

# Current Opinion in Rheumatology

**Editor-in-Chief:** John Varga

**Raynaud phenomenon, scleroderma, overlap  
syndromes and other fibrosing syndromes**

Edited by Monique Hinchcliff

**Crystal deposition diseases**

Edited by Sara Tedeschi

**Myositis and myopathies**

Edited by Marie Hudson, Didem Saygin and Angeles Galindo-Feria

*Current Opinion in Rheumatology* was launched in 1989. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of Rheumatology is divided into 15 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal's Section Editors for this issue.

## SECTION EDITORS

### Monique Hinchcliff

Dr. Monique Hinchcliff is Director of Clinical and Translational Research for Rheumatology, Allergy & Immunology at the Yale School of Medicine and the Director of the Yale Scleroderma Program. She received her medical degree from the Rosalind Franklin University Chicago Medical School and completed her medicine residency at Norwalk Hospital in Connecticut. She completed rheumatology fellowship training at Northwestern University Feinberg School of Medicine in Chicago, IL while earning a Master of Science degree in Clinical Investigation.

Her research program includes clinical, interventional and observational studies, with the goal of better understanding systemic sclerosis and identifying new and repurposed treatments for patients with systemic sclerosis. She has many active research collaborations both in the US and abroad. Clinically, Dr. Hinchcliff leads a team of multidisciplinary specialists with expertise in caring for patients with systemic sclerosis. She participates in ongoing clinical trials in order to give patients access to the latest treatments that may be beneficial.

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Sara Tedeschi, MD, MPH is a rheumatologist and clinical investigator at Brigham and Women's Hospital and Assistant Professor of Medicine at Harvard Medical School. Her primary research focus is calcium pyrophosphate deposition (CPPD) disease. Dr. Tedeschi serves as



Head of Crystalline Arthritic Diseases at Brigham and Women's Hospital, where she established the prospective Brigham CPPD (BRIC) Registry in 2022. She co-led the development of the ACR/EULAR 2023 CPPD Disease Classification Criteria, serves as Co-Chair of the OMERACT CPPD Working Group, and is Section Editor for Crystal Deposition Diseases for *Current Opinion in Rheumatology*. Dr. Tedeschi also serves as Director of the Brigham and Women's Hospital Giant Cell Arteritis Fast Track Clinic and is a member of the ACR Quality of Care Criteria Subcommittee.

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# Advanced imaging in systemic sclerosis: distinguishing activity from damage across organ systems

*Alana Haussmann and Elizabeth R. Volkman*

## Purpose of review

A central challenge in systemic sclerosis (SSc) is the inability to distinguish active, potentially reversible disease, from damage, irreversible fibrosis. Current imaging modalities, including high-resolution computed tomography (HRCT) and echocardiography, predominantly capture structural damage and cannot resolve this distinction. This review outlines next generation imaging modalities for SSc with focus on quantitative machine learning algorithms and molecular imaging.

## Recent findings

The unifying advance across organ systems is a shift from documenting damage to measuring disease activity directly. Machine-learning-derived quantitative HRCT detects radiological patterns of ILD sensitive to change in SSc-associated interstitial lung disease. Parametric cardiac magnetic resonance mapping resolves diffuse interstitial fibrosis missed by late gadolinium enhancement. Fibroblast activation protein inhibitor PET (FAPI-PET) visualizes active fibrogenesis in lung and myocardium, identifying biologically active disease even before structural distortion occurs. [<sup>18</sup>F]Sodium fluoride PET detects metabolically active calcinosis. High-frequency ultrasound, elastography, and optical coherence tomography (OCT)-angiography extend objective assessment of cutaneous and microvascular involvement.

## Summary

Emerging imaging modalities in SSc may enable earlier detection of active disease amenable to treatment modification and yield more sensitive endpoints for SSc clinical trials.

## Keywords

imaging biomarkers, molecular imaging, quantitative imaging, systemic sclerosis

## INTRODUCTION

Systemic sclerosis (SSc) is a clinically heterogeneous disease, and manifestations can differ not only between patients but also across organ systems within the same patient [1]. Disease activity and damage in SSc are currently assessed through a combination of clinical examination, patient-reported symptoms, organ-specific physiologic testing, and serologic markers. These measures are pragmatic but have substantial limitations. Most are nonspecific to SSc [e.g. N-terminal pro-B-type natriuretic peptide (NT-proBNP)], are influenced by extra-pulmonary or non-SSc comorbidities (e.g. pulmonary function testing), and lack the sensitivity to detect early or subclinical involvement [e.g. modified Rodnan skin score (mRSS)] [2<sup>••</sup>,3]. Fundamentally, few of these tools reliably distinguish ongoing biologic activity from accumulated structural damage, a distinction that informs therapeutic decision-making across the disease course [3].

Imaging can address this gap, but the modalities in routine use share consistent limitations [4–6]. For example, high-resolution computed tomography (HRCT) of the chest and transthoracic echocardiography capture structural damage rather than biologic activity and cannot reliably separate active, potentially reversible disease from established fibrosis. These constraints not only affect clinical practice but have also hindered our ability to effectively include radiological outcomes as primary endpoints for SSc clinical trials.

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## KEY POINTS

- Existing and emerging imaging modalities for SSc play an important role in establishing organ system involvement and predicting prognosis.
- New imaging tools, including molecular imaging, may serve as surrogate markers of disease activity by tracking ongoing fibrotic remodeling.
- Integrating imaging studies into clinical development models for SSc may expand therapeutic discovery for SSc disease features with no disease modifying interventions available (e.g. calcinosis, gastrointestinal disease).
- Future research is needed to define clinically meaningful changes in imaging endpoints both for clinical practice and research application.

A new generation of quantitative and molecular imaging addresses these gaps (Fig. 1). Machine-learning-derived quantitative CT and ultrasound metrics, parametric cardiac magnetic resonance (MR) mapping, and PET employing radiotracers that target fibroblast activation protein (FAP) represent emerging imaging modalities to advance our ability to measure disease activity. Distinguishing active disease from damage may improve our ability to personalize treatment [7,8]. For example, in SSc-associated interstitial lung disease (ILD), two patients with comparable extents of fibrosis on HRCT may have divergent levels of fibroblast activation on FAPI-PET; the patient with high tracer uptake may benefit from intensified immunomodulatory therapy, whereas the patient with low uptake despite similar structural disease may not derive incremental benefit from escalation. The research implications are equally consequential. Trials enriched for patients with active disease may be more likely to capture treatment effects [9].

This review describes novel imaging approaches across the lung, heart, skin, peripheral vasculature, and calcinosis, with additional notes on emerging gastrointestinal, renal, and cerebrovascular applications (Table 1). These novel imaging modalities hold promise for clinical practice and trial application, addressing specific clinical questions across organ systems (Table 2).

## METHODS

A targeted literature search was conducted via MEDLINE/PubMed for articles published from January 2020 through April 2026. Search terms included 'systemic sclerosis', 'scleroderma', 'imaging', and

'biomarker' combined with their Medical Subject Headings (MeSH) terms and modality-specific keywords 'high-resolution computed tomography', 'magnetic resonance imaging', 'optical coherence tomography', 'fibroblast activation protein inhibitor positron emission tomography (FAPI-PET)', 'sodium fluoride PET', 'dual-energy computed tomography', 'ultrasound', 'ultrasound elastography', and 'high-frequency ultrasound'. Boolean operators (AND, OR) were applied across each modality-specific searches. Inclusion criteria comprised clinical trials, observational studies, and case series ( $N \geq 9$ ) reporting imaging or biomarker applications in SSc. Select foundational studies published before 2020 were included to provide historical context. Exclusion criteria included non-English articles, isolated case reports without broader applicability, and studies lacking clearly defined imaging or biomarker endpoints.

## PULMONARY IMAGING

ILD accounts for the largest share of SSc-related mortality, a pressure that has driven rapid development of novel pulmonary imaging biomarkers [10].

However, neither conventional radiological assessment with HRCT, nor pulmonary function testing can distinguish disease damage from activity in patients with SSc-ILD. HRCT visualizes the structural sequelae of fibrogenesis (reticulation, traction bronchiectasis, ground-glass opacity) but cannot resolve whether the fibrotic process is ongoing or quiescent. Forced vital capacity (FVC) and diffusing capacity (DLCO) reflect the cumulative physiologic consequence of interstitial expansion and alveolar loss; however, both decline only after meaningful architectural injury has occurred. Visual HRCT scoring is subject to interobserver bias and can be insensitive to subtle change [4]. Furthermore, the FVC, the accepted primary endpoint for SSc-ILD trials, can be confounded by extrapulmonary contributions [2<sup>nd</sup>,11]. Reliable detection of early, active disease would open the most meaningful therapeutic window.

## Quantitative imaging analysis

Quantitative imaging analysis (QIA) and radiomics address this gap by extracting automated, fine-grained measurements of lung density and texture from standard HRCT acquisitions. Machine-learning classifiers generate quantitative lung fibrosis (QLF) and quantitative interstitial lung disease (QILD) scores that correlate with FVC, DLCO, and patient-reported dyspnea across independent SSc cohorts, including Scleroderma Lung Studies I and II [12,13]. Short-interval QLF change predicts long-

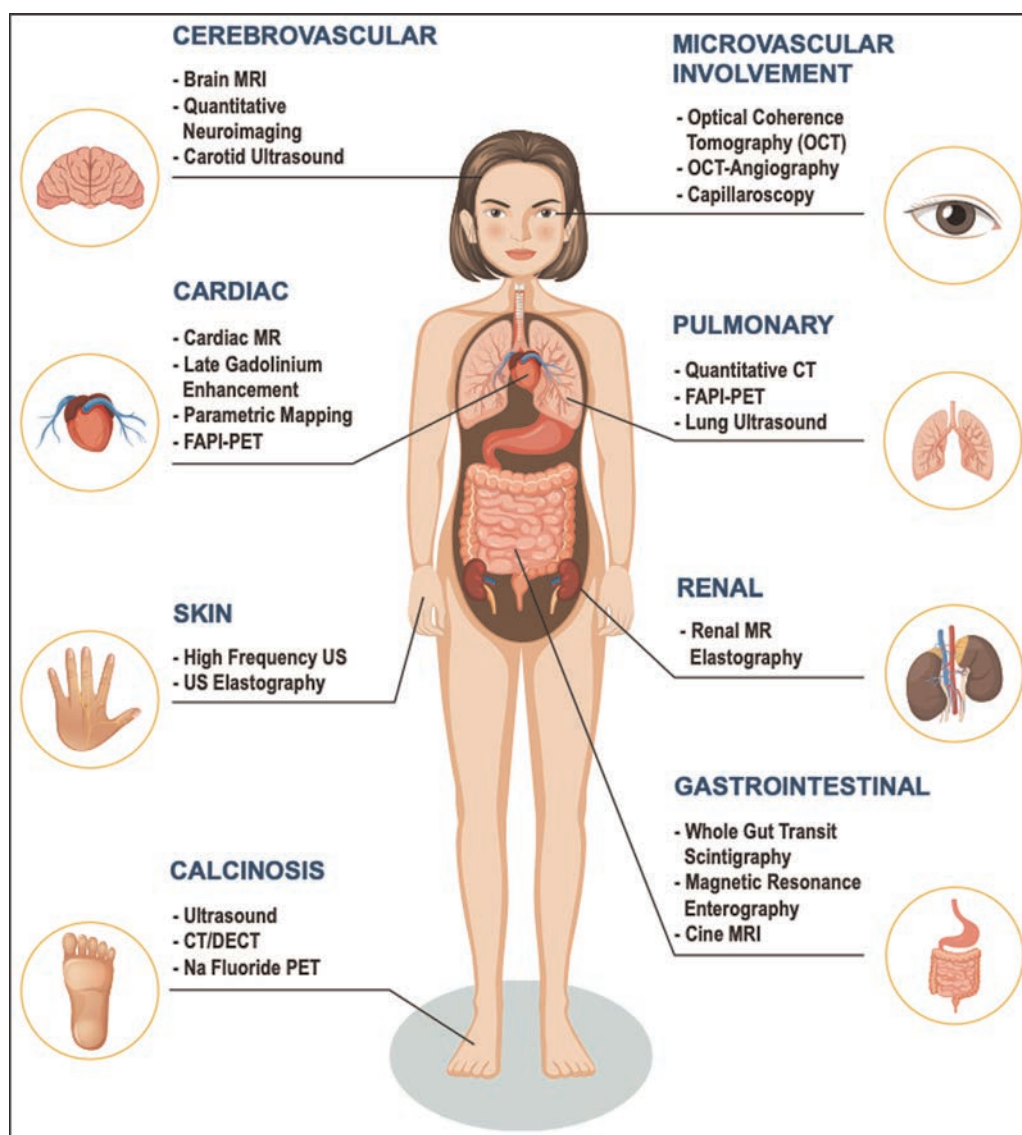


**FIGURE 1.** Emerging and existing advanced imaging in systemic sclerosis by organ system.

term mortality and progression-free survival, supporting earlier identification of progressors and enrichment of disease-modifying trials [9]. Post hoc QILD analyses of the focuSSced tocilizumab trial detected treatment-attributable change invisible to FVC, supporting QILD's emergence as a candidate trial endpoint [14]. Baseline HRCT-derived radiomic signatures further improve early-disease progression prediction, outperforming visual scoring [15].

### Pulmonary molecular imaging

Where QIA measures structural damage, FAPI-PET targets FAP, a serine protease expressed on reactive myofibroblasts, enabling direct in-vivo visualization of active fibrogenesis [16]. FAPI uptake may

identify biologically active disease even before structural distortion accrues (Fig. 2). Furthermore, prospective studies have demonstrated an association between FAPI uptake with subsequent radiological and physiologic progression of ILD in patients with SSc and idiopathic inflammatory myositis [17<sup>••</sup>,18]. A translational study conducted on patients with end-stage ILD confirmed a robust correlation between FAPI uptake and the histopathological expression of FAP in explanted lung tissue of patients who underwent lung transplantation [19<sup>••</sup>]. Clinically, FAPI uptake may define an earlier therapeutic window; for trials, it represents a candidate pharmacodynamic biomarker for agents targeting fibroblast activation. FAPI tracers remain investigational in SSc.

**Table 1.** Novel imaging modalities in systemic sclerosis by organ system

| Organ system           | Standard tool                   | Novel modality                                                                                                                                | Disease state captured                                                              | Current status                                                                            |
|------------------------|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Lung (ILD)             | Visual HRCT, FVC                | Quantitative CT (QLF, QILD) [12,13]; HRCT-derived radiomics [15]; [ <sup>68</sup> Ga]Ga-FAPI-04 PET [16,17 <sup>■</sup> ,18,19 <sup>■</sup> ] | Cumulative fibrosis burden, short-term progression risk, active fibrogenesis        | Specialized centers; FAPI-PET investigational                                             |
| Heart                  | Echocardiography, LGE-CMR       | Parametric CMR mapping (T1, ECV, T2) [26–29]; FAPI-PET [30]                                                                                   | Diffuse interstitial fibrosis, active myocardial inflammation, ongoing fibrogenesis | Expert centers; FAPI-PET investigational                                                  |
| Skin                   | Modified Rodnan skin score      | High-frequency ultrasound [45,46], ultrasound elastography [46,47]                                                                            | Subclinical fibrosis, mechanical stiffness, treatment-responsive change             | Research; multicenter feasibility shown                                                   |
| Peripheral vasculature | Nailfold capillaroscopy         | Optical coherence tomography (OCT), OCT-angiography [55,56,57 <sup>■</sup> ]                                                                  | Quantitative capillary density, perfusion, preclinical microvasculopathy            | Research; SLE precedent established                                                       |
| Calcinosis             | Plain radiography, SCTC scoring | Musculoskeletal ultrasound [41,42]; Dual-energy CT with AI quantification [37,39,40]; [ <sup>18</sup> F]NaF-PET [43,44]                       | Volumetric calcinosis burden; active, metabolically driven calcification            | Research; AI proof-of-concept; pilot stage for [ <sup>18</sup> F]NaF                      |
| Gastrointestinal       | Endoscopy, manometry            | Whole-gut transit scintigraphy [59]; MR enterography; cine MRI [61,62]                                                                        | Multisegment dysmotility, bowel wall pathology, esophageal peristalsis              | Specialized centers; cross-disease borrowing from IBD                                     |
| Renal                  | Ultrasound, serum creatinine    | MR elastography; BOLD MRI; diffusion-weighted imaging [64]                                                                                    | Renal fibrosis, oxygenation, microstructural change                                 | Investigational (validated in CKD); unvalidated in SSs                                    |
| Cerebrovascular        | Standard brain MRI              | Diffusion tensor imaging, quantitative perfusion MRI [66,67]; carotid intimal-medial thickness [65]                                           | Subclinical white matter disease, perfusion deficits, cerebrovascular event risk    | Investigational; cross-disease borrowing from cerebral small vessel disease and neuro-SLE |

AI, artificial intelligence; BOLD, blood oxygen level-dependent; CKD, chronic kidney disease; CMR, cardiovascular magnetic resonance; CT, computed tomography; ECV, extracellular volume; FAPI, fibroblast activation protein inhibitor; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IBD, inflammatory bowel disease; ILD, interstitial lung disease; LGE, late gadolinium enhancement; NaF, sodium fluoride; OCT, optical coherence tomography; QILD, quantitative interstitial lung disease score; QLF, quantitative lung fibrosis score; SCTC, Scleroderma Clinical Trials Consortium; SLE, systemic lupus erythematosus; SSs, systemic sclerosis.

## Lung ultrasound

Semi-quantitative scoring of pleural B-lines provides a low-cost, radiation-free bedside screening tool that correlates with HRCT-defined ILD extent in SSs [20,21]. Absence of ionizing radiation supports frequent serial monitoring in younger patients in whom cumulative radiation exposure is a particular concern.

## CARDIAC IMAGING

Cardiac involvement accounts for approximately 20% of SSs-related deaths and frequently remains subclinical until presentation with fatal arrhythmia [22,23,24<sup>■</sup>].

### Late gadolinium enhancement

Principal diagnostic and prognostic biomarker. Cardiovascular magnetic resonance (CMR) imaging with LGE was the first tool to detect cardiac involvement attributable to SSs. LGE detects focal replacement fibrosis in

up to 60% of SSs patients and independently predicts arrhythmia and heart failure, with event-free survival below 50% at 5 years in LGE-positive individuals [25]. However, LGE relies on signal-intensity contrast between scarred and normal myocardium and therefore requires a normal reference region. The dominant cardiac feature of SSs is patchy diffuse interstitial fibrosis from recurrent microvascular ischemia rather than focal infarction; when fibrosis is uniformly distributed, no reference region exists [6,26]. LGE thus captures replacement scar but may miss the earlier diffuse interstitial phase, which is the window in which immunomodulatory and antifibrotic therapy are most likely to be effective.

### Parametric mapping

Native T1 and extracellular volume (ECV) measurements, both reflecting expansion of the interstitial

**Table 2.** Clinical questions in systemic sclerosis answered by novel imaging

| Clinical question                                                           | Best modality                                                         | Quantitative readout                             | Action it informs                                                                                            | References                                 |
|-----------------------------------------------------------------------------|-----------------------------------------------------------------------|--------------------------------------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Is this patient's SSc-ILD progressing despite stable spirometry?            | Quantitative CT (QLF/QILD change over 6–12 months)                    | $\Delta$ % lung involvement                      | Escalate to antifibrotic or immunomodulatory therapy                                                         | [9,12,14]                                  |
| Is the patient's interstitial lung disease still actively forming fibrosis? | FAP-PET                                                               | Tracer uptake (SUVmax)                           | Candidate for early antifibrotic intervention (research stage)                                               | [16,17 <sup>***</sup> ,19 <sup>***</sup> ] |
| Will this patient with early SSc-ILD progress in the next year?             | Baseline HRCT-derived radiomic signature                              | Radiomic risk classifier                         | Risk stratification; trial enrichment; closer surveillance                                                   | [15]                                       |
| Does this asymptomatic SSc patient have subclinical myocardial fibrosis?    | Parametric CMR (native T1, ECV)                                       | Native T1 (ms); ECV (%)                          | Closer cardiac surveillance; consider therapy escalation                                                     | [26,28,29]                                 |
| Is there active myocardial inflammation?                                    | T2 mapping (CMR)                                                      | T2 (ms)                                          | Initiate or escalate immunosuppression for myocarditis                                                       | [27]                                       |
| Is myocardial fibrosis still being actively built?                          | Cardiac FAPI-PET                                                      | Tracer uptake (SUVmax)                           | Candidate for early antifibrotic intervention (research)                                                     | [30]                                       |
| Is the patient's skin disease progressing despite a stable mRSS?            | High-frequency ultrasound; ultrasound elastography                    | Dermal thickness (mm); shear wave velocity (m/s) | Detect subclinical fibrosis; objectively assess therapy response                                             | [45–47]                                    |
| Is microvascular disease worsening despite vasodilator therapy?             | Optical coherence tomography angiography (OCT-A)                      | Vessel density; vascular perfusion               | Escalate or switch vasodilator therapy, consider workup for digital ulcer or pulmonary arterial hypertension | [55,56,57 <sup>***</sup> ]                 |
| Is this patient's calcinosis metabolically active?                          | [ <sup>18</sup> F]NaF-PET                                             | Tracer uptake (SUVmax)                           | Identify previsible active disease (research stage)                                                          | [43,44]                                    |
| Where in the GI tract is the patient's dysmotility most severe?             | Whole-gut transit scintigraphy                                        | Segmental transit times                          | Targeted prokinetic therapy by region; trial endpoint                                                        | [59]                                       |
| Is this patient at increased cerebrovascular event risk?                    | Carotid intimal–medial thickness; brain MRI (white matter, perfusion) | Carotid IMT (mm); white matter lesion burden     | Cardiovascular risk modification; consider antiplatelet therapy                                              | [65–67]                                    |

CMR, cardiac magnetic resonance; CT, computed tomography;  $\Delta$ , change; ECV, extracellular volume; FAP, fibroblast activation protein; FAPI, fibroblast activation protein inhibitor; FAPI-PET, fibroblast activation protein inhibitor PET; GI, gastrointestinal; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IMT, intima–media thickness; mRSS, modified Rodnan skin score; NaF, sodium fluoride; OCT-A, optical coherence tomography angiography; QILD, quantitative interstitial lung disease; QLF, quantitative lung fibrosis; SSc, systemic sclerosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease; SUVmax, maximum standardized uptake value.

space, quantify diffuse fibrosis, and T2 mapping captures active myocardial inflammation. Together these sequences nearly double the diagnostic sensitivity of LGE alone [27]. Abnormal mapping values are present in over half of SSc patients, predict adverse cardiac events in asymptomatic individuals, and are the only CMR abnormality in roughly one-third of cases [25,28,29]. CMR carries no ionizing radiation and has been progressively integrated into routine cardiac risk stratification at expert centers.

### Cardiac molecular imaging

Where LGE and parametric mapping characterize damage and inflammation, FAPI-PET visualizes

ongoing myocardial fibrogenesis [30]. In a proof-of-concept study of 14 SSc patients, myocardial FAPI uptake correlated with arrhythmia burden, N-terminal pro-B-type natriuretic peptide (NT-proBNP) elevation, and LGE positivity, with histologic confirmation of FAP-expressing myofibroblasts in FAPI-avid regions; serial imaging additionally captured dynamic changes in fibrogenic activity not reflected by parametric CMR [30].

The integration of CMR with FAPI-PET separates cumulative fibrosis from ongoing fibrogenesis, and patients with cardiac FAPI uptake in the absence of LGE may define the most actionable group for disease-modifying therapy.

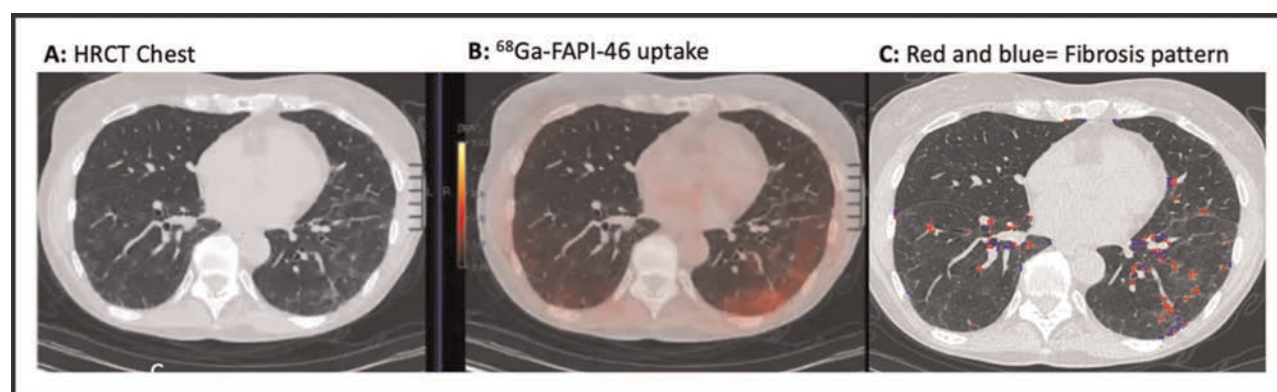


**FIGURE 2.** Evidence of increased uptake of  $^{68}\text{Ga}$ -FAPI-46 (panel b, red coloring) in structurally normal areas of the lung on HRCT (panel a) in patient with early systemic sclerosis-associated interstitial lung disease (<2 years disease duration) who is Scl-70 positive. Panel c demonstrates the areas of fibrosis represented in red and blue. Quantitative Lung Fibrosis (QLF) score for the whole lung was only 2.2%. SUVmax was increased at 2.3.

## CALCINOSIS

Calcinosis cutis is a painful and disfiguring complication of SSc that causes chronic refractory pain, functional limitation, and recurrent soft tissue infections [31,32]. It affects up to 40% of patients and is particularly prevalent in those with anticentromere antibodies [31,33]. Clinical development for this manifestation has been hindered by the lack of objective endpoints to measure calcinosis activity.

### Plain radiography and computed tomography

Plain radiography remains the principal diagnostic and longitudinal monitoring biomarker for calcinosis but cannot quantify lesion volume, depth, or distinguish active from quiescent disease [34,35]. The Scleroderma Clinical Trials Consortium (SCTC) radiographic scoring system has improved standardization for hand calcinosis, demonstrating inter-rater reliability and sensitivity to longitudinal change [36].

Conventional CT extends structural assessment by enabling three-dimensional segmentation and volumetric quantification of calcinosis lesions (Fig. 3). Open-source segmentation tools allow direct measurement of lesion volume and radiodensity, providing objective endpoints that radiography alone cannot generate [37]. Building on this approach, the Scleroderma Calcinosis Cutis Score (SC2S) provides a standardized imaging metric to quantify systemic sclerosis-associated calcinosis cutis [38]. Dual-energy computed tomography (DECT) refines structural assessment by differentiating calcium from bone and dense soft tissue, enabling compartment mapping within subcutaneous, intramuscular, and fascial planes [39,40]. Early work

integrating U-Net-based convolutional neural networks with DECT imaging supports the feasibility of automated volumetric quantification [37].

### Musculoskeletal ultrasound

Musculoskeletal ultrasound serves as a bedside, non-ionizing diagnostic tool that provides precise anatomic localization within subcutaneous, intramuscular, and fascial planes, useful for longitudinal monitoring [31,41,42]. Ultrasound can also identify calcinosis in atypical sites such as the ureter, kidney, and parotid gland, and provide guidance for sodium thiosulfate injection [41]. Operator dependence and reduced reproducibility for high-burden disease remain limitations.

### Functional imaging

[ $^{18}\text{F}$ ]Sodium fluoride ([ $^{18}\text{F}$ ]NaF) PET targets hydroxyapatite turnover and serves as a candidate prognostic biomarker for active mineralization [43]. In a pilot study of nine patients with SSc, [ $^{18}\text{F}$ ]NaF-PET demonstrated uptake in 70% of CT-detected lesions and identified additional subclinical calcifications not detected by CT, suggesting detection of an early, metabolically active disease phase [44].

Most interventions have been evaluated in established disease; whether treatment at an earlier, active stage alters progression is unknown. Analogous to FAPI-PET in SSc-ILD, [ $^{18}\text{F}$ ]NaF-PET may define a window in which calcification can be identified and intervened upon prior to tissue destruction [16,19<sup>\*\*\*</sup>]. Prospective studies with standardized imaging protocols are needed to validate these approaches and establish trial-ready endpoints.

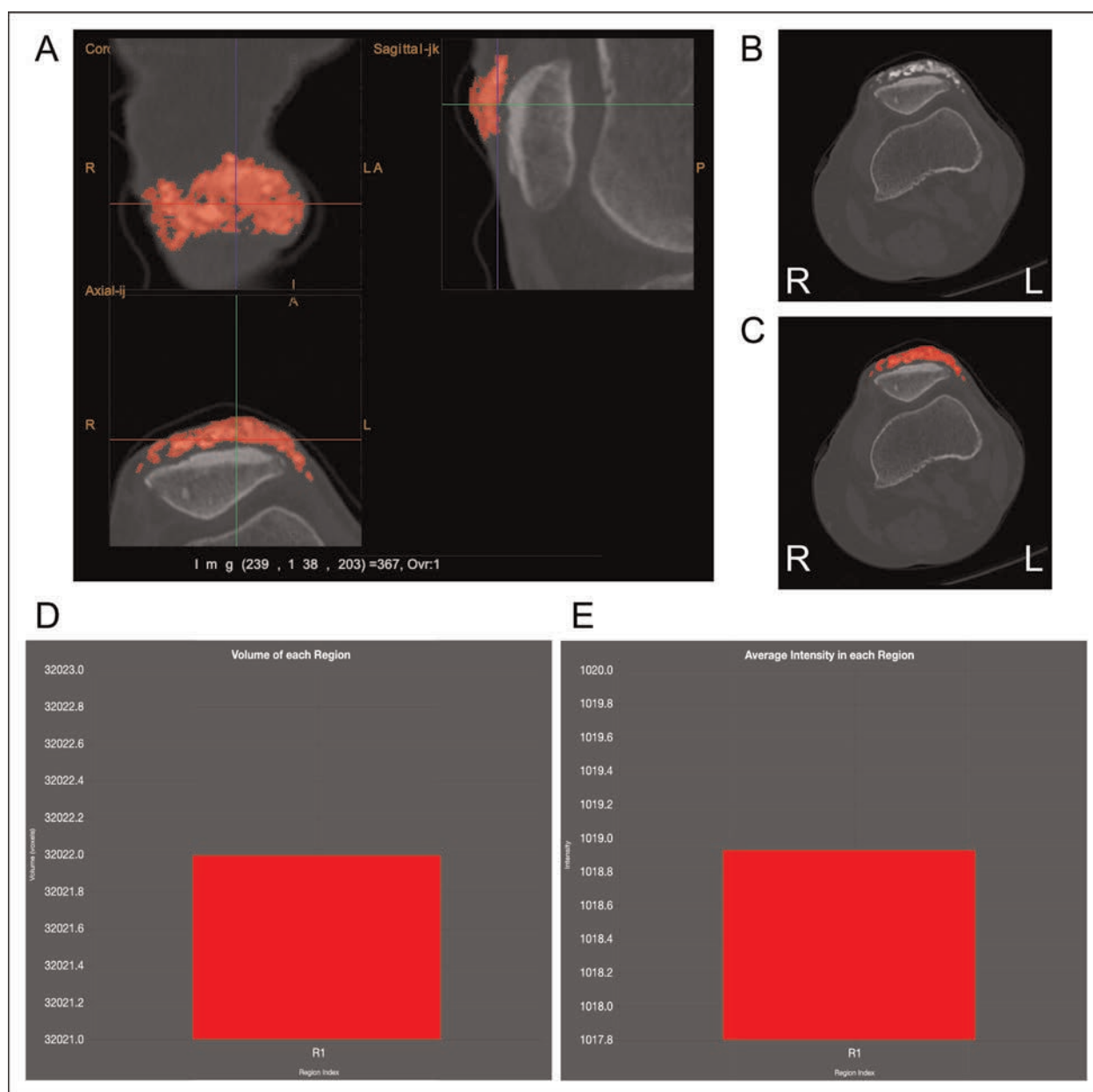


**FIGURE 3.** Open-source BiImageSuite (BIS) Web software used to annotate patellar calcinosis cutis in a patient with systemic sclerosis. (a) Three-dimensional view on the software dashboard of computed tomography (CT) exam with calcinosis cutis (CC) painted red. (b) Rasterized CT image of CC lesion without CC painted. (c) Rasterized CT image of CC lesion with CC painted red on axial image. (d) Voxel count of painted CC lesion. Volume ( $\text{mm}^3$ ) was quantified by multiplying painted voxel counts by the voxel volume ( $\text{mm}^3/\text{voxel}$ ) listed in BIS WEB software 'viewer information'. (e) Radiodensity (Hounsfield units) of painted CC area.

### CUTANEOUS SCLEROSIS

Skin involvement is a defining feature of SSc, and the mRSS has anchored its diagnosis, classification, and longitudinal stratification for decades. The mRSS serves as the principal clinical and trial biomarker for cutaneous disease but has well recognized limitations as a measure of active fibrogenesis. It shows interobserver variability that limits sensitivity to subtle change, and it quantifies cumulative skin

thickness rather than measures underlying fibrogenic activity [5]. These limitations have practical consequences: no phase 3 randomized controlled trial in SSc has demonstrated a treatment effect on mRSS as a successfully met primary endpoint, including high-dose D-penicillamine, recombinant relaxin, oral type I collagen, and tocilizumab in the focuSSced trial [5,7].

High-frequency ultrasound (HFUS) and ultrasound elastography offer objective, examiner-independent

diagnostic and longitudinal monitoring biomarkers for cutaneous sclerosis. HFUS measures dermal thickness with submillimeter resolution and detects increased dermal echogenicity correlating with histologic fibrosis, with feasibility and reproducibility demonstrated across multicenter SSc cohorts [45,46]. Ultrasound elastography quantifies skin stiffness, a mechanical correlate of fibrosis that detects abnormalities before they are palpable and tracks change with treatment [46]. Together these modalities may identify subclinical fibrosis missed by clinical scoring and could ultimately complement or replace mRSS as both a clinical and trial-ready outcome [45,47].

## MICROVASCULAR INVOLVEMENT

Micro-vasculopathy is an early and ubiquitous manifestation of SSc and frequently precedes overt clinical fibrosis by several years [48,49]. Nailfold capillaroscopy serves as the principal diagnostic classification and prognostic biomarker for this domain. It distinguishes primary from secondary Raynaud phenomenon, supports SSc diagnosis, and tracks disease evolution through progression of established capillaroscopic patterns [50]. In patients with Raynaud phenomenon and SSc-specific autoantibodies, capillaroscopic abnormalities are central to emerging frameworks defining pre-SSc and identifying at-risk patients for preventive intervention [51]. Validated scoring systems such as the NEMO score also predict subsequent development of digital ulcers [52]. The NEMO score was initially defined as the number of microhemorrhages and was later used to denote the combined number of microhemorrhages and microthromboses [53]. Capillaroscopy is, however, qualitative, examiner-dependent, and provides limited perfusion data [54].

Optical coherence tomography (OCT) and OCT-angiography (OCT-A) extend microvascular assessment with quantitative, examiner-independent measures of capillary density and perfusion [55,56]. Recent work in SSc patients has demonstrated that OCT-A detects retinal microvascular changes that correlate with nailfold capillaroscopic findings, suggesting OCT-A may identify SSc microvasculopathy before clinical manifestations appear, including digital ulcers or pulmonary arterial hypertension [57<sup>\*\*\*</sup>].

## GASTROINTESTINAL IMAGING

Gastrointestinal involvement affects up to 90% of SSc patients, yet validated imaging biomarkers have lagged behind [58]. Standard evaluation depends on upper endoscopy and colonoscopy, both of which are invasive and burdensome to patients while

providing only mucosal information from single anatomical segments. Manometry and breath testing add functional readouts but are similarly limited to one organ at a time and provide little capacity to track disease activity over time.

Cross-segment molecular imaging is beginning to address these gaps. Whole-gut transit scintigraphy, a single radionuclide-based examination that quantifies transit across the esophagus, stomach, small bowel, and colon, serves as a candidate diagnostic and longitudinal monitoring biomarker for the multisegment dysmotility characteristic of SSc [59]. Magnetic resonance enterography, validated in inflammatory bowel disease, has been applied to SSc-related small bowel disease and pseudo-obstruction [60,61]. Its sensitivity to change in SSc has not been established and needs to be tested and confirmed in longitudinal studies. Cine MRI, a rapid sequential MR acquisition that visualizes motion in real time, offers a complementary assessment of esophageal peristalsis and bolus transit [62]. Together, these modalities may finally provide the objective, trial-ready endpoints that SSc gut disease has lacked.

## EMERGING INSIGHTS IN RENAL AND CEREBROVASCULAR IMAGING IN SYSTEMIC SCLEROSIS

Renal and cerebrovascular involvement remain among the least-imaged SSc manifestations despite their growing recognition as contributors to long-term morbidity. Renal involvement extends beyond scleroderma renal crisis to include chronic renal disease [63,64]. Renal magnetic resonance elastography and blood oxygen level-dependent MRI quantify renal fibrosis and microstructural change but remain unvalidated in SSc cohorts [65].

Stroke risk in SSc is elevated and linked to both small vessel ischemic injury and macrovascular atherosclerosis [66]. Brain MRI demonstrates white matter abnormalities and regional hypoperfusion correlating with nailfold capillaroscopy findings, and carotid intima-media thickness on ultrasound predicts cerebrovascular event risk [66]. Quantitative neuroimaging including diffusion tensor imaging and perfusion MRI, established in cerebral small vessel disease and neuropsychiatric SLE, may enable systematic detection of subclinical cerebrovascular disease in SSc [67,68].

## CONCLUSION

Advanced imaging stands to fundamentally accelerate clinical research in SSc and improve patient outcomes. Quantitative imaging biomarkers can enrich trial cohorts with patients most likely to progress and

respond, increasing statistical efficiency [9,14]. Imaging-defined endpoints detect treatment-attributable change earlier than physiologic measures [14]. Targeted radiotracers such as FAPI-PET offer a candidate pharmacodynamic biomarker class for novel therapies, providing a mechanistic readout of drug-target engagement that clinical trials in SSc have historically lacked [16,30]. Activity-versus-damage stratification additionally permits proof-of-concept studies at the stage of disease most likely to respond to intervention.

The unifying advance across these modalities is one shift: from documenting damage to measuring fibrogenesis and disease activity directly. The next decade will be defined by whether composite imaging phenotypes integrating these measures across organs can capture SSc as a unified multiorgan disease, and whether prospective data confirm that such phenotypes predict trajectory and treatment response. Standardization across vendors, institutions, and trial protocols is the principal bottleneck. Together, these advances open a path toward earlier diagnosis, earlier treatment, and meaningfully better outcomes for patients with SSc.

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## Conflicts of interest

There are no conflicts of interest.

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# Redefining systemic sclerosis-associated pulmonary hypertension as an immune-mediated vasculopathy across the cardiopulmonary circulation

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## Purpose of review

Systemic sclerosis-associated pulmonary hypertension (SSc-PH) is a heterogeneous, difficult-to-treat condition in which multiple pulmonary hypertension groups frequently overlap. Recent evidence suggests that vascular involvement may contribute to multiple SSc-PH phenotypes. This review highlights recent advances in understanding vascular features and emerging therapeutic strategies beyond vasodilation.

## Recent findings

Pathological and imaging studies demonstrate that vascular remodeling in SSc-PH extends beyond pulmonary arteries to pulmonary veins, capillaries, and coronary microcirculation, consistent with widespread immune-mediated vascular dysfunction. These features are increasingly recognized across various SSc-PH phenotypes: pulmonary arterial hypertension and pulmonary veno-occlusive disease; pulmonary hypertension associated with left heart disease, most commonly heart failure with preserved ejection fraction (PH-HFpEF); and pulmonary hypertension-associated with interstitial lung disease (PH-ILD); each of which is often accompanied by intrinsic right ventricular (RV) dysfunction. Emerging therapies targeting activin signaling, macrophage–vascular crosstalk, B-cell immunity, and endothelial-to-mesenchymal transition require further study but may be essential to identifying disease-modifying approaches across SSc-PH phenotypes.

## Summary

There is increasing recognition that vascular remodeling across the cardiopulmonary circulation may underlie multiple SSc-PH phenotypes, providing novel insight into SSc-PH disease mechanisms and rationale for the development of therapies targeting vascular remodeling, fibrosis, inflammation, and intrinsic RV dysfunction beyond conventional vasodilator treatment.

## Keywords

inflammation, pulmonary vascular disease, right ventricular dysfunction, scleroderma

## INTRODUCTION

Pulmonary hypertension is clinically classified into five groups according to the World Symposium on Pulmonary Hypertension (WSPH) classification, and therapeutic strategies differ by cause [1]. Pulmonary hypertension is also categorized according to hemodynamic features as precapillary, isolated postcapillary, or combined precapillary and postcapillary pulmonary hypertension. Systemic sclerosis-associated pulmonary hypertension (SSc-PH) represents a heterogeneous condition in which multiple pulmonary hypertension phenotypes, including WHO Group 1 pulmonary arterial hypertension (PAH)/pulmonary veno-occlusive disease (PVOD), WHO Group 2 pulmonary hypertension associated with left heart disease, most commonly heart failure with preserved ejection fraction (PH-HFpEF), and WHO

Group 3 pulmonary hypertension associated with interstitial lung disease (PH-ILD), frequently overlap and may evolve during the disease course [2]. This clinical heterogeneity is characterized by overlapping precapillary and postcapillary hemodynamic features, reflecting vascular remodeling across multiple pulmonary vascular compartments. Despite

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## KEY POINTS

- SSc-PH may be better understood as a spectrum of immune-mediated cardiopulmonary vasculopathy rather than distinct pulmonary hypertension subtypes.
- Vascular remodeling involving pulmonary arteries, veins, capillaries, and myocardial microcirculation may contribute to multiple SSc-PH phenotypes and intrinsic right ventricular dysfunction.
- Exercise-based assessment and immune profiling may facilitate earlier detection and more mechanism-based treatment strategies in SSc-PH.

advances in therapies for both SSc and PAH, the overall prognosis of SSc-PH remains poor [3,4]. Therefore, improved understanding of the complex pathobiology of SSc-PH is essential for the development of more effective therapeutic strategies.

## RECONSIDERING SYSTEMIC SCLEROSIS-ASSOCIATED PULMONARY HYPERTENSION AS A VASCULOPATHY

Accumulating evidence suggests that vasculopathy in SSc-PH is not limited to WHO Group 1 PAH/PVOD, but contributes broadly across multiple forms of SSc-PH, including WHO Group 2 PH-HFpEF, and WHO Group 3 PH-ILD, which share heightened right ventricular (RV) afterload sensitivity (compared to idiopathic PAH), due to coronary microvascular dysfunction leading to intrinsic RV dysfunction (Table 1). In this context, SSc-PH may be better understood as a spectrum of immune-mediated cardiopulmonary vasculopathy involving the pulmonary arteries, capillaries, veins, and myocardial microcirculation (Fig. 1).

## WHO GROUP 1 PULMONARY HYPERTENSION: ARTERIAL AND VENOUS REMODELING

Although vasodilator therapy has improved outcomes in idiopathic PAH, patients with SSc-PAH have substantially poorer survival and reduced treatment responsiveness [4], which are due to differences in pulmonary vascular abnormalities in SSc-PAH compared to idiopathic PAH. Instead of the common plexiform lesions with endothelial and smooth muscle cell growth found in idiopathic PAH or non-SSc connective tissue diseases such as systemic lupus erythematosus, SSc-PAH often presents with a more fibrous intimal thickening, and in some cases, small-vessel collapse [5]. Pulmonary vascular remodeling extends beyond arteries to veins and venules. Histopathological studies have demonstrated fibrous remodeling of the pulmonary venous system, and imaging studies have identified frequent PVOD-like features [6–8]. These widespread arterial, small-vessel, and venous vascular changes, coupled with intrinsic RV dysfunction, may contribute to poor responsiveness to pulmonary vasodilator therapy in SSc-PAH.

## WHO GROUP 2 PULMONARY HYPERTENSION: HEART FAILURE WITH PRESERVED EJECTION FRACTION AS PULMONARY VASCULAR DISEASE

In SSc, WHO Group 2 pulmonary hypertension is most commonly associated with HFpEF, which is frequently accompanied by pulmonary hypertension and poor clinical outcomes [9,10]. In HFpEF, elevated left-sided filling pressures are transmitted backward through the pulmonary venous circulation to pulmonary capillaries and arteries. This hemodynamic burden initiates a cascade of pulmonary vascular remodeling involving veins, capillaries, and small arterioles. Histopathological studies demonstrate that

**Table 1.** Vasculopathic features across systemic sclerosis-associated pulmonary hypertension phenotypes

| Phenotype                | Vascular involvement         | Pathological features                                                                          |
|--------------------------|------------------------------|------------------------------------------------------------------------------------------------|
| PAH/PVOD                 | Arteries, capillaries, veins | Intimal fibrosis, small-vessel collapse                                                        |
| PH-HFpEF                 | Arteries, capillaries, veins | Venous and small-vessel intimal thickening, PVOD-like changes proliferation, PVOD-like changes |
| PH-ILD                   | Arteries, capillaries, veins | Diffuse vascular remodeling, capillary                                                         |
| Intrinsic RV dysfunction | Coronary microcirculation    | Microvascular ischemia, concentric intimal hypertrophy                                         |

PAH/PVOD, pulmonary arterial hypertension/pulmonary veno-occlusive disease; PH-HFpEF, heart failure with preserved ejection fraction; PH-ILD, pulmonary hypertension associated with interstitial lung disease; RV, right ventricle.

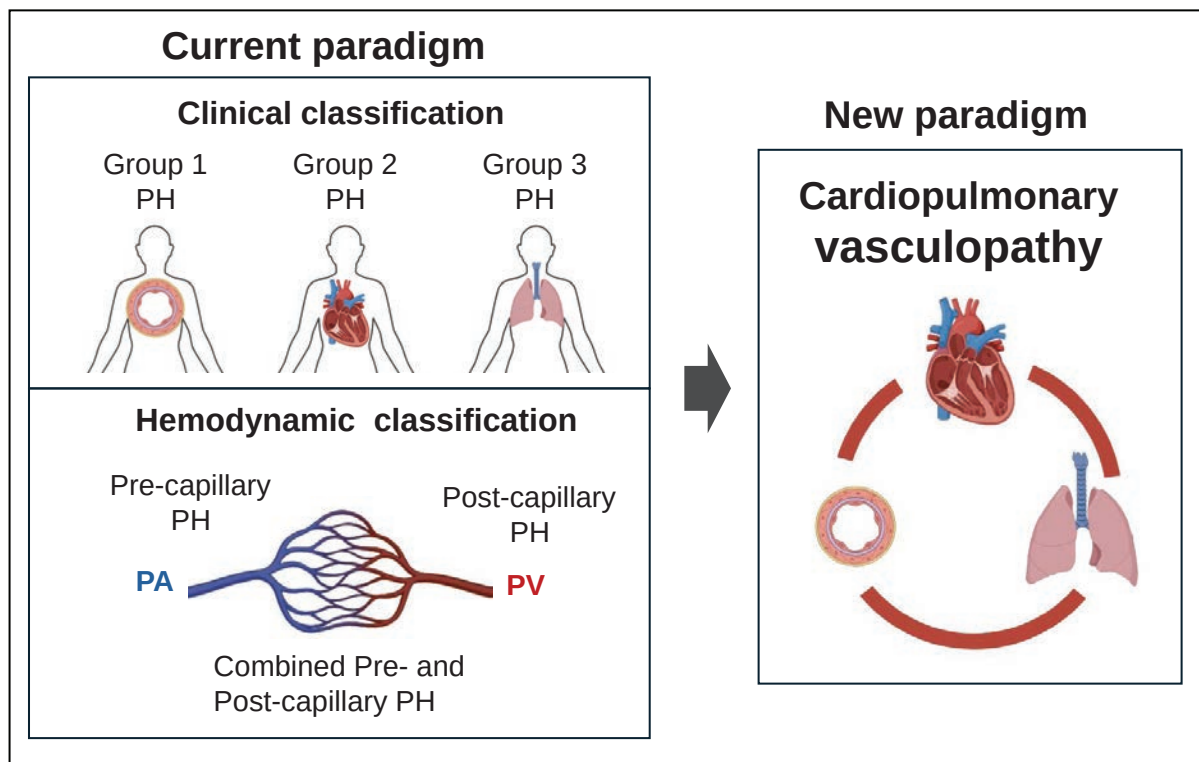


**FIGURE 1.** Redefining systemic sclerosis-associated pulmonary hypertension: toward cardiopulmonary vasculopathy. Systemic sclerosis-associated pulmonary hypertension (SSc-PH) is clinically classified into WHO Group 1 pulmonary arterial hypertension/pulmonary veno-occlusive disease (PAH/PVOD), WHO Group 2 pulmonary hypertension associated with heart failure with preserved ejection fraction (HFpEF-PH), and WHO Group 3 pulmonary hypertension associated with interstitial lung disease (ILD-PH). Hemodynamically, SSc-PH is categorized as precapillary, isolated postcapillary, or combined precapillary and postcapillary pulmonary hypertension. Rather than representing distinct disease entities, these clinical and hemodynamic manifestations may reflect different expressions of a common cardiopulmonary vasculopathy involving the pulmonary arteries, capillaries, veins, and myocardial microcirculation. This figure presents cardiopulmonary vasculopathy as a new unifying paradigm for SSc-PH. Created with BioRender.com.

the severity of pulmonary hypertension correlates closely with venous and microvascular intimal thickening, supporting vascular impairment as an important contributor to HFpEF-associated pulmonary hypertension [11]. Moreover, HFpEF is increasingly recognized as a systemic inflammatory and microvascular disease characterized by endothelial dysfunction, impaired myocardial microcirculation, and, particularly in SSc, with myocardial fibrosis [12,13]. These findings support the concept that both HFpEF and PH-HFpEF involve vascular dysfunction.

#### **WHO GROUP 3 PULMONARY HYPERTENSION: PULMONARY HYPERTENSION-ASSOCIATED INTERSTITIAL LUNG DISEASE BEYOND PULMONARY FIBROSIS AND HYPOXIC PULMONARY VASOCONSTRICTION**

In patients with ILD, pulmonary hypertension has been thought to arise from the fibrotic destruction of

the lung tissue, resulting in a reduction of the pulmonary vascular bed and impaired gas exchange. Together with hypoxic pulmonary vasoconstriction, these changes lead to elevated pulmonary vascular resistance (PVR). However, current studies reveal that there is no direct link between the severity of fibrosis, such as the extent of disease on pulmonary function tests or fibrotic change on high-resolution computed tomography, and the development of pulmonary hypertension or its severity [14,15], indicating PH-ILD is not solely explained by lung tissue damage or hypoxia.

Histopathological studies in patients with PH-ILD due to SSc demonstrate vascular remodeling throughout the pulmonary vascular tree, ranging from the primary arteries to the arterioles, encompassing capillaries and pulmonary veins [16<sup>22</sup>,17<sup>2</sup>,18]. Furthermore, capillary proliferation and PVOD-like lesions are frequently observed in these patients [17<sup>2</sup>,18]. In addition, molecular differences between ILD and PH-ILD suggest that distinct vasculocentric pathways may contribute to pulmonary hypertension development [19,20].

## INTRINSIC RIGHT VENTRICULAR DYSFUNCTION DUE TO CORONARY MICROVASCULAR DYSFUNCTION

RV function is the most important determinant of pulmonary hypertension prognosis, regardless of cause [21]. Notably, RV dysfunction in SSc-PH appears disproportionately severe compared with the other forms of PH [22,23,24], with increased afterload sensitivity of the RV (i.e. at any given increase in PVR or total pulmonary resistance, RV function is worse in SSc compared to patients with idiopathic PAH). Accumulating evidence indicates that RV dysfunction in SSc is not solely a consequence of pressure overload but reflects intrinsic myocardial involvement that may occur even before overt pulmonary hypertension develops [25,26]. In SSc patients without pulmonary hypertension, impaired RV function correlates with left ventricular systolic and diastolic dysfunction, but not with pulmonary function or pulmonary arterial pressure, suggesting intrinsic cardiac dysfunction involving both ventricles [25].

The pathogenesis of intrinsic cardiac involvement in SSc is thought to involve recurrent coronary microvascular ischemia and reperfusion injury, due to endothelial dysfunction and microvascular inflammation, leading to interstitial myocardial fibrosis [27]. Coronary vasospasm and impaired coronary flow reserve are considered major contributors to recurrent ischemia–reperfusion injury [28–30]. Histopathological analysis similarly demonstrates diffuse, patchy myocardial fibrosis in both ventricular walls, contraction band necrosis, and concentric intimal thickening in intramural coronary arteries with immune cell infiltration [31–33]. These findings support intrinsic RV dysfunction as a manifestation of systemic microvascular disease in SSc, such as the skin, lungs, and kidneys.

## SCREENING ALGORITHMS

Given the risk of pulmonary hypertension in SSc patients, early screening is critical. Doppler echocardiography with tissue Doppler and strain imaging is the primary screening tool recommended for all SSc patients [1]. Among echocardiographic parameters, tricuspid regurgitation velocity is used to estimate RV systolic pressure, which equals pulmonary artery systolic pressure in the absence of pulmonic stenosis. However, a measurable tricuspid regurgitation jet is not present in all patients with pulmonary hypertension [34,35], limiting reliance on tricuspid regurgitation velocity alone for pulmonary hypertension screening. Therefore, tricuspid regurgitation velocity should be combined with other echocardiographic parameters and clinical features [1]. SSc-PAH-specific screening algorithms, such as DETECT and the Australian

Scleroderma Interest Group (ASIG) algorithm, are the most commonly used [36–38]. Although originally developed for SSc patients with disease duration of more than 3 years and DLCO of less than 60%, the DETECT algorithm has demonstrated utility in patients with earlier disease and preserved DLCO (>60%) [39]. Similarly, the updated 2022 ESC/ERS PH guidelines now define pulmonary hypertension using a lower mean pulmonary artery pressure threshold of more than 20 mmHg, with the goal of identifying at-risk patients (such as those with SSc) who have pulmonary vascular disease [40].

In clinical practice, the prognosis of SSc patients with WHO Groups 2 and 3 pulmonary hypertension may be even worse than that of patients with WHO Group 1 SSc-PAH [10,41]. Although DETECT and ASIG were primarily aimed at detecting SSc-PAH, they may also identify patients with WHO Groups 2 and 3 pulmonary hypertension [42]. This observation suggests that the physiological abnormalities captured by these screening algorithms may reflect shared vascular dysfunction across multiple SSc-PH phenotypes rather than WHO Group 1 disease alone.

## EXERCISE ECHOCARDIOGRAPHY

Despite efforts toward early diagnosis, pulmonary hypertension and RV dysfunction are often detected at an advanced stage, when treatment is difficult. Owing to the substantial capacitance of the pulmonary circulation, early pulmonary vascular disease may remain clinically silent at rest. Resting pulmonary hypertension (mPAP >20 mmHg) may not develop until more than 50% of the pulmonary vascular bed has been lost [43]. As exertional dyspnea is often the earliest symptom of pulmonary hypertension or RV dysfunction, exercise echocardiography may identify occult pulmonary hypertension and RV dysfunction earlier [44,45,46]. Exercise-induced elevation of pulmonary artery systolic pressure and reduced RV contractile reserve may identify early pulmonary vascular disease and RV dysfunction [47–49]. In addition, exercise echocardiography detects exercise-induced elevation in left atrial pressure (indicative of left ventricular diastolic dysfunction) in SSc [50]. Exercise echocardiography may be particularly valuable because it enables integrated assessment of pulmonary vascular, RV, and LV reserve across the SSc-PH spectrum.

## VASODILATORY PATHWAYS

Pulmonary vasodilators remain the cornerstone of therapy for PAH. However, patients with SSc-PAH have poorer outcomes and treatment responses than those with idiopathic PAH, potentially reflecting

more extensive fibrotic vascular remodeling and worse RV function and RV reserve. These observations suggest that earlier intervention, before irreversible fibrotic vascular remodeling becomes established, may provide greater therapeutic benefit. Interestingly, observational data from a large SSc registry showed that bosentan treatment for digital ulcer prevention was associated with reduced subsequent PAH development, supporting the potential benefit of early intervention [51<sup>11</sup>].

The effectiveness of vasodilator therapy is limited in WHO Group 2 and Group 3 pulmonary hypertension. In PH-ILD, systemic delivery of pulmonary vasodilators is generally discouraged because of worsening ventilation–perfusion mismatch [1]. Inhaled treprostinil, a prostacyclin, preferentially targets better ventilated lung regions and improves exercise capacity and reduces clinical worsening in patients with PH-ILD [52]. Similarly, pulmonary vasodilator therapy is not recommended for WHO Group 2 pulmonary hypertension, as pulmonary vasodilator therapy increases pulmonary venous return to a left heart that is unable to accommodate the increased preload, thereby further elevating left-sided filling pressures and increasing the risk of pulmonary edema. In WHO Group 2 PH-HFpEF, numerous randomized trials of pulmonary vasodilators, including PDE5 inhibitors, sGC stimulators, inhaled prostacyclin, and endothelin receptor antagonists, have failed to demonstrate consistent clinical benefit, including in combined precapillary and postcapillary pulmonary hypertension [53–55].

### TARGETING BMP AND ACTIVIN SIGNALING AS DISEASE-MODIFYING THERAPY IN SYSTEMIC SCLEROSIS-ASSOCIATED PULMONARY HYPERTENSION

BMPT2 signaling maintains pulmonary vascular homeostasis, and impaired BMPT2 signaling shifts the balance toward enhanced TGF- $\beta$ /activin-mediated proliferative and inflammatory pathways, promoting vascular remodeling [56–60]. BMPT2 mutations are identified in many familial PAH and a subset of idiopathic PAH patients, while reduced BMPT2 expression is also observed in pulmonary vascular lesions across multiple forms of PAH [61–64].

Sotatercept, an activin ligand trap, has emerged as a novel therapy targeting this signaling imbalance. In the STELLAR trial, sotatercept significantly improved exercise capacity and PVR in PAH [65<sup>12</sup>]. Preclinical studies further suggest that activin signaling inhibition reduces macrophage infiltration and proinflammatory gene expression in experimental PAH lungs, while preventing pulmonary

hypertension [66<sup>13</sup>]. However, the efficacy and safety of sotatercept in SSc-PAH remain uncertain. In STELLAR, telangiectasia and bleeding occurred in approximately 20 and 10% of treated patients, respectively [65<sup>12</sup>]. Although STELLAR did not demonstrate an increased overall risk of pericardial effusion with sotatercept, recent real-world reports have raised concerns regarding new or worsening pericardial effusions, particularly in SSc-PAH [67,68]. Therefore, careful risk–benefit assessment is required when considering sotatercept in SSc-PAH. Beyond PAH, the CADENCE phase II trial demonstrated reductions in both PVR and pulmonary capillary wedge pressure in patients with combined precapillary and postcapillary pulmonary hypertension associated with HFpEF, suggesting benefit across both pulmonary vascular and cardiac dysfunction [69]. Patients at the lower dose of sotatercept did better than those at the higher dose of sotatercept, possibly due to poor tolerability at the higher dose, suggesting a narrow therapeutic window. In addition, a recent case series of five patients with PVOD reported that sotatercept improved hypoxemia and clinical status [70], suggesting a potential benefit in conditions characterized by the pulmonary venopathy that is present across SSc-PH subtypes.

### TARGETING MACROPHAGE–VASCULAR CROSSTALK

Chronic inflammation contributes to the pathogenesis of PAH. Circulating inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1 $\beta$  (IL-1 $\beta$ ), and tumor necrosis factor, are elevated in PAH and SSc and are associated with worse survival [71<sup>14</sup>,72,73]. Increasing evidence indicates that macrophages are a major source of these pathogenic cytokines [74,75]. Mechanistically, IL-6 and platelet-derived growth factor (PDGF) induce proliferation and resistance to apoptosis in pulmonary artery smooth muscle cells [[74,76]]. We recently demonstrated that Regnase-1, RNase, in alveolar macrophages regulates PAH by degrading mRNA of IL-6 and PDGF [77<sup>15</sup>]. Recent single-cell transcriptomic analysis further demonstrated pronounced macrophage-to-endothelial cell signaling in SSc-PAH compared with idiopathic PAH, supporting a central role for macrophage–vascular crosstalk in SSc-PAH [78<sup>16</sup>].

Although imatinib demonstrated efficacy in PAH, its clinical development was limited by systemic toxicity. Seralutinib was therefore developed as an inhaled inhibitor of PDGF receptor, colony-stimulating factor 1 receptor (CSF1R), and c-KIT [79] to improve tolerability and target both vascular proliferation and macrophage activation. Although the phase 3 PROSERA trial failed to meet its primary

endpoint, subgroup analyses suggested greater treatment effects in connective tissue disease (CTD)-associated PAH [80], supporting continued interest in servalutinib for SSc-PAH. Similarly, in the phase 2 TRANSFORM-UK trial of tocilizumab in WHO Group 1 PAH, IL-6 inhibition did not significantly improve PVR overall but showed potential benefit in CTD-PAH, including SSc-PAH [81<sup>\*</sup>]. These findings suggest multiple immune pathways may be more effective than inhibition of a single cytokine.

## AUTOIMMUNITY AND B-CELL-DIRECTED THERAPY

The association of specific autoantibodies with distinct clinical phenotypes supports an important role for autoimmunity in SSc pathogenesis. Functional autoantibodies may directly contribute to vascular remodeling and vasculopathy in SSc-PH. Antiendothelial cell antibodies (AECAs) are detected in 22–86% of SSc patients, depending on the detection method and on patient selection [82], and are associated with vascular manifestations, including digital ischemia and PAH [83,84]. In addition, antiangiotensin II type 1 receptor and antiendothelin-1 type A receptor autoantibodies may promote vasoconstriction and vascular remodeling [85,86], while antifibroblast antibodies amplify vascular inflammation and remodeling in SSc.

These observations have prompted interest in B-cell-targeted therapy. In a randomized, placebo-controlled trial in SSc-PAH, rituximab did not meet the primary endpoint, although extended follow-up suggested possible benefit [87]. CD19-targeted CAR-T cells have recently been shown to improve disease activity, as assessed by the EUSTAR activity index, and skin fibrosis, as assessed by the modified Rodnan skin score, in patients with severe refractory SSc [88<sup>\*\*\*</sup>], supporting immune resetting as a potential disease-modifying strategy. Whether immune-resetting therapies can modify pulmonary vascular remodeling or intrinsic RV dysfunction remains an important future research question.

## ENDOTHELIAL TO MESENCHYMAL TRANSITION

Endothelial to mesenchymal transition (EndoMT) is increasingly acknowledged as a pivotal mechanism driving fibrotic vasculopathy in SSc. During EndoMT, endothelial cells lose endothelial characteristics and acquire mesenchymal and myofibroblastic features, leading to impaired vascular barrier function, enhanced immune cell transmigration, and increased extracellular matrix production [89,90]. EndoMT cells also secrete proinflammatory cytokines, including

IL-6, IL-8, and TNF- $\alpha$ , further amplifying vascular inflammation [89].

TGF- $\beta$  is a strong driver of EndoMT; however, TGF- $\beta$  alone is not sufficient to induce EndoMT to promote disease progression *in vivo*. TGF- $\beta$ -induced EndoMT is enhanced by inflammatory cytokines, ET-1, hypoxia, and shear stress [89,91]. ET-1 receptor antagonists such as bosentan and macitentan have been shown to inhibit EndoMT *in vitro*. Despite strong mechanistic rationale, therapeutic targeting of TGF- $\beta$  signaling has proven challenging. Metelimumab, a monoclonal antibody targeting TGF- $\beta$ 1, failed to improve clinical outcomes in early SSc and was associated with increased adverse events [92]. Fresolimumab, targeting all three TGF- $\beta$  isoforms, reduced TGF- $\beta$ -regulated gene expression and modified Rodnan skin scores in an open-label trial of 15 early dcSSc patients [93], but further trials have not been conducted.

## POTENTIAL FUTURE RESEARCH

Future research in SSc-PH should focus on combining immune-based patient stratification with earlier detection for cardiopulmonary vascular dysfunction. Longitudinal immune profiling combined with exercise echocardiography may identify patients at risk for progression before resting pulmonary hypertension develops, facilitating earlier mechanism-based intervention before irreversible vascular remodeling occurs.

## CONCLUSION

SSc-PH is a heterogeneous condition characterized by complex interactions between immune dysregulation and progressive vascular remodeling. Pulmonary and cardiac involvement in SSc-PH reflects a systemic microvasculopathy extending beyond traditional WSPH classification. Reframing SSc-PH as a spectrum of immune-mediated vasculopathy may improve patient stratification and facilitate development of mechanism-based therapies.

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# Hyper-aging in systemic sclerosis: linking genome instability, mitochondrial dysfunction, and inflammaging to fibrosis

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## Purpose of review

Systemic sclerosis (SSc) is a progressive autoimmune disease characterized by fibrosis, vasculopathy, and immune dysregulation. Emerging evidence indicates that SSc shares multiple hallmarks of accelerated biological aging, including genomic instability, telomere attrition, mitochondrial dysfunction, cellular senescence, and chronic innate immune activation. This review summarizes recent advances published during the last 18 months supporting the concept of SSc as a disorder of maladaptive or 'hyper-aging'.

## Recent findings

Recent epigenetic clock studies, including DunedinPACE and other DNA methylation-based aging models, demonstrate accelerated biological aging in SSc, particularly in patients with interstitial lung disease and severe organ involvement. Gene expression meta-analysis has confirmed that aging and senescence signatures are markedly enriched in SSc-ILD lung tissue. Multiple aging-associated mechanisms contribute to disease progression, including telomere shortening, mitochondrial dysfunction, micronuclei formation, and chromosomal instability. Cytosolic DNA derived from damaged nuclei or mitochondria activates the cGAS-STING pathway, sustaining type I interferon signaling, inflammaging, and fibrotic remodeling. Recent transcriptomic and spatial studies further support a close relationship between metabolic collapse, mitochondrial stress, immune dysregulation, and tissue fibrosis in SSc.

## Summary

Current evidence supports the concept that SSc represents a state of accelerated and dysregulated biological aging involving persistent innate immune activation, mitochondrial stress, and defective genome surveillance. Therapeutic strategies targeting aging-associated pathways, particularly mitochondrial dysfunction, cGAS-STING signaling, and cellular senescence, may provide new opportunities to modulate fibrosis, inflammation, and immune imbalance in SSc.

## Keywords

cyclic GMP-AMP synthase-stimulator of interferon genes, hyper-aging, inflammaging, mitochondrial dysfunction, systemic sclerosis

## INTRODUCTION

Systemic sclerosis (SSc) is a complex autoimmune connective tissue disease characterized by progressive fibrosis, vasculopathy, and chronic immune dysregulation affecting the skin, lungs, gastrointestinal tract, heart, and vasculature [1<sup>•</sup>, 2<sup>••</sup>, 12<sup>•</sup>]. Despite advances in understanding immune-mediated fibrosis, the mechanisms linking chronic immune activation with progressive tissue fibrosis and multisystem organ involvement remain incompletely understood. Increasing evidence now suggests that SSc shares several biological features with accelerated aging disorders, including genomic instability, mitochondrial dysfunction, cellular senescence, and

chronic low-grade inflammation [3<sup>•</sup>]. Indeed, biological aging is a complex, multihallmark process encompassing epigenetic drift, telomere attrition, mitochondrial dysfunction, loss of proteostasis,

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## KEY POINTS

- Systemic sclerosis exhibits several hallmarks of accelerated biological aging, including genomic instability, telomere attrition, mitochondrial dysfunction, and cellular senescence.
- DNA methylation-based aging clocks such as DunedinPACE and GrimAge demonstrate accelerated biological aging in SSc patients, particularly in SSc-associated interstitial lung disease; gene expression meta-analysis further confirms striking enrichment of senescence and aging signatures in SSc-ILD lung tissue, with telomere shortening confirmed at the tissue level.
- Chromosomal instability and micronuclei formation contribute to cytosolic DNA accumulation and activation of the cGAS-STING innate immune pathway.
- Mitochondrial dysfunction and mtDNA release amplify inflammaging, immune dysregulation, and fibrotic remodeling.
- Targeting aging-associated pathways, including cellular senescence, mitochondrial stress responses, and cGAS-STING signaling, represents a promising therapeutic strategy in SSc.

cellular senescence, and altered intercellular communication [7]. The remarkable overlap between these aging hallmarks and the pathological features of SSc has raised the possibility that SSc involves a fundamentally dysregulated aging program.

Recent studies have expanded the conceptual framework of SSc beyond a purely autoimmune fibrotic disease to include maladaptive or accelerated biological aging as an important contributor to disease pathogenesis [2<sup>22</sup>,3<sup>3</sup>]. Importantly, SSc does not simply recapitulate chronological aging; rather, it appears to involve a compressed and dysregulated aging phenotype characterized by persistent cellular stress, defective genome maintenance, and sustained innate immune activation. This concept of ‘hyper-aging’ may help explain the coexistence of fibrosis, vascular injury, chronic inflammation, and progressive organ dysfunction in SSc [2<sup>22</sup>,3<sup>3</sup>].

Several hallmarks of aging have now been implicated in SSc pathogenesis, including epigenetic drift, telomere attrition, mitochondrial dysfunction, chromosomal instability, immunosenescence, and altered intercellular communication [3–6<sup>6</sup>,7,8,9<sup>9</sup>]. Among these processes, activation of the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway has emerged as a major link connecting genome damage, mitochondrial stress, inflammaging, and fibrosis. Cytosolic DNA released from micronuclei or damaged mitochondria activates

innate immune signaling pathways that sustain type I interferon production and chronic inflammatory remodeling [2<sup>22</sup>].

This review summarizes recent advances linking accelerated aging biology with SSc pathogenesis, with particular emphasis on genomic instability, mitochondrial dysfunction, inflammaging, and cGAS-STING signaling. The major hallmarks of hyper-aging implicated in SSc and their therapeutic relevance are summarized in Table 1. An integrated model linking genomic instability, mitochondrial dysfunction, inflammaging, and fibrosis in SSc is shown in Fig. 1.

## EPIGENETIC CLOCKS REVEAL ACCELERATED BIOLOGICAL AGING IN SYSTEMIC SCLEROSIS

DNA methylation-based aging clocks have emerged as important tools for quantifying biological aging and evaluating age acceleration in chronic inflammatory diseases. First-generation clocks, including the Horvath pan-tissue clock and the Hannum blood-based clock, estimate biological age from methylation at specific CpG sites and established the principle that epigenetic age can diverge from chronological age in disease states [10<sup>10</sup>]. Second-generation models, including GrimAge and DunedinPACE, integrate DNA methylation patterns with clinical biomarkers associated with morbidity and mortality, providing improved assessment of physiological aging and the rate at which it is occurring [10<sup>10</sup>,11<sup>11</sup>]. Recent studies indicate that SSc patients exhibit accelerated epigenetic aging compared with healthy individuals, supporting the concept that biological aging contributes directly to disease progression.

Preliminary data suggest that patients with SSc-associated interstitial lung disease (SSc-ILD) exhibit increased DunedinPACE scores, indicating accelerated epigenetic aging rates in SSc-ILD [11<sup>11</sup>]. Accelerated aging correlated with disease severity and pulmonary involvement. To directly validate these aging signatures at the tissue level, Yang and colleagues performed a gene expression meta-analysis of lung tissue from 38 SSc-ILD patients and 18 healthy controls, demonstrating that epithelial and fibroblast senescence signatures were enriched 3.6-fold and 3.7-fold, respectively, in SSc-ILD [13<sup>13</sup>]. Key aging genes including *CDKN2A* and senescence markers *GDF15* and *COMP* were significantly upregulated, and telomere length in type II alveolar cells was shortened in SSc-ILD to levels comparable to idiopathic pulmonary fibrosis, a disease of established aberrant aging [13<sup>13</sup>]. These findings are particularly relevant because SSc and idiopathic pulmonary fibrosis (IPF) share multiple molecular aging signatures,

**Table 1.** Key mechanisms linking accelerated aging with systemic sclerosis and therapeutic implication

| Hallmark                  | Key mechanism in SSc                                                                         | Pathogenesis                                                                             | Evidence/markers                                                                          | Therapeutic implications                                             | Refs                                                                                                                                                                          |
|---------------------------|----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Epigenetic aging          | DNA methylation-based age acceleration (DunedinPACE, GrimAge)                                | Reflects increased biological age and disease severity; accelerated pace in SSc-ILD      | Horvath clock, GrimAge, DunedinPACE; 3.6–3.7× senescence enrichment in SSc-ILD lung       | Epigenetic modulators; aging reversal strategies                     | [10 <sup>■</sup> ,11,12 <sup>■</sup> ,13 <sup>■</sup> ,14,15,16,17]                                                                                                           |
| Telomere attrition        | Shortened telomeres in immune and epithelial cells; accelerated rate in early SSc            | Replicative senescence, impaired tissue repair, fibrosis, worse survival                 | Reduced PBL-TL; tissue telomere shortening comparable to IPF                              | Telomerase-targeted therapies                                        | [18 <sup>■</sup> ,19,20 <sup>■</sup> ]                                                                                                                                        |
| Genomic instability       | Chromosomal instability and micronuclei formation                                            | Cytosolic DNA release and innate immune activation via cGAS-STING                        | Micronuclei, centromere abnormalities                                                     | Genome stability restoration strategies                              | [2 <sup>■</sup> ,19 <sup>■</sup> ,21 <sup>■</sup> ,22 <sup>■</sup> ]                                                                                                          |
| cGAS–STING activation     | Cytosolic DNA sensing due to nuclear and mitochondrial damage                                | Type I IFN production, chronic inflammation, SASP amplification                          | STING pathway activation, interferon signatures, ISG upregulation                         | cGAS inhibitors, STING antagonists                                   | [2 <sup>■</sup> ,21 <sup>■</sup> ,22 <sup>■</sup> ,26 <sup>■</sup> ]                                                                                                          |
| Mitochondrial dysfunction | Mitochondrial damage and mtDNA release into cytosol                                          | ROS production, inflamming, immune activation, cGAS-STING triggering                     | Elevated cytosolic mtDNA, oxidative stress markers, metabolic collapse in fibrotic niches | Mitochondrial protectants, mitophagy enhancers, metabolic modulators | [2 <sup>■</sup> ,24 <sup>■</sup> ,25 <sup>■</sup> ,26 <sup>■</sup> ,27 <sup>■</sup> ,28 <sup>■</sup> ,29 <sup>■</sup> ,30 <sup>■</sup> ,31,32 <sup>■</sup> ,33 <sup>■</sup> ] |
| Immunosenescence          | Decline in adaptive immunity; expansion of senescent immune cells and age-associated B cells | Chronic inflammation ('inflamming'); autoantibody production; impaired immune resolution | Senescent T cells, age-associated B cells, reduced naïve T cells                          | Immunomodulatory therapies                                           | [37 <sup>■</sup> –39]                                                                                                                                                         |
| Metabolic dysregulation   | Altered TCA cycle and mitochondrial metabolism; fumarate–mtDNA axis disruption               | Fibrosis and immune activation via metabolic-immune crosstalk                            | FH-fumarate-mtDNA axis disruption; metabolic collapse in SSc-ILD                          | Metabolic reprogramming therapies                                    | [30 <sup>■</sup> ,31,32 <sup>■</sup> ,33 <sup>■</sup> ]                                                                                                                       |
| SASP activation           | Senescence-associated secretory phenotype; senescent cells in SSc skin and lung              | Pro-inflammatory cytokine release (IL-6, IFNs); fibrotic ECM remodeling                  | Elevated p16, p21, GDF15; senescent fibroblasts and endothelial cells in SSc tissue       | Senolytics, senomorphics, anti-inflammatory agents                   | [26 <sup>■</sup> ,37 <sup>■</sup> ,39 <sup>■</sup> ,40 <sup>■</sup> ]                                                                                                         |

including telomere shortening, mitochondrial dysfunction, and senescence-associated transcriptional programs.

Epigenetic drift may also contribute to altered immune-cell function in SSc. Studies have demonstrated both global DNA hypomethylation and gene-specific hypermethylation in fibroblasts, peripheral blood mononuclear cells, and endothelial cells from SSc patients, supporting a systemic dysregulation of aging-associated pathways [3<sup>■</sup>,13<sup>■</sup>,14–17]. Hypomethylation of profibrotic genes, together with hypermethylation-mediated silencing of genes involved in immune regulation, vascular homeostasis, and anti-fibrotic signaling, has been reported, suggesting widespread dysregulation of DNA methylation-dependent gene expression in SSc. These methylation abnormalities are consistent with aging-associated epigenetic drift and support the concept of systemic disruption of pathways governing fibrosis, inflammation, and vascular injury [13<sup>■</sup>,14–17].

Collectively, these findings suggest that epigenetic age acceleration may serve as both a biomarker and a mechanistic contributor to SSc progression, with SSc-ILD representing an organ manifestation in which accelerated aging is particularly pronounced.

### TELOMERE ATTRITION AND REPLICATIVE STRESS IN AGING-MEDIATED FIBROSIS

Telomeres are specialized nucleoprotein structures located at chromosome ends that preserve genomic integrity during DNA replication. Progressive telomere shortening limits cellular proliferative capacity and promotes senescence, tissue dysfunction, and age-related disease.

Recent studies continue to support a strong relationship between telomere attrition and fibrotic lung disease [18<sup>■</sup>,19<sup>■</sup>]. Patients with SSc-ILD exhibit significantly shortened peripheral blood leukocyte telomere length (PBL-TL) compared with non-ILD SSc

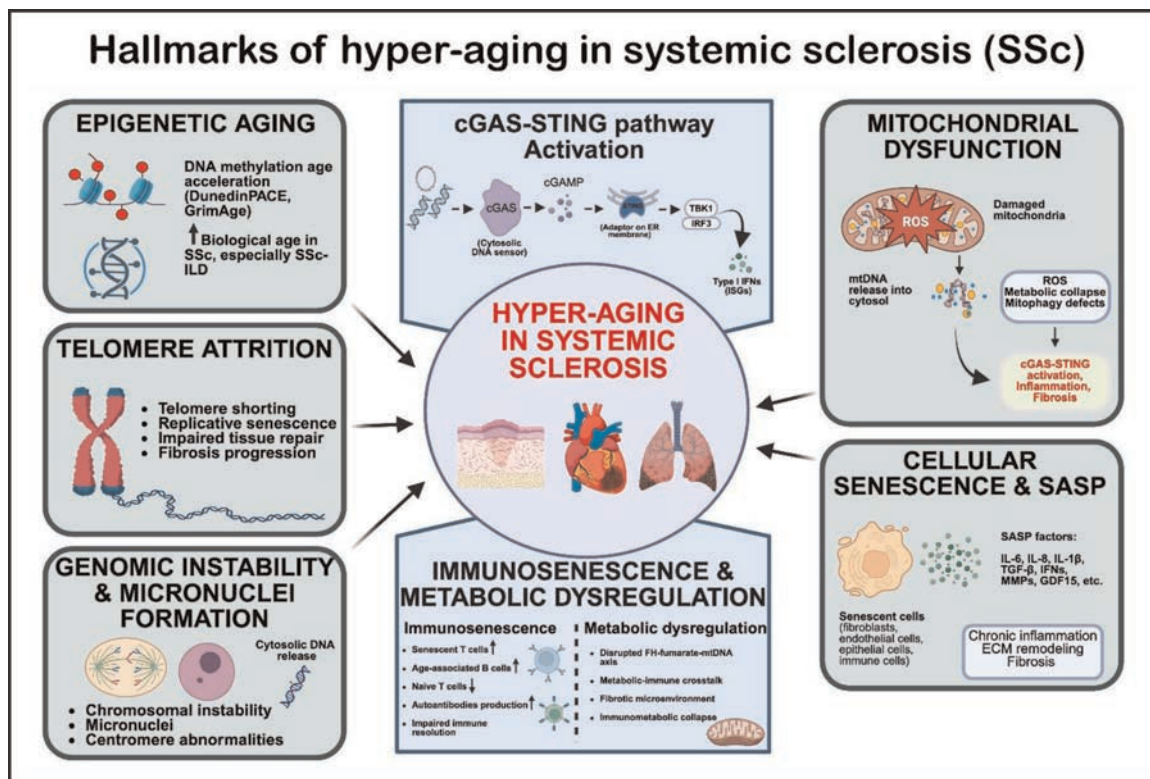


**FIGURE 1.** Hallmarks of hyper-aging in systemic sclerosis. This schematic summarizes seven interconnected mechanisms driving hyper-aging in SSc: eEpigenetic aging with DNA methylation changes and accelerated biological age, particularly in SSc-associated interstitial lung disease (SSc-ILD); telomere attrition leading to replicative senescence, impaired repair, and fibrosis; Genomic instability with chromosome defects and micronuclei formation causing cytosolic DNA release; cGAS–STING activation by nuclear and mitochondrial DNA, inducing TBK1–IRF3 signaling and type I interferon (IFN-I) responses; Mitochondrial dysfunction with increased ROS, impaired oxidative phosphorylation, defective mitophagy, and mtDNA leakage; Cellular senescence and SASP-mediated secretion of IL-6, IL-8, IL-1 $\beta$ , MCP-1, and GM-CSF promoting inflammation and fibrosis; and immunosenescence with T/B/NK cell dysfunction, TCA cycle impairment, fumarate accumulation, and disrupted HIF-1 $\alpha$  signaling. Collectively, these pathways drive chronic inflammation, fibrosis, immune dysfunction, and accelerated aging in SSc. cGAS, cyclic GMP–AMP synthase; DNA, deoxyribonucleic acid; GM-CSF, granulocyte–macrophage colony-stimulating factor; HIF-1 $\alpha$ , hypoxia-inducible factor 1-alpha; IFN-I, type I interferon; IL, interleukin; IRF3, interferon regulatory factor 3; MCP-1, monocyte chemoattractant protein-1; mtDNA, mitochondrial DNA; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SSc, systemic sclerosis; SSc-ILD, SSc-associated interstitial lung disease; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1; TCA, tricarboxylic acid cycle.

patients and healthy controls [18<sup>•</sup>,20<sup>••</sup>]. The clinical significance of telomere shortening in SSc was further established by a large prospective cohort study of 244 SSc patients demonstrating that shorter PBL-TL was independently associated with pulmonary disease severity, hospitalizations, and worse event-free survival [20<sup>••</sup>]. Notably, patients in early disease stages exhibited faster rates of PBL-TL shortening compared with those with longer disease duration, suggesting that telomere attrition may be particularly active during the early and most damaging phase of SSc [20<sup>••</sup>]. These findings establish telomere shortening as a clinically meaningful biomarker in SSc, and provide direct evidence linking telomere biology to disease outcomes beyond ILD.

Telomere dysfunction may contribute directly to SSc pathogenesis through multiple mechanisms. Critically short telomeres induce DNA damage signaling, replicative senescence, and impaired tissue repair. Senescent fibroblasts and epithelial cells accumulate proinflammatory and profibrotic secretory programs that sustain chronic fibrosis [19<sup>••</sup>]. Telomere dysfunction may also promote chromosomal instability and micronucleus formation, thereby linking replicative stress to innate immune activation.

Although senescent phenotypes have been consistently observed in SSc dermal fibroblasts, direct evidence for telomere shortening in skin-resident cells is less robust than that observed in peripheral

blood leukocytes and lung epithelial cells. Recent tissue-level analyses have demonstrated significant telomere shortening in SSc-ILD lung epithelial cells, but not in skin epithelial cells, suggesting that telomere dysfunction may be particularly relevant to pulmonary manifestations of the disease rather than uniformly present across all affected tissues. Accordingly, telomere-associated abnormalities in SSc may be organ-specific rather than generalized, which may help explain why SSc-ILD exhibits particularly pronounced aging-associated signatures relative to other disease manifestations [18<sup>22</sup>,20<sup>22</sup>].

### GENOME INSTABILITY, CENTROMERE DYSFUNCTION, AND MICRONUCLEI FORMATION IN SYSTEMIC SCLEROSIS

Genomic instability is a central hallmark of aging and is increasingly recognized as an important contributor to autoimmune and fibrotic diseases [7]. One of the most prominent manifestations of genomic instability is the formation of micronuclei, small extranuclear structures containing whole chromosomes or chromosome fragments generated during defective mitosis or unresolved DNA damage [21<sup>22</sup>,22<sup>22</sup>].

Recent studies have identified micronuclei as potent activators of innate immune signaling because rupture of micronuclear membranes exposes chromosomal DNA to cytosolic DNA sensors [21<sup>22</sup>,22<sup>22</sup>,23<sup>22</sup>]. In SSc, there is strong historical and contemporary evidence of chromosomal instability, manifested by micronuclei, translocations, and chromosomal breaks, driven by clastogenic factors, oxidative stress, and centromere dysfunction [19<sup>22</sup>]. Examples of clastogenic factors implicated in SSc include reactive oxygen species, inflammatory cytokines, and immune complex-associated mediators, all of which can induce DNA damage and chromosomal abnormalities. Chromosomal instability and micronuclei formation may contribute directly to chronic inflammation and fibrosis through activation of cGAS-STING signaling [2<sup>22</sup>,19<sup>22</sup>].

Centromere dysfunction represents another emerging mechanism linking genome instability with SSc pathogenesis. Recent evidence suggests that centromeric alterations and chromosomal instability contribute to abnormal chromosome segregation and micronuclei formation in SSc fibroblasts [2<sup>22</sup>,19<sup>22</sup>,21<sup>22</sup>]. These alterations promote cytosolic DNA accumulation and sustain chronic type I interferon signaling.

Recent studies further indicate that genomic instability intersects closely with cellular senescence and inflammaging. Persistent DNA damage responses, defective mitotic surveillance, and cytosolic DNA accumulation amplify chronic inflammatory signaling and

reinforce senescence-associated secretory phenotypes (SASPs). These findings support the concept that defective genome maintenance may represent a major driver of hyper-aging in SSc.

### MITOCHONDRIAL DYSFUNCTION AND MTDNA-DRIVEN INFLAMMAGING IN SYSTEMIC SCLEROSIS

Mitochondrial dysfunction is increasingly recognized as a central mediator of aging-associated inflammation and fibrosis [2<sup>22</sup>,24<sup>22</sup>]. Mitochondria regulate oxidative phosphorylation, redox homeostasis, apoptosis, and innate immune signaling. During aging and chronic inflammatory disease, mitochondrial stress results in excessive reactive oxygen species production, impaired bioenergetics, and release of mitochondrial DNA (mtDNA) [24<sup>22</sup>,25<sup>22</sup>].

Recent studies demonstrate that damaged mitochondria release mtDNA into the cytosol, where it functions as a damage-associated molecular pattern capable of activating cGAS-STING signaling and other innate immune pathways [24<sup>22</sup>,26<sup>22</sup>,27<sup>22</sup>]. Cytosolic mtDNA amplifies inflammatory cytokine production, promotes interferon signaling, and sustains chronic inflammatory remodeling [26<sup>22</sup>]. Mitochondrial DNA also bridges cellular senescence and chronic inflammation: as mitochondrial integrity declines with aging, persistent mtDNA leakage drives continuous innate immune activation and SASP amplification [28<sup>22</sup>]. Defective mitophagy further exacerbates this cycle by preventing clearance of damaged mitochondria and limiting restriction of cytosolic mtDNA release, a mechanism with direct relevance to aging-associated inflammaging [29<sup>22</sup>].

Spatial transcriptomic studies in SSc skin have identified metabolic collapse and mitochondrial dysfunction as defining features of fibrotic tissue niches [30<sup>22</sup>]. These findings support a close relationship between mitochondrial injury, immune dysregulation, and progressive fibrosis. Consistent with the clinical consequences of metabolic dysfunction, patients with connective tissue diseases, including SSc, frequently exhibit exercise intolerance. Reduced systemic vascular dilation and impaired peripheral oxygen uptake have been associated with diminished exercise capacity, suggesting that abnormalities in vascular function and mitochondrial energy metabolism may directly contribute to fatigue and reduced functional performance in these patients [31]. This metabolic-immune axis is particularly relevant in SSc-ILD, where metabolic dysfunction and senescence converge as drivers of lung aging and disease [32<sup>22</sup>]. The fumarate-mitochondrial-cGAS-STING axis, in which loss of metabolic intermediates

destabilizes mitochondria and triggers innate immune activation, illustrates how metabolic collapse in inflammatory tissue may amplify inflammation through mitochondrial mechanisms, with potential relevance to SSc [33<sup>22</sup>].

Collectively, these findings position mitochondrial dysfunction as a major convergence point linking metabolic stress, innate immunity, and fibrotic remodeling in SSc.

## CELLULAR SENESENCE AND INFLAMMAGING IN SYSTEMIC SCLEROSIS

Cellular senescence is a stable stress-associated state characterized by irreversible cell-cycle arrest and acquisition of a SASP [34<sup>22</sup>]. Senescent cells accumulate during aging and contribute to chronic inflammation, tissue dysfunction, and fibrosis. In SSc, cellular senescence has emerged as a central pathogenic mechanism affecting multiple cell types including fibroblasts, endothelial cells, epithelial cells, and immune cells [34<sup>22</sup>,35<sup>22</sup>].

Direct evidence for the role of senescence in SSc tissue has been provided by studies demonstrating that senescent fibroblasts, endothelial cells, and immune cells accumulate in SSc skin and lung [13<sup>22</sup>,35<sup>22</sup>]. Gene expression meta-analysis of SSc-ILD lung tissue revealed 3.6-fold to 3.7-fold enrichment of epithelial and fibroblast senescence signatures, with upregulation of key senescence markers including p16 (CDKN2A), p21, GDF15, and COMP [13<sup>22</sup>]. In SSc skin, senescence signatures correlate with the degree of skin involvement, and endothelial-to-mesenchymal transition (EndMT), a process closely linked to senescence, is more abundant in SSc tissue and associated with fibrotic remodeling [35<sup>22</sup>]. Senescent cells produce inflammatory mediators including IL-6, interferons, chemokines, and profibrotic cytokines that reinforce chronic inflammation and extracellular matrix remodeling.

Activation of cGAS-STING signaling has emerged as an important regulator of senescence-associated inflammation [22<sup>22</sup>,36<sup>22</sup>]. Cytosolic DNA generated from damaged nuclei, micronuclei, or mitochondria activates innate immune pathways that sustain SASP signaling and inflammaging [34<sup>22</sup>]. This creates a self-amplifying cycle linking genome instability, mitochondrial dysfunction, and chronic inflammation [26<sup>22</sup>,36<sup>22</sup>].

Recent studies also support a role for immunosenescence in SSc. Aging-associated immune alterations include reduced naïve T-cell populations, expansion of differentiated effector T cells, accumulation of age-associated B cells (ABCs), and chronic innate immune activation [37–39<sup>22</sup>]. ABCs are a distinct B-cell population that expands with aging and

has been implicated in autoantibody production and autoimmune pathogenesis, including in SSc [37–39<sup>22</sup>]. These immune alterations may contribute to impaired immune resolution and persistent inflammation.

Importantly, SSc-associated inflammaging differs from physiological aging because inflammatory pathways become chronically amplified and spatially mislocalized within fibrotic tissues. This distinction further supports the concept of SSc as a disorder of maladaptive hyper-aging rather than normal aging alone.

## THERAPEUTIC TARGETING OF AGING-ASSOCIATED PATHWAYS IN SYSTEMIC SCLEROSIS

The recognition of SSc as a disorder involving accelerated biological aging has important therapeutic implications. Multiple experimental approaches are now being explored to target aging-associated pathways, particularly cGAS-STING signaling, mitochondrial dysfunction, and cellular senescence.

Several cGAS inhibitors and STING antagonists have demonstrated promising preclinical activity in inflammatory and autoimmune models [2<sup>22</sup>,23,40–43<sup>22</sup>]. Agents including G150, RU.521, C-176, C-178, H-151, and ISD017 suppress type I interferon signaling and inflammatory cytokine production by inhibiting cGAS-STING activation. Recent reviews have further characterized the mechanistic basis of these inhibitors and their potential across aging-associated inflammatory diseases [40<sup>22</sup>]. Naturally derived STING antagonists, including anhydrotuber- osin, have also demonstrated efficacy in autoimmune disease models [43<sup>22</sup>].

Therapeutic targeting of mitochondrial dysfunction represents another promising strategy. Approaches focused on reducing mitochondrial stress, improving mitophagy, limiting mtDNA release, and restoring metabolic homeostasis may attenuate inflammaging and fibrosis [24<sup>22</sup>,28<sup>22</sup>,32<sup>22</sup>].

Interest in senolytic therapies is increasing rapidly, as the evidence for senescence in SSc pathogenesis accumulates [34<sup>22</sup>,35<sup>22</sup>]. A comprehensive review of senescence in tissue fibrosis with emphasis on SSc concluded that targeting senescent cells, using senolytics or senomorphics that modulate SASP, represents a viable and underexplored therapeutic avenue in SSc [34<sup>22</sup>]. Clinically, a study of SSc patients undergoing treatment with cyclophosphamide or autologous hematopoietic stem cell transplantation demonstrated that markers of cellular senescence and endothelial-to-mesenchymal transition (EndMT) have been linked to therapeutic outcomes. Specifically, low baseline vascular p21

expression and persistence or increase in p21 expression following treatment were associated with poorer skin responses, whereas reductions in p21-positive vascular cells and EndMT markers were observed in patients with more favorable responses, particularly following stem cell transplantation [39<sup>■</sup>]. These findings suggest that senescence-associated markers may have prognostic value in SSc and support the rationale for therapeutic strategies targeting senescent cell populations. However, additional prospective studies are required to determine the safety and efficacy of dedicated senolytic therapies in SSc.

Overall, therapeutic strategies targeting aging-associated pathways may provide opportunities to simultaneously modulate fibrosis, chronic inflammation, and immune dysregulation. Emerging therapeutic approaches targeting cGAS-STING signaling and aging-associated pathways are summarized in Table 2.

## CONCLUSION

Recent advances support the concept that SSc represents a state of hyper-aging characterized by accelerated and dysregulated biological aging. Epigenetic drift, telomere attrition, genomic instability, mitochondrial dysfunction, cellular senescence, and inflammaging converge to promote fibrosis, vascular injury, and chronic innate immune activation. Central to this process is activation of the cGAS-STING pathway by cytosolic DNA derived from damaged nuclei and mitochondria. Emerging clinical evidence linking telomere shortening to SSc prognosis and senescent cell accumulation to treatment response reinforces the therapeutic relevance of the hyper-aging framework. Future studies integrating aging biology with immune and fibrotic mechanisms will further refine the hyper-aging framework in SSc, facilitating the development of novel biomarkers and mechanism-based therapeutic strategies.

**Table 2.** Therapeutic approaches targeting the cGAS-STING axis in systemic sclerosis and autoimmune diseases

| Therapeutic class               | Agent                                             | Mechanism of action                                                                                                                                                            | Disease findings                                                                                                                       | Refs                                                 |
|---------------------------------|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| cGAS inhibitors                 | G150                                              | Inhibits cGAS enzymatic activity; reduces ISG and pro-inflammatory cytokine expression                                                                                         | Demonstrated efficacy in SSc-related immune activation models                                                                          | [2 <sup>■</sup> ]                                    |
| cGAS inhibitors                 | A151                                              | Suppressive oligodeoxynucleotide (TTAGGG motif); competitively blocks cGAS by binding dsDNA-binding domain, reducing enzymatic activity and downstream IFN- $\beta$ production | Inhibits cGAS in human monocytes; studied in Trex1-deficient and SLE models; reduces IFN- $\beta$ in autoimmune contexts               | [2 <sup>■</sup> ,38 <sup>■</sup> ]                   |
| cGAS inhibitors                 | PF-06928215                                       | High-affinity small-molecule inhibitor binding directly to cGAS catalytic active site (KD=200nmol/l); identified via fluorescence polarization screening                       | Preclinical characterization of cGAS active-site inhibition; established proof of cGAS druggability                                    | [2 <sup>■</sup> ,38 <sup>■</sup> ]                   |
| cGAS inhibitors                 | RU.521                                            | Selective cGAS inhibitor targeting the enzyme catalytic site; effective in Trex1-deficient interferonopathy models                                                             | Demonstrated therapeutic benefit in murine type I interferonopathy models; reduces STING-dependent inflammation                        | [2 <sup>■</sup> ]                                    |
| STING antagonists               | C-176, C-178, H-151                               | Block STING palmitoylation and prevent active conformational transition of STING                                                                                               | Suppress STING signaling in-vitro and in-vivo models; H-151 effective in neovascular AMD model                                         | [2 <sup>■</sup> ,38 <sup>■</sup> ,41 <sup>■</sup> ]  |
| STING inhibitors                | ISD017                                            | Small-molecule STING inhibitor that reduces autoantibody formation and renal injury                                                                                            | Effective in murine lupus-prone (Fcgr2b-deficient) mice with proteinuria and autoimmune features                                       | [38 <sup>■</sup> ,42 <sup>■</sup> ]                  |
| Natural STING antagonist        | Anhydrotuberosin (ATS)                            | Potent natural STING antagonist identified via high-throughput screening; suppresses STING-dependent interferon signaling                                                      | Demonstrates efficacy in Trex1-deficient autoimmune models; total synthesis achieved                                                   | [38 <sup>■</sup> ,43 <sup>■</sup> ]                  |
| Mitochondrial targeting therapy | Mitophagy enhancers (e.g. rapamycin, urolithin A) | Promote clearance of damaged mitochondria, reduce cytosolic mtDNA release, and attenuate cGAS-STING activation                                                                 | Preclinical evidence that improving mitophagy curtails mtDNA-driven cGAS-STING inflammaging; relevant to SSc mitochondrial dysfunction | [22 <sup>■</sup> ,34 <sup>■</sup> ,35 <sup>■</sup> ] |

cGAS, cyclic GMP-AMP synthase; ECM, extracellular matrix; IFN, interferon; IPF, idiopathic pulmonary fibrosis; ISG, interferon-stimulated genes; mtDNA, mitochondrial DNA; PBL-TL, peripheral blood leukocyte telomere length; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SBS, single-base substitution; SSc, systemic sclerosis; SSc-ILD, SSc-associated interstitial lung disease; STING, stimulator of interferon genes; TCA, tricarboxylic acid.

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## Conflicts of interest

There are no conflicts of interest.

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- This review discusses telomere shortening in fibrotic interstitial lung disease including connective tissue disease-associated ILD.
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This mechanistic study demonstrates how defective mitophagy promotes mtDNA release and cGAS-STING-mediated inflammaging during aging.

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This spatial transcriptomic study identifies mitochondrial dysfunction and metabolic collapse as defining features of fibrotic skin niches in SSc.

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This comprehensive physiological review details how metabolic dysfunction and cellular senescence converge as primary drivers of lung aging and fibrotic disease, with direct relevance to SSc-ILD pathogenesis.

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This study identifies a metabolic-mitochondrial-cGAS-STING axis linking mitochondrial instability with chronic inflammatory signaling.

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This high-impact review focusing on SSc demonstrates that senescent cells drive fibrotic remodeling across multiple organs and that targeting cellular senescence with senolytics or senomorphics represents a viable therapeutic strategy in SSc, supported by early clinical trial data.

35. Chiu YH, van Dijk M, Goldschmeding R, *et al*. Dermal cellular senescence and EndMT in patients with systemic sclerosis undergoing cyclophosphamide or aHSCT treatment. *Rheumatology (Oxford)* 2025; 64:3957.

This clinical study from the ASTIS trial demonstrates that senescent cells (p21+) and endothelial-to-mesenchymal transition markers in SSc skin biopsies are

modulated by treatment and predict clinical response, supporting cellular senescence as both a biomarker and therapeutic target in SSc.

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This review characterizes cGAS-STING signaling as a central regulator of the senescence program and the SASP, with implications for both aging and inflammatory disease.

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This review provides an updated overview of immunosenescence and inflammaging mechanisms relevant to chronic inflammatory disease.

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This review characterizes ABCs and their expanding role in autoimmune pathogenesis across rheumatic diseases.

39. Xie G, Chen X, Gao Y, *et al*. Age-associated B cells in autoimmune diseases: pathogenesis and clinical implications. *Clin Rev Allergy Immunol* 2025; 68:18.

This review discusses the pathogenic role of ABCs in autoimmune diseases, including their contribution to autoantibody production and chronic immune activation relevant to SSc.

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This review discusses cGAS-STING signaling as a central mediator of aging-associated inflammatory disease and therapeutic target.

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This study demonstrates that pharmacological inhibition of STING with H-151 suppresses pathological inflammation, supporting STING inhibition as a potential therapeutic strategy.

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This study shows that the STING inhibitor ISD-017 ameliorates autoimmune glomerulonephritis in vivo, providing preclinical evidence for targeting STING in autoimmune disease.

43. Guo F, Zhang J, Gao Y, *et al*. Discovery and total synthesis of anhydrotuberosin as a STING antagonist for treating autoimmune diseases. *Angew Chem Int Ed Engl* 2025; 64:e202407641.

This study reports the discovery of a novel small-molecule STING antagonist with therapeutic potential for the treatment of autoimmune diseases.



# Artificial intelligence for lung disease quantification in systemic sclerosis-associated interstitial lung disease and other connective tissue disease-associated interstitial lung disease

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## Purpose of review

Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is the leading cause of disease-related mortality in systemic sclerosis and the connective tissue disease-associated ILD (CTD-ILD) in which artificial intelligence imaging has advanced most rapidly. Visual high-resolution CT (HRCT) scoring is reader-dependent and limits clinical decision-making. This review summarizes clinically relevant artificial intelligence and radiomics publications from approximately the last 18 months, focusing on quantification, diagnosis and classification, response assessment, and prognosis.

## Recent findings

The field has moved from visual-score emulation toward outcome-oriented quantitative imaging biomarkers. In SSc-ILD, deep-learning usual interstitial pneumonia (UIP) probability stratifies FVC decline and long-term survival, while whole-chest quantitative imaging biomarkers extend risk prediction beyond lung involvement alone. Automated SSc-specific segmentation, explainable Goh-equivalent scoring, slice-reduced radiomics, and open datasets have strengthened the methodological base. Parallel work in CTD-ILD, RA-ILD, and IIM-ILD shows that artificial intelligence-derived HRCT parameters correlate with DLCO/TLC, predict mortality, and support disease-pattern classification. In broader fibrosing ILD, qCT definitions of progressive pulmonary fibrosis and clinically meaningful CT thresholds provide the most important conceptual advance for future SSc-ILD trials.

## Summary

Artificial intelligence-based CT quantification is becoming a credible adjunct for rheumatology and radiology practice, but the most defensible deployment model is human-in-the-loop decision support. Prospective multicenter validation, protocol harmonization, calibration, version control, and integration into multidisciplinary discussion remain essential before artificial intelligence outputs can be used as treatment-triggering biomarkers.

## Keywords

artificial intelligence, connective tissue disease, interstitial lung disease, quantitative computed tomography, systemic sclerosis

## INTRODUCTION

Interstitial lung disease (ILD) develops in approximately one-half of patients with systemic sclerosis (SSc) and is now the leading cause of SSc-related mortality, with 10-year survival in extensive disease below 70% [1,2]. SSc-ILD is also the connective tissue disease-associated ILD (CTD-ILD) in which artificial intelligence imaging has matured most rapidly. The reasons are historical and structural: SSc-ILD is the only CTD-ILD with a long-standing reference visual-scoring system (the Goh extensive-versus-limited classification), a well defined natural history, and a series of randomized antifibrotic and immunomodulatory

trials (SLS II, SENSICIS, focuSSced, DESIRES) that provide imaging-linked outcomes [3–6].

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## KEY POINTS

- Artificial intelligence in SSc-ILD has matured from proof-of-concept segmentation to clinically interpretable quantitative imaging biomarkers linked to FVC trajectory, pulmonary function, organ manifestations, treatment response, and survival.
- Deep-learning UIP probability is best interpreted as a continuous risk biomarker rather than a replacement for expert radiologic pattern classification.
- The strongest recent methodological shift in fibrosing ILD is outcome-oriented qCT: qctPPF, meaningful CT-change thresholds, and multimodal survival models provide a template for SSc-ILD trials.
- Cross-CTD studies show that SSc-derived quantification strategies generalize to RA-ILD, IIM-ILD, and heterogeneous inflammatory rheumatic disease populations, although subtype-specific calibration remains necessary.

Nevertheless, visual HRCT interpretation remains reader-dependent, semi-quantitative and relatively insensitive to small but clinically meaningful longitudinal change. The 2022 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Asociación Latinoamericana de Tórax (ATS/ERS/JRS/ALAT) guideline operationalized progressive pulmonary fibrosis (PPF) as the unifying outcome across non-IPF fibrosing ILDs, including SSc-ILD, anchored in a composite of symptoms, physiology, and imaging progression [7]. Of these three pillars, the imaging component is the most subjective and the most amenable to artificial intelligence-derived improvement.

This review surveys clinically meaningful primary research published since mid-2024, written from a chest-radiology perspective for the practicing rheumatologist, with earlier studies retained only when foundational. The principal focus is SSc-ILD; advances in other CTD-ILDs are surveyed in a dedicated subsection because they share methodologic infrastructure with SSc-ILD.

The contemporary AI-ILD literature can be organized into four overlapping tasks: segmentation and quantification of disease burden; diagnosis and pattern classification; response assessment and PPF definition; and prognosis or treatment selection. These tasks are not independent. For example, a usual interstitial pneumonia (UIP)-probability score may be diagnostically informative, but its strongest value in SSc-ILD may be prognostic. Similarly, ground-glass opacity may represent potentially reversible inflammation in one CTD-ILD phenotype

but fine fibrosis or volume-averaging artifact in another. The emerging generation of models is therefore useful only if its outputs remain anatomically interpretable, technically reproducible and clinically actionable.

## FROM VISUAL SCORING TO DEEP-LEARNING QUANTIFICATION

The first wave of ILD artificial intelligence (ILD AI) used convolutional neural networks (CNN) for slice-level pattern recognition. The second wave addressed a practical bottleneck: having experts annotate individual cross-sectional images is a laborious process and can only be done to a limited extent. Multi-instance learning and weakly supervised learning allow a model to be trained using a single classification for the entire patient (e.g. 'UIP' or 'progressed') without having to specify where in the scan it should look; the model synthesizes information from many layers into a probability at the patient level and can then display the regions that led to that result.

The current wave is no longer built on a single architecture. Self-configuring segmentation networks outline lung structures and disease voxel by voxel, adapting their own settings to each new dataset. Transformer-based classifiers weigh relationships across the entire scan rather than local texture alone. Multimodal models read the CT alongside clinical variables such as forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DLCO), and autoantibody status.

For the clinician, this means a change in the output itself. Earlier models provided only a rough classification ('UIP' versus 'not UIP'). Current models return quantifiable values: the percentage of lung involved, the extent of each individual pattern, a continuous probability rather than a yes/no category, an overlay map showing the location of the disease, and values that can be measured again on the next CT to assess progression.

Foundational SSc-ILD segmentation work showed that deep learning can quantify total disease extent and major radiologic patterns with expert-level agreement, while newer annotated datasets, although still small, begin to address the scarcity of disease-specific training data [8,9].

Recent non-SSc studies support translational generalizability. Lin *et al.* [10] used self-configuring nnU-Net, a U-Net framework that automatically adapts preprocessing, network configuration and training settings to the dataset, to quantify ILD features with strong expert agreement. Hoffmann *et al.* evaluated artificial intelligence-based quantification of pulmonary HRCT (AIqPHRCT) in inflammatory rheumatic disease-associated ILD, showing

excellent reproducibility without operator adjustment (manual correction of artificial intelligence-generated lung or lesion segmentations by the reader/operator) and significant inverse correlations between artificial intelligence-derived disease extent and DLCO, total lung capacity (TLC), and FVC [11<sup>■</sup>,12<sup>■</sup>]. Because such manual operator adjustment increased variability, particularly for ground-glass opacity and honeycombing, these data support using artificial intelligence-derived disease burden as a standardized structural complement to pulmonary function testing, not as a substitute for expert interpretation [11<sup>■</sup>,12<sup>■</sup>]. Multimodal classifiers extend quantification toward outcome prediction; for example, CT, pulmonary function, and demographic features predicted mortality across three independent ILD cohorts [13<sup>■</sup>]. In SSc-ILD, automated UIP probability is best understood as a continuous risk score rather than a binary diagnostic label [14<sup>■■</sup>]. Used with radiologist oversight, such outputs may improve pattern classification and prognostic alignment, but they remain decision-support inputs for multidisciplinary interpretation rather than replacements for it [15,16].

### SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE: THE MOST MATURE CONNECTIVE TISSUE DISEASE-ASSOCIATED INTERSTITIAL LUNG DISEASE USE CASE

SSc-ILD now has the densest body of disease-specific artificial intelligence imaging literature among CTD-ILDs. Among the first publications on deep learning in SSc-ILD was a seminal 2020 study by Chassagnon *et al.*, who trained a multicomponent deep neural network based on AtlasNet [8]. Radiological lung patterns [i.e. ground-glass opacities (GGO), reticulations (RET), traction bronchiectasis, and honeycombing] were segmented jointly, covering the total extent of disease (TED). Their model achieved Dice agreement with expert radiologists in the same range as inter-reader agreement (0.74–0.75 versus 0.68–0.71) and correlations with DLCO of  $\rho = -0.76$  [8]. Following along the same research lines, Vahdani *et al.* [9<sup>■</sup>] reported comparable automated segmentation of GGO and established fibrosis in a smaller SSc-ILD cohort and released expert-annotated HRCT labels, a useful step toward shared benchmarking despite the limited sample size.

While Chassagnon and Vahdani evaluated single time points, Guiot *et al.* augmented their work through a longitudinal component by assessing radiological manifestations in relation to 24-month follow-up of pulmonary function testing [17<sup>■</sup>].

To correspond to clinical practice, which relies heavily on the Goh score [1], Jia *et al.* developed a

two-step deep learning framework, which first selects the axial CT slices to score, and then outputs Goh-equivalent extent scores for TED, GGO, and RET. In their study, the proposed framework's agreement with the ground truth (human expert consensus) was  $\kappa = 0.54$  for TED, 0.39 for GGO, and 0.84 for RET, while the human rater's agreement was 0.51–0.74 for TED, 0.44–0.62 for GGO and 0.76–0.90 for RET [18<sup>■</sup>]. Additionally, their framework generated saliency maps that allow clinicians to interrogate the prediction at the slice level for improved explainability.

One of the most important SSc paper of the review period was by Stock *et al.* Using the SOFIA deep-learning algorithm, the authors showed that artificial intelligence-derived UIP probability in 522 SSc-ILD patients was associated with lower baseline FVC, faster FVC decline, and increased 15-year mortality, despite the fact that NSIP is more common than UIP in SSc-ILD [14<sup>■■</sup>]. The finding supports interpreting UIP probability as a continuous risk biomarker rather than a binary label. In practical terms, patients with high scores, meaning CT features more similar to UIP than to other ILD patterns, may warrant closer longitudinal surveillance and earlier consideration of treatment escalation, while the final diagnosis remains anchored in multidisciplinary assessment.

Although changes to the lung parenchyma are most commonly investigated in SSc-ILD, Sieren *et al.* focused on extrapulmonary structures on chest CT. With a regression model using markers of body composition analysis, they predicted survival with an AUC of 0.75 [19<sup>■■</sup>]. This study is especially interesting, as it widens the perspective from lung-only to a more systemic approach.

Table 1 summarizes key SSc-ILD AI studies, prioritizing work from 2024 to 2026 and retaining earlier studies only when foundational.

### ADVANCES IN OTHER CONNECTIVE TISSUE DISEASE-ASSOCIATED INTERSTITIAL LUNG DISEASE

The methodologic infrastructure built for SSc-ILD has begun to be transferred to other CTD-ILDs. Humphries *et al.* [24<sup>■■</sup>] delivered the first rigorous quantitative CT analysis specifically in rheumatoid arthritis (RA)-ILD using data-driven texture analysis in 289 patients with external validation in 50, documenting moderate negative correlation with FVC% predicted ( $\rho = -0.55$  to  $-0.50$ ) and DLCO% predicted ( $\rho = -0.67$  to  $-0.65$ ) and prognostic value beyond visual scoring. A clinical-radiomics integrated nomogram has since been published estimating 5-year survival in RA-ILD, demonstrating that imaging-only

**Table 1.** Overview of studies on artificial intelligence for the assessment of systemic sclerosis-associated interstitial lung disease, with a focus on work published 2024–2026

| First author               | Year | Cohort size  | Model architecture                                                                                                                       | Main finding                                                                                                                                                                  |
|----------------------------|------|--------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chassagnon [8]             | 2020 | 208 patients | Multicomponent deep neural network based on AtlasNet, augmented through dual autoencoder architecture.                                   | DICE agreement between model and experts matches inter-expert variability for overall disease extent segmentation.                                                            |
| Jia [18 <sup>¶</sup> ]     | 2024 | 230 patients | Framework constituting two separate models: a level-selection network based on VGG11 and a 2D segmentation network based on ConvNeXt.    | Kappa agreement between model and ground truth was higher for RET than for GGO and overall comparable with expert raters.                                                     |
| Joye [20 <sup>¶</sup> ]    | 2024 | 166 patients | In-house developed radiomics software, ZRad, for feature extraction. Multiple different models for feature selection and classification. | Radiomics-based SSc-ILD characterization can be obtained from slice-reduced rather than full-chest CT.                                                                        |
| Guiot [17 <sup>¶</sup> ]   | 2025 | 75 patients  | Icolung software: commercial software developed for the quantification of lung involvement in COVID-19 patients.                         | Modifications of FVC and DLCO over time were correlated with longitudinal radiological ILD modifications ( $r = -0.40$ , $p < 0.01$ ; $r = -0.40$ , $P < 0.01$ respectively). |
| Kuzumi [21 <sup>¶¶</sup> ] | 2025 | 48 patients  | Causal tree model.                                                                                                                       | Identification of predictors of rituximab efficacy among clinical and laboratory parameters. No analysis of CT imaging.                                                       |
| Sieren [19 <sup>¶¶</sup> ] | 2025 | 128 patients | CNN, not otherwise specified, to segment nonlung body compartments.                                                                      | Nonlung findings on chest CT carry prognostic value for SSc-ILD patients, with markers of body composition predicting survival with an AUC of 0.75.                           |
| Singh [22 <sup>¶</sup> ]   | 2025 | 92 patients  | Multiple segmentation and classification algorithms, including an adaptive border marching algorithm to segment the lungs on CT.         | Identification of predictors of primary graft dysfunction in SSc-ILD lung transplant recipients.                                                                              |
| Stock [14 <sup>¶¶</sup> ]  | 2025 | 522 patients | Systematic Objective Fibrotic Imaging analysis Algorithm (SOFIA), a convolutional neural network algorithm.                              | Higher probability for UIP pattern correlated with lower FVC, faster loss of FVC and increased 15-year mortality.                                                             |
| Vahdani [9 <sup>¶</sup> ]  | 2026 | 40 patients  | U-Net variant inspired by the ConvNeXt V2 family of models.                                                                              | DICE agreement between model and expert consensus between 0.70 for established fibrosis and 0.78 for established fibrosis + GGO.                                              |
| Zhang [23 <sup>¶</sup> ]   | 2026 | 43 patients  | Not described.                                                                                                                           | Comparison of different CT acquisition protocols, including HRCT, VNC, and monoenergetic 70 keV CT.                                                                           |

CNN, convolutional neural network; CT, computed tomography; DICE, Dice similarity coefficient; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; GGO, ground-glass opacities; HRCT, high-resolution CT; ILD, interstitial lung disease; keV, kiloelectronvolt; RET, reticulations; SSc-ILD, systemic sclerosis-associated interstitial lung disease; UIP, usual interstitial pneumonia; VNC, virtual noncontrast.

radiomics is meaningful but augmentation with clinical and laboratory variables (in particular Krebs von den Lungen-6) is decisive for individualized risk estimation [25<sup>¶</sup>]. Quantitative imaging now also addresses idiopathic inflammatory myopathies (IIM): deep-learning classifiers distinguish characteristic IIM-ILD imaging patterns [26<sup>¶</sup>], Artificial intelligence quantification of pulmonary vasculature in anti-MDA5+ disease identifies patients at risk of rapid progression [27<sup>¶</sup>], artificial intelligence-quantified

change tracks tofacitinib response in MDA5+ dermatomyositis [28<sup>¶</sup>], an interpretable model integrates radiomic and clinical features for IIM-ILD detection [29<sup>¶</sup>], and longitudinal quantitative CT addresses antisynthetase syndrome with follow-up beyond 24 months [30<sup>¶</sup>]. Liu and colleagues extended HRCT radiomics to juvenile dermatomyositis [31].

Cross-CTD frameworks complete the picture. AIqPHRCT applies a single locked algorithm across inflammatory rheumatic diseases and identifies

DLCO and TLC as key physiologic correlates of artificial intelligence-derived severity [11<sup>■</sup>,12<sup>■</sup>]. Long *et al.*[32] derived a CT deep-learning radiomics model that staged CTD-ILD against the gender–age–physiology (GAP) framework, a clinical ILD risk framework incorporating sex, age, FVC, and DLCO. Chu *et al.* [33<sup>■</sup>] then showed in a longitudinal cohort that artificial intelligence-derived HRCT parameters independently predict all-cause mortality in CTD-ILD across CTD subtypes, which is the strongest survival-anchored evidence to date that artificial intelligence-derived imaging biomarkers should inform follow-up frequency and treatment escalation. Ito *et al.*[34] applied novel deep-learning analysis to ILD extent across CTDs; Zhang *et al.*[35<sup>■</sup>] addressed imaging-defined lesion reversibility under treatment, an under-explored axis relevant to immunosuppression decisions; and Colligiani *et al.*[36<sup>■</sup>] introduced radiomic separability of fibrosing versus inflammatory ILD patterns, an axis that more closely mirrors the rheumatologist's treatment decision than fibrosis extent alone.

### BEYOND EXTENT: PROGNOSIS, TREATMENT RESPONSE, AND BIOLOGY

Artificial intelligence-derived imaging biomarkers increasingly anchor treatment decisions beyond simple fibrosis extent and are oriented toward three phenotypic aspects. Vascular phenotyping: artificial intelligence quantification of pulmonary vasculature in anti-MDA5+ IIM-ILD identifies patients at risk of rapid progression and is mechanistically relevant across all fibrosing CTD-ILDs, particularly given the SSc-specific overlap between ILD and pulmonary arterial hypertension [27<sup>■</sup>]. Airway phenotyping: quantitative airway analysis derived from HRCT provides independent prognostic information in IPF and is plausibly transferable to traction-bronchiectasis-driven progression in SSc-ILD, although dedicated CTD validation is still pending [37<sup>■</sup>]. Body composition: CT-derived sarcopenia and adipose-tissue measures predict mortality in IPF and may have downstream relevance to CTD-ILD frailty assessment, particularly in patients on chronic glucocorticoids or antifibrotic therapy [38]. Lauer *et al.* introduced 'radioproteomics', linking radiomic signatures to molecular response to antifibrotic treatment in pulmonary fibrosis using both bleomycin-model mice and a human cohort that explicitly included SSc-ILD; this is a particularly intriguing avenue for rheumatology, as it enables imaging-derived monitoring of pathway-level treatment effects without serial biopsy [39].

Plasma proteomic signatures associated with high-attenuation areas on CT provide a biologically

grounded link between quantitative imaging and systems biology. Candidate proteins include junctional adhesion molecule-like protein and GTP cyclohydrolase 1 feedback regulatory protein, both of which localized to areas of fibrosis in ILD lung tissue, suggesting a potential pathway toward nonimaging biomarkers that could be measured longitudinally at routine visits [40<sup>■</sup>]. Multimodal artificial intelligence integrating histopathology with CT has been proposed to enhance ILD diagnosis when biopsy material remains available, although clinical applicability is currently constrained to research and reference-center settings [41<sup>■</sup>]. Together, these developments mean that the artificial intelligence-quantified HRCT report of 2026 carries substantially more information than the percentage-fibrosis number that dominated the 2018-2022 literature.

### STANDARDIZATION, HARMONIZATION, AND REPRODUCIBILITY

The reproducibility of artificial intelligence-quantified CT remains constrained by variability across scanners, reconstruction kernels (mathematical filters applied during CT image reconstruction that influence image sharpness, noise, and texture), and acquisition protocols, with direct implications for longitudinal SSc-ILD assessment and harmonized data pooling [42<sup>■</sup>,43<sup>■</sup>,44]. One key methodologic contribution of the period comes from Choe *et al.* [42<sup>■</sup>]. Using generative adversarial network-based style conversion, they harmonized CT acquisitions across vendors and restored functional correlations between artificial intelligence quantification and pulmonary function, a prerequisite for reliable multicenter trials [42<sup>■</sup>]. Beyond vendors, a second source of variability comes from detector technology itself. Koo *et al.* compared photon-counting detector CT (PCD-CT) with conventional CT on paired same-day scans, finding high feature-level concordance. Locked models therefore transfer broadly to PCD-CT, although local discrepancies still warrant recalibration before clinical deployment [43<sup>■</sup>]. In SSc-ILD specifically, Happe *et al.* [44] recently extended this comparison to automated lung texture analysis on paired PCD-CT and energy-integrating-detector CT, confirming preserved diagnostic accuracy across detector technologies and providing the first SSc-targeted evidence base for the photon-counting transition. A further driver of heterogeneity lies in the reconstruction algorithm, which shapes image texture and therefore the output of any artificial intelligence model. Evidence on this point comes from Hamada *et al.*[45], who showed that for honeycombing specifically, deep-learning reconstruction kernels improve inter-observer agreement relative to hybrid

iterative reconstruction. The clinical implication has been formalized by Yu *et al.* [46<sup>\*</sup>], who tested locked deep learning models for fibrosing-ILD diagnosis across multiple acquisition protocols and documented performance drift, underscoring the need for institutional benchmarking before deployment.

The studies cited above tackle specific sources of variability, but a fully standardized pipeline for SSc-ILD quantification does not yet exist. Beyond these individual contributions, three methodologic priorities now stand out: Image Biomarker Standardization Initiative compliance for cross-registry feature comparability, federated learning to enable multisite training without patient-level data exchange, and postmarket drift monitoring as scanner generations and patient populations evolve [47–49]. Each is established in the broader radiology-artificial intelligence literature but has yet to be operationalized within SSc-ILD registries.

## FOUNDATION MODELS AND GENERALIST CHEST COMPUTED TOMOGRAPHY ARTIFICIAL INTELLIGENCE

Foundation models are an emerging direction in thoracic imaging, but they have not yet been validated specifically for SSc-ILD or CTD-ILD cohorts [50–52]. In contrast to conventional artificial intelligence tools designed for a single task, such as fibrosis segmentation or UIP classification, foundation models are trained on very large imaging and report datasets and may then be adapted to multiple clinical questions with less disease-specific annotation [53]. For clinicians, their potential value is practical: they may help identify visually similar cases, reduce the need for manual labeling, support more consistent quantification across heterogeneous ILD phenotypes, and eventually improve robustness across scanners and institutions [50,54]. At present, however, their role in SSc-ILD remains investigational, and they should be viewed as a future platform for artificial intelligence-assisted imaging rather than as established biomarkers for diagnosis, monitoring, or treatment decisions.

## IMPLEMENTATION IN CLINICAL PRACTICE

The safest implementation model is human-in-the-loop decision support and helps to improve inter-reader agreement and pattern-classification accuracy in fibrotic ILD [15,16]. Artificial intelligence can prepopulate structured reports with lung volume, normal parenchyma, total ILD extent, fibrotic extent, GGO, reticulation, honeycombing, traction bronchiectasis, UIP probability and longitudinal change. The radiologist then verifies or corrects

the output and contextualizes it within image quality and differential diagnosis. Because patients with SSc-ILD carry an increased risk of lung cancer, the same chest CT can additionally be reviewed for pulmonary nodules and malignancy, which artificial intelligence tools can flag alongside ILD quantification. The multidisciplinary ILD board then integrates these imaging biomarkers with symptoms, FVC, DLCO, autoantibodies, treatment history, comorbid pulmonary hypertension, frailty and patient preference.

Regulatory and reporting requirements are becoming stricter. Prediction models should follow TRIPOD +AI [55]; diagnostic accuracy studies should align with STARD-AI [56]; interventional deployment studies should consider CONSORT-AI [57]; and radiomics feature definitions should follow Image Biomarker Standardization Initiative principles. In Europe, medical diagnostic artificial intelligence falls within a high-risk governance environment, requiring data provenance, bias analysis, version control, and post-market monitoring (EU AI Act) [58]. For SSc-ILD registries and trials, federated learning and centralized audit of qCT outputs may allow multicenter model development without unrestricted patient-level data transfer.

## CONCLUSION

Artificial intelligence-based CT quantification in SSc-ILD has advanced from proof-of-concept research to a clinically credible adjunct for measuring disease burden, estimating UIP-probability risk along a continuum, assessing longitudinal qCT change, and supporting multimodal prognostication.

Important limitations remain, particularly the sensitivity of artificial intelligence outputs to CT acquisition parameters, scanner hardware, and dose; robust harmonization, calibration, and quality-control procedures are therefore essential before these tools can be used reliably across centers.

For current practice, artificial intelligence should remain a human-in-the-loop decision-support tool rather than an autonomous determinant of diagnosis, progression, or treatment escalation. For rheumatologists and radiologists, the practical message is to use artificial intelligence-derived CT metrics as structured quantitative inputs to clinical judgment. A single absolute score is less informative than a verified longitudinal trajectory interpreted alongside pulmonary function, biomarkers, treatment history, and multidisciplinary expertise. If validated prospectively, integrated artificial intelligence imaging workflows could refine treatment escalation, improve trial design, and individualize follow-up in SSc-ILD and the broader CTD-ILD spectrum.



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# Erosive gout: update on mechanisms, impact and treatment

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## Purpose of review

Erosive gout refers to the presence of at least one gouty bone erosion in a person with gout. This review provides an update on the update on mechanisms, impact, and treatment of erosive gout.

## Recent findings

Erosive gout is usually the consequence of long-standing tophaceous disease. However, bone erosions in association with tophi can be detected on ultrasound before onset of clinical symptoms in some people with asymptomatic hyperuricaemia. SPP1 (osteopontin)-expressing macrophages have been implicated in pathogenesis of tophaceous gout and SPP1-mediated cellular interactions may influence bone remodelling in the context of erosive gout. In addition to joint deformity, people with erosive gout experience more frequent gout flares and have low rates of disease remission, even with intensive urate-lowering therapy. Oral urate-lowering therapy using a treat to target serum urate approach can prevent progression of erosive gout, and small serial imaging studies have demonstrated infilling of monosodium urate crystal-related bone erosion in pegloticase responders.

## Summary

Erosive gout is a consequence of tophaceous gout and causes joint deformity which is difficult to reverse once established. Collectively, these findings provide a rationale for urate-lowering therapy for people with gout to prevent the consequences of tophaceous gout including joint damage.

## Keywords

erosion, gout, tophus

## INTRODUCTION

Erosive gout refers to the presence of at least one gouty bone erosion in a person with gout [1]. These erosions have characteristic appearances on medical imaging, appearing as a cortical break with an overhanging edge and sclerotic margin, as demonstrated in an imaging atlas of gout [2<sup>•</sup>] (Fig. 1). There are also characteristic sites of involvement of gouty bone erosion on imaging, with most frequent involvement in the lower limbs, particularly at the medial aspect of the 1st metatarsal head [3]. These sites align with preferential sites of monosodium urate (MSU) crystal deposition in the feet [3,4<sup>•</sup>].

In people with gout, bone erosion is the consequence of tophaceous gout and typically occurs late in the disease following prolonged exposure to hyperuricaemia. For example, in the people with gout attending the Vien Gut Medical Center in Ho Chi Minh City, Vietnam, baseline bone erosion scores in the feet associated with gout disease duration ( $P < 0.05$ ) presence of subcutaneous tophi on physician examination ( $P < 0.001$ ), and ultrasound measures of index tophus size ( $P = 0.01$ ) [5<sup>••</sup>].

## ASSESSMENT FOR EROSIVE GOUT

Gouty bone erosions can be identified by all the major imaging modalities: plain radiography, computed tomography, ultrasound (Fig. 2) and magnetic resonance imaging [2<sup>•</sup>,6,7]. A comparison study of hand-held ultrasound and cart-based ultrasound showed that, despite lower resolution and clarity, the handheld device identified bone erosion in most people with gout, with similar or higher sensitivity than the cart-based device [7].

The European Alliance of Associations for Rheumatology (EULAR) has recently published recommendations about the role of imaging in diagnosis

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## KEY POINTS

- Bone erosion is a consequence of tophaceous gout and causes joint deformity and disability.
- Bone erosion with associated tophi can be observed on ultrasound in some people with asymptomatic hyperuricaemia who have not experienced clinical symptoms of gout.
- SPP1 (osteopontin)-expressing macrophages play an important role in tophus formation and may represent a treatment target for prevention or treatment of erosive gout.
- Treat to serum urate target with oral urate-lowering therapy can prevent bone erosion progression, but there is limited evidence of erosion healing with oral urate-lowering therapy.
- Bone remodelling including erosion in-filling can be observed in pegloticase responders with erosive gout.



**FIGURE 1.** Plain radiograph left 1st metatarsophalangeal joint in a person with tophaceous gout, demonstrating bone erosions with overhanging edges and sclerotic margins. Note the involvement of the various sites within the joint, including the medial metatarsal head.

and management of crystal-induced arthropathies in clinical practice [8]. These recommendations include advice about the role of imaging in assessing structural damage due to gout. EULAR advised that “In case ultrasound/DECT are not available, conventional radiography can be used to assess structural damage due to gout.” The EULAR taskforce noted that structural damage such as bone erosion can be identified by imaging modalities including conventional radiography in longstanding disease. The role of serial imaging in clinical practice was considered uncertain and requiring further study. However, a 1-year interval was considered reasonable to monitor imaging changes in gout.

## QUANTIFICATION OF EROSIVE GOUT

Scoring methods have been described to qualify the extent of bone erosion in gout. These systems have generally been modified from existing scoring systems initially developed for assessing bone erosion in rheumatoid arthritis, such as the Sharp-van der Heijde scoring system for plain radiography [9], the RAMRIS scoring system modified for both MRI and computed tomography (CT) for gout [10,11], and the OMERACT/EULAR rheumatoid arthritis ultrasound scoring system [12].

An advantage of the Sharp-van der Heijde plain radiography scoring system is that it allows quantification of plain radiographic changes, noting that plain radiography is widely available in most health-care systems and less observer-dependent than ultrasound. An example is the Vien Gut Medical Center cohort in which serial plain radiographs of the feet were obtained and bone erosion subsequently quantified over a twelve-month period of urate-lowering therapy [5<sup>22</sup>].

While dual energy CT is mostly viewed as a preferred modality for detection of MSU crystals, the conventional CT images obtained as part of dual energy CT protocols provide excellent resolution of bone erosion [13<sup>2</sup>,14]. A gout-specific semi-quantitative CT scoring system with excellent inter-reader reproducibility has been utilized in clinical trials [6,11,15,16]. Individual bone erosions have also been assessed in more detail by measurement of size the transverse and longitudinal planes on CT [14]. In addition to assessment of bone erosion, this approach has allowed a qualitative assessment of bone remodelling with recortication and new bone formation that can occur during intensive serum urate-lowering. Recortication has been defined as “increased thickening and/or density at the erosion margin” and new bone formation defined as “increased density and/or development of bony spurs at the erosion margin” [14].

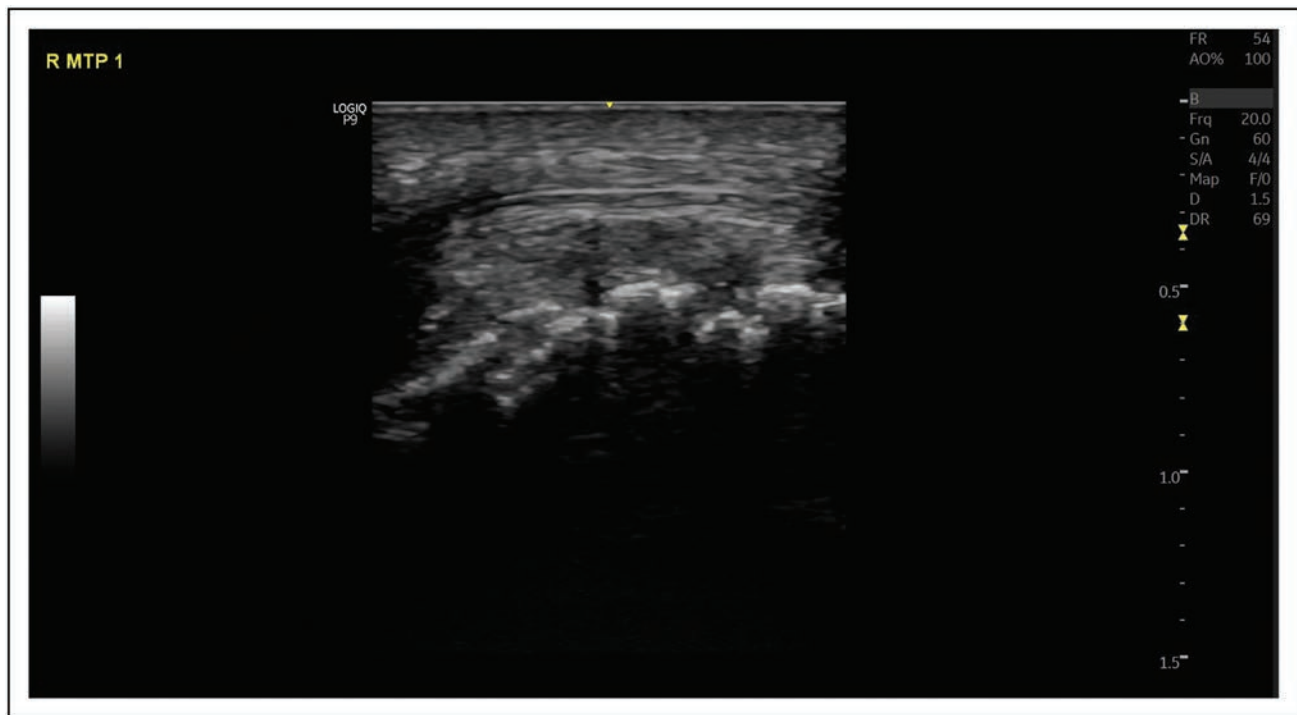


**FIGURE 2.** Ultrasound right 1st medial metatarsal head demonstrating bone erosion in contact with a tophus (GE Logiq P9, L10-22-RS transducer).

### MECHANISMS OF EROSIIVE GOUT

Prior imaging studies of people with established gout have demonstrated a close spatial relationship between tophus and bone erosion within the joint and support an ‘outside-in’ mechanism of bone erosion due to MSU crystal deposition and tophus formation within the synovial space. [17,18]. The distribution of bone erosion in gout aligns closely with the distribution of MSU crystal deposition measured by dual energy CT with preferential sites of deposition at the medial metatarsal head [3,4<sup>■</sup>]. Bone erosion represents a focal intra-articular lesion with maintenance of skeletal bone mineral density [19].

While bone erosion is typically a feature of long-standing gout, imaging studies of people with asymptomatic hyperuricemia have demonstrated that bone erosion can occur prior to development of clinically apparent gout. In the multinational TIGER study of 269 people with serum urate  $\geq 0.48$  mmol/l (8 mg/dl), no previous gout flares, and no subcutaneous tophi, bone erosion was present on ultrasound in 11.9% of participants and at least one tophus on ultrasound in 17.1% [20<sup>■</sup>]. These ultrasound lesions were primarily at the 1st metatarsophalangeal (MTP) joint. Furthermore, 1st MTP joint ultrasound tophus was associated with an odds ratio of 11.6 [95% confidence interval (CI) 4.1–33.0] for the presence of radiographic bone erosion and the

presence of Doppler activity (score  $> 1$ ) on ultrasound was also associated with an odds ratio of 11.4 (95% CI 3.2–40.5) for radiographic bone erosion. This study indicates that that subclinical tophi and bone erosion can develop much earlier than previously appreciated in those with asymptomatic hyperuricemia.

Immunohistochemistry analysis of the tophus has identified macrophages expressing osteoclast markers within the tophus, and multiple osteoclast-like cells at the bone–tophus interface [21]. The tophus is an organized structure comprising islands of MSU crystals (crystalline core), surrounded by a corona zone of innate and adaptive immune cells including multinucleated macrophages, which is in turn surrounded by a fibrovascular zone [22,23].

Recent work has highlighted the importance of SPP1<sup>+</sup> macrophages in tophaceous gout with implications for tophus formation and bone erosion in gout [24<sup>■</sup>]. Spatial analysis of different sites within the tophus identified enrichment of SPP1 (osteopontin)-expressing macrophages within the corona region. Osteopontin plays a key role in bone remodelling through multiple mechanisms including anchoring osteoclasts to the bone surface [25]. SPP1<sup>+</sup> macrophages were identified as a unique subset specific to the tophus with osteoclast differentiation potential and active involvement in extracellular matrix remodelling. Tophaceous gout-associated macrophages

showed marked upregulation of SPP1, MMP9, CHI3L1 and COL6A2 compared to gout flare-associated synovial fluid macrophages. Some SPP1+ tophaceous gout-associated macrophages co-expressed MMP9 and chitinase-3 like-protein-1 (CHI3L1), a protein that plays an important role in tissue injury, inflammation, tissue repair, and remodelling responses. MMP9, which is well known for its role in cell migration and tissue remodelling, is regulated by SPP1 [26]. Stromal cells within the tophus exhibited a phenotype similar to SPP1+ macrophages in tophi, characterized by increased expression of SPP1 and MMP9, together with CD68. The corona zone adjacent to the tophus core exhibited an elevated proportion of triple-positive (S100A4+SPP1+CD68+) cells, indicative of potential macrophage-fibroblast intermediate states, while this co-expression was not common in the fibrovascular zone. In the SPP1-related pathway within the corona zone, the most prominent receptor-ligand pair identified was SPP1-CD44, with macrophages, fibroblasts, and osteoblasts as senders or receivers. The potential importance of osteopontin in bone erosion is further supported by a report that people with erosive gout have higher circulating osteopontin concentrations than people with nonerosive gout [27].

### IMPACT OF EROSIIVE GOUT

The presence of bone erosion often reflects longstanding disease and high MSU crystal deposition, as reflected in the Vien Gut cohort study [5<sup>\*\*\*</sup>]. In a retrospective analysis of 1204 people with gout who had undergone a dual energy CT, elevated Sharp-van der Heijde scores on the CT images and tarsal bone erosion were independently associated with frequent gout flares over the 12 months after the dual energy CT. These associations were independent of the MSU crystal volumes on dual energy CT, suggesting that the presence of bone erosion may be a risk for flare in addition to MSU crystal burden [28].

Bone erosions can lead to joint deformity with consequent functional problems. In an analysis of 100 people with tophaceous gout, radiographic hand bone erosion scores were the strongest predictor of grip strength and independently explained 35% of the variance in grip strength, with a total explained variance of 56% with the inclusion of sex, age and tophus count [29]. Additionally, bone erosion and osteolysis in small joints can lead to joint instability and digit shortening, which may become clinically apparent once tophus regression has been achieved with urate-lowering therapy [30].

G-CAN has recently endorsed a definition of clinical remission in gout, consisting of no gout flares over 12 months, absence of subcutaneous tophi and serum urate <0.36 mmol/l (6 mg/dl) over 12 months

[31]. In an analysis of a 2-year, double-blind randomized-controlled trial of people with erosive gout treated with oral urate-lowering therapy, randomized to a serum urate target of <0.20 mmol/l (3.3 mg/dl) or <0.30 mmol/l (5 mg/dl) this definition was achieved in 27% of participants in year 1 and 44% in year 2 [32]. These results indicate that remission is not achieved by the majority of people with erosive gout, even after 2 years of serum urate-lowering well below the saturation concentration of urate. In this study, dual energy CT MSU volume was the only statistically significant independent predictor of gout remission at year 2; each 1-cm<sup>3</sup> increase in the baseline dual energy CT MSU volume decreased the odds of fulfilling the gout remission definition [odds ratio (OR) 0.57, 95% CI 0.41–0.78; *P* < 0.001] [32].

### MANAGEMENT OF EROSIIVE GOUT

Erosive gout is a definite indication for long-term urate-lowering therapy, according to both EULAR and ACR gout management guidelines [33,34]. For people with tophi, MSU crystal volumes measured on dual energy CT significantly reduce over 1 year when mean serum urate levels were <0.24 mmol/l and between 0.24–0.29 mmol/l. In comparison, MSU crystal volumes increased when the mean serum urate was ≥0.48 mmol/l [35].

While urate-lowering therapy improves gout flares and tophus size in people with erosive gout, bone erosion is slow to change with conventional oral urate-lowering therapy. In the Vien Gut Medical Center cohort, only small improvements in foot radiographic bone erosion scores were observed over a 1-year period of urate-lowering therapy (serum urate target <0.30 mmol/l for erosive gout); in 70 people with erosive gout; mean baseline foot erosion score was 10.24 (SD 10.61) and significantly decreased after 1 year in the 46 patients with follow-up radiographs [mean (SD) change – 1.17 (1.72), *P* < 0.001] [5<sup>\*\*\*</sup>]. In a randomized clinical trial, treat to target allopurinol dose escalation (to a serum urate target of <0.36 mmol/l, 6 mg/dl) did prevent progressive bone erosion but did not reverse bone erosion over 2 years [6]. Furthermore, oral urate-lowering therapy aiming for lower serum urate targets (<0.20 mmol/l compared with <0.30 mmol/l) did not lead to improvement in bone erosion scores [15].

Pegloticase leads to rapid dissolution of MSU crystals and tophi in people with gout, and bone erosions associated with tophaceous gout can fill in and remodel following this therapy. In a small case series of patients receiving pegloticase, improvements in conventional radiographic bone erosion

scores, but not joint space narrowing, have been reported [36]. More recent dual energy CT studies have confirmed these findings. In an analysis of eight MIRROR trial participants receiving pegloticase with or without methotrexate, rapid depletion of MSU crystal deposition was observed, together with bone remodelling at 29/42 (69%) evaluated bone erosions. Remodelling included reduction in bone erosion size in 69%, recortication in 10%, and new bone formation in 7% [14].

Likewise, in the open-label PROTECT study that examined the efficacy and safety of pegloticase in immunosuppressed kidney transplant recipients with uncontrolled gout serial dual energy CT over 24 weeks demonstrated marked depletion of the MSU crystal volume in four pegloticase responders [13<sup>■</sup>]. Of note, three types of bone erosions were observed in the kidney transplant population: MSU crystal-adjacent, unknown mineral deposit-adjacent, and deposit-independent bone erosions. On serial scanning, reduction of bone erosion size was only observed in MSU crystal-adjacent bone erosions.

Clinical trials examining therapeutic approaches for established erosive gout have shown that anti-resorptive agents that target osteoclasts with either zoledronate or denosumab do not have clinical benefits on bone erosion scores [16,37].

Surgical management of tophaceous gout may be required, in addition to intensive urate-lowering therapy. The Chinese Medical Doctor Association has developed a Multidisciplinary Expert Consensus Statement and Recommendations for tophaceous gout severity grading and surgical treatment [38<sup>■</sup>]. This represents the first consensus guidance on surgical management of tophaceous gout. It is strongly recommended that clinicians assess severity of disease through radiological examinations (conventional radiography, ultrasound, dual energy CT or MRI), with selection of the imaging modality based on diagnostic purpose. The authors recommend grading the severity of tophaceous gout based on patient pain, functional impact and extent of bone erosion on imaging tests. The presence of mild bone or joint erosion reflects grade 2 severity, extensive joint surface erosion and subchondral bone collapse reflects grade 3 severity, and end-stage joint destruction with fixed deformity or near-complete bone destruction (e.g., pathologic fracture) reflects grade 4 severity. In addition to urate-lowering therapy, surgical management should be guided by disease severity, with debulking and joint reconstruction (arthrodesis, bone grafting, arthroplasty) or amputation for nonsalvageable digits recommended for grade 4 disease.

## CONCLUSION

Erosive gout is a consequence of tophaceous gout. Erosive gout is most often observed in the context of prolonged exposure to hyperuricaemia but can be observed before onset of symptomatic gout. SPP1 (osteopontin) represents a new therapeutic target in tophaceous gout and SPP1-mediated cellular interactions may contribute to bone erosion at the bone-tophus interface. Erosive gout causes joint deformity which is difficult to reverse once established. Collectively, these findings provide further rationale for urate-lowering therapy in people with gout before onset of tophaceous disease, to prevent the consequences of poorly controlled tophaceous gout and irreversible joint damage.

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## Conflicts of interest

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# Colchicine-related effects on gene and protein expression in gout

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## Purpose of review

Gout is an inflammatory arthritis mediated by monosodium urate deposition in synovial tissue. Colchicine is a common treatment for acute gout flares and prophylaxis, with well established efficacy but an incompletely understood mechanism. Investigating colchicine's impact at a proteomic and transcriptomic level may highlight these mechanisms. Interest in colchicine's effect on atherosclerotic cardiovascular disease (ASCVD) has stimulated additional research in this area.

## Recent findings

Proteomic studies have helped identify gout's inflammatory signature, supporting prior evidence of nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome activation and involvement of inflammatory signaling pathways. Comparing recent 'omics studies between gout and colchicine use in ASCVD models reveals an overlap in inflammatory pathways. Colchicine reduced innate immune system activation in four separate ASCVD models, with notable overlap in mediators of the NLRP3 inflammasome [interleukin (IL)-1 $\beta$ , IL-6, IL-18, and monocyte chemoattractant protein-1] and others.

## Summary

Building on recent studies of colchicine's effect in ASCVD and the overlap seen with pathways implicated in gout, proteomic and transcriptomic studies in gout could further our understanding of the mechanisms driving colchicine's effectiveness. A more complete understanding of colchicine's mechanisms of action in gout may help guide future efforts at development of more targeted approaches to gout treatment.

## Keywords

cardiovascular disease, colchicine, gout, proteomics, transcriptomics

## INTRODUCTION

Gout is the most common inflammatory arthritis worldwide [1–4]. Gout pathogenesis is predominantly driven by the innate immune system response to monosodium urate (MSU) crystal deposition [5]. In addition to the risk of recurrent flares, untreated or inadequately treated gout contributes to a chronic inflammatory state and is associated with cardiometabolic comorbidity [1,6]. Colchicine has been successfully used for treatment of acute gout flares and prophylaxis against flares for decades. Colchicine is known to act against microtubules in rapidly dividing cells, and its mechanism in gout is multifactorial, with inhibition of the NLRP3 inflammasome, alteration of cytokine release and function, suppression of genes involved in cell regulation, and others [7]. However, the full biological mechanism and resultant protective effect against gout flares and systemic inflammation is incompletely understood.

With the development of novel proteomic and transcriptomic methodologies, there have been increasing efforts to fully uncover the pathways

involved in gout pathogenesis. Transcriptomics refers to the measurement and evaluation of RNA transcripts at a given timepoint, whereas proteomics focuses on characterization of proteins transcribed from these messenger RNA (mRNA) transcripts using a targeted- or broad-spectrum approach. In gout, these methods may reflect the biological mechanisms and pathophysiology underlying important disease-related aspects, such as the inflammatory signature during and between flares, the inflammatory milieu that predisposes to gout, and mechanistic pathways which represent potential treatment targets. Such studies also provide insight into how a medication such as colchicine, with its myriad

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## KEY POINTS

- The full mechanism of colchicine in gout treatment is incompletely understood, though recent applications in cardiovascular disease have stimulated renewed interest in colchicine.
- Proteomics studies in gout, both in case-control and gout-specific outcomes, consistently demonstrate key mediators of innate immunity and inflammatory pathways in gout pathogenesis.
- Evaluation of colchicine's effect at a transcriptomic and proteomic level in atherosclerotic cardiovascular disease models demonstrates colchicine's myriad effects on inflammation and innate immunity across disease states.
- Interleukin (IL)-1 $\beta$ , IL-6, and monocyte chemoattractant protein-1 are overexpressed in gout, demonstrate joint-localization with overexpression in the synovial fluid of gout patients, and respond with decreased expression following exposure to colchicine in two different cardiovascular disease models.
- Accumulating data on mechanisms driving colchicine response in cardiovascular literature may help guide further investigations in gout treatment.

biologic mechanisms and effects, may impart clinical benefit in gout.

Although direct examination of colchicine's effects on gene and protein expression in gout has been very limited, there is growing evidence of these effects in models of atherosclerotic cardiovascular disease (ASCVD) that may ultimately translate to gout as well. This review article will summarize recent proteomic research in gout, explore the increasing evidence for the mechanisms of colchicine in ASCVD, and examine the potential overlaps. Our goal is that this review will be useful in guiding further research into colchicine's role in gout treatment.

## TRANSCRIPTOMIC RESEARCH IN GOUT

Transcriptomic assessments in gout have been very limited to-date. One case-control study evaluated single-cell transcriptomics between peripheral blood mononuclear cells of eight gout patients and six age- and sex-matched controls [8]. Differential expression was validated for 116 genes, among which the key findings included higher mRNA levels of *IL-1 $\beta$* , *NLRP3*, and *PTGS2* and lower levels of *CLEC12A* and *IRF1* in gout. Although other analyses of publicly available datasets have been performed [9–11], other primary transcriptomic studies in gout are lacking. Therefore, in our comparisons of studies across gout

and colchicine outcomes we have elected to focus on gout proteomics research, highlighting the need for additional transcriptomic research and validation of findings in gout.

## PROTEOMIC RESEARCH IN GOUT

Numerous studies have used proteomics to explore the inflammatory profile of gout. These include case-control and gout-specific comparisons, including normouricemic vs. hyperuricemic states, before and after urate lower therapy (ULT), and acute flare vs. intercritical gout, providing insight into disease pathophysiology and treatment responses. Given the directionality of mRNA transcription into protein, these findings provide insight into expected gene expression patterns as well. Terminology useful in the discussion of proteomic methodologies is described in Table 1. Consistent findings across the gout proteomics literature are summarized in Table 2 (full reports in Table S1, Supplemental Digital Content, <https://links.lww.com/COR/A65>).

Targeted proximity extension assay (PEA)-based proteomics has been used in case-control studies to evaluate differences between the serum proteome of gout patients and controls [12<sup>11</sup>,13]. One study, which included 8 gout patients and 8 healthy controls, revealed 20 proteins with increased expression in gout, including many inflammatory mediators; with the largest differences seen in interleukin (IL)-8, IL-1 $\beta$ , oncostatin M (OSM), tissue growth factor (TGF) $\alpha$ , vascular endothelial growth factor A (VEGFA), and matrix metalloproteinase (MMP)-1 [12<sup>11</sup>]. In evaluation for use as potential biomarkers in gout diagnosis, four of these proteins (VEGFA, MMP-1, TGF $\alpha$ , and OSM) each demonstrated an area under the receiver operating characteristic curve >0.90 for gout. Another case-control study included 193 gout patients and 215 normouricemic controls and therefore had a substantial improvement in power [13]. In that analysis, there were 37 proteins with increased expression. The largest differences were seen with fibroblast growth factor (FGF)-21, IL-6, S100A12, IL-10, 4E-BPI, and tumor necrosis factor (TNF). Consistent findings of increased expression in gout across both of these studies include IL-8, monocyte chemoattractant protein (MCP)-3, IL-6, OSM, TGF $\alpha$ , VEGFA, and hepatocyte growth factor (HGF).

This same approach was also used to compare gout patients to individuals with asymptomatic hyperuricemia. Asymptomatic hyperuricemia has been associated with a subclinical inflammatory state [14], and in comparisons with normouricemic controls, hyperuricemia demonstrates inflammatory proteomic signatures even in the absence of gout [13]. In comparison to those with asymptomatic

**Table 1.** Terminology in the description of proteomic methods

| Proteomics term           | Description                                                                                                                                                                                                                                                                                                                                           |
|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Targeted                  | Investigation of a predefined list of protein analytes, which are typically hypothesis-based and/or selected from prior literature. This precision facilitates higher throughput assays for larger sample sizes.                                                                                                                                      |
| Broad-spectrum            | Proteome-wide investigation with the goal of identifying differences between different disease states or outcomes. This approach is often used for the exploratory identification of biologic pathways or proteins of importance where existing knowledge is limited.                                                                                 |
| Bottom-up                 | Proteins are cleaved into peptides using proteases. Peptides are measured and quantified via mass spectrometry, and the precleaved proteins are inferred from this data. This approach is very effective for complex samples with a large number of proteins, such as broad-spectrum analyses.                                                        |
| Top-down                  | Mass spectrometry-based quantification is performed on whole proteins without cleavage. Analysis can be technically challenging, particularly for more complex samples, but can provide additional information on the composition of individual proteoforms, including posttranslational modifications [39].                                          |
| Proximity Extension Assay | Targeted antibody probes tagged with DNA are used to bind specific proteins of interest. DNA tags are then quantified via quantitative polymerase chain reaction or sequencing approaches. This approach allows for very-high throughput proteomics on small-volume samples, though all protein analytes must be prespecified for antibody targeting. |

hyperuricemia, gout was associated with a reduction in inflammatory mediators such as 4E-BP1, C-X-C motif chemokine ligand (CXCL)9, CXCL10, and IL-17C. The largest decrease in gout was in 4E-BP1, an effector of mTOR that reprograms macrophages towards a pro-inflammatory phenotype. It is not clear how treatment factors differing between these groups may have impacted the inflammatory response in this comparison.

In comparison of hyperuricemic to normouricemic (treated) gout, there was a significant increase of FGF-21 in the presence of hyperuricemia. This metabolic hormone is hypothesized to play a role in regulation of the inflammatory response in gout [15]. It was also noted in one of the two case-control analyses as increased in gout, prompting further investigation in *ex vivo* stimulation studies that support its pro-inflammatory role [13]. CCL25 was similarly increased in hyperuricemic gout (and gout vs. controls) [13], supporting the role of this inflammatory mediator in gout pathophysiology [16].

In a small number of individuals with gout with serum samples before and after treat-to-target ULT, there was a significant reduction in inflammatory markers following achievement of goal serum urate (SU), including leukemia inhibitory factor receptor (LIF-R), IL-18, IL-10RB, chemokine C-C ligand motif (CCL)11 and CCL28 [12<sup>\*\*\*</sup>]. Differences in the serum inflammatory proteome following effective treat-to-target ULT have also been demonstrated in a comparison of participants from the STOP Gout clinical trial with matched controls, where it was shown that an inflammatory biomarker score of 11 proteins was elevated in gout before treat-to-target ULT and improved over time on ULT to approach controls [17,18]. In addition to these targeted approaches, the

effect of treat-to-target ULT has also been examined using broad-spectrum bottom-up proteomics [19<sup>\*</sup>]. Two separate cohorts were evaluated after 48 weeks of ULT treatment to target SU, identifying 24 and 32 proteins altered by ULT, respectively. These did not overlap with those identified in the previous study, though the difference in technique (PEA-based vs. broad-spectrum) likely impacts comparability of these results. In addition to the differences seen between normouricemic and hyperuricemic gout [13], this evidence supports the notion of a unique inflammatory signature in gout, specifically involving the innate immune response and cytokine regulation, and that this may be mitigated by treat-to-target ULT.

Among individuals with gout, the acute changes accompanying gout flares are of important clinical interest and have been examined in two cohorts with targeted PEA-based proteomics. In one, differential expression of 21 biomarkers was revealed, with 16 increased and 5 decreased during acute flare [20]. TNF superfamily (TNFSF)14, IL-6, and OSM, all increased, were associated with the largest fold changes in expression during flare. In the second, 6 proteins differed in the presence of flares (4 increased, 2 decreased) [13]. Increased expression of MMP-1, IL-6, CEGFA, and CCL23 during flare was seen in both studies. Of proteins increased during flare, IL-6, TNFSF14, OSM, CCL23, MMP-1, colony stimulating factor (CSF)-1, HGF, EN-RAGE, TGF $\alpha$ , VEGFA, CXCL1, IL-7, and CCL23 have also been shown to be increased in gout compared to healthy controls [12<sup>\*\*\*</sup>,13].

Comparing sera to synovial fluid in gout patients revealed seven proteins, which were increased in serum and seven, which were increased in the synovium, providing evidence of a distinct inflammatory

signature within the gout-affected joint [12<sup>22</sup>]. It is important to note that while the same assay was used, this PEA-based approach has not been validated for direct comparison across different sample types. However, the synovial fluid of 8 gout patients also differed from 8 osteoarthritis controls in expression of 6 proteins, findings which overlapped with the previous comparison in increased levels of IL-6, IP-10, IL-17F, and MIP-3 $\beta$  in the gout-affected joints [12<sup>22</sup>].

These proteomic studies have furthered understanding of the inflammatory signature of gout, with many supporting innate immune activation through the NLRP3 inflammasome, IL-6-related pathways, and multiple cell-signaling pathways (Table 2). It is important to note that comparison of PEA-based proteomic studies is limited by the targeted nature of these panels, as proteins must be included on the panel in order to be measured. However, many of these studies used similar panels. While there are currently no manuscripts detailing colchicine-specific effects in gout, the proteomic signatures of acute gout flares and those of chronic gout that respond to treatment with ULT may both highlight important mechanisms of interest.

### IMPACT OF COLCHICINE ON GENE EXPRESSION: LESSONS FROM CARDIOVASCULAR DISEASE

Given the accumulating proteomic data demonstrating the inflammatory and immunologic pathways implicated in gout and the persistent uncertainty regarding the mechanisms by which colchicine exerts its clinical effect, omics-level characterization of colchicine response presents an opportunity to advance our understanding of gout treatment. Unfortunately, colchicine-directed investigation in gout literature remains an unmet need.

However, low-dose colchicine was also approved for secondary prevention of ASCVD in 2023, based on the results of the LoDoCo2 and COLCOT clinical trials [21,22]. Although tempered by results of the CLEAR-SYNERGY trial [23], there remains strong evidence for colchicine's potential in cardiovascular risk reduction. Resulting from continued interest in colchicine's ability to reduce ASCVD risk through anti-inflammatory effects, there have been numerous studies in cardiovascular literature exploring colchicine-related gene and protein expression that provide opportunities to examine potential effects in gout (Table 3).

Cholesterol crystals are known to have the ability to activate the NLRP3 inflammasome [24], suggesting a potential link between ASCVD and gout pathophysiology, and evidence of colchicine's suppression of

NLRP3 inflammasome activity has fueled investigation into its role in atherosclerotic disease [25,26]. A proteomic substudy of 174 participants of the LoDoCo2 trial in 2020 demonstrated that treatment with 30 days of colchicine was associated with differential expression of 60 serum proteins (37 decreased, 23 increased) in a PEA-based targeted analysis, including reductions in many innate immune markers and inflammasome-related cytokines, such as IL-18, IL-1RA, and IL-6 [27]. There was also reduced expression of markers of the adaptive immune response and hemostasis (glycoprotein VI, CD40 ligand, pro-IL-16, CCL17). However, the largest reductions were noted in neutrophil degranulation markers, such as myeloblastin, CEA-related cell adhesion molecule 8 (CEACAM8), azurocidin, and myeloperoxidase. As colchicine preferably accumulates within granulocytes [28], these findings suggest that colchicine acts beyond the inflammasome to interfere with neutrophil chemotaxis, superoxide production, mobilization, and adhesion in ASCVD.

Other atherosclerotic disease models have also been used to evaluate the effects of colchicine. A transcriptomic evaluation using a mouse aortic dissection model after exposure to colchicine revealed lower levels of several proinflammatory genes in the treatment group, including *IL-1 $\beta$* , *IL-6*, *CCL2*, and *MMP9* [29<sup>29</sup>]. This decrease in *IL-1 $\beta$*  mRNA with colchicine exposure again supports attenuation of the NLRP3 inflammasome. *CCL2*, also known as MCP1, acts as a chemoattractant for monocytes and basophils, but not neutrophils [30]. *CCL2* has previously been implicated in pathogenesis of diseases mediated by monocyte infiltration, such as rheumatoid arthritis, atherosclerosis, and psoriasis, and was identified as preferentially expressed in the synovium vs. serum among individuals with gout [12<sup>22</sup>]. *MMP9* assists in the degradation and remodeling of the extracellular matrix and has also been implicated in regulating neutrophil migration across the basement membrane [31]. Decreased *MMP9* mRNA levels further support colchicine's role in attenuating neutrophil action in ASCVD models [29<sup>29</sup>].

A multiomic approach including both tissue transcriptomics and serum proteomics has also been utilized to investigate colchicine's effect on human atherosclerotic plaques [32<sup>32</sup>]. Tissue transcriptomics of plaques revealed decreased mRNA levels of *S100A9*, *MMP9*, *MMP12*, *IL-18*, osteopontin (*SPP1*), and *CD36* after colchicine exposure [32<sup>32</sup>]. The pro-inflammatory implications of *S100A9* [33] and replication of colchicine's impacts on *IL-1 $\beta$* , *IL-6*, *IL-18*, *MMP9*, *SPP1*, and *ACTA2* with the previous aortic dissection model suggest a consistent neutrophil-attenuating effect with colchicine exposure (Table 3) [29<sup>29</sup>,32<sup>32</sup>]. Gene ontology analysis for all down-regulated genes

**Table 2.** Differentially expressed proteins with overlap across recent gout proteomic studies

| Serum                                    |                                                 |                                                  |                                          |                          | Synovium                                 |                                          |
|------------------------------------------|-------------------------------------------------|--------------------------------------------------|------------------------------------------|--------------------------|------------------------------------------|------------------------------------------|
| Gout (increased) vs. controls            | Gout (decreased) vs. asymptomatic hyperuricemia | Hyperuricemic (increased) vs. normouricemic gout | After ULT (increased) vs. before         | Acute flare (increased)  | Gout synovium (increased) vs. serum      | Gout (increased) vs. OA                  |
| Huang <i>et al.</i> [12 <sup>***</sup> ] | Cabau <i>et al.</i> [13]                        | Cabau <i>et al.</i> [13]                         | Sanchez <i>et al.</i> [19 <sup>†</sup> ] | Ea <i>et al.</i> [20]    | Huang <i>et al.</i> [12 <sup>***</sup> ] | Huang <i>et al.</i> [12 <sup>***</sup> ] |
| IL-8                                     | 4E-BP1                                          | FGF-21                                           | No overlap                               | IL-6                     | IL-6                                     | IL-6                                     |
| MCP-3                                    | IL-18R1                                         | CCL25                                            | After ULT (decreased) vs. before         | TNFSF14                  | MIP-3β                                   | IL-8                                     |
| IL-1β                                    | CASP-8                                          |                                                  |                                          | OSM                      | IP-10                                    | IP-10                                    |
| IL-6                                     | CSF-1                                           |                                                  |                                          | CCL23                    | IL-17F                                   | IL-17F                                   |
| EGF                                      | CXCL9                                           |                                                  | Sanchez <i>et al.</i> [19 <sup>†</sup> ] | CASP-8                   | IL-1β                                    | MIP-3β                                   |
| OSM                                      | PD-L1                                           |                                                  | No overlap                               | MMP-1                    | HGF                                      | VEGFA                                    |
| MMP-1                                    | CCL25                                           |                                                  | Cabau <i>et al.</i> [13]                 | CSF-1                    | MCP-1                                    |                                          |
| TGFα                                     | IL-17C                                          |                                                  | IL-10RB                                  | HGF                      | Gout synovium (decreased) vs. serum      |                                          |
| VEGFA                                    | IL-10RB                                         |                                                  | CCL11                                    | EN-RAGE                  |                                          |                                          |
| MIP-1β                                   |                                                 |                                                  | CCL28                                    | TGFα                     |                                          |                                          |
| IL-7                                     |                                                 |                                                  | SLAMF1                                   | VEGFA                    | Huang <i>et al.</i> [12 <sup>***</sup> ] |                                          |
| MCP-2                                    |                                                 |                                                  | CDCP1                                    | SLAMF1                   | IL-17C                                   |                                          |
| MCP-1                                    |                                                 |                                                  |                                          | CXCL1                    | MCP-2                                    |                                          |
| HGF                                      |                                                 |                                                  |                                          | IL-7                     | TRAIL                                    |                                          |
| Cabau <i>et al.</i> [13]                 |                                                 |                                                  |                                          | IL-18R1                  | TGFα                                     |                                          |
| VEGFA                                    |                                                 |                                                  |                                          | Cabau <i>et al.</i> [13] | IL-7                                     |                                          |
| FGF-21                                   |                                                 |                                                  |                                          | MMP-1                    | MIP-1β                                   |                                          |
| IL-18R1                                  |                                                 |                                                  |                                          | IL-6                     | EGF                                      |                                          |
| CXCL1                                    |                                                 |                                                  |                                          | VEGFA                    |                                          |                                          |
| CCL25                                    |                                                 |                                                  |                                          | CCL23                    |                                          |                                          |
| EN-RAGE                                  |                                                 |                                                  |                                          | Acute flare (decreased)  |                                          |                                          |
| IL-17C                                   |                                                 |                                                  |                                          |                          |                                          |                                          |
| CSF-1                                    |                                                 |                                                  |                                          | Ea <i>et al.</i> [20]    |                                          |                                          |
| CXCL9                                    |                                                 |                                                  |                                          | TRAIL                    |                                          |                                          |

**Table 2 (Continued)**

| Serum                         |                                                 | Synovium                                                |                                  |                          |                                     |                         |
|-------------------------------|-------------------------------------------------|---------------------------------------------------------|----------------------------------|--------------------------|-------------------------------------|-------------------------|
| Gout (increased) vs. controls | Gout (decreased) vs. asymptomatic hyperuricemia | Hyperuricemic (increased) vs. normouricemic gout before | After ULT (increased) vs. before | Acute flare (increased)  | Gout synovium (increased) vs. serum | Gout (increased) vs. OA |
| IL-10RB                       |                                                 |                                                         |                                  | CCL11                    |                                     |                         |
| MCP-3                         |                                                 |                                                         |                                  | Cabau <i>et al.</i> [13] |                                     |                         |
| PD-L1                         |                                                 |                                                         |                                  | DNER                     |                                     |                         |
| TGFα                          |                                                 |                                                         |                                  |                          |                                     |                         |
| 4E-BPI                        |                                                 |                                                         |                                  |                          |                                     |                         |
| CCL23                         |                                                 |                                                         |                                  |                          |                                     |                         |
| SLAMF1                        |                                                 |                                                         |                                  |                          |                                     |                         |
| HGF                           |                                                 |                                                         |                                  |                          |                                     |                         |
| TNFSF14                       |                                                 |                                                         |                                  |                          |                                     |                         |
| IL-6                          |                                                 |                                                         |                                  |                          |                                     |                         |
| IL-8                          |                                                 |                                                         |                                  |                          |                                     |                         |
| DNER                          |                                                 |                                                         |                                  |                          |                                     |                         |

Proteins shown were observed in at least two different reports. Full description of proteins identified as significant within each study (including nonoverlapping) is shown in Table S1. 4E-BPI, eukaryotic translation initiation factor 4E binding protein 1; CASP-8, caspase-8; CCL, C-C motif chemokine ligand; CDCP1, CUB domain-containing protein 1; CSF, colony stimulating factor; CXCL, C-X-C motif chemokine ligand; DNER, delta/notch-like epidermal growth factor-related receptor; EGF, epidermal growth factor; EN-RAGE, extracellular newly identified receptor for advanced glycation end-products binding protein; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; IL, interleukin; IL-10RB, IL-10 receptor subunit beta; IP-10, interferon gamma-induced protein 10; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; OSM, oncostatin M; PD-L1, programmed death-ligand 1; SLAMF1, signaling lymphocytic activation molecule family member 1; TGF, transforming growth factor; TNFSF14, tumor necrosis factor superfamily member 14; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; VEGFA, vascular endothelial growth factor A.

**Table 3.** Summary of reported transcriptomic and proteomic changes following exposure to colchicine in cardiovascular studies

| Proteomics                                 |                                            | Transcriptomics                            |                                            |
|--------------------------------------------|--------------------------------------------|--------------------------------------------|--------------------------------------------|
| Decreased (serum)                          | Increased (serum)                          | Decreased (plaque)                         | Increased (plaque)                         |
| Opstal <i>et al.</i> [27]                  | Opstal <i>et al.</i> [27]                  | Von Ehr <i>et al.</i> [32 <sup>***</sup> ] | Von Ehr <i>et al.</i> [32 <sup>***</sup> ] |
| PRTN3                                      | FABP2                                      | IL1RN                                      | INMT                                       |
| CEACAM8                                    | MB                                         | MMP9                                       | NEXN                                       |
| AZU1                                       | TGM2                                       | IL-18*                                     | MYL9                                       |
| MPO                                        | FGF-21                                     | SPP1                                       | NR2F2                                      |
| U-PAR                                      | IGFBP-1                                    | RNASE1                                     | ACTA2                                      |
| NEMO                                       | Increased (plaque)                         | WFDC21P                                    | CALD1                                      |
| GP6                                        |                                            | LSP1                                       | CAMK2N1                                    |
| SRC                                        | Von Ehr <i>et al.</i> [32 <sup>***</sup> ] | S100A9                                     | PLN                                        |
| CD40-L                                     | COL6A3                                     | CD36                                       | FMO2                                       |
| IL-16                                      | LUM                                        | Decreased (aortic dissection model)        | MRAP2                                      |
| CCL17                                      | IGLC2                                      |                                            | EIF3J                                      |
| IL-18*                                     | WDR11                                      | Jiang <i>et al.</i> [29 <sup>■</sup> ]     | MBNL1-AS1                                  |
| IL-1RA                                     | BLVRB                                      | CXCL14                                     | Increased (aortic dissection model)        |
| IL-6*                                      | IGFBP7                                     | CXCL10                                     |                                            |
| IKBKG                                      | TGFB1                                      | IL-1 $\beta$                               | Jiang <i>et al.</i> [29 <sup>■</sup> ]     |
| Decreased (plaque)                         | LGALS3                                     | IL-6*                                      | MYOCD                                      |
|                                            | CST3                                       | MMP8                                       | MYH11                                      |
| Von Ehr <i>et al.</i> [32 <sup>***</sup> ] | C1QA                                       | CXCL2                                      | TNXB                                       |
| TKT                                        | PCOLCE                                     | IL-1 $\alpha$                              | CCN3                                       |
| HSPA5                                      | IGHV4-38-2                                 | MMP9                                       | CNN1                                       |
| LYZ                                        | IGHG1                                      | SPP1                                       | ACTA2                                      |
| CAP1                                       | TUBB                                       | FN1                                        | TAGIN                                      |
| PDIA3                                      |                                            | IL-18*                                     |                                            |
| MYH10                                      |                                            | MCP1 (CCL2)                                |                                            |
| CAPN2                                      |                                            | Decreased (macrophage)                     |                                            |
| ALDOA                                      |                                            |                                            |                                            |
| PDLIM1                                     |                                            | Wang <i>et al.</i> [35 <sup>■</sup> ]      |                                            |
| CB96L                                      |                                            | IL-1 $\beta$                               |                                            |
| OGN                                        |                                            | IL-6*                                      |                                            |
| JCHAIN                                     |                                            | PIM2                                       |                                            |
| ECM1                                       |                                            | TNF $\alpha$                               |                                            |
| COL6A1                                     |                                            | MMP9                                       |                                            |
| TLN1                                       |                                            | CXCL8                                      |                                            |

**Table 3** (Continued)

| Proteomics        |                   | Transcriptomics    |                    |
|-------------------|-------------------|--------------------|--------------------|
| Decreased (serum) | Increased (serum) | Decreased (plaque) | Increased (plaque) |
| TPI1              |                   | ICAM-1             |                    |
| ARPC2             |                   | MCP1 (CCL2)        |                    |
| WDR1              |                   |                    |                    |
| CD5L              |                   |                    |                    |
| ANG               |                   |                    |                    |
| VCP               |                   |                    |                    |
| CLIC4             |                   |                    |                    |
| PRDX1             |                   |                    |                    |
| PEBP1             |                   |                    |                    |
| SEPTIN7           |                   |                    |                    |
| HSPA1B            |                   |                    |                    |
| HSP90             |                   |                    |                    |

Genes with consistent findings across both tissue transcriptomic colchicine models are highlighted in red. Genes with consistent findings across serum proteomic and tissue transcriptomic CVD models are annotated with \*. Genes/proteins are based on reported associations within primary manuscripts and supplementary material, <https://links.lww.com/COR/A65>, which are not fully comprehensive of all genes/proteins evaluated.

ACTA2, actin alpha 2 smooth muscle; ALDOA, aldolase A; ANG, angiogenin; ARPC2, actin related protein 2/3 complex subunit 2; AZU1, azurocidin 1; BLVRB, biliverdin reductase B; C1QA, complement C1q subcomponent subunit A; CALD1, caldesmon 1; CAMK2N1, calcium/calmodulin dependent protein kinase II inhibitor 1; CAP1, adenylyl cyclase-associated protein 1; CAPN2, calpain 2; CB96L, cancer/testis antigen 96L; CCL, C-C motif chemokine ligand; CCN3, cellular communication network factor 3; CD36, cluster of differentiation 36; CD40L, CD40 ligand; CD5L, CD5 antigen-like; CEACAM8, carcinoembryonic antigen-related cell adhesion molecule 8; CLIC4, chloride intracellular channel 4; CNN1, calponin 1; COL6A1, collagen type VI alpha 1 chain; COL6A3, collagen type VI alpha 3 chain; CST3, cystatin C; CXCL, C-X-C motif chemokine ligand; ECM1, extracellular matrix protein 1; EIF3J, eukaryotic translation initiation factor 3 subunit J; FABP2, fatty acid binding protein 2; FGF-21, fibroblast growth factor 21; FMO2, flavin containing dimethylaniline monooxygenase 2; FN1, fibronectin 1; GP6, glycoprotein VI; HSP90, heat shock protein 90; HSPA1B, heat shock protein family A member 1B; HSPA5, heat shock protein family A member 5; ICAM-1, intercellular adhesion molecule 1; IGFBP-1, insulin-like growth factor binding protein; IGHG1, immunoglobulin heavy constant gamma 1; IGHV4-38-2, immunoglobulin heavy variable 4-38-2; IGLC2, immunoglobulin lambda constant 2; IKBKG, inhibitor of nuclear factor kappa-B kinase subunit gamma; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; IL1RN, Interleukin-1 receptor antagonist; INMT, indolethylamine N-methyltransferase; JCHAIN, immunoglobulin J chain; LGALS3, galectin 3; LSP1, lymphocyte-specific protein 1; LUM, lumican; LYZ, lysozyme; matrix metalloproteinase 9 MMP; MB, myoglobin; MBNL1-AS1, muscleblind-like splicing regulator 1 antisense RNA 1; MPO, myeloperoxidase; MRAP2, melanocortin 2 receptor accessory protein 2; MYH10, myosin heavy chain 10; MYH11, myosin heavy chain 11; MYL9, myosin light chain 9; MYOCD, myocardin; NEMO, NF-kappa-B essential modulator; NEXN, nexilin F-actin binding protein; NR2F2, nuclear receptor subfamily 2 group F member 2; OGN, osteoglycin; PCOLCE, procollagen C-endopeptidase enhancer; PDIA3, protein disulfide isomerase family A member 3; PDLIM1, PDZ and LIM domain protein 1; PEBP1, phosphatidylethanolamine binding protein 1; PIM2, Pim-2 proto-oncogene serine/threonine kinase; PLN, phospholamban; PRDX1, peroxiredoxin 1; PRTN3, proteinase 3; RNASE1, ribonuclease 1; S100A9, S100 calcium binding protein A9; SEPTIN7, septin 7; SPP1, secreted phosphoprotein 1; SRC, proto-oncogene tyrosine-protein kinase Src; TAGLN, transgelin; TGFBI, transforming growth factor beta induced; TGM2, transglutaminase 2; TKT, transketolase; TLN1, talin 1; TNXB, tenascin XB; TPI1, triosephosphate isomerase 1; TUBB, tubulin beta chain; u-PAR, urokinase plasminogen activator receptor; VCP, valosin-containing protein; WDR, WD repeat domain; WFDC21P, WAP four-disulfide core domain 21 pseudogene.

revealed neutrophil degranulation as the most altered term. Proteomic analysis also revealed significant changes with both low- and high-dose colchicine exposure, primarily with a decrease in proteins involved in neutrophil degranulation, such as LYZ, CD44, heat shock protein A1B (HSPA1B), and adenylyl-cyclase associated protein (CAP)-1, as well as HSP90, a known inflammatory signaling regulator [34].

In an atherosclerosis and diabetes model, colchicine-treated mice showed decreased levels of serum IL-1 $\beta$  and IL-6 in biomarker analysis, and immunofluorescence analysis of plaque lesions identified markedly decreased PIM2 levels [35<sup>¶</sup>], which is a

serine/threonine kinase involved in macrophage polarization and activation of the NF- $\kappa$ B signaling pathway [36]. Evidence points towards a role of PIM2 in IL-6-mediated inflammation, though data in gout is lacking [37]. Macrophage cell models corroborated these findings and differential transcriptomics revealed decreased expression of *IL-1 $\beta$* , *IL-6*, *MCP1*, and *MMP9* following colchicine exposure, replicating colchicine's effects in other ASCVD models at a cellular level. Gene ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses of genes from the GSE11841 dataset, which includes data from macrophage-rich regions of carotid plaque samples in diabetic and nondiabetic populations,

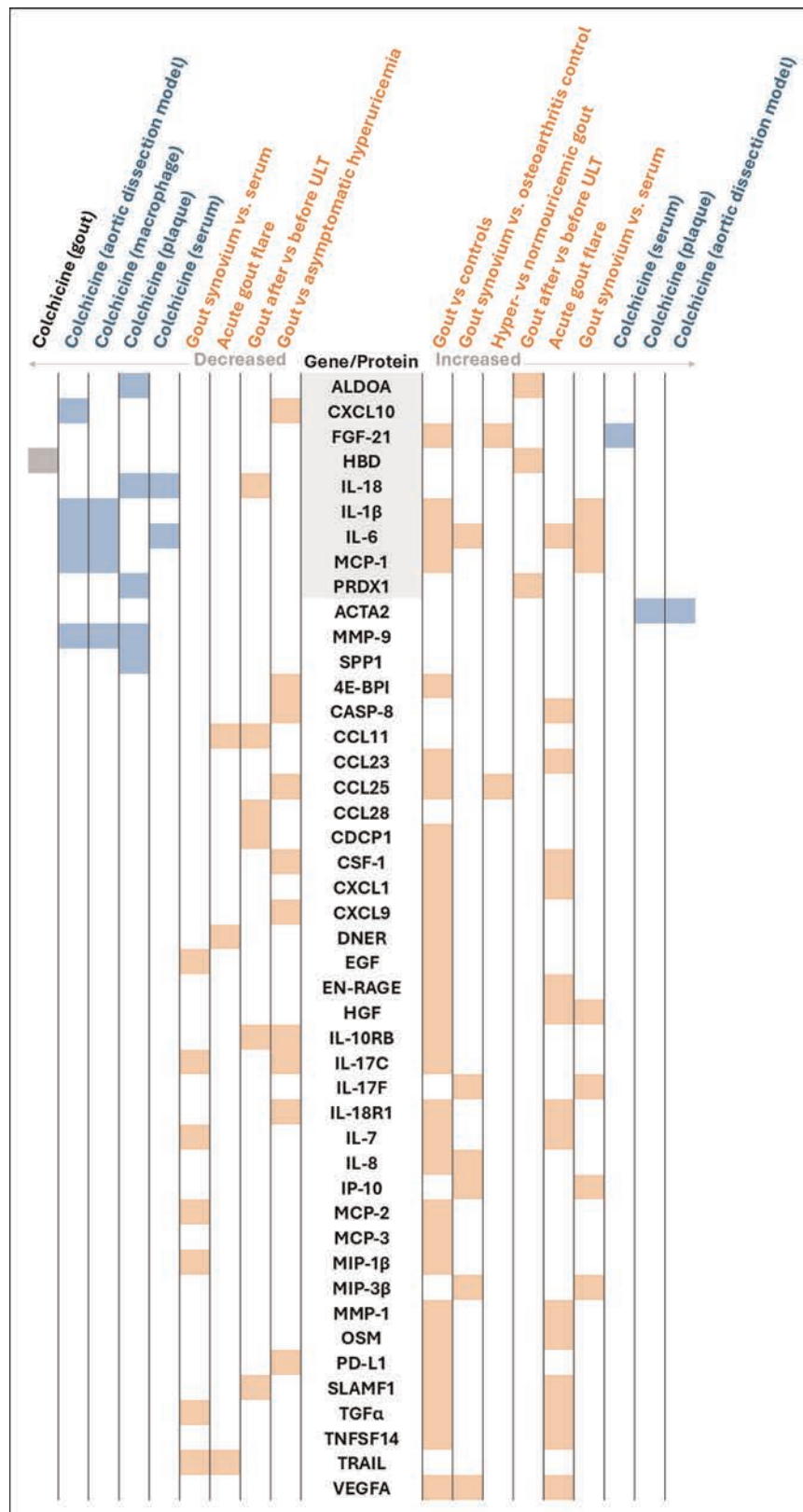


**FIGURE 1.** Figure summarizing all genes/proteins which were reported as significant in at least two different transcriptomic/proteomic studies of gout pathophysiology and/or colchicine response. Genes/proteins which were observed in studies of both gout and colchicine response are highlighted. 4E-BP1, eukaryotic translation initiation factor 4E binding protein 1; ACTA2, actin alpha 2 smooth muscle; ALDOA, aldolase A; CASP-8, caspase-8; CCL, C-C motif chemokine ligand; CDCP1, CUB

also identified PIM2 as possible target of colchicine [35<sup>■</sup>]. Inhibiting PIM2 in macrophages resulted in a similar reduction in inflammatory biomarkers compared to colchicine, thus revealing yet another potential mechanism for colchicine's impact in ASCVD and gouty inflammation.

### THE IMPACT OF COLCHICINE IN GOUT: EARLY APPLICATIONS AND FUTURE DIRECTIONS

The application of transcriptomic and proteomic approaches has provided key insight into colchicine-driven changes in inflammatory and immune pathways in ASCVD models, suggesting areas for possible translation to gout research. Innate immune system activation is a critical factor in the pathophysiology of gout, but also in ASCVD, where the invasion of macrophages into the vascular endothelium mediates plaque formation. When comparing proteomic characteristics of gout to transcriptomic/proteomic responses to colchicine in ASCVD, there are significant overlaps in markers of macrophage/inflammasome activation, cell signaling pathways, and neutrophil chemotaxis (Fig. 1). Perhaps the most intriguing of these are IL-1 $\beta$ , IL-6, and MCP-1, all three of which are increased in gout vs. controls, demonstrate joint-localization with overexpression in the synovial fluid of gout patients, and respond with decreased expression following exposure to colchicine in two different ASCVD models [12<sup>■</sup>,13, 29<sup>■</sup>,32<sup>■</sup>].

The impact of colchicine on gene expression in gout has been reported in one abstract, a subgroup analysis of the STOP Gout clinical trial including nonflaring participants treated with ULT at 24 and 48 weeks, which investigated differences in the serum transcriptome according to colchicine use [38<sup>■</sup>]. Findings implicated the innate immune response, as well as cell signaling pathways, adaptive immunity, and cardiovascular function [38<sup>■</sup>]. In comparing significant findings of that abstract to the reviewed literature, overlap was limited to

hemoglobin subunit delta (*HBD*), for which levels were decreased in those on colchicine (vs. not on colchicine) and also increased following 48 weeks of ULT [19<sup>■</sup>,38<sup>■</sup>]. This overlap occurred between two studies using STOP Gout clinical trial data, though different subgroups of patients were used. Beyond individual analytes, significant overlaps exist in the innate immune and cell signaling functions implicated by these results [38<sup>■</sup>,39], supporting the common patterns observed in our examination of the cardiovascular and gout literature.

Our comparison of proteomic and transcriptomic findings across colchicine and gout suggests that the effect of colchicine in gout likely extends far beyond its proposed primary mechanism of microtubule inhibition. Studies in ASCVD have supported colchicine's impact on innate immune system activation, neutrophil degranulation, monocyte chemotaxis, and other pathways. Markers of NLRP3 inflammasome activation, a major component of gout pathogenesis, were also commonly reduced with colchicine exposure. Further research will be needed to more fully elucidate these mechanisms, of which an important component will be closing the evidence gap in gout-specific transcriptomics. Such work may ultimately lead to valuable insights into therapeutic targets, treatment strategies, and gout pathophysiology.

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*The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.*

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### FIGURE 1. Continued.

domain-containing protein 1; CSF-1, colony stimulating factor 1; CXCL, C-X-C motif chemokine ligand; DNER, delta/notch-like epidermal growth factor-related receptor; EGF, epidermal growth factor; EN-RAGE, extracellular newly identified receptor for advanced glycation end-products binding protein; FGF-21, fibroblast growth factor 21; HBD, hemoglobin subunit delta; HGF, hepatocyte growth factor; IL, interleukin; IP-10, interferon gamma-induced protein 10; macrophage inflammatory protein (MIP); MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; OSM, oncostatin M; PD-L1, programmed death-ligand 1; PRDX1, peroxiredoxin 1; SLAMF1, signaling lymphocytic activation molecule family member 1; SPP1, secreted phosphoprotein 1; TGF $\alpha$ , transforming growth factor alpha; TNFSF14, tumor necrosis factor superfamily member 14; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; ULT, urate-lowering therapy; VEGFA, vascular endothelial growth factor A.

## Conflicts of interest

There are no conflicts of interest.

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# Systemic effects of gout flares beyond the joints

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## Purpose of review

A gout flare is an episode of intense inflammation caused by the activation of NLR family pyrin domain containing 3 (NLRP3) inflammasome and production of interleukin (IL)-1 $\beta$ . This pathway is involved in pathogenesis of cardiovascular events and provides a plausible mechanism linking gout flares to cardiovascular diseases.

## Recent findings

Gout flares are associated with a transient increased risk of cardiovascular events (myocardial infarction, stroke, and cardiovascular death), venous thromboembolism, and tachyarrhythmia in the subsequent 30–60 days – a finding comparable to that observed after other acute inflammatory states, such as influenza and pneumonia. Treat-to-target urate-lowering therapy lowered the risk of major adverse cardiovascular events in an emulated target trial. It also reduced systemic inflammation in observational studies. Additionally, gout flare prophylaxis with colchicine was associated with lower rates of major adverse cardiovascular events in a nationwide cohort study without evidence of residual confounding.

## Summary

Patients with gout are at a high risk of cardiovascular diseases. Recent data suggest that patients presenting with gout flares warrant heightened vigilance for cardiovascular events, venous thromboembolism, and tachyarrhythmia over the following 30–60 days. Treating gout to the target serum urate level could prevent cardiovascular events and renal function decline. Gout flare prophylaxis with colchicine may have a similar effect.

## Keywords

arrhythmia, cardiovascular events, chronic kidney disease, colchicine, depression, gout, treat-to-target, urate-lowering therapy

## INTRODUCTION

Gout is the most common inflammatory arthritis, affecting 2–4% of adults in Europe and North America [1,2] and its global prevalence continues to rise [3]. Gout has traditionally been conceptualized as an episodic inflammatory arthritis characterized by flares and symptom-free inter-critical periods. However, recent evidence suggests that gout is a chronic inflammatory disease with serious extra-articular consequences [4,5].

This review summarizes evidence on the systemic effects of gout flares, with a focus on cardiovascular diseases, chronic kidney disease, and depression. It examines the inflammatory mechanisms that may link flares to these outcomes and discuss whether treating gout to target might translate into improved outcomes.

## GOUT FLARES: DEFINITION, BURDEN, AND PATIENT PERSPECTIVE

A gout flare is an episode of acute inflammatory arthritis caused by the innate immune response to monosodium urate crystals deposited in articular and periarticular tissues [6,7]. Most patients with gout have recurrent flares before initiating urate-lowering

therapy, as evidenced in a recent NOR-Gout study [8]. From the patient perspective, flares impose a substantial burden of disability, lost productivity, and impaired quality of life [9]. Qualitative research consistently documents that fear of flares is the dominant driver of disease-related anxiety [10].

## CHALLENGES WITH THE IDENTIFICATION OF GOUT FLARES IN ELECTRONIC HEALTH RECORDS

Large datasets originated from consultation based electronic healthcare records provide a feasible and relatively inexpensive opportunity to evaluate the

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## KEY POINTS

- Gout flares are associated with a short-term increased risk of major adverse cardiovascular events, tachyarrhythmia, and venous thromboembolism.
- Treating gout to the target serum urate with urate-lowering drugs lowered the five-year risk of major adverse cardiovascular events.
- Gout flare prophylaxis with colchicine reduced major adverse cardiovascular events compared with no prophylaxis in a study, while non-steroidal anti-inflammatory drugs' (NSAIDs) use was associated with an increased risk of cardiovascular events compared with colchicine.

consequences of gout flares. However, this is hampered by the fact that not all gout flares require medical attention, and there are a range of definitions proposed and used. The positive predictive value of a definition using consultation and prescription/procedure within 7 days was 95% [11]. However, in other studies, the positive predictive value of this definition ranged between 50% and 68% [12,13]. We and others defined gout flares as a primary care consultation for gout flare care, or a primary care consultation for gout and a prescription for colchicine, corticosteroids, or NSAIDs on the same date, or hospitalization for gout as the primary discharge diagnosis [14–17]. We modified the original definition [11,18] to minimize the chances of misclassification, as steroids and NSAIDs may be prescribed for other reasons such as asthma and pain due to osteoarthritis, respectively. Indeed, restricting the window from 7 days to 1 day improved the positive predictive value of a similar gout flare definition [12]. Furthermore, we included hospitalization for gout in the definition as hospitalizations for gout based on ICD codes have been validated, and their positive predictive value was 100% [19].

## GOUT FLARES AND SYSTEMIC COMPLICATIONS: EPIDEMIOLOGICAL EVIDENCE

Gout is well known to be associated with a range of cardiovascular diseases such as myocardial infarction, stroke, atrial fibrillation, and venous thromboembolism after adjusting for traditional cardiovascular risk factors [20–25].

However, the mechanistic basis of this excess risk has long been debated. Hyperuricemia was considered to be the principal driver. However, this hypothesis is not supported by findings from Mendelian

randomization studies, that found no evidence for a causal role of serum urate levels in the pathogenesis of cardiovascular diseases [26,27].

Consistent with this, the ALL-HEART trial, a randomized controlled trial of urate-lowering therapy in people with ischemic heart disease but without gout, found no cardiovascular benefit from allopurinol despite achieving a large magnitude of serum urate reduction [28]. Together, these findings raised a question as to whether an alternate explanation, that is, acute inflammation from gout flares (Fig. 1) and chronic inflammation in inter-critical gout may contribute to excess cardiovascular risk in people with gout as observed in other inflammatory diseases such as infections, rheumatoid arthritis and inflammatory bowel diseases [29–33].

## Major adverse cardiovascular events

The temporal association between gout flares and major adverse cardiovascular events (MACEs) is supported by two large epidemiological studies across different populations and methodological designs [15,34]. Using UK-wide linked primary-care, hospitalization, and cause of death data, we showed a temporal association between MACE [i.e., fatal and non-fatal myocardial infarction and stroke] and gout flares in the preceding 60 days (adjusted odds ratio: 1.93, 95% confidence interval (CI): 1.57–2.38] compared with remote (i.e., >180 days) or no flares [15]. When examined individually, both acute myocardial infarction and stroke were each independently elevated in the 60 days following a gout flare, with adjusted odds ratios of 1.88 (95% CI: 1.42–2.49) and 1.80 (95% CI: 1.35–2.41), respectively [15]. The magnitude of risk was particularly pronounced for fatal cardiovascular events, with an adjusted odds ratio of 4.76 (95% CI: 1.69–8.43) in the 60 days after a flare [15]. Similar findings were observed using a self-controlled case-series analysis where the adjusted incidence rate ratio was 1.89 (95% CI: 1.54–2.30) in the 60 days after a gout flare compared with the baseline period [15], with comparable elevations observed for myocardial infarction (adjusted incidence rate ratio: 1.95, 95% CI: 1.50–2.53) and stroke (adjusted incidence rate ratio: 1.70, 95% CI: 1.27–2.27) as separate outcomes. Importantly, these findings were robust across key subgroups: the association was consistent in sensitivity analyses restricted to patients with high or very-high baseline cardiovascular risk as per European Society of Cardiology recommendations [35], and persisted after excluding individuals with preexisting cardiovascular disease [15]. Subsequent work by our group extended this association in a population of patients with early gout, observing that even in people newly diagnosed

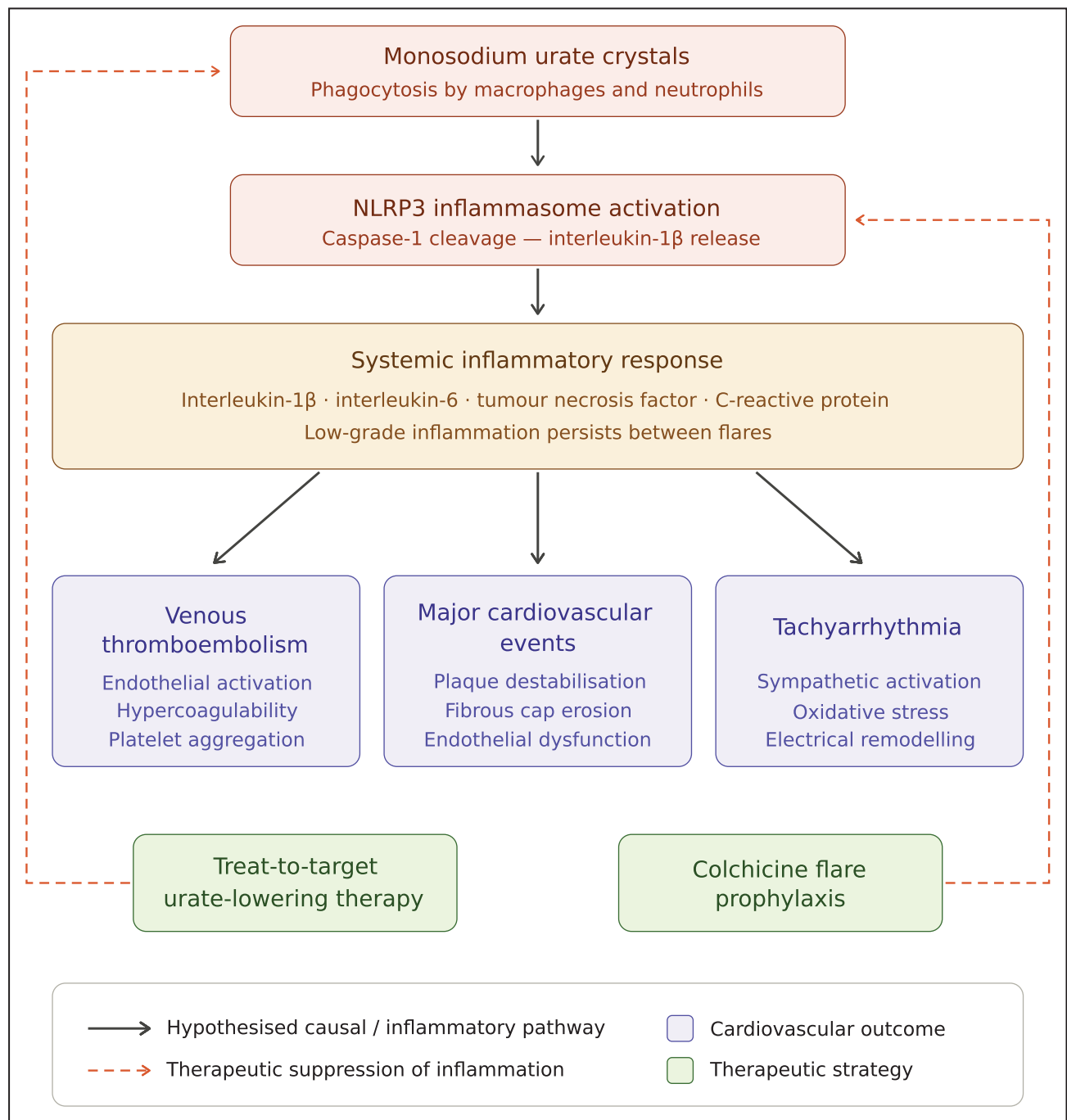


**FIGURE 1.** Proposed relationship between monosodium urate crystals, inflammation, and cardiovascular outcomes in gout.

with gout, there was a transient elevation in the incidence of MACEs in the subsequent 30 days (adjusted incidence rate ratio: 1.55, 95% CI: 1.33–1.83) [36]. A similar association was observed in a Western Australian population, where Lopez and colleagues reported an increased risk of MACEs (i.e., composite of acute coronary syndrome, stroke, heart failure, or cardiovascular death) in the first 30 days after an incident hospital admission for acute

gout (adjusted incidence rate ratio: 1.67, 95% CI: 1.38–2.03) [34]. Even though hospitalizations for gout may capture most severe flares, or flares occurring in comorbid individuals, or both; this study provides external validation of the association between gout flares and major adverse cardiovascular events. More recently, dose–response effect between the number of gout flares and the risk of cardiovascular events was reported using data from the

TriNetX Global Collaborative Research Network [37<sup>¶</sup>]. Compared with those experiencing  $\leq 3$  flares/year, patients with 4–6 or  $\geq 7$  flares/year had a higher risk of major adverse cardiovascular events (myocardial infarction, stroke, heart failure), with adjusted hazard ratios of 1.24 (95% CI: 1.15–1.33) and 1.45 (95% CI: 1.37–1.53).

### Venous thromboembolism

Our study using linked primary-care, hospitalization, and cause of death data from the UK identified a transient increase in the risk of venous thromboembolism (i.e., deep vein thrombosis and/or pulmonary embolism) in the first 30 days following a gout flare, with an adjusted incidence rate ratio of 2.31 (95% CI: 1.39–3.83) [16] and no statistically significant increase observed beyond the first month. The absolute excess risk was modest (4.70 vs. 3.65 per 1000 person-years in the 90 days after a flare compared with the overall postdiagnosis period), but the association might warrant attention to venous thromboembolism prophylaxis in high-risk patients presenting with severe or prolonged flares.

### Tachyarrhythmia

The most recent addition to this landscape is the demonstration of a temporal association between gout flares and tachyarrhythmia. We conducted nested case-control studies and self-controlled case-series analyses using linked primary care, hospitalization, and cause of death data from England ( $N=260\,254$  patients with gout) and Sweden ( $N=19\,346$ ) [38<sup>¶</sup>]. A new diagnosis of tachyarrhythmia – predominantly atrial fibrillation/flutter, which accounted for 88.6% of outcomes – was associated with a gout flare in the preceding 30 days (adjusted odds ratio: 1.41, 95% CI: 1.07–1.85 in England; 1.71, 95% CI: 1.10–2.65 in Sweden). Multivariable models included age, sex, ethnicity, body mass index, smoking status, alcohol intake, socioeconomic status, cardiovascular comorbidities, latest serum urate level, number of hospitalizations and primary care consultations within 12 months of the index date, number of prescriptions for anti-inflammatory medications within 12 months of the index date, Charlson comorbidity index, and recent prescription of cardioactive drugs, colchicine, NSAIDs, and corticosteroids. Self-controlled case-series analyses suggested the increased risk extended to 60 days post-flare (adjusted incidence rate ratio: 1.44, 95% CI: 1.26–1.64 and 1.34, 95% CI: 1.17–1.54 for days 0–30 and 31–60 in the English cohort, and 4.15, 95% CI: 2.47–6.97 and 2.25, 95% CI: 1.13–4.48 for days 0–30 and 31–60 in the Swedish cohort). Results were consistent when we restricted the analyses to

tachyarrhythmias ascertained in secondary care or death records.

### Depression and anxiety

In a systematic review and meta-analysis of 20 studies, Howren *et al.* reported that depression and anxiety were more common in people with gout than in comparators, with pooled odds ratios of 1.29 (95% CI: 1.07–1.56) and 1.29 (95% CI: 0.96–1.73), respectively [39]. Of note, the frequency of flares was identified as a significant determinant of depression, alongside the number of tophi and oligo/polyarticular gout.

### Chronic kidney disease

A positive association has also been described between the burden of gout flares and the incidence of chronic kidney disease. Using data from the TriNetX Global Collaborative Research Network, Wang *et al.* followed 29 321 adults with gout who had at least one treated gout flare and preserved baseline kidney function ( $\text{eGFR} \geq 60 \text{ ml/min/1.73 m}^2$ ) for up to 7 years [40<sup>¶</sup>]. Compared with those experiencing one flare per year, patients with  $\geq 5$  flares per year had a higher risk of incident chronic kidney disease stage 3–5 or end-stage renal disease, with adjusted hazard ratios ranging from 1.20 to 1.46. In contrast to the cardiovascular associations described above, this reflects the cumulative flare burden over several years rather than a transient post-flare window, and it is difficult to disentangle from repeated exposure to the nephrotoxic effect of NSAIDs.

## INFLAMMATION IN GOUT AND CARDIOVASCULAR DISEASES: SHARED PATHWAYS

The activation of the NLRP3 inflammasome by monosodium urate crystals phagocytized by resident macrophages and infiltrating neutrophils triggers an inflammatory response during a gout flare [7]. Inflammasome leads to the production of IL-1 $\beta$  which, in turn, initiates a self-amplifying inflammatory cascade, which stimulates synoviocytes and endothelium to express adhesion molecules and produce chemokines, driving further neutrophil recruitment and amplifying local cytokine production.

While the inflammatory response is most intense within the joint, it is not confined to it. Systemic inflammation during gout flares manifests as fever, leukocytosis, and elevated C-reactive protein.

NLRP3 inflammasome/IL-1 $\beta$ -driven systemic inflammation may promote atherosclerotic plaque destabilization and rupture through several converging

mechanisms. IL-1 $\beta$  directly stimulates endothelial dysfunction and oxidative stress, increasing vascular permeability and promoting the recruitment of neutrophils and macrophages into pre-existing atherosclerotic plaques [41,42]. Within the plaque, activated inflammatory cells, particularly neutrophils, upregulate matrix metalloproteinases that degrade collagen within the fibrous cap, thinning it and rendering it vulnerable to rupture [42–45]. For tachyarrhythmia, IL-1 $\beta$  and related mediators promote sympathetic nervous system activation and oxidative stress that directly modulates atrial and ventricular electrophysiology, a pathway supported by experimental animal studies linking NLRP3/IL-1 $\beta$  activation to atrial fibrillation susceptibility [46–48] and by the reduction in post-operative atrial fibrillation observed with colchicine [49]. For venous thromboembolism, systemic inflammation during flares promotes endothelial activation, transient hypercoagulability, and platelet aggregation, compounded by the vascular stasis resulting from reduced mobility during flares that predominantly affect the lower limb joints [50,51].

This inflammatory hypothesis has direct therapeutic implications. The CANTOS trial demonstrated that blockade of IL-1 $\beta$  with canakinumab significantly reduced incident MACE (hazard ratio: 0.85, 95% CI: 0.74–0.98) in patients with prior myocardial infarction and elevated high sensitivity C reactive protein, independently of lipid lowering [52]. The COLCOT and LoDoCo2 trials of low-dose colchicine (0.5 mg daily) in patients with established coronary disease showed reductions in MACEs with hazard ratios of 0.77 (95% CI: 0.61–0.96) and 0.69 (95% CI: 0.57–0.83) respectively [53,54]. Mechanistically, colchicine stabilizes vulnerable atherosclerotic plaques by increasing their fibrous cap thickness and significantly reduces high sensitivity C reactive protein [55<sup>\*\*\*</sup>]. The cardiovascular benefit of colchicine is reinforced by the most recent Cochrane systematic review of colchicine in secondary cardiovascular prevention, which pooled data from 10 randomized controlled trials and found high-certainty evidence that low-dose colchicine reduces the risk of myocardial infarction (risk ratio: 0.74, 95% CI: 0.57–0.96) and stroke (risk ratio: 0.67, 95% CI: 0.47–0.95) [56<sup>\*\*\*</sup>].

### **VASCULAR INFLAMMATION, ATHEROSCLEROSIS, AND CARDIOVASCULAR OUTCOMES IN OTHER DISEASES**

There is parallel between gout flares and other acute inflammatory states. Kwong *et al.* demonstrated that the risk of acute myocardial infarction was significantly elevated in the seven days after confirmed influenza infection, attenuating over the following

weeks [32]. Comparable elevations were observed following hospitalization for pneumonia [33], urinary tract infections [31], active rheumatoid arthritis [29], and inflammatory bowel diseases [30].

The gout population represents a particularly compelling subgroup in whom suppressing inflammasome/IL-1 $\beta$ -driven inflammation may simultaneously improve joint and cardiovascular outcomes through shared biological pathways. Whether prolonged colchicine use in gout confers cardiovascular benefit analogous to that observed in dedicated cardiovascular trials remains an important open question. Nevertheless, the next section of this review provides current evidence supporting the validity of this hypothesis.

### **DOES TREATING GOUT TO TARGET PREVENT SYSTEMIC COMPLICATIONS?**

If gout flares drive systemic cardiovascular risk, then strategies that reduce flare burden might translate into better outcomes.

#### **Treat-to-target urate-lowering therapy**

To address this question, we conducted an emulated target trial using linked primary care, hospitalization, and mortality data from 109 504 people with gout from England [57<sup>\*</sup>] due to ethical concerns about not offering treat-to-target urate-lowering therapy to people with gout. We found that among patients with gout newly prescribed urate-lowering therapy, those managed with a treat-to-target approach – with dose titration to achieve serum urate below the recommended treatment target of <360  $\mu$ mol/l (6 mg/dl) within 12 months – had a significantly lower risk of MACEs (i.e., non-fatal stroke, non-fatal myocardial infarction, or cardiovascular death) at 5 years compared with those who were prescribed urate-lowering therapy without reaching the treatment target or without further serum urate measurement within 12 months (weighted hazard ratio: 0.91, 95% CI: 0.89–0.92). A greater reduction in cardiovascular events was observed in the subgroup of patients achieving the more stringent treatment target of <300  $\mu$ mol/l (5 mg/dl), with a weighted hazard ratio of 0.77 (95% CI: 0.72–0.81). Importantly, no differences were observed for negative control outcomes – acute bronchitis, cataract, and appendicitis – reducing the likelihood that the findings were attributable to residual confounding. As there was a significantly lower incidence of flares in the treat-to-target arm (weighted incidence rate ratio: 0.97, 95% CI: 0.95–0.99), we hypothesized that this might explain, at least in part, the cardiovascular benefit of treat-to-target urate-lowering therapy, consistent with the

inflammatory hypothesis linking recurrent flares to excess cardiovascular risk. However, we did not directly evaluate this proposed mechanism, and this should be addressed in future studies. Similar findings were observed in two emulated target trials evaluating the risk of MACEs (i.e., non-fatal stroke, non-fatal myocardial infarction, or cardiovascular death) comparing different urate-lowering strategies (e.g., prescribing urate-lowering therapy without any dose adjustment/serum urate monitoring vs. treat-to-target strategies) using Medicare claims in the United States [58] and data from the Western Sweden Healthcare (VEGA) dataset [59]. Despite substantially smaller sample sizes of 4402 [58] and 7014 [59] patients, the authors observed comparable point estimates (hazard ratio estimates ranging between 0.88 and 0.94 compared with prescribing urate-lowering therapy without any dose adjustment/serum urate monitoring), offering important corroborating evidence from other countries.

Interestingly, Wheeler and colleagues provided the mechanistic underpinning for this observation [5<sup>•</sup>]. In their cohort study, systemic inflammatory markers – including high sensitivity C reactive protein – significantly reduced in patients achieving and maintaining serum urate at target compared with those who did not, at both 24 and 48 months of follow-up. This further reinforces the hypothesis that treat-to-target urate-lowering therapy reduces systemic inflammatory burden – the proposed driver of cardiovascular risk.

The benefits of treating gout to target may extend beyond the cardiovascular system. Wang *et al.* emulated a target trial in 14 792 people aged 40–89 years with gout and stage 3 chronic kidney disease who initiated urate-lowering therapy in UK general practice [60<sup>••</sup>]. A lower risk of severe or end-stage kidney disease was observed in those who achieved the target serum urate of 360  $\mu\text{mol/l}$  (6 mg/dl) (adjusted risk difference of –2.41% (95% CI: –4.61 to –0.21) and adjusted hazard ratio of 0.89 (95% CI: 0.80–0.98)) compared with those who did not. Although this study was designed to test non-inferiority, the upper bound of the confidence interval excluded unity, so the data suggest that treat-to-target urate-lowering therapy is associated not only with the absence of nephrotoxicity but with a reduction in the risk of kidney disease progression.

### Colchicine for flare prophylaxis

Beyond its role in flare treatment, colchicine – the preferred agent for flare prophylaxis during urate-lowering therapy initiation – might confer cardiovascular benefits in gout populations. In an emulated

target trial using linked primary care, secondary care, and mortality data from 99 800 patients in the UK [17], we showed that patients with gout initiating urate-lowering therapy with colchicine prophylaxis had significantly lower rates of MACEs (i.e., fatal and non-fatal stroke and myocardial infarction) compared with those receiving no prophylaxis (weighted hazard ratio: 0.82, 95% CI: 0.69–0.94) over a follow-up of up to 180 days, the recommended duration of gout flare prophylaxis, in an intention-to-treat analysis.

Yokose *et al.* performed another emulated target trial using population-level data from British Columbia, Canada, directly comparing colchicine with NSAIDs as the prophylactic agent at urate-lowering therapy initiation [61<sup>••</sup>]. Among 18 120 propensity score-matched adults with gout starting allopurinol, NSAID users had a 56% higher risk of MACEs (i.e., non-fatal stroke, non-fatal myocardial infarction, or cardiovascular death) compared with colchicine users (hazard ratio: 1.56, 95% CI: 1.11–2.17). When each agent was compared with no prophylaxis, colchicine was not associated with any increase in cardiovascular risk, whereas NSAIDs were associated with a 50% higher risk of MACEs (hazard ratio: 1.50, 95% CI: 1.17–1.91). This finding is consistent both with the cardioprotective anti-inflammatory effects of colchicine and the potentially deleterious cardiovascular effects of chronic NSAIDs use in this comorbid population.

The duration of prophylaxis in routine practice falls far short of guideline recommendations. While ACR and EULAR guidelines recommend at least 3–6 months, mean prophylaxis duration in UK primary care is approximately 45 days [17]. Among 43 926 individuals with gout in South Korea who initiated urate-lowering therapy with colchicine prophylaxis, only 7.6% remained on colchicine at three months [62]. As previous studies have shown that a shorter flare prophylaxis is associated with an increased number of flares [63,64], premature cessation of prophylaxis may expose patients to both recurrent flares and their associated systemic cardiovascular consequences.

### LIMITATIONS OF CURRENT EVIDENCE

Despite the growing evidence linking gout flares with cardiovascular diseases, several limitations remain. First, most studies are observational and rely on routine healthcare data, which cannot completely prove causality, despite methods used to reduce confounding. Second, most studies were carried out in the UK, although findings have been replicated in independent populations from Australia, Sweden, Canada, and the United States.

Further validation across ethnic populations remains necessary. Third, the contribution of gout medications themselves to cardiovascular risk remains difficult to disentangle from the inflammatory effects of flares. NSAIDs, corticosteroids, and colchicine each exert distinct cardiovascular effects that may modify outcomes independent of inflammation. Finally, while the inflammatory hypothesis is biologically plausible and supported by mechanistic evidence, direct interventional evidence is lacking. Randomized trials are required to confirm whether treat-to-target urate lowering treatment and flare prophylaxis reduces cardiovascular morbidity and mortality.

## CONCLUSION

Gout flares are acute inflammatory events that transiently elevate the risk of a range of cardiovascular diseases in the short term. Treat-to-target urate-lowering therapy reduced the risk of MACEs, potentially by reducing flare frequency and systemic inflammation. Colchicine flare prophylaxis might confer additional cardiovascular protection.

For the clinician, these data support several practical points: consider patients with gout at high cardiovascular risk, optimize primary/secondary cardiovascular prevention, recognize the 30–60 day post-flare period as a high-risk window warranting vigilance about cardiovascular events, prescribe colchicine for gout flare prophylaxis when starting treat-to-target urate lowering treatment, and pursuing a treat-to-target approach not only for gout specific outcomes but potentially as a strategy for reducing the risk of cardiovascular events.

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## Conflicts of interest

*A.A. reports personal fees from UpToDate (Royalty), SOBI (Lecture fees), Novartis (Consulting), Alesta Pharmaceuticals (Consulting) and Eli Lilly (Consulting) outside the submitted work.*

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*M.A.M. has nothing to disclose.*

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- of outstanding interest

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## Updates on idiopathic inflammatory myopathies: partnering with patients, making progress

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Whitaker and Engel were among the earliest investigators to use the term ‘idiopathic inflammatory myopathy (IIM)’ in the early 1970s to refer to polymyositis and dermatomyositis [1]. The term gradually became the accepted umbrella term for these and other related acquired inflammatory myopathies over the 1980s–1990s. By the early 2000s, the term had become standard [2,3]. Since then, publications in PubMed indexed with the term ‘idiopathic inflammatory myopathy’ have tripled (Fig. 1). Research in IIM is thriving!

The scope of research in IIM has also expanded dramatically over this time. Around the year 2000, the field was largely centered on describing clinical phenotypes, histopathology and empiric treatment. Today, IIM research spans, among other things, patient-centered care, etiology, pathogenesis, immunology, and clinical trials of novel therapies. These advances have led the way to identification of novel subsets using clinico-sero-pathologic integration and informed clinical decision-making. Some notable advances in these areas are highlighted in a series of papers in this issue.

The landscape of patient engagement in IIM research described by Cheng and Leclair (pp. 423–430) is surprisingly rich. This shows clearly that involvement of patients has moved from mere tokenism to active participation in research and advocacy, notably in the drug development process. Although the authors highlight ongoing challenges [e.g., perceived lack of confidence on the part of patient research partners (PRP), time constraints, financial burden and lack of skills among both PRP and researchers to build and maintain effective collaborations], they also present several examples of training and capacity building programs that are designed to empower patients to contribute effectively as PRPs. PRPs are now recognized as equal stakeholders by major funding bodies and international networks in many but not all parts of the world. Expanding this to underrepresented regions should be a priority. Cheng and Leclair (pp. 423–430) argue that, through early patient involvement, investment in training, and increased global representation, the myositis research community can generate knowledge that is more relevant, inclusive, and impactful.

Patient-centered care has become an integral component of high-quality healthcare, extending beyond the traditional biomedical model to include the psychological, social, and emotional aspects of health. Lodin *et al.* (pp. 431–436) highlight research showing that pain and fatigue are key drivers of patient-perceived disease burden in IIM. Other aspects of the patient lived-experience that have the potential to significantly impact health-related quality of life among patients with IIM include depression, incontinence, sleep disturbance, cognitive dysfunction and sexual dysfunction. However, research in these other domains remains scarce. Of particular importance, Lodin *et al.* (pp. 431–436) provide examples of available patient-reported outcome measures that can enhance research in these domains by facilitating inter-study comparability. Finally, this paper is distinctive in this issue because it looks across IIM subsets. Where the companion papers tend to split myositis by subset and autoantibody, this one highlights symptoms that are shared across the disease. That crosscutting perspective is a meaningful contribution.

Talreja *et al.* (pp. 437–447) provide a narrative review of environmental exposures and risks for IIM. The breadth of exposures is striking, covering ultraviolet radiation, smoking, occupational exposures, infections, and pharmacological triggers. Interestingly, they highlight that exposures in IIM operate preferentially in specific serological and genetic contexts, supporting discrete exposure-antibody pairings, rather than uniform disease-level risk. The integration of juvenile and adult-onset disease with attention to critical exposure windows is particularly valuable. The comparison with systemic lupus

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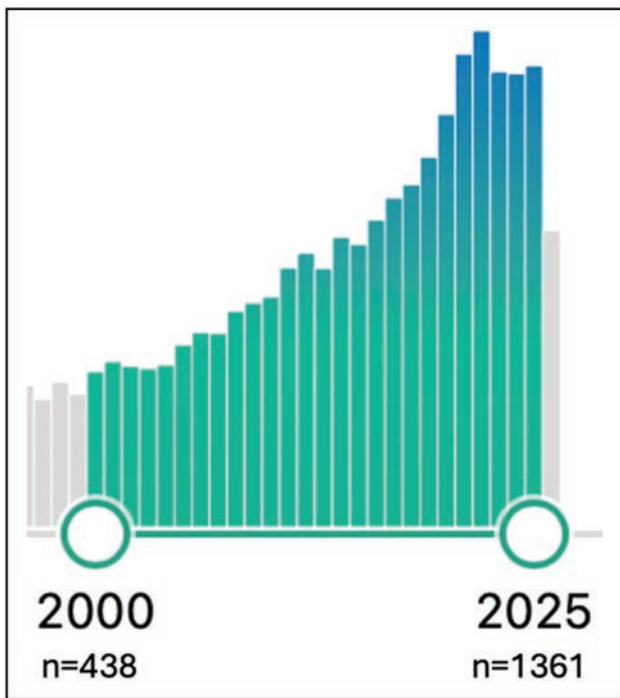


**FIGURE 1.** PubMed citations for “idiopathic inflammatory myopathy” per year over the last 25 years (retrieved July 24, 2026).

erythematosus effectively positions IIM findings within the broader autoimmunity literature, and the identification of potentially high-risk populations (e.g., HLA-DRB103:01-positive smokers with occupational silica exposure) has translational relevance.

Since the discovery of the first myositis-specific autoantibody (MSA) in the mid-1970s [4], autoantibodies have transformed IIM from a heterogeneous group of broadly defined inflammatory muscle diseases into a collection of biologically and clinically distinct subsets. The importance of autoantibodies in IIM is highlighted by the inclusion of three papers in this issue. Chung *et al.* (pp. 448–455) highlight seminal findings on the pathogenicity of MSA. Although many questions persist, there is compelling data accumulating that some MSA with intra-cellular targets may indeed have a direct pathogenic effect on myocytes. This finding has important implications not only in terms of understanding the biology underlying IIM, but also in terms of therapeutic development. Aguilar-Vazquez and Galindo-Feria (pp. 456–469) extend the observations on the direct pathogenicity of MSA to include indirect effects as amplifiers of inflammation. These authors also add a new layer of complexity, that patients sharing the same autoantibody may differ in epitope recognition, coexisting reactivities, prognosis, and organ-specific risk. This provides rationale for further

serological stratification (i.e., subsets within subsets). Future histopathological and molecular research will be useful to validate these findings. Careful clinico-sero-pathological phenotyping has paved the way to the recognition of scleromyositis (SM) as a distinct IIM subset, as reviewed by Landon-Cardinal *et al.* (pp. 470–480) In this setting, transcriptomic profiling has indeed identified a unique genomic signature for SM, thereby supporting the view that SM is a distinct IIM subset. Given the multiplicity of autoantibodies that are seen across SM, future studies stratified on autoantibody status may again bring attention to the idea of “subsets within subsets”.

Inclusion body myositis has unique clinico-sero-pathological features among IIM. One of the many striking differences is its lack of response to conventional immunosuppression. The review by Fer and Benveniste bridges the gap between our evolving understanding of IBM pathogenesis and the development of mechanism-based therapeutic strategies, highlighting how advances in disease biology are reshaping the therapeutic landscape. At the pathogenic level, the authors highlight a more complex immune microenvironment than what has until recently been appreciated and propose an integrated (as opposed to a dichotomous) model in which chronic immune activation and muscle-intrinsic degenerative defects in proteostasis and protein aggregation pathways intersect to create a self-amplifying pathogenic loop. The authors highlight two ongoing trials, one of ruxolitinib targeting interferon- $\gamma$ -driven inflammation and another of sirolimus, which may have the added advantage of targeting both immune activation and intrinsic muscle dysfunction.

Therapeutic development is arguably the most exciting area of progress in IIM in recent years, particularly from the patient perspective. In large part because of advances in the understanding of IIM pathogenesis, novel therapeutic targets directed against key immune pathways, including B cells, T cells, type I interferon and JAK signaling, and neonatal Fc receptor (FcRn) have been identified. Chimeric antigen receptor (CAR) cell approaches represent a particularly promising strategy, offering the potential to reset the immune system and allowing the discontinuation of chronic immunosuppressive therapy, though many questions related to accessibility, safety and durability remain to be answered. Wilk *et al.* (pp. 488–498) summarize the recent and ongoing clinical trial landscape in their comprehensive paper.

Refractory interstitial lung disease (ILD) can be one of the most severe manifestation of several IIM subsets, in particular antisynthetase syndrome (ASyS) and anti-melanoma differentiation-associated gene 5 (anti-MDA5) syndrome. While there have been several trials for patients with IIM-associated

ILD, there have been none in patients with treatment-resistant disease. This may be, at least in part, due to the absence of a standard definition for ‘refractory’, as pointed out by Poirier-Blanchette *et al* (pp. 499–508). This is likely compounded by other factors, including the challenge of conducting trials in rare diseases and in seriously ill patients. Thus, most of the evidence for the management of this subset of patients comes from case reports, case series and retrospective observational studies. These authors summarize this evidence in their paper and highlight the urgent need for prospective studies with well defined patient populations and treatment sequencing. An international registry could play a pivotal role in accelerating research for this life-threatening condition.

Coming back to the term IIM, most but not all of the papers in this issue used that term. Instead, two papers referred to “inflammatory myopathy” and one to “autoimmune myositis”. Given the increasing understanding of the etiopathogenesis of IIM, as expertly reviewed in this issue, is the term “idiopathic” still appropriate? Also, the term “myopathy” is broad and encompasses inherited, metabolic, toxic and endocrine etiologies. Is it time to update the terminology to autoimmune myositis (AIM), as used

by Landon-Cardinal *et al.* (pp. 470–480)? An elegant case for this novel nomenclature has already been made by S  n  cal *et al.* almost 10 years ago [5]. As our understanding of the diseases evolves, so too should our nomenclature.

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# Partners in discovery: building equal and proactive patient engagement in inflammatory myopathies

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## Purpose of review

Patient engagement in research has evolved from passive participation and inclusion toward active partnership and co-leadership. This review examines the current landscape of patient involvement in myositis research, highlights existing initiatives and frameworks, and identifies persistent gaps and overlaps.

## Recent findings

In myositis, or inflammatory myopathies, early onboarding and integration of patients as research partners in preclinical and clinical studies offer invaluable opportunities to improve relevance, feasibility, and impact of research. The findings presented emphasize the importance of early partnership with patient research partners (PRPs), bidirectional training to foster mutual understanding, and expanded outreach to underrepresented regions.

## Summary

Patient engagement in myositis research has advanced considerably, yet its integration remains inconsistent worldwide. Several existing resources can be leveraged to facilitate patient engagement in myositis research, but achieving meaningful PRP integration requires deliberate effort, adequate resources, and a commitment to cultural change.

## Keywords

myositis, patient and public involvement, patient engagement

## INTRODUCTION

Over the past two decades, the paradigm of patient involvement in biomedical research has shifted significantly. The Canadian Institute for Health Research defines patient engagement as “patients, researchers, healthcare providers and decision makers actively collaborating to build a sustainable, accessible, and equitable healthcare system to bring about positive changes in the health of people” [1]. Patients are increasingly no longer viewed only as study participants, but becoming active collaborators who contribute experiential knowledge to complement scientific expertise. The European Alliance of Associations for Rheumatology (EULAR) Task Force that developed recommendations for the inclusion of patient research partners (PRPs) in scientific projects define PRPs as “persons with a relevant disease who operate as active research team members on an equal basis with professional researchers, adding the benefit of their experiential knowledge to any phase of the project” [2]. PRPs can be the patients themselves or their care partners or caregivers, and may be referred to as patient partners, patient experts, advisors, patient and public involvement (PPI) contributors, or caregivers.

Given the rarity and heterogeneity of myositis, a spectrum of chronic autoimmune diseases characterized by muscle inflammation, weakness, and multi-organ involvement, patient engagement in research is required to capture the full patient experience. Patients’ insights can help understand symptom burden and variability, treatment priorities and tolerability, quality-of-life outcomes and barriers to care. Earlier patient involvement can improve study design, recruitment, and dissemination, ultimately accelerating translational science into clinical practice.

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## KEY POINTS

- Patient engagement initiatives in inflammatory myopathies demonstrate the feasibility and value of patient research partner (PRP) integration.
- Several barriers exist to meaningful patient engagement, but there are also available resources to support researchers and PRPs when faced with those challenges.
- By integrating patient perspectives early, investing in training, and expanding global representation, the myositis research community can co-create knowledge that is more relevant, impactful, and equitable.

Despite growing recognition of the value of patient engagement in myositis, implementation remains inconsistent across geographical locations and myositis disease subsets. While several international initiatives have incorporated PRPs, challenges persist in achieving equitable, early, and sustained involvement. This review explores the current state of patient engagement in myositis research, identifies barriers and opportunities, and outlines strategies to foster meaningful collaboration.

## CURRENT LANDSCAPE OF PATIENT ENGAGEMENT IN INFLAMMATORY MYOPATHIES RESEARCH

Patient engagement in myositis research has grown through international collaborations and advocacy organizations. The recent proceedings of the 6th Global Conference on Myositis (GCOM) showcased the evolution of patient engagement in the myositis community. Patients, care partners and representatives from more than 15 patient organizations worldwide constituted 8.1% (55/679) of GCOM 2026 participants. They contributed significantly to the program and shared their voices in scientific sessions and patient-led workshops, which focused on current topics of interests such as diet and lifestyle, emotional health and wellbeing, artificial intelligence and cellular therapies [3].

Several inflammatory myopathies clinical and research networks now include patients as board and/or advisory board members or as research collaborators (Table 1) [4–13]. Notably, patient involvement has been central to the work of the Outcome Measures in Rheumatology (OMERACT) Myositis Working Group, which defined a research agenda to develop patient-reported outcome measures (PROM) in myositis. OMERACT worked collaboratively with myositis patients to help identify the

**Table 1.** Examples of patient engagement initiatives in inflammatory myopathies [4–13]

| Organizations                                                                                | Examples of PRP roles                           | Examples of initiatives                                                                                                   |
|----------------------------------------------------------------------------------------------|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| Outcome Measures in Rheumatology (OMERACT)                                                   | Myositis Working Group members co-investigators | Collaboration to the development of patient-focused outcome measures                                                      |
| International Myositis Assessment and Clinical Studies Group (IMACS)                         | Associate members <sup>a</sup>                  | Contribution to scientific interest groups                                                                                |
| Myositis International Health & Research Collaborative Alliance (MIHRA)                      | Patient advisory board members                  | FDA Center for Drug Evaluation and Research Public–Private Partnership (MIHRA PATH)                                       |
| International Myositis Society (iMyoS)                                                       | Board and associate board members               | Contribution to governance, projects and biennial GCOM meetings                                                           |
| European Reference Network on Connective Tissue and Musculoskeletal Diseases (ERN ReCONNECT) | Elected patient representatives (ePAG)          | Contribution to the development and dissemination of information (e.g., policy, good practice, care pathways, guidelines) |
| European Reference Network on Neuromuscular Diseases (ERN EURO-NMD)                          | Patients Advisory Board Members                 | Representation of patient needs and perspectives in network discussions and activities                                    |
| European Neuromuscular Center (ENMC)                                                         | Mandatory inclusion of patients in workshops    | Participation to workshops, consensus meetings and recommendations elaboration                                            |
| Pediatric Rheumatology European Association (PreS)                                           | Core members of the JDM working party           | Contribution to PreS JDM working group annual meeting                                                                     |
| Childhood Arthritis and Rheumatology Research Alliance (CARRA)                               | Associate members                               | Contribution to JDM calcinosis workgroup                                                                                  |

<sup>a</sup>Patient support group leaders. JDM, juvenile dermatomyositis.

symptoms and life impacts which mattered most to them, such as fatigue, pain, and physical function [4,5]. Similarly, a recent patient-led study from Australia used a mixed method approach to identify priorities for patients living with inclusion body myositis and their carers where more specific unmet needs for this myositis subset were identified, such as support for carers and mental health needs [14<sup>22</sup>]. This study shows how PRPs can lead projects that are meaningful and can impact the myositis research agenda.

In the last decade, patient organizations worked to ensure that the journeys of adult dermatomyositis and inclusion body myositis patients were heard at U.S. Food and Drug Administration (FDA) listening sessions and Externally Led Patient-Focused Drug Development (EL-PFDD) meetings [15–17]. These initiatives were opportunities for patients to highlight important unmet therapeutic needs, including the lack of available personalized therapies, the limitations of drug delivery mechanisms and the burden of treatment side-effects [18]. Since 2023, the Myositis International Health & Research Collaborative Alliance (MIHRA) Foundation, has embedded patients as active partners in both research and governance [6]. Patients help set research priorities, interpret qualitative data, and ensure that patient perspectives are authentically represented. In 2025, the FDA Center for Drug Evaluation and Research (CDER) launched MIHRA PATH (Partnership to Advance Therapeutic Horizons), a myositis public–private partnership [7]. Built on a 360-degree stakeholder model, MIHRA PATH brings together patients, academics, industry, patient organizations, and FDA scientists as equal partners. Its Patient Voice Council and patient co-chairs in every scientific working group ensure meaningful patient influence through governance and engagement policies. These structures enable patients to directly shape therapeutic development including clinical trial design, endpoint development, and the interpretation of meaningful change in myositis. Other examples of patient engagement initiatives in inflammatory myopathies are presented in Table 1. These demonstrate the feasibility and value of patient engagement in inflammatory myopathies, underscore the growing recognition of patients as experts in their lived experience, but also highlight the variability in engagement models.

## CHALLENGES FOR MEANINGFUL PATIENT ENGAGEMENT IN MYOSITIS RESEARCH

Although researchers are recognizing the benefits of patient engagement notably in improving the quality of their research work, they also report obstacles to PRP collaboration. A 2025 study exploring

researchers' perspectives on patient engagement using semi-structured interviews, identified some of the challenges including recruitment issues, PRPs health-related constraints, poor PRP retention rate, increased administrative workload, and delays in onboarding process [19<sup>23</sup>]. In addition, needs assessments have shown that researchers sometimes lack the skills and knowledge necessary to build and maintain effective collaborations with PRPs [20<sup>24</sup>].

On the other hand, while many patients are motivated to share their lived experiences and perspectives in research, their participation is often limited by barriers such as lack of confidence in their scientific knowledge, unclear roles, unfamiliarity with research processes, time constraints, and financial burdens [21]. Ambiguous roles, and insufficient recognition of the contribution of PRPs can be potentially disempowering [22]. In a cross-sectional survey of PRPs across Canadian health system settings, participants were primarily motivated by a desire to improve the health system, often influenced by personal experiences [23]. Although many felt valued and engaged in their roles, common challenges included inadequate compensation, power imbalances, and limited visibility of their impact, with 40% considering quitting. Challenges to patient engagement and possible solutions are summarized in Table 2.

An important goal of patient engagement in research is that the patients' experience is represented. In inflammatory myopathies there is often a lack of engagement of patients early in their disease course, an important period during which patients can provide critical insights into initial information gaps, diagnostic journey challenges, and early treatment concerns. With the perspective that not all periods of a patient's journey are favourable to becoming a PRP, Schoemaker *et al.* discuss patient engagement in rheumatology research through the lens of adversarial growth [24]. They identify four stages: lived experience, personal story, collective perspective and PRP, proposing the idea that patients can be involved in research at all stages but with different levels of engagement. Their approach emphasizes the need to consider where the patients are in their disease path and what are their life circumstances when discussing possible contribution in research which can ultimately lead to more fruitful collaborations.

## TRAINING AND CAPACITY BUILDING

Important gaps remain in patients' understanding of current evidence, research methodologies, and the evolving scientific landscape of myositis, highlighting the need for further evaluation of PRP training

**Table 2.** Summary of current challenges and potential solutions in patient partnership

| Challenges                                                                               | Potential solutions                                                                                                                                                                                        |
|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Late involvement of patients after key research decisions have been made                 | Involve PRPs from earliest point of research question, then priority setting, study design, outcome selection, and dissemination.                                                                          |
| PRP recruitment and retention difficulties                                               | Develop structured recruitment strategies, simplify onboarding, provide mentorship, and maintain long-term engagement.                                                                                     |
| Limited researcher knowledge and skills to work with PRPs                                | Offer researcher training on patient engagement, communication, co-design, and partnership principles.                                                                                                     |
| Limited PRP scientific knowledge and confidence in research methods                      | Provide accessible training programs (e.g., research methods, ethics, scientific communication) and disease-specific education.                                                                            |
| Unclear roles and power imbalance                                                        | Clearly define roles and responsibilities, promote shared decision-making, recognize contributions through authorship and leadership roles.                                                                |
| Financial and practical barriers                                                         | Provide fair compensation, flexible participation options (including virtual meetings), and accessibility options.                                                                                         |
| Inconsistent patient engagement across countries, research settings, or disease subtypes | Standardize patient engagement practices, adopt established frameworks (e.g., EULAR, ERN), require participation of PRPs before project initiation.                                                        |
| Underrepresentation of diverse populations                                               | Build partnerships with regional organizations (e.g., Asia-Pacific, Africa, Latin-America, Middle East), invest in local capacity building, and recruit diverse patient voices.                            |
| Low PRPs involvement in preclinical or translational research despite potential benefits | Expand patient engagement into laboratory and translational research through participation in laboratory team meetings, discussion of patient-centered priorities, and collaboration in specific projects. |
| Limited measures to assess whether engagement is meaningful or merely symbolic           | Develop quality indicators and metrics to monitor patient engagement, accountability, and impact over time.                                                                                                |
| Multiple frameworks create uncertainty                                                   | Choose existing frameworks or modify to fit local contexts through co-evaluation with patients.                                                                                                            |
| Lack of ongoing resources and institutional support for sustainable patient engagement   | Allocate dedicated funding, appoint PRP coordinators, integrate engagement into governance, and embed requirements in funding and publication processes.                                                   |

needs and support frameworks. To empower patients to contribute effectively as PRPs, structured and accessible training programs are essential.

The EULAR began increasing collaboration with health professionals and social leagues in the early 1990s, creating a foundation for patient-led advocacy. In 2008, a network of national organizations of patients called the EULAR People with Arthritis/Rheumatism in Europe (PARE) was established. EULAR PARE paved the way for patients to become active voices in scientific strategy in rheumatic and musculoskeletal diseases, thereby strengthening their influence and creating a powerful alliance among European decision makers. The EULAR Online Course for PRPs was officially launched in late 2023, with over 100 trained PRPs internationally to date [25].

The European Patients' Academy of Therapeutic Innovation (EUPATI) has also been offering a Patient Expert Training Programme since 2014, which provides comprehensive training on the medicines research and development lifecycle, including clinical

trials, regulatory processes, health technology assessment, and patient involvement at every stage [26]. Its goal is to empower patients with the knowledge and skills to actively collaborate with stakeholders in therapeutic development. To date, there are more than 500 graduates (i.e., EUPATI Fellows) from more than 60 countries, forming a vast international network. A large database of EUPATI Fellows called EUPATIConnect links researchers with EUPATI Fellows from over 100 disease areas. EUPATI also offers a multilingual online library with reliable, easy-to-understand educational resources for PRPs. Although these initiatives are useful resources, some patients and experts in the field have raised some concerns that having "expert" PRPs might in fact reduce the diversity of patients' voices as all patients will not be willing or have the capacity to go through such extensive training [27].

Despite their potential shortcomings, these existing programs can equip patients with essential skills in research methodology, ethics, and scientific communication, enabling meaningful engagement with research teams as well as active participation in

scientific discussions and dissemination activities. In the context of myositis, this broad foundational training could be complemented by myositis-specific education to further strengthen effective collaboration. In addition, mentorship from more experienced PRPs could help to accelerate project onboarding and provide practical experience to orient newly trained PRPs.

## RECOMMENDATIONS AND FRAMEWORKS FOR COLLABORATION BETWEEN PATIENTS AND RESEARCHERS

PRPs can be identified through clinical care by clinician-researchers, but also through patient organizations [e.g., The Myositis Association (TMA)], clinical networks [e.g., International Myositis Assessment & Clinical Studies Group (IMACS)], or international societies [e.g., International Myositis Society (iMyoS)]. Selected individuals should have relevant lived experience, an interest in collaborative research and the ability to contribute constructively as equal members of the research team. Researchers should aim to involve at least two PRPs where feasible, recruit them early in the study design phase, ensure diversity of perspectives, clarify roles and expectations, and provide appropriate training and support to enable meaningful participation [28–30,31<sup>11</sup>]. Some emerging guidelines and frameworks provide practical direction for embedding PRPs within research teams, emphasizing principles of respect, transparency, co-learning, and shared decision-making.

In 2011, EULAR published the first-ever international recommendations for PRP involvement in rheumatology research [2]. This framework defined PRPs as equal partners bringing lived experience to the research cycle, rather than simply as study subjects. Following their publication, a scoping review of clinical trials and translational studies in the rheumatology field published in the 2016–2020 period revealed an increase from 2% to 20% in PRP involvement in randomized controlled trials for the 2016–2020 period [28]. However, none of the translational studies reviewed by the authors ( $n=40$ ) involved a PRP which underscores a significant gap between recommendations and clinical practice. PRP involvement in basic science and translational studies can bring important insights and help bridge the gap between fundamental discoveries and clinical implementation [30].

Similarly, the OMERACT group, that involve patients in their meetings since 2002, developed in 2016 a set of recommendations on how to involve PRPs as equal members in their working groups [32]. The OMERACT recommendations provided the practical foundation for involving PRPs in rheumatology

research, focusing on equal partnership and meaningful participation within their working groups [31,32]. The 2023 updated EULAR recommendations expand this framework into a comprehensive, evidence-based model that emphasizes diversity, support, researcher training, coordination, continuous evaluation and implementation across the entire spectrum of rheumatology research, including basic and translational research [33<sup>12</sup>]. A summary of the OMERACT and EULAR recommendations are presented in Table 3.

Following the publication of the updated 2023 EULAR guidelines, a group of PRPs and researchers shared the results of the iPREPARE study which aimed to understand the perceptions of PRP involvement in rheumatology research in an era where PRP involvement is encouraged. Based on surveys and semi-structured interviews, the authors showed important training gaps with 38% of PRPs reporting no specialized training to perform their roles, whilst 63% of researchers reporting no training on how to work with PRPs [34<sup>13</sup>]. To help move the field further and address some of these remaining gaps, the EULAR PARE INSPIRE Taskforce was assembled to develop metrics and quality indicators to assess patient engagement (e.g., authorship, leadership roles), help support accountability, and track progress [35]. By improving data collection on patient engagement in rheumatology research, it will help to understand how those recommendations are implemented, and if the increase in PRP involvement reflects impactful engagement, or a form of tokenism.

In the neuromuscular diseases field, a Dutch collaborative framework combining the perspectives of patients, clinicians and researchers successfully aligned research priorities with patients lived experiences [36<sup>14</sup>]. Patients identified fatigue, pain, and mobility as key unmet needs, which directly informed research funding priorities, clinical guidelines, and targeted rehabilitation programs. By positioning patients as active partners in setting the research agenda, this type of model ensures that real-world priorities drive scientific inquiry, while offering a scalable and ethically grounded approach to meaningful patient engagement. In the field of rare connective tissue diseases, the European Reference Network ReCONNECT involves patients as equal stakeholders in research, education, governance, and care development through structured patient partnership which improves the relevance and impact of healthcare initiatives while providing a transferable model for patient-centred innovation in rare disease settings [37<sup>15</sup>]. As digital innovations continue to grow, the Innovative Health Initiative (IHI) UNIFIED public–private partnership is developing and testing a framework in oncology, neurology and pediatric

**Table 3.** Summary of the 2015 OMERACT and 2023 EULAR recommendations for PRP involvement

| OMERACT (2015) [32]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | EULAR (2023 update) [31]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Leadership responsibility for meaningful PRP involvement.</li> <li>• Involving at least two PRPs per project.</li> <li>• Selecting PRPs for experiential knowledge and interest.</li> <li>• Agreeing on roles and expectations early.</li> <li>• Involving PRPs throughout the project.</li> <li>• Providing tailored information and support.</li> <li>• Reporting how PRPs were involve.</li> <li>• Recognizing contributions through acknowledgement, presentations and authorship where appropriate.</li> </ul> | <ul style="list-style-type: none"> <li>• Involve PRPs in all types of research, including basic and translational science.</li> <li>• Engage PRPs from project inception through dissemination.</li> <li>• Include at least two PRPs per project.</li> <li>• Recruit diverse PRPs with clearly defined mutual roles.</li> <li>• Provide a supportive and accessible research environment.</li> <li>• Appoint a PRP coordinator where possible.</li> <li>• Train both researchers and PRPs.</li> <li>• Evaluate the partnership regularly during the project</li> <li>• Recognize PRP contributions through authorship, acknowledgement and appropriate financial compensation where feasible.</li> </ul> |

rheumatology that integrate patient preferences, patient-centered clinical-study endpoints and digital health technologies (e.g. wearables) to better capture what matters most to patients. One of the goals of this European initiative is to determine minimally clinically important difference for patient-centered clinical study endpoints derived from digital health technologies. Learnings from this initiative may be helpful for future applications of digital health technologies in myositis studies to improve and perhaps facilitate clinical research, regulatory decision-making, and health technology assessments [38,39].

These are only a snapshot of recommendations and frameworks emerging from different groups and countries. Navigating patient research partnership frameworks can be challenging, creating uncertainty around which guidance to follow and where researchers and patients should begin their partnership journey. A systematic review of 65 frameworks for supporting, evaluating, and reporting patient and public involvement in research, concluded that no single framework fits all settings [40]. Instead, myositis researchers should adapt existing resources or collaborate with patients through co-design workshops to develop locally relevant frameworks.

### **FUTURE DIRECTIONS AND STRATEGIES FOR ADVANCING PATIENT ENGAGEMENT IN MYOSITIS**

Meaningful patient research partnership requires resource planning to support sustained involvement of PRPs within research groups. PRPs should be engaged from the earliest stages of research and remain continuously involved throughout the research lifecycle, including in priority setting, study design, outcome selection, interpretation of findings, and dissemination activities, to ensure that research remains relevant, inclusive, and aligned with patient needs and lived experiences.

Governance leaders and international networks are crucial in selecting, facilitating and integrating PRPs and PRP coordinators as equal stakeholders, and establishing patient involvement as a standard and mandatory component of research teams at every stage of research. There is an important gap to bridge to increase patient engagement in preclinical studies, where PRPs are not expected to make technical scientific decisions, but should contribute to prioritize research questions such as identifying which part of their history, symptoms or disease manifestations have the greatest impact on their lives to help researchers decide which biological mechanisms to study. They can also share what type of interventions are acceptable to them or what unmet needs exists in how medications are administered to them (e.g., daily vs. twice daily administration, oral vs. subcutaneous formulation). PRP involvement can also help to build meaningful grant applications and can have a beneficial impact on knowledge transfer activities [41].

Equal recognition of PRPs contribution through co-authorship, and fair compensation of PRPs for their participation in a range of different activities (e.g., working group member, event participation, presentation, advisory role) are also important components of successful patient engagement [42,43].

Finally, expanding global representation and strengthening engagement in underrepresented regions such as Asia-Pacific, Africa, Latin America, and the Middle East should be a priority. However, this will require additional resources and sustained capacity-building efforts to effectively support and amplify all patients' voices and needs. Collaboration with regional rheumatology organizations and consortia, such as Asia Pacific League of Associations for Rheumatology, African League of Associations for Rheumatology, and Pan American League of Associations for Rheumatology, could further facilitate local engagement, infrastructure development, and culturally relevant patient partnership initiatives.

## CONCLUSION

Patient engagement in myositis research has progressed substantially, but meaningful integration remains inconsistent across regions and research domains. Advancing from consultation to true partnership requires embedding patient engagement throughout the research lifecycle, investing in training for both researchers and PRPs, ensuring equitable recognition and compensation, adopting flexible engagement frameworks, and expanding global representation. By embracing co-creation as the standard, the myositis research community can generate more relevant, impactful, and equitable research that better reflects patients' lived experiences and ultimately improves outcomes.

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# Beyond weakness: pain and other under-studied symptoms in adults with inflammatory myopathies

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## Purpose of review

Idiopathic inflammatory myopathies (IIM) are heterogeneous autoimmune diseases with a broad and often underappreciated symptom burden extending beyond organ-specific manifestations. While traditional research has emphasized muscle weakness and other clinical features, less visible symptoms remain insufficiently captured. This review highlights these under-recognized but impactful domains for patients living with IIM.

## Recent findings

Pain, fatigue, depression, incontinence, sleep disturbance, cognitive dysfunction, and sexual dysfunction are common, inter-related, and closely linked to disease activity and functional impairment, and significantly impact health-related quality of life among patients with IIM. While recent studies increasingly demonstrate pain and fatigue as the key drivers of patient-perceived disease burden, the research studies on other domains are scarce.

## Summary

This review highlights the importance and prevalence of several under-recognized patient-prioritized symptoms and identifies the areas of critical knowledge gaps that warrant further investigation. Holistic and patient-centered management approach in IIM involves adoption of patient reported outcome measures assessing these key disease aspects and multidisciplinary teams that are equipped with diverse skillsets to improve patient outcomes.

## Keywords

fatigue, incontinence, myositis, pain, sleep

## INTRODUCTION

Idiopathic inflammatory myopathies (IIM), also commonly referred as myositis, are a heterogeneous group of autoimmune diseases characterized by skeletal muscle involvement and different extra-muscular manifestations [1]. The major IIM subgroups are dermatomyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy, inclusion body myositis, polymyositis and overlap myositis. These subtypes differ in clinical manifestations and disease courses, contributing to a broad and diverse symptom spectrum across IIM subtypes.

Previous studies with surveys and interviews have identified key domains that are both prevalent and meaningful to patients with IIM, including muscle symptoms and reduced muscle endurance, cutaneous manifestations, pain, pulmonary manifestations, dysphagia, incontinence, and fatigue [2]. While most IIM studies focus on manifestations that directly reflect organ involvement, such as muscle weakness, rash, arthritis, and dyspnea, less visible but highly impactful symptoms that do not reflect a

specific organ manifestation such as pain and fatigue remain under-recognized and under-studied.

This narrative review focuses on symptom domains that are not routinely captured in conventional myositis assessment tools but are central to patient experience, including pain, fatigue, depression, incontinence, sleep disturbance, cognitive dysfunction, and sexual dysfunction. Highlighting

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## KEY POINTS

- Beyond muscle weakness and rash, several symptoms have been prioritized by patients as important including pain, fatigue, sleep disturbance, sexual dysfunction, and incontinence.
- Patient reported symptoms of cognitive dysfunction, pain, fatigue, depression, and sleep disturbance frequently cluster together which may be due to a coordinated set of behavioral and psychological changes triggered by inflammatory signals.
- For a holistic management approach in idiopathic inflammatory myopathies, adoption of patient reported outcome measures assessing these key aspects of disease and working with multidisciplinary teams is critical.

these domains may help bridge the gap between clinical measures of disease activity and patient-perceived disease burden in IIM, which reflect different, and not always concordant, dimensions of disease.

## PAIN IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

Pain has been recently recognized as a common and important symptom in patients with IIM, representing a clear shift from the earlier view of myositis as a largely painless condition. This change was formally acknowledged at the OMERACT 2018 meeting, where pain was endorsed as a mandatory life impact domain for adult myositis clinical trials along with fatigue and physical function [3]. Since then, several studies have consistently shown that pain is highly prevalent and clinically relevant in IIM.

Across studies, pain is reported by the majority of patients [4<sup>■</sup>]. In a U.S. registry-based study, 86% of patients with IIM described pain, with a mean score of 3.5 out of 10 on a visual analog scale [5]. A large survey study showed that patients with IIM report more pain compared with individuals without rheumatic disease, although slightly less than in other systemic autoimmune rheumatic diseases [6].

In a qualitative interview study with patients with IIM, a variability in pain quality, location, and duration among patients was noted [7]. Pain may be chronic or fluctuating and often worsens during disease flares [7]. Pain can be a first symptom of myositis and corticosteroid treatment can worsen or improve the pain; however, there is a risk that pain resurfaces or worsens with tapering of corticosteroid doses. It is therefore important to assess pain continuously over the disease course and address adequately when needed. Both muscle and joint pain

are common, reported by up to 63% of patients [5], however, skin symptoms such as mechanic hands or digital ulcers can also contribute to pain [7].

Mechanism of myositis-related pain is currently poorly understood. Similar to other systemic rheumatic diseases, it may be multifactorial, reflecting inflammatory muscle, joint and skin involvement and possibly central and/or peripheral sensitization [4<sup>■</sup>,8]. Further studies are needed to understand the factors that may contribute to variability and persistence of pain among patients with IIM.

Importantly, pain is closely associated with patient-reported disease activity with higher pain levels strongly correlating with worse patient global disease activity in several studies [5,8]. Longitudinal data also show that pain improves in parallel with improvement in disease activity, supporting that pain could at least be partially related to underlying inflammation [8]. Pain is also a common feature during disease flares. Up to 64% of patients with dermatomyositis and polymyositis report muscle discomfort during these periods, which is associated with increased disability, reduced productivity, and higher healthcare utilization [9]. At the same time, pain contributes significantly to discordance between patient- and physician-reported disease activity, reflecting its strong influence on the patient perspective; therefore, future studies that examine association between objective measures of disease activity and pain levels could further shed light into this relationship [10,11].

Pain also has a substantial impact on daily life. Around 71% of IIM patients report that their pain interferes with daily activities [12]. In qualitative interviews, patients report that their pain affects all aspects of their life, such as their social roles, relationships, and self-perception [7]. In addition, patients express an urgent need for more studies to understand pain as a disease manifestation.

Taken together, these findings show that pain in IIM is common, significantly impairs daily life, and may be linked to disease activity. Therefore, systematic and longitudinal assessment of pain in routine practice and clinical studies is essential to better recognize and adequately address this symptom. The PROMIS Pain Interference (6a) scale is an instrument that has been shown to be reliable, valid, and responsive in patients with IIM; therefore, it can be used to assess the impact of pain in adult IIM in future studies [12–14].

## FATIGUE IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

Fatigue is a common and burdensome symptom among patients with IIM and is frequently reported

by patients as having a major impact on daily life and overall well being [15]. In a prospective observational study, the majority of patients with IIM ranging between 52% and 67% reported moderate to severe fatigue [16<sup>■</sup>]. Patients often report fatigue as disabling, and persistent as it may not improve even when other disease manifestations improve [15]. Importantly, fatigue contributes substantially to subjective perceived disease severity and is, together with physical function, one of the main drivers of patient global disease activity [10]. In longitudinal analyses, fatigue levels showed moderate to strong correlations with muscle and extra-muscular disease activity, physician global disease activity, pain, physical function, and health-related quality of life [16<sup>■</sup>]. Similar to pain, fatigue also shows improvement over time in parallel with improvement in disease activity, suggesting that it could be, at least partially, driven by the underlying inflammation. Besides disease activity, fatigue can also be related to cumulative damage as a result of disease and medications; however, future studies are required to examine this question. Other factors that have been associated with higher levels of fatigue among patients with IIM include reduced physical function, increased pain, poorer quality of life, and psychological factors such as anxiety and depression [15,16<sup>■</sup>,17<sup>■</sup>] as well as female sex, overlap myositis, and autoimmune multimorbidity [18].

As a common symptom of IIM, assessment of fatigue with the appropriate instruments is important. The PROMIS Fatigue short form (7b) has been shown as a reliable, valid, and responsive instrument in patients with IIM and could be used for consistent and adequate assessment of fatigue across clinical studies [12–14].

## MENTAL HEALTH PROBLEMS IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

Mental health impairment is increasingly recognized as an important contributor to the disease burden in IIM. However, research in this topic is scarce in IIM compared to other autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. In a large study conducted with MIHRA (Myositis International Health & Research Collaborative Alliance) collaboration, probable anxiety and depression [defined as  $\geq 8$  on Hospital Anxiety and Depression Scale (HADS)] were observed in 25% and 14% of patients with IIM, respectively [17<sup>■</sup>]. Concordant with these results, another cohort study showed significantly poorer global mental health among patients with IIM compared to the individuals without autoimmune disease [18].

Several patient-reported outcomes and disease-related factors could be contributing to development and persistence of mental health problems in IIM. Fatigue appears to be a key factor, with increasing fatigue associated with a progressively higher risk of both anxiety and depression [17<sup>■</sup>]. Additional contributing factors include muscle weakness, physical impairment, other comorbidities, pain, and psychosocial factors such as isolation, trauma exposure, and loss of control [19]. Glucocorticoids can also cause anxiety, especially at higher doses, and can contribute to physical inactivity by causing weight gain. Physical inactivity is associated with worse mental health scores, whereas higher levels of physical activity are linked to a lower risk of depression, suggesting a potential protective role [17<sup>■</sup>]. Twenty-four weeks of strength training program in patients with established IIM improved self-reported depression compared to the nonexercising control group [20]. These results further support a link between physical activity and depression. Disease-related factors associated with lower global mental health scores include active disease, interstitial lung disease, and overlap myositis [17<sup>■</sup>,18].

In clinical studies, mental health in IIM was assessed using the PROMIS Global Mental Health domain and HADS [17<sup>■</sup>,18]; however, further studies are needed to assess the measurement properties of these instruments in patients with IIM to facilitate future research on mental health problems in IIM.

## SLEEP DISTURBANCE IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

Similar to mental health impairment, sleep disturbance is an under-studied problem that is frequently reported by patients with IIM [21]. In a large national cross-sectional dataset from the German National Database, 51% of patients with IIM reported sleep disturbance, making this one of the most frequently reported symptoms alongside fatigue [22]. In repeated cross-sectional assessment from 1997 to 2017 showed that sleep disturbance has improved over time to 41% but remained common. Importantly, these improvements occurred in concordance with improvements in physician-reported disease control, reductions in glucocorticoid use, and improvements in pain and fatigue [22]. The frequency of sleep disturbance also varies by IIM subtype and is the highest in patients with overlap myositis [22]. This could be due to potentially increased symptom burden among the patients with overlap myositis. Sleep problems were assessed using numeric rating scale in one study with IIM [22]; however, future studies should explore the utility

of more comprehensive sleep instruments beyond unidimensional scales.

### **COGNITIVE DYSFUNCTION IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES**

Cognitive dysfunction in IIM is increasingly recognized as an important patient-reported problem, although it remains poorly understood in terms of its underlying mechanisms [21]. Available data suggest that what patients describe as cognitive dysfunction likely reflects subjective difficulties with concentration, memory, and mental clarity, often referred to as “cognitive impact”, rather than defined neurological disorders such as dementia. Qualitative work from OMERACT Myositis Working Group supports that cognitive difficulties are part of lived experience and contribute to daily limitations and reduced well being [23].

In a large survey study, patients prioritized cognitive difficulties as an important symptom alongside fatigue and sleep problems [21]. Clustering of cognitive symptoms with other patient-reported domains, particularly fatigue and sleep disturbance, suggest that cognitive difficulties may arise as part of a broader symptom complex and/or these symptoms are closely interconnected from the patient perspective. This observation may also be interpreted within the framework of sickness behavior, a coordinated set of behavioral and psychological changes triggered by inflammatory signals. This evolutionarily conserved response can be driven by pro-inflammatory cytokines that affect the central nervous system and can potentially give rise to symptoms such as fatigue, malaise, anhedonia, depression, lassitude, anxiety, and increased pain sensitivity [24,25]. While sickness behavior is considered adaptive during acute illness by promoting energy conservation and recovery, persistent activation has been linked to chronic conditions, including depression, chronic pain, and fatigue [24,26]. These mechanisms may partly explain the symptom patterns observed in IIM; however, further studies are needed to understand the applicability of the sickness behavior framework to patients with IIM.

### **SEXUAL DYSFUNCTION IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES**

Despite being an important aspect of quality of life, sexual health has historically received limited attention in IIM with very few studies conducted to date. Sexual activity was identified as a key area for improvement by patients with polymyositis and

dermatomyositis, yet remains insufficiently studied and discussed [27]. A cross-sectional study comparing patients with IIM to matched healthy controls demonstrated that sexual dysfunction is common, affecting 59% of women with IIM compared with 40% of controls, and 64% of men compared with 9% of controls [28]. Sexual dysfunction was defined using instruments assessing multiple domains of sexual health, including desire, arousal, lubrication, orgasm, erectile function, satisfaction, and sexual quality of life, all of which were significantly impaired in patients with IIM. Sexual dysfunction was associated with muscle weakness, disability, physical inactivity, fatigue, depression, and reduced quality of life [28]. Besides the management of these closely associated domains, sexual dysfunction may be treated with a tailored physiotherapy program that has been associated with improvements in sexual function and quality of life [29].

Assessment of sexual dysfunction in one study [28] was performed with a comprehensive battery of questionnaires including Female Sexual Function Index, Brief Index of Sexual Function for Women, Sexual Function Questionnaire, Sexual Quality of Life Questionnaire – Female for women and International Index of Erectile Dysfunction, Male Sexual Health Questionnaire, and Sexual Quality of Life Questionnaire – Men for men with IIM. Future studies should focus on assessment of measurement properties of these instruments in patients with IIM to facilitate further research in this important area.

### **INCONTINENCE IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES**

Incontinence has rarely been studied in IIM but appears to be more common than previously recognized. A cross-sectional study demonstrated significantly higher prevalence of both urinary and bowel incontinence in patients with myositis compared with the general population [30]. Urinary incontinence was reported by 88% of women and 66% of men, while bowel incontinence was reported by 74% and 54%, respectively, indicating a substantial burden. The study population consisted predominantly of patients with inclusion body myositis (77%), while other IIM subtypes were less represented. However, prevalence of incontinence was not reported separately by subtype, limiting conclusions regarding differences between IIM subtypes [30].

Incontinence in IIM is not well understood given that IIM primarily affects skeletal muscles rather than smooth muscles responsible for anal and bladder sphincter function. However, indirect mechanisms

such as impaired mobility may contribute to the high prevalence. For example, since IIM leads to progressive skeletal muscle weakness and impairment in physical function, it may affect mobility, transfers, and timely access to toileting facilities [30]. Importantly, patients more often attribute incontinence symptoms to medications and environmental or accessibility factors rather than limb weakness alone. Two-thirds of affected patients reported never seeking help, highlighting unmet clinical needs [30]. Taken together, incontinence represents an important but often overlooked aspect of disease burden in IIM that warrants greater attention in clinical care.

## IMPLICATIONS FOR MULTIDISCIPLINARY MANAGEMENT OF THESE PATIENT-REPORTED OUTCOMES

As complex diseases, the management of IIM requires multidisciplinary team care to successfully address all aspects of the disease including the most under-recognized symptoms discussed here. An optimal disease activity control with medical treatments through rheumatology and/or neuromuscular specialties is a key aspect of IIM management, but not sufficient to address all of the symptoms that impair the quality of life of patients living with IIM. Therefore, asking about the symptoms in clinical encounters and referring patients to the appropriate specialists in the multidisciplinary team including occupational and physical therapists, a speech and language therapist, a nutritionist, a social worker, specialists in pelvic floor physical therapy and sexual dysfunction, psychologists, and psychiatrists are essential for a holistic management approach. Incorporating patient-reported outcome measures in routine practice can help to capture this multidimensional burden and identify the symptoms that require further discussion and attention during clinical encounters.

Besides multidisciplinary care, self-management and self-efficacy are also important and understudied areas for management in IIM. High self-efficacy is associated with high life-satisfaction and physical function and lower fatigue levels compared to individuals with low self-efficacy [31]. Individuals achieving or exceeding recommended physical activity levels have lower anxiety, depression, and fatigue and better muscle function compared to those who are less physically active [17<sup>■</sup>,32].

## CONCLUSION

In this narrative review, we reported the potential mechanisms, prevalence, and assessment of several important but underrecognized aspects of IIM including pain, fatigue, mental health problems,

sleep disturbances, cognitive dysfunction, incontinence, and sexual dysfunction. The findings underscore the limited research on these symptoms and identify important knowledge gaps that warrant further investigation for a comprehensive and patient-centered understanding of disease burden in IIM.

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## Conflicts of interest

*There are no conflicts of interest.*

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# Environmental exposures and risks for the idiopathic inflammatory myopathies and its phenotypes: a narrative review

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## Purpose of review

The delineation of myositis-specific autoantibody (MSA) subgroups over the past two decades has reframed environmental research in idiopathic inflammatory myopathies (IIMs), making it plausible to examine discrete exposure-phenotype pairings within serologically defined subgroups. This review synthesises evidence on environmental, occupational, infectious, and pharmacological exposures, with attention to phenotypic specificity.

## Recent findings

Ultraviolet radiation shapes MSA-specific geographic distributions at the population level and associates with dermatomyositis onset at the individual level. Disease onset follows MSA-specific seasonal patterns, replicated across geographically independent cohorts. Smoking amplifies antisynthetase syndrome risk through a gene-environment interaction with HLA-DRB1\*03:01, whilst protecting against anti-TIF1- $\gamma$  autoantibodies. Gestational and early-life tobacco smoke exposure is consistently implicated as risks for juvenile IIM. Occupational silica exposure associates with antisynthetase syndrome and overlap myositis, with synergistic lung disease risk when combined with smoking. Statins, immune checkpoint inhibitors, anti-TNF $\alpha$  agents, and interferons each induce immunopathologically distinct myositis phenotypes. Postpandemic surveillance has documented a rise in anti-MDA5 autoantibody-positive disease following SARS-CoV-2 infection.

## Summary

Environmental exposures in IIM act preferentially in specific serological and genetic contexts, consistent with discrete exposure-phenotype pairings shaped by genetic background and age at exposure. Prospective, MSA-stratified studies with direct exposure quantification represent priority directions for the field.

## Keywords

autoantibodies, dermatomyositis, environmental exposures, idiopathic inflammatory myopathies, myositis

## INTRODUCTION

The development of autoimmune disease is now understood as the product of cumulative environmental exposures interacting with genetic susceptibility over time [1,2]. Gene-environment and exposure-exposure interactions, unfolding across the lifespan from the prenatal period through adulthood, are thought to drive the immunological changes that ultimately manifest as clinically apparent disease [1].

The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of systemic autoimmune diseases in which immune-mediated muscle inflammation, systemic organ involvement, and a spectrum of disease-specific autoantibodies define clinically and serologically distinct subgroups [3<sup>a</sup>,4]. A growing body

of evidence in IIM has implicated environmental, occupational, and infectious factors in disease risk

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## KEY POINTS

- Environmental exposures in idiopathic inflammatory myopathy (IIM) operate preferentially in specific serological and genetic contexts, supporting discrete exposure-phenotype pairings, rather than uniform disease-level risk.
- UV radiation, cigarette smoking, and occupational silica exposure show subgroup specific associations, reinforcing the importance of myositis-specific autoantibody (MSA)-based stratification in environmental research.
- Gestational and early-life tobacco smoke exposure are consistently implicated as risk factors for juvenile IIM, whilst occupational inhalational exposures predominate in adult-onset disease, indicating that critical exposure windows are age-dependent.
- Priority research directions include prospective MSA-stratified studies, identification of high-risk populations, direct exposure quantification, and characterization of dose-response relationships and critical exposure windows.

and phenotypic expression [5,6]. The progressive characterisation of myositis-specific autoantibodies (MSAs) over the past two decades has transformed the classification of IIM, revealing not a single condition, but a family of diseases with distinct clinical features, immunogenetic associations, and disease trajectories [7]. This classification has opened the way for environmental research in IIM to define discrete exposure-phenotype pairings, examining which exposures act in which subgroups, through which mechanisms, and in which genetic contexts.

This review examines environmental influences on IIM across five domains: external exposures, internal exposures, occupational exposures, infectious exposures, and pharmacological triggers. Agents capable of inducing immune-mediated inflammatory myopathy are considered within the latter category; non-inflammatory toxic myopathies, which are pathologically and mechanistically distinct, are not included. Where evidence permits, we examine exposure-phenotype specificity across clinical and MSA-defined subgroups, proposed mechanistic pathways, and the positioning of IIM findings within the broader landscape of environmental autoimmunity.

## RESULTS

The proposed mechanisms underlying selected exposure-phenotype associations, where evidence in IIM permits, are summarised in Table 1.

## External exposures

### Ultraviolet radiation

Ultraviolet (UV) radiation demonstrates consistent associations with IIM, at both population and individual levels. UV intensity is the strongest geoclimatic predictor of anti-Mi-2 autoantibody distribution across geographically independent cohorts, with anti-TIF1- $\gamma$  autoantibodies showing a similar latitudinal pattern [13–15]. The same relationship holds at the individual level: higher occupational and recreational sun exposure and greater sunburn frequency in the year preceding diagnosis have each been associated with dermatomyositis (DM) onset and flare [16,17]. In juvenile IIM (JIIM), higher UV index within 30 days of symptom onset has been associated with anti-TIF1- $\gamma$  autoantibody positivity and the juvenile dermatomyositis (JDM) phenotype [18], disease severity [19], and a chronic disease course [20]. Higher ambient residential UV exposure has been associated with anti-MDA5 autoantibody-positive JDM compared with MSA-negative counterparts [21]. Latitudinal gradients in IIM may not be attributable solely to UV radiation; geomagnetic activity has been proposed as a contributory determinant, based on observed correlations with the incidence of other systemic autoimmune rheumatic diseases (SARDs) in population-based cohorts [22]. This association has not, to date, been directly demonstrated in IIM.

### Seasonal and geoclimatic factors

The seasonality of IIM onset follows an MSA-specific pattern, replicated across geographically independent cohorts. Anti-synthetase syndrome (ASyS) autoantibody-positive patients cluster in spring, with a March–April peak in adults [23,26] and a May–July peak in JIIM [21]. An autumn clustering previously associated with anti-SRP-positive patients [23] has not been reproduced in larger analyses, in which this subgroup showed no identifiable seasonal pattern [26]. Anti-MDA5 autoantibody-positive patients cluster predominantly between October and March, consistent across Asian and Western cohorts [24,25<sup>\*</sup>]; MSA-negative adults peak in summer, with onset concentrated in June–July [26], while no seasonal pattern has been identified in MSA-negative JIIM [21]. In terms of geography, anti-MDA5-positive patients resided significantly closer to freshwater at disease onset, and geographic clustering of IIM phenotypes has been observed at a national level in the United States [24,27].

### Smoking and air pollution

Cigarette smoking has been independently associated with polymyositis (PM), anti-Jo-1 positivity, and

**Table 1.** Environmental exposures in idiopathic inflammatory myopathies (IIM): subgroup associations and proposed mechanisms

| Exposure                                                                   | IIM subtype/MSA                                             | Proposed mechanism                                                                                                                                                                                                                                                                       |
|----------------------------------------------------------------------------|-------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| External exposures                                                         |                                                             |                                                                                                                                                                                                                                                                                          |
| UV radiation                                                               | DM, JDM/anti-Mi-2, anti-TIF1- $\gamma$ , anti-MDA5 Ab       | UV upregulates Mi-2 protein via translational mechanisms in cell culture; UV-induced keratinocyte apoptosis with autoantigen release demonstrated in DM skin biopsies [8,9]                                                                                                              |
| Cigarette smoking                                                          | PM, ASyS/anti-Jo-1 Ab; protective for anti-p155/140 (TIF1). | HLA-DRB1*03:01 interaction with smoking implicates antigen presentation at the bronchial mucosa; inhaled antigens proposed to initiate ASyS through NK cell dysregulation and neutrophil extracellular traps formation [10,28,29]                                                        |
| Vaccines                                                                   | All major IIM subtypes                                      | Distinct HLA profile (DQA1*03:03 risk; DRB1*03:01 protective) implicates a specific antigen presentation pathway; aluminium hydroxide adjuvant persistence in muscle macrophages demonstrated in macrophagic myofasciitis [35,37]                                                        |
| Silicone breast implants                                                   | Postimplant myositis phenotype                              | Distinct HLA profile (DQA1*01:02 enriched; DRB1*03:01 reduced) demonstrates activation of a different immunogenetic pathway from spontaneous IIM [41,42]                                                                                                                                 |
| Internal exposures                                                         |                                                             |                                                                                                                                                                                                                                                                                          |
| Gestational and early life exposures (maternal smoking)                    | JIM                                                         | In utero maternal smoking induces epigenetic modifications including foetal DNA methylation changes that may persist into adulthood; maternal microchimeric cells identified in JDM muscle and peripheral blood, with smoking proposed as a modulator of maternal microchimerism [44,45] |
| Psychosocial stress                                                        | All major IIM subtypes                                      | HPA axis dysregulation with glucocorticoid resistance drives augmented proinflammatory cytokine production, lymphocyte activation, and immune cell mobilisation. [50]                                                                                                                    |
| Occupational exposures                                                     |                                                             |                                                                                                                                                                                                                                                                                          |
| Occupational inhalational exposures (silica, mineral dust, chemical fumes) | ASyS, overlap myositis/anti-Jo-1 Ab                         | Silica activates innate immune pathways through macrophage-mediated inflammation, driving proinflammatory cytokine production and adaptive immune activation; inhaled antigens have additionally been proposed to initiate ASyS through NK cell dysregulation [10,11]                    |
| Drug exposures                                                             |                                                             |                                                                                                                                                                                                                                                                                          |
| Statins                                                                    | IMNM/anti-HMGCR                                             | HMGCR upregulation in regenerating muscle fibres renders the enzyme immunogenic; immune-mediated perpetuation persists after drug withdrawal; anti-HMGCR Ab positivity in statin-naïve patients indicates an independently arising autoimmune process [57–59]                            |
| Immune checkpoint inhibitors                                               | ICI-associated myositis                                     | PD-1/CTLA-4 blockade removes peripheral self-tolerance, unleashing autoreactive T-cells against shared tumour and muscle antigens [60]                                                                                                                                                   |
| Hydroxyurea                                                                | Drug-induced DM                                             | Mechanism uncertain; interface dermatitis without true myositis on biopsy suggests a distinct pathogenic pathway from immune-mediated inflammatory myopathy [61]                                                                                                                         |
| TNF- $\alpha$ inhibitors                                                   | Drug-induced DM/PM                                          | Mechanism uncertain; increased production of IFN- $\gamma$ after TNF- $\alpha$ blockage might play a role in development of DM/PM [62]                                                                                                                                                   |
| IFN therapy                                                                | Drug-induced DM/PM                                          | Mechanism uncertain; activation of the type-I IFN pathway is implicated in the pathogenesis of PM/DM, with heightened type-I IFN signature expression. Recurrence of myositis has been reported in such patients on re-administration of IFN therapy [63].                               |
| Infectious Exposures                                                       |                                                             |                                                                                                                                                                                                                                                                                          |
| SARS-CoV-2                                                                 | Anti-MDA5 Ab+ DM                                            | SARS-CoV-2 epitopes show structural homology to DM autoantigens in TIF1- $\gamma$ -positive patient sera; sustained MDA5-interferon pathway activation implicated in anti-MDA5 DM [69,70,71,72,73]                                                                                       |

**Table 1** (Continued)

| Exposure                          | IIM subtype/MSA                    | Proposed mechanism                                                                                                                                                                           |
|-----------------------------------|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Coxsackie B1 virus                | PM-like histology (animal models)  | Viral RNA persists in muscle as a double-stranded complex; T-cell competence required for chronicity; host MHC haplotype determines susceptibility independently of viral load [74–76]       |
| HCV                               | IBM                                | Viral RNA detectable in IBM muscle at rates exceeding systemic viraemia, implicating local tissue persistence as a driver of endomysial inflammation [80]                                    |
| West Nile virus                   | PM-like histology                  | WNV induces sixfold MHC class I upregulation and de novo MHC class II expression in human myoblasts, rendering fibres susceptible to CD8-mediated cytotoxic killing [81]                     |
| HIV                               | PM                                 | Endomysial CD8+ infiltration of MHC class I-expressing nonnecrotic fibres histologically indistinguishable from idiopathic PM, without demonstrable direct muscle infiltration by virus [82] |
| Gut and lung microbiome dysbiosis | IMNM, ASyS, DM-associated ILD, JDM | Specific gut bacterial genera causally linked to PM and DM risk; dysbiosis also present in JDM; MSA-specific microbial signatures identified across IIM subtypes [12,83,84–86 <sup>¶</sup> ] |

Ab, autoantibody; ASyS, antisynthetase syndrome; CVB1, Coxsackie B1 virus; DM, dermatomyositis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HMGR, 3-hydroxy-3-methylglutaryl-CoA reductase; HPA, hypothalamic pituitary axis; IBM, inclusion body myositis; ICI, immune checkpoint inhibitor; IFN, interferon; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; IMNM, immune-mediated necrotising myopathy; JDM, juvenile dermatomyositis; MDA5, melanoma differentiation-associated protein 5; MHC, major histocompatibility complex; MSA, myositis-specific autoantibody; NK, natural killer; PM, polymyositis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor; UV, ultraviolet; WNV, West Nile virus.

ASyS, with HLA-DRB1\*03:01 carriage amplifying this risk [28], particularly in Caucasian patients [29]. Notably, cigarette smoking has been found to be protective against anti-TIF1- $\gamma$  (p155/140) autoantibodies, with a dose-response relationship evident across pack-years [29]. The pattern mirrors, in reverse, the smoking–HLA-DRB1\*03:01 relationship already described for ASyS and anti-Jo-1, though the original study did not find a statistically significant interaction between the two factors for any outcome; the mechanism underlying the anti-TIF1- $\gamma$  association remains unestablished. Smoking has further been associated with overlap myositis and extra-muscular manifestations including interstitial lung disease (ILD), dysphagia, and cardiac involvement [30].

Evidence linking air pollution to IIM remains limited and largely indirect. Clinically amyopathic DM (CADM) prevalence has shown correlations with fixed-point airborne emission sources [31], and SO<sub>2</sub> exposure has been associated with hospitalisation for paediatric rheumatic diseases including JDM [32]. Residential proximity to major roadways was associated with higher IIM prevalence in registry data, with the largest effect observed in inclusion body myositis (IBM); roadway proximity may serve as a proxy for ambient particulate exposure, though confirmation in larger studies is required [27]. Fine particulate matter  $\leq 2.5 \mu\text{m}$  in diameter (PM<sub>2.5</sub>) has been associated with SARD risk in population-level studies, though data specific to IIM are absent [33,34].

## Vaccines

Vaccination represents a recognised, but uncommon trigger for IIM across all major subtypes. Temporal associations have been reported following hepatitis B, influenza, smallpox, and HPV vaccines [35]. Immunization within one year of diagnosis was more frequently reported in JDM and juvenile overlap myositis compared with juvenile PM [36]. Immunogenetic analysis of myositis after vaccination in the pre-COVID-19 era identified HLA-DQA1\*03:03 as a risk factor, while HLA-DRB1\*03:01, the principal genetic risk factor for spontaneous IIM, was protective, suggesting that vaccine-triggered myositis is immunogenetically distinct from idiopathic disease [37<sup>¶</sup>]. New-onset and relapsed DM has been reported following both SARS-CoV-2 infection and COVID-19 vaccination, though these observational associations have not been substantiated in large register-based studies [38,39,40<sup>¶</sup>]. The absolute risk remains low, a reassuring finding in the context of the well established public health benefits of vaccination.

## Implants

A large population-level meta-analysis has found no significant association between silicone breast implants and connective-tissue disease, including IIM [41]. In the small subset of women in whom myositis does develop after implantation, however, a HLA association has been identified that is HLA DQA1\*01:02 enriched, and with a reduced presence of DRB1\*03:01 which is associated with idiopathic IIM [42].

## Internal exposures

### Pregnancy and early life exposures

Pregnancy-associated IIM, referring to DM or PM with onset during pregnancy or the period immediately following delivery or pregnancy loss, presents with a distinct clinical profile, often associated with delayed diagnosis, poor steroid response, and adverse foetal outcomes, and has been reported across multiple MSA subgroups [43]. Whether pregnancy itself confers risk for IIM onset, as opposed to coinciding with it temporally, remains unresolved. In JIIM, in-utero and early-life exposures contribute meaningfully to disease risk. Tobacco smoke exposure, particularly smoking during pregnancy and early household smoke exposure, is associated with elevated odds of JIIM onset across independent cohorts [44<sup>■</sup>,45]. Early-life household smoking exposure has similarly been associated with adult-onset systemic autoimmune rheumatic disease, including IIM, although the IIM subgroup analysis was underpowered to reach significance [44<sup>■</sup>]. Maternal occupational inhalational exposures and ozone exposure in early childhood have been identified as independent risk factors for JDM in Brazilian cohorts, with earlier symptom onset observed in children with greater prenatal environmental burden [46,47<sup>■</sup>]. Birthdate clustering in serologically and genetically defined JIIM subgroups further supports the existence of seasonally structured pre or perinatal triggers [48]. Twin discordance studies represent one of the most robust forms of evidence for environmental contributions to complex disease, and discordance in MSA positivity between affected and unaffected twins further substantiates the role of environmental factors in autoantibody development in IIM [49].

### Psychosocial stress

Psychosocial stress has been linked with both disease onset and flare across the IIM spectrum, in adult and juvenile populations alike. Adults diagnosed with systemic autoimmune rheumatic diseases, predominantly myositis, experience a higher frequency of negative, uncontrollable, and highly stressful life events, such as a serious accident or failing an important exam, along with greater perceived stress, in the year preceding diagnosis compared with healthy controls [50<sup>■</sup>]. In JIIM, a stressful life event precedes illness onset in a minority of patients, most often a single major stressor relating to social, family, or academic circumstances [51]. Among patients who flare, stressful events, including a recent house move and financial difficulties, are more frequently reported than among those without flare [17].

## Occupational exposures

High lifetime occupational exposure to biological or mineral dust and chemical fumes has been reported in a greater proportion of ASyS patients compared with myositis controls, with exposed patients showing higher rates of ILD, mechanic's hands, and HLA-DRB1\*03 carriage [52]. Silica exposure has been associated with DM and overlap myositis, with a dose-response trend across phenotypes and synergistic increase in lung disease risk when combined with smoking [53<sup>■</sup>,54]. Heavy metal exposure has been associated with overlap myositis and lung disease-positive myositis [53<sup>■</sup>]. Environmental toxin exposure more broadly, including asbestos, fiberglass, solvents, and coal dust, has been more frequently reported in IBM, with additional associations noted with cardiac involvement and ILD [30,53<sup>■</sup>]. World Trade Center dust exposure has been associated with IIM and other SARDs, with anti-Jo-1 autoantibodies identified among affected cases [55]. Inorganic dust exposure during military service has been associated with SARD risk, including myositis, in a large veteran cohort [56].

## Drug exposures

Drugs may cause muscle injury through two distinct mechanisms: direct, nonimmune-mediated injury to muscle fibres which constitutes a toxic myopathy and resolves on withdrawal, or induction of true immune-mediated inflammatory myopathy which may be clinically and histopathologically indistinguishable from spontaneously arising IIM. Once established, the latter may persist independently of the triggering agent, and is classified within the IIM spectrum. Statins are the most thoroughly studied example, causing either a self-limiting toxic myopathy that resolves on discontinuation, or anti-HMGCR-associated immune-mediated necrotizing myopathy (IMNM), which is progressive and persistent despite drug withdrawal, and requires immunosuppressive therapy [57–59]. Notably, anti-HMGCR positivity occurs in some statin-medication naïve patients and in JIIM.[57]. Immune checkpoint inhibitors represent an increasingly recognised pharmacological trigger, with a phenotype notable for ocular and proximal weakness, respiratory failure, and concurrent myocarditis, collectively accounting for significant morbidity and mortality [60<sup>■</sup>]. Among drug-induced DM cases, hydroxyurea is the most commonly implicated agent, followed by immune checkpoint inhibitors and statins [61]. New-onset DM has also been reported in association with antitumour necrosis factor- $\alpha$  agents and interferon- $\alpha$  therapy [62,63]. Proton pump inhibitors and carbimazole have also been associated with inflammatory myopathy, though the evidence base remains limited [64,65].

Prediagnosis medication exposure has been more frequently reported in MSA-negative IIM patients compared with anti-MDA5-positive patients [36].

### Infectious exposures

Epidemiological evidence supports a role for preceding infections in IIM onset across clinical and MSA-defined subgroups. Respiratory and gastrointestinal infections in the twelve months preceding diagnosis have been associated with increased odds of IIM, with differential associations noted across DM, PM, and IBM phenotypes [66<sup>■</sup>,67<sup>■</sup>]. In IIM, pharyngitis and upper respiratory infections are among the most commonly reported antecedent exposures, and a polycyclic disease course has been associated with a higher infection burden prior to onset [20,51,68].

The experimental literature identifies several, not mutually exclusive, mechanisms through which infectious agents may initiate or sustain muscle inflammation. Molecular mimicry between viral epitopes and muscle autoantigens has been proposed on the basis of structural homology between SARS-CoV-2 epitopes and DM-associated autoantigens, with cross-reactive antibodies identified in TIF1- $\gamma$ -positive DM patients [69]. Postpandemic surveillance has documented a rise in anti-MDA5 autoantibody-positive DM following SARS-CoV-2 infection [70,71<sup>■</sup>], alongside increased flare risk across IIM subtypes [72]. A distinct but related mechanism is nonreplicative viral persistence. Coxsackie B1 virus is the best-characterised example: animal models demonstrate that viral RNA persists in muscle in double-stranded form in genetically susceptible hosts, with T-cell competence required for chronicity and myopathic determinants mapping to specific viral genomic regions [73–75]. Supporting human evidence is limited [76], and certain muscle biopsy-based PCR studies report conflicting results [77,78]. Hepatitis C Virus (HCV) shows a similar pattern, with viral RNA detectable in IBM muscle at rates exceeding systemic viraemia [79]. Human T-lymphotropic virus type 1 (HTLV-1) is associated with PM, DM and IBM, reported across geographically distinct cohorts with resultant myositis showing poor response to immunosuppressive therapy [80]. Independently, certain viruses appear to trigger autoimmunity through direct upregulation of MHC class I on muscle fibres. West Nile virus and HIV each induce this response in human myoblasts, rendering fibres susceptible to CD8-mediated cytotoxic killing in a pattern histologically indistinguishable from idiopathic PM [81,82]. Gut, lung, and oral microbiome dysbiosis has been consistently identified across IIM subtypes [83<sup>■</sup>], with MSA-specific patterns identified in IMNM [84], ASyS [85], and DM-associated ILD [86],

although IBM may represent an exception [88<sup>■</sup>]. Whether dysbiosis represents a precipitating exposure, a consequence of disease, or a marker of shared household environmental exposures remains uncertain [87,88<sup>■</sup>].

### DISCUSSION

The evidence reviewed here points to a consistent pattern: environmental exposures in IIM act preferentially in particular serological and genetic contexts rather than conferring uniform disease-level risk. The characterisation of MSA subgroups has changed what is visible: discrete exposure-phenotype pairings in which UV radiation, smoking, silica, and infectious triggers each act preferentially in particular subgroups. Exposures such as psychosocial stress and prenatal tobacco smoke appear to confer risk more broadly across the disease spectrum, though whether this reflects genuinely nonspecific effects or insufficient power to detect MSA-specific associations within these categories remains unresolved. Establishing that these associations exist is, however, only the first step. The subsequent questions concern when in the lifespan exposures exert their effects, and through which mechanisms [89].

The age at which exposures operate is itself a structuring variable. In adult-onset disease, occupational inhalational exposures and cigarette smoking have been associated with disease risk; in IIM, the evidence points towards gestational and early-life tobacco smoke exposure. Certain exposures, including UV radiation and psychosocial stress, have been implicated across age groups, suggesting that the relevant triggers may differ by age even where the broader exposure-phenotype framework applies throughout the lifespan.

A shared immunogenetic pattern is apparent across exposure-associated subtypes. In both vaccine-triggered and silicone implant-associated IIM, HLA-DRB1\*03:01, the principal genetic risk factor for spontaneous IIM, is not only absent as a risk allele but appears protective or underrepresented, with distinct alleles (DQA1\*03:03 and DQA1\*01:02, respectively) characterising each phenotype [37<sup>■</sup>,41,42]. This suggests that potent environmental triggers may act via different genetic pathways than ordinarily required for idiopathic disease initiation. Patients with exposure-associated IIM may not carry the HLA markers typical of idiopathic disease. Implant-associated myositis is rare and shows a distinct HLA profile, warranting a low index of suspicion in recipients with a compatible HLA type rather than population-level screening or advice against implantation.

Disease onset follows an MSA-specific seasonal pattern: ASyS autoantibody-positive patients cluster

**Table 2.** Comparison of environmental exposures in idiopathic inflammatory myopathies (IIM) and systemic lupus erythematosus (SLE)

| Exposure                                | Idiopathic inflammatory myopathies                                                                                                                                                                                                                                                           | Systemic lupus erythematosus                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| External exposures                      |                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                            |
| UV radiation/<br>latitudinal Clustering | Well established as trigger for DM/JDM; MSA-specific clustering with DM autoantibodies (anti-TIF1- $\gamma$ , anti-Mi-2, anti-MDA5). Higher individual UV exposure associated with DM onset, flare, and anti-MDA5-positive JDM. Latitudinal gradients in MSA distribution documented [13–17] | Implicated in SLE flares via ROS generation; UV exposure upregulates type I interferons in SLE skin and induces keratinocyte apoptosis, leading to surface translocation of SLE autoantigens; susceptibility amplified in individuals with impaired oxidative detoxification capacity. [90–94]                                                                                                             |
| Other geoclimatic factors               | MSA-specific seasonal clustering noted: ASyS antibody-positive patients cluster in spring, anti-MDA5-positive patients predominantly in autumn and winter, and MSA-negative adult patients in summer. [23,24,25 <sup>■</sup> ,26]                                                            | Seasonal peaks in disease activity documented in spring/summer, driven by photosensitive rash and arthritis; autumn rise in antidsDNA noted. No autoantibody-level subgroup structure identified. [95,96]                                                                                                                                                                                                  |
| Smoking                                 | Cigarette smoking amplifies anti-Jo-1 and ASyS risk through a gene-environment interaction with HLA-DRB1*03:01; protective for anti-TIF1- $\gamma$ autoantibodies. Associated with overlap myositis and extra-muscular manifestations including ILD and cardiac involvement [28–30]          | Cigarette smoking is consistently associated with incident SLE risk, with a particularly strong association in the antidsDNA positive subgroup. Active smoking is also associated with higher disease activity. [91,92,97]                                                                                                                                                                                 |
| Air pollution                           | CADM prevalence correlates with fixed-point airborne emission sources; residential proximity to major roadways associated with IIM prevalence, with the largest effect in IBM; SO <sub>2</sub> exposure associated with JDM hospitalisation. [27,31,32]                                      | Exposure to air pollutants (PM <sub>2.5</sub> , PM <sub>10</sub> , NO <sub>2</sub> , and NO <sub>x</sub> ) and polycyclic aromatic hydrocarbons is associated with incident SLE risk; individuals with high genetic susceptibility and high air pollution exposure show the greatest risk. PM <sub>2.5</sub> has additionally been associated with short-term variation in SLE disease activity [92,98,99] |
| Vaccines                                | Reported in association with multiple vaccine types including COVID-19; population-level data have not established a significant increase in IIM incidence. Distinct immunogenetic profile from spontaneous disease identified. [35,37 <sup>■</sup> ,38,39,40 <sup>■</sup> ]                 | Infrequently reported following multiple vaccine types including COVID-19 mRNA vaccines; not confirmed in epidemiological studies or case-control data. [91,100]                                                                                                                                                                                                                                           |
| Internal exposures                      |                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                            |
| Pregnancy and early life exposures      | Gestational tobacco smoke and occupational inhalational exposures have been associated with JDM onset; early household smoke exposure increases JIIM risk. Twin studies demonstrate MSA discordance between affected and unaffected twins. [44 <sup>■</sup> ,45,49]                          | Maternal farm work and pesticide exposure during pregnancy associated with SLE risk; childhood residential pesticide exposure additionally implicated. Peripartum flares are well documented in established SLE [101]                                                                                                                                                                                      |
| Psychosocial stress                     | Stressful life events, particularly job loss and financial difficulty, have been associated with IIM onset and disease flare [50 <sup>■</sup> ,51]                                                                                                                                           | PTSD, depression, childhood abuse, and stressful life events have each been associated with incident SLE risk across multiple large cohort studies. Sleep disturbance and inadequate sleep duration (<7 h) has been associated with the development of SLE [102,103]                                                                                                                                       |
| Occupational exposures                  |                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                            |
| Silica                                  | Associated with DM and overlap myositis, with an additive risk of lung disease when combined with smoking. [53 <sup>■</sup> ,54]                                                                                                                                                             | Well established risk factor with dose-response associations across intensity and duration of exposure; elevated risk documented across construction, mining, and quarrying occupations. [91,92,104]                                                                                                                                                                                                       |
| Organic solvents                        | Isolated evidence suggests association between solvent exposure and IIM, with higher prevalence observed in IBM than in other subtypes [30,53 <sup>■</sup> ].                                                                                                                                | Fragmented evidence has found association between solvents (paints, thinners) and SLE [91,92,104]                                                                                                                                                                                                                                                                                                          |
| Heavy metals                            | Increased risk of overlap myositis and lung disease. [53 <sup>■</sup> ]                                                                                                                                                                                                                      | Mercury exposure has been associated with elevated ANA levels and SLE risk; evidence for other heavy metals remains largely experimental. [91,92,104]                                                                                                                                                                                                                                                      |

Table 2 (Continued)

| Exposure             | Idiopathic inflammatory myopathies                                                                                                                                                                                                                                                                  | Systemic lupus erythematosus                                                                                                                                                                                                           |
|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Infectious exposures |                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                        |
| Viruses              | SARS-CoV-2 demonstrates molecular mimicry and strong overlap with anti-MDA5 DM, with increased flare risk, ILD, and mortality. CVB1 and HCV show persistent viral presence in IBM muscle. WNV and HIV induce MHC class I upregulation and PM-like inflammation [70,71,72,74–77,80–82 <sup>■</sup> ] | EBV is an established risk factor; prospective data link EBV IgG to subsequent SLE risk. SARS-CoV-2 associated with new-onset SLE in case reports. Evidence for CMV, parvovirus B19, HTLV-1, and HIV remains inconsistent. [91,92,105] |
| Bacteria             | Pharyngitis and GI infections associated with JIIM onset and DM flare. Gut microbiome dysbiosis consistently identified across IIM subtypes with MSA-specific patterns in IMNM and ASyS. [66 <sup>■</sup> ,67 <sup>■</sup> ,68]                                                                     | Gut microbiome dysbiosis influences ANA production and is associated with SLE risk; <i>H. pylori</i> may be protective in SLE [92]                                                                                                     |
| Parasites            | Limited evidence; <i>Trypanosoma cruzi</i> induces PM-like histology with MHC class I upregulation in experimental models [109]                                                                                                                                                                     | <i>Toxoplasma gondii</i> implicated as a risk factor, however, mechanistic evidence remains limited [106].                                                                                                                             |
| Other exposures      |                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                        |
|                      | Silicone breast implants (limited evidence) [41,42]                                                                                                                                                                                                                                                 | Alcohol (protective) [91]; Pesticides (risk) [92]; Hair dye and cosmetic products [92]; PFAS exposure [107]; Combined oral contraceptive pills [108]                                                                                   |

ANA, antinuclear antibody; ASyS, antisynthetase syndrome; CADM, clinically amyopathic dermatomyositis; CMV, cytomegalovirus; CVB1, Coxsackie B1 virus; DM, dermatomyositis; EBV, Epstein-Barr virus; GI, gastrointestinal; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HTLV, human T-lymphotropic virus; IBM, inclusion body myositis; ICI, immune checkpoint inhibitor; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; IMNM, immune-mediated necrotising myopathy; JDM, juvenile dermatomyositis; JIIM, juvenile idiopathic inflammatory myopathy; MDA5, melanoma differentiation-associated protein 5; MHC, major histocompatibility complex; MSA, myositis-specific autoantibody; PFAS, per- and polyfluoroalkyl substances; PM, polymyositis; PTSD, posttraumatic stress disorder; PUFA, polyunsaturated fatty acids; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus; UV, ultraviolet; WNV, West Nile virus; WNV, West Nile virus.

in spring, and anti-MDA5-positive patients predominantly between October and March [23,24,25<sup>■</sup>], whilst MSA-negative adult patients show a summer clustering [26]. This suggests that environmental triggers may act within defined time windows rather than uniformly across the year, though whether the relevant variable is the seasonal trigger itself or a window of host susceptibility remains unclear. Similarly, whilst UV irradiance and latitude account for some of the geographic variation in MSA distributions [13], the observation in RA that solar cycles and geomagnetic activity contribute to incidence variation independently of UV [22] raises the possibility that geoclimatic determinants of IIM are not fully captured by UV exposure alone.

The JIIM literature extends this question across the lifespan. The most consistently implicated exposures in juvenile disease operate before or shortly after birth: paternal and maternal smoking during pregnancy, maternal occupational inhalational exposures, and early childhood ozone exposure each associate with JIIM onset across independent cohorts [44<sup>■</sup>,45]. Twin discordance in MSA positivity supports the role of environmental rather than purely genetic factors in autoantibody development [49]. Taken together, these findings suggest that the

critical exposure window in JIIM may precede clinical disease by years.

The subtype-specificity of environmental associations carries practical implications. In ASyS, the convergence of occupational inhalational exposures, smoking, HLA-DRB1\*03:01 carriage, and lung-predominant disease raises the possibility of an identifiable high-risk population; prospective MSA surveillance in occupationally-exposed smoking individuals with this genetic background would represent a plausible predisease detection strategy, though this remains to be evaluated [52,53<sup>■</sup>]. The observed rise in anti-MDA5-positive IIM following SARS-CoV-2 infection, frequently presenting with rapidly progressive ILD, suggests a potential role for MSA testing in patients with new-onset ILD in whom a preceding viral trigger is suspected [71<sup>■</sup>,72].

The environmental triggers of IIM and systemic lupus erythematosus (SLE) overlap considerably across exposure domains, making SLE the most instructive SARD comparator; the findings are summarised in Table 2. The comparison reveals that identical exposures produce distinct immunological outcomes depending on serological and genetic context. UV radiation is a shared exposure across both conditions; it is strongly implicated in SLE pathogenesis and shapes

MSA-specific latitudinal gradients in IIM. Epstein-Barr Virus is an established infectious trigger in SLE, whilst SARS-CoV-2 and Coxsackie B1 viruses carry substantial mechanistic evidence in IIM. This pattern supports condition-specific and serologically stratified study designs in future environmental research [89,110].

Several methodological limitations constrain the current evidence base. Retrospective study designs predominate, lack of healthy control populations for comparison, small sample sizes, inconsistent MSA ascertainment in older cohorts, and direct biological quantification of exposures is largely absent. Inconsistent subsetting is another limitation, as IMNM and ASyS were previously not separated from PM and DM and continue to have changes to their definitions which can contribute to changes in observed risk factors.

Prospective research in this field requires, as a prior step, the identification of populations at sufficient risk to make such designs feasible; occupationally-exposed HLA-DRB1\*03:01 carriers represent one such candidate group. Future research priorities include defining critical exposure windows across the lifespan, characterising dose-response relationships within MSA-defined subgroups, and quantifying cumulative exposures through validated assays and biosensors. The potential contributions of climate change, worsening pollution, and lifestyle factors to the frequency and severity of IIM represent an emerging dimension that environmental research in the field has yet to fully engage with [111].

## CONCLUSION

Environmental exposures in IIM act in a largely subtype-specific manner, shaped by genetic background and serological context. The characterisation of MSAs and preliminary evidence on environmental exposures forms the basis on which prospective, exposure-phenotype stratified research can now be meaningfully designed.

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## Conflicts of interest

*There are no conflicts of interest.*

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# Pathogenesis of autoantibodies in inflammatory myopathies

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## Purpose of review

While autoantibodies targeting extracellular antigens, such as those in myasthenia gravis, are established mediators of disease, autoantibodies recognizing intracellular antigens in inflammatory myopathies have traditionally been considered nonpathogenic. This review examines evidence challenging that paradigm and highlights recent advances in understanding the origins and pathogenic functions of autoantibodies in myositis.

## Recent findings

In several forms of myositis, immunoglobulin accumulates within muscle fibers in a distribution mirroring that of the cognate autoantigen. Muscle biopsies demonstrate functional consequences consistent with disruption of the targeted autoantigen, as well as secondary muscle damage and inflammation. These effects are reproduced in vitro by forced autoantibody internalization. Local plasma cells may facilitate this process by releasing cytoplasmic contents into neighboring cells, including immunoglobulin RNA. In paraneoplastic dermatomyositis, genetic alterations of the targeted autoantigen are frequently identified in tumors, suggesting that immune responses to somatic tumor mutations may initiate autoantibody production. In immune checkpoint inhibitor-associated myositis, autoantibodies may contribute to disease by acting as chemoattractants for drug-activated T cells.

## Summary

Recent findings support a direct pathogenic role for autoantibodies in several autoantibody-defined myositis subtypes and provide new insights into their origins and contribution to immune-mediated muscle injury, while also suggesting broader roles.

## Keywords

autoantibody internalization, cancer-associated myositis, immune checkpoint inhibitor myopathy, immune-mediated necrotizing myopathy, inflammatory myopathies

## INTRODUCTION

Autoantibodies are a defining feature of the inflammatory myopathies (IMs), a heterogeneous group of autoimmune muscle diseases that includes dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM), antisynthetase syndrome (ASyS), and overlap myositis (OM) [1]. In contrast to disorders such as myasthenia gravis (MG), in which autoantibodies target extracellular proteins and directly mediate tissue dysfunction, most myositis autoantibodies recognize intracellular antigens [2]. Because antibodies are generally thought to have limited access to the intracellular compartment, these autoantibodies have traditionally been considered diagnostic biomarkers rather than pathogenic effectors.

This view is increasingly being challenged. Recent studies have demonstrated intracellular accumulation of immunoglobulin in affected muscle fibers, colocalization with the corresponding autoantigen, molecular

signatures consistent with disruption of autoantigen function, and reproduction of these effects after experimental intracellular delivery of patient-derived immunoglobulin [3<sup>••</sup>,4<sup>••</sup>,5,6]. Together, these observations support a model in which autoantibodies directly contribute to disease pathogenesis in several forms of myositis.

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## KEY POINTS

- Myositis autoantibodies targeting intracellular antigens are increasingly recognized as pathogenic effectors rather than merely diagnostic biomarkers.
- Evidence supporting their pathogenicity includes intracellular immunoglobulin accumulation, colocalization with cognate autoantigens, disruption of autoantigen function with downstream tissue damage and inflammation, and reproduction of these effects in experimental models.
- Distinct myositis subtypes exhibit antibody-driven mechanisms linked to disruption of autoantigen function, including transcriptional derepression in anti-Mi2, RNA-processing defects in anti-PM/Scl, interferon activation in anti-MDA5, and lipid accumulation in anti-HMGCR.
- In cancer-associated dermatomyositis, somatic tumor alterations affecting autoantigens such as TIF1 $\gamma$  may trigger autoantibody responses that subsequently target normal tissues.
- These findings support therapeutic strategies aimed at lowering pathogenic autoantibody burden, either by reducing autoantibody production or accelerating antibody clearance, including intravenous immunoglobulin, FcRn inhibitors, B-cell- and plasma-cell-targeted therapies, and B-cell lineage-directed chimeric antigen receptor (CAR) T-cell approaches.

At the same time, important advances have been made in understanding how autoantibodies arise. Studies of cancer-associated myositis have identified somatic genetic alterations affecting the targeted autoantigen within tumors, providing strong support for neoantigen-driven autoimmunity [7<sup>••</sup>,8,9].

This review summarizes current evidence regarding the origins and pathogenic functions of autoantibodies in inflammatory myopathies (Fig. 1, Table 1). We contrast classical extracellular antibody-mediated mechanisms with emerging evidence supporting intracellular pathogenicity and discuss the implications of these findings for disease classification and therapy.

## ORIGINS OF AUTOANTIBODIES

Understanding how autoantibodies develop is essential for identifying preventive strategies and designing interventions that can be applied before irreversible tissue injury occurs. Although the precise mechanisms remain incompletely understood, recent evidence provided important clues.

A longstanding hypothesis proposes that autoimmunity arises when tissue injury releases

intracellular proteins into the extracellular environment, exposing previously hidden antigens to the immune system. While tissue damage may amplify ongoing immune responses, this explanation alone is insufficient. Many conditions associated with chronic tissue injury do not result in autoimmune disease, and the remarkable specificity of myositis autoantibodies is difficult to reconcile with a nonspecific response to released cellular contents.

An alternative and increasingly supported model is molecular mimicry or neoantigen-driven immunity. In this framework, immune responses initially directed against foreign or altered proteins become cross-reactive with structurally related self-antigens. One of the strongest examples comes from cancer-associated autoimmunity. Studies of systemic sclerosis demonstrated that tumors from patients with anti-RNA polymerase III antibodies frequently harbor somatic mutations affecting the targeted autoantigen, suggesting that antitumor immunity may trigger autoantibody formation [10].

Similar observations have now been made in dermatomyositis. Anti-TIF1 $\gamma$  autoantibodies are strongly associated with cancer, and tumors from affected patients frequently contain somatic mutations, loss of heterozygosity, or other genetic alterations involving TIF1 $\gamma$  [8,9]. Independent studies have confirmed these findings and extended them to additional cancer-associated myositis autoantibodies [7<sup>••</sup>]. Collectively, these observations suggest that altered tumor proteins may serve as initiating antigens that trigger immune responses which subsequently spread to the corresponding self-protein expressed in normal tissues.

Genetic susceptibility is another major determinant of autoantibody development. The strongest genetic associations in myositis involve HLA class II alleles and correlate more closely with autoantibody specificity than with clinical phenotype. A classic example is the association between HLA-DRB1\*11:01 and anti-HMGCR myopathy [11].

Traditionally, these associations have been interpreted as evidence for autoreactive CD4<sup>+</sup> T-cell responses. However, HLA class II molecules are also central to B-cell survival. Autoreactive B cells that efficiently internalize an autoantigen through their B-cell receptor can present peptides derived from that antigen to helper T cells. B cells expressing HLA molecules capable of presenting these peptides more effectively may receive stronger survival signals and preferentially differentiate into plasma cells. Thus, HLA associations may reflect not only T-cell susceptibility but also a congenital survival advantage conferred to autoreactive B-cell clones.

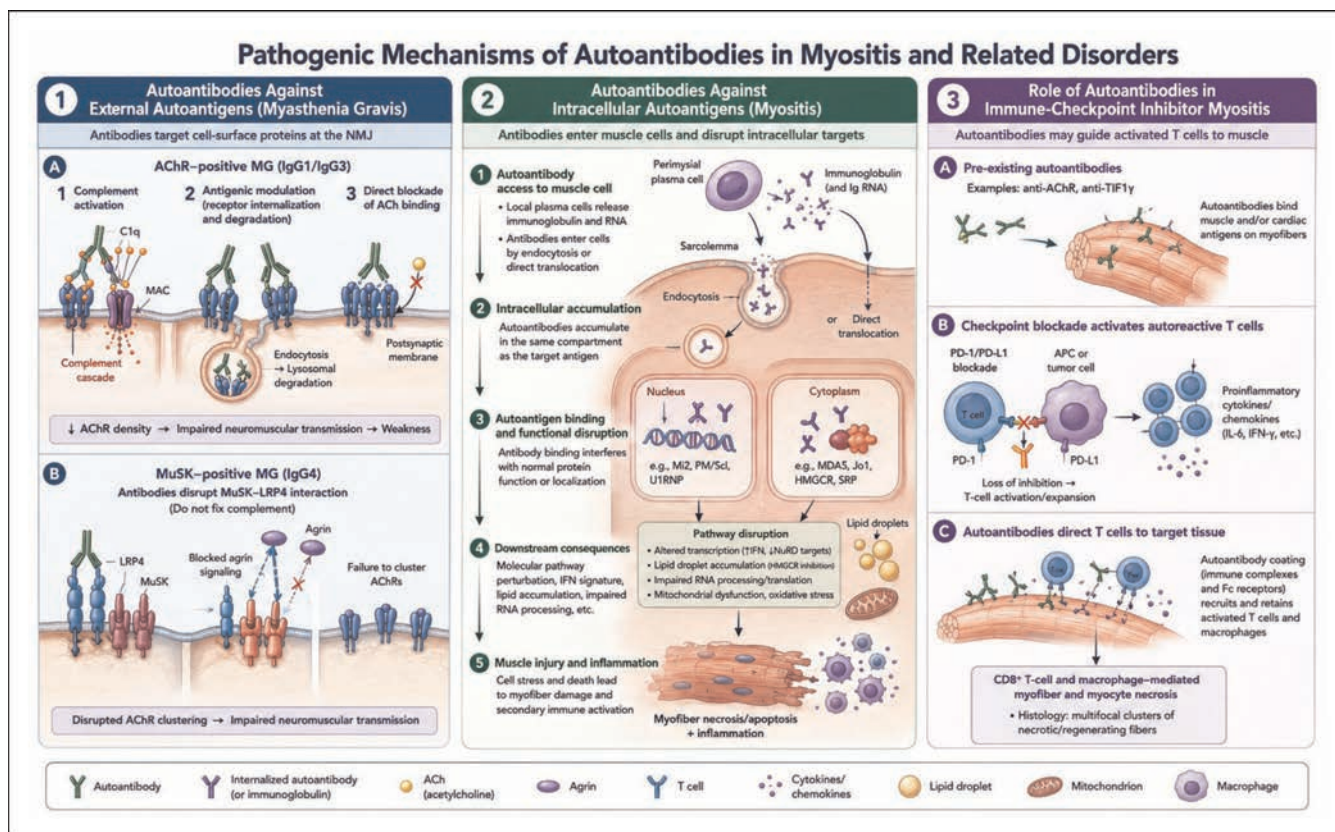


**FIGURE 1.** Three distinct mechanisms by which autoantibodies contribute to muscle diseases: (1) classical extracellular autoantibodies in myasthenia gravis act at the neuromuscular junction; (2) autoantibodies in myositis enter muscle cells and disrupt intracellular proteins, leading to downstream functional alterations and muscle injury; (3) in immune-checkpoint inhibitor myositis, preexisting autoantibodies may help recruit and retain activated T cells at muscle, directing and amplifying T-cell-mediated tissue damage.

## EXTRACELLULAR AUTOANTIBODIES: LESSONS FROM MYASTHENIA GRAVIS

MG provides the prototypical example of antibody-mediated disease and serves as a useful contrast to inflammatory myopathies [2].

In acetylcholine receptor (AChR)-positive MG, immunoglobulin G1 (IgG1), and IgG3 autoantibodies target the extracellular domain of the receptor at the neuromuscular junction [2]. Disease results from three complementary mechanisms: activation of the classical complement pathway, accelerated receptor internalization and degradation, and direct blockade of acetylcholine binding. Together, these processes reduce receptor density and impair neuromuscular transmission.

In MuSK-positive MG, the mechanism differs substantially. Predominantly IgG4 autoantibodies disrupt interactions between MuSK and LRP4, preventing agrin-mediated clustering of acetylcholine receptors. Because IgG4 antibodies do not efficiently activate complement, pathology results primarily from disruption of signaling pathways rather than inflammatory injury [2].

The success of complement inhibitors in MG reflects the direct pathogenic role of circulating antibodies [12]. These observations are particularly relevant when contrasting them with inflammatory myopathies where complement inhibitors have not shown efficacy [13]. If pathogenic mechanisms differ fundamentally, therapeutic responses should also differ.

## INTRACELLULAR AUTOANTIBODIES IN MYOSITIS

The possibility that antibodies can enter living cells and alter intracellular function was first proposed nearly five decades ago. In 1978, Alarcón-Segovia *et al.* reported that antiribonucleoprotein antibodies could enter living mononuclear cells [14]. Although provocative, these findings were difficult to reconcile with prevailing concepts of antibody biology and remained largely unexplored [15].

Recent studies have revived interest in this mechanism by providing several converging lines of evidence [3<sup>xx</sup>,4<sup>xx</sup>,5,16,17<sup>xx</sup>,18<sup>xx</sup>]. First, immunoglobulin

**Table 1.** Overview of the key mechanistic differences across inflammatory myopathies, myasthenia gravis, and immune checkpoint inhibitor myopathy

| Feature                       | Inflammatory myopathies (myositis)                                                     | Myasthenia gravis                                                   | ICI myopathy                                                                                         |
|-------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Primary target                | Intracellular antigens (cytoplasmic/nuclear)                                           | Cell-surface antigens at NMJ (AChR, MuSK, LRP4)                     | Muscle fibers (via T-cell attack)                                                                    |
| Key autoantibodies            | Mi2, MDA5, NXP2, TIF1 $\gamma$ , HMGCR, SRP, Jo1, PM/Scl                               | Anti-AChR (IgG1/IgG3), anti-MuSK (IgG4)                             | AChR, TIF1 $\gamma$                                                                                  |
| Dominant effector mechanism   | Autoantibody internalization $\rightarrow$ intracellular target disruption             | Complement activation, antigenic modulation, receptor blockade      | CD8+ T-cell and macrophage-mediated necrosis probably attracted by autoantibodies against the muscle |
| Complement role               | Present but noncontributory based on results of clinical trials                        | Central in AChR-MG (MAC at NMJ); absent in MuSK-MG                  | Not believed to be a primary mechanism                                                               |
| Complement inhibitor efficacy | Failed in IMNM (zilucoplan phase 2)                                                    | Effective in AChR-MG (eculizumab, ravulizumab, zilucoplan approved) | Not applicable                                                                                       |
| Interferon signature          | Type I IFN (DM); Type II IFN (ASyS, IBM)                                               | Not prominent                                                       | Type II IFN (ICI-MYO1); Type I IFN (ICI-DM); IL-6 in all subtypes                                    |
| Histopathology                | Perifascicular atrophy (DM); scattered necrosis (IMNM); perimysial inflammation (ASyS) | NMJ structural simplification; muscle fibers intact                 | Multifocal clusters of necrotic/regenerating fibers                                                  |
| FcRn inhibitor efficacy       | Effective (efgartigimod phase 2/3)                                                     | Approved (efgartigimod, rozanolixizumab, nipocalimab)               | Not established                                                                                      |
| Emerging therapies            | CAR-T, BCMA                                                                            | Complement inhibitors, FcRn inhibitors                              | JAK inhibitors, CTLA4                                                                                |

NMJ, neuromuscular junction.

accumulates intracellularly in muscle biopsies from patients with multiple myositis subtypes. Second, the distribution of immunoglobulin closely mirrors that of the corresponding autoantigen. Third, affected tissues exhibit molecular changes consistent with loss or alteration of autoantigen function. Fourth, experimental intracellular delivery of patient-derived immunoglobulin reproduces these abnormalities in cultured cells. Finally, plasma cells within affected muscle appear capable of transferring immunoglobulin-associated material to neighboring cells, potentially providing a mechanism for antibody entry.

Related to this point, several nonmutually exclusive mechanisms have been proposed to mediate autoantibody internalization independently of local plasma cell transfer, including Fc receptor-mediated uptake and brush border myosin 1-dependent entry, as described for antidsDNA and anti-U1RNP antibodies [3<sup>22</sup>,4<sup>22</sup>,6,14,15]. However, these mechanisms alone are unlikely to explain the limited intracellular uptake and functional effects observed following passive antibody exposure in vitro or the tissue specificity of diseases with autoantibodies targeting ubiquitously expressed

intracellular autoantigens. By contrast, local transfer from tissue-resident plasma cells could account for both observations. In this model, intracellular delivery would require the active packaging and transfer of immunoglobulin-containing material by plasma cells rather than passive exposure to extracellular antibodies, while tissue specificity would arise because plasma cell survival, maturation, and persistence depend on tissue-specific microenvironments that differ markedly among affected organs such as muscle, lung, and skin. Nevertheless, the mechanisms by which autoantibodies gain intracellular access remain an active area of investigation.

Together, these findings support a model in which intracellular autoantibodies contribute directly to tissue injury.

### Dermatomyositis

Among dermatomyositis autoantibodies, the strongest evidence for pathogenic intracellular activity exists for anti-Mi2 and anti-MDA5 antibodies [3<sup>22</sup>,4<sup>22</sup>,5,19<sup>22</sup>,20<sup>22</sup>].

Mi2 is a component of the nucleosome remodeling deacetylase (NuRD) complex, which regulates chromatin accessibility and transcriptional repression. Muscle biopsies from anti-Mi2-positive patients demonstrate intranuclear accumulation of immunoglobulin together with overexpression of genes normally suppressed by the NuRD complex [3<sup>''</sup>,4<sup>''</sup>]. Experimental delivery of purified IgG from anti-Mi2 patients into cultured myoblasts reproduces these transcriptional abnormalities, supporting a direct functional effect [3<sup>''</sup>,4<sup>''</sup>].

Recent work has further expanded understanding of anti-Mi2 antibodies by demonstrating recognition of conserved plant homeodomain (PHD) zinc finger motifs present in multiple proteins [19<sup>''</sup>,20<sup>''</sup>]. In addition to Mi-2, these autoantibodies can bind the PHD domains of multiple proteins such as AIRE, SP140L, and TIF1 $\gamma$  (whereas anti-TIF1 $\gamma$  autoantibodies bind non-PHD regions of TIF1 $\gamma$ ). This observation highlights an important principle: antibodies recognize three-dimensional structural epitopes, which may be shared by different proteins. Consequently, a single antibody may recognize multiple proteins that share a common structural motif, while distinct antibodies can bind to different epitopes within the same protein. The pathogenic relevance of this broader reactivity remains an active area of investigation.

Interestingly, epitope mapping of anti-Mi-2 autoantibodies showed that, although most target the PHD domain, some also bind other regions of PHD-containing proteins [19<sup>''</sup>,20<sup>''</sup>]. This may explain why some patients remain seropositive despite achieving drug-free remission, as antibodies directed against nonpathogenic epitopes can lead to persistent or false-positive autoantibody detection [21]. Likewise, many patients remain autoantibody-positive at low titers after achieving remission with treatment, suggesting that a threshold of pathogenic autoantibody activity is required for clinical disease. These observations likely reflect broader principles applicable to other autoantibody-mediated diseases.

Anti-MDA5 antibodies target a cytoplasmic RNA sensor involved in antiviral immunity. MDA5 detects double-stranded RNA and activates signaling pathways that culminate in type I interferon production. In anti-MDA5 dermatomyositis, immunoglobulin accumulates within the cytoplasm of muscle fibers, and intracellular delivery of purified IgG from patients induces marked activation of interferon-responsive genes [4<sup>''</sup>]. These findings suggest that intracellular autoantibody binding to MDA5 activates the protein, inducing the characteristic interferon signature observed in this disease.

Evidence for anti-NXP2 and anti-TIF1 $\gamma$  antibodies remains less definitive [4<sup>''</sup>]. Both proteins participate in transcriptional regulation and suppression of

interferon signaling, making them biologically plausible pathogenic targets. However, experimental studies have not yet consistently demonstrated functional consequences following intracellular antibody delivery. In anti-NXP2 disease, abnormal redistribution of NXP2 from the nucleus to the cytoplasm has been reported, raising the possibility that antibodies may alter protein localization. Additional studies are needed to clarify these mechanisms.

### Immune-mediated necrotizing myopathy

IMNM is characterized by autoantibodies against HMGCR or SRP and currently provides some of the strongest evidence supporting intracellular antibody pathogenicity [4<sup>''</sup>,17<sup>''</sup>,18<sup>''</sup>].

HMGCR is the rate-limiting enzyme of cholesterol synthesis and the pharmacological target of statins. Muscle biopsies from anti-HMGCR-positive patients demonstrate cytoplasmic immunoglobulin accumulation together with prominent lipid droplet deposition. Recent studies have shown that anti-HMGCR antibodies inhibit HMGCR activity, leading to intracellular lipid accumulation and myofiber necrosis [4<sup>''</sup>,17<sup>''</sup>].

Experimental systems have provided important mechanistic support. Intracellular delivery of anti-HMGCR immunoglobulin into cultured muscle cells reproduces lipid accumulation and cellular injury [17<sup>''</sup>,18<sup>''</sup>]. Similarly, passive transfer studies have demonstrated reduced muscle strength and increased muscle pathology following exposure to anti-HMGCR antibodies [22].

Anti-SRP antibodies target the signal recognition particle, a ribonucleoprotein complex required for translocation of newly synthesized proteins into the endoplasmic reticulum. Muscle biopsies demonstrate cytoplasmic immunoglobulin accumulation consistent with localization of the target antigen [4<sup>''</sup>]. Animal models further demonstrate muscle weakness and cardiac abnormalities following antibody exposure [22].

Historically, complement activation was proposed as a major pathogenic mechanism in IMNM because membrane attack complex deposition can be detected on muscle fibers [22,23]. However, the failure of complement inhibition in clinical trials suggests that complement activation is unlikely to represent the primary disease mechanism [13]. Instead, complement deposition may reflect secondary injury occurring after intracellular pathogenic processes have already been initiated.

### Antisynthetase syndrome

Antisynthetase (ASyS) is characterized by antibodies against aminoacyl-tRNA synthetases, most commonly

Jo1. These enzymes play essential roles in protein translation by attaching amino acids to their corresponding transfer RNAs.

Several observations support direct pathogenicity of anti-Jo1 antibodies [4<sup>22</sup>]. Immunoglobulin colocalizes with the target antigen in cultured cells, and intracellular delivery of patient-derived purified IgG reproduces a substantial portion of the disease-associated transcriptional signature. Furthermore, many of these changes overlap with those induced by pharmacological inhibition of Jo1, suggesting that antibody binding interferes with normal protein function.

This finding builds on seminal observations from the 1980s demonstrating that anti-Jo-1 autoantibodies can impair the enzymatic function of histidyl-tRNA synthetase [24,25].

### Overlap myositis and anti-Ro52 autoantibodies

Overlap myositis includes several autoantibody-defined syndromes, among which anti-PM/Scl disease provides particularly compelling evidence for intracellular pathogenicity.

PM/Scl autoantigens are components of the nuclear RNA exosome complex, which degrades non-coding RNAs, including divergent and antisense transcripts. Muscle biopsies from anti-PM/Scl-positive patients demonstrate nucleolar immunoglobulin accumulation corresponding to the location of the RNA exosome complex. Transcriptomic analyses reveal accumulation of RNA species normally degraded by the exosome, suggesting impaired complex function. These abnormalities can be reproduced experimentally through intracellular delivery of purified patient-derived IgG [3<sup>22</sup>,4<sup>22</sup>].

Anti-U1RNP antibodies also provide evidence for intracellular antibody accumulation. Earlier studies demonstrated nuclear localization of immunoglobulin in living cells, and more recent observations have confirmed similar findings in skeletal muscle [3<sup>22</sup>,14]. However, direct evidence linking antibody binding to disruption of RNA splicing remains limited.

Anti-Ro52 antibodies deserve separate consideration because they frequently coexist with other myositis autoantibodies and are associated with more severe disease, particularly interstitial lung disease [26,27]. Ro52 functions as an intracellular Fc receptor that promotes degradation of antibody-containing immune complexes through ubiquitination pathways [28,29]. Autoantibodies directed against Ro52 can inhibit this activity. Consequently, anti-Ro52 antibodies may amplify disease by preventing degradation of other pathogenic intracellular

antibodies, thereby enhancing their persistence and biological effects.

### THERAPEUTIC IMPLICATIONS

The intracellular autoantibody model has important therapeutic implications. Most importantly, it predicts that treatments directed solely against extracellular effector mechanisms may have limited efficacy. The negative zilucoplan trial in IMNM is consistent with this prediction [13].

In contrast, therapies that reduce autoantibody production or accelerate antibody clearance would be expected to provide benefit. Intravenous immunoglobulin (IVIG), which is effective in several forms of myositis [30,31], acts in part by blocking the neonatal Fc receptor (FcRn), thereby enhancing IgG clearance, and also engage the inhibitory FcγRIIb receptor on plasma cells, potentially suppressing antibody production. Rituximab targets B-cell precursors of antibody-secreting cells and has demonstrated clinical utility despite mixed trial results.

FcRn inhibitors represent another promising strategy because they reduce circulating immunoglobulin concentrations irrespective of antigen specificity. Their success in MG has stimulated evaluation in inflammatory myopathies, with preliminary data showing encouraging results [32<sup>22</sup>].

Perhaps most strikingly, emerging experience with CD19-directed CAR T-cell therapy [33] and BCMA-directed CAR T-cell therapy [34<sup>22</sup>], together with BCMA-targeted monoclonal antibody therapies [35<sup>22</sup>], has demonstrated dramatic responses in severe autoimmune diseases, including myositis. These approaches directly target the cellular source of pathogenic antibodies and may ultimately provide durable disease control.

Recognition that specific autoantibodies disrupt defined biological pathways also creates opportunities for mechanism-based therapies. For example, supplementation of downstream metabolites of the mevalonate pathway, previously investigated in limb-girdle muscular dystrophy associated with HMGCR mutations [36], has been proposed as a potential therapeutic approach in anti-HMGCR disease. Similar approaches may become possible as the functional consequences of additional autoantibodies are clarified.

### IMMUNE CHECKPOINT INHIBITOR MYOPATHY

Immune checkpoint inhibitor (ICI)-associated myositis differs fundamentally from conventional myositis. Blockade of PD-1, PD-L1, or CTLA-4 pathways disrupts immune tolerance and promotes autoreactive T-cell responses. Histopathology is dominated

by T cells and macrophages rather than autoantibody-mediated changes [37–39].

Nevertheless, autoantibodies may still contribute to disease. Muscle-directed antibodies, such as anti-AChR, anti-TIF1 $\gamma$ , and antistriational antibodies, are frequently detectable in patients who go on to develop immune checkpoint inhibitor-induced myositis. Anti-AChR and antistriational antibodies are each detected in approximately 40–50% of patients, while additional muscle-directed autoantibodies are present in smaller subsets of patients, resulting in approximately 80% of patients harboring at least one muscle-directed autoantibody [37–40]. These autoantibodies are present prior to the initiation of therapy and typically do not cause clinically apparent disease in the absence of immune checkpoint inhibition [37–40]. Following immune checkpoint blockade, however, these preexisting antibodies may help direct activated immune cells toward specific tissues [37,40].

Several observations support this possibility. Patients with anti-AChR antibodies treated with immune checkpoint inhibitors frequently develop muscle and cardiac involvement resembling myasthenia gravis despite often lacking the classical electrophysiological features of neuromuscular junction dysfunction [37,39]. This observation is consistent with studies indicating that, unlike in classical myasthenia gravis, anti-AChR autoantibodies in ICI-associated disease do not impair ligand–receptor function [41]. Moreover, myositis and myocarditis occur at exceptionally high rates in patients with thymoma and anti-AChR antibodies receiving checkpoint inhibitors, [39] and a similar phenotype has also been described in patients with thymoma and high anti-AChR antibody titers in the absence of ICI exposure [42]. Finally, other autoimmune conditions associated to ICI have been also linked to preexisting tissue-specific autoantibodies [43,44].

Although alternative explanations remain possible, these findings suggest a model in which checkpoint inhibition provides the necessary T-cell activation, while preexisting autoantibodies contribute to tissue specificity by identifying target tissues for the activated immune response.

## CONCLUSION

The understanding of autoantibodies in inflammatory myopathies has evolved substantially during the past decade. Accumulating evidence indicates that several myositis autoantibodies directed against intracellular autoantigens are not merely biomarkers but active participants in disease pathogenesis. Intracellular accumulation, colocalization with target antigens, disruption of biological pathways, and reproducibility in experimental systems support

direct pathogenic roles for antibodies such as anti-Mi2, anti-MDA5, anti-HMGCR, anti-SRP, anti-Jo1, and anti-PM/Scl.

These findings challenge traditional concepts of antibody biology and expand the spectrum of mechanisms through which autoantibodies can cause disease. They also provide a framework for understanding therapeutic responses and identifying novel treatment strategies aimed at preventing antibody production, blocking intracellular antibody activity, or restoring autoantigen function.

Future studies will determine how broadly these mechanisms apply across autoimmune diseases and whether targeting intracellular autoantibody pathogenicity can improve outcomes for patients with myositis and related disorders.

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## Conflicts of interest

*There are no conflicts of interest.*

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# Myositis autoantibodies: from new specificities to new paradigms

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## Purpose of review

Myositis-specific autoantibodies have long been used to classify patients into clinically meaningful subsets; however, recent studies show that the field is moving beyond the simple question of which autoantibody is present. This review examines how emerging specificities, epitope architecture, autoantibody coexistence, pathogenic mechanisms, and detection platforms are reshaping the interpretation of myositis serology.

## Recent findings

Recent work has expanded the autoantibody repertoire through the identification of additional autoantibody specificities, multiprotein antigenic complexes, and transcriptional regulators. At the same time, epitope-level studies reveal that patients sharing the same autoantibody specificity may recognize different antigenic regions, with potential implications for phenotype, prognosis, and assay interpretation. Evidence also challenges the view of myositis autoantibodies as passive biomarkers: selected specificities may mediate complement-dependent muscle injury, amplify inflammatory circuits, or interfere with intracellular antigen function. Meanwhile, new detection platforms have not only improved discovery but also exposed limitations related to conformational epitopes, cross-reactivity, false seronegativity, and assay standardization.

## Summary

Novelty in myositis autoantibodies should be understood not only as new targets but also as new paradigms linking antigen structure, immune mechanisms, detection methods, and clinical actionability.

## Keywords

autoantibody pathogenicity, epitope diversity, idiopathic inflammatory myopathies, myositis autoantibodies, novel autoantibodies

## INTRODUCTION

The history of autoantibodies in idiopathic inflammatory myopathies (IIM) has evolved substantially over the past decades. Early myositis classification criteria, such as the Bohan and Peter classification criteria in 1975 were developed at a time when the existence and clinical significance of myositis autoantibodies were still unknown and could therefore not be incorporated into disease classification [1,2]. However, this perspective shifted with the identification of anti-Mi-2 as the first myositis-specific autoantibody (MSA) [3–5], marking the beginning of serological characterization in myositis (Fig. 1).

Nearly 50 years later, the myositis autoantibody repertoire has expanded to approximately 40 specificities, including ~30 MSAs, multiple myositis-associated autoantibodies (MAAs), and emerging co-reactivities (Fig. 1). Several of these autoantibodies are now recognized as key tools for patient stratification, organ-risk assessment, prognosis and prediction of treatment response (Supplementary Table 1, <https://links.lww.com/COR/A66>).

However, their clinical meaning cannot be reduced to the presence or absence of a single specificity. In this context, the term ‘specificity’ refers to the individual autoantigenic target recognized (e.g. histidyl-tRNA synthetase in anti-Jo-1), and not to the diagnostic specificity of the assay for myositis. Key challenges remain in interpreting subset

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## KEY POINTS

- Novel myositis autoantibodies extend beyond new specificities to encompass new paradigms of antigen recognition, pathogenicity, and clinical interpretation.
- Quantitative and longitudinal serology may refine risk assessment in selected autoantibody subsets (e.g. anti-MDA5, anti-Jo-1, anti-HMGCR, anti-SRP), although assay standardization and prospective validation remain required.
- Patients sharing the same autoantibody may differ in epitoperecognition, coexisting reactivities, prognosis, and organ-specific risk, supporting further serological stratification.
- Selected autoantibodies may act as pathogenic effectors or pathway amplifiers rather than passive biomarkers.

heterogeneity, coexisting reactivities, epitope diversity, and functional relevance. Thus, the concept of 'novelty' now encompasses beyond only new specificities. In this structured narrative review, we summarize how recent advances are shifting the field from autoantibody discovery toward broader paradigms in myositis autoantibody research.

## EXPANDING REPERTOIRE OF MYOSITIS AUTOANTIBODIES

The discovery of novel autoantibodies has progressively expanded the serological boundaries of IIM. Emerging autoantibodies have revealed previously unrecognized antigenic targets, challenged the concept of monospecific and truly seronegative disease, and uncovered additional layers of heterogeneity within established MSA-defined subsets.

### Novel anti-aminoacyl-tRNA synthetase: specificities identified since 2020

Anti-aminoacyl-tRNA synthetase autoantibodies (anti-ARS) define antisynthetase syndrome (ASyS), a distinct IIM subtype characterized by myositis, interstitial lung disease (ILD), mechanic's hands, Raynaud's phenomenon, and nonerosive arthritis [6].

For decades, eight anti-ARS specificities were recognized: anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-Ks, anti-Ha, and anti-Zo. Conventional line-blot or commercial immunoassay panels targeting this classical specificities leave up to 40% of clinically defined ASyS patients appear seronegative [7]. However, the use of expanded technologies including Immunoprecipitation coupled to Mass Spectrometry (IP-MS), and Phage Immunoprecipitation Sequencing (PhIP-Seq), have dramatically broadened

the repertoire, identifying reactivity to nearly all 20 ARS [7,8] (Fig. 1). These platforms have revealed that many 'seronegative' cases harbor antibodies to rare or previously unrecognized ARS targets, indicating that apparent seronegativity often reflects detection limitations rather than true antibody absence [7,9–11].

This expansion also highlights the structural complexity of ARS autoantigens. Some ARS enzymes exist as relatively independent proteins, whereas others are embedded within multiprotein assemblies, such as the OJ multisynthetase complex [12]. Since 2020, newly reported or expanded anti-ARS reactivities illustrate how improved antigen discovery and screening technologies are reshaping the serological boundaries of ASyS beyond the classical eight specificities, including patients previously classified as seronegative [7,9–11]. From a practical perspective, these newly reported or expanded anti-ARS reactivities are not yet included in clinically available, regulatory-approved antibody panels. Most commercial LB, chemiluminescent and particle-based myositis panels most consistently cover anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ and anti-OJ, with anti-Ks, anti-Ha and anti-Zo included inconsistently and with lower analytical reliability [13,14]. Testing for remaining synthetases is currently performed on a research basis in specialized laboratories, mainly by immunoprecipitation, IP-MS, PhIP-Seq, or in-house ELISA, within research collaborations or reference-center networks [15]. Prototype multiplex assays incorporating additional synthetases are under evaluation, but harmonized cut-offs and clinical validation studies are still required before these specificities can be recommended for routine diagnostic testing [16].

### Other novel specificities and the challenge of seronegative myositis

Additional emerging autoantibody specificities have recently been described in IIM, including antibodies targeting FHL1 [17], eIF3 [18], HSC70 [19,20], TPM4 [21], and NDUFA11 [22] (Fig. 1, Supplementary Table 1, <https://links.lww.com/COR/A66>). Although many of these findings remain preliminary, they suggest that additional autoantibody subsets may remain unidentified.

This issue is particularly relevant in seronegative IIM subsets. Seronegative immune-mediated necrotizing myopathy (IMNM), has been associated with more aggressive muscle damage and poorer outcomes than anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) or antisignal recognition particle (SRP) seropositive subsets [23]. Notably, seronegative ASyS has been described in up to 40% of patients despite the presence of characteristic clinical

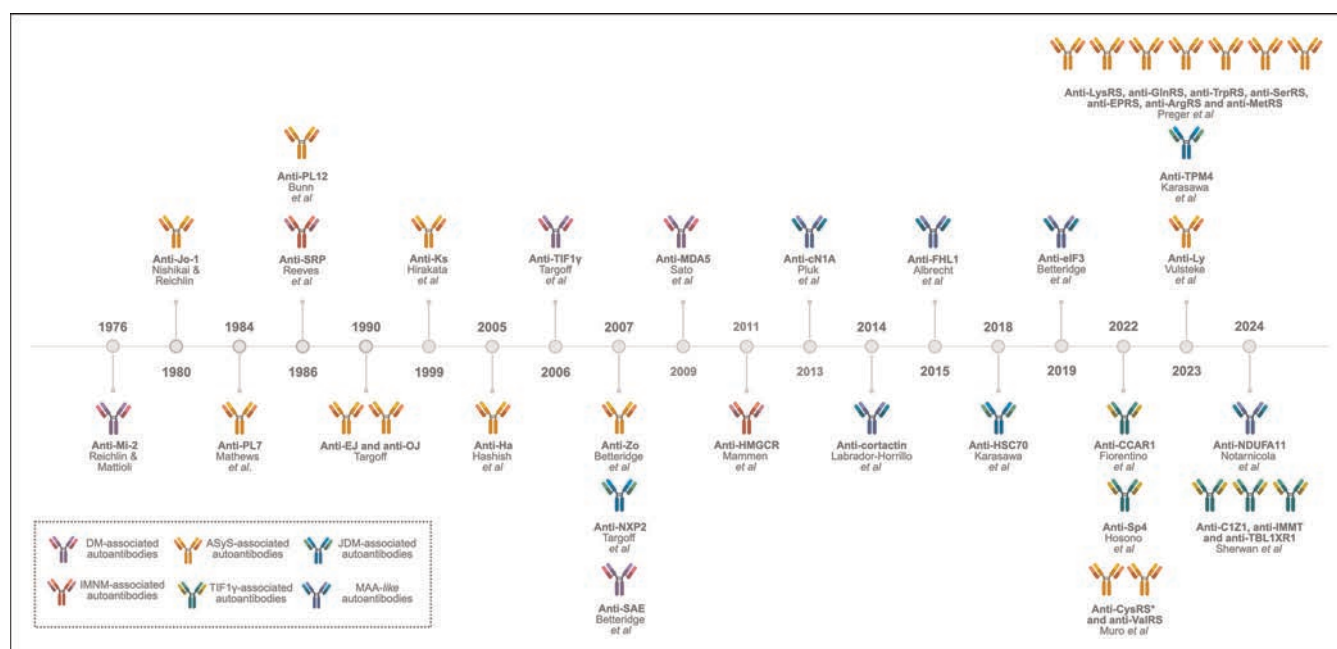


**FIGURE 1.** Timeline of selected myositis autoantibody milestones. The timeline summarizes representative milestones in the description, identification, or clinical characterization of established and emerging myositis autoantibodies. Anti-Mi-2 is shown with the 1976 early PM/DM serological reaction, although the Mi-1/Mi-2 systems were identified in 1980 and anti-Mi-2 was later linked to dermatomyositis in 1985. Anti-Jo-1 was first described in 1980, and Jo-1 was identified as histidyl-tRNA synthetase in 1983. Anti-TIF1γ was initially described as antip155/140 or antip155, anti-NXP2 as anti-MJ. \*Anti-CysRS was first reported with anti-ValRS in 2022 before being named anti-Ly in 2023. Colors indicate the main clinical or serological grouping of each autoantibody. ArgRS, arginyl-tRNA synthetase; ARS, aminoacyl-tRNA synthetase; ASyS, antisynthetase syndrome; C1Z1, Cip1-interacting zing finger protein; CCAR1, cell cycle and apoptosis regulator 1; cN1A, cytosolic 5'-nucleotidase 1A; CysRS, cysteinyl-tRNA synthetase; DM, dermatomyositis; eIF3, eukaryotic translation initiation factor 3; EPRS, glutamyl-prolyl-tRNA synthetase; FHL1, four-and-a-half LIM domains protein 1; GlnRS, glutaminyl-tRNA synthetase; HisRS, histidyl-tRNA synthetase; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HSC70, heat shock cognate 70 kDa protein; IleRS, isoleucyl-tRNA synthetase; IMMT, MICOS complex subunit MIC60; IMNM, immune-mediated necrotizing myopathy; JDM, juvenile dermatomyositis; LysRS, lysyl-tRNA synthetase; MAA, myositis-associated autoantibody; MDA5, melanoma differentiation-associated protein 5; MetRS, methionyl-tRNA synthetase; NDUFA11, NADH oxidoreductase subunit A11; NXP2, nuclear matrix protein 2; PM, polymyositis; SAE, small ubiquitin-like modifier activating enzyme; SerRS, seryl-tRNA synthetase; Sp4, specificity protein 4; SRP, signal recognition particle; TBL1XR1, transducin β-like 1 X-linked receptor 1; TIF1γ, transcription intermediary factor 1-gamma; TPM4, tropomyosin alpha-4 chain; TrpRS, tryptophanyl-tRNA synthetase; ValRS, valyl-tRNA synthetase. Created with BioRender.

manifestations when evaluated using conventional autoantibody assays. Although expanded anti-ARS screening can reclassify some of these patients [24], persistent seronegativity, together with distinct HLA associations [25] and elevated cytokine levels [26], suggest that unrecognized autoantibodies may still be present in subsets currently classified as seronegative.

### Beyond primary myositis-specific autoantibody positivity: contributors to disease heterogeneity

The heterogeneity of clinical manifestations among patients sharing the same MSA challenges the traditional concept of homogeneous, monospecific

autoantibody-defined subsets. This is particularly evident in anti-TIF1γ-positive and anti-MDA5-positive disease, where coexisting reactivities and clinical modifiers may refine prognosis beyond primary MSA status alone.

### Emerging coexisting autoantibodies in anti-TIF1γ-positive dermatomyositis

Anti-TIF1γ-positive dermatomyositis is not a homogeneous serological entity, it comprises distinct subgroups defined by autoantibody coexistence, reported in up to seven different serological combinations [27].

Among these, anticell cycle and apoptosis regulator 1 (CCAR1) and antispecificity protein 4 (Sp4) have emerged as clinically relevant co-reactivities.

CCAR1 is a multifunctional transcriptional co-activator involved in cell growth, apoptosis, and steroid receptor signaling [28,29], whereas Sp4 is a zinc finger transcription factor involved in gene regulation [30]. In adult-onset dermatomyositis, both autoantibodies are associated with a lower cancer risk compared with isolated anti-TIF1 $\gamma$  positivity [31–34], while anti-TIF1 $\gamma$ -positive patients lacking both anti-Sp4 and anti-CCAR1 may represent a higher risk subgroup requiring more intensive cancer surveillance [35]. In juvenile-onset dermatomyositis, these autoantibodies occur at lower frequencies (anti-Sp4 in 7–9%, anti-CCAR1 in 13–19% of anti-TIF1 $\gamma$ -positive patients) and are associated with less severe muscle disease, though cancer risk is not a primary concern in this age group given the rarity of malignancy in juvenile dermatomyositis [27,34]. Additional coexisting specificities, including anti-TBL1XR1, anti-IMMT, anti-C1Z1, anti-SOX5, and others, further support the serological complexity of this subset [27].

In contrast to anti-CCAR1 and anti-Sp4, these additional reactivities have not yet been consistently linked to a defined clinical profile in adult-onset dermatomyositis: they have been reported mainly in single cohorts, occur at low frequencies, and have not been independently validated as modifiers of cancer risk or organ involvement. In JDM, anti-TBL1XR1 has also been associated with milder muscle disease, though data remain limited to single cohorts [27]. Their present implication is therefore mainly conceptual, indicating that anti-TIF1 $\gamma$ -positive dermatomyositis often reflects a broader, multi-antigen response against nuclear transcriptional regulators rather than a strictly monospecific one. Whether these reactivities represent bystander markers of a diversified antibody response or carry independent prognostic weight remains to be determined in larger prospective cohorts.

These findings suggest that additional autoantibody positivities in anti-TIF1 $\gamma$ -positive adult-onset dermatomyositis could, in principle, modify cancer screening intensity. However, current guidelines have not incorporated these autoantibodies into clinical algorithms, in part because neither anti-CCAR1 nor anti-Sp4 testing is yet clinically available, and in part because prospective multicenter validation (particularly across non-US populations and in diverse adult cohorts) is still lacking.

### Clinical heterogeneity within anti-MDA5-positive myositis

Antimelanoma differentiation-associated gene 5 (MDA5)-positive myositis also illustrates that a single MSA-defined subset may contain clinically distinct

phenotypes. The French Myositis Network identified three separate entities within anti-MDA5-positive myositis: rapidly-progressive ILD (RP-ILD); severe skin vasculopathy and myositis, and; dermatorheumatologic phenotype [36].

Within this subset, coexisting autoantibody reactivities are a major contributor to heterogeneity. Anti-Ro52 co-positivity, further stratify risk; anti-MDA5/anti-Ro52 double-positive patients show more severe ILD, more frequent ground-glass opacities on HRCT, and lower survival than patients with anti-MDA5 alone [37]. Cluster analysis of anti-MDA5-positive dermatomyositis identified three phenotypic subgroups with markedly different outcomes; the high-risk cluster, defined by high anti-MDA5 titer together with anti-Ro52 positivity, carried 60% all-cause mortality compared with 3.7% in the low-risk cluster [38].

Epitope-level differences may further contribute to heterogeneity: comparative B-cell epitope profiling in Japanese and North American cohorts showed that reactivity against the N-terminal tandem CARD region (fragment A, amino acids 1–155) was associated with RP-ILD and pulmonary mortality in Japanese patients, whereas North American patients preferentially recognized a C-terminal fragment (fragment H, amino acids 905–1026), suggesting that patients sharing anti-MDA5 positivity may differ in the antigenic regions they target, with potential prognostic implications [39<sup>22</sup>] discussed further in Section ‘Epitope specificity and intra-autoantibody heterogeneity’.

### REFINING ESTABLISHED AUTOANTIBODY SUBSETS: QUANTITATIVE, PATHOLOGICAL AND PROGNOSTIC ASSOCIATIONS

Established myositis autoantibodies require multi-dimensional interpretation beyond binary presence or absence. Antibody titers, temporal dynamics, IgG subclasses, co-existing specificities, histopathological patterns, and immune signatures collectively refine risk stratification, disease monitoring, and prognosis.

### Quantitative serology in anti-MDA5 dermatomyositis

Anti-MDA5-positive dermatomyositis exemplifies the shift from binary autoantibody classification to quantitative, longitudinal serological assessment. In this subset, rising anti-MDA5 titers may predict ILD progression and mortality, while declining levels may correlate with remission; persistent or rebounding titers may indicate refractory disease or relapse [40]. However, standardized monitoring intervals,

assay calibration, and validated actionable thresholds, remain undefined [41].

Prognostic refinement also extends to IgG subclasses: investigational thresholds for anti-MDA5 IgG1 (>13 U/ml) and IgG3 (>11 U/ml) levels have been associated with mortality [42], and IgG1 titers may improve RP-ILD prediction, particularly when combined with the neutrophil-to-lymphocyte ratio [43].

Quantitative serological behavior has been described for other MSAs: anti-Jo-1 levels may correlate with disease activity, particularly on longitudinal assessment [44–46], and anti-HMGCR and anti-SRP titers may correlate with CK levels and decline with treatment, though in some cases anti-HMGCR levels do not fully normalize even with clinical improvement [47,48]. Together, these findings underscore that longitudinal quantitative serology may complement clinical assessment across myositis subtypes.

### Histopathological signatures and prognostic stratification

Antibody-specific histopathological signatures extend serological stratification to the tissue level. In 256 dermatomyositis muscle biopsies positive for myxovirus resistance protein A (MxA, an interferon-induced marker), distinct patterns segregate by autoantibody: anti-Mi-2 was associated with perifascicular atrophy, necrosis, and inflammation; anti-NXP2 with microinfarction; anti-TIF1 $\gamma$  with perifascicular ‘punched-out’ fibers; and anti-MDA5 with minimal muscle pathology despite extramuscular severity [49]. These findings suggest that muscle biopsy may carry autoantibody-predictive information, reinforcing that each MSA defines a biologically distinct entity.

Beyond tissue-level signatures, large cohort studies have further quantified the prognostic weight of established autoantibodies. Anti-MDA5 independently predicts RP-ILD, anti-TIF1 $\gamma$  predicts malignancy [50], and anti-MDA5/anti-Ro-52 coexistence identifies poorer survival [51].

### MAPPING ANTIGENIC TARGETS AND EPIOTOPE DIVERSITY

Beyond the identification of autoantibody specificities, epitope architecture and antigen conformation provide a refined framework for understanding serological heterogeneity, patient stratification, and limitations of discovery platforms.

#### Molecular targets and epitope diversity

Myositis autoantibodies recognize diverse self-antigens, including cytoplasmic aminoacyl-tRNA synthetases,

nucleic-acid sensors, and chromatin-remodeling proteins. Antigenic diversity operates across and within target proteins. Histidyl-tRNA synthetase (HisRS/Jo-1) exemplifies this: anti-Jo-1 antibodies recognize multiple linear and conformation-dependent epitopes, with the N-terminal/WHEP region representing an immunodominant target. HisRS can also be cleaved by granzyme B, potentially contributing to autoantigen exposure, although the relationship between cleavage sites and domain epitopes remains incompletely defined [52,53].

MDA5 provides a parallel example in which antigen structure shapes antibody recognition. The MDA5 central helicase region comprising Hel1, Hel2i, Hel2, and the pincer domain (collectively termed 3Hel), contains dominant conformational epitopes, and recognition is largely conformation-dependent [54,55]. Thus, for both prototypic myositis autoantigens, antibody recognition depends substantially on intact three-dimensional structure rather than linear sequence alone.

This structural biology has direct methodological consequences. PhIP-Seq and other peptide-display platforms are powerful discovery tools but rely on linear peptide libraries and may therefore be inherently unable to detect conformational epitopes [15,56]. A negative PhIP-Seq result does not exclude an autoantibody but identifies a structural blind spot. Conversely, linear epitopes within MDA5 helicase domains have been identified [57<sup>\*\*\*</sup>], underscoring that conformational and linear approaches are complementary rather than interchangeable. Together, these observations indicate that myositis autoantibody specificity is shaped not only by the identity of the target autoantigen, but also by the structural nature of the recognized epitope.

#### Epitope specificity and intra-autoantibody heterogeneity

Beyond which antigen is recognized, patients with the same autoantibody specificity may differ in which epitopes are targeted. In HisRS/Jo-1, insertion mutagenesis demonstrated multiple conformational and linear epitopes [53]. In MDA5, depletion experiments and patient-derived monoclonal antibodies have shown distinct reactivities against individual helicase subdomains, indicating that multiple patient-specific epitope profiles can coexist within the same serological subset [54,57<sup>\*\*\*</sup>]. Whether these profiles evolve over time through epitope spreading, in which an initially focused response expands toward subdominant or cryptic epitopes within the same antigen or across different proteins [58,59], remains unexplored in IIM. While cross-sectional

data suggest epitope diversity among patients, direct longitudinal evidence documenting intra-patient epitope evolution in myositis is limited [55–56].

Epitope-level resolution can also distinguish true coexistence from structural cross-reactivity. Anti-Mi-2 autoantibodies recognize plant homeodomain zinc finger 1 (PHD1)-containing regions in TIF1 $\gamma$ , whereas canonical anti-TIF1 $\gamma$  autoantibodies predominantly target the N-terminal region. Removal of the PHD finger from TIF1 $\gamma$  constructs eliminates anti-Mi-2 cross-reactivity and may improve anti-TIF1 $\gamma$  assay specificity [60<sup>¶</sup>,61<sup>¶</sup>]. Thus, domain-level mapping can refine both biological interpretation and diagnostic assay design.

Epitope diversity also extends beyond B-cell recognition. In anti-Jo-1 disease, HisRS-specific CD4<sup>+</sup> T-cell responses are antigen-driven and MHC class II-dependent, with key determinants in the N-terminal region [62]. HisRS-specific Th1 cells have been identified in blood and bronchoalveolar lavage fluid (BALF), and germinal center-like structures in lung biopsies suggest local T-cell–B-cell collaboration against HisRS [63]. Most recently, HisRS<sub>41–55</sub> was identified as an HLA-DRB1\*03:01-restricted CD4<sup>+</sup> T-cell epitope, linking genetic susceptibility to antigen-specific cellular immunity and potential B-cell epitope diversification [64<sup>¶</sup>,65,66].

Clinically, the clearest evidence that epitope specificity may refine stratification comes from anti-MDA5<sup>+</sup> dermatomyositis. Comparative B-cell epitope profiling showed that antifracture A (aa 1–155) reactivity corresponding to the N-terminal, tandem CARD region was associated with RP-ILD and pulmonary mortality in Japanese patients, whereas North American patients preferentially recognized fragment H (aa 905–1026), with geographic differences in epitope profiles correlating with distinct outcomes [39<sup>¶</sup>]. Because CARD and helicase domains mediate different aspects of MDA5 signaling, domain-specific antibodies could plausibly have distinct functional consequences (either inhibiting or aberrantly enhancing pathway activation) [67–69]. However, no study has yet directly compared the functional consequences of anti-CARD versus antihelicase antibodies on MDA5–MAVS signaling, and whether domain-specific epitope profiles shift during disease progression or treatment remains unknown. Future structure-aware discovery pipelines incorporating longitudinal epitope tracking may help refine stratification within clinically heterogeneous MSA-defined subsets.

### Multiprotein autoantigenic complexes

Antigenic complexity in myositis extends beyond single-protein targets. Anti-OJ represents one of

the clearest examples: initially associated with isoleucyl-tRNA synthetase (IleRS) [70], anti-OJ sera can react with additional components of the multisynthetase complex, indicating a broader macromolecular antigenic target [12]. This complex architecture complicates interpretation, as clinically relevant reactivity may be directed against IleRS, other complex components such as lysyl-tRNA synthetase (LysRS), or conformational epitopes generated by the assembled complex. Therefore, recombinant single-antigen platforms may underdetect anti-OJ if dominant epitopes depend on native conformation or complex integrity. Recent studies showing anti-OJ reactivity against both IleRS and LysRS, with ELISA assays displaying high agreement with IP, support the concept that anti-OJ represents recognition of an antigenic complex rather than a strictly monospecific response [71].

Anti-OJ, though rare, is associated with ASyS, particularly ILD [72], yet commercial line immunoassays show limited detection accuracy [73]. This illustrates how antigenic architecture directly impacts clinical serology and diagnostic test performance.

### MOVING BEYOND BIOMARKERS: FUNCTIONAL RELEVANCE OF MYOSITIS AUTOANTIBODIES

Although MSAs have traditionally been regarded as diagnostic and prognostic biomarkers, accumulating evidence suggests that selected specificities may contribute to disease pathogenesis. The strength of this evidence varies, from direct muscle injury in anti-HMGCR and anti-SRP, to extracellular IFN amplification in anti-MDA5, and potential intracellular target interference. Pathogenic relevance should be interpreted in the context of antigen biology, tissue vulnerability, effector mechanisms, and the strength of available experimental evidence.

### Pathogenic evidence in immune-mediated necrotizing myopathy-associated autoantibodies

The strongest evidence supporting a pathogenic role for myositis autoantibodies comes from IMNM, characterized by severe muscle weakness, marked CK elevation and substantial long-term disability [74]. Anti-HMGCR and anti-SRP titers [23] correlate with disease severity and CK levels, rising with active disease and declining with treatment response [47,48].

Anti-HMGCR autoimmunity involves environmental exposure, antigen availability, and genetic risk. HMGCR, the pharmacological target of statins,

is upregulated by statin exposure and highly expressed in regenerating muscle fibers, potentially sustaining antigen availability even after statin discontinuation [75–77]. Proposed mechanisms include enhanced antigen presentation, conformational changes or generation of cryptic epitopes, and presentation of HMGCR-derived peptides in the context of HLA-DRB1\*11:01 and HLA-DRB1\*07:01 [78] (Fig. 2). Purified anti-HMGCR IgG can inhibit HMGCR enzymatic activity *in vitro*, resembling the pharmacological effect of statins [79<sup>\*\*\*</sup>]. Moreover, anti-HMGCR-positive muscle biopsies show lipid

accumulation within myocytes [79<sup>\*\*\*</sup>], supporting a model of metabolic interference in addition to immune-mediated injury.

Anti-SRP represents a complementary model of IMNM pathogenicity. SRP is a ribonucleoprotein complex involved in targeting newly synthesized proteins to the endoplasmic reticulum. Anti-SRP autoantibodies accumulate inside myofibers, and may inhibit SRP function, disturbing protein and lipid metabolism [80,81]. Anti-SRP-positive serum enriched with complement reduces myoblast survival and induces C3c and C5b-9 deposition [82,83]. Consistently, purified

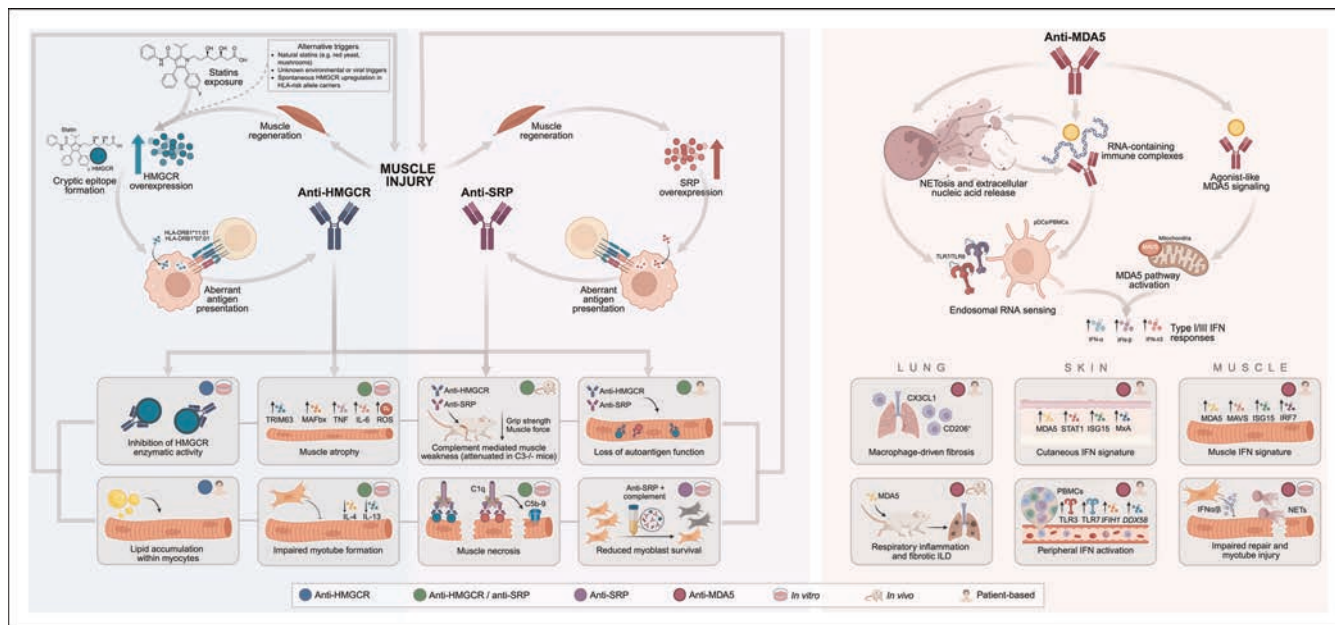


**FIGURE 2.** Distinct pathogenic models proposed for anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase, anti-signal recognition particle, and anti-melanoma differentiation-associated protein 5 autoantibodies. Anti-HMGCR and anti-SRP provide the strongest evidence for direct autoantibody pathogenicity in myositis. For anti-HMGCR, statin exposure, muscle regeneration, and alternative triggers may increase HMGCR expression and antigen availability in genetically susceptible individuals, favoring aberrant antigen presentation and sustained autoimmunity. Downstream effects include inhibition of HMGCR enzymatic activity, lipid accumulation within myocytes, muscle atrophy, impaired myotube formation, complement-mediated weakness, and myofiber necrosis. Anti-SRP autoimmunity is similarly linked to aberrant antigen presentation and SRP overexpression, with subsequent loss of autoantigen function, reduced myoblast survival, muscle atrophy, complement-mediated injury, and necrosis. By contrast, anti-MDA5 is best interpreted as a model of inflammatory amplification rather than direct myonecrotic injury. Anti-MDA5 may promote disease through three nonmutually exclusive pathways: NETosis with extracellular nucleic acid release, RNA-containing immune complex formation, and agonist-like MDA5 signaling. These pathways converge on endosomal RNA sensing and MDA5-pathway activation, driving type I/III interferon responses. Tissue-level consequences are represented by macrophage-driven fibrosis and respiratory inflammation/fibrotic ILD in lung, cutaneous and peripheral interferon activation in skin/systemic compartments, and IFN-associated stress with impaired repair and myotube injury in muscle. Colored circles indicate the type of supporting evidence for each mechanism (patient-based, *in vitro*, or *in vivo*). DDX58, DExD/H-box helicase 58; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IFIH1, interferon-induced with helicase C domain 1; IFN, interferon; IL-13, interleukin-13; IL-4, interleukin-4; IL-6, interleukin-6; ILD, interstitial lung disease; ISG15, interferon-stimulated gene 15; MAFbx, muscle atrophy F-box; MAVS, mitochondrial antiviral signaling protein; MDA5, melanoma differentiation-associated protein 5; MxA, myxovirus resistance protein A; NETs, neutrophil extracellular traps; PBMcs, peripheral blood mononuclear cells; ROS, reactive oxygen species; SRP, signal recognition particle; STAT1, signal transducer and activator of transcription 1; TLR, Toll-like receptor; TNF, tumor necrosis factor; TRIM63, tripartite motif-containing 63. Created with BioRender.

anti-HMGCR and anti-SRP autoantibodies can induce myofiber atrophy and necrosis *in vitro* [83,84], associated with increased MAFbx and TRIM63 expression, IL-6, TNF, and reactive oxygen species (ROS) production [84]. Myofiber necrosis appears to be predominantly complement-mediated [83]. Both autoantibodies have been reported to impair myotube formation through reduced of IL-4 and IL-13 secretion [84].

Animal studies support a pathogenic role for IMNM-associated autoantibodies, and identify complement activation is a key mediator of muscle injury [85]. Together, these findings indicate that anti-HMGCR and anti-SRP autoantibodies are not merely biomarkers but may actively contribute to muscle damage through complement activation, impaired muscle regeneration, metabolic dysfunction, oxidative stress, and inflammatory signaling.

### **Alternative models of pathogenicity: anti-MDA5, neutrophil extracellular traps, and extracellular immune amplification**

MDA5 is a cytosolic RNA sensor that recognizes long double-stranded RNA and signals through mitochondrial antiviral signaling protein (MAVS), activating IRF3, IRF7, and NF- $\kappa$ B, leading to transcription of type I interferons (IFN-I) and pro-inflammatory cytokines [86–90]. Anti-MDA5 autoantibodies are strongly associated with clinically amyopathic dermatomyositis, RP-ILD, and vasculopathic skin lesions [91], suggesting a primarily vasculopathic and pneumotropic rather than myonecrotic phenotype.

Consistently, anti-MDA5-positive muscle often lacks classic dermatomyositis histopathological features [92], although MDA5, MAVS, IRF7, and ISG15 expression may be increased [93], suggesting indirect or limited IFN-mediated stress rather than primary antibody-mediated myofiber necrosis.

Anti-MDA5 autoantibodies should be interpreted as a potential amplifier of inflammation rather than a definitive effector of direct muscle injury (Fig. 2). Anti-MDA5 has been linked to neutrophil extracellular trap (NET)-driven inflammation with increased circulating NET markers (cell-free DNA and LL-37) [94], detection of NETs in affected tissues (skin, muscle, and lung), and induction of NET formation by anti-MDA5-positive sera or purified IgG *in vitro*. Functionally, NETs injure differentiated myotubes without impairing myoblast proliferation, suggesting that NETs may contribute to tissue damage once formed [95].

Anti-MDA5 may amplify inflammation through RNA-containing immune complexes. MDA5/anti-MDA5/RNA complexes activate plasmacytoid dendritic cells (pDCs) through an RNA-dependent TLR7 pathway and induce IFN- $\alpha$  [69]. RNA-containing

immune complexes from IIM patients can activate peripheral blood mononuclear cells (PBMCs) through TLR7/8, inducing IFN- $\alpha$  and IL-6 and generating soluble mediators that negatively affect human myoblasts and satellite cells [96,97]. This model aligns with the dysregulated type I/III IFN profile of anti-MDA5-positive dermatomyositis, including increased IFN- $\beta$  and IFN- $\lambda$ 3 [98].

The clinical predominance of skin and lung disease supports a tissue-specific extracellular amplification model. Patients frequently develop palmar papules, cutaneous ulcerations, and RP-ILD; skin lesions show pauci-inflammatory vasculopathy, vessel-wall inflammation, and thrombi [99]. Increased MDA5 expression in dermatomyositis skin [100], together with STAT1, ISG15, and MxA upregulation [101] supports an IFN-centered process involving target-antigen enrichment, immune complexes, endothelial injury, and inflammatory signaling that may perpetuate disease in skin and lung compartments [102]. Pulmonary injury may also involve macrophage-driven profibrotic pathways, supported by increased levels of macrophage-related mediators, including soluble CD163, chitotriosidase, ferritin, neopterin, and CX3CL1, as well as CD206-positive M2 macrophage accumulation in fatal MDA5-associated ILD [102–105]. Consistently, an IFN-I score has been proposed to predict short-term mortality, with higher scores associated with reduced 3-month survival [106].

Experimental data further support a context-dependent model. In mice, MDA5 immunization induces anti-MDA5 antibodies and MDA5-reactive T cells. After poly(I:C)-induced lung injury, these mice developed prolonged respiratory inflammation and fibrotic ILD, attenuated by CD4+ T-cell depletion [107], suggesting, MDA5-directed autoimmunity cooperates with innate immune activation rather than proving anti-MDA5 antibodies are directly pathogenic. In parallel, IFN-I can impair muscle repair by reducing muscle stem cell proliferation and inhibiting myoblast differentiation and myotube formation *in vitro* [108,109].

Overall, anti-MDA5 autoimmunity is best understood as a model of extracellular inflammatory amplification. NET formation, RNA-containing immune complexes, type I/III IFN activation, endothelial dysfunction, macrophage activation, and profibrotic pulmonary inflammation form a feed-forward loop preferentially affecting skin and lung, contributing to the vasculopathic and pneumotropic phenotype.

### **Pathogenic internalization and intracellular target interference**

A major unresolved question in myositis autoantibody pathogenicity is how circulating antibodies

access intracellular autoantigens and alter their function. Recent studies have shown that immunoglobulins can localize within muscle fibers in patterns corresponding to their cognate autoantigens: cytoplasmic deposition for anti-HMGCR, anti-SRP, anti-MDA5, and anti-Jo-1, and nuclear deposition for anti-Mi-2 [110]. Functional data suggest that intracellular localization may have biological consequences, although the magnitude and nature of these effects vary by specificity (Fig. 3).

Anti-Mi-2 provides one of the clearest examples of intracellular target interference. In anti-Mi-2-positive muscle biopsies, nuclear immunoglobulin deposition is associated with overexpression of genes normally repressed by the Mi-2/NuRD complex, and electroporation of anti-Mi-2 immunoglobulins into cultured muscle cells reproduces this transcriptional pattern [110,111]. Additionally, anti-Mi-2 autoantibodies can cross-recognize autoimmune regulator (AIRE) through a homologous PHD1 epitope

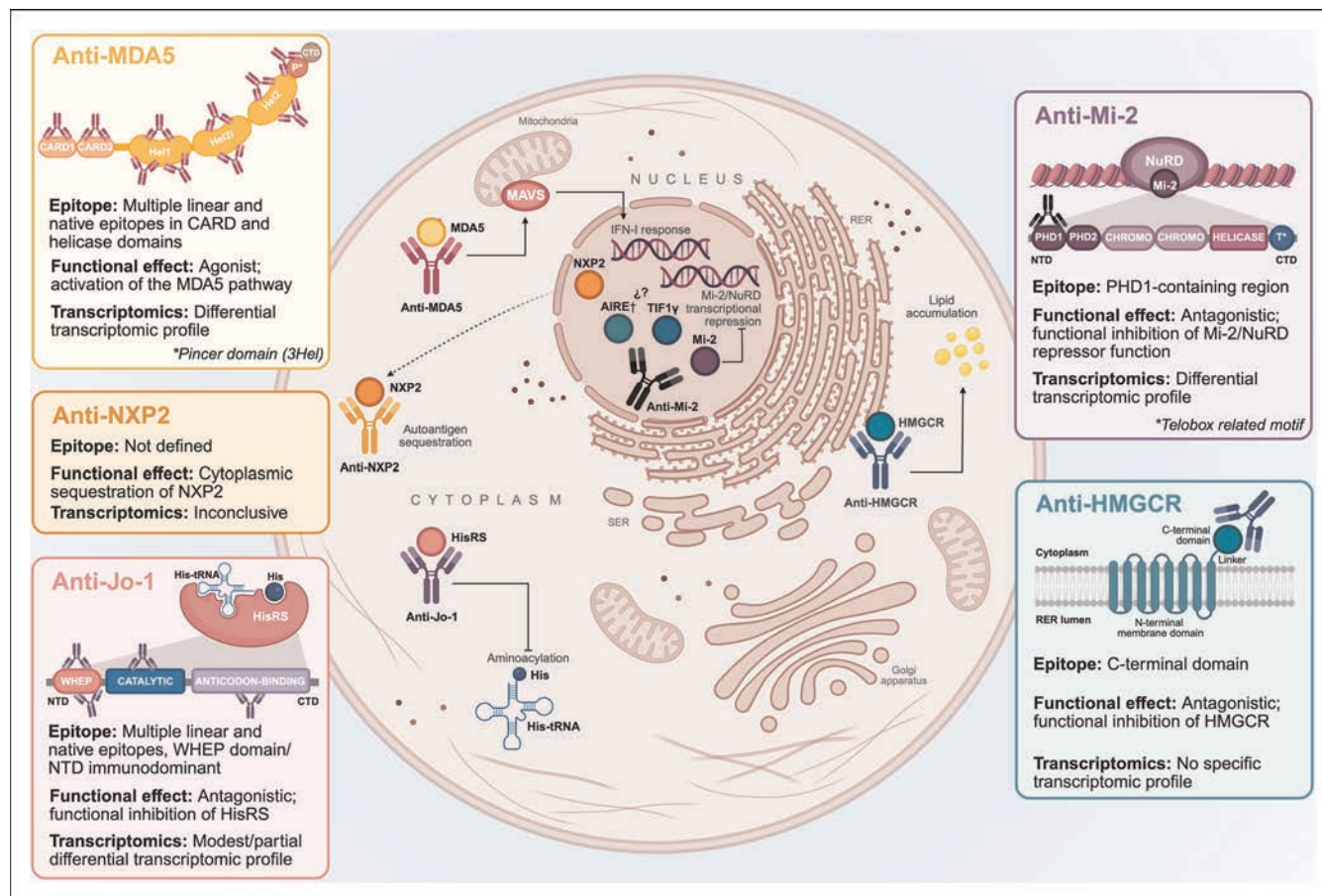


**FIGURE 3.** Intracellular target interference and functional effects of selected myositis autoantibodies. Schematic representation of proposed intracellular localization, epitope architecture, and functional consequences of selected myositis autoantibodies. Anti-MDA5, anti-Mi-2, anti-Jo-1, anti-HMGCR, and anti-NXP2 are shown according to their main target localization and proposed mechanism: agonist-like activation of the MDA5 pathway, Mi-2/NuRD functional inhibition, HisRS inhibition, HMGCR metabolic interference, or NXP2 cytoplasmic sequestration. 'Differential transcriptomic profile' refers to autoantibody-associated gene-expression changes observed in patient muscle biopsies and/or reproduced after experimental intracellular delivery of patient IgG compared with control IgG or nonmatching autoantibody conditions. The question mark (?) indicates that the functional consequences of anti-Mi-2 recognition of PHD1-containing regions in TIF1 $\gamma$  and AIRE remain unknown. The dagger symbol (†) indicates that AIRE is physiologically expressed in medullary thymic epithelial cells and is included only as a schematic putative cross-reactive target. AIRE, autoimmune regulator; CARD, caspase activation and recruitment domain; CTD, C-terminal domain; Hel, helicase domain; HisRS, histidyl-tRNA synthetase; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IFN- $\gamma$ , type I interferon; MAVS, mitochondrial antiviral-signaling protein; MDA5, melanoma differentiation-associated protein 5; NuRD, nucleosome remodeling and deacetylase; NXP2, nuclear matrix protein 2; PHD1, plant homeodomain finger 1; RER, rough endoplasmic reticulum; SER, smooth endoplasmic reticulum; TIF1 $\gamma$ , transcription intermediary factor 1-gamma; WHEP, TrpRS-HisRS-GluProRS domain. Created with BioRender.

[60<sup>\*\*\*</sup>]. As AIRE is essential for thymic negative selection and central immune tolerance, recognition of shared PHD1-containing regulatory proteins raises the possibility that anti-Mi-2 autoimmunity may extend beyond Mi-2/NuRD interference alone. However, whether anti-Mi-2 autoantibodies can access AIRE-expressing cells *in vivo* or functionally perturb AIRE-dependent tolerance mechanisms remains unknown.

Other specificities illustrate distinct and less definite models. Anti-Jo-1 produces a more modest transcriptomic effect despite evidence that anti-Jo-1 can inhibit HisRS activity *in vitro* [110,112]. Anti-HMGCR-positive biopsies suggest metabolic interference, supported by lipid accumulation and enzymatic inhibition of HMGCR rather than prominent transcriptional reprogramming [79<sup>\*\*\*</sup>,110]. Anti-MDA5 appears to represent an agonist-like model, with cytoplasmic immunoglobulin deposition and enrichment of IFN $\beta$ 1-inducible genes, supporting inflammatory amplification rather than direct myofiber necrosis, as discussed above. Anti-NXP2 may involve cytoplasmic sequestration of a normally nuclear autoantigen, although this mechanism has not been consistently reproduced *in vitro* [110].

Overall, intracellular target interference should be interpreted as a plausible but still emerging pathogenic model. Electroporation experiments show that intracellular delivery of patient immunoglobulins can reproduce selected tissue transcriptomic patterns, but spontaneous antibody entry into living muscle fibers and trafficking to specific intracellular compartments remain incompletely demonstrated. Thus, this model complements rather than replaces, established mechanisms such as complement-mediated necrosis, immune complex formation, extracellular inflammatory amplification, and metabolic dysfunction.

### ADVANCING AUTOANTIBODY DETECTION: FROM ASSAY PERFORMANCE TO BIOLOGICAL INTERPRETATION

The expanding complexity of the myositis autoantibody landscape has important implications for detection. Novel specificities, coexisting autoantibodies, conformational epitopes, and multiprotein complexes mean that assay choice affects both diagnostic accuracy and biological interpretation. Differences in antigen source, conformation, multiplexing capacity, and cut-off definition determine whether a result reflects true positivity, assay-specific noise, structural cross-reactivity, or failure to detect a native target.

Immunoprecipitation remains a reference method because it preserves native antigens and macromolecular complexes, but it is technically demanding,

difficult to standardize, and poorly suited for routine clinical use [113]. More accessible platforms, including ELISA, line blot, indirect immunofluorescence (IIF), chemiluminescent immunoassays (CLIA), particle-based multianalyte technologies (PMAT), and discovery methods are widely used, though no single platform performs equally [8].

Line blot is particularly common but shows variable agreement with immunoprecipitation and substantial dependence on positivity thresholds [114]; adjusted band-intensity approaches and stricter cut-offs can improve specificity, and reduce apparent false-positive results, particularly for anti-PL-7, anti-MDA5, and anti-Mi-2 $\beta$  [115,116].

Newer platforms have expanded the detectable repertoire while exposing structural blind spots. PMAT and CLIA allow high-throughput profiling and may improve detection of anti-Mi-2, anti-MDA5, anti-TIF1 $\gamma$ , anti-HMGCR, and complex-associated anti-OJ through combined anti-LysRS and anti-IleRS reactivity [117,118]. PhIP-Seq has enabled proteome-wide discovery, including anti-AIRE in anti-Mi-2-positive [60<sup>\*\*\*</sup>] and Sp4 in anti-TIF1 $\gamma$ -positive patients [33], but may miss conformational or complex-dependent epitopes, such as anti-Jo-1, anti-MDA5, and anti-OJ [56,119]. Conversely, IP-MS can capture conformational and multiprotein determinants but requires careful validation [8,119].

Persistent inter-platform and inter-laboratory discordance, particularly for anti-TIF1 $\gamma$ , rarer anti-ARS, and anti-SAE (even among laboratories using the same commercial assay [14,120,121]) affects interpretation of mutual exclusivity, coexistence, and seronegativity. Robust characterization of novel myositis autoantibodies therefore requires combining discovery platforms with confirmatory assays capable of preserving the relevant antigenic architecture. In this context, the role of ANA IIF on HEp-2 cells deserves specific comment. IIF has limited sensitivity as a screening test in IIM: several major autoantigens are cytoplasmic (aminoacyl-tRNA synthetases, SRP, HMGCR, MDA5) and are missed when only nuclear fluorescence is reported, and some nuclear specificities, such as anti-TIF1 $\gamma$  and anti-NXP2, may yield weak or atypical patterns. Reporting IIF simply as 'ANA-negative', therefore, risks excluding truly seropositive patients. Nevertheless, when cytoplasmic patterns are systematically read and reported, IIF retains practical value: it is inexpensive, widely available, uses a native antigen substrate that preserves conformational epitopes and can flag reactivities that solid-phase panels can miss, prompting targeted confirmatory testing or referral to specialized laboratories. The International Consensus on ANA Patterns (ICAP) nomenclature makes this approach operational by defining standardized anticell pattern codes, including

cytoplasmic patterns relevant to myositis such as AC-19 and AC-20 (cytoplasmic patterns suggestive of anti-ARS reactivity) and AC-18 (discrete cytoplasmic dots), alongside nuclear AC-1 to AC-14 patterns [122,123]. Pattern-oriented algorithmic testing strategies based on ICAP have been proposed to improve selection of downstream confirmatory assays and reduce unnecessary testing [124]. We would therefore argue that ANA IIF, read and reported according to ICAP criteria and explicitly including cytoplasmic patterns, remains complementary to modern multiplex and discovery platforms; importantly, a clinically suggestive phenotype should prompt myositis-specific autoantibody testing irrespective of the IIF result.

## CONCLUSION

Recent advances in myositis autoantibody research extend beyond the identification of new specificities. Emerging evidence supports broader paradigms: additional anti-ARS reactivities expand the serological boundaries of ASyS; MSAs may not always be strictly monospecific; epitope-level heterogeneity may influence phenotype, prognosis, and assay interpretation; and selected autoantibodies may contribute directly or indirectly to disease pathogenesis.

Clinical actionability varies substantially across these advances. Quantitative anti-MDA5 monitoring is increasingly used in specialized centers to guide treatment decisions, supported by consistent associations between titer dynamics and disease activity [40–42,43<sup>¶</sup>]. Anti-Ro52 co-testing in anti-MDA5-positive patients provides validated prognostic stratification and is feasible with commercially available assays [38,51]. In contrast, epitope-level profiling, co-reactivities such as anti-CCAR1 and anti-Sp4 in anti-TIF1 $\gamma$ -positive disease [27–31], and functional assays of antibody internalization [110,111] remain research tools pending standardized platforms and prospective multicenter validation. Current guidelines have not yet incorporated these emerging biomarkers into formal algorithms, and their adoption should be guided by local expertise, assay availability, and evolving evidence.

Future studies should integrate standardized, structure-aware detection platforms with longitudinal clinical cohorts, tissue-based analyses, and functional models across diverse populations to determine which autoantibodies are biomarkers, pathogenic effectors, or indicators of targetable immune pathways.

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*There are no conflicts of interest.*

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# Uncovering scleromyositis: no myth, just missed

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## Purpose of review

Scleromyositis (SM), the muscle-specific manifestation of scleroderma, is increasingly recognized as a distinct myositis subset, yet it remains poorly captured by existing classification criteria and absent from therapeutic guidelines. This review provides recent advances in SM with emphasis on challenging presentations and propose a pragmatic diagnostic framework integrating clinical, serological, capillaroscopic, and histopathological data.

## Recent findings

Recent studies identify capillaropathy as the unifying pathological hallmark of SM across muscle biopsy subtypes. Nailfold videocapillaroscopy reveals a predominantly scleroderma-active or scleroderma-like microangiopathy discriminating SM from potential myositis mimickers. Recent cohort studies demonstrate that SM confers independent mortality burden and substantial cardiac risk warranting immediate cardiac evaluation at diagnosis regardless of autoantibody profile or histological pattern. Pericyte dysfunction may link capillaropathy to fibrosis in SM, while autoantibodies appear to directly disrupt intracellular pathways, contributing to the shared vasculopathic and profibrotic signature that defines SM as a distinct entity.

## Summary

SM represents a clinically severe and underrecognized disease spectrum that frequently escapes current classification frameworks. Early SM diagnosis requires systematic integration of clinical, serological, capillaroscopic, and histopathological data, with capillaropathy as the unifying thread. Establishing a consensus SM definition and securing clinical trial inclusion remain the most urgent research priorities.

## Keywords

capillaropathy, myopathy, scleroderma, scleromyositis, systemic sclerosis

## INTRODUCTION

Systemic sclerosis (SSc) is the most lethal rheumatic disease and is defined by a pathogenic triad of vasculopathy, immune dysregulation, and fibrosis [1]. While its major organ manifestations are well characterized, muscle involvement has remained comparatively understudied. Muscle involvement in SSc is not incidental but represents a primary target organ manifestation reflecting the same pathogenic triad [2]. Although various terminologies have been used, most notably the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) defined SSc-associated myopathy [3], we adopt the term scleromyositis (SM) to encompass a broader phenotypic spectrum, including predominant muscle disease at disease onset with accompanying vasculopathy and sometimes subtle SSc features. Within the broader landscape of autoimmune myositis (AIM), SM constitutes a distinct clinico-sero-pathological subset that remains incompletely captured by existing classification frameworks. Indeed, substantial proportions of patients fail to meet either SSc [4] or AIM

criteria [5] despite expert-defined SM [6]. In a recent cohort of 250 AIM patients classified by expert opinion, SM accounted for 20% of cases, underscoring its prevalence within the AIM spectrum [7<sup>a</sup>].

Herein we review recent advances in SM with emphasis on challenging presentations and propose a pragmatic diagnostic framework integrating

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## KEY POINTS

- Scleromyositis (SM) routinely escapes existing classification frameworks underscoring the indispensable role of expert clinical recognition integrating clinical, serological, capillaroscopic, and histopathological data.
- Up to half of SM patients are seronegative on commercial solid-phase assays, making interpretation of indirect immunofluorescence pattern on HEp-2 cells an indispensable first step in serological assessment.
- Nailfold videocapillaroscopy reveals a predominantly scleroderma-active or scleroderma-like microangiopathy in 75% of SM patients, providing strong binary discriminating capacity against immune mediated necrotizing myopathy and inclusion body myositis and supporting its routine integration into the diagnostic workup.
- Muscle capillary vasculopathy, ideally screened by collagen-4 staining and confirmed ultrastructurally by marked basement membrane reduplication, is the cardinal histopathological hallmark of SM, unifying four dominant patterns carrying direct therapeutic implications.
- Skeletal myopathy independently increases mortality in systemic sclerosis (HR 1.60), and cardiac complications, including myocarditis, represent the leading cause of death in SM, warranting systematic cardiac screening at diagnosis.

clinical, serological, capillaroscopic, and histopathological data.

### CLINICAL PHENOTYPE: A BROAD SPECTRUM THAT ESCAPES CURRENT CLASSIFICATION CRITERIA

The clinical phenotype of SM is broader and more heterogeneous than classical descriptions suggest. While symmetric limb-girdle weakness represents the prototypic presentation in classic SSc [3,8<sup>•</sup>] a substantial proportion of patients with SM exhibit atypical muscle involvement including distal weakness, axial weakness (head drop/campyocormia) and diaphragmatic weakness [6,9,10<sup>•</sup>,11]. Crucially, many SM patients lack the hallmark SSc skin fibrosis (i.e. '*sine scleroderma*') and careful interrogation and examination for Raynaud's phenomenon, fingertip ulcers or pitting scars, and nailfold capillary abnormalities but also other, sometimes subtle, SSc features is therefore essential. These include lower esophageal and/or small bowel dysmotility, calcinosis, trigeminal neuropathy, and scleroderma renal crisis [2,6]. Of note, all these last-mentioned SSc

features are not included in the ACR/EULAR criteria. Because these criteria are heavily weighted toward skin fibrosis and a limited set of three SSc-specific autoantibodies [4], and AIM criteria emphasize proximal weakness without capturing SSc features [5], many SM patients fulfil neither set of criteria at presentation. Notably, in a large Italian SSc cohort ( $n=1480$ ), nearly 20% of patients lacked all three prototypical SSc autoantibodies, and this subgroup exhibited a higher prevalence of myopathy [12<sup>•</sup>].

Serological coverage is equally incomplete, with up to half of patients lacking identifiable fine specificities (i.e. '*seronegative*') [9]. Many of these *seronegative* SM patients present *sine scleroderma* and a nonnegligible proportion initially lack Raynaud's phenomenon [6], placing them at particularly high risk of under-recognition. In a series of *seronegative* SM defined by expert opinion, only 55% of patients met SSc classification criteria, 50% met myositis criteria, and just 10% fulfilled both at presentation [6]. After six years of follow-up, however, 80% ultimately met SSc criteria, underscoring that myositis may represent the inaugural manifestation of SSc long before classification thresholds are reached. These findings indicate that relying solely on the concomitant fulfillment of SSc and AIM criteria lacks sensitivity, particularly in early, muscle-dominant disease. Identifying red flags suggestive of SM therefore remains indispensable, enabling an expert-opinion-based diagnosis (Fig. 1).

### SEROLOGY: HIGH SERONEGATIVITY, NOVEL AUTOANTIBODIES, AND THE ROLE OF INDIRECT IMMUNOFLUORESCENCE

The serological landscape of SM is anchored by three SSc-overlap autoantibodies (anti-PM/Scl, anti-U1RNP, and anti-Ku) defining the most recognized clinical phenotypes, alongside SSc-specific antibodies such as antitopoisomerase I and anti-RNA polymerase III, which may associate with muscle involvement but typically with lower inflammatory activity and a greater tendency toward fibrosis [13]. Yet perhaps, the most clinically consequential serological observation is that up to half of SM patients lack identifiable fine specificities by solid-phase immunoassay [9]. This serological gap has driven the identification of novel autoantibodies, including anti-RuvBL1/2 [14] and anti-SMN [6]. Against this backdrop of incomplete commercial panel coverage, antinuclear antibody (ANA) testing by indirect immunofluorescence (IIF) on HEp-2 cells becomes indispensable as the primary screening step (Fig. 2). A negative ANA is incompatible with most SSc antibodies and should prompt diagnostic reconsideration, while a high-titer nucleolar pattern is strongly suggestive of SSc. The International

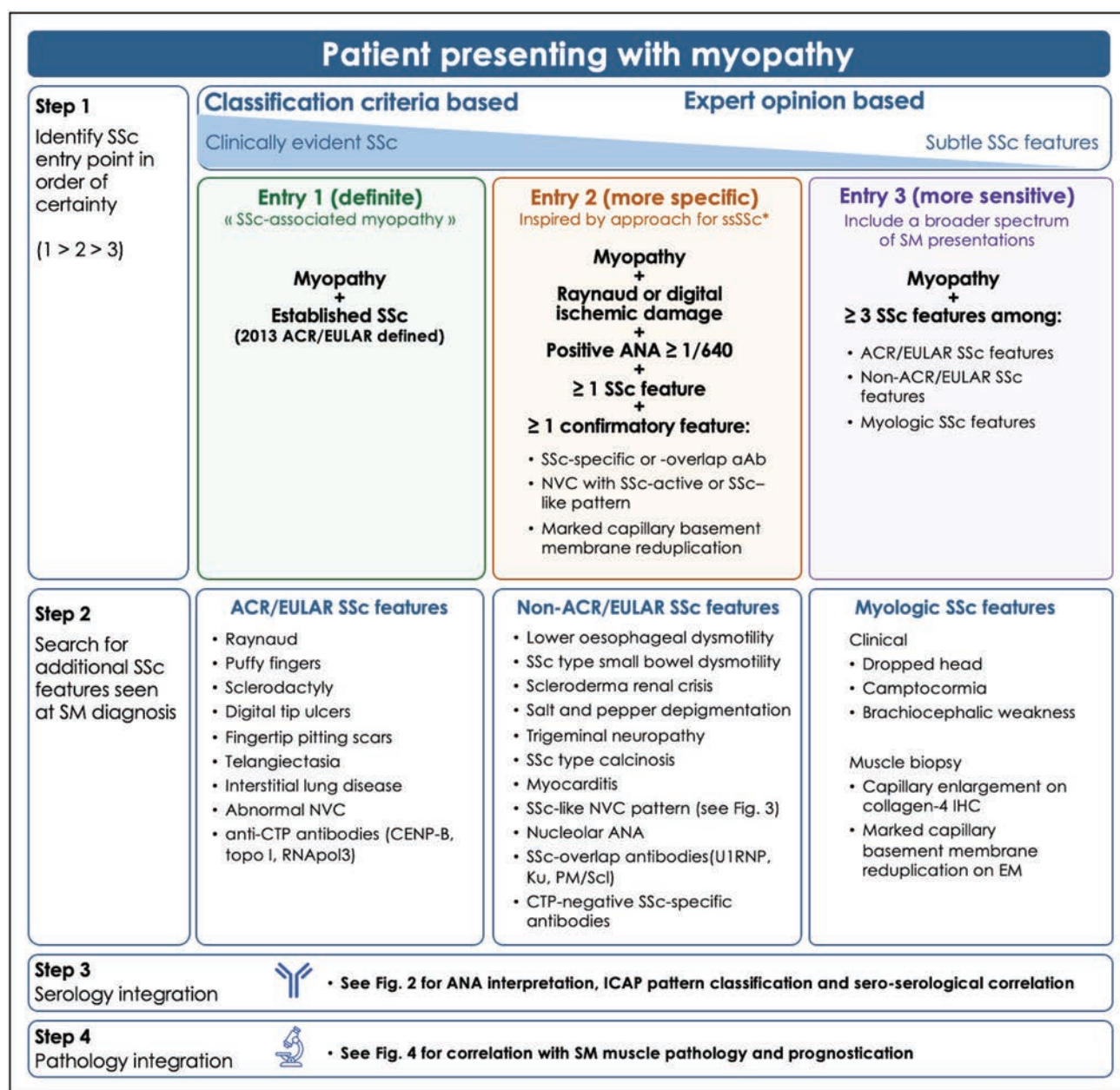
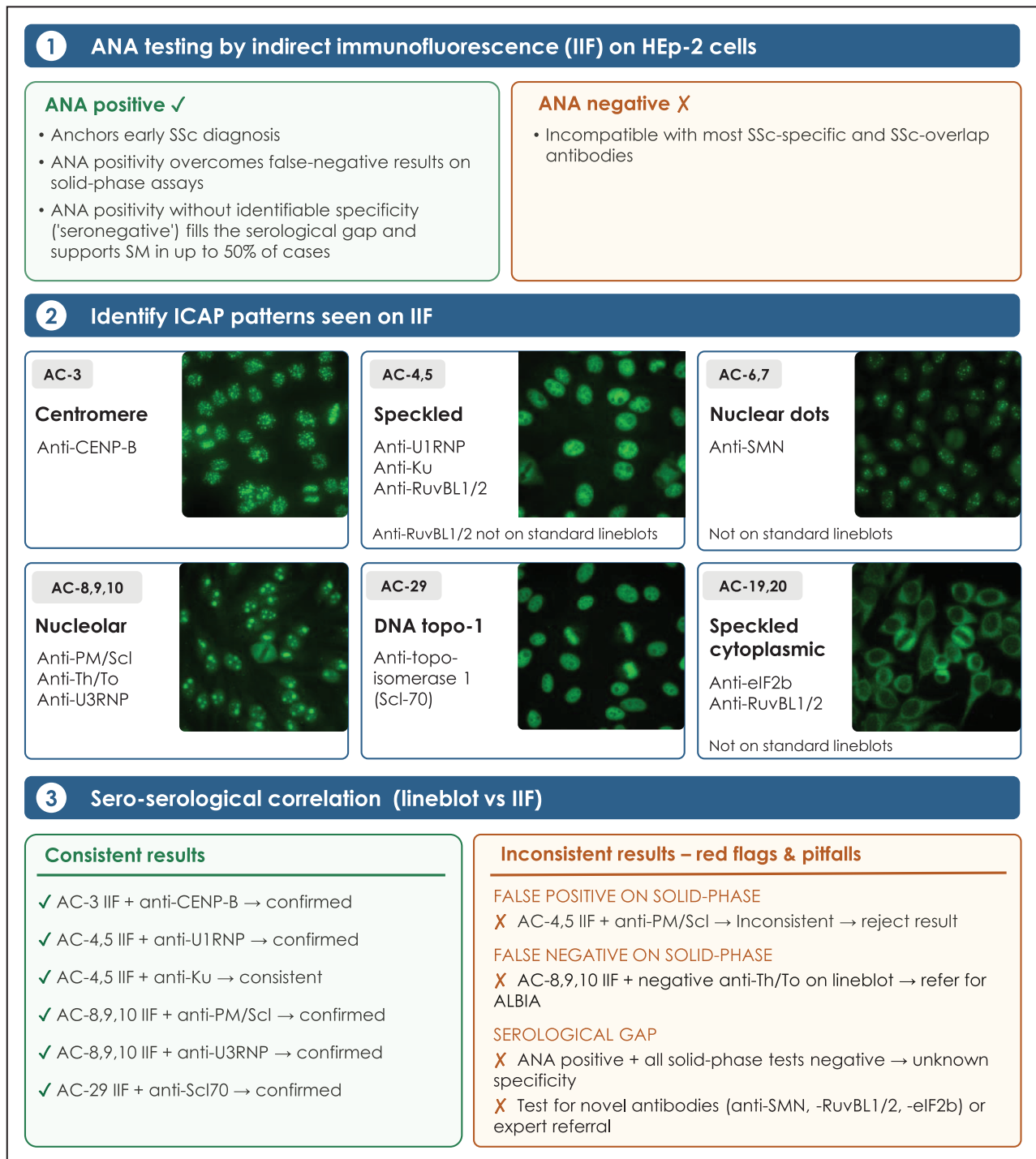


**FIGURE 1.** Practical approach to consider scleromyositis diagnosis in clinical practice.

\*Inspired by the proposed definition of SSc sine scleroderma by Poormoghimi *et al.* [58]. Digital ischemic damage includes digital pitting scar, ulceration or gangrene as defined by Hudson *et al.* [59]. See Fig. 2 for ANA interpretation and pattern classification. Dermatomyositis, antisynthetase syndrome, and seropositive immune-mediated necrotizing myopathy should always be excluded, as they share overlapping clinical features with SM. The exact number of SSc features required for an expert-opinion-based diagnosis has not yet been tested for classification purposes. At this stage, individual SSc features are not weighted; each is counted equally and systematically, so that future studies can determine the optimal threshold. This proposed expert-opinion-based diagnostic approach reflects the authors' accumulated clinical experience and should be considered preliminary. Formal classification or diagnostic criteria await validation in future studies. aAb, autoantibody; ACR, American College of Rheumatology; ANA, antinuclear antibody; CTP antibodies, anti-Centromere, -Topoisomerase I, -RNA Polymerase III; EM, electron microscopy; EULAR, European League Against Rheumatism; ICAP, International Consensus of ANA Patterns; IHC, immunohistochemistry; NVC, nailfold videocapillaroscopy; SM, scleromyositis; SSc, systemic sclerosis; ssSSc, systemic sclerosis sine scleroderma.

**FIGURE 2.** Stepwise approach to serology interpretation in scleromyositis.

Antisynthetase antibodies should be excluded in the presence of an AC-19/20 IIF pattern. More rarely, an AC-1 pattern may also be observed in scleromyositis patients. Of note, anti-Ro52 antibodies are frequently detected either in isolation or in combination with an SSc-associated autoantibody. ALBIA, addressable laser bead immunoassay; ANA, antinuclear antibodies; ICAP, International Consensus on ANA Pattern; IIF, indirect immunofluorescence. Images reproduced from [www.anapatterns.org](http://www.anapatterns.org) with permission.

Consensus on ANA Patterns (ICAP) framework provides structured IIF interpretation in SM [15], highlighting key patterns: nucleolar (AC-8/9/10), centromere (AC-3), speckled (AC-4/5), nuclear dots (AC-6), and the complex multicompartmental pattern (AC-29). Sero-serological correlation between IIF and solid-phase results further serves to detect false negatives, as illustrated by lineblot failure to reliably detect anti-Th/To [16], or to flag false positives such as anti-PM/Scl [17].

### NAILFOLD VIDEOCAPILLAROSCOPY: A WINDOW INTO SCLEROMYOSITIS VASCULOPATHY

Nailfold videocapillaroscopy (NVC) is an accessible, low-cost, noninvasive tool with major diagnostic relevance in SM, as it provides direct visualization of the microangiopathy central to its pathogenesis [18,19]. Cutolo *et al.* described three canonical scleroderma NVC patterns: the early, active and late patterns [20]. Another category, the scleroderma-like pattern, describes mixed findings that share qualitative features of SSc-type vasculopathy without satisfying the criteria for any single canonical stage [21–23] (Fig. 3). This pattern was essentially described in dermatomyositis (DM), in which capillary abnormalities characteristic of different SSc stages appear simultaneously [24]; a combination essentially absent in classic SSc as supported by a large Italian cohort of 1689 SSc patients where none displayed scleroderma-like patterns [25<sup>■</sup>]. SM substantially reframes this paradigm.

In a recent cohort of 99 AIM patients including 24 with SM [26<sup>■</sup>], capillary density was lowest in SM (mean  $5.3 \pm 2.1$  capillaries/mm), numerically below DM ( $5.7 \pm 2.1$ ) and significantly lower than immune mediated necrotizing myopathy (IMNM)/polymyositis (PM)/inclusion body myositis (IBM) ( $8.6 \pm 1.4$ ,  $P < 0.001$ ), placing SM at the severe end of the microvascular injury spectrum. Giant ramified capillaries were present in 29% of SM cases vs. 17% in DM, 6% in antisynthetase syndrome (ASyS), and none in IMNM/PM/IBM. Strikingly, 75% of SM patients displayed scleroderma-active (33%) or scleroderma-like (42%) patterns, while no early or late canonical SSc patterns were identified, supporting the concept that acute immune injury in SM drives accelerated, disorganized microvascular remodeling that does not follow the orderly sequential progression of classic SSc [20].

The mechanistic basis of NVC abnormalities in SM may involve type I interferon-driven vascular injury, as NVC parameters correlate with interferon-stimulated genes in DM [27], and patients with scleroderma-like patterns in the above-mentioned

cohort [26<sup>■</sup>] were predominantly DM or anti-PM/Scl-positive SM. The latter has historically been termed as “sclerodermatomyositis” [28] and upregulation of genes associated with type I interferon signaling has been reported in SM muscle biopsies, particularly in anti-PM/Scl-positive patients [29].

From a diagnostic standpoint, no single NVC pattern reliably distinguishes SM from DM or ASyS [26<sup>■</sup>]. However, NVC retains strong binary discriminating capacity against myopathies likely to be confused with SM as scleroderma-active or scleroderma-like patterns were present in none of IMNM or IBM patients. This distinction is particularly valuable in clinically ambiguous *sine scleroderma* presentations with IBM-like distal weakness [30] or an IMNM-like biopsy pattern [31<sup>■</sup>]. These findings support routine integration of NVC into the diagnostic evaluation of any patient in whom SM is under consideration or needs to be excluded.

### CAPILLARY PATHOLOGY AS THE HISTOPATHOLOGICAL HALLMARK OF SM: A TOOL TO SUPPORT AN EARLY DIAGNOSIS

Muscle biopsy in SM reveals a heterogeneous histopathological spectrum [32] in which vasculopathy is the cardinal and unifying lesion that distinguishes SM from other AIM [31<sup>■</sup>].

A systematic, stepwise approach to muscle pathology to screen for SM is therefore recommended (Fig. 4):

- (1) The first step is screening for capillary vasculopathy using collagen-4 immunohistochemistry (ideally by immunofluorescence), which simultaneously demonstrates capillary enlargement, dropout, and sometimes hints at basement membrane reduplication (see Fig. 4); CD31 immunohistochemistry is another practical, although less sensitive, alternative when collagen-4 is unavailable.
- (2) The second step is screening by electron microscopy for the ultrastructural hallmark of SM: marked capillary basement membrane reduplication defined as  $\geq 4$  thin layers in  $>50\%$  of capillaries. In the largest ultrastructural study published thus far, this finding was present in 65% of SM cases and absent in all AIM controls ( $P < 0.001$ ) [31<sup>■</sup>]. It was identified in similar proportions in SM patients not fulfilling the ACR/EULAR SSc criteria, in SM presenting *sine scleroderma*, and in *seronegative* SM. Importantly, milder capillary basement membrane reduplication of fewer than 4 layers is less specific, observed in up to 32% of AIM controls in that

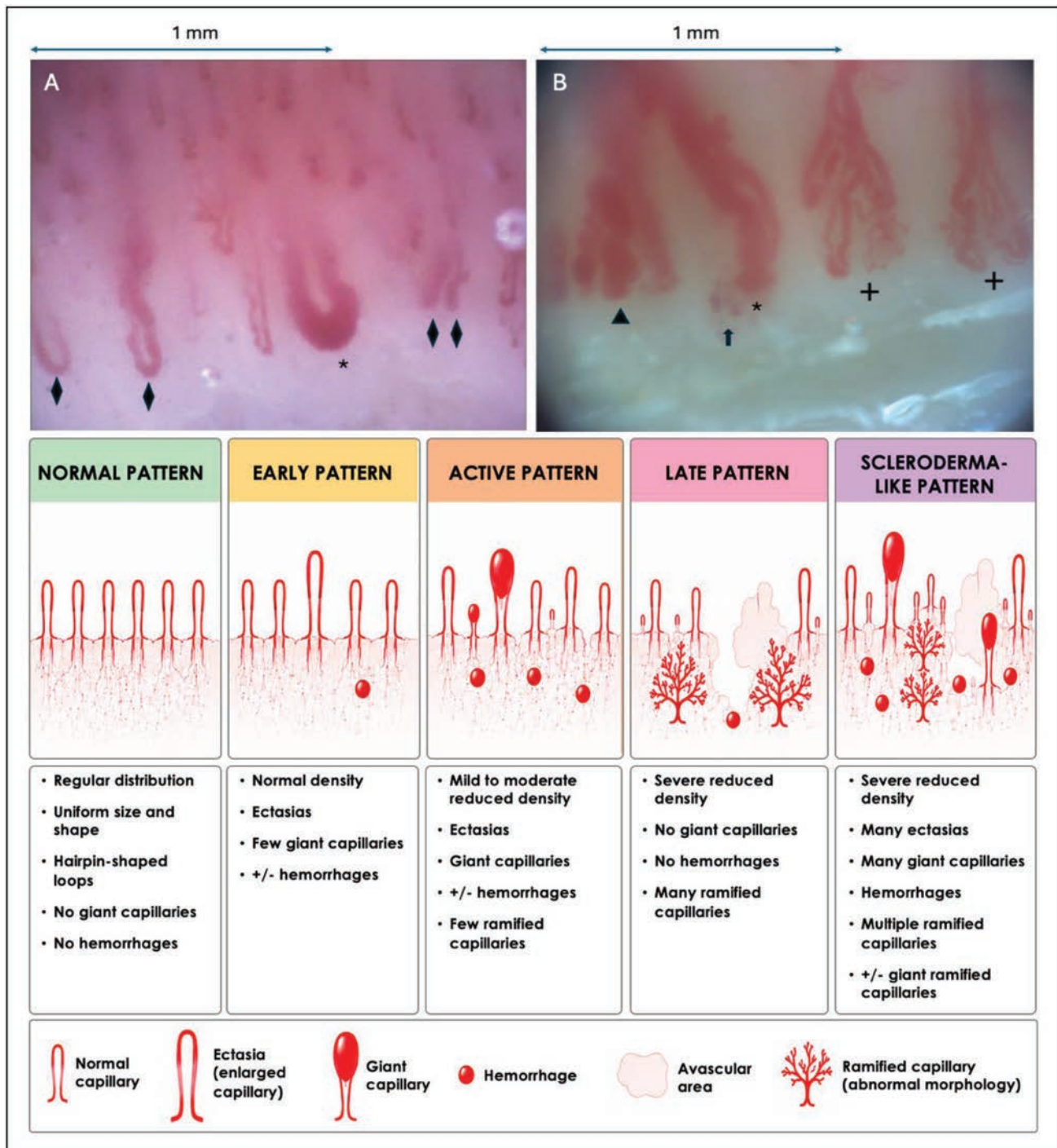


**FIGURE 3.** Identifying the scleroderma-active (A) and the 'scleroderma-like' (B) NVC pattern in a myopathic patient. The early pattern is characterized by preserved capillary density with giant capillaries ( $>50\mu\text{m}$ ); the active pattern by mild-to-moderate capillary loss ( $4\text{--}6/\text{mm}$ ) with giant capillaries and abnormal morphologies; and the late pattern by severely reduced capillary density ( $\leq 3/\text{mm}$ ), abnormal morphologies, and absence of giant capillaries. The scleroderma-like pattern is characterized by the simultaneous presence of multiple abnormal capillary morphologies, giant capillaries, and severely reduced density; these findings are not expected in the early, active or late pattern. Schematic representation of nailfold videocapillaroscopy patterns were created using OpenAI's ChatGPT. Panel A: \* giant capillary, ♦ ectasia, density: 5 capillaries/1 linear mm. Panel B: \* giant capillary, ▲ giant ramified capillary, + ramified capillary ('abnormal morphology'), † hemorrhage, density: 2 capillaries/1 linear mm.

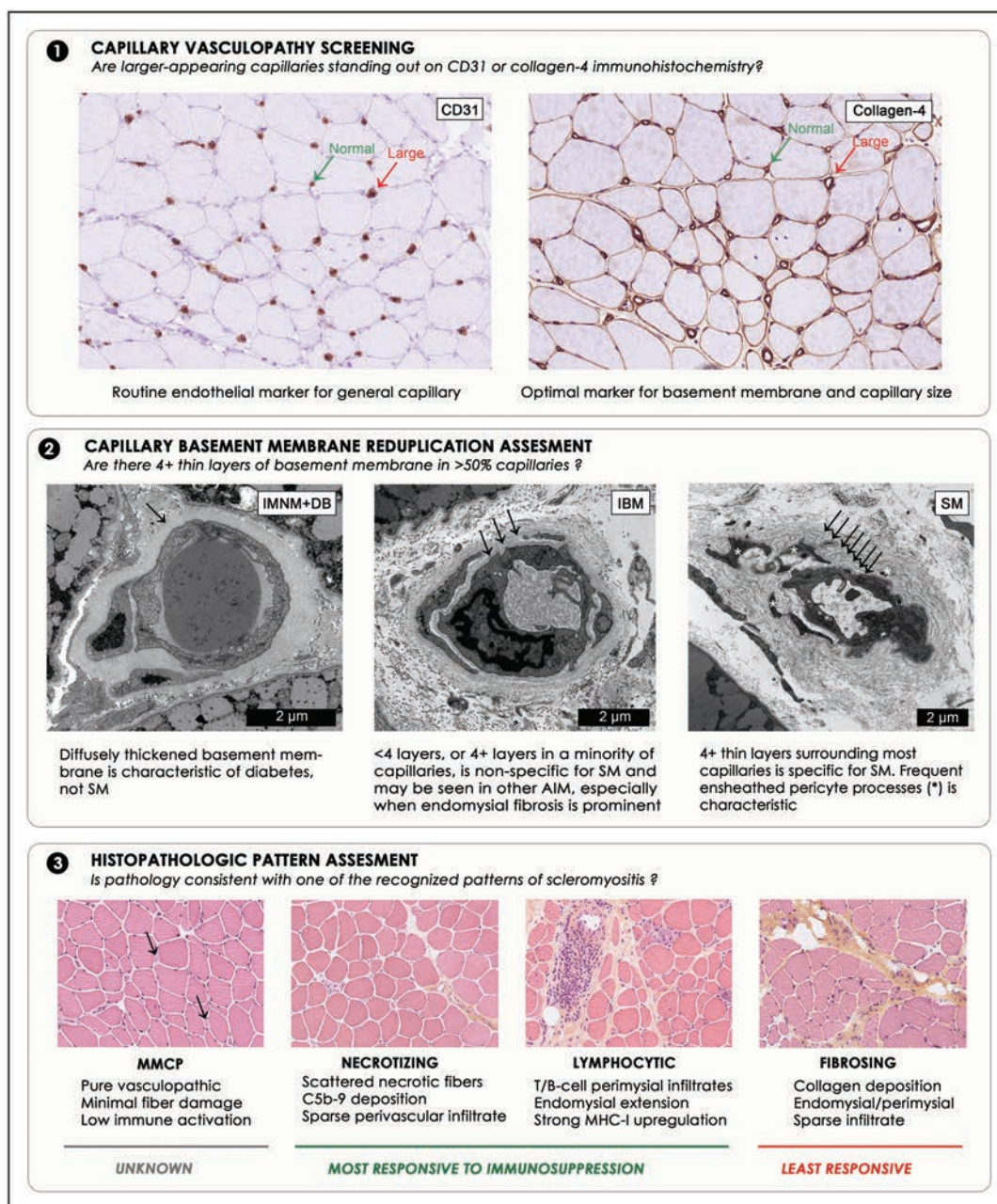


**FIGURE 4.** Stepwise screening for scleromyositis on muscle pathology.

Step 1: CD31 can be used to screen for capillary dropout but collagen-4 better defines capillary contours and basement membrane (BM), especially when used when used on IF. Step 2:  $\geq 4$  thin concentric BM layers reliably distinguish scleromyositis (SM) from other autoimmune myositis (AIM) subsets. Milder or less frequent BM reduplication, present in ~30% of SM and in other AIM subsets, is nonspecific and requires light-microscopic and clinico-serological correlation. Step 3: Histopathologic patterns may occur alone or in combination and may reflect sampling or disease duration. Arrows indicate capillaries (Step 1), BM (Step 2), and large capillaries in MMCP (Step 3). IBM, inclusion body myositis; IMNM, immune-mediated necrotizing myopathy; MMCP, minimal myopathy with capillary pathology.

series and known to occur in certain nonimmune myopathies [33], underscoring the importance of assessing its extent rather than its mere presence.

- (3) The third step is classification by light microscopy into one of four currently recognized SM histopathological patterns, all sharing the underlying vasculopathic substrate: minimal myositis with capillary pathology 'MMCP' [34]; inflammatory (i.e. *lymphocytic*) myopathy [35]; IMNM-like necrotizing myopathy [36]; and fibrosing myopathy [36]. These patterns carry direct therapeutic implications as available data suggest that inflammatory and necrotizing patterns are most responsive to immunosuppressive treatment, whereas isolated fibrosing myopathy are less responsive [13,35,37]. The efficacy of immunosuppressive therapy on the vasculopathy component of SM remains uncertain; however, recent data from the Systemic sclerosis Progression INvestiGation (SPRING) registry show that mycophenolate mofetil was associated with a 95% reduction in the risk of vasoactive treatment escalation in patients with SSc [38], raising the possibility that immunosuppression may confer collateral vascular protection in SM.

Histopathological features in SM also appear to track with autoantibody specificity [32]. Anti-Ku SM has recently been examined more extensively and, in addition to the IMNM-like and lymphocytic patterns, has been shown to exhibit hallmark capillary features and distinctive sarcoplasmic protein aggregates linked to dysregulated autophagy and immunoproteasome function [39<sup>■</sup>]. Histopathological data remain scarce for more recently identified autoantibodies in SM. Recent case reports and small series have described anti-RuvBL1/2-positive SM presenting with an IMNM-like histological pattern in patients with subtle SSc features [40,41], further broadening the differential diagnosis of necrotizing myopathy and reinforcing the importance of systematic clinical assessment in patient who lacks IMNM-specific antibodies.

When the histopathological pattern is lymphocytic/inflammatory, SM may manifest as brachio-cervical inflammatory myopathy (BCIM), a distinctive clinico-pathological phenotype also described in association with other systemic autoimmune diseases, including Sjögren's disease, myasthenia gravis, and rheumatoid arthritis [30]. A recent study comparing BCIM patients with and without ACR/EULAR defined SSc reported similar ultrastructural capillary pathology across both groups, including endothelial activation and capillary basement membrane reduplication [42]. However, it remains uncertain whether the

changes observed in non-SSc BCIM correspond to the above-mentioned marked capillary basement membrane reduplication characteristic of SM, or instead to a milder nonspecific reduplication that may accompany chronic endomysial inflammation/fibrosis, as reported in IBM [31<sup>■</sup>], or even fibrosis alone as reported in Duchenne muscular dystrophy [33]. As discussed above, the low sensitivity of ACR/EULAR SSc criteria for atypical muscle-dominant presentations further complicates this boundary.

## RECENT ADVANCES IN SCLEROMYOSITIS PATHOGENESIS

Capillaropathy, a major histopathological hallmark of SM [31<sup>■</sup>,34], is the entry point into its poorly understood pathophysiology. SM vasculopathy is characterized by endothelial activation and pericyte proliferation [34], and the close correlation between the number of reduplicated basement membrane layers and ensheathed pericyte processes supports a central role for pericytes in microvascular–basement membrane remodeling [31<sup>■</sup>]. Pericytes can further migrate into the interstitial space and differentiate into myofibroblasts, thereby contributing not only to microvascular destabilization but also to fibrosis [43<sup>■</sup>,44<sup>■</sup>] and positioning pericyte dysfunction as a mechanistic link between capillaropathy and fibrosis in SM. These observations are consistent with our preliminary bulk RNA sequencing analysis performed on muscle biopsies from 23 treatment-naïve SM patients, compared with 31 other AIM patients and 7 nonneuromuscular controls from a bicentric Strasbourg–Montreal cohort. SM muscle displayed 239 uniquely dysregulated genes enriched in pathways related to collagen formation and extracellular matrix remodeling [45], further confirming SM as a distinct entity within AIM.

More recently, growing evidence suggests that autoantibodies may directly participate in disease pathogenesis. Autoantibodies from myositis patients, including anti-PM/Scl and anti-Ku antibodies associated with SM, have been shown to be internalized into myofibers and to localize within the same subcellular compartment as their corresponding autoantigen, potentially disrupting the physiological function of the targeted protein [46<sup>■</sup>,47]. In muscle from anti-PM/Scl-positive patients, nucleolar immunoglobulin deposition and transcriptomic alterations involving long noncoding RNAs and divergent transcripts suggest dysfunction of the nuclear RNA exosome complex [46<sup>■</sup>]. Anti-Ku antibodies may also contribute to vascular injury through endothelial reactivity [48] and interfere with Ku70/Ku80-dependent pathways involved in DNA repair, cellular stress responses, and autophagy [46<sup>■</sup>,49].

Altogether, these findings suggest that SM represents a distinct AIM subgroup characterized by a shared vasculopathic and profibrotic signature, while part of its biological heterogeneity may depend on the specific intracellular pathways disrupted by individual autoantibodies.

### **SCLEROMYOSITIS PROGNOSIS: INDEPENDENT MORTALITY BURDEN AND CARDIAC RISK**

Recent cohort studies have demonstrated that cardiac involvement is among the strongest determinants of disease severity and long-term outcomes in SM. Three Johns Hopkins cohort studies [8<sup>22</sup>, 50<sup>22</sup>, 51<sup>22</sup>] establishes SM as a clinically severe phenotype with independent and substantial prognostic burden. Skeletal myopathy in SSc confers a 1.6-fold independent hazard of death (HR 1.60,  $P < 0.0001$ ) persisting after adjustment for age, race, disease duration, SSc subtype, serology and cardiopulmonary confounders, confirming that muscle involvement is a primary disease manifestation rather than a proxy for overall severity. Cardiac complications represent the most immediate prognostic threat, with anti-Ku emerging as a potentially higher-risk autoantibody associated with myocarditis (43% ( $n = 3/7$ ),  $P = 0.003$ ) [50<sup>22</sup>] and, alongside skeletal myopathy, as one of the two strongest predictors of severe left ventricular systolic dysfunction across 2303 SSc patients [51<sup>22</sup>]. A large cohort of 154 anti-Ku patients [52<sup>22</sup>] further corroborates this trajectory, identifying a muscle-dominant SM cluster with a cumulative myocarditis rate of 22% ( $n = 9/41$ ) at follow-up; as this cohort was selected on the basis of anti-Ku positivity, the observed rate reflects the burden within this specific serological subset rather than a direct comparison of risk across autoantibody profiles. In a recent single-center retrospective cohort, myocarditis was identified in 9 of 142 myositis cases (6%) and was associated with Raynaud phenomenon, antiphospholipid antibody positivity and anti-Ro52 coexistence [53<sup>22</sup>]. The presence of myopathy in SSc should therefore be treated as a high-risk profile warranting immediate cardiac evaluation irrespective of autoantibody profile. A retrospective study of 71 SM patients found no difference in overall mortality across histological patterns, with a 10-year mortality rate of 20% and cardiac events as the leading cause of death [54<sup>22</sup>], further reinforcing that cardiac surveillance is warranted in all SM patients regardless of biopsy subtype. Based on these findings, a cardiac screening strategy comprising troponin I, NT-ProBNP, EKG and, if any result is abnormal, a cardiac MRI has been proposed at the time of SM diagnosis [50<sup>22</sup>].

### **AN EMPIRICAL TREATMENT LANDSCAPE PENDING CONSENSUAL DISEASE DEFINITION AND CLINICAL TRIAL INCLUSION**

No dedicated randomized controlled trials exist in SM; management relies on observational data, expert opinion, and extrapolation from SSc and AIM studies, with uniformly low levels of evidence [55]. The 2023 EULAR SSc recommendations do not specifically address SM [56]. Future efforts to establish a consensus definition of SM and ensure its inclusion in clinical trials [57] will be essential to improve the evidence base and guide management.

### **CONCLUSION**

SM is an underrecognized but clinically severe myositis subset that carries independent mortality burden, high cardiac risk, and a broad phenotypic spectrum that routinely escapes existing classification frameworks. Early diagnosis requires systematic integration of clinical, serological, capillaroscopic, and histopathological data, with capillary vasculopathy as the unifying pathological thread across all disease manifestations. Establishing a consensus SM definition and securing its inclusion in clinical trials represent the most urgent priorities to translate this growing evidence base into improved patient outcomes.

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## Conflicts of interest

There are no conflicts of interest.

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# Inclusion body myositis: new insights into pathogenesis and therapeutic perspectives

*François Fer and Olivier Benveniste*

## Purpose of review

Inclusion body myositis (IBM) is the most common acquired myopathy in individuals over 50 years of age and remains refractory to conventional immunosuppressive therapies. This review summarizes recent advances in the understanding of IBM pathogenesis and highlights emerging therapeutic strategies.

## Recent findings

Recent studies have refined the understanding of the interplay between degenerative and immune-mediated mechanisms in IBM. Abnormal protein aggregation, impaired proteostasis, and alterations of the autophagic pathway contribute to muscle fiber degeneration. In parallel, increasing evidence supports a central role for highly differentiated cytotoxic CD8<sup>+</sup> T cells invading major histocompatibility complex class I-expressing muscle fibers. Recent immunophenotyping studies have identified expanded populations of terminally differentiated killer cell lectin-like receptor G1-expressing CD8<sup>+</sup> T cells in blood and muscle, suggesting a potential role for these cells in sustaining chronic muscle injury. These findings have prompted the development of targeted immunotherapies aimed at selectively modulating pathogenic cytotoxic T-cell populations.

## Summary

IBM appears to result from a complex interaction between degenerative and immune-mediated pathways. Improved characterization of the immune effector cells involved in muscle injury is opening new avenues for targeted therapies and may ultimately lead to treatments for this condition that currently lacks disease-modifying therapy.

## Keywords

CD8<sup>+</sup> T cells, killer cell lectin-like receptor G1, muscle degeneration, sporadic inclusion body myositis, targeted immunotherapy

## INTRODUCTION

Inclusion body myositis (IBM) predominantly affects individuals over 50 years of age and is the most common acquired myopathy in this population. The diagnosis is based on a combination of clinical, histopathological, and increasingly serological features. Clinically, the disease is characterized by slowly progressive muscle weakness preferentially affecting the quadriceps and deep finger flexors [1], often leading to difficulties with climbing stairs, rising from a chair, or performing fine motor tasks. Dysphagia is also common and may develop during the course of the disease [2].

Serum creatine kinase levels are typically normal or only mildly elevated [3]. Muscle biopsy remains the cornerstone of diagnosis with a distinctive combination of inflammatory and degenerative changes, including endomysial infiltrates composed predominantly of CD8<sup>+</sup> cytotoxic T lymphocytes invading nonnecrotic muscle fibers [4,5] expressing major

histocompatibility complex class I (MHC-I) and class II (MHC-II) [6], together with degenerative abnormalities such as rimmed vacuoles [7], protein aggregates [8], and mitochondrial alterations [9,10]. Muscle imaging, particularly magnetic resonance imaging, may also support the diagnosis by demonstrating a characteristic pattern of muscle involvement [11,12].

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## KEY POINTS

- Inclusion body myositis is increasingly viewed as a disease driven by interactions between immune-mediated and degenerative mechanisms.
- Highly differentiated cytotoxic CD8<sup>+</sup> T cells, including killer cell lectin-like receptor G1<sup>+</sup> populations, have emerged as key effectors in inclusion body myositis (IBM) muscle injury.
- Recent multiomics and single-cell studies have refined the understanding of innate immune activation, mitochondrial dysfunction, and TDP-43-related pathology in IBM.
- Emerging therapeutic strategies will likely need to target both persistent immune activation and muscle-intrinsic degenerative pathways.
- Improved understanding of IBM pathogenesis may facilitate the development of effective disease-modifying therapies.

In contrast to other idiopathic inflammatory myopathies, IBM typically responds poorly to conventional immunosuppressive therapies [2,13] and currently lacks effective disease-modifying treatment.

This coexistence of immune and degenerative features in the muscle biopsy has long fueled debate regarding the primary mechanisms driving the disease. Increasing evidence suggests that IBM results from a complex interplay between immune-mediated muscle injury and intrinsic degenerative processes affecting muscle fibers [14]. In the past decade, advances in immunophenotyping, the development of new experimental models, and the emergence of targeted therapeutic strategies have further refined our understanding of the disease. This review summarizes recent progress in the pathogenesis of IBM and discusses the implications of these findings for future therapeutic approaches.

## RECENT ADVANCES IN THE IMMUNOPATHOLOGY OF INCLUSION BODY MYOSITIS

### Highly differentiated cytotoxic T cells and immunosenescence

Recent studies have refined the characterization of immune effector cells involved in IBM, highlighting the central role of highly differentiated cytotoxic CD8<sup>+</sup> T cells. These cells exhibit features of terminal differentiation, including low proliferative activity

[15], expression of cytotoxic mediators such as perforin and granzyme B [15,16], and persistence within affected muscle tissue.

This phenotype is consistent with immunosenescent or TEMRA (terminally differentiated effector memory T-cells)-like T cells [15], which accumulate during chronic antigen exposure and aging. Their accumulation in IBM muscle suggests that the disease is driven, at least in part, by long-lived effector populations capable of maintaining a chronic cytotoxic response. This may provide a mechanistic explanation for the limited efficacy of conventional immunosuppressive therapies, which primarily target proliferating immune cells but may spare these terminally differentiated populations.

### Killer cell lectin-like receptor G1-expressing T cells as pathogenic effectors

Among these populations, expanded CD8<sup>+</sup> T cells expressing killer cell lectin-like receptor G1 (KLRG1) have emerged as a particularly relevant subset. KLRG1 is associated with terminal differentiation and sustained cytotoxic function, and KLRG1<sup>+</sup> T cells have been identified both in peripheral blood and within IBM muscle tissue [15,16].

These cells frequently co-express additional markers of terminal differentiation and cytotoxicity, including CD57, perforin, and granzyme B [17], supporting the concept that they represent antigen-experienced, long-lived effector cells. Their persistence within muscle tissue and resistance to regulation suggest that they may play a key role in sustaining myofiber injury over time. In addition, KLRG1 expression may serve not only as a phenotypic marker but also as a potential therapeutic target, with emerging strategies aiming to selectively deplete these highly differentiated effector cells. However, whether KLRG1<sup>+</sup> T cells represent true drivers of disease or a downstream consequence of chronic antigenic stimulation remains to be fully established.

Altogether, these findings support a model in which IBM is not characterized by acute inflammation, but rather by a chronic, antigen-driven immune response maintained by immunosenescent cytotoxic T cells.

### Increasing complexity of the immune microenvironment

Recent single-nuclei analyses have identified infiltrating dendritic cells, macrophages, plasma cells, and distinct T-cell subsets within IBM muscle tissue, indicating a more complex immune microenvironment than previously appreciated.

In particular, myeloid dendritic cells expressing interferon-related programs may contribute to local activation and maintenance of cytotoxic T-cell responses [18<sup>\*\*\*</sup>]. In parallel, transcriptomic and repertoire analyses provide evidence of local immunoglobulin production [19], suggesting that local humoral immune responses may also occur in a subset of patients.

## Innate immunity

Beyond adaptive immune responses, increasing evidence points to a contribution of innate immune pathways in IBM. Multiple studies have identified a prominent interferon (IFN) signature within affected IBM muscle tissue, predominantly involving IFN $\gamma$ -related pathways, including STAT1 activation and CXCL9/CXCL10-associated chemokine programs [8,20]. IFN $\gamma$  may contribute to disease pathogenesis by promoting major histocompatibility complex class I upregulation on myofibers and sustaining local immune activation [21]. Recent studies also identified abnormal MHC class II/HLA-DR expression patterns in IBM muscle tissue, supporting activation of IFN $\gamma$ -associated antigen-presentation pathways [22].

Emerging data also suggest that IFN-driven signaling may influence muscle fiber homeostasis, including effects on muscle regeneration and cellular stress responses. In particular, IFN $\gamma$  has been associated with impaired myogenic differentiation and satellite cell regenerative capacity, potentially limiting muscle repair in experimental models [23<sup>\*</sup>], which could contribute to progressive muscle degeneration.

In parallel, recent studies suggest activation of innate immune sensing pathways, particularly cGAS–STING (cyclic GMP–AMP synthase – stimulator of interferon genes) signaling, potentially triggered by mitochondrial damage and the release of mitochondrial DNA-associated danger signals [24<sup>\*</sup>]. These findings support a model in which muscle-intrinsic stress signals engage innate immune pathways, thereby sustaining and amplifying local inflammation.

Together, these data indicate that IBM immunopathology extends beyond classical adaptive immunity and involves a self-reinforcing interaction between cytotoxic T cells and innate immune activation.

## EMERGING EXPERIMENTAL MODELS AND MOLECULAR INSIGHTS

### New experimental models

The development of novel experimental systems has begun to address longstanding limitations in modeling IBM. Xenograft models, in which human IBM muscle tissue is transplanted into immunodeficient

mice [25], have provided valuable insight into the persistence of human immune cells and their interactions with muscle fibers in vivo.

In parallel, induced pluripotent stem cell-derived muscle models have enabled the study of muscle-intrinsic mechanisms in a controlled environment. Recent work has shown that patient-derived iPSC myotubes can reproduce several key features of the disease, including alterations in protein homeostasis, mitochondrial dysfunction, and stress-related pathways [26], supporting the concept that muscle fibers are not merely passive targets but may actively contribute to disease pathogenesis.

## Multomics approaches and integrated pathogenic pathways

Advances in high-throughput technologies, including transcriptomics, proteomics, and single-cell sequencing, have significantly refined our understanding of IBM. These approaches have revealed coordinated alterations in inflammatory signaling, cellular stress responses, protein degradation pathways, and myofiber homeostasis within affected muscle tissue. In particular, single-cell and single-nucleus analyses have highlighted the coexistence of multiple pathogenic processes across distinct cellular populations, supporting a model of IBM as a multicellular disease ecosystem in which immune cells, stressed myofibers, and degenerative pathways interact dynamically rather than operating as isolated processes [20].

Among muscle-intrinsic mechanisms, increasing attention has focused on the role of TDP-43 (TAR DNA-binding protein 43), a DNA/RNA-binding protein implicated in several neurodegenerative disorders. In IBM muscle fibers, TDP-43 is frequently mislocalized from the nucleus to the cytoplasm, where it forms abnormal aggregates. This mislocalization is associated with a loss of nuclear TDP-43 function, leading to abnormal RNA splicing and processing, including the inclusion of normally repressed “cryptic” exons within mRNA transcripts [27<sup>\*\*\*</sup>], potentially resulting in the production of dysfunctional proteins [28]. These alterations may contribute to muscle fiber stress and degeneration beyond immune-mediated injury.

Notably, experimental data indicate that TDP-43-related abnormalities may persist even in the absence of ongoing immune cell activity, supporting the concept that degenerative processes can become, at least in part, self-sustaining [25]. In this context, recent work has identified seeding-competent TDP-43 species in both human IBM muscle and experimental models, capable of inducing TDP-43 aggregation in vitro. These seeding-competent conformers

can persist even after the resolution of overt aggregate pathology, suggesting that pathogenic TDP-43 conformers may be maintained independently of visible inclusions [29]. These findings provide support for a prion-like mechanism of TDP-43 aggregation, although the extent to which such processes contribute to disease propagation *in vivo* remains to be established.

Together, these findings position TDP-43 dysfunction as a central node linking impaired proteostasis, cellular stress responses, and muscle fiber degeneration, within a broader framework in which immune-mediated injury and muscle-intrinsic mechanisms interact in a self-amplifying pathogenic loop.

### Conceptual advances: toward an integrated model of inclusion body myositis pathogenesis

The traditional view of IBM has long been structured around a dichotomy between immune-mediated and degenerative mechanisms. However, recent advances challenge this binary framework and instead support a more integrated model of disease pathogenesis.

Accumulating data suggest that IBM arises from interactions between highly differentiated cytotoxic T cells, interferon-driven innate immune pathways, and muscle-intrinsic stress responses, including impaired proteostasis, mitochondrial dysfunction, and abnormal RNA processing. In this model, chronic immune activation and IFN $\gamma$  signaling promote myofiber stress, major histocompatibility complex class I upregulation, and protein aggregation within muscle fibers, while degenerative alterations such as mitochondrial damage and TDP-43 dysfunction may further stimulate innate immune sensing pathways, including cGAS–STING signaling, thereby sustaining local inflammation and creating a self-amplifying pathogenic loop (Fig. 1).

This integrated perspective is supported by recent multiomics and single-cell studies demonstrating the coexistence of inflammatory, stress-response, and degenerative programs across distinct cellular populations within IBM muscle tissue. Importantly, this framework may help explain the limited efficacy of therapies targeting a single pathway and supports the rationale for combined therapeutic approaches addressing both immune and muscle-intrinsic mechanisms [20,24\*].

### THERAPEUTIC PERSPECTIVES

The limited efficacy of conventional immunosuppressive therapies in IBM highlights the complexity of disease mechanisms and supports the concept that

IBM cannot be explained solely by classical autoimmunity. Recent therapeutic strategies have therefore increasingly focused on selectively targeting highly differentiated cytotoxic T-cell populations, interferon-related pathways, and muscle-intrinsic degenerative mechanisms.

### Emerging targeted immunotherapies

Advances in immunophenotyping have opened the possibility of therapies targeting specific pathogenic immune cell subsets. In particular, strategies directed against highly differentiated cytotoxic T cells are being explored. Monoclonal antibodies targeting KLRG1 represent one such approach, aiming to selectively deplete terminally differentiated effector T cells while sparing other immune compartments. Although a phase 2/3 study (ClinicalTrials.gov identifier NCT05721573) evaluating the anti-KLRG1 antibody ulviprubart did not reach statistical significance in the overall population for its primary endpoint (change from baseline in the IBMFRS total score at week 76) or for its main secondary endpoints (MMT-12, hand-grip and quadriceps strength, and the modified Timed Up and Go test), subgroup analyses suggested potential benefits in patients with mild to moderate disease [30].

Beyond cell-targeted strategies, the identification of interferon-driven pathways and innate immune activation has highlighted upstream inflammatory signaling as a therapeutic target. Ruxolitinib, a JAK inhibitor modulating the IFN $\gamma$  pathway, is currently under investigation (NCT06536166) following promising *in vitro* and preclinical data [23\*].

### Targeting muscle-intrinsic degenerative pathways

In addition to immune-targeted strategies, growing attention has focused on therapeutic approaches addressing muscle-intrinsic mechanisms of disease. The identification of impaired proteostasis, including TDP-43 dysfunction and protein aggregation, provides a strong rationale for interventions aimed at restoring cellular homeostasis. Modulation of autophagy, lysosomal function, and protein degradation pathways may help limit the accumulation of misfolded proteins within muscle fibers.

However, the extent to which these pathways can be effectively targeted *in vivo* remains uncertain, and clinical translation has so far been limited. More broadly, the recognition that muscle fibers actively contribute to disease pathogenesis through stress responses and metabolic dysfunction further supports the need to address intrinsic vulnerability in addition to immune-mediated injury.

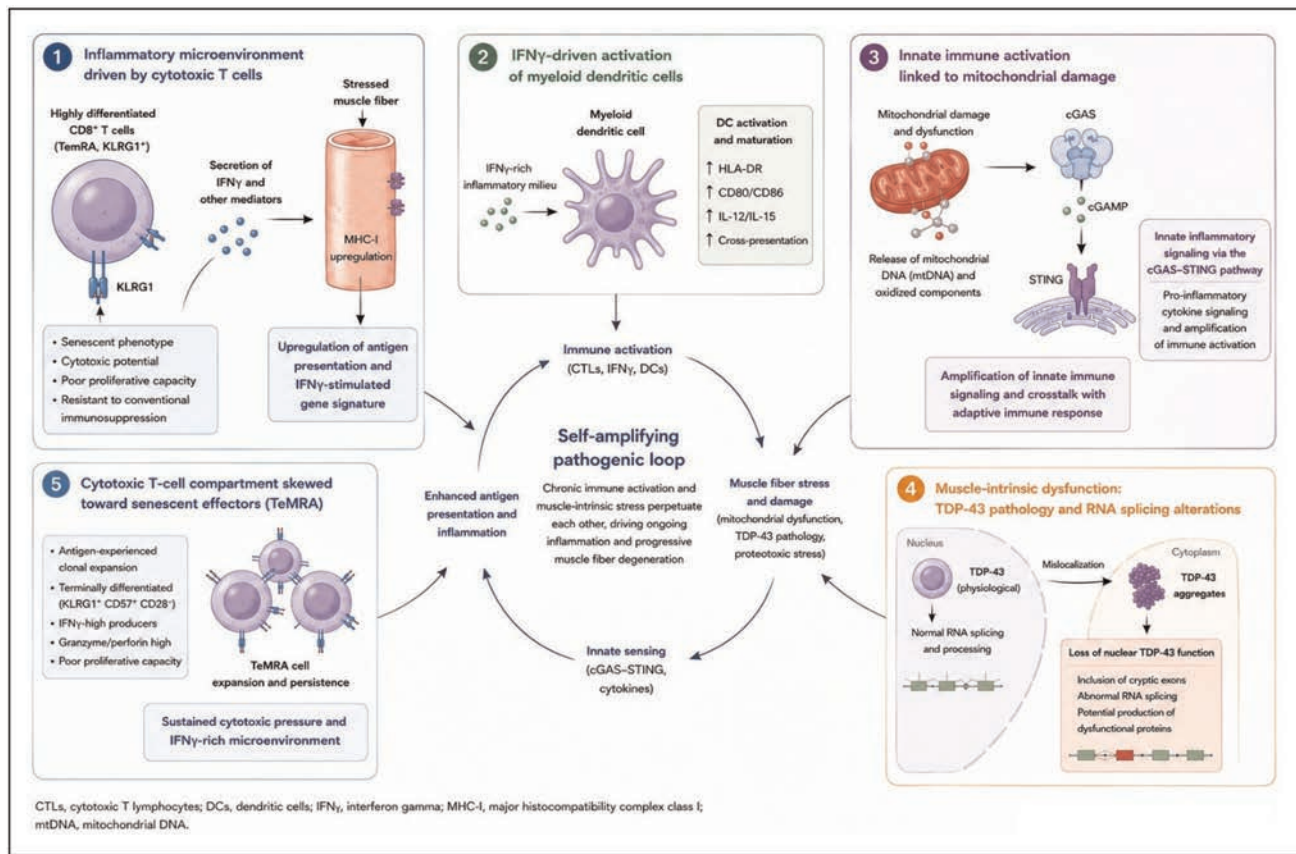


**FIGURE 1.** New insights into the pathophysiology of inclusion body myositis. Recent findings support a model in which chronic cytotoxic T-cell activation, IFN $\gamma$ -associated inflammatory signaling, innate immune sensing, mitochondrial dysfunction, and impaired proteostasis interact in a self-amplifying pathogenic loop within IBM muscle tissue. Highly differentiated KLRG1<sup>+</sup>/TEMRA-like CD8<sup>+</sup> T cells and myeloid immune populations contribute to persistent immune activation, while muscle-intrinsic alterations including TDP-43 dysfunction, abnormal RNA processing, mitochondrial damage, and impaired autophagy promote cellular stress and innate immune pathway activation, including cGAS–STING signaling. Together, these interconnected mechanisms may sustain progressive myofiber degeneration and contribute to therapeutic resistance.

### Integrating therapeutic strategies

Taken together, these findings suggest that effective disease modification will likely require therapeutic approaches targeting both immune and muscle-intrinsic pathogenic mechanisms.

This framework may help explain the limited success of previous clinical trials and highlights

the importance of mechanism-based and potentially stage-specific therapeutic strategies in IBM.

Sirolimus, an mTOR inhibitor with dual effects on immune modulation and autophagy regulation, represents a particularly interesting example of a strategy targeting both pathogenic axes in IBM. By modulating T-cell activation while simultaneously

**Table 1.** Emerging therapeutic strategies targeting distinct pathogenic pathways in IBM

| Pathogenic axis               | Targeted pathway                     | Example     | Rationale                          |
|-------------------------------|--------------------------------------|-------------|------------------------------------|
| Adaptive immunity             | KLRG1 <sup>+</sup> cytotoxic T cells | Ulviprubart | immunosenescent T cells            |
| Innate/inflammatory signaling | IFN-related pathways                 | Ruxolitinib | IFN $\gamma$ -driven inflammation  |
| Muscle-intrinsic degeneration | mTOR/autophagy pathways              | Sirolimus   | proteostasis and immune modulation |

IBM, Inclusion body myositis; IFN $\gamma$ , interferon gamma.

enhancing autophagic pathways, sirolimus may address both persistent immune responses and impaired proteostasis within muscle fibers.

In a phase IIb study [31], sirolimus did not meet its primary endpoint; however, stabilization of the 6-min walk distance (6MWD) and of muscle fatty replacement evaluated by quantitative MRI was observed, suggesting a potential effect on disease progression. A phase IIb/III trial is ongoing (NCT04789070) [32] and may help clarify whether targeting converging immune and degenerative pathways can translate into meaningful clinical benefit.

Emerging therapeutic strategies targeting different pathogenic axes in IBM are summarized in Table 1.

## CONCLUSION

Inclusion body myositis is a complex disorder characterized by the interplay between immune-mediated muscle injury and intrinsic degenerative processes, resulting in progressive and disabling muscle weakness. Recent advances have refined the characterization of pathogenic immune effector populations, particularly highly differentiated cytotoxic CD8<sup>+</sup> T cells, including KLRG1-expressing subsets, which appear to play a central role in sustaining chronic muscle fiber injury. In parallel, emerging experimental models and molecular studies have provided new insights into muscle-intrinsic defects in proteostasis and protein aggregation pathways. Collectively, these findings support a more integrated view of IBM pathogenesis and are beginning to inform the development of targeted therapeutic strategies. Although effective disease-modifying treatments remain elusive, these advances represent an important step toward more mechanism-based therapeutic approaches.

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None.

## Conflicts of interest

*There are no conflicts of interest.*

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# The current clinical trial landscape in idiopathic inflammatory myopathies

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## Purpose of review

In recent years, advances in the understanding of idiopathic inflammatory myopathies (IIM) pathogenesis have led to the development of targeted therapies directed against key immune pathways. This review highlights recent advances in clinical trials, emerging therapeutic strategies, and the rapidly evolving treatment landscape in IIM, reflecting the continued expansion of the therapeutic armamentarium.

## Recent findings

Multiple clinical trials have evaluated therapeutics directed against key immune pathways implicated in IIM, including B-cell depletion, T-cell co-stimulation, type I interferon (IFN) signaling, fragment crystallizable receptor (FcRn) inhibition and Janus kinase (JAK) /STAT blockade. Promising results have been reported with agents such as JAK inhibitors, FcRn antagonists, anti-IFN therapies, and chimeric antigen receptor (CAR) T-cell approaches in selected patients. Several additional experimental trials are ongoing to evaluate novel therapeutic agents.

## Summary

Several recent landmark clinical trials in IIM suggest that targeted therapies directed at key immune pathways may improve disease control beyond conventional immunosuppression, supporting a shift toward mechanism-based treatment approaches in clinical practice. The rapid and expanding growth of clinical studies in IIM reflects an unprecedented acceleration in therapeutic development, underscoring the progress in the field.

## Keywords

chimeric antigen receptor, clinical trial, emerging treatments, idiopathic inflammatory myopathy

## INTRODUCTION

The idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of systemic autoimmune diseases with skeletal muscle involvement [1,2]. IIMs may present with multiple other organs involvement such as skin, lung, heart and joints and may overlap with other systemic autoimmune rheumatic diseases [2–4]. Despite experiencing significantly higher mortality compared to the general population [5–7], with risk profiles differing according to specific myositis-related antibodies [6], therapeutic options for IIM are largely dependent on broad immunosuppression.

In recent years, advances in the understanding of IIM pathogenesis have led to targeted therapies directed against key immune pathways, including B cells, T cells, type I interferon (IFN) signaling, fragment crystallizable receptor (FcRn) and Janus kinase (JAK)/STAT pathways. This review highlights the rapidly evolving treatment landscape in IIM.

## OVERVIEW OF ONGOING TRIALS

A summary of the active clinical trials in IIM and search strategy is provided in Table 1. A detailed

overview of active clinical trials in IIM is provided in Table S1, Supplemental Digital Content, <https://links.lww.com/COR/A64>. For the purpose of this review, we have excluded active trials in inclusion

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## KEY POINTS

- The therapeutic landscape in idiopathic inflammatory myopathies (IIM) is rapidly evolving, with an unprecedented number of active clinical trials.
- Recent clinical trials in IIM demonstrate a rapidly expanding pipeline of targeted and mechanism-based therapies, including B-cell, T-cell, interferon, FcRn, and JAK/STAT pathway inhibitors.
- Significant challenges remain for future clinical trials in IIM, including disease rarity, clinical heterogeneity and limited patient stratification.

body myositis and those not pertaining to investigational new drugs.

## INTRAVENOUS IMMUNOGLOBULINS

Intravenous immunoglobulins (IVIg) was first reported to be useful against a patient with IIM in 1987 [8]. Although the precise mechanisms underlying the therapeutic effects of IVIg in IIM are not fully elucidated, it is thought to act through multiple immunomodulatory pathways [9]. The safety and therapeutic benefit in dermatomyositis (DM) were first established in a randomized, double-blind, placebo-controlled trial in 1993 [10].

**Table 1.** Ongoing clinical trials in idiopathic inflammatory myopathies

| Mechanism of action                           | Number of active trials | Study drug(s)                                 | Phase I                                       | Phase II                                    | Phase III   |
|-----------------------------------------------|-------------------------|-----------------------------------------------|-----------------------------------------------|---------------------------------------------|-------------|
| CAR therapy                                   | 49                      | *                                             | #                                             | N/A                                         | N/A         |
| Complement inhibitors                         | 4                       | Anti-C1s;<br>Anti-C2;<br>Anti-Bb              | NCT06371417;<br>NCT06723106                   | NCT06284954;<br>NCT06887738                 |             |
| IFN inhibition                                | 3                       | Dazukibart; Anifrolumab                       | N/A                                           | NCT05895786;<br>NCT06698796;<br>NCT06455449 | N/A         |
| FcRn antagonist                               | 3                       | Nipocalimab; Efgartigimod                     | N/A                                           | NCT05379634;<br>NCT05523167                 | NCT05979441 |
| BiTE therapy                                  | 3                       | CD20 × CD8; CD19 ×<br>CD3;<br>BCMA × CD3      | NCT06916806;<br>NCT07284797;<br>NCT07229144   | N/A                                         | N/A         |
| TriTE therapy                                 | 3                       | CD19 × CD20 × CD3;<br>CD19 × CD28 × CD3       | NCT07371468 ;<br>NCT06888960 ;<br>NCT07193810 | N/A                                         | N/A         |
| JAK inhibitors                                | 2                       | Filgotinib; Baricitinib                       | N/A                                           | NCT06285539                                 | NCT04972760 |
| B-cell blockade                               | 2                       | Ublituximab; V001-BCMA                        | NCT07339540                                   | NCT07103746                                 | N/A         |
| Stem-cell transplantation                     | 2                       | MSC; UCLSC                                    | NCT06888973                                   | NCT07160205                                 | N/A         |
| Interleukin-2                                 | 2                       | Interleukin-2                                 | N/A                                           | NCT04237987;<br>NCT04062019                 | N/A         |
| Sodium Thiosulfate                            | 2                       | Sodium Thiosulfate                            | N/A                                           | NCT03582800;<br>NCT06672822                 | N/A         |
| IVIg                                          | 2                       | IVIg                                          | N/A                                           | NCT05832034;<br>NCT06599697                 | N/A         |
| MSC-exos-P1 Nebulized<br>MSC-derived exosomes | 1                       | MSC-exos-P1 Nebulized<br>MSC-derived exosomes | NCT06919380                                   | N/A                                         | N/A         |
| GLP-1 agonist                                 | 1                       | Froniglutide                                  | N/A                                           | NCT05833711                                 | N/A         |
| Allogeneic Cord Blood NK                      | 1                       | AlloNK                                        | N/A                                           | NCT06991114                                 | N/A         |
| Omega-3 Fatty Acid                            | 1                       | Omega-3 Fatty Acid                            | N/A                                           | NCT07111065                                 | N/A         |
| Topical Ruxolitinib                           | 1                       | Topical Ruxolitinib                           | N/A                                           | NCT06857240                                 | N/A         |
| mRNA-LNP                                      | 1                       | mRNA-LNP                                      | NCT07526350                                   |                                             | N/A         |

Table 1 (Continued)

| Mechanism of action     | Number of active trials | Study drug(s) | Phase I | Phase II    | Phase III |
|-------------------------|-------------------------|---------------|---------|-------------|-----------|
| Allogeneic Mitochondria | 1                       | PN-101        | N/A     | NCT07122648 | N/A       |

To identify clinical trials evaluating therapies for IIM, we performed a search of ClinicalTrials.gov on April 24, 2026. The search strategy included the terms "Myositis," "IIM," "Idiopathic inflammatory myopathies," and "Idiopathic inflammatory myopathy." Trials with a terminated status were excluded. Relevant trials were reviewed, and information regarding study design, population, interventions, and recruitment status was extracted.

[\*] CD19 CAR-T; CD19 STAR-T; CRISPR-Cas9-Engineered CD19T Cells; CD19/CD3E CAR-T; CD19/IL15 CAR-NK; CD19/IL-10/IL15 CAR-NK; CD19/PD-1 CAR- $\gamma\delta$  T; CD20  $\gamma\delta$  CAR-T; CD19/CD20 CAR-T; CD19/CD70 CAR-T; BCMA/CD70 CAR-T; BCMA CAR T; CD19/BCMA CAR T; CD19/CD22/BCMA CAR-T; BAFF-R CAR-T;  $\gamma\delta$  CAR-T; in vivo CAR-T; CAR-Treg.

[#] NCT06347718; NCT06154252; NCT06298019; NCT06152172; NCT05869955; NCT06685042; NCT06665256; NCT07212322; NCT06569472; NCT06686524; NCT06056921; NCT06361745; NCT06417398; NCT06986018; NCT07115745; NCT06308978; NCT06828042; NCT07526493; NCT06316076; NCT06733935; NCT07439029; NCT06379646; NCT06978647; NCT06925542; NCT06373081; NCT06255028; NCT06614270; NCT06970951; NCT06375993; NCT07038447; NCT07085104; NCT07184450; NCT07085676; NCT04561557; NCT07089121; NCT07295847; NCT07361094; NCT06548607; NCT06794008; NCT07086404; NCT07072884; NCT06350110; NCT06941129; NCT07315087; NCT07174843; NCT07022197; NCT06980597; NCT07413341; NCT07331272; NCT07527936.

BiTE, bi-specific T-cell engager; CAR, chimeric antigen receptor; FcRn, neonatal Fc receptor; IFN, interferon; IVIg, intravenous immunoglobulins; JAK, Janus kinase; LNP, lipid nanoparticle; mRNA, messenger ribonucleic acid; MSC, mesenchymal stem cells; NK, natural killer; TriTE, tri-specific T cell engager; UCLSC, umbilical cord lining stem cells.

A more recent investigator-initiated, phase II, open-label, single-arm pilot study (NTR6160) using IVIg (Privigen) monotherapy over 9 weeks demonstrated that first-line IVIg led to at least moderate response in 42% (8/19) of DM, immune-mediated necrotizing myopathy (IMNM), overlap myositis and antisynthetase syndrome (ASyS) patients, and within 3 weeks of IVIg in 6/8 responders, indicating a fast mode of action [11]. However, 37% of patients required rescue medication due to insufficient efficacy, and likely due to the absence of concomitantly administered treatment [11]. In contrast, the landmark phase III clinical trial *ProDERM* study (NCT02728752) allowed stable doses of concomitant background therapy [12]. In this double-blind, placebo-controlled trial, a total of 95 adults with active DM were randomized 1:1 to receive IVIg (Octagam 10%) at 2.0 g/kg or placebo every 4 weeks for 16 weeks, and patients meeting confirmed deterioration criteria could cross over [12]. This trial met its primary endpoint, with 79% (37/47) of IVIg patients vs. 44% (21/48) of placebo patients achieving at least minimal response ( $P < 0.01$ ) [13]. This trial led to the first FDA-approved therapy for DM based on the results of a randomized controlled trial. A post hoc analysis of the *ProDERM* trial found that IVIg showed clinically meaningful benefits beyond muscular and cutaneous symptoms, including dysphagia and other organ involvement, supporting its broader therapeutic role in DM [14].

The *Time Is Muscle* trial is an active phase II double-blind placebo-controlled randomized trial (NCT05832034). Enrolled patients with IIM will be within 1 week of diagnosis and treatment-naïve, allowing evaluation of whether early add-on IVIg can achieve more rapid disease control and reduce the risk of long-term disability [15]. The *MIGHT* trial

(NCT06599697) is another active phase II double-blind placebo-controlled randomized trial, enrolling HMGCR-positive IMNM patients. Enrolled participants in this trial will be randomized 1:1 to either IVIg 2 g/kg or placebo, and the percentage change in serum creatine kinase (CK) will be evaluated at week 12.

### NEONATAL Fc RECEPTOR INHIBITOR

Autoantibodies are detectable in approximately 70% of patients with myositis [16<sup>■</sup>]. By competitively blocking FcRn-mediated recycling of immunoglobulin G (IgG), this can promote lysosomal degradation of IgG and thereby selectively reduce circulating IgG levels, including pathogenic ones (Fig. 1) [17<sup>■</sup>, 18<sup>■</sup>]. Nipocalimab, a fully human IgG1 monoclonal antibody, and efgartigimod, an engineered human IgG1 antibody Fc fragment, are both designed to selectively block FcRn. A case series of three patients with anti-SRP IMNM reported that early treatment with efgartigimod in combination with methylprednisolone was associated with marked reductions in CK levels and significant improvement in muscle strength [19]. In an open-label pilot study of seven patients with refractory IMNM, efgartigimod achieved clinical responses in 4/7 patients within 4 weeks of treatment, with significant reductions in IgG and autoantibody levels and only mild adverse events [20].

The *ALKIVIA* trial (NCT05523167) is a phase II/III, double-blind, placebo-controlled study in adult patients with active IIM. Patients were randomized 1:1 to receive weekly efgartigimod PH20 subcutaneous (SC) or placebo, in addition to background standard of care treatment for IIM. Preliminary results from the phase II demonstrated that mean

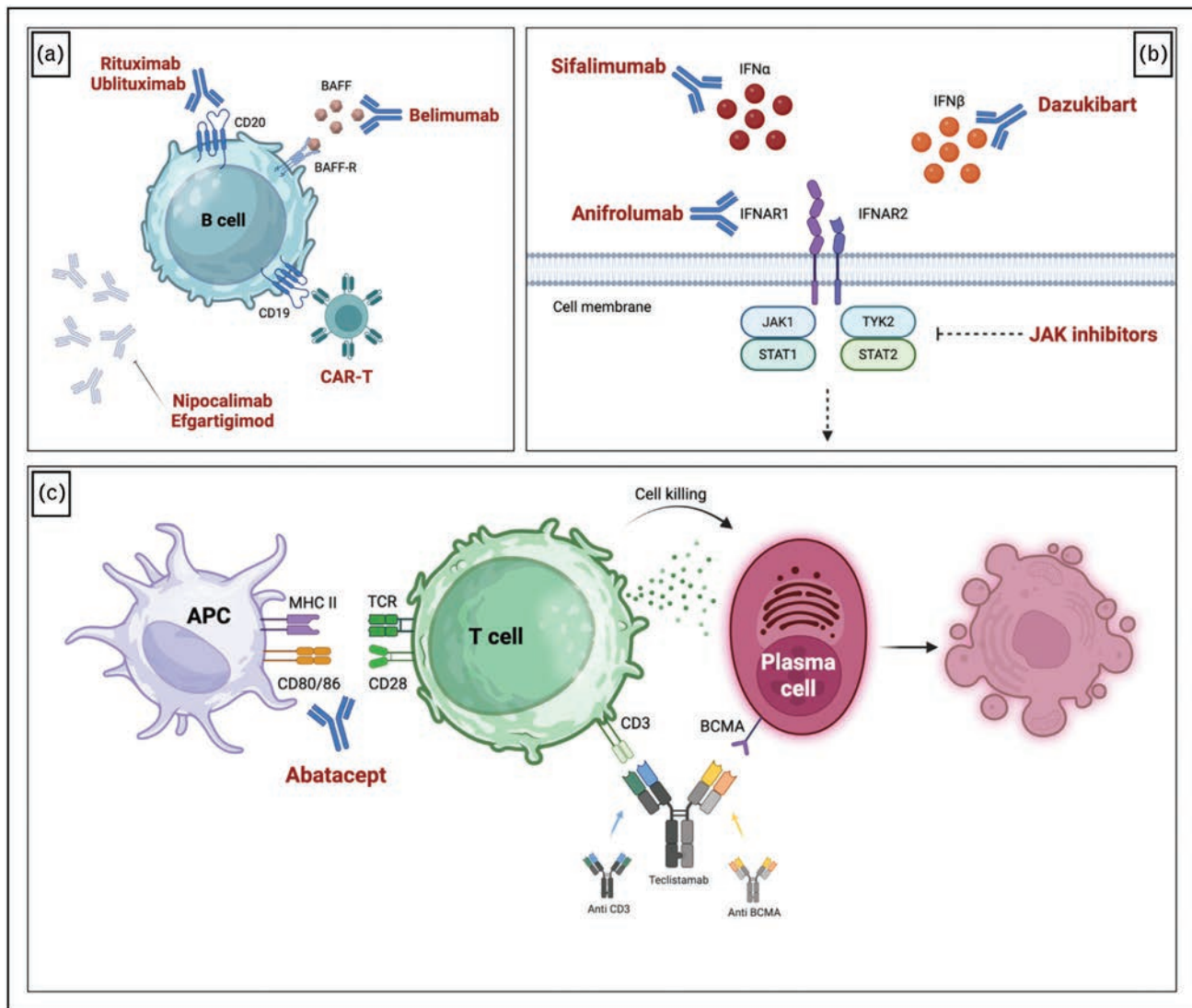


**FIGURE 1.** Overview of select therapeutic targets and drug mechanisms in IIM. BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; IFN, interferon; JAK, Janus kinase; MHC, major histocompatibility complex; TCR, T-cell receptor. Created in BioRender. Wilk, N. (2026) <https://BioRender.com/wiqejnu>. Panel a: B cell-targeted therapies in IIM include anti-CD20 monoclonal antibodies, BAFF inhibition with belimumab, FcRn antagonists, and CAR-T therapies, which act through depletion of B cells, suppression of B-cell survival and differentiation, reduction of pathogenic IgG autoantibodies, or elimination of autoreactive B-cell populations. Panel b: Therapies targeting the interferon (IFN) pathway in IIM include agents directed against interferon- $\alpha/\beta$ , blockade of IFNAR1, and JAK inhibitors, which suppress downstream IFN-mediated inflammatory signalling. Panel c: T cell-directed therapies include co-stimulation blockade with abatacept, which inhibits CD80/CD86–CD28 signalling to reduce T cell activation, and T cell engagers, which redirect cytotoxic T cells toward target cells to promote selective immune cell elimination.

total improvement score (TIS) at week 24 was statistically significantly higher in the efgartigimod PH20 SC arm than the placebo arm (50.45 vs. 35.65,  $P < 0.01$ ), with good safety and tolerability [17<sup>\*\*\*</sup>, 18<sup>\*\*\*</sup>]. A 28-week open-label extension (ALKI-VIA+; NCT05979441) from the phase II study is currently ongoing. The SPIREA trial (NCT05379634), a phase II, multicenter, randomized, double-blind,

placebo-controlled, parallel-group trial will explore the efficacy of nipocalimab in adults with IIM. Participants will be assigned to nipocalimab or placebo, and the primary endpoint will be the proportion achieving minimal response with a prednisone dose of  $\leq 5$  mg/day during weeks 44–52. While the study is still listed as active, it is no longer recruiting patients.

## JANUS KINASE INHIBITORS

It is well established that type I IFN inducible genes are upregulated in IIM [21]. JAK inhibitors are orally administered small molecules that interfere with a broad range of cytokine and growth factor signaling cascades [Fig. 1] [21]. A landmark case report published in 2014 demonstrated the efficacy of ruxolitinib in a patient with refractory dermatomyositis and myelofibrosis [22]. This followed key clinical observations of the efficacy of tofacitinib in refractory dermatomyositis [23]. A seminal proof-of-concept investigation by Ladislau *et al.* demonstrated that JAK inhibition could reverse type I IFN-induced muscle and vascular damage in DM, providing the clinical evidence for JAK inhibition as a targeted therapy in this patient population [24]. This catalyzed subsequent studies, including an open-label tofacitinib pilot trial in active, treatment-refractory DM (STIR; NCT03002649). All 10 patients (100%) completing the study met the primary outcome of interest, the International Myositis Assessment Clinical Studies (IMACS) definition of improvement (DOI) at 12 weeks, with additionally significant CDASI reduction from 28 to 9.5,  $P < 0.01$  [25]. Additional long-term efficacy was demonstrated in the STIR trial of up to 92 weeks [26]. Multiple additional case reports and small case series have supported the safety and clinical efficacy of tofacitinib in patients with refractory or skin-predominant DM [22,23,27,28].

The phase III VALOR trial (NCT05437263) evaluated brepocitinib, an oral TYK2/JAK1 inhibitor, in adults with refractory DM. A total of 241 patients were randomized to brepocitinib 30 mg, brepocitinib 15 mg, or placebo for 52 weeks. The 30 mg dose significantly improved their TIS compared with placebo (46.5 vs. 31.2;  $P < 0.01$ ), with benefits also observed in skin and muscle disease activity and glucocorticoid tapering. It is important to highlight that brepocitinib demonstrated efficacy as early as 4 weeks with sustained durability to 52 weeks. In contrast, the 15 mg dose did not achieve significant superiority over placebo. Serious infections were more common with the 30 mg dose, although no deaths occurred during the study [29<sup>■</sup>]. A smaller randomized, treatment delayed-start clinical trial with baricitinib ( $n = 15$ ) demonstrated that most patients achieved at least minimal response by 12 weeks, and 60% attained a moderate response by 24 weeks following active treatment (MYOJAK; NCT04208464). No significant difference in response was observed between the immediate- and delayed-start treatment groups at 24 weeks [30].

An open-label phase II study with a 26-week treatment period using filgotinib (a selective JAK1 inhibitor) is ongoing for refractory DM or ASyS patients (NCT06285539). Primary outcomes at 26

weeks include the 2016 ACR/EULAR Myositis Response Criteria and a quality of life measure using the EuroQol 5D-5L questionnaire [31]. Another phase III double-blind, randomized, placebo-controlled trial will evaluate baricitinib (a JAK1/2 inhibitor) in adults with active DM (BIRD; NCT04972760) and will include naïve DM patients. Primary outcomes at 24 weeks will include the proportion of patients that achieve moderate response.

## INTERFERON BLOCKADE

Beyond JAK inhibitors, other IFN blockade strategies have included neutralizing monoclonal antibody against IFN signaling proteins or IFN receptors [Fig. 1]. For instance, a phase IB randomized, double-blind, placebo-controlled trial evaluated sifalimumab, a fully human anti-IFN- $\alpha$  monoclonal antibody (NCT00533091) [32]. The trial showed that sifalimumab reduced the type I interferon gene signature (IFNGS) by 53–66% in peripheral blood and by 47% in muscle tissue, with a positive correlation between IFNGS suppression and clinical response [32].

Dazukibart is a potent, selective, humanized IgG1 neutralizing monoclonal antibody directed against IFN $\beta$ . A double-blind, randomized, placebo-controlled phase II trial (NCT03181893) demonstrated highly significant improvement in cutaneous disease and was generally well tolerated [33<sup>■</sup>]. In the smaller muscle cohort ( $n = 18$ ), dazukibart 600 mg showed numerically higher but nonsignificant improvement in TIS and MMT-8 as the study was not powered for the muscle cohort [33<sup>■</sup>]. An ongoing phase III trial (NCT05895786; NCT06698796) is evaluating dazukibart in a larger population to address the limitations of this previous phase II study.

In comparison, anifrolumab is a fully human monoclonal antibody that targets the type I IFN receptor subunit 1 (IFNAR1). Several case series suggest that anifrolumab could be effective in DM, especially with predominant skin involvement [34–37]. The JASMINE trial (NCT06455449) is a phase III, double-blind trial in adults with DM or polymyositis (PM) with moderate to severe disease activity. Its primary endpoint is moderate response at 52 weeks.

## B-CELL BLOCKADE

B-cell and plasma-cell play a central role in the pathophysiology, especially in certain subtypes such as ASyS [16<sup>■</sup>]. The landmark rituximab in myositis (RIM) trial (NCT00106184) was a randomized, double-blind, placebo-phase, treatment delayed-start trial that enrolled 200 patients with refractory adult PM/DM and juvenile DM (JDM). Patients were

randomized to rituximab early (rituximab at weeks 0 and 1, placebo at weeks 8 and 9) or rituximab late (placebo at weeks 0 and 1, rituximab at weeks 8 and 9) [38]. Although the study did not achieve its primary endpoint of demonstrating a difference in time to IMACS DOI between early and delayed rituximab initiation, the majority of participants (83%) nevertheless reached the DOI by week 44. In addition, a significant steroid-sparing effect was observed [38]. Post hoc analyses suggested that rituximab response was more pronounced in patients with detectable autoantibodies compared with seronegative patients [39]. A phase II, randomized, double-blind controlled trial (NCT07103746) is ongoing and will explore the role of a third generation anti-CD20 antibody ublituximab in adults with early, active IMNM with positive anti-SRP or anti-HMGCR. In contrast to the *RIM* trial, its primary endpoint will be the effect of ublituximab as first add-on combination therapy at 24 weeks using the 2016 ACR/EULAR Myositis Response Criteria, aligning with the expected onset of anti-CD20 efficacy. Furthermore, the SUMMIT (Study of ublituximab in IMNM) is based on the key hypothesis that early treatment at critical time of disease trajectory (<1 year disease duration) will lead to a durable clinical response in anti-SRP/HMGCR positive IMNM.

Another B-cell depleting agent, belimumab, is currently under study in refractory IIM. This fully human IgG1 monoclonal antibody targets B-cell activating factor (BAFF/BLyS), a cytokine critical for B cell survival and maturation (Fig. 1). A phase

II/III, randomized, parallel assignment, double-blind proof-of-concept trial explored the efficacy of belimumab (NCT02347891) [40]. The study was underpowered and did not reach its primary endpoint; however, a greater proportion of patients receiving belimumab achieved moderate response compared with placebo (55.5% vs. 33.3%, NS) [40].

In recent years, advances in therapies capable of achieving profound B-cell depletion - most notably chimeric antigen receptor (CAR) T-cell approaches - have generated promising early clinical results. These developments have increasingly popularized the idea of an “immune reset” to describe the therapeutic reprogramming of the immune system [41]. The extent of cellular depletion achieved with B-cell-directed therapies depends on the specific lineage marker targeted. This ranges from more restricted approaches, such as CD20 (affecting a subset of B cells) and BCMA (primarily targeting plasmablasts and plasma cells), to broader strategies like CD19 (encompassing B cells and plasmablasts) and CD38 (covering B cells, plasmablasts, and plasma cells) (Fig. 2) [42].

The current autologous strategy used to produce CAR cell therapies is associated with limitations, including substantial cost, lengthy manufacturing times, and restricted patient access. In contrast to autologous approaches, there is growing momentum toward the development of allogeneic CAR-T cell therapies. These “off-the-shelf” products are designed to be readily available, enabling more rapid treatment initiation. By leveraging large-scale

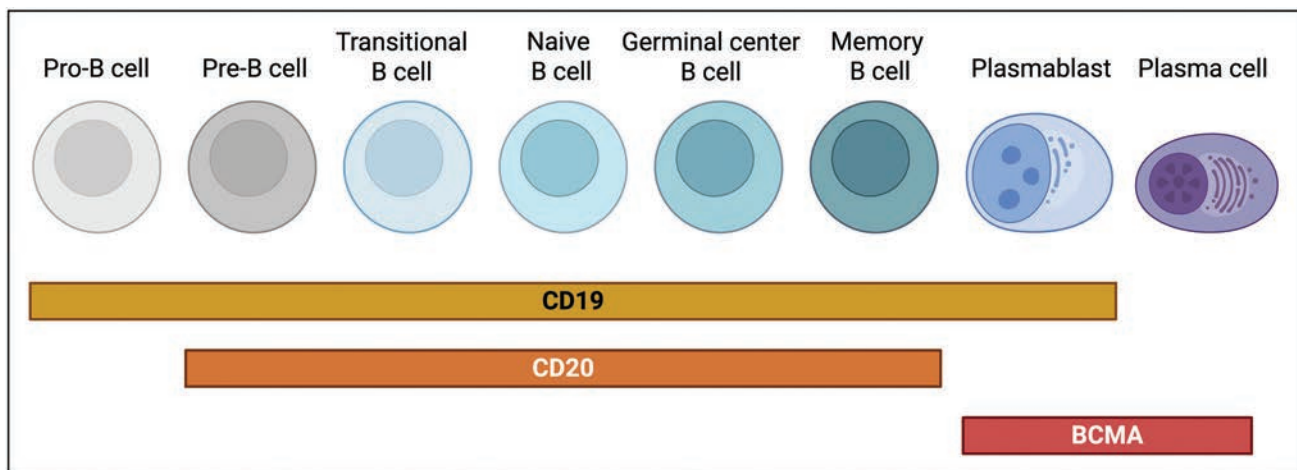


**FIGURE 2.** B-cell maturation and stage-specific expression of CD19, CD20, and BCMA. BCMA, B-cell maturation antigen; CD, cluster of differentiation. Created in BioRender. Wilk N. (2026) <https://BioRender.com/dw2r7qy>. B-cell development is characterized by dynamic changes in surface marker expression across maturation stages. Early and naïve B cells express CD19 throughout most stages of development, while CD20 is primarily present on mature naïve and memory B cells but is absent on early precursors and differentiated plasma cells. As B cells terminally differentiate into antibody-secreting plasmablasts and plasma cells, CD20 expression is lost and BCMA becomes the dominant survival receptor, supporting long-lived plasma cell survival.

manufacturing, they have the potential to reduce per-dose costs, ensure more uniform product quality, and support scalable distribution, thereby expanding access to a wider patient population [43<sup>¶</sup>]. Concerns remain regarding the risk of graft-vs.-host disease and host-mediated alloreactivity with allogeneic CAR-T therapy [43<sup>¶</sup>].

A growing number of phase I/II clinical trials are actively investigating CAR cell therapies, many designed as open-label or basket studies that include a range of autoimmune conditions to facilitate enrolment. The rapid expansion of these programs has created an environment reminiscent of a “gold rush”, with numerous companies entering the field simultaneously and driving intense competition to establish effective and scalable CAR approaches [Table 1].

CAR-T therapy represents the predominant modality in this field, with CD19 consistently serving as the principal antigen targeted across most constructs. In the phase I/II basket *CASTLE* study (NCT06347718) including five IIM patients, CD19 CAR-T cell therapy was generally well tolerated, with mostly mild grade 1 cytokine release syndrome (CRS), no immune effector cell-associated neurotoxicity syndrome, manageable infectious and hematologic complications. In a phase I/II open-label study, autologous CD19 CAR-T therapy (NCT06154252) demonstrated encouraging early efficacy and tolerability in patients with active DM, ASyS, and IMNM. Among the first six treated patients, five achieved a drug-free clinical response, while treatment-related toxicity was limited to grade 1 CRS in three patients, with no severe CRS or neurotoxicity observed. CAR-T expansion led to rapid and profound B-cell depletion followed by reconstitution with predominantly transitional naïve B cells within 8–12 weeks after infusion [44]. Several other cases have reported successful treatment of IIM cases with CD19-targeted CAR T cell therapy [45,46]. A case report described the use of BCMA-targeted CAR T-cell therapy in a patient with relapsing IIM following prior CD19 CAR T-cell treatment, highlighting its potential role in refractory disease [47]. Current evidence of CAR-T therapy in IIM remains limited by short follow-up durations. Consequently, the durability of clinical responses and the potential for long-term toxicities remain uncertain and will require evaluation in larger cohorts with extended follow-up. Further details about other types of CAR therapy is provided in Table S2, Supplemental Digital Content, <https://links.lww.com/COR/A64> and Figure S3, Supplemental Digital Content, <https://links.lww.com/COR/A64>.

T-cell engagers (TCEs), antibodies that redirect cytotoxic T cells toward B cells or plasma cells, have emerged as a novel “off-the-shelf” immunotherapeutic

strategy with potential applications in autoimmune disease [48<sup>¶</sup>]. By simultaneously targeting CD3 on T cells and B-cell antigens such as CD19, CD20, or BCMA, these TCEs promote selective elimination of autoantibody-producing cells [48<sup>¶</sup>]. Several reports have demonstrated successful use of TCEs in autoimmune diseases, including IIM [49,50]. Several ongoing clinical trials will evaluate the role of TCEs either as bispecific T-cell engager (BiTE) (NCT06916806; NCT07284797; NCT07229144) or tri-specific T cell engager (TriTE) therapy (NCT07371468; NCT06888960; NCT07193810), allowing for more precise immune targeting, regulated T-cell engagement, and sustained therapeutic activity [Fig. 1] [48<sup>¶</sup>].

## T-CELL BLOCKADE

The costimulatory molecules cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and CD28, together with T cells, contribute significantly to the pathogenesis of IIM (Fig. 1) [51]. The *ARTEMIS* trial (NCT01315938) was a phase IIB pilot study with a randomized treatment delayed-start design of intravenous abatacept in 20 adults with refractory DM ( $n=9$ ) or PM ( $n=11$ ) [52]. This small pilot study with no placebo control found that 8 of 19 evaluable patients (42%) achieved the IMACS DOI after 6 months of treatment and abatacept was generally well tolerated [52]. A subsequent larger phase III trial (NCT02971683) of SC abatacept for patients with active, treatment-refractory IIM did not meet its primary endpoint overall (IMACS DOI: 56.0% abatacept vs. 42.5% placebo,  $P=0.083$ ), though a subgroup analysis suggested potential benefit in non-DM subtypes [53<sup>¶¶</sup>].

The *ATackMy-ILD* trial (NCT03215927) was a randomized, placebo-controlled pilot trial in 20 patients with active ASyS-Interstitial lung disease (ILD) [54]. At week 24, there was no significant difference in the primary endpoint of percentage forced vital capacity change between abatacept and placebo [54]. However, trends at 48 weeks in the open-label extension and improvements in select secondary measures may suggest potential longer-term benefits, and a larger, long-term randomized controlled trial is warranted to determine the efficacy for abatacept in ASyS-ILD [54].

## ALTERNATIVE TREATMENTS UNDER CLINICAL INVESTIGATION

### Stem-cell transplantation

Stem cell transplantation has been investigated as a therapeutic strategy for severe, treatment-refractory autoimmune diseases [55]. Few successful reports

have been published to date in IIM patients [56–58]. Two clinical trials are currently evaluating stem cell-based therapies in IIM. A phase I/II randomized, double-blind, placebo-controlled basket trial is assessing allogeneic bone marrow-derived mesenchymal stem cell therapy vs. placebo on time to IMACS DOI up to 48 weeks in refractory DM and PM (NCT06888973). In addition, a phase II/III randomized, crossover, quadruple-blinded trial (IIM-PACT; NCT07160205) is investigating umbilical cord lining-derived stem cells (ULSC) in adults with refractory IIM, assessing safety over 12 months postinfusion and efficacy based on TIS at 7 months.

### Mitochondrial transplantation

In a phase I/IIA, nonrandomized exploratory trial (NCT04976140) of nine adults with refractory PM or DM, patients received a single intravenous dose of mitochondria isolated from ULSC (PN-101) alongside stable background therapy. The treatment was generally well tolerated, with 77.8% reporting mild adverse events and no serious adverse events observed, and at least minimal response compared with baseline [59]. A phase II, randomized, double-blind, placebo-controlled trial will compare single-dose PN-101 (300 mg or 600 mg) with placebo in a 1:1 allocation (NCT07122648).

### Inhibitors of toll-like receptors

Given the central role of toll-like receptors (TLRs) 7 and 9 in interferon pathway activation, TLR7/9 antagonism has been explored as a potential therapeutic strategy in DM [60]. A phase II, double-blind, placebo-controlled trial of IMO-8400 (bazlitoran), an antagonist of TLR 7, 8, and 9 in patients with DM did not demonstrate significant efficacy over placebo for either skin or muscle endpoints at 29 weeks (NCT02612857). This study was underpowered, enrolling only 30 of the planned 48 patients and limited by the use of concomitant medications [60].

### Interleukin-2

At low doses, interleukin-2 (IL-2) selectively expands regulatory T cells, suggesting a potential therapeutic role in IIM. A prospective pilot study (NCT04062019) showed that low-dose IL-2 was safe and led to clinical improvement in active IIM, with 14/18 patients (77.8%) achieving IMACS DOI at 3 months, including all DM and ASyS cases. Improvements included 50% median reduction in extra-muscular disease activity (mainly skin), alongside expansion of regulatory T cells and no serious adverse events [61]. A phase II RCT (NCT04237987) is ongoing.

### Interleukin-12/23 blockade

Previous studies have identified IL-23 blockade as a potential therapeutic target in IIM [62]. A phase III, randomized, double-blind, placebo-controlled study, evaluated the efficacy ustekinumab, a human monoclonal antibody targeting the p40 subunit shared by IL-12 and IL-23, in adults with refractive PM or DM. This study failed to meet its primary endpoint, with no statistically significant difference in the proportion of participants achieving minimal response at week 24 (NCT03981744) [63].

### Phosphodiesterase-4 inhibitor

Previous reports have described the successful use of apremilast, a phosphodiesterase-4 (PDE-4) inhibitor, in recalcitrant cutaneous DM [64,65]. A phase IIA, open-label, single-arm nonrandomized controlled trial with apremilast 30 mg twice daily in 8 women with recalcitrant cutaneous DM demonstrated that 87.5% (7/8) achieved a CDASI decrease  $\geq 4$  points at 3 months (NCT03529955) [66]. No patients had active muscle disease at enrollment, and all study patients were resistant to multiple lines of therapy [66].

### Complement pathway inhibition

Complement activation, particularly via the classical pathway leading to membrane attack complex deposition in muscle microvasculature, is a key component of the pathophysiology of IIM [67]. An anti-C1s monoclonal antibody (RAY121) has been shown to be well tolerated and suppressed the classical complement pathway up to 4 weeks after a single dose in a phase IA, placebo-controlled, double-blind, single ascending dose trial [68]. A phase IB, open-label single-arm trial and an extension study for adults with refractive DM/IMNM are currently underway (NCT06371417; NCT06723106).

### Nutritional supplementation

Large observational studies have indicated that omega-3 polyunsaturated fatty acids (PUFAs) may have beneficial effects in rheumatoid arthritis, and a systematic review and meta-analysis further showed that omega-3 PUFA supplementation is associated with a significant improvement in disease severity markers [69]. A systematic review of omega-3 supplementation in systemic lupus erythematosus (SLE) also suggests improvements in disease activity [70]. An active phase II, randomized, double-blind, placebo-controlled trial will be exploring the effect of omega-3 supplementation (fish oil) on TIS at week 24 in adult patients with active DM/JDM (NCT07111065).

## Immunoproteasome inhibitor

Zetomipzomib (KZR-616) is a selective inhibitor of the immunoproteasome with anti-inflammatory and immunomodulatory potential which has been studied in highly active SLE (NCT03393013) [71]. This drug has since been studied in DM and PM patients in the *PRESIDIO* trial (NCT04033926), a phase II, randomized, double-blind, placebo-controlled crossover study. Over 16 weeks, both the zetomipzomib and placebo groups showed clinically meaningful improvements in TIS, but there was no significant difference between groups. After crossover, modest additional improvements were seen in both arms, and the drug was generally well tolerated. Overall, while effective symptom improvement was observed, zetomipzomib did not demonstrate clear superiority over placebo [72].

## Sodium thiosulfate and topical Janus kinase inhibition

IIM often present with characteristic cutaneous features, particularly in DM, and may also be associated with SC or soft-tissue calcifications [1,73–75]. Two phase II, open-label and single-arm trials are investigating the role of SC sodium thiosulfate injection in DM with ectopic calcification (NCT03582800; NCT06672822). Results from a completed single-arm, open-label trial of sodium thiosulfate to treat JDM-related calcinosis have yet to be published (NCT03267277). Another phase II, open-label, single-arm study is exploring the role of a ruxolitinib cream (JAK1/JAK2 inhibition) in adult DM patients with refractory cutaneous manifestations, with its primary endpoint being the CDASI score improvement at 8 weeks (NCT06857240).

## CONCLUSION

Recent clinical trials have substantially reshaped the therapeutic landscape of IIM, with emerging targeted and mechanism-based therapies showing encouraging signals of efficacy. Important recent positive clinical trials include the *ProDERM* trial, the *ALKIVIA* trial, the *VALOR* trial, and a phase II trial evaluating dazukibart [12,17<sup>11</sup>,18<sup>11</sup>,29<sup>11</sup>,33<sup>11</sup>]. We are now in an era of targeted therapeutic agents directed toward key mechanistic pathways driving disease pathogenesis, in particular in dermatomyositis. Several challenges remain however when conducting clinical trials in IIM, which is certainly linked to the rarity of the disease and the heterogeneity of conditions falling under the umbrella of IIM [76,77].

Small sample sizes and insufficient statistical power remain common limitations, often compounded by confounding from background immunosuppressive therapies and unexpectedly high placebo responses,

which can obscure true treatment effects and limit subgroup analyses. Innovative trial designs may help address the persistent challenge of small sample sizes such as adaptive platform trials, including the potential for shared placebo arms across treatment domains. Additional challenges arise from evolving disease classification frameworks, as current criteria do not fully capture the breadth of IIM subtypes or adequately distinguish key entities such as IMNM and ASyS syndrome, further complicating patient stratification. Given the increasing recognition of differences in underlying aetiopathogenesis across subgroups, patient selection into future clinical trials will be essential to avoid heterogeneity diluting treatment effects and to ensure that emerging therapies are tested in mechanistically relevant populations. Finally, variability in outcome measures, particularly in cutaneous disease and steroid-sparing endpoints, highlights the need for standardized, sensitive, and clinically meaningful endpoints to improve comparability across studies.

In conclusion, the emergence of targeted therapies in IIM is transforming the therapeutic landscape, but continued efforts are required to refine clinical trial methodology, enhance disease classification, and standardize outcome assessment. The future of IIM treatment will likely be defined by pathway-specific, targeted immunotherapies and mechanism-driven disease control.

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N.W. conceptualized and designed the review, collected the data, analyzed the data, drafted the manuscript, and adjusted the manuscript according to the comments of the co-authors.

J.P., M.N. and H.C. critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Conflicts of interest

*H.C. has received grant support from Pfizer; advisory board member for Astra Zeneca, Pfizer, Argenx, J&J; Data and Science Monitoring Board chair for Horizon Therapeutics; speaker fees from UCB.*

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# Novel therapies for refractory idiopathic inflammatory myopathy-associated interstitial lung disease

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## Purpose of review

Idiopathic inflammatory myopathies (IIM) are systemic autoimmune rheumatic diseases in which interstitial lung disease (ILD) is a frequent extra-muscular manifestation and a major driver of morbidity and mortality. ILD occurs most commonly in antisynthetase syndrome and anti-melanoma differentiation-associated gene 5 (anti-MDA5) dermatomyositis syndrome, the latter carrying a high risk of rapidly progressive ILD (RP-ILD). Although recent guidelines outline conventional immunosuppressive strategies, a subset of patients progress despite escalation, and the definition of refractory IIM-ILD remains poorly standardized.

## Recent findings

Because type I and II interferon signaling, other cytokines, and aberrant B-cell activity have been implicated in the pathogenesis of IIM-ILD, novel therapies have been used off-label to target these mechanisms in treatment-resistant disease. This review summarizes emerging off-label and investigational therapies, including Janus kinase inhibitors, direct cytokine inhibitors (anifrolumab, dazukibart, tocilizumab, basiliximab), B-cell- and plasma-cell-targeted approaches (anti-CD20 antibodies, daratumumab, chimeric antigen receptor T-cell therapy, bispecific T-cell engagers), intravenous immunoglobulin, and antifibrotics, and rescue measures.

## Summary

Across these agents, evidence is confined to case reports, small series, and observational cohorts, with few randomized trials reporting IIM-ILD-specific outcomes. Prospective studies are needed to define patient selection, treatment sequencing and combinations, durability, and safety of novel therapies in IIM-ILD.

## Keywords

idiopathic inflammatory myopathies, interstitial lung disease, novel therapies, progressive pulmonary fibrosis, rapidly progressive-interstitial lung disease

## INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are systemic autoimmune rheumatic diseases (SARD) with frequent autoimmune myositis and extra-muscular manifestations [1,2<sup>¶</sup>]. IIM-associated interstitial lung disease (ILD) (IIM-ILD) is a common manifestation associated with significant morbidity and mortality [1]. ILD occurs frequently in antisynthetase syndrome (ASyS) and anti-melanoma differentiation-associated gene 5 dermatomyositis (DM) syndrome (anti-MDA5 syndrome), but also manifests in other DM subtypes, anti-signal recognition particle (anti-SRP)-associated immune-mediated necrotizing myopathy (IMNM), and overlap myositis (OM) [1,2<sup>¶</sup>]. Recently, American [3] and European [4<sup>¶¶</sup>] guidelines have been published regarding the management of SARD-ILD, which include recommendations for the management of IIM-ILD. Although many IIM-ILD

patients respond to conventional therapies, some patients progress despite therapeutic escalation. Therefore, reports of novel off-label therapies have

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## KEY POINTS

- Idiopathic inflammatory myopathy (IIM)-interstitial lung disease (ILD) can continue to progress despite guideline-based immunosuppression; therefore, novel off-label therapies have been trialed in the literature.
- Janus kinase inhibitors, including tofacitinib, baricitinib, upadacitinib, and brepocitinib interrupt type I and II interferon signaling, as well as other cytokines, and have shown improved survival and lung function in refractory IIM-ILD.
- The direct cytokine inhibitors anifrolumab (type I IFN receptor), dazukibart (IFN- $\beta$ ), along with tocilizumab (IL-6) and basiliximab (IL-2r) have also shown benefit in refractory IIM-ILD.
- B-cell and plasma cell targeted therapies, including next-generation anti-CD20 antibodies, daratumumab, CAR-T cells, and bispecific T-cell engagers, have improved disease activity in highly refractory cases.
- Antifibrotics (nintedanib, pirfenidone) and IVIG complement standard immunomodulation, while plasma exchange and lung transplantation can be used as rescue measures in refractory IIM-ILD.

emerged in the literature and are discussed in this review.

## REFRACTORY IIM-ILD: DISEASE COURSE AND CONVENTIONAL MANAGEMENT

The definition of “refractory” IIM-ILD is not well established and varies in the literature. Most define refractory as progressive or relapsing ILD despite conventional immunosuppressive agents, including glucocorticoids, mycophenolate mofetil (MMF), azathioprine, calcineurin inhibitors and rituximab [3,4<sup>22</sup>]. Furthermore, in real-world practice, it is important to determine whether persistent disease activity is due to irreversible damage (fibrosis) rather than ongoing inflammation, which can be a challenging task [5].

Refractory IIM-ILD can present abruptly, which is termed rapidly progressive ILD (RP-ILD). Anti-MDA5 positivity is the strongest risk factor for RP-ILD [6], but RP-ILD has been described in other IIM subtypes [7,8]. Recent guidelines define RP-ILD as progression to respiratory failure within days to weeks, indicated by high oxygen requirements or intubation [3]; however, this definition may miss patients with early disease who still require upfront intensive therapy. In high-risk patients, especially those positive for anti-MDA5, ILD progression over one to three months may better capture early RP-ILD [9,10].

RP-ILD is inherently aggressive and requires multi-agent therapy; therefore, recent publications have focused on optimizing combinations of therapies. Most publications focus on anti-MDA5 syndrome, given the increased prevalence of RP-ILD in this subtype. The first prospective combination-therapy study treated 29 anti-MDA5 patients with upfront high dose glucocorticoids, a calcineurin inhibitor (CNI; tacrolimus in this study), and cyclophosphamide, showing improved 6-month survival compared to stepwise escalation [11]. Following this original “triple therapy” regimen, more recent work has focused on mechanism-based strategies.

In contrast to RP-ILD, IIM-ILD can progress over months to years or relapse after a period of stability despite guideline-directed therapy. Several terms have been proposed in the literature including progressive fibrosing ILD [12] and postmyopathic progressive pulmonary fibrosis [13<sup>23</sup>]; however, the most commonly used definition is progressive pulmonary fibrosis (PPF), which refers to fibrosing ILD other than idiopathic pulmonary fibrosis with at least two of the following three criteria within the past year: worsening respiratory symptoms, physiologic decline [forced vital capacity (FVC)  $\geq 5\%$  predicted or diffusing capacity for carbon monoxide (DLCO)  $\geq 10\%$  predicted], and/or radiologic progression [14]. PPF cases often have evidence of fibrotic radiologic changes, yet IIM-ILD progression can present with both inflammatory and fibrotic imaging features. Despite this, the assumption in IIM-ILD, similar to other SARD-ILD, is that treating the underlying disease using immunosuppression escalation is preferred.

When IIM-ILD progresses, standard therapies can be escalated [3,4<sup>22</sup>]; however, emerging therapies have also shown benefit in case reports and series (Table 1). While a precise definition of refractory IIM-ILD falls outside the scope of this review, it is an important topic that deserves further consideration in the future. For the purposes of this review, we will discuss the recent literature on novel agents for the treatment of IIM-ILD in patients, which could be considered in patients who have failed conventional therapies.

## JANUS KINASE INHIBITORS

Type I and type II interferon (IFN) signaling has been implicated in certain IIM subtypes, including anti-MDA5 syndrome and ASyS [15,16]. Both type I and type II IFN signal through the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway; therefore, JAKi have been used in the treatment of refractory IIM-ILD. Other cytokines, including interleukin (IL)-2, IL-6 and granulocyte-macrophage colony-stimulating factor, also signal through JAK–STAT; therefore, the effects of JAKi

**Table 1.** Novel therapies in the management of refractory myositis-related interstitial lung disease

| Drug class                                 | Therapy      | Mechanism                                  | Suggested dose in IIM-ILD*                                                                                                                                                          | Route/schedule | Key side Effects                                                                                                    | References (studies in IIM-ILD)                                                   |
|--------------------------------------------|--------------|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|---------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Janus kinase inhibitors                    | Tofacitinib  | JAK1/JAK3 inhibitor                        | 5–10 mg p.o. b.i.d. or 11 mg p.o. daily                                                                                                                                             | p.o.           | Leukopenia, herpes zoster, infections, MACE, malignancy, VTE, hepatotoxicity                                        | [18,19,20 <sup>■</sup> ,21 <sup>■</sup> ,25,26 <sup>■</sup> ,27]                  |
|                                            | Baricitinib  | JAK1/JAK2 inhibitor                        | 2–4 mg p.o. daily                                                                                                                                                                   | p.o.           | Leukopenia, herpes zoster, infections, MACE, malignancy, VTE, hepatotoxicity                                        | [22 <sup>■</sup> ,25,26 <sup>■</sup> ,29]                                         |
|                                            | Upadacitinib | Selective JAK1 inhibitor                   | 15–30 mg p.o. daily                                                                                                                                                                 | p.o.           | Leukopenia, herpes zoster, infections, MACE, malignancy, VTE, hepatotoxicity                                        | [23 <sup>■</sup> ,24,26 <sup>■</sup> ]                                            |
|                                            | Brepocitinib | TYK2/JAK1 inhibitor                        | 15 or 30 mg p.o. daily (30 mg optimal in VALOR trial)                                                                                                                               | p.o.           | Serious infections, herpes zoster, cytopenias, MACE, VTE, malignancy                                                | [28 <sup>■</sup> ] [VALOR DM trial; ILD subgroup, no significant FVC change]      |
| Cytokine inhibitors                        | Anifrolumab  | Anti-IFNAR1 mAb                            | 300 mg i.v. every 4 weeks                                                                                                                                                           | i.v.           | Infections (upper respiratory, herpes zoster), infusion reactions                                                   | [34 <sup>■</sup> ,35 <sup>■</sup> ]                                               |
|                                            | Dazakibart   | Anti-IFNβ mAb                              | 600 mg i.v. every 4 weeks                                                                                                                                                           | i.v.           | Infections, HLH/MAS (1 case, unlikely related), headache                                                            | [38 <sup>■</sup> ] (phase 2 DM trial [37 <sup>■</sup> ] reported no ILD outcomes) |
|                                            | Tocilizumab  | Anti-IL-6 receptor mAb                     | 8 mg/kg i.v. every 4 weeks; or 162 mg s.c. weekly                                                                                                                                   | i.v. or s.c.   | Infections, neutropenia, transaminitis, hyperlipidemia, GI perforation (rare), infusion/injection reactions         | [42,43] (phase 2 IIM trial [41] reported no ILD outcomes)                         |
|                                            | Basiliximab  | Anti-IL-2 receptor (CD25) mAb              | 20 mg i.v. every 7 days for 2 doses                                                                                                                                                 | i.v.           | Hypersensitivity/anaphylaxis (rare, especially on re-exposure), infections                                          | [44]                                                                              |
| B-cell- and plasma-cell-targeted therapies | Rituximab    | Anti-CD20 mAb (chimeric, first-generation) | 1000 mg i.v. on day 1 and day 15, then every 6 months (or 375 mg/m <sup>2</sup> i.v. weekly x 4 doses)                                                                              | i.v.           | Infusion reactions, infections, hypogammaglobulinemia, late-onset neutropenia, PML (rare), hepatitis B reactivation | [45,46]; guideline-supported [3,4 <sup>■</sup> ]                                  |
|                                            | Ofatumumab   | Anti-CD20 mAb (fully human)                | MS protocol: 20 mg s.c. x 3 doses on weeks 0, 1, 2, then every 4 weeks<br>CLL + WM protocol: 300 mg i.v. on day 1, 1000–2000 mg i.v. on day 8, then 1000–2000 mg i.v. every 4 weeks | s.c. or i.v.   | Injection-site reactions, infections, hypogammaglobulinemia, PML (rare)                                             | Potential benefit; untested in IIM-ILD (anti-SRP IMNM cases without ILD [51])     |
|                                            | Ocrelizumab  | Anti-CD20 mAb (humanized)                  | 300 mg i.v. x 2 doses (day 1 and day 15), then 600 mg i.v. every 6 months                                                                                                           | i.v.           | Infusion reactions, infections, hypogammaglobulinemia, PML (rare)                                                   | Potential benefit; untested in IIM-ILD                                            |
|                                            | Obinutuzumab | Anti-CD20 mAb (glycoengineered)            | 1000 mg i.v. on weeks 0, 2, 24, 26, then 1000 mg i.v. every 6 months                                                                                                                | i.v.           | Infusion reactions, infections, hypogammaglobulinemia, cytopenia, PML (rare)                                        | [50]                                                                              |

Table 1 (Continued)

| Drug class             | Therapy                | Mechanism                                                                                                        | Suggested dose in IIM-ILD*                                                                                                                                                                                          | Route/schedule             | Key side Effects                                                                                                                          | References (studies in IIM-ILD)                                                                            |
|------------------------|------------------------|------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
|                        | Daratumumab            | Anti-CD38 mAb                                                                                                    | 1800 mg s.c. weekly x 4 doses or 16 mg/kg i.v., weekly x 8 doses, then every 2 weeks x 7 weeks, then maintenance every 4 weeks                                                                                      | s.c. or i.v.               | Infection reactions, hypogammaglobulinemia, infections, cytopenias                                                                        | [52, 53–55]                                                                                                |
|                        | CAR-T (CD19)           | Chimeric antigen receptor T cells targeting CD19                                                                 | ~1 × 10 <sup>6</sup> viable CAR-T cells/kg i.v. (single infusion); preceded by lymphodepletion with fludarabine 25 mg/m <sup>2</sup> on days –5, –4, –3 + cyclophosphamide 1000 mg/m <sup>2</sup> on day –3         | i.v., single infusion      | CRS, ICANS, infections, cytopenias, hypogammaglobulinemia                                                                                 | [58, 59]                                                                                                   |
|                        | CAR-T (BCMA)           | Chimeric antigen receptor T cells targeting BCMA                                                                 | ~6 × 10 <sup>6</sup> viable CAR-T cells/kg i.v. (single infusion); preceded by lymphodepletion with fludarabine 30 mg/m <sup>2</sup> on days –5, –4, –3 + cyclophosphamide 300 mg/m <sup>2</sup> on days –5, –4, –3 | i.v., single infusion      | CRS, ICANS, infections, cytopenias, hypogammaglobulinemia                                                                                 | [60]                                                                                                       |
|                        | Teclistamab            | Bispecific T-cell engager (BCMA × CD3)                                                                           | Hagen et al. protocol: 0.06 mg/kg s.c. on day 1, then 0.3 mg/kg on day 3, then 2 target doses of 1.5 mg/kg on day 5 and day 28                                                                                      | s.c.                       | CRS, infections, hypogammaglobulinemia, cytopenias, transient CRP/cytokine elevation                                                      | [61]                                                                                                       |
|                        | Blinatumomab           | Bispecific T-cell engager (CD19 × CD3)                                                                           | 9 µg/day i.v. continuous infusion × 5 days, then 14 µg/day × 7 days; often followed by RTX maintenance                                                                                                              | Continuous i.v. infusion   | CRS, ICANS, infections, hypogammaglobulinemia, neurotoxicity                                                                              | [62]                                                                                                       |
| IVIG                   | IVIG                   | Immunomodulation (multiple mechanisms: Fc receptor blockade, complement inhibition, autoantibody neutralization) | 2 g/kg i.v. divided over 2–5 days, every 4 weeks                                                                                                                                                                    | i.v.                       | Headache, pyrexia, nausea, VTE, aseptic meningitis, anaphylaxis                                                                           | [64–67]                                                                                                    |
| Antifibrotic therapies | Nintedanib             | Intracellular tyrosine kinase inhibitor (antifibrotic)                                                           | 150 mg p.o. b.i.d. (reduce to 100 mg p.o. b.i.d. if not tolerated)                                                                                                                                                  | p.o.                       | Diarrhea, nausea, hepatotoxicity (elevated transaminases), weight loss, bleeding risk, GI perforation (rare)                              | [12] (IIM-ILD outcomes not specifically reported) [68–70]                                                  |
|                        | Pirfenidone            | Antifibrotic (modulates TGF-β; reduces fibroblast proliferation and collagen synthesis)                          | Titrated to 801 mg p.o. TID (2403 mg/day)                                                                                                                                                                           | p.o.                       | Photosensitivity/rash, GI upset (nausea, anorexia), hepatotoxicity, fatigue, weight loss                                                  | [72]                                                                                                       |
|                        | Nerandomilast          | Oral preferential phosphodiesterase 4B (PDE4B) inhibitor (antifibrotic and anti-inflammatory)                    | 9 mg or 18 mg p.o. b.i.d. (doses used in FIBRONEER-ILD)                                                                                                                                                             | p.o.                       | Diarrhea, nausea, headache, upper respiratory tract infection                                                                             | [73] (FIBRONEER-ILD: autoimmune-ILD subgroup nonsignificant; however, trial was not powered to see effect) |
| Rescue measures        | Plasma exchange (PLEX) | Extracorporeal removal of circulating autoantibodies, cytokines, and inflammatory mediators                      | ~1–1.5 plasma volumes per session; multiple sessions (e.g., 3–7) on consecutive/alternate days as rescue (protocols vary)                                                                                           | Extracorporeal (apheresis) | Hypotension, hypocalcemia/citrate reactions, coagulopathy, catheter-related infection/thrombosis, allergic reactions to replacement fluid | [75–81]                                                                                                    |

Table 1 (Continued)

| Drug class | Therapy              | Mechanism                                                                                    | Suggested dose in IIM-ILD*                     | Route/schedule               | Key side Effects                                                                                      | References (studies in IIM-ILD) |
|------------|----------------------|----------------------------------------------------------------------------------------------|------------------------------------------------|------------------------------|-------------------------------------------------------------------------------------------------------|---------------------------------|
|            | Lung transplantation | Surgical replacement of end-stage fibrotic lung                                              | Single or bilateral lung transplant            | Surgical                     | Graft rejection, infection, primary graft dysfunction, chronic lung allograft dysfunction, malignancy | [82 <sup>***</sup> ]            |
|            | ECMO                 | Extracorporeal gas exchange providing respiratory support (bridge to recovery or transplant) | Venovenous ECMO; continuous, duration variable | Extracorporeal (cannulation) | Bleeding, thrombosis, hemolysis, infection, cannula/limb complications                                | [83 <sup>***</sup> ]            |

Reference numbers correspond to the manuscript reference list. "Potential benefit; untested in IIM-ILD" denotes agents with a mechanistic rationale or efficacy in other diseases (or in IIM without ILD) but no published IIM-ILD data. \*Suggested doses based on previous experience, published literature in IIM-ILD or other contexts, most protocols are not standardized, and evidence is limited regarding optimal dosing in IIM-ILD. anti-MDA5, anti-melanoma differentiation-associated gene 5; anti-SRP, anti-signal recognition particle; BCMA, B-cell maturation antigen; b.i.d., twice daily; CAR-T, chimeric antigen receptor T-cell; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; CRP, C-reactive protein; CRS, cytokine release syndrome; DM, dermatomyositis; ECMO, extracorporeal membrane oxygenation; FGFR, fibroblast growth factor receptor; FVC, forced vital capacity; GI, gastrointestinal; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; IFN $\beta$ , interferon beta; IFN, interferon; IFNAR1, type I interferon receptor subunit 1; IIM, idiopathic inflammatory myopathy; IIM-ILD, IIM-associated interstitial lung disease; IL-2R $\alpha$ , interleukin-2 receptor alpha; IL-6, interleukin-6; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathy; i.v., intravenous; IVIG, intravenous immunoglobulin; JAK, Janus kinase; mAb, monoclonal antibody; MACE, major adverse cardiovascular events; MAS, macrophage activation syndrome; MS, multiple sclerosis; PDE4B, phosphodiesterase 4B; PDGFR, platelet-derived growth factor receptor; PLEX, plasma exchange; PML, progressive multifocal leukoencephalopathy; p.o., per os (orally); RTX, rituximab; s.c., subcutaneous; STAT, signal transducer and activator of transcription; TGF- $\beta$ , transforming growth factor beta; TID, three times daily; TYK2, tyrosine kinase 2; VEGFR, vascular endothelial growth factor receptor; VTE, venous thromboembolism; WM, Waldenström macroglobulinemia.

may not be entirely mediated through IFN inhibition [17]. Each JAKi also has variable affinity for the individual JAK enzymes and thus variably inhibits upstream signaling.

Tofacitinib, a JAK1/JAK3 inhibitor, was first used in IIM-ILD as a rescue therapy in treatment refractory anti-MDA5-associated RP-ILD [18]. Five patients with refractory RP-ILD received tofacitinib after failing combination therapy with cyclophosphamide, cyclosporine A and steroids, and three survived. Tofacitinib was then evaluated as first-line therapy in anti-MDA5-associated ILD and was associated with a 100% survival rate, significantly higher than 78% in historical controls [19]. Recent larger studies have shown superior 1-year lung transplantation-free survival with tofacitinib vs. calcineurin inhibitors [20<sup>\*\*\*</sup>]. Combination tofacitinib and CNi therapy also improved survival over CNi monotherapy, with a favorable infection profile compared to cyclophosphamide-based regimens [21<sup>\*</sup>].

Baricitinib, a JAK1/JAK2 inhibitor, has also been used in refractory IIM-ILD. Tokunaga *et al.* evaluated a combination regimen of baricitinib, rituximab, and tacrolimus (the BRT regimen) vs. conventional therapy with cyclophosphamide and tacrolimus in a small cohort of patients with anti-MDA5 syndrome. Survival was 100% in the BRT group compared with 42% in the cyclophosphamide-based regimen treatment group [22<sup>\*\*\*</sup>].

Upadacitinib, a selective JAK1 inhibitor, was noninferior to tofacitinib in a large observational study and there was a nonsignificant trend towards improved 6-month lung transplantation-free survival in patients with anti-MDA5 syndrome [23<sup>\*\*\*</sup>]. In a cohort of IIM patients treated with upadacitinib, two with ASyS-associated ILD and three with anti-MDA5-associated ILD, four of five patients showed improvements on pulmonary function tests (PFTs) and stability on computed tomography (CT), while one anti-MDA5 patient had mild asymptomatic ILD progression [24].

In a recently published cohort of ASyS patients with PPF, treatment with either tofacitinib or baricitinib improved respiratory symptoms and CT scores [25]. In another cohort of treatment-refractory IIM patients, 50% of whom had ASyS, treatment with baricitinib, tofacitinib, or upadacitinib improved DLCO but not FVC in the six patients with ILD [26<sup>\*</sup>]. However, in a patient with anti-PL12 ASyS, tofacitinib showed good initial effect but ILD progressed after tapering steroids [27]. These results show that JAKi has some benefit in ASyS; however, larger cohort studies are needed to clarify the durability of this effect.

The recently published VALOR trial evaluated brepocitinib, a tyrosine kinase 2 (TYK2)/JAK1 inhibitor,

in dermatomyositis. Although 19% of participants had ILD, no significant change in FVC was observed; however, the study was not powered for this outcome and the percentage of patients with ILD was slightly different between groups [28<sup>\*\*\*</sup>]. Given the effectiveness of other JAKi in IIM-ILD, future studies are needed to assess the efficacy of brepocitinib in IIM-ILD.

Clinical trials on JAK2 inhibitors such as baricitinib (NCT04208464, NCT04972760) and fedratinib/ruxolitinib (NCT04966884) are currently ongoing in IIM and IIM-ILD. Given the differences in JAKi specificities [16,29,30], further studies are needed to identify predictive biomarkers that might allow more personalized JAKi selection.

## CYTOKINE INHIBITORS

As mentioned above, both type I and II IFN, as well as other cytokines, signal through the JAK-STAT pathway and play a role in IIM-ILD [1,2<sup>\*</sup>,30]. As such, direct IFN and other cytokine inhibitors have been trialed in IIM-ILD.

Anifrolumab is a monoclonal antibody targeting subunit 1 of the type I IFN receptor. Case reports and small series show cutaneous improvement in DM with anifrolumab [31,32,33<sup>\*</sup>], though ILD-specific data remain limited. Retuerto-Guerrero *et al.* recently reported outcomes in 30 IIM patients treated with anifrolumab, which included three IIM-ILD patients with available PFT and CT data. ILD remained stable or improved with anifrolumab treatment [34<sup>\*\*</sup>]. Pettorossi *et al.* reported a patient with anti-MDA5 syndrome refractory to multiple lines of treatment, including JAKi, who responded after seven anifrolumab infusions with improvements in CT and DLCO [35<sup>\*</sup>]. A clinical trial evaluating anifrolumab in dermatomyositis is ongoing (NCT06455449).

Dazukibart is a monoclonal antibody that selectively binds IFN $\beta$  [36<sup>\*</sup>]. In a phase 2 randomized placebo-controlled trial in dermatomyositis, dazukibart significantly improved cutaneous disease activity, creatine kinase levels and muscle strength; however, no ILD outcomes were reported [37<sup>\*\*</sup>]. In a case series, dazukibart improved pulmonary disease in one pediatric patient with severe multisystem DM including ILD and one adult with anti-MDA5 RP-ILD [38<sup>\*</sup>]. Given the proposed central role of IFN $\beta$  in IIM-ILD pathogenesis, dazukibart could represent a potential therapy for refractory disease.

Tocilizumab is a direct IL-6 inhibitor used in SARD [39] that has also shown benefit in systemic sclerosis-associated ILD [40]. When tested in a phase 2 trial in IIM, the primary endpoint was not met; however, the trial was not designed to test ILD efficacy and lung outcomes were not specifically reported [41]. Recent

case reports describe efficacy in treatment-resistant RP-ILD in adult [42] and pediatric [43] patients, and a clinical trial is recruiting for tocilizumab in anti-MDA5 syndrome (NCT07377058).

One of the earliest signals for direct cytokine-receptor blockade in anti-MDA5 RP-ILD comes from a case series in which four patients were treated with basiliximab, a monoclonal antibody targeting the IL-2 receptor (CD25) expressed on activated T lymphocytes [44]. Three of the four patients showed a beneficial response and a phase 2 trial was proposed in 2017; however, the progress of this trial is unknown at this time and results have not been published (NCT03192657).

## B-CELL- AND PLASMA-CELL-TARGETED THERAPIES

Rituximab, a first-generation anti-CD20 antibody, was the first biologic tested in a clinical trial in IIM but had negative results, as disease activity improved in both early and late treatment groups [45]; however, subsequent reports, including recent guidelines, support rituximab use in IIM-ILD [3,4<sup>\*\*</sup>,46]. Next-generation anti-CD20 agents like ofatumumab (fully human type I anti-CD20), ocrelizumab (humanized type I anti-CD20), and obinutuzumab (glycoengineered type II anti-CD20) may achieve more profound B-cell depletion than rituximab [47<sup>\*</sup>,48<sup>\*</sup>,49]. Although reports in IIM-ILD remain limited, these agents are effective in other rheumatic diseases [47<sup>\*</sup>]. In a case series of five treatment-resistant IIM patients (rituximab failure or allergy), obinutuzumab produced physiologic and radiologic stabilization in those with ILD [50]. Ofatumumab also showed benefit in two anti-SRP-positive IMNM cases, though neither had ILD [51]. Given the evidence supporting rituximab in IIM-ILD [48<sup>\*</sup>], next-generation anti-CD20 agents, particularly obinutuzumab, warrant further investigation [49].

Daratumumab is a monoclonal antibody targeting CD38-positive plasma cells, which is particularly relevant in patients who fail rituximab, as anti-CD20 agents may not adequately deplete pathogenic plasma cells [52<sup>\*</sup>]. Although approved for multiple myeloma, emerging reports support its use in refractory IIM [47<sup>\*</sup>,48<sup>\*</sup>]. Patients with refractory anti-MDA5-associated RP-ILD showed marked respiratory improvement after daratumumab [53,54], including successful extracorporeal membrane oxygenation (ECMO) weaning in one case [55]. Benefit has also been reported in anti-SRP IMNM [56], though that patient did not have ILD. However, daratumumab responses are variable, and one refractory ASyS case failed to respond, primarily due to recurrence of muscle disease [52<sup>\*</sup>]. Although more evidence is

needed, daratumumab may represent a potential option in refractory IIM-ILD.

Chimeric antigen receptor T-cell therapies (CAR-T) use genetically engineered T cells targeting specific cell-surface antigens, typically B-cell-lineage antigens such as CD19 or B-cell maturation antigen (BCMA) [57<sup>■</sup>]. Emerging evidence supports CAR-T therapy in IIM-associated ILD [47<sup>■</sup>,48<sup>■</sup>,58,59]. In a case series of three patients with ASyS-associated ILD treated with CD19 CAR-T cells, all demonstrated clinical improvement, including ILD, with sustained remission for up to 18 months off immunosuppressive therapy [58]. However, long-term durability data remain limited. One ASyS patient relapsed nine months after CD19 CAR-T but was successfully retreated with BCMA-targeted CAR-T, highlighting the importance of plasma cell targeting in refractory disease [60<sup>■</sup>]. At the time of writing, there are over 43 active CAR-T clinical trials in IIM (clinicaltrials.gov).

Teclistamab is a bispecific T-cell engager that binds both BCMA on plasma cells and CD3 on T cells, thereby redirecting T-cell-mediated cytotoxicity against BCMA-expressing cells [47<sup>■</sup>,48<sup>■</sup>,61,62<sup>■</sup>]. Four patients with SARD-ILD (anti-MDA5 syndrome, rheumatoid arthritis, Sjögren's disease, and systemic sclerosis) have been treated with teclistamab. In the patient with anti-MDA5 syndrome, DLCO remained stable; however, FVC was not reported [61].

Blinatumomab, a CD19/CD3 bispecific T-cell engager, was evaluated in five patients with treatment-refractory ASyS, including four with ILD, and was associated with rapid improvement in myositis, as well as stabilization or improvement in FVC in patients with ILD [62<sup>■</sup>]. However, the durability of response appeared limited to 3–8 months in some patients [62<sup>■</sup>]. Similar findings have also been reported in patients with systemic sclerosis after a single dose of blinatumomab [63<sup>■</sup>].

## INTRAVENOUS IMMUNOGLOBULIN

The ProDERM trial demonstrated significant benefits of intravenous immunoglobulin (IVIG) in IIM, primarily for cutaneous and muscular manifestations; however, only one patient with ILD was included in the IVIG arm [64]. Observational studies support IVIG combined with other immunosuppressants in IIM-ILD. Wang *et al.* reported higher 3-month remission and lower 6-month mortality in anti-MDA5-associated RP-ILD treated with IVIG [65]. In ASyS, IVIG has been associated with significant improvement in FVC and DLCO [66], with similar findings in another cohort of 26 IIM-ILD patients, predominantly ASyS and anti-MDA5 syndrome [67]. Although current evidence is largely observational, IVIG is now part of the guideline-recommended

therapeutic armamentarium for IIM-ILD [3,4<sup>■</sup>]. In our experience, IVIG is usually combined with other agents rather than used as monotherapy in refractory IIM-ILD. Because IVIG does not increase infectious risk, it is particularly attractive in patients receiving combination regimens or when infection has yet to be ruled out [3].

## ANTIFIBROTIC THERAPIES

Antifibrotics have an adjunctive role in IIM-ILD with PPF. Randomized controlled trial data for nintedanib, an intracellular tyrosine kinase inhibitor, are extrapolated from the INBUILD trial of patients with PPF [12], whose autoimmune subgroup ( $n=170$ ) showed slower FVC decline with nintedanib treatment; however, IIM-ILD-specific outcomes were not reported [68]. A three-center real-world study of patients with IIM-ILD ( $n=36$  treated with nintedanib vs.  $n=115$  without nintedanib) found that nintedanib was independently protective against the development of RP-ILD and was associated with improved survival in this retrospective study [69]. In another anti-MDA5 cohort ( $n=14$  treated with nintedanib vs.  $n=56$  without nintedanib), nintedanib-treated patients had higher 12-month survival in the overall cohort (100% vs. 73.2%) and within the RP-ILD subgroup (100% vs. 54.5%) [70]; however, patients receiving less than three months of nintedanib were excluded, so results may be confounded by survivor bias. Pirfenidone, an antifibrotic that primarily exerts its effect through TGF $\beta$  inhibition but also has other mechanisms of action [71], showed a non-significant trend towards mortality benefit in subacute anti-MDA5 ILD, but no trend was seen in patients with acute disease [72]. The recently published FIBRONEER-ILD trial tested nerandomilast in PPF and showed slower FVC decline in the treatment arms compared with placebo. In the autoimmune-ILD subgroup, this trend was nonsignificant; however, this trial was not powered to see an effect in this subgroup and IIM-ILD outcomes were not specifically reported [73]. Antifibrotics are currently indicated in recent guidelines as sequential add-on in refractory IIM-associated PPF [3,4<sup>■</sup>]; however, more evidence is needed to clarify the role of earlier antifibrotic use in IIM-ILD [74].

## RESCUE MEASURES

Plasma exchange (PLEX) is used mainly as rescue therapy in progressive or refractory anti-MDA5 RP-ILD, with mixed survival data. Several small studies suggest improved survival when added to combination therapy [75–78]. In contrast, Bay *et al.* found worse 1-year transplant-free survival with rescue

PLEX; however, this result is likely confounded by indication, as patients with more severe disease received PLEX [79]. Other small series report inconsistent or nonsignificant mortality effects [80,81].

In patients with progressive disease, especially those with RP-ILD, lung transplantation may represent the only life-saving option. Previous studies have shown similar outcomes in IIM patients compared to patients with systemic sclerosis and idiopathic pulmonary fibrosis [82<sup>■</sup>], and ECMO has been used as successful bridging therapy to transplant in IIM RP-ILD [83<sup>■</sup>]. The window for lung transplant is narrow in some cases, and consultation with lung transplant specialists should be early if RP-ILD is suspected.

## CONCLUSION

Refractory IIM-ILD remains a major therapeutic challenge associated with significant morbidity and mortality, particularly in anti-MDA5 syndrome and RP-ILD. Conventional immunosuppressive therapies remain the cornerstone of treatment, and emerging targeted therapies are expanding the landscape for treatment-refractory disease. However, current evidence remains limited by small sample sizes, heterogeneous patient populations, and the absence of randomized controlled trials specifically evaluating IIM-ILD outcomes. Prospective studies are urgently needed to define optimal patient selection, treatment sequencing and combinations, long-term safety, and durability of response in refractory IIM-ILD.

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