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Vasculitis syndromes
Edited by Hasan Yazici and Yusef Yazici

Medical physiology and rheumatic diseases
Edited by Mirko Manetti

Wolters Kluwer

Editorial introductions

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.

EDITOR IN CHIEF

John Varga

John Varga MD is the Frederick G. Huetwell Professor at the University of Michigan Medical School in Ann Arbor, Michigan.

Dr Varga was born in Budapest, Hungary, and came to the United States at the age of fifteen as a refugee. He matriculated at Columbia University in New York City, and obtained his medical degree from New York University. Following Rheumatology fellowship in Boston, he pursued research training with Professor Sergio Jimenez at the University of Pennsylvania. He served on the faculty at Jefferson Medical College, the University of Illinois and Feinberg School of Medicine. In 2020 he was recruited as Chief of Rheumatology at the University of Michigan Medical School. Dr Varga's research focuses on the biology and treatment of scleroderma and fibrosis, and bridges clinical and laboratory-based investigation.

Dr Varga has mentored over 20 trainees, several of whom are now independent academic investigators. He is the author of more than 400 original articles and book chapters and four books. His research has been continuously funded by the National Institutes of Health. He is an elected member of the Association of American Physicians, AOA and the Henry Kunkel Society, and is Master of the American College of Rheumatology and member of its Board of Directors.

SECTION EDITORS

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Hasan Yazici, MD, is a retired professor of medicine and the founder of the Division of Rheumatology at Cerrahpaşa Medical Faculty of University of Istanbul - Cerrahpaşa. He currently practices rheumatology at Academic Hospital in Istanbul. His main research interests are Behçet syndrome, clinical research methodology and ethics.

Prof. Yazici has published widely on Behçet syndrome. The dedicated Behçet syndrome multidisciplinary outpatient clinic he has started with a group of colleagues 46 years ago continues to give patient care and conduct clinical research. He has published many original articles in peer reviewed journals (the most quoted author on Behçet syndrome / Web of Science) in addition to his text book contributions, editorials and reviews. He has recieved a number of prestigious awards and has a long list of memberships in the editorial boards and scientific societies which includes being a member of the Science Academy (Turkey) and Academia Europaea; a Master of the American College of Rheumatology and a recipient of the EULAR award for Meritorious Service in Rheumatology.

Yusuf Yazici

Yusuf Yazici, MD, is a Clinical Associate Professor of Medicine at the New York University School of Medicine.

Dr Yazici earned his medical degree from Cerrahpasa Medical Faculty of Istanbul University in Istanbul, Turkey. He completed his internship and residency at Creighton University in Nebraska, USA and his fellowship in rheumatology at the Hospital for Special Surgery of Weill Medical College of Cornell University, USA.

His areas of interest are rheumatoid arthritis, early arthritis, patient reported outcomes, database and registry management and monitoring of arthritis patients in regard to clinical response and adverse events related to treatment and Behcet's syndrome. He has published over 200 articles and presented at various national and international meetings over 100 times.

Dr Yazici divides his time between seeing patients and conducting both industry and investigator-initiated trials, in the areas of RA and Behcet's syndrome.

Mirko Manetti

Dr Manetti, PhD was born in Florence, Italy, and is Associate Professor of Human Anatomy at the Department of Experimental and Clinical Medicine, University of Florence. He received the single-cycle master's degree in Biological Sciences with full marks and honors in 2003, and the PhD degree in Human Morphology and Morphogenesis in 2007 at the University of Florence. In 2006–2007 he was Visiting Scientist at the Department of Internal Medicine of the Justus-Liebig-University of Giessen, Germany. He was Postdoctoral Research Fellow from 2007 to 2017 and Assistant Professor from 2017 to 2021 at the University of Florence, where he currently teaches Human Anatomy to undergraduate students as Associate Professor. In 2018 he obtained the National Scientific Habilitation for Full Professor of Human Anatomy from the Italian Ministry of Education, University and Research. Since 2023 he is member of the Scientific Strategic Committee of the Italian World Scleroderma Foundation.

Dr Manetti is author of numerous scientific publications in peer reviewed journals and proceedings of national and international congresses, and currently serves as reviewer and editorial board member for numerous peer reviewed journals. His main research interests are microscopic anatomy of human organs, morphological and functional aspects of stromal cells, endothelial cell biology and angiogenesis, cellular and molecular mechanisms of tissue fibrosis, and pathogenesis of autoimmune, chronic inflammatory and connective tissue diseases such as scleroderma.

Vasculitis associated with nonhematological malignancies

Zeynep Hande Turna

Purpose of review
There is a complex relationship between nonhematological malignancies and vasculitis Paraneoplastic vasculitis may present in many different forms. Cancer risk is high in patients with some types of vasculitis. Also, immune checkpoint inhibitors (ICIs) used in treatment of many solid tumors may cause vasculitis.

Recent findings
Vasculitis associated with solid tumors is less frequently seen when compared to vasculitis associated with hematological malignancies. Cutaneous leukocytoclastic vasculitis (vasculitis of small vessels) is the most frequently encountered paraneoplastic vasculitis type. Paraneoplastic vasculitis is usually seen in patients with lung, genitourinary and gastrointestinal system tumors. The timing of paraneoplastic vasculitis varies as before, after or concurrently with the diagnosis of malignancy. Vasculitis is usually considered to be paraneoplastic when time gap between the onset of vasculitis and diagnosis of cancer is within 12 months. ICIs used frequently in treatment of many solid tumors may cause vasculitis by stimulating T cell activation. They usually cause large vessel (temporal arteritis and single organ vasculitis), central nervous system vasculitis or small vessel vasculitis.

Summary
Close monitoring of patients with vasculitis is essential for early recognition of an underlying malignancy and directing treatment options towards cancer specific treatments. Vasculitis due to ICIs should be recognized as early as possible when ICIs should be stopped, and immunosuppressives should be started to avoid severe complications of immune adverse events diagnosed to with- hold ICIs and start immunosuppressive treatments precluding severe complications of immune adverse events.

Keywords
central nervous system vasculitis, immune check-point inhibitors, immune related adverse events, leukocytoclastic vasculitis, paraneoplastic vasculitis

INTRODUCTION

The relationship between vasculitis and malignant disease is sometimes complex and needs clarification Paraneoplastic vasculitis may be an early messenger of a developing malignancy or may be encountered concurrently or after the diagnosis of a malignant disease. Vasculitis, like other diseases with chronic inflammation, may be associated with increased cancer risk; Immune checkpoint inhibitors (ICIs) frequently used in the treatment of many solid tumors stimulate immune system and can cause immune related adverse events (IRAEs)-like vasculitis.

Paraneoplastic vasculitis

Vasculitis may occur during malignancies in 2.3–8% of the patients [1].

Vasculitis associated with malignancy may be a paraneoplastic syndrome. and may occur at the same time or within a certain time gap before or after the diagnosis of cancer [2,3].

Paraneoplastic vasculitis (PNV) is less frequently associated with solid tumors compared to hematological malignancies. PNV represents 2–5% of all types of vasculitis and occurs in approximately 1 in 1800 hematological malignancies and 1 in 80 800 solid tumors [4,5]. Lung, urogenital and gastrointestinal tract tumors are the most frequent tumors associated with vasculitis. PNV also have been

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KEY POINTS

- Vasculitis associated with solid tumors is less frequently seen when compared to vasculitis associated with hematological malignancies.
- Cutaneous leukocytoclastic vasculitis (vasculitis of small vessels) is the most frequently encountered paraneoplastic vasculitis type.
- Paraneoplastic vasculitis may precede the diagnosis of cancer by weeks, months, or even years and is generally associated with a bad prognosis.
- Small vessel vasculitis not responsive to glucocorticoids is an alarm sign for a concurrent or developing malignancy.
- Patients with solid tumors receiving immune checkpoint inhibitors (ICIs) should be monitored closely for early recognition of immune related vasculitis when ICIs should be stopped and glucocorticoids should be started to prevent severe complications.

documented as isolated case reports in a variety of solid tumors [6–10].

Paraneoplastic vasculitis shows a temporal relationship with the diagnosis of malignancy. Hutson *et al.* identified 2800 patients with vasculitis and 69 000 patients with cancer over an 18.5-year period and identified 69 patients with a malignancy and systemic vasculitis (2.5% of patients with vasculitis and 0.1% of patients with cancer); only17% of the patients were diagnosed with vasculitis and cancer within 12 months and were considered to have a malignancy associated vasculitis [11]. In a study by Loricera *et al.*, vasculitis and malignancy identified within a period of 12 months were considered to be paraneoplastic and almost half of all cases were in the form leukocytoclastic vasculitis (LCV) [12].

Fain *et al.* in a retrospective analysis of sixty patients observed that the cutaneous LCV (45%), and polyarteritis nodosa (36.7%) were the most frequent vasculitis types in patients with a malignancy. Vasculitis associated malignancies were hematologic in 63.1% and solid tumors in 36.9% of the patients. Churg–Strauss syndrome, microscopic polyangiitis, Wegener's granulomatosis, and Henoch–Schonlein purpura are the other reported vasculitis types in patients with malignant diseases [2,13].

Cutaneous (LCV), a vasculitis of small vessels presenting with small purpuric papules on lower extremities, was found to be the most frequent type of vasculitis associated with solid tumors. LCV can be triggered usually with Infections, drugs, allergies and collagen vascular diseases [2,9,14,15].

The time between the onset of vasculitis and diagnosis of malignancy is variable. LCV may precede the diagnosis of cancer by weeks, months, or even years and is generally associated with a worse prognosis [2,8,9,15].

Vasculitis may sometimes be thought to be an adverse drug reaction, but the progression of the cutaneous findings despite glucocorticoid therapy and withdrawal of the suspicious agents are suggestive of a paraneoplastic process. Several case reports related LCV to chemotherapy or hormonal therapy such as cisplatin etoposide, vinorelbine, tamoxifen, aromatase inhibitors, and targeted drugs.

Concurrent onset and parallel course of the leukocytoclastic vasculitis with the malignancy may support the diagnosis a paraneoplastic vasculitis [16–19].

Paraneoplastic vasculitis usually fails to respond to steroids but resolves following the effective treatment of the linked malignancy, Recurrence of vasculitis heralding tumor recurrence or progression, provide strong evidence for vasculitis being a true paraneoplastic syndrome [16,20].

Concurrent malignancy in patients with temporal arteritis has been observed in up to 7.4% of the cases. In a study by Kardaş *et al.*, among the patients with cancer giant cell arteritis was the most common type of vasculitis [21]. There was no statistically significant association between different cancer and vasculitis subtypes but there was an increased trend for association between lung cancer and giant cell arteritis [21]. In a study by Liozon *et al.*, giant cell arteritis was associated with cancers of the gastrointestinal tract, a site where cancer incidence increases with age. Nevertheless, hematological malignancies emerged as the major group (45%) [22].

In elderly patients, a fortuitous association is probable in patients with cancer and giant cell arteritis. Myklebust *et al.* demonstrated no increased frequency of malignancy in patients with giant cell arteritis in their prospective study with matched population controls [23].

Nonhematological malignancy risk in patients with vasculitis

Vasculitis, like other diseases with chronic inflammation, may be associated with increased cancer risk. Cancer incidence is significantly higher in patients with vasculitis and the timing of diagnosis between vasculitis and cancer may be variable [22,24–26]. Kardaş *et al.* observed that among 684 patients with a mean age of 46 years and with a median follow up time of 2.5 years, cancer was detected in 5.6% of the patients. Colon and lung cancers were the most common forms [22].

The diagnosis of vasculitis requires a search for cancer as well as other potential etiologies. PNV may occur before malignancy becomes manifest. The search for a cancer is particularly mandatory when the vasculitis becomes chronic and treatment is no longer effective Tumor relapse should come to mind when vasculitis develops in a patient followed for a malignancy.

Vasculitis occurring during malignancy presents distinctive features according to the vasculitis subtype and also the nature of the malignancy. In a study by Fain *et al.*, patients with vasculitis associated with solid tumors more frequently had peripheral neuropathies, arthralgias, and renal involvement than those with vasculitis associated with lymphoid malignancies [13].

The malignancy rate in patients with small-vessel vasculitis (microscopic polyangiitis or Wegener's granulomatosis) was significantly higher than that of a normal age-matched general population [relative risk (RR) 7.5]. The risk was higher for patients with ANCA-associated vasculitis than for those with Henoch–Schonlein purpura (RR 6.02 and 5.25, respectively, compared with controls). The malignancy rate was also higher in patients with ANCA-associated vasculitis than in those with systemic lupus erythematosus [27]. The search for a cancer is recommended in elderly men with Henoch–Schonlein purpura, especially when joint manifestations are present [28].

Wegener's granulomatosis and renal cancer appeared simultaneously in 60% of the cases described by Tatsis *et al.* Renal cancer developed significantly more frequently in patients with Wegener's granulomatosis than those with rheumatoid arthritis [29].

Vasculitis associated with immune check point inhibitors

ICIs are approved by the Food and Drug Administration and the European Medicines Agency for treatment of a large range of cancers. The mechanism of action of ICI differs from traditional cytotoxic therapies and targeted molecules.

ICIs block the major inhibitory pathways in T cells, resulting in an augmented antitumor response. T-cell surface receptors programmed cell death-1 (PD-1), its ligand PD-L1, and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) are the most important inhibitor molecules or brakes of T-cell activation. Several monoclonal antibodies against these molecules have been approved and are now in clinical use for the treatment of various cancers [30–32].

Although ICIs have a beneficial role in activating tumor antigen-specific T cells, they can also lead to aberrant activation of autoantigen-reactive T cells leading to IRAEs that resemble autoimmune diseases. The adverse effects associated with immunotherapy are generally inflammatory in nature, because of uninhibited T cell activation IRAEs of any grade may occur in about 90% and 70% of patients treated monotherapy with anti-CTLA-4 inhibitor and with any anti-PD-1 or anti-PD-L1 antibody respectively. The rates of grade 3 or greater toxicities reported may approach 50% and 10–15% with anti-CTLA-4 and anti-PD-1/-L1 inhibitor therapies respectively. IRAEs are more frequent, more severe and appear earlier in patients who have received combination ICIs [31–33].

Most IRAES occur within 3 months of ICI initiation. Dermatologic adverse events have been reported within 24 h of treatment initiation. In contrast, late IRAES can occur more than 1 year after initiation of treatment or even months or years after discontinuation of therapy [30–32].

IRAEs can affect any organ system frequently skin, gastrointestinal, endocrine, hepatic and neurological systems, For grade 1 toxicities, close monitoring of the patient is required. For grade 2 IRAEs, immune checkpoint inhibitors should generally be with hold while symptomatic treatment for the adverse event is initiated. If a patient experiences a grade 3 or greater IRAEs immunotherapy should usually be discontinued and glucocorticoid treatment started. If improvement is still not noted other immunosuppressive therapy is recommended. Depending on the organ system involved, treatments including, Infliximab, azathioprine, mycophenolate, tacrolimus, cyclosporine, rituximab, plasmapheresis, and antithymocyte globulin have been used [30–32].

In a review by Abdel-Wahab *et al.*, 123 patients with cancer and preexisting autoimmune diseases (AID) who were receiving ICIs were analyzed. They found that 75% had exacerbation of preexisting AIDs, IRAEs, or both. Among these patients, 41% had recurrence or worsening of prior clinical manifestations. De novo IRAEs developed in 25% of patients. Rate of IRAEs were similar in patients with active or inactive AIDs (67% vs. 75%). Patients who were receiving treatment for preexisting AIDs when ICI therapy was initiated had fewer AEs than those who were not receiving treatment (59% vs. 83%). Compared with patients treated with the anti-CTLA-4 antibody ipilimumab, patients treated with anti-PD-1/PD-L1 inhibitors reported more AID flares (62% vs. 36%) and more de novo IRAEs [33].

The rheumatic IRAEs include arthralgia, arthritis, myalgia, myositis, vasculitis, polymyalgia rheumatica (PMR)-like syndrome, and sicca syndrome, The Incidence of rheumatic IRAEs is 0.4–16%. Occurrence of adverse events is usually between 5 and

11 months after the initiation of ICIs. Autoantibodies are mostly negative [33].

Vasculitis induced by ICIs is rare, and as I previously mentioned mainly involves large vessels (giant cell arteritis, single organ vasculitis) or the nervous system (primary angiitis of the central nervous system and isolated vasculitis of the peripheral nerves [33].

The median time from ICI initiation to vasculitis onset is about 3 months Daxini *et al.* reported patients treated with PD-1/PD-L1/CTLA-4-targeting ICIs who developed vasculitis. Of the 53, 20 were confirmed to have ICI-associated vasculitis. In that study, large vasculitis (giant cell arteritis, isolated aortitis) and vasculitis of the nervous system (primary angiitis of the central nervous system and isolated vasculitis of the peripheral nervous system) were the commonly reported types of vasculitis [33,34].

Patients receiving ICIs have also been reported to develop small-vessel vasculitis, such as eosinophilic granulomatosis, which is characterized by asthma, nazo sinusi-tis, eosinophilia, lung shadows, and arthritis. About 2.9% of ICI-treated patients have asymptomatic eosinophilia [33,34].

Chanson *et al.* conducted a review, analyzing the ImmunoCancer International Registry (ICIR) network. Vasculitis was detected in 28 patients who had received ICIs for cancer treatment. Small vessel vasculitis was predominant (75%) followed by large vessel (14%) vasculitis. Complete response of vasculitis was achieved in 78% of the patients with corticosteroids and other drugs [35▪].

Other reported presentations include small-vessel vasculitis in both hands causing finger pain and ischemia, mesenteric vasculitis causing stomach pain and skin vasculitis causing purpura. Comont *et al.* reported case reports of four patients with acral vasculitis. Combination ICI treatments had been used in three of four patents ICI related acral vasculitis presented with subungual or periungual skin necrosis in all of the cases and two of them needed finger amputations despite glucocorticoids. Antinuclear antibodies (ANA) were found to be positive in two of the cases. Small vessel vasculitis with digital necrosis may also be seen in ICI treatments while close monitoring and early initiation of immunosuppressive treatment is mandatory to avoid necrosis and other complications [36].

Treatment of ICI-induced skin vasculitis may involve withdrawal of ICIs and initiation of glucocorticoid therapy. Skin vasculitis may benefit from hydroxychloroquine. Plasma exchange is also an option for concomitantly removing the circulating ICIs, pathogenic autoantibodies and inflammatory cytokines [33,34].

Gallan *et al.* reported four cases of renal vasculitis in patients who were treated with ICIs Onset of symptoms varied between 2 weeks to 24 months after the initiation of treatment Three patients had renal small-to medium-vessel vasculitis and 1 had focally crescentic pauci-immune glomerulonephritis Three patients presented with acute renal failure and one with nephrotic syndrome and hematuria. All patients respond to glucocorticoids [37].

Neurological immune-related adverse events are rare and affect 1–2% of ICI-treated patients. One of the neurologic IRAE is immune-related vasculitis (IRV) which is observed in 0.1–0.3% of all patients. The symptomatology is unspecific, and a broad spectrum of neurologic symptoms can occur, depending on the location and how severely the vessel is affected. Erritzøe-Jervild reported in a systemic review of 20 cases of neurologic IRV, who had received PD1/PDL1 İnhibitor [38▪]. Recent studies showed that PD-1 deficiency plays a key role in the development of idiopathic medium and large vessel vasculitis (e.g., giant cell arteritis), These data may support a causal relationship between PD-1 inhibition and vasculitis [38▪].

Symptoms with neurologic IRV were systemic symptoms like fever or headache in 45% of the patients [38▪]. Onset of symptoms varied widely, occurring either soon after ICI initiation or up to months after discontinuation. Laboratory findings frequently showed pleocytosis and elevated CSF protein levels. MRI abnormalities were present in all cases, with 58% showing white matter hyperintensities, Because of the difficulties and invasiveness of biopsy for diagnosis central nervous system (CNS) vasculitis neurologic IRV diagnosis should rely on CNS imaging showing multifocal concentric vessel wall enhancement or segmental stenosis ("beading") on angiography without requiring a biopsy. Stabilization or improvement of CNS inflammation (e.g. CSF pleocytosis) with immunomodulatory treatment supports the diagnosis [38▪] Newer imaging modalities with vessel wall imaging (VWI) such as black blood MRI offer improved detection of inflammatory vasculitis by visualizing concentric vessel wall enhancement in addition to luminal narrowing [38▪].

Ischemic stroke can be an end-stage manifestation of CNS vasculitis. Cancer patients are also at increased stroke risk due to cancer-associated hypercoagulability. Cerebral vasculitis can also occur as a paraneoplastic syndrome or due to previous cranial radiotherapy if previously received All these pathologies complicate the determination of causality in cerebral vasculitis [38▪].

Diagnostic workup for CNS vasculitis should include contrast-enhanced brain MRI, angiography with vessel wall imaging, and CSF analysis. Additionally, EEG and paraneoplastic panels should be

performed, and infection and cancer associated potential causes of symptoms must be excluded [38▪].

CONCLUSION

Close monitoring of patients with vasculitis is essential for early recognition of an underlying malignancy to change treatment options toward cancer specific treatments. Vasculitis due to ICIs should be diagnosed as early as possible to stop such treatment and to start immunosuppressive treatments to avoid severe complications of immune adverse events.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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This paper highlights the association of vasculitis with immune check point inhibitors frequently used in treatment of solid tumors recently.

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This paper is focused on the CNS vasculitis one of the most difficult topics in differential diagnosis of heterogeneous neurological symptoms.

Treatment of systemic vasculitis

Yusuf Yazici

Purpose of review
This review will attempt to summarize the most potentially impactful new data on the treatment of systemic vasculitic conditions, including ANCA-associated vasculitis (AAV), giant cell arteritis, polymyalgia rheumatica and Takayasu arteritis.

Recent findings
Rituximab, cyclophosphamide, upadacitinib, baricitinib, mepolizumab, benralizumab and tocilizumab have all had new clinical trials and observational data from real world registries showing their treatment benefit in various vasculitic conditions. The recently developed classification criteria for five different vasculitic conditions (AAV, giant cell arteritis, and Takayasu arteritis), very important for clinical trial recruitment, have serious methodological issues that continue to be present in the new criteria sets and these need to be addressed before they can be widely adopted.

Summary
Important new data over the last several years for the treatment of systemic vasculitis have the potential to change how these conditions are managed. The remaining issues outlined in this review still need to be addressed to best serve vasculitis patients.

Keywords
ANCA-associated vasculitis, classification criteria, giant cell arteritis, polymyalgia rheumatica, Takayasu arteritis, treatment guidelines

INTRODUCTION

Treatment and long-term management of systemic vasculitic conditions, including ANCA-associated vasculitis (AAV), giant cell arteritis (GCA), polymyalgia rheumatica (PMR) and Takayasu arteritis (TA) have been an active area of research in recent years. This review will attempt to summarize the most potentially impactful new data and publications over the last 18–24months and try to discuss some of the controversy surrounding these with the aim to improve patient care in systemic vasculitis.

CLASSIFICATION CRITERIA

2022 saw publications for the new classification criteria for the five major vasculitic syndromes, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), GCA ,and TA [1–5]. As previously discussed, an important methodological issue was that these criteria were not appropriately validated in independent validation sets of patients [6▪,7].

Tomelleri *et al.* undertook the validation of the TA criteria in their cohort [8]. They demonstrated that the new criteria set had decreased specificity compared to the old criteria set, significantly different than what had been published in the original criteria paper [4], with the 2022 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) criteria having better sensitivity (95.83% vs. 82.94%) and a negative predictive value, but a markedly decreased specificity (63.51% vs. 90.54%) and a positive predictive value, which further emphasize the issues with the new criteria development process. In rare conditions such as AAV, the specificity of classification criteria is more important than the sensitivity, especially when they are used for research purposes, as the increased likelihood of misdiagnosing someone with AAV when they have another condition is increased with a set of criteria that have lower specificity, which seems to be case with the new criteria. This has ethical implications, as well. In a research setting,

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KEY POINTS

- The 2022 AAV classification criteria need proper validation studies before they are widely adopted for clinical research.
- Baricitinib, upadacitinib, tocilizumab, mepolizumab, and benralizumab have new data suggesting they will become part of the treatment options for patients.
- As always, more data, especially longer term follow up, are needed on these medications before they are more widely used in the treatment of vasculitis.

patients may be exposed to drugs that have not yet been proven to help AAV patients, so being as certain as we can that these patients actually have AAV is critical [9]. The compliance with the important issue of independent validation cohorts has thus far not been vigilantly evaluated by ACR and EULAR in preparation of the AAV criteria. Revalidation of these criteria are urgently needed by both ACR and EULAR before they are widely incorporated into research projects.

TREATMENT

Granulomatosis with polyangiitis and microscopic polyangiitis

Rituximab

Use of reduced dose glucocorticoids (redGC) along with rituximab in the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) was studied by Nagle *et al.* [10▪]. This was a retrospective, multicenter descriptive study in 19 university and general hospitals in France and Luxembourg. They showed that the subgroup of patients treated with rituximab and redGC, had a higher risk of experiencing the primary study outcome (a composite outcome that included minor relapse, major relapse, progression before achieving remission, occurrence of end-stage kidney disease (ESKD) requiring dialysis for >12 weeks and/or kidney transplantation and death) with a hazard ratio (HR) of 2.36 [95% confidence interval (CI) 1.18–4.71]. In the original PEXIVAS study, where this redGC regimen was studied, rituximab with redGC showed a trend towards less efficacy as well, with a HR of 1.86 (95% CI 0.83–4.14) for meeting the primary outcome of death from any cause or ESKD [11]. Comparing the differences between the two patient populations offers clues as to why this was the case. The PEXIVAS study enrolled both GPA (40%) and MPA (60%) patients, defined by their ANCA antibodies, myeloperoxidase (MPO) and proteinase 3 (PR3). PR3 positivity is a known risk factor for more severe disease and more closely associates with a diagnosis of GPA. In the PEXIVAS study rituximab was used for remission induction in about 15% of patients. In the real-world study by Nagle *et al.* 60% of patients had GPA and 40% had MPA, and 53% were positive for PR3 while 45% were positive for MPO. Rituximab was the drug used for remission induction in 74% of the patients (78% for standard GC vs. 71% for redGC). Compared to the PEXIVAS study, there were more GPA patients in the real-world study, more patients were started on rituximab for remission induction, and the worst outcome was seen in the rituximab with redGC group. With fewer GPA (using PR3 as a proxy) patients and fewer patients using rituximab for remission induction in the PEXIVAS study, there was still a trend for worse outcome in those who used rituximab with redGC for remission induction.

These worse outcomes are likely due to several issues we currently have with AAV trials [12]. First, GPA and MPA patients probably should not be enrolled into the same trial; if they are, the results should be analyzed and reported separately. GPA and MPA are different conditions and GPA patients commonly have a more severe disease course. Diluting the severity of the pool patients in a trial by enrolling MPA patients along with GPA patients, would not unexpectedly favor rituximab as a remission induction agent. This has, it seems, to have led majority of patients with AAV to be treated with rituximab, as shown in the real-world report by Nagle *et al.* leading to worse outcomes for some patients who may have done better with cyclophosphamide as their remission induction medication. Evidence for this is also present in the PEXIVAS study itself, where administration of oral cyclophosphamide as induction therapy was associated with lower risks of relapse [13]. Additionally, the relentless push to decrease GC use in vasculitis treatment seems to have led to a potentially weaker option for sicker patients, rituximab, to be used also with reduced doses of GC, compounding the potential harm to patients, probably leading to worse outcomes. There needs to be a frank discussion of these accumulating data to potentially revise our approach to treating AAV and the guidelines that impact clinical practice.

Abatacept

Langford *et al.* compared the efficacy of abatacept to placebo for the treatment of relapsing, nonsevere GPA, as a potential safer option [14]. The primary end point was the rate of treatment failure, defined as

relapse, disease worsening, or failure to get to a Birmingham Vasculitis Activity Score (BVAS) score of 0 or 1 by 6 months. Sixty-five patients were studied, and no statistical difference in the treatment failure rate was found between the abatacept and placebo groups. Treatment with abatacept did not show any benefit in any of the secondary outcomes, either; there was no difference in the frequency or severity of adverse events between treatment arms. In conclusion, even though safety of abatacept was similar to the placebo group overall, abatacept failed to help control the disease activity and did not reduce the risk of relapse, severe worsening, or help achieve remission.

Eosinophilic granulomatosis with polyangiitis

Mepolizumab

Weschler *et al.* [15]. reported the open label extension study (OLE) of MIRRA, which had shown the efficacy of mepolizumab, a humanized monoclonal antibody that specifically targets interleukin (IL)-5 to reduce proliferation, activation and survival of eosinophils, and is approved for the treatment of eosinophilic granulomatosis with polyangiitis (EGPA) [16]. MIRRA study, a phase 3 placebo-controlled trial, showed that mepolizumab was associated with higher rates of remission and had significantly fewer relapses over 52 weeks of treatment, in addition to glucocorticoid sparing benefits, compared to placebo. The OLE study that enrolled patients from MIRRA who continued to require oral glucocorticoids $\geq$ 5 mg/day after the conclusion of MIRRA. All 100 patients who enrolled in the OLE received mepolizumab 300 mg subcutaneously every four weeks plus standard of care until mepolizumab was discontinued. No new safety signals were identified compared to the mother trial and the median glucocorticoid dose decreased from 10.0 mg/day to 5.0 mg/day at study exit. Furthermore, the percentage of patients using glucocorticoids >7.5 mg/day decreased from 75% at baseline to 32% while 28% of the patients discontinued them. The OLE study showed that mepolizumab continued to be well tolerated and led to further decrease in glucocorticoid use.

Benralizumab

In another study, benralizumab was compared to mepolizumab for the treatment of EPGA [17▪].

This was a randomized, double blind noninferiority trial to evaluate the efficacy and safety of benralizumab as compared with mepolizumab, with the primary endpoint of remission at weeks 36 and 48. One hundred forty patients were treated and the percentage of patients with remission at weeks 36 and 48 was 58% in the benralizumab group and 56% in the mepolizumab group, showing noninferiority but not superiority of benralizumab over mepolizumab. The accrued duration of remission and the time to first relapse were similar in the two groups. Adverse events were also similar between the two drugs, along with the efficacy data, suggesting that benralizumab may potentially be a good treatment option for patients with EPGA.

Rituximab

Another study looked at the comparison of rituximab to conventional therapy for remission induction in EGPA [18]. This randomized double-blind study enrolled 105 patients with active disease defined as a BVAS of 3 or greater and compared glucocorticoids plus rituximab with conventional therapy (glucocorticoids alone or in combination with cyclophosphamide in severe forms) for induction of remission, a BVAS of 0 and a prednisone dose of 7.5 mg/day or less at day 180. Thirty-three (63.5%) patients in the rituximab group achieved the primary end point compared with 32 (60.4%) in the control group (relative risk, 1.05 [95% CI, 0.78–1.42]; $P=0.75$); results were similar at day 360. There was no difference noted in duration of remission, either, between the two strategies (48.5 ± 6.51 weeks in the rituximab group and 49.1 ± 7.42 weeks in the conventional strategy group, $P=0.41$). All relapse and major relapse rates were similar between the two groups, as well as glucocorticoid use. In conclusion, rituximab was not superior to a conventional remission induction therapy in EGPA. Authors discuss that this study was not designed to test the two treatment strategies in severe EGPA and state that rituximab and cyclophosphamide cannot be considered equivalent in patients with severe disease. This assessment is consistent with the data, as rituximab was not even superior to glucocorticoids alone which was used by majority in the comparison group. An emulation trial by the same group has shown that addition of cyclophosphamide to glucocorticoids led to reduced risk of vasculitis flares [19]. The totality of these data suggest, as is the case with other AAV as will be discussed elsewhere in this paper, cyclophosphamide should be the preferred treatment option for severe cases.

Giant cell arteritis

Upadacitinib

One of the major developments in the treatment of giant cell arteritis (GCA) was the approval of upadacitinib recently by the FDA for this condition. This

approval came after the phase 3 trial of upadacitinib trial by Blockmans *et al.* [20▪]. Patients with new-onset or relapsing GCA were assigned to upadacitinib 15 mg ($n=209$) or 7.5 mg ($n=107$) with a 26 week glucocorticoid taper or placebo ($n=112$) with a 52 week glucocorticoid taper. The primary end point was sustained remission between weeks 12 and 52. Upadacitinib 15 mg arm was statistically significantly better than placebo in meeting the primary end point (46.4% [95% CI, 39.6–53.2] vs. 29.0% [95% CI, 20.6–37.5]; $P=0.002$). It was also better for sustained complete remission, time to a disease flare, cumulative glucocorticoid exposure, and patient-reported outcomes. Interestingly, upadacitinib 7.5 mg dose was also better than placebo numerically with 41.1% vs. 29.0% of patients achieving sustained remission, but this was not statistically significant. However, when the actual response difference between the two doses of upadacitinib are compared, there is only about a 5% difference, 41.1% vs. 46.4%. There were no major differences in adverse events, except serious adverse events were lower in the upadacitinib 7.5 mg compared to upadacitinib 15 mg, 12.1% vs. 22.5%, along with 2 deaths in upadacitinib 15 mg and no deaths in upadacitinib 7.5 mg. Based on this study upadacitinib was approved for the treatment of GCA for the 15 mg dose, however, it is hard to argue that there was no benefit from the lower dose, upadacitinib 7.5 mg, as it was close to significance and in a larger patient population, which will be the case when it is used in the real world, it may have also reached significance. It would be good to have the option of using the lower dose, too, for the treatment of GCA, especially as it was also overall associated with fewer serious adverse events compared to upadacitinib 15 mg.

Tocilizumab

Tocilizumab had been approved for the treatment of GCA after the successful GiACTA trial [21]. Since then, there have been efforts to assess if lower doses and/or a shorter duration of glucocorticoids may be used in the first year along with tocilizumab to achieve remission.

Two groups have been trying to answer this question. The GUSTO trial [22▪] was an open label, small proof of concept trial that aimed to evaluate the efficacy and safety of tocilizumab monotherapy for 52 weeks and then stopping it, along with initial ultra-short-term glucocorticoid treatment at baseline only, in patients with new-onset GCA. It showed that 14/18 (78%) of the patients achieved remission within 24 weeks and 13 of 18 showed no relapses up to 52 weeks (72%) after an ultra-short pulse of glucocorticoids of 500 mg methylprednisolone intravenously (IV) for three consecutive days only.

The same group now looked at the role of MRI in disease activity monitoring in GCA as part of the GUSTO trial [23]. They examined vascular and musculoskeletal inflammation using MRI; cranial, thoracic and abdominal MRI exams were performed at baseline and at weeks 24, 52, and 104.Vasculitic vessels were still detectable in one in four cranial segments at week 24. These were resolved at weeks 52 and 104, however, large vessels, except for the ascending aorta, showed ongoing inflammatory activity over time, suggesting that while vasculitic manifestations in the cranial vessels normalized after 52 weeks of treatment, large vessel findings persisted despite the lasting full clinical remission. This, of course, questions the decision about stopping tocilizumab treatment once clinical remission is achieved at week 52. If there is ongoing inflammation in the large vessels, while the patient is clinically silent, it may mean further treatment is needed to prevent future disease manifestations and damage. A further question is if "true" remission needs to be defined as remission in signs and symptoms of GCA along with normal imaging, a concept that requires additional studies.

The TOPAZIO study also looked at the same issue [24]. The goal of the study was to assess the impact of tocilizumab monotherapy after ultra-short-pulse glucocorticoids on clinical manifestations, and vessel inflammation and damage in large vessel-GCA (LV-GCA). This was a prospective observational study, where 18 patients received 500 mg per day IV methylprednisolone for three consecutive days at baseline only and weekly tocilizumab injections from day 4 until week 52. PET/CT was performed on all patients at baseline and at weeks 24 and 52, with reduction in the PET vascular activity score (PETVAS) as the primary end point. Both at weeks 24 and 52, a significant reduction in PETVAS was seen, with about 56% (10/18) and 47% (8/17) of patients in relapse free remission at weeks 24 and 52, respectively. There were no patients who had new aortic dilation, however, 4 patients with aortic dilation at baseline showed increases in aortic dilation.

Next, Muratore *et al.* followed these patients off treatment to assess the maintenance of efficacy in the next 26 weeks out to week 78 for the 17 patients who were available for analysis [25]. PETVAS still showed a significant decrease compared to baseline at week 78, however, compared with week 52, PETVAS significantly increased, 6 months after tocilizumab discontinuation. Relapse-free clinical remission at week 78 was 65% (11/17), and age and sex-adjusted hazard ratio (95% CI) for each unit increase of PETVAS indicating subsequent relapse was 1.36 (0.92–2.00).

Both of these studies suggest that while ultrashort glucocorticoids at baseline along with tocilizumab for

a year and then discontinuation was able to provide very good clinical remission. There seems to be, at least in some patients, ongoing large vessel inflammation, initially subclinical but potentially leading to future relapses. This needs to be considered before stopping tocilizumab after a year of treatment even if the patients are in clinical remission and tocilizumab may need to be continued; how much longer remains unknown.

Polymyalgia rheumatica

Baricitinib

Saraux *et al*. looked at baricitinib in the treatment of polymyalgia rheumatica (PMR), which has been traditionally treated with glucocorticoids and there remains an unmet need for treatments that can limit or end the use of glucocorticoids, which are associated with adverse events [26]

BACHELOR was a randomized, double-blind, placebo-controlled, parallel-group trial at six centers in France. All patients ($n=34$) had new onset PMR and were randomized to 4 mg baricitinib orally or placebo (with oral glucocorticoids as rescue treatment) for 12 weeks, which was later followed by 2 mg baricitinib or placebo for another 12 weeks. The primary endpoint (CRP PMR-AS of 10 or less) was reached at week 12 by 14 of 18 (78%) participants in the baricitinib group and 2 of 15 (13%) participants in the placebo group (relative risk 5·8, 95% CI 3·2–10·6; adjusted $P<0·0001$). There were no deaths and no major adverse cardiovascular events in either group.

This small study suggests that, compared with placebo, patients with PMR receiving 4 mg baricitinib are less likely to need oral glucocorticoids to have low disease activity and without any new safety signals.

Tocilizumab

Efficacy of tocilizumab had been previously shown for the treatment of PMR [27].

Assaraf *et al*. [28]. conducted a multicenter retrospective analysis of use of tocilizumab in PMR patients requiring glucocorticoid-sparing treatment. They had 53 patients; 31 had active disease despite conventional synthetic DMARD treatment. Glucocorticoid dose was down to less than or equal to 5 mg/day in 77% of the patients at 6 months, and in 97% of the patients at 12 months. Proportions of glucocorticoid-free patients 6 and 12 months after the first tocilizumab infusion were 22.5% and 58.3%, respectively. In addition, tocilizumab infusion spacing rather than discontinuations seemed to be a better tapering strategy.

Guidelines

British Society for Rheumatology published their guidelines for the management of AAV in 2025 [29]. Recommendations were updated from the published 2014 guideline mainly in treatment for GPA and MPA, management of subglottic stenosis and ear, nose, and throat (ENT) manifestations of AAV, and management and treatment for EGPA. For GPA and MPA, both rituximab and cyclophosphamide were recommended for remission induction, with a preference for rituximab in active relapsing disease. In cases of no evidence of life-threatening organ involvement, methotrexate or mycophenolate mofetil are also suggested. For maintenance of remission, rituximab was preferred, with azathioprine and methotrexate as alternatives in select cases, at least for 24–48 months. Avacopan was suggested as an additional option to help decrease glucocorticoid related issues. Similar recommendations, in addition to teamwork with ENT specialists are noted for GPA with ENT involvement. For EGPA, anti-IL-5/5R biologics were recommended for nonlife threatening disease, with rituximab and cyclophosphamide reserved for more serious involvement. Overall, these recommendations mirror similar ones from other rheumatology societies and also reflect what the current practice is. As discussed elsewhere here, there is still some controversy about the role of rituximab and cyclophosphamide in severe GPA and this was not addressed in this guideline.

CONCLUSION

There continues to be issues with the 2022 vasculitis classification criteria that need to be addressed before more and more clinical trials continue to use them for selecting patients. A frank discussion of the methodological issue by the societies which sponsored the development of these criteria, ACR and EULAR, is urgently needed.

We now have new options in upadacitinib, for the treatment of GCA, baricitinib for PMR and mepolizumab and benralizumab for EGPA. Better understanding the role of rituximab cyclophosphamide in GPA and MPA is also provided with new data, suggesting that cyclophosphamide may be the preferred agent for severe cases, and potentially the first agent for GPA, which tends to have worse activity and outcomes compared to MPA. Tocilizumab continues to be a good agent for GCA, with potentially allowing for only limited glucocorticoid use, however, longer term large vessel involvement needs to be studied further after discontinuation of tocilizumab after a year. Tocilizumab also seems to be beneficial for PMR management.

Rituximab for EGPA and abatacept for nonsevere GPA did not show benefit over current treatment with glucocorticoids.

As always, totality of the data needs to be taken into account when we apply the new information to our individual patients. In this line, the new classification criteria need to be properly validated before they are fully adopted, the new treatment recommendation communicated widely and the newly approved drugs for the treatment of vasculitic conditions used in the appropriate patients, providing new options for better outcomes.

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Conflicts of interest

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Vasculitis in autoinflammatory diseases

Emilie Bohbot and Eldad Ben-Chetrit

Purpose of review
This review aims to explore the relationship between autoinflammatory diseases (AIDs) and vasculitis, with a focus on recently identified syndromes and newly published data since 2016.

Recent findings
While the connection between innate immune dysregulation and systemic inflammation is well established in AIDs, the occurrence of vasculitis in these disorders remains underrecognized and often misclassified. We discuss vasculitic manifestations in a wide range of AIDs, including familial Mediterranean fever, DADA2, HA20, VEXAS, CAPS, TRAPS, HIDS/MKD, Blau syndrome, and others. Each condition presents a unique pattern of vascular involvement, ranging from incidental cutaneous findings to life-threatening systemic vasculitis. The underlying mechanisms often involve overactivation of inflammatory pathways such as IL-1β, or NF-κB, and in some cases, novel genetic mutations affecting non-inflammatory pathways such as purine metabolism. The histologic, clinical, and genetic features often differ from classic vasculitic syndromes.

Summary
Recognizing vasculitis in the context of AIDs is critical for early diagnosis, especially in pediatric patients or those with treatment-resistant or atypical presentations. Genetic testing should be considered in such cases. Understanding these distinct disease patterns allows physicians to tailor management strategies, including biologic therapies or hematopoietic stem cell transplantation, improving outcomes in these complex and often severe disorders.

Keywords
autoinflammatory diseases, deficiency of adenosine deaminase 2, familial Mediterranean fever, vasculitis, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome

INTRODUCTION

The term autoinflammatory disease (AID) has been used since 1999 to describe a group of disorders of the innate immune system characterized by recurrent episodes of inflammation. In contrast to autoimmune diseases, in AIDs, there is no primary role for specific autoreactive T- or B-lymphocytes or autoantibodies in their pathogenesis [1,2]. Some of these diseases, such as familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndromes (CAPS), and hyper-immunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD), are monogenic in origin and lead to hereditary periodic fever syndromes [3]. Others may have polygenic or multifactorial etiologies, such as periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA), or Behcet's syndrome (BD).

Vasculitis refers to inflammation of blood vessel walls with subsequent damage to organs and tissues. It may be a dominant feature of some autoinflammatory disorders, such as adenosine deaminase 2 deficiency (DADA2) and haploinsufficiency of A20 (H20) [4]. In other autoinflammatory disorders, the association between vasculitis and autoinflammation is not always obvious.

In this review, we describe the prevalence and types of vasculitis in some AIDs, focusing on new diseases and recent evidence published since our last review in 2016 [5▪].

VASCULITIS IN AIDs

Familial Mediterranean fever

FMF is the most common AID, presenting with recurrent episodes of fever, serositis, and rash lasting

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KEY POINTS

- Vasculitis is a key feature in several autoinflammatory diseases (AIDs) such as familial Mediterranean fever, deficiency of adenosine deaminase 2 (DADA2), HA20, and vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome (VEXAS), and may be underrecognized or misclassified in clinical practice.
- The patterns of vasculitis in AIDs often differ from classical forms, with distinct clinical features, histopathology, and genetic backgrounds, requiring tailored diagnostic approaches.
- Genetic testing should be considered in patients with early-onset, atypical, or treatment-refractory vasculitis, especially when associated with systemic inflammation or family history.
- Targeted therapies, including interleukin-1 and tumor necrosis factor inhibitors, JAK inhibitors, and hematopoietic stem cell transplantation, may be necessary and effective in managing vasculitic manifestations in AIDs.
- Raising clinical awareness of vasculitis within AIDs can enhance diagnostic accuracy and patient outcomes, especially in pediatric groups and complex multisystem inflammatory cases.

24–72 h [6]. It is associated with pathogenic mutations in the *MEFV* gene, which encodes pyrin. The characteristic skin rash of FMF, erysipelas-like erythema, is not vasculitic. However, protracted febrile myalgia (PFM), a severe form of disabling myalgia with high fever in FMF patients, may have a vasculitic etiology. Previous skin and muscle biopsies failed to show vasculitis, but a recent study revealed vasculitis involving the fasciae and myofascial areas, with minimal muscle involvement [7,8].

The most common vasculitides described in FMF are Henoch–Schonlein purpura (HSP)/immunoglobulin A vasculitis (IgAV) and polyarteritis nodosa (PAN), with a prevalence of 2.7–7% and 1%, respectively [9]. In a large pediatric FMF cohort including 1687 patients, IgAV was the second most common comorbid condition, after juvenile idiopathic arthritis [10]. *MEFV* mutations have also been found to be more common among IgA vasculitis patients [11▪]. IgA-associated vasculitis in the context of FMF often follows an atypical course, characterized by a younger age of onset, frequent recurrences, and rashes that may appear in uncommon locations such as the face and trunk [12]. Compared to patients with IgAV alone, IgAV-FMF patients had significantly higher gastrointestinal and renal involvement, a higher median pediatric vasculitis activity score, and a greater need for steroids, cyclophosphamide, IVIG, and plasma exchange therapy [13]. Furthermore, the IgAV-FMF patients seem to have an increased prevalence of intussusception [14]. It seems that *MEFV* variants, on exon 10, trigger a more severe form of IgAV [13,15▪]. In cases where skin biopsy was performed, histological examination revealed leukocytoclastic vasculitis without IgA deposition. This raised the hypothesis that HSP-like vasculitis may represent a distinct manifestation of FMF itself [12] (Table 1).

As for PAN, FMF-PAN patients have an earlier onset of disease, increased male-to-female ratio, more abdominal pain, more frequent perirenal hematomas, glomerular and central nervous system involvement compared to PAN alone [14,16]. Overall, it has a more favorable prognosis. Due to these distinctive features, it is not clear if these patients suffer from classical PAN or if these clinical findings represent a unique vasculitis specific to FMF [14] (Table 2).

Large vessel vasculitides such as Takayasu arteritis (TAK) or Cogan syndrome have been rarely described to co-occur with FMF [9]. There are 5 case reports of FMF together with TAK; most patients carried pathogenic variants of p.M694V. A recent report describes a 29-year-old man treated with tocilizumab, controlling both diseases [17].

Additionally, Behcet's syndrome (BS) may co-occur with FMF, which may be partially explained by the common ethnic and geographic distribution of these diseases. In these patients, cutaneous, gastrointestinal, and central nervous system involvement is more frequent than in isolated Behcet's. Interestingly, in cohorts of BS, FMF is more common than in the general population of the same region [9].

Finally, although FMF is a relapsing disease, most reports of vasculitis in FMF patients describe single episodes with good response to immunosuppressive therapy [18].

Cryopyrin-associated periodic syndromes

Cryopyrin-associated periodic syndromes (CAPS) encompasses a group of disorders historically divided into familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease/chronic infantile neurological cutaneous articular syndrome (NOMID/CINCA). All three disorders are associated with mutations in the *NLRP3* gene, coding for the NLRP3 protein, or cryopyrin [5▪]. These syndromes are characterized by periodic fever, urticarial rash, arthritis, conjunctivitis, and neurological involvement, including hearing loss and aseptic meningitis [11▪]. The typical skin lesion is a neutrophilic urticarial

Table 1. Comparison of IgA vasculitis (HSP) with and without FMF

Features	IgA vasculitis (HSP) only	IgA vasculitis + FMF
Age of onset	Typical childhood onset	Younger than usual
Clinical course	Generally self-limited	Atypical, recurrent episodes
Distribution of rash	Buttocks, lower extremities	Includes face and trunk (atypical)
Gastrointestinal involvement	Common	More frequent and severe
Intussusception	Rare	Increased prevalence
PVAS (Pediatric Vasculitis Activity Score)	Lower median	Higher median
CRP (C-reactive protein)	Lower median	Higher median
Treatment requirements	Less intensive (steroids may suffice)	More intensive: steroids, cyclophosphamide, IVIG, plasma exchange
Histology on skin biopsy	Leukocytoclastic vasculitis with IgA deposition	Leukocytoclastic vasculitis without IgA deposition
MEFV mutations	Absent or incidental	Common, especially exon 10 variants
Possible interpretation	Classic IgAV	May represent FMF-related vasculitis, possibly distinct from classic IgAV

IgA, immunoglobulin A; IgAV, immunoglobulin A vasculitis.

dermatosis without vasculitis. There are case reports of CAPS patients with small-vessel vasculitis of the skin and testis [5▪], retinal vasculitis [19,20], and one report of a young CINCA patient with pauci-immune crescentic glomerulonephritis [21]. A recent review described a Muckle–Wells patient who developed recurrent fever and severe vasculitis with intestinal perforations shortly after birth and died at age 15 from alveolar hemorrhage [22]. Consequently, vasculitis is not considered a primary feature of CAPS but may occur as a coincidental or coexisting condition.

Hyper-immunoglobulin D syndrome/ mevalonate kinase deficiency

Hyper-immunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD) is characterized by recurrent fever, rash, lymphadenopathy, and gastrointestinal manifestations; in severe forms, it results in Mevalonic aciduria, causing neurological, ocular, and auditory disorders [4,18]. The most common types of rash are erythematous macules, papules, nodules, and urticarial lesions [5▪,11▪]. In a cohort of 44 patients, 10 underwent skin biopsy, which

Table 2. Comparison of PAN with and without FMF

Feature	Isolated PAN (classical PAN)	PAN associated with FMF (FMF-PAN)
Age of onset	Later onset	Earlier onset
Sex ratio (male:female)	Balanced or slight male predominance	Increased male-to-female ratio
Abdominal pain	Present in some cases	More frequent and prominent
Perirenal hematomas	Rare	More frequent
Glomerular involvement	Uncommon (PAN usually spares glomeruli)	More frequent glomerular involvement
Central nervous system Involvement	Variable	More frequent CNS involvement
Prognosis	Variable, can be severe	More favorable prognosis overall
Nosological status	Recognized systemic medium-vessel vasculitis	Unclear: may represent a unique FMF-related vasculitis

CNS, central nervous system; FMF, familial Mediterranean fever; PAN, polyarteritis nodosa; TNF, tumor necrosis factor.

showed mild features of vasculitis [23]. There are additional case reports of HIDS patients with vasculitis in skin biopsies, strengthening the theory that cutaneous vasculitis may be a component of the disease [11▪]. Omoyinmi *et al.* recently published the case of a 2-year-old boy presenting with high fever, abdominal pain, diarrhea, rectal bleeding, and extensive purpuric and necrotic lesions predominantly in the lower limbs. Next-generation sequencing revealed compound heterozygous mutations in the *MVK* gene. The patient had a rapid and complete recovery with IL-1 blockade [24]. IgA vasculitis, Kawasaki-like, and Behcet-like syndromes were rarely described in MKD [15▪]. Taken together, these findings suggest that cutaneous vasculitis may represent one of the clinical manifestations of MKD, although its occurrence appears variable.

Tumor necrosis factor receptor-associated periodic syndrome

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant disease associated with mutations in the *TNFRSF1A* gene. It presents as recurrent fever, serositis, periorbital edema, and myalgia with an overlying migratory rash [5▪,11▪]. Most skin biopsies do not show evidence of vasculitis. There is a case report of a 66-year-old female with TRAPS whose skin biopsy demonstrated small vessel vasculitis and panniculitis; she was positive for anti neutrophilic cytoplasmic antibody (ANCA) against neutrophil elastase [25]. There is also a report of a 4-year-old child with TRAPS who presented with a clinical syndrome consistent with IgA vasculitis [26]. In a review of adult patients diagnosed with autoinflammatory disease, one out of six TRAPS patients had leukocytoclastic vasculitis [27]. An additional autopsy report of a 26-year-old patient with TRAPS showed pronounced intimal thickening and medial hypertrophy of medium and small vessel walls without inflammatory cell involvement, suggesting a systemic vasculopathy [28]. These observations suggest that, although not a defining feature, vasculitic manifestations and systemic vasculopathy may occur in TRAPS patients.

Blau syndrome

Blau syndrome is a rare autoinflammatory disease associated with mutations in the *NOD2* (*CARD15*) gene, which causes autoactivation of the NF-κB pathway. The disorder presents with granulomatous dermatitis, arthritis, and uveitis, typically with onset before the age of four years [29▪,30]. A recent retrospective study of 47 Chinese patients with Blau syndrome demonstrated an incidence of vasculitis in 28% of patients, mostly with medium and large vessel involvement, such as the abdominal aorta, common carotid, and renal arteries [29▪]. In another series of 44 patients, 34% had cardiovascular involvement, which included Takayasu-like arteritis and/or cardiopathy. These patients had a higher incidence of recurrent fever and were treated more frequently with anti-TNFα agents [31]. Because of the insidious onset of vasculitis in Blau syndrome, clinicians should maintain a high level of suspicion for this complication [30]. Thus, Blau syndrome does have features of vasculitis, especially of large arteries.

Otulipenia/Otulin-related autoinflammatory syndrome

Otulipenia/OTULIN-related autoinflammatory syndrome (ORAS) is an autosomal recessive disease associated with mutations in the *FAM105B* gene, which encodes Otulin, a de-ubiquitinase acting as a down-regulator of the NF-κB signaling pathway. It was first described in 2016 by two separate groups [32,33]. Patients present with early-onset prolonged episodes of fever, failure-to-thrive, erythematous skin rash with nodules, lipodystrophy, arthralgia, abdominal pain, diarrhea, and lymphadenopathy [32–34]. The flares are prolonged and do not resolve without treatment [35]. Skin biopsies usually show different types of panniculitis and neutrophilic dermatoses, but small- and medium-sized vessel vasculitis has also been reported [32,34]. The disease seems to respond well to TNF inhibition [33,36].

Haploinsufficiency of A20

Haploinsufficiency of A20 (H20), is associated with heterozygous loss-of-function mutations in the *TNFAIP3* gene (coding for TNFα-induced protein 3, or A20). It was first described as a monogenic form of Behcet's syndrome, presenting with oral and genital ulcers, uveitis, skin, joint, and gastrointestinal inflammation [37]. H20 is also associated with autoimmunity (such as thyroiditis or systemic lupus erythematosus) [38,39▪,40] and lymphoproliferation [15▪,39▪]. As in BS, it may be accompanied by a variable vessel vasculitis with a preference for the venous side of the vasculature [15▪]. A review of 16 H20 patients revealed retinal vasculitis in one patient, CNS vasculitis in another, and CNS vasculitis together with pulmonary artery emboli in a third [38]. Another review of 45 patients compares H20 patients to classical BS, highlighting the differences between the two diseases; in H20, there is a reversal of the male-to-female ratio to 1 : 2, early appearance of symptoms with a median age of 5.5 years, recurrent fever, lower prevalence of HLA-B51, more

Table 3. Comparison: Behçet's syndrome vs. haploinsufficiency of A20 (HA20)

Feature	Behçets syndrome	HA20 (haploinsufficiency of A20)
Genetic basis	Polygenic; no single associated gene	Monogenic: heterozygous TNFAIP3 loss-of-function mutations
Pathogenic mechanism	Aberrant immune regulation; unclear etiology	Dysregulated NF-κB signaling due to defective ubiquitin-editing enzyme (A20)
Disease classification	Variable-vessel vasculitis, autoinflammatory/ autoimmune overlap	Monogenic autoinflammatory disease (AID), mimicking variable-vessel vasculitis
Age of onset	Typically, adolescence or early adulthood	Early-onset, often in childhood
Oral ulcers	Recurrent	Recurrent, typically early and prominent
Genital ulcers	Common	Common
Gastrointestinal symptoms	Present in some cases	Frequent
Fever	Not a consistent feature	Periodic fevers common
Arthritis/arthralgia	Often present	Polyarthralgia or arthritis is common
Skin involvement	Erythema nodosum, pseudofolliculitis, etc.	Cutaneous involvement common
Eye involvement	Uveitis, retinal vasculitis	Retinal vasculitis has been reported in some patients
CNS involvement	May occur	CNS vasculitis was documented in several patients
Thrombosis	Common (venous > arterial)	Pulmonary artery emboli reported; possible thromboembolic risk

CNS, central nervous system.

abdominal symptoms and less response to colchicine [40] (Table 3). Next-generation genetic sequencing should be considered for the work-up of young patients with suspected BS, especially those with a positive family history, early disease onset, or atypical features [41].

Deficiency of adenosine deaminase 2

Deficiency of adenosine deaminase 2 (DADA2) is a monogenic disease resulting from biallelic loss-of-function mutations in the *ADA2* gene. It is unique in the AIDs as the gene associated with the disease is not involved in inflammatory pathways but rather affects purine metabolism and signaling [42]. DADA2 causes small- and medium-vessel necrotizing vasculitis, mimicking classical polyarteritis nodosa (PAN) [15▪,43] (Table 4). The onset of disease is usually in childhood, with 77% of patients presenting before the age of 10 years [44]. The clinical features include livedo racemosa, digital ischemia, renal or gastrointestinal infarcts, early-onset stroke (ischemic and hemorrhagic), and systemic vasculitis. Indeed, the predilection of DADA2 for central nervous system involvement (up to 50–77% of patients) is a distinguishing feature from classic PAN [15▪,39▪]. In addition to vasculitis, DADA2

Table 4. Vasculitis in DADA2 vs. classic polyarteritis nodosa

Feature	DADA2-associated vasculitis	Classic PAN
Age of onset	Early childhood or infancy	Mostly adulthood
Genetic cause	ADA2 mutations	Idiopathic, possibly HBV-related
Stroke	Frequent (ischemic and hemorrhagic)	Rare
Response to TNF inhibitors	Excellent	Variable
Immunodeficiency	Present in some patients	Absent
Hematologic involvement	Frequent (anemia, neutropenia)	Uncommon

DADA2, deficiency of adenosine deaminase 2; PAN, polyarteritis nodosa; TNF, tumor necrosis factor.

may cause hematological disorders, such as pure red cell aplasia, refractory thrombocytopenia, and even bone marrow failure [15▪,42]. Furthermore, immune dysregulation may present as autoimmune lymphoproliferative syndrome (ALPS), lymphoma, or common variable immunodeficiency [15▪]. The wide phenotypic variability is partly explained by specific mutations and by residual enzyme activity of *ADA2*, with higher levels presenting with a vasculitic phenotype and lower levels with prominent hematological disease [39▪,42]. Retrospective studies have demonstrated a clear beneficial role of TNF inhibitors, particularly for stroke prevention, although this strategy is less effective for controlling hematological manifestations. Allogeneic hematopoietic stem cell transplantation (HSCT) is reserved for patients with severe inflammatory and hematological disease who have not responded to conventional therapy [42,45▪].

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome

VEXAS, first described in 2020, is a highly heterogeneous monogenic disease associated with somatic mutations in the *UBA1* gene located on the X chromosome, occurring almost exclusively in men over the age of 50 [46]. It is a life-threatening disease with a 5-year mortality rate of 30–40% [47]. There are rare reports of women with VEXAS, the majority of which have Turner syndrome or acquired monosomy X [48]. Typical features of the disease are fever, weight loss, relapsing polychondritis, various cutaneous manifestations (livedo racemosa, neutrophilic urticarial dermatosis, erythema nodosum, Sweet-syndrome-like eruptions), ocular and lung involvement, progressive bone marrow failure, and vasculitis [15▪,48,49] (Table 5). There are multiple forms of systemic vasculitis associated with VEXAS, including leukocytoclastic vasculitis, Polyarteritis nodosa, and Giant-cell arteritis. There is a high prevalence of thrombosis (35–45%), mostly unprovoked and recurrent venous thrombosis, as described in BS and H20 [15▪,48]. Macrocytic anemia and myelodysplastic syndrome are key features of VEXAS, which may help diagnose patients with unexplained, recurrent, or treatment-refractory inflammatory disorders [49]. Various treatments, including glucocorticoids, conventional disease-modifying antirheumatic drugs, biological agents, and JAK inhibitors (especially ruxolitinib) have been used with variable results [49–51]. Additional treatment options target the UBA1-mutant clone with hypomethylating agents such as azacytidine. Allogeneic HSCT is currently the only curative treatment for VEXAS, sometimes with considerable mortality and morbidity [48].

In summary, vasculitis in VEXAS spans a spectrum from skin-limited disease to systemic polyarteritis nodosa-like vasculitis and occasionally large-vessel arteritis. The syndrome challenges traditional classifications of vasculitis, requiring genetic confirmation of UBA1 mutations for diagnosis and consideration of targeted therapies beyond traditional immunosuppressants.

CONCLUSION

In this review, we explored the intersection between autoinflammatory diseases (AIDs) and vasculitis, focusing on emerging evidence since 2016. AIDs are disorders of the innate immune system, often driven by genetic mutations affecting inflammatory

Table 5. Vasculitis in VEXAS vs. classic vasculitic syndromes

Feature	VEXAS-associated vasculitis	Classic PAN/ANCA vasculitis
Age of onset	Late adulthood (>50 years)	Typically younger in PAN, variable in ANCA vasculitis
Gender predominance	Strong male predominance	No gender preference in PAN; slight male bias in GPA
Genetics	Somatic UBA1 mutations	Typically idiopathic or autoimmune
Hematologic features	Macrocytic anemia, thrombocytopenia	Uncommon
Bone marrow	Myeloid vacuoles	Normal
Response to immunosuppression	Often refractory to steroids alone	Variable
Treatment	Requires steroid-sparing agents, hypomethylating agents, and JAK inhibitors under study	Cyclophosphamide, rituximab, steroids

PAN, polyarteritis nodosa; VEXAS, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome.

pathways, particularly inflammasomes, NF-κB signaling, or purine metabolism.

Vasculitis has emerged as a key and in some cases central feature of several monogenic autoinflammatory diseases, particularly FMF, DADA2, HA20, and VEXAS. The underlying mechanisms likely involve dysregulation of innate immunity, with central roles for IL-1β and NF-κB, resulting in endothelial dysfunction and vascular inflammation. Histopathologic and clinical features may differ from those of classic vasculitides, requiring a high index of suspicion and integration of clinical, genetic, and immunologic data.

Although vasculitis is not universally present in all AIDs, it is a prominent or recurrent feature in several conditions:

(1) FMF is often associated with IgA vasculitis and PAN, frequently presenting with atypical features and greater severity. Vasculitis-like manifestations may also occur during prolonged febrile myalgia.
(2) DADA2 is a prototypical monogenic vasculitis mimicking PAN, characterized by early-onset strokes and involvement of small- to medium-sized vessels.
(3) HA20, initially described as a Behçet-like syndrome, exhibits variable-vessel vasculitis and systemic inflammation, often starting in early childhood.
(4) CAPS, TRAPS, HIDS/MKD, and ORAS may present with vasculitic features in selected patients, although vasculitis is not their primary manifestation.
(5) VEXAS is notable for its severe, life-threatening inflammatory and vasculitic features, often necessitating hematologic monitoring and targeted treatment.

Genetic testing should be considered in young patients with vasculitis, especially in cases with early onset, systemic involvement, or poor response to standard immunosuppressive therapies. Targeted treatments – such as IL-1 or TNF inhibitors, JAK inhibitors, or hematopoietic stem cell transplantation – show promise in managing vasculitic features of AIDs, though treatment must be tailored to the individual's genotype, phenotype, and organ involvement. Some forms of vasculitis seen in AIDs do not align with current vasculitis classification systems, highlighting the need to reconsider existing diagnostic frameworks.

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Conflicts of interest

There are no conflicts of interest.

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Vasculitis associated with haematologic malignancies

Ayse Salihoglu and Muhlis Cem Ar

Purpose of review
This review examines the complex bidirectional relationship between vasculitis and hematologic malignancies, highlighting the importance of meticulous diagnostic assessment.

Recent findings
Vasculitis may emerge in the setting of hematologic malignancies via mechanisms such as paraneoplastic inflammation, immune dysregulation, drug exposure, and clonal hematopoiesis. Myeloid neoplasms – especially myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML) – show a stronger association than lymphoid malignancies, with cutaneous small vessel vasculitis being the most common subtype. VEXAS syndrome exemplifies the overlap between autoinflammation and hematologic disease, often presenting with vasculitic features and macrocytic anemia.
In lymphoproliferative disorders and plasma cell dyscrasias, vasculitis may precede, mimic, or complicate the malignancy. Entities such as intravascular lymphoma, angioimmunoblastic T-cell lymphoma, and monoclonal gammopathies – including MGUS and multiple myeloma – can manifest with vasculitic symptoms, requiring histopathologic and molecular evaluation. Emerging concepts like monoclonal gammopathy of cutaneous and rheumatologic significance highlight the need for interdisciplinary care. Drug-induced vasculitis, particularly from immunomodulatory agents and biologics, adds diagnostic complexity. Atypical features – such as unexplained cytopenias, dual autoantibody positivity, or poor response to immunosuppression – should prompt evaluation for underlying hematologic disease. Conversely, vasculitis may signal complications in patients with known hematologic disorders.

Summary
Early suspicion of vasculitis associated with hematologic malignancies and accurate diagnosis are important in guiding therapeutic approaches.

Keywords
Behçet syndrome, chronic myelomonocytic leukemia, myelodysplastic syndrome, MGUS, monoclonal gammopathy of cutaneous significance, vasculitis, VEXAS

INTRODUCTION

Patients with hematologic malignancies may initially present to rheumatology clinics due to a variety of inflammatory manifestations that overlap with autoimmune and vasculitic syndromes. Hematologic neoplasms – particularly those of myeloid and lymphoid origin – can mimic, coexist with, or even underlie vasculitic processes. Although the majority of patients diagnosed with vasculitis do not harbor an underlying malignancy, certain hematologic cancers may present with features suggestive of vasculitis or may emerge as a consequence of autoimmune dysregulation.

Referral to hematology is often prompted by laboratory abnormalities such as cytopenias, monocytosis, eosinophilia, or acquired bleeding diatheses in patients with suspected vasculitis. Notably, autoimmune phenomena – including vasculitis – occur in up to 30% of patients with myeloid or lymphoid malignancies. Among these, myeloid disorders such as MDS and chronic myelomonocytic leukemia (CMML) exhibit a stronger association with vasculitis compared to lymphoproliferative diseases [1].

The vasculitic involvement in hematologic malignancies typically affects small cutaneous or

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KEY POINTS

- Presenting with unexplained vasculitis should lead the clinicians to investigate underlying hematologic malignancies and collaboration between hematologists and rheumatologists is important.
- The vasculitis diagnosis and treatment in the context of hematologic malignancies is difficult because of the clinical heterogeneity, lack of specific serologic tests or markers and challenges in obtaining tissue samples.
- Integration of myeloid driver gene features like TET2 in hematologic malignancy associated vasculitis diagnosis may be more commonly used in the future.

medium-sized muscular arteries, whereas ANCA-associated and large-vessel vasculitis are less frequently observed. Conversely, approximately one-third of patients with autoimmune diseases may have an underlying MDS or CMML, underscoring the bidirectional relationship between these entities [2].

Diagnostic differentiation between primary vasculitis and paraneoplastic or malignancy-associated vasculitis requires a comprehensive approach, including complete blood count with differential, PET, histopathological evaluation, and clonal analyses, particularly via next-generation sequencing (NGS). Despite growing recognition of these associations, therapeutic data remain limited and largely anecdotal [3▪▪].

MYELOID MALIGNANCIES

Autoimmune and inflammatory manifestations are increasingly recognized in patients with MDS and *CMML*. These include vasculitis, connective tissue diseases, and inflammatory arthritis. Vasculitis in the context of MDS/CMML may arise as a paraneoplastic phenomenon, but infectious and drug-induced etiologies [4] must also be considered. Interestingly, progression to acute leukemia appears to be less frequent in MDS/CMML patients who develop vasculitis [5]. No consistent correlation has been identified between MDS subtypes, cytogenetic abnormalities, and the presence of autoimmune manifestations, and the prognostic impact of coexisting autoimmune disease remains unclear [6,7].

Myelodysplastic syndrome

Autoimmune and systemic inflammatory conditions are observed in approximately 10–25% of patients with MDS, encompassing neutrophilic dermatoses, connective tissue disorders, arthritis, and vasculitis [8]. Among vasculitic presentations, cutaneous small vessel vasculitis – particularly leukocytoclastic vasculitis (LCV) – is the most frequently reported subtype [7]. Giant cell arteritis (GCA) associated with MDS tends to exhibit attenuated clinical features compared to idiopathic GCA.

A systematic review of cutaneous manifestations in MDS identified vasculitis in 15.4% of cases (21/134 patients), with subtypes including cutaneous polyarteritis nodosa (PAN), LCV, Behçet syndrome, and unclassified vasculitides. Notably, MDS had a fatal course in 50% of these patients, with a median survival of 7.5 months following vasculitis onset [9].

Renal involvement in MDS-associated vasculitis was evaluated in a multicenter retrospective study by Lafargue *et al*. [8], which identified ANCA-associated glomerulonephritis as the predominant cause of renal injury. The therapeutic impact of hypomethylating agents on renal outcomes remains to be elucidated [8].

VEXAS syndrome

VEXAS syndrome (Vacuoles, E1 enzyme, X-linked, Autoinflammation, Somatic) is a recently characterized monogenic autoinflammatory disorder caused by somatic mutations in the UBA1 gene, predominantly affecting men over 40 years of age. The syndrome manifests with multisystem inflammation involving the skin, lungs, and bone marrow, and frequently mimics vasculitic diseases [10]. Vasculitis occurs in approximately 25% of patients and spans all vessel sizes, with PAN and LCV being the most common subtypes. Cutaneous involvement is present in 85% of cases, while visceral small vessel vasculitis affecting the lungs and kidneys is rare [11▪]. Hematologic abnormalities in VEXAS syndrome typically include macrocytic anemia and other cytopenias, with frequent progression to MDS or plasma cell dyscrasias. A hallmark diagnostic feature is cytoplasmic vacuolization in erythroid and myeloid precursors, warranting careful hematopathological evaluation [12].

Patients with VEXAS syndrome are often misdiagnosed with atypical, treatment-resistant vasculitis. Distinguishing features include leukocytoclasia without true vasculitis, neutrophilic alveolitis, non-vasculitic ocular and neurologic symptoms, and poor response to conventional immunosuppression. Clinical clues such as male sex, age at least 40 years, and cytopenias (macrocytic anemia, thrombocytopenia, monocytopenia) should prompt consideration of VEXAS [13▪▪].

Case reports have highlighted diverse presentations, including large vessel vasculitis refractory to steroids and granulomatosis with polyangiitis (GPA) with cartilage involvement responsive to methotrexate and infliximab [14,15]. In a cohort of 89 male patients with VEXAS syndrome, Sullivan *et al.* [14] identified vasculitis in 21 individuals, predominantly cutaneous LCV. Only one patient had GCA despite frequent cranial symptoms, and no association with thrombosis was observed [14]. Importantly vasculitis was not found to be correlated to thrombosis. The authors suggested that men at least 50 years of age with atypical and steroid-dependent vasculitis should be considered for evaluation of VEXAS syndrome.

Therapeutic strategies for VEXAS syndrome include high-dose corticosteroids and steroid-sparing agents such as JAK inhibitors (ruxolitinib, baricitinib), IL-6 inhibitors, hypomethylating agents, and allogeneic hematopoietic stem cell transplantation (HSCT) [16]. Durable glucocorticoid-free remissions are rare without hypomethylating therapy or HSCT. Reduction in UBA1 allele burden has been observed in responders to hypomethylating agents, suggesting a potential role for molecular monitoring in guiding treatment decisions [17].

Behçet syndrome and myelodysplastic syndromes

Behçet syndrome is a chronic, relapsing, multisystem vasculitis of unknown aetiology, characterized by mucocutaneous, ocular, vascular, and gastrointestinal involvement. A distinct clinical entity has emerged in patients with concurrent Behçet syndrome and myelodysplastic syndrome (BS-MDS), exhibiting features that diverge from either condition alone. Patients with BS-MDS tend to be older, display less frequent ocular involvement, and more commonly present with gastrointestinal manifestations compared to those with idiopathic Behçet syndrome. Notably, trisomy 8 is a recurrent cytogenetic abnormality in BS-MDS, particularly in cases with intestinal involvement [18].

Park *et al.* [6] conducted a multicenter retrospective analysis of 35 patients with intestinal BS-MDS across four Korean centers, comparing them to patients with intestinal Behçet syndrome without MDS. The BS-MDS cohort demonstrated higher mortality rates and greater refractoriness to conventional immunosuppressive therapies. In such cases, targeting the underlying MDS – especially when intestinal Behçet syndrome is refractory – has shown therapeutic benefit. Allogeneic HSCT may offer disease control, though its implementation requires multidisciplinary evaluation and careful consideration of risks, including graft-versus-host disease and infectious complications [6]. The efficacy of HSCT in BS-MDS has also been supported by case reports and literature reviews [19].

Chronic myelomonocytic leukemia

CMML, a clonal hematopoietic disorder classified within the spectrum of myelodysplastic/ myeloproliferative neoplasms, is frequently associated with autoimmune phenomena, occurring in approximately 15–25% of patients. Vasculitis is the most common autoimmune manifestation, with medium-sized vessel vasculitis (e.g., polyarteritis nodosa) and large-vessel vasculitis (e.g., GCA, Takayasu arteritis) being particularly prevalent. Large-vessel vasculitis may precede the diagnosis of CMML and serve as an early clinical clue.

In a multicenter French study, GCA emerged as the most frequent vasculitis subtype among patients with MDS/CMML, likely reflecting the shared demographic profile of older age [5]. Vasculitis may occur before or after CMML diagnosis, and its presence often correlates with distinct clinical and molecular features. Clonal hematopoiesis, driven by somatic mutations such as TET2, plays a pivotal role in both hematologic malignancy and inflammatory disease trajectories. Robinette *et al.* [20▪] recently demonstrated an increased incidence of GCA in patients with clonal hematopoiesis, particularly those harboring TET2 mutations and cytopenias. Intriguingly, TET2 mutations were associated with vision loss in GCA patients, even in the absence of elevated C-reactive protein, suggesting a genotype-specific inflammatory phenotype [20▪].

Patients with CMML-associated vasculitis tend to be younger than the general CMML population and exhibit a male predominance [21]. Although rare in adults, IgA vasculitis with cutaneous involvement has been reported in CMML, further highlighting the spectrum of vasculitic presentations. Altered monocyte/macrophage gene expression profiles have also been implicated in IgA nephropathy, suggesting a shared immunopathogenic mechanism [2].

LYMPHOID MALIGNANCIES

The association between vasculitis and lymphoproliferative disorders is rare but clinically significant. Various lymphoma subtypes may mimic vasculitic syndromes, leading to diagnostic challenges and potential delays in appropriate treatment.

Lymphoproliferative disorders

LCV, characterized by neutrophilic infiltration of small vessels, has diverse etiologies including

infections, medications, cryoglobulinemia, and neoplastic conditions. LCV is associated with lymphoproliferative diseases in approximately 1% of cases and may precede, coincide with, or follow the diagnosis of the underlying hematologic malignancy [22].

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis has been reported in conjunction with lymphomas and multiple myeloma. Proposed mechanisms include malignant infiltration of tissues (e.g., in chronic lymphocytic leukemia), monoclonal plasma cell production of ANCA, or vasculitis triggered by prior immunosuppressive therapy. Multiple myeloma may clinically mimic ANCA-associated vasculitis with features such as palpable purpura, peripheral neuropathy, and hemorrhagic nasal crusts, often in the absence of ANCA seropositivity [22]. Clues for underlying multiple myeloma include monoclonal gammopathy and C4 hypocomplementemia [23].

Intravascular lymphoma (IVL), a rare and aggressive subtype of non-Hodgkin lymphoma, frequently involves the skin, lungs, and central nervous system (CNS). IVL may be misdiagnosed as vasculitis due to its cutaneous and neurologic manifestations. Multiple biopsies from active lesions are essential for diagnosis. ANCA-positive IVL has also been described, further complicating the differential diagnosis [24]. Fever, neurologic symptoms, elevated LDH, and atypical ANCA positivity should prompt consideration of IVL and warrant skin or bone marrow biopsy [25–30].

Angioimmunoblastic T-cell lymphoma (AITL) has been reported following IgA vasculitis, suggesting a possible pathogenic link via tumor antigen-driven T-cell activation and aberrant IgA production [31]. NK/T-cell lymphoma may present with eosinophilia and systemic symptoms mimicking eosinophilic granulomatosis with polyangiitis, with vasculitis resulting from direct vascular infiltration by tumor cells [32].

Paraneoplastic urticarial vasculitis has been described in Hodgkin lymphoma, presenting with acute urticaria and resolving with chemotherapy. Proposed mechanisms include immune complex deposition, histamine release, and mast cell degranulation [33].

Large granular lymphocyte (LGL) leukemia, a rare indolent lymphoproliferative disorder of clonal T or NK cells, is associated with autoimmune conditions in 25–32% of cases, including vasculitis. Cryoglobulinemia, LCV, and ANCA-negative microscopic polyangiitis have been reported [34]. Patients often present with neutropenia, anemia, polyclonal hypergammaglobulinemia, splenomegaly, and increased circulating LGLs. A case of T-LGL leukemia presenting with necrotic bullous LCV was differentiated from reactive LGL proliferation by bone marrow infiltration and TCR αβ expression [35].

Hairy cell leukemia may rarely underlie cutaneous LCV. Cladribine, a standard treatment, may exacerbate vasculitic symptoms, while vemurafenib and corticosteroids have been used in combination [36].

Plasma cell disorders

Monoclonal gammopathies span a spectrum from asymptomatic monoclonal gammopathy of undetermined significance (MGUS) to aggressive plasma cell leukemia. MGUS, though premalignant, may lead to renal, neurologic, and cutaneous complications. The concept of monoclonal gammopathy of cutaneous significance (MGCS) has emerged to describe dermatologic conditions associated with monoclonal gammopathies not meeting criteria for hematologic intervention [37].

MGCS is categorized by underlying pathophysiologic mechanism. Group 1 involves direct effects of immunoglobulin products, such as cryoglobulinemia, which causes vasculitis through immune complex deposition [38]. Cryoglobulins are classified into type I (monoclonal IgM, IgG, or IgA) and mixed types II and III. Type I cryoglobulinemia is commonly associated with hematologic malignancies, including Waldenström's macroglobulinemia, multiple myeloma, MGUS, non-Hodgkin lymphoma, and chronic lymphocytic leukemia [39].

Group 2 MGCS involves indirect mechanisms, where monoclonal gammopathies trigger autoantibody production, cytokine release, and complement activation, leading to dermal inflammation. LCV is a common manifestation, typically presenting as palpable purpura on the lower extremities [40]. Differentiating incidental monoclonal gammopathies from pathogenic monoclonal gammopathies requires hematologic collaboration. Brummer *et al.* [41] described a patient with LCV mimicking ulcus cruris as the initial sign of smoldering multiple myeloma, with complete remission following plasma cell-directed therapy. LCV arising in the context of plasma cell diseases has been documented mostly in the form of case reports and the published cases are summarized by Brummer *et al.* [41]. LCV occurred typically as diffuse palpable purpura on the limbs or the trunk and was the initial manifestation of these multiple myeloma patients. In fewer patients, LCV developed over the course of multiple myeloma and was attributed to immunomodulatory drugs and/or proteasome inhibitors. Immune complex deposition, altered cytokine production, endothelial dysfunction, and complement system activation cause

inflammation and blood vessel infiltration by neutrophils [41].

IgA paraproteinemia may cause IgA-associated LCV. Cryoglobulinemia is present in approximately 20% of IgA vasculitis cases but is not required for diagnosis in patients with M-protein [42]. Marginal zone lymphoma has been reported with type II cryoglobulinemia vasculitis involving the intestines, skin, and lungs, with cryocrit used for response monitoring [43].

Monoclonal gammopathy has also been linked to renal pathology, termed monoclonal gammopathy of renal significance (MGRS) [44]. In a recent study of ANCA-negative pauci-immune crescentic glomerulonephritis (PICGN), eight of 14 patients had MG. Proposed mechanisms include monoclonal protein deposition, complement activation, endothelial injury, and neutrophil extracellular trap formation. The patients with MG were older and had lower eGFR, proteinuria, hemoglobin and complement levels but higher erythrocyte sedimentation rate. Kidney biopsies of patients with monoclonal gammopathy revealed a higher degree of fibrosis compared to patients without monoclonal gammopathy and patients with monoclonal gammopathy had a higher mortality rate. In ANCA-negative PICGN, monoclonal gammopathy should be investigated [45].

Plasma cell dyscrasias, particularly MGUS and multiple myeloma, are also among the hematologic manifestations of VEXAS syndrome [3▪▪]. Importantly, monoclonal gammopathy may arise in rheumatologic diseases, including those treated with biologics, prompting the recent proposal of monoclonal gammopathy of rheumatologic significance [46▪].

MISCELLANEOUS HEMATOLOGIC CONDITIONS ASSOCIATED WITH VASCULITIS

Vasculitis may arise in the context of various hematologic conditions and treatments, often presenting diagnostic and therapeutic challenges [47]. LCV, in particular, can be drug-induced, with immunomodulatory agents such as lenalidomide – commonly used in multiple myeloma – implicated in its pathogenesis.

Rituximab, a monoclonal anti-CD20 antibody widely employed in both B-cell lymphomas and autoimmune vasculitis, has paradoxically been associated with LCV. This adverse effect may occur days to weeks postadministration and is hypothesized to result from rituximab-antirituximab immune complex formation, B-cell depletion, and cytokine release [48].

Cryoglobulinemic vasculitis affects approximately 3% of patients with Sjögren's syndrome and confers an elevated risk for progression to non-Hodgkin lymphoma. It is to be noted that in a small cohort of 13 patients with Sjögren's syndrome-associated cryoglobulinemic vasculitis, rituximab therapy did not appear to influence lymphoma evolution [49].

Autoimmune phenomena, including vasculitis, may also develop following allogeneic HSCT.

WHEN TO SUSPECT UNDERLYING HEMATOLOGIC MALIGNANCY IN VASCULITIS

Recognition of hematologic malignancy in patients presenting with vasculitis requires vigilance, especially when clinical or laboratory features deviate from typical autoimmune patterns. Key red flags include unexplained cytopenias, dual autoantibody positivity, poor response to immunosuppression, and bone marrow infiltration on MRI [50].

Conversely, in patients with established hematopoietic disorders, the emergence of atypical systemic symptoms – such as prolonged fever, polymyalgia rheumatica-like manifestations, sensorineural hearing loss, nephropathy, or unexplained eosinophilia – should raise suspicion for vasculitic involvement.

CONCLUSION

Recognizing atypical presentations, serologic anomalies, and treatment-resistant vasculitis is essential for timely identification of underlying hematologic disease.

Multidisciplinary collaboration, integration of molecular diagnostics, and individualized therapeutic strategies remain pivotal in optimizing outcomes for this diagnostically challenging and clinically heterogeneous group of patients.

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Conflicts of interest

There are no conflicts of interest.

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Pathophysiologic implications and therapeutic potentials of telocytes in multiorgan fibrosis

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Purpose of review
Telocytes (TCs) are unique stromal cells with distinctive morphology, ultrastructural features, and intercellular communication abilities. Accumulating evidence supports their critical roles in tissue homeostasis, regeneration, and stem cell niche maintenance through both cell-to-cell contacts and delivery of paracrine signals. The purpose of this review is to provide an up-to-date overview of the current knowledge regarding the pathophysiologic implications and therapeutic potentials of TCs in multiorgan fibrosis.

Recent findings
Loss and/or structural degeneration of TCs have been implicated in the pathogenesis of fibrotic conditions affecting the skin, gastrointestinal tract, heart, lungs, kidneys, and reproductive organs. TC depletion has often been associated with extracellular matrix remodeling, aberrant fibroblast activation, disruption of stem cell support, and altered tissue architecture. Experimental evidence suggests that TCs may possess antifibrotic therapeutic potentials, with TC transplantation or administration of TC-derived secretome/extracellular vesicles mitigating fibrosis progression in different preclinical models.

Summary
TCs are emerging as pivotal regulators of stromal homeostasis across several organs and their loss appears to be a unifying feature in the pathogenesis of tissue fibrosis in different anatomical districts. Targeting TCs, either by preserving their function or restoring their networks/paracrine signals, may open new therapeutic avenues for managing various fibrotic diseases.

Keywords
antifibrotic therapy, intercellular signaling, multiorgan fibrosis, telocytes, tissue homeostasis

INTRODUCTION

Telocytes (TCs) represent a distinct population of interstitial cells ubiquitously distributed within the stromal compartment of numerous organs and characterized by unique morphologic, ultrastructural, and functional properties [1–6]. TCs are easily identifiable by their small piriform, spindle or triangular cell body and by their extremely thin, long, and branched telopodes, characteristic cytoplasmic processes with a typical moniliform aspect due to the alternation of very slim segments (podomers) and small enlarged portions (podoms) [1–6]. Within tissues, telopodes are usually organized in intricate 3D networks, which makes them highly specialized for both homocellular and heterocellular communications [1–6]. Moreover, telopodes can also establish contacts with the extracellular matrix (ECM) [7]. Under transmission electron microscopy (TEM), which is considered the gold standard technique to observe TCs, these stromal cells are characterized by a relatively small cell body containing scarce perinuclear cytoplasm, with mitochondria and endoplasmic reticulum cisternae mainly harbored within podoms [1–6]. In addition, telopodes are frequently surrounded by various types of extracellular vesicles, including exosomes, ectosomes, and multivesicular bodies, supporting a role for TCs in paracrine signaling and local cellular regulation [7,8,9▪▪]. In terms of immunophenotype, although TCs lack a distinctive antigenic profile, expression of CD34 alone or in combination with platelet-derived growth factor receptor α (PDGFRα) currently

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KEY POINTS

- Telocytes are a distinct population of stromal cells characterized by long and moniliform telopodes and a strategic position within the tissue microenvironment across various organs, where they contribute to tissue homeostasis, regeneration, stem cell niches maintaining, and intercellular signaling.
- Quantitative and/or structural alterations of telocytes have been closely associated with the onset and progression of fibrosis in several disorders including systemic sclerosis, inflammatory bowel disease, liver and cardiac fibrosis, suggesting a role for telocyte impairment in driving aberrant fibroblast activation and extracellular matrix accumulation.
- Emerging preclinical evidence demonstrated that telocyte transplantation or administration of telocyte-derived secretome/extracellular vesicles can attenuate fibrosis and restore tissue architecture, supporting their potential as novel antifibrotic therapeutic tools.

represents the most reliable label for their identification under light microscopy [1–6]. Nevertheless, the specific TC immunophenotype may vary across different tissue or organ systems, and heterogeneous TC subpopulations exhibiting distinct immunohistochemical features may coexist within the stroma of a single anatomical site [4,7,10,11]. Beyond these ultrastructural and immunophenotypic features, emerging data reveal that TCs also possess unique microRNA signatures and gene/protein expression profiles, which clearly distinguish them from classical fibroblasts and other stromal cell types [4,7,10,11]. While the full spectrum of TC functions remains to be fully elucidated, their characteristic spatial organization, extensive cell-to-cell communications, and paracrine activity via extracellular vesicle release suggest that these peculiar stromal cells may play significant roles in a wide range of physiological processes [2,4,7,10,11]. First, by forming 3D labyrinthine networks with their long and interconnecting telopodes, TCs may serve as a structural scaffold, guiding tissue morphogenesis, promoting postnatal repair, and maintaining tissue integrity [2,4,7,10,11]. Second, TCs have been proposed to mediate cellular signaling both via direct cell-to-cell contacts and indirectly through vesicle-mediated delivery of cytokines, growth factors, and RNAs (e.g., mRNAs, microRNAs and other noncoding RNAs) [2,4,7,10,11]. Third, TCs were also identified as an emerging component of stem cell niches of several organs, where they are thought to be crucial for stem cell survival, renewal, differentiation, maturation, and guidance [2,4,7,10,11]. Lastly, TCs are commonly regarded as active participants in immunomodulation/immunosurveillance, electrical signal conduction especially in the myometrium and myocardium, and regulation of intestinal motility, likely through the diffusion of the slow waves generated by the interstitial cells of Cajal within the enteric neuromuscular compartment [2,4,7,10,11].

Given their broad distribution and multifaceted functions, increasing interest has focused on the involvement of TCs in pathologic conditions, particularly fibrotic diseases, which are characterized by excessive ECM deposition and remain a challenging clinical problem due to their unclear pathogenesis and limited therapeutic options [4,6,7,10–14]. In this context, a growing body of evidence has recently established a strong association between TC morphologic and numerical impairment and the progression of a wide range of disorders featuring tissue fibrosis, including systemic sclerosis (SSc or scleroderma), ulcerative colitis (UC), Crohn's diseases (CD), liver fibrosis, myocardial fibrosis, and endometriosis among others (Fig. 1) [4,6,7,10–14]. Nonetheless, it should be considered that TC damage and loss may either be a consequence of the fibrotic process or precede the initial stages of fibrosis, and that a reciprocal causation between fibrosis establishment and TC impairment cannot be excluded (Fig. 1). However, since accumulating literature reported that TC transplantation and/or TC-derived secretome/extracellular vesicle administration were able to mitigate ECM deposition in preclinical models of several fibrotic diseases, TCs may be regarded as a promising innovative antifibrotic therapeutic tool [7,12,15▪,16▪,17,18].

In the present review, we will provide a comprehensive overview of the most important findings regarding TC involvement in different fibrotic conditions, and critically examine TC therapeutic potential for the management of these challenging pathologies.

TELOCYTES IN SKIN FIBROSIS

In healthy skin, TCs establish an extensive 3D interstitial network that compartmentalizes the dermal layer, with their telopodes closely surrounding microvascular structures, peripheral nerve fibers, and cutaneous adnexa, including hair follicles and sweat glands [19]. In the setting of cutaneous fibrosis, and particularly in SSc, a complex autoimmune connective tissue disorder characterized by microvasculopathy and progressive fibrosis of the skin and internal organs, remarkable alterations in the TC network have been documented [19]. Specifically, a significant reduction and degenerative changes in cell morphology of dermal TCs have been

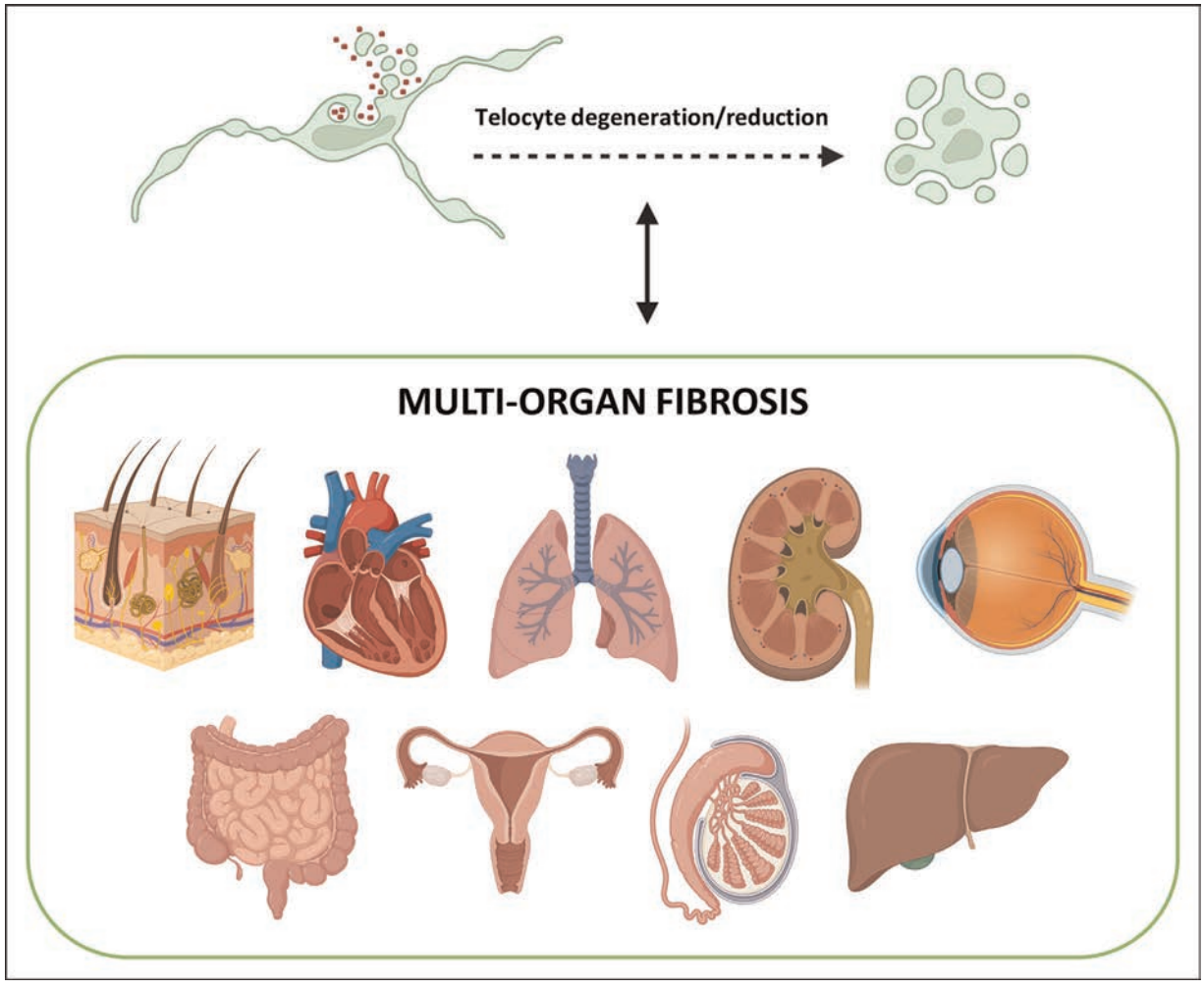

FIGURE 1. Degeneration and reduction of telocytes, a distinctive stromal cell population possessing unique morphologic features and intercellular communication abilities, have been associated with the onset and progression of multiorgan fibrosis, including the skin, heart, lungs, gastrointestinal tract, kidneys, liver, organs of the reproductive systems, and cornea. Telocyte damage or loss may either be a consequence of the fibrotic process or precede the initial stages of fibrosis, and a reciprocal causation between fibrosis establishment and telocyte impairment may exist.

observed in fibrotic skin biopsies from SSc patients, correlating with the extent of dermal fibrosis and featuring ultrastructural abnormalities such as mitochondrial swelling, cytoplasmic vacuolization, and accumulation of lipofuscin bodies [19]. Similar findings have been replicated in the bleomycin-induced murine model of scleroderma-like dermal fibrosis [20]. Different hypotheses have been proposed to explain the relationship between TC damage/loss and the onset/progression of dermal fibrosis. First, TC damage/loss may either be a consequence of ECM remodeling during fibrogenesis or disrupt the regulatory role of TCs over fibroblasts, thus contributing to abnormal fibroblast activation and consequent differentiation into profibrotic myofibroblasts [7,9▪▪,19,20]. Second, TCs themselves might undergo a phenotypic conversion into myofibroblasts, thus directly contributing to the fibrotic stromal cell pool [7,13]. However, experimental evidence overwhelmingly supports the first hypothesis as the dominant mechanism. Indeed, while few cells co-expressing the TC marker CD34 and the myofibroblast marker α-smooth muscle actin (α-SMA) have been detected in fibrotic SSc skin and in bleomycin-treated mouse skin at early stages of the fibrogenic process [13,20], in dermal lesions of both SSc patients and bleomycin-induced mouse model TEM analysis provided clear evidence of progressive degenerative ultrastructural changes and necrosis of TCs rather than their transdifferentiation into profibrotic myofibroblasts [19,20]. In addition, a recent clinical case study by Pereira de Godoy *et al*. described pronounced dystrophic changes in dermal TCs (i.e., telopode fragmentation, cytoplasmic disintegration, apoptotic nuclear

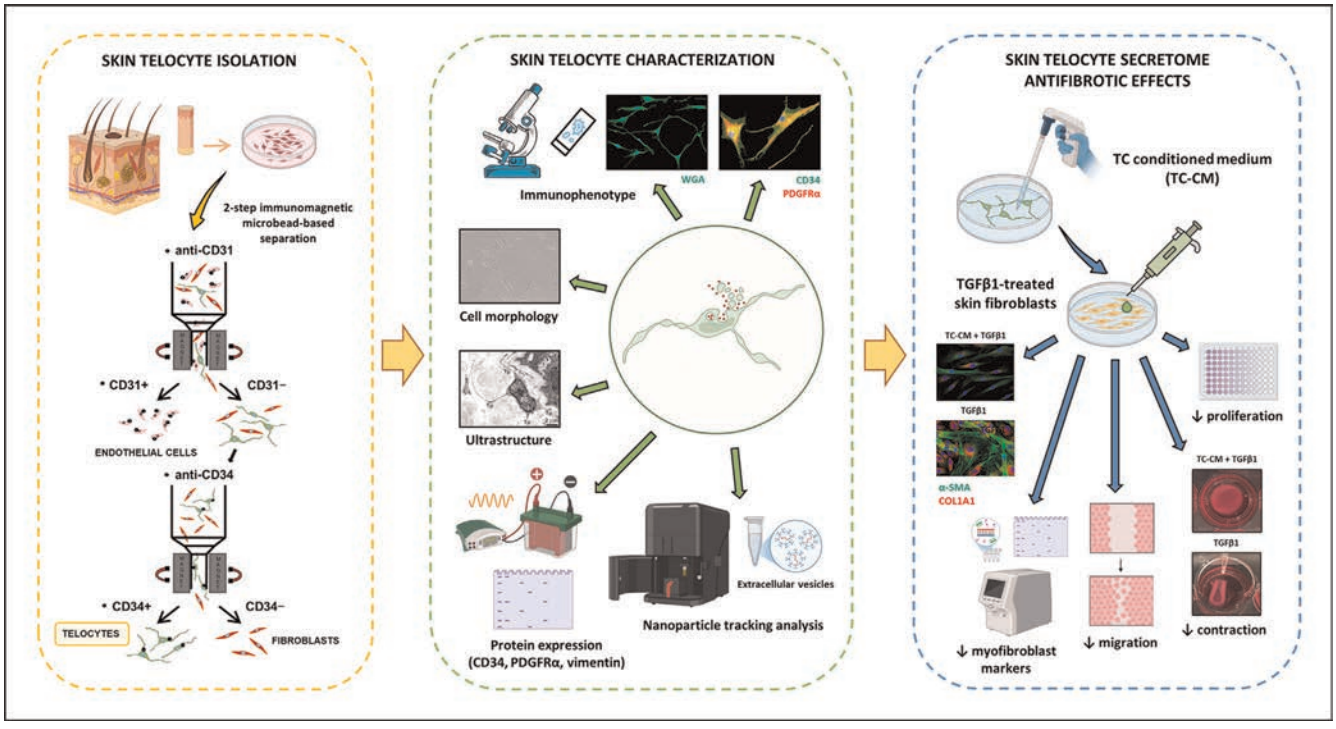

FIGURE 2. Skin telocyte isolation, characterization, and in vitro assessment of their antifibrotic effects. Skin telocytes were isolated from human healthy skin biopsies by using a two-step immunomagnetic microbead-based cell separation method, in which total dermal cells were subjected to magnetic-activated cell sorting: in the first step, anti-CD31-conjugated beads were used to isolate CD31+ endothelial cells that share CD34 expression with telocytes, while in the second step, performed on the remaining CD31− cells, anti-CD34-conjugated beads were used to further separate CD31−/CD34− fibroblasts from CD31−/CD34+ telocytes. Skin telocytes were subsequently cultured and characterized using different methodologies: (i) morphologic features were assessed via phase-contrast microscopy and wheat germ agglutinin (WGA) fluorescent staining of the plasma membrane; (ii) immunophenotypic profiling was performed by double immunofluorescence staining for CD34 and PDGFRα; (iii) CD34, PDGFRα, and vimentin protein expression was evaluated by immunoblotting; and (iv) extracellular vesicle content in telocyte conditioned medium (TC-CM) was analyzed using nanoparticle tracking analysis. Skin TC-CM exerted antifibrotic effects by effectively preventing transforming growth factor β1 (TGFβ1)-induced skin fibroblast-to-myofibroblast differentiation. Indeed, TC-CM significantly prevented the proliferative and migratory responses of skin fibroblasts to TGFβ1 stimulation, as well as their phenotypic differentiation into profibrotic and contractile COL1A1+/α-SMA+ myofibroblasts.

morphology, and nuclear extrusion) during the progression of lower limb lymphedema-associated fibrosis [21]. Notably, intensive lymphatic stimulation therapy resulted in a marked increase in TC density and was associated with clinical reversal of dermal fibrosis [21]. Finally, recent in vitro findings highlighted important antifibrotic properties of skin TCs, which could be exploited in the near future to develop novel therapeutic strategies against cutaneous fibrosis [9▪▪]. In fact, through a combination of morphologic, gene/protein expression, and functional investigations, TC secretome as conditioned medium collected from cultured healthy dermal TCs isolated using a two-step immunomagnetic microbead-based protocol was shown to be rich in extracellular vesicles and effective in preventing transforming growth factor β1 (TGFβ1)-induced skin fibroblast-to-myofibroblast profibrotic differentiation (Fig. 2) [5,9▪▪]. Indeed, the administration of TC-conditioned medium not only significantly suppressed the proliferative, migratory, and contractile responses of fibroblasts to TGFβ1 stimulation, but also attenuated their profibrotic phenotypic differentiation into myofibroblasts, as evidenced by a marked decrease in *FAP*, *ACTA2*, *COL1A1*, *COL1A2*, *FN1*, and *CTGF* gene expression levels, along with reduced α-SMA, N-cadherin, COL1A1, and fibronectin containing extra domain A (FN-EDA) protein levels (Fig. 2) [9▪▪]. Collectively, these promising findings pave the way for further preclinical research to understand in-depth the skin TC-derived paracrine signals that are crucial in the control of fibroblast behavior and might be suitable as novel targets for antifibrotic therapies. Besides TC paracrine functions, whether transplantation of skin TCs directly within fibrotic skin lesions might

represent an additional therapeutic option deserves thorough investigation.

TELOCYTES IN GASTROINTESTINAL TRACT FIBROSIS

TCs are widely distributed across all the layers of the gastrointestinal tract wall, where they contribute to maintaining structural integrity and functional regulating the local microenvironment [7,10,11]. Within intestinal stem cell niches, particularly in the mucosal compartment, TCs play a pivotal role by delivering paracrine signals such as Wnt ligands, which are essential for stem cell maintenance/renewal and epithelial turnover [7,10,11,22,23]. In the context of inflammatory bowel disease (IBD), including CD and UC, two complex pathologies in which chronic relapsing and remitting intestinal inflammation finally results into extensive tissue fibrosis and consequent intestinal stiffness and dysmotility, TC morphology and distribution undergo significant pathologic alterations that are closely associated with the degree of fibrotic remodeling and structural disorganization of the intestinal wall [7,10–12,24. In CD, inflammation and fibrosis may involve the entire gastrointestinal tract, from the oral cavity to the colon, though the terminal ileum is most commonly affected, while in UC they are restricted to the colon, spreading from distal to proximal and always involving the rectum [7,10–12].

The terminal ileum of patients with CD is characterized by transmural fibrosis and discontinuous inflammatory and fibrotic areas known as “skip lesions”. In disease-free ileal segments, TCs were found to exhibit a distribution comparable to healthy controls, whereas in disease-affected portions they were reported to be significantly reduced, especially in those areas with the most extensive fibrotic remodeling and severe intestinal wall architectural disruption [25,26]. In addition, in the muscularis propria of affected CD segments, the TC network appeared fragmented or even totally missing within both circular and longitudinal muscle layers, as well as around the myenteric plexus ganglia [25].

In UC, where fibrotic changes are typically confined mostly to the mucosal and submucosal layers of the colon, TCs were found to be significantly reduced even in early stages of the disease [27]. Such TC reduction closely paralleled colon fibrotic changes, as TC depletion was initially restricted to the muscularis mucosae and submucosa, while the muscularis propria, typically spared from fibrosis, remained unaffected, while in more advanced stages, TC loss also extended to deeper muscle layers and the myenteric plexus [27]. Interestingly, these findings align with those reported in “skip lesions” of disease-affected CD specimens, in which TC loss is found only in areas with pronounced fibrosis and architectural damage [27].

Notably, the reduction in TC numbers in both CD and UC was paralleled by a significant decline in interstitial cells of Cajal, which are considered the principal mediators of gut neurotransmission and motility and with which TC telopodes form intermingling networks in order to coordinate smooth muscle cell peristaltic activity [25,27]. The structural and functional impairment of this complex interstitial cell network at the myenteric plexus was thus supposed to account for IBD-associated gastrointestinal dysmotility [12,24,25,27].

Similar to dermal fibrosis, even in IBD the impairment of the intestinal network of TCs might be due to their entrapment in the fibrotic ECM, with consequent cell sufferance and significant alterations in the spatial relationships between telopodes and neighboring cells such as tissue-resident fibroblasts, thus favoring their uncontrolled activation and profibrotic transition into myofibroblasts [10,11,25,27]. Interestingly, although it has been suggested that TCs may also directly contribute to the increase in α-SMA+ myofibroblast population by transdifferentiating themselves and changing their immunophenotype [28], CD34/α-SMA double immunostaining failed to detect significant numbers of transitioning cells, which is in favor of a scenario in which TC degeneration predominates over transdifferentiation into myofibroblasts [10,11].

Finally, a recent study investigated TC distribution in tissue specimens from subjects affected by oral submucous fibrosis, a premalignant condition characterized by epithelial atrophy and progressive submucosal fibrosis [29]. In particular, the authors’ quantitative analysis of CD34+ stromal cells revealed a considerable decrease in TC number in the early stages of the disease, with a further decline in the advanced stages, prompting them to suggest the loss of TCs may contribute to the development of oral submucous fibrosis [29].

Although TC transplantation has not yet been explored as a possible treatment strategy for gastrointestinal pathologies, intestinal TCs exhibit considerable therapeutic potential as nonepithelial sources of Wnt ligands and R-Spondin 3 (RSPO3), two important regulators of the Wnt signaling cascade, which is known to be essential for intestinal stem cell self-renewal and proliferation within the gastrointestinal epithelium [23,30,31]. Indeed, conditional knockdown of Porcupine or Wntless genes, which are required for functional maturation of all Wnt proteins, in intestinal TCs led to a rapid interruption of Wnt signaling, a significant reduction of the stem

cell population, and the consequent intestinal crypt collapse, underscoring the role of TCs as central mediators of intestinal homeostasis [23,30,31]. Furthermore, by using single-cell RNA sequencing, Kinchen *et al.* have identified a mesenchymal cell population located adjacent to the colonic crypt niche and characterized by a high Wnt signaling activity [32]. Interestingly, the decline of this population, presumed to be functionally analogous to TCs, was associated with the disruption of the intestinal epithelial architecture in UC, further supporting the notion that restoring TC function could be a promising therapeutic strategy for IBD [32].

TELOCYTES IN LIVER AND BILIARY TRACT FIBROSIS

Liver fibrosis, primarily resulting from chronic hepatic injury due to viral hepatitis and alcoholic or nonalcoholic steatohepatitis, is characterized by excessive activation of hepatic stellate cells (HSCs) and abnormal ECM deposition leading to progressive disruption of liver parenchymal structures [7,10,11]. Hepatic TCs, which are predominantly located in the space of Disse, where they provide structural support to HSCs, hepatocytes, and stem cells, and are thought to contribute to the integrity of the organ architecture and cellular interactions [33], have been shown to undergo a significant depletion during hepatic fibrogenesis [34]. This finding, along with the concomitant increase in HSCs in fibrotic liver tissue, supports the notion that TCs constitute a distinct interstitial cell population within the hepatic stroma and that their reduction may contribute to HSC dysregulation, possibly fostering their profibrotic function [34]. In addition, since in a murine model of partial hepatectomy TCs have been demonstrated to exhibit close spatial proximity to both hepatocytes and hepatic progenitor cells, which are critical for liver regeneration, their disappearance in the context of liver fibrosis has been supposed to potentially lead to impaired hepatocyte function and stem cell niches compromise, further exacerbating the hepatic injury [35]. Interestingly, in the same study the authors reported that the posthepatectomy raise in hepatocyte proliferation coincided with a peak in both TC and hepatic stem cell numbers, suggesting a potential role for TCs in supporting hepatocyte and stem cell-driven liver regeneration [35]. Finally, TC displaying ultrastructural damages have been observed in a rat model of aflatoxin B1-induced liver injury [36].

As far as the biliary system, where TCs are broadly distributed within the muscular layer and are believed to contribute to biliary motility through electrical coupling with smooth muscle cells, histopathologic analyses on tissues affected by gallbladder stone disease and biliary dilation syndrome were performed to explore the possible relationship between TCs and such biliary disorders [37]. In particular, through immunohistochemical comparative approaches, the authors described a significant TC reduction in the fibrotic regions of both diseased gallbladder and bile duct compared to healthy control tissues, suggesting that such a decrease may disrupt the TC regulatory balance over fibroblast/myofibroblast activity, ultimately resulting into ECM alterations and progressive tissue fibrosis [37].

TELOCYTES IN CARDIAC FIBROSIS

Within the human heart, TCs have been described in multiple anatomical compartments, including the myocardial interstitium, endocardium, epicardial stem cell niches, and cardiac valves [10,11,38]. Despite constituting a minor subset of cardiac interstitial cells, through their telopodes TCs are known to form an extensive 3D network in close association with cardiomyocytes, with which they interact via specialized junctions potentially facilitating electrical coupling and contributing to the formation of functional cellular units [10,11,38]. In epicardial stem cell niches, TCs have been found in intimate contact with resident cardiac stem cells, putative cardiomyocyte progenitors, as well as capillaries, nerve endings, and other stromal components [10,11,38,39]. This spatial organization suggests that TCs may play a critical role in maintaining a supportive microenvironment conducive to stem cell differentiation and maturation, thereby promoting myocardial regeneration [10,11,38,39]. Of note, the results of experimental studies in murine models further support a developmental role for TCs, implicating them in the regulation of myocardial compaction during embryogenesis [10,11]. Moreover, the shared expression of surface markers such as c-kit/CD117 between cardiac TCs and epicardium-derived progenitor cells has led to the hypothesis that TCs may also represent a specialized subpopulation within the cardiac progenitor cell hierarchy, with potential implications for both cardiac development and regenerative processes [10,11].

TC depletion has been documented across a wide spectrum of cardiac disorders [10,11,38,39]. During heart failure associated with dilated, ischemic, or inflammatory cardiomyopathies, TCs have been reported to be significantly reduced, with their number correlating with the extent and severity of alterations in ECM composition [10,11,38,40]. In particular, the TC network was found to be markedly diminished or even totally absent in the fibrotic regions of the failing myocardium, characterized

by densely packed fibrillar collagen, with TCs exhibiting severe ultrastructural degenerations including cytoplasmic vacuolization and telopodal retraction [10,11,40]. Conversely, TCs appeared relatively preserved in myocardial regions rich in amorphous ECM components, where telopodes were indeed still elongated and displayed their typical branched morphology [10,11,40]. Interestingly, quantitative analyses revealed an inverse correlation between TC/telopode abundance and mature fibrillar collagen content, as well as a positive association with collagen degradation products [10,11,40]. These observations, supported by further in vitro studies demonstrating that ECM components can influence telopode behavior in cardiac TC cultures, collectively indicate that TC dynamics are closely linked to ECM composition and remodeling [10,11]. Though the full spectrum of pathophysiologic consequences resulting from TC loss remains to be elucidated, it has been postulated that their depletion may disrupt myocardial structural integrity and intercellular communications, ultimately impairing the spatial organization and signaling networks within the myocardium [10,11,40]. Specifically, the reduction of TCs may compromise the function and maintenance of cardiac stem cell niches, thereby limiting the pool of cardiomyocyte progenitors and impeding regenerative responses [10,11,40]. Of note, a significant TC loss was additionally documented in fibrotic areas of experimental rat models of myocardial infarction, further underscoring their sensitivity to fibrotic remodeling [10,11,17]. In the context of SSc, the fibrotic remodeling of the myocardium is similarly associated with a substantial reduction in the TC network, which may impair regenerative capacity and cardiomyocyte electrical coupling, thereby contributing to arrhythmogenesis and progressive heart failure [10,11,41].

Several preclinical studies have demonstrated the therapeutic potential of TCs in the heart [7,10–12,15▪,17,42▪▪]. In a rat model of myocardial infarction, intramyocardial injection of cardiac CD34+/c-kit+ TCs into the infarcted and peri-infarcted regions of the animals led to a substantial reduction in infarct size and improved postinfarction cardiac functions [17,42▪▪]. Since these beneficial effects were attributed to the reconstruction of the TC interstitial network and to the attenuation of myocardial fibrosis, restoring the TC network in infarcted myocardium may contribute to functional cardiac repair [17,42▪▪]. More recently, by using the same animal model, Liao *et al.* demonstrated that the administration of miR-21-5p, the most abundant microRNA identified in TC-derived exosomes, was able to reduce infarct size and fibrosis, improve cardiac function, and enhance angiogenesis [15▪]. These findings suggest that both TC-based and TC-derived exosome-based therapeutic approaches may hold promise for the treatment of ischemic heart disease and consequent myocardial fibrosis.

TELOCYTES IN PULMONARY FIBROSIS

Pulmonary TCs, located within the interstitial spaces of intralobular bronchioles, terminal and respiratory bronchioles, and alveolar ducts, have been found to be significantly reduced in SSc-associated interstitial lung disease, possibly contributing to the progressive thickening of the alveolar septa and airspace obliteration [41]. Interestingly, lung TCs exhibit distinct gene and protein expression profiles that distinguish them from other mesenchymal cell populations [7,43,44]. Transcriptomic analyses have identified a set of genes selectively regulated in TCs [7,44]. Among the most upregulated are *FHL2*, a gene associated with anti-inflammatory responses and attenuation of fibrotic pathways, and *QSOX1*, which is involved in cell cycle regulation and ECM remodeling. Conversely, *PDE5A*, a gene whose overexpression is linked to the progression of pulmonary fibrosis, was found to be among the most downregulated in TCs [7,44]. These molecular signatures suggest a potential protective role for TCs in modulating both inflammation and fibrosis in pulmonary diseases [7,44].

The therapeutic potential of TCs against pulmonary fibrosis has been recently reported in an in vitro study by Zhang *et al.*, where the authors demonstrated that TCs were able to attenuate pulmonary fibrosis by preventing the epithelial-to-mesenchymal transition (EMT) in rat tracheal epithelial cells treated with TGFβ, mainly through the paracrine release of hepatocyte growth factor (HGF) [45]. Moreover, in a rat model of lipopolysaccharide-induced lung acute injury, which exhibits diffuse alveolar damage with interstitial fibrosis as its clinical hallmark, co-transplantation of CD34+ TCs and mesenchymal stem cells resulted in significantly reduced lung injury scores, supporting a synergistic therapeutic effect [46].

TELOCYTES IN KIDNEY AND URINARY TRACT FIBROSIS

In the urinary system, TCs are primarily located in the renal cortical interstitium, particularly in the periglomerular and pericapillary regions, adjacent to Bowman's capsule, as well as within the upper lamina propria of the renal pelvis, ureter, and urinary bladder [7,47].

Loss or structural damage of TCs was reported to be closely associated with the occurrence of ureteral

wall fibrosis. In a study by Wolnicki *et al.* a significant reduction in TC density and a concomitant increase in collagen deposition have been described in the thickened ureteral wall of pediatric patients with hydronephrosis, a prevalent condition affecting fetuses and neonates [48]. Similarly, in patients diagnosed with ureteropelvic junction obstruction, a decreased number of TCs has been correlated with an elevated collagen/muscle content ratio, indicating disrupted tissue architecture and fibrotic remodeling [49]. By combining immunohistochemical and double immunofluorescence staining with TEM techniques, Valente *et al.* also identified a significant increase in α-SMA expressing TCs in diabetic renal samples exhibiting periglomerular fibrosis [47]. Under TEM these TCs also exhibited ultrastructural changes such as dilated rough endoplasmic reticulum and electron-transparent niches containing proteoglycans, features suggestive of a synthetic, ECM-modifying phenotype [47]. On these bases, the authors suggested a potential role of TCs in the pathogenesis of diabetic nephropathy, possibly through their direct involvement in ECM composition regulation and fibrotic progression [47].

As far as their possible therapeutic potential, the in vivo administration of renal TCs in a model of renal ischemia-reperfusion injury mitigated histopathologic damages and improved renal function [50]. These protective effects were attributed to the paracrine activity of TCs, including the secretion of growth factors able to promote proliferation and inhibit apoptosis in renal tubular epithelial cells [50]. Moreover, in a rat model of unilateral ureteral obstruction-induced renal fibrosis, tail vein administration of cultured TCs was shown to upregulate HGF expression, inhibit EMT, suppress the TGFβ1/Smad signaling pathway, and ultimately attenuate the progression of fibrosis [18]. However, in vitro studies using a TGFβ1-induced fibrosis model failed to demonstrate any significant impact of TCs on EMT inhibition or HGF expression, suggesting that multiple in vivo interactions and environmental cues may be essential for TCs to be able to exert their antifibrotic effects [18]. Nonetheless, collectively these results support the notion that TCs may offer a novel therapeutic avenue for the treatment of renal fibrosis [18].

TELOCYTES IN REPRODUCTIVE ORGAN FIBROSIS

TCs have been identified throughout the female reproductive system (i.e., vagina, uterus, fallopian tubes, ovaries, mammary glands and placenta), where many reports pointed out at their potential role in the regulation of local microenvironment, myogenic contractile mechanism, immunomodulation, bioelectrical signaling, and regulation of blood flow [51]. Additional studies also reported that TCs express steroid hormone receptors, suggesting that they might act as hormonal sensors, particularly in the context of reproductive physiology and pregnancy maintenance [51]. For instance, the ciliary beating frequency within the fallopian tube varies indeed in response to cyclical fluctuations of estrogen and progesterone, with low levels estrogen enhancing ciliary activity frequency, and high progesterone levels suppressing it [52].

Gynecological disorders such as premature ovarian failure, acute salpingitis, endometriosis, intrauterine adhesions, uterine leiomyoma, and ectopic pregnancy, are commonly associated with pathologic fibrosis [7]. In a murine model of cyclophosphamide-induced premature ovarian failure, apoptotic degeneration of ovarian parenchymal cells was observed in conjunction with a decrease in TC density in the fibrotic stroma, a phenomenon that was associated with lower estrogen levels and consequent disruption of the ovarian microenvironment and functionality [53]. Moreover, in rat oviduct tissues affected by endometriosis or acute salpingitis, TCs displayed severe ultrastructural abnormalities including organelle loss, nuclear and mitochondrial swelling, cytoplasmic vacuolization, endoplasmic reticulum dilation, and distension of intercellular junctions. These pathologic features led to the collapse of the interstitial TC network and the disruption of TC-stem cell niches, ultimately contributing to oviductal fibrosis and infertility [54,55]. Comparable findings were reported in human fallopian tube specimens from patients with endometriosis and tubal ectopic pregnancy, where damage and loss of TCs were associated with fibrotic remodeling and impaired tubal motility [56]. Further evidence of TC involvement in reproductive pathology comes from placental tissue in preeclamptic pregnancies [57]. Combined immunohistochemical and ultrastructural analyses, indeed, revealed a significant loss and morphologic abnormalities/degeneration of TCs within the fibrotic stroma of placental villi [57]. Similarly, a marked reduction in the c-kit+ TC population, with loss of TC-mediated homeostatic control and subsequent fibrotic development, was found in human samples of uterine leiomyoma, a benign myometrial tumor characterized by ECM overproduction [58]. In contrast to these findings, Karasu *et al.* reported an increased number of TCs in the muscular layer and serosa of tubal tissues from patients with ectopic pregnancy [59]. This was hypothesized to enhance the progesterone-mediated inhibition of tubal motility, potentially impairing the transport of the blastocyst to the uterine cavity [59]. A significantly higher number of TCs predominantly expressing progesterone receptors was similarly

described in oviductal tissue samples from patients with uterine myoma, prompting the authors to propose that TC disturbance may contribute to infertility through both direct and indirect effects on smooth muscle contractility and ciliary motility within the oviduct [52]. Furthermore, recent studies in mammary gland tissue have identified TCs as potential precursors of cancer-associated fibroblasts in invasive lobular breast carcinoma, where they are thought to support tumor progression through ECM remodeling, promotion of tumor growth, invasion, and metastatic spread [60].

In the male reproductive system, TCs are widely distributed throughout the internal genital organs, including the prostate, testes, epididymis, and seminal vesicles [61–64]. In particular, in the testes TCs have been found to form an extensive reticular network within both peritubular and intertubular stromal compartments, where they are believed to contribute to testicular morphogenesis and homeostasis, as well as to the regulation of spermatogenesis and androgen secretion [65]. In tissue sections of seminoma, one of the most frequent malignant testicular cancers in humans, Marini *et al.* reported a significant TC depletion accompanied by a severe disruption of the normal testicular architecture and the presence of interstitial fibrosis [65]. Interestingly, TC disappearance coincided with an expansion of α-SMA+ myoid cells, which may facilitate tumor progression and metastasis [65].

Notably, TCs from organs of the reproductive system have been shown to express and secrete matrix metalloproteinase-9, which may suggest a role of these stromal cells in ECM degradation and remodeling which are profoundly disturbed during tissue fibrogenesis [63,66].

Regarding the emerging therapeutic roles of TCs in the context of genital system disorders, initial evidence indicated that TCs enhance the in vitro proliferation, adhesion, and motility of endometrial stromal cells (ESCs), processes implicated in the pathogenesis of endometriosis [67]. Nevertheless, more recent studies have demonstrated that TCs may also promote in vitro decidualization by inducing mesenchymal-to-epithelial transition (MET) in ESCs via Wnt/β-catenin signaling pathway, which suggests a potential therapeutic application of TCs for reproductive disorders associated with impaired decidualization [68]. Indeed, proper decidualization and MET are fundamental for the cyclic renewal and regeneration of the endometrium, facilitating embryo implantation and regulating trophoblast invasion [68]. Finally, in a murine model of lipopolysaccharide-induced intrauterine adhesions and endometrial fibrosis, treatment with TC-derived exosomes was shown to reduce uterine fibrosis and enhance MET [16▪]. In addition, in vitro administration of either TC-conditioned medium or TC-derived exosomes inhibited TGFβ1-induced profibrotic differentiation of ESCs by providing a source of Wnts, as testified by a significant reduction in the expression of α-SMA, COL1A1, and fibronectin, an effect that was blocked in the presence of Wnt/β-catenin signaling inhibitors [16▪]. Taken together, these experimental findings further support the regenerative potential of TCs in uterine pathology.

TELOCYTES IN CORNEAL FIBROSIS

By using an integrated immunohistochemical and TEM approach, CD34+/PDGFRα+ TCs have been identified throughout the full thickness of the corneal stroma, where they have been described to be aligned parallel to the corneal surface and interspersed among the ECM lamellae [69]. This regular spatial organization was hypothesized to contribute to the proper assembly and maintenance of the highly organized collagenous matrix, which is essential for ensuring corneal transparency and mechanical stability [69]. Notably, in the same study the authors also reported the existence of distinct TC subpopulations based on the co-expression of the stem cell marker c-kit/CD117, distinguishing between c-kit+ and c-kit– TC subpopulations [69]. Moreover, a comparative analysis between healthy corneas and corneas affected by keratoconus, a condition that leads to corneal fibrosis with disease progression, revealed a significant reduction in TC density within the pathologic tissues, particularly of the c-kit+ TC subset that likely represents a pool of progenitor cells with regenerative functions [69]. Of note, most of the remaining TCs in keratoconic corneas exhibited pronounced ultrastructural abnormalities, including organelle loss, cytoplasmic vacuolization, and telopode shrinkage or shortening, indicating not only a quantitative loss of these cells, but also a functional TC impairment during pathologic remodeling of corneal stroma [69].

CONCLUSION

Compelling evidence accumulated over the last decade has highlighted TCs as a distinct and functionally relevant stromal cell population with crucial roles in maintaining tissue architecture, mediating intercellular signaling, and supporting local stem cell niche renewal and regenerative properties [1–8,9▪▪,10,11]. Across a wide range of fibrotic disorders including SSc, IBD, liver and cardiac fibrosis, and fibrotic conditions affecting the reproductive, urinary, respiratory systems and the cornea, progressive loss or structural impairment of the TC network

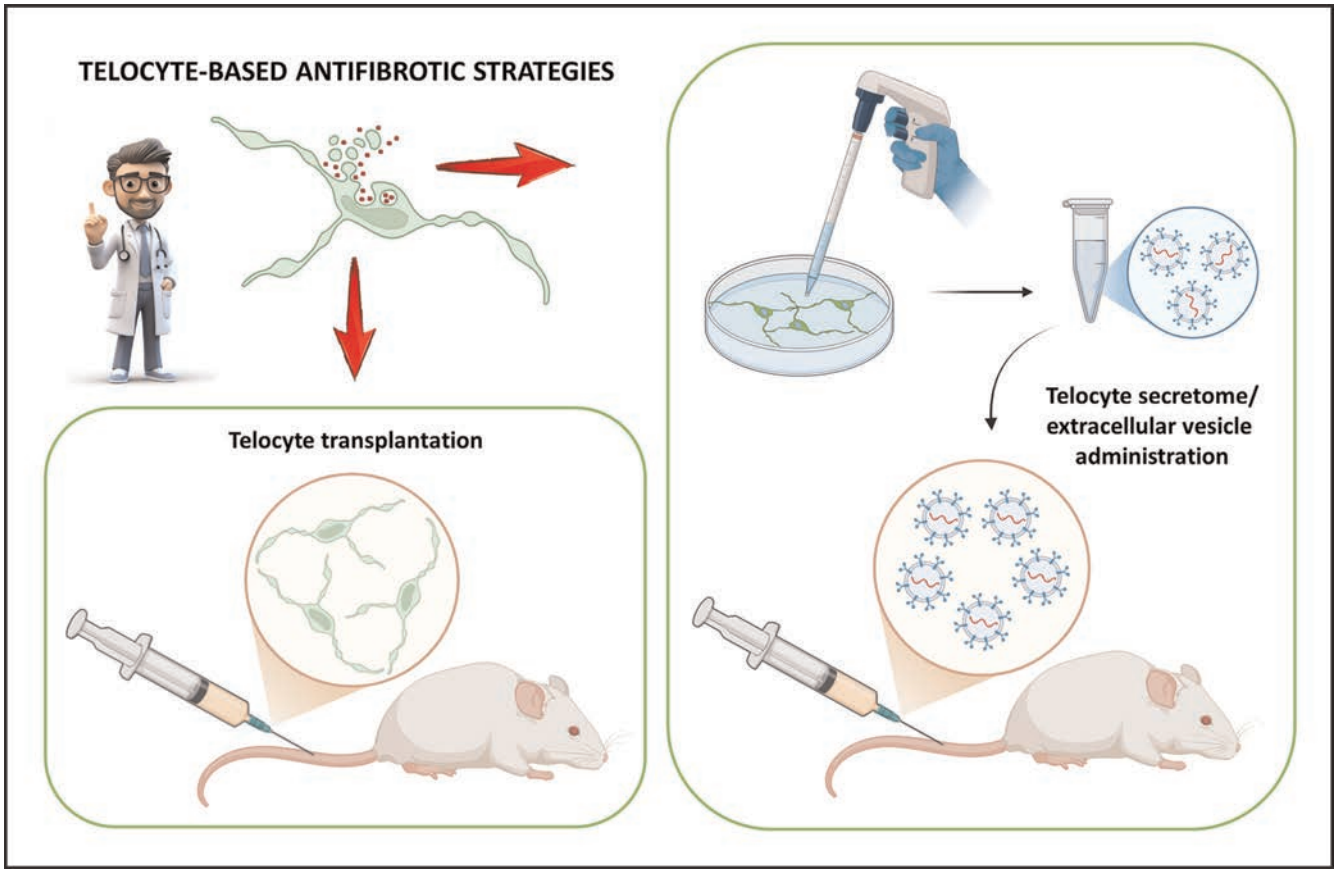

FIGURE 3. Potential telocyte-based antifibrotic strategies. Several preclinical studies demonstrated that telocyte transplantation or administration of telocyte-derived secretome/extracellular vesicles can attenuate tissue fibrosis and restore normal tissue architecture, supporting their potential as novel antifibrotic therapeutic tools.

consistently emerged as a pathologic hallmark [4,6, 7,10–14]. While the causative relationship between TC dysfunction and tissue fibrosis remains to be fully elucidated, current data suggest that TC depletion may represent either a trigger or a consequence of aberrant fibrotic cascades, primarily through the loss of homeostatic regulation over fibroblast activation, and ECM turnover [4,6,7,10–14]. Notably, in vitro and in vivo preclinical models have demonstrated that TC transplantation and/or administration of TC-derived secretome or exosomes can mitigate fibrogenesis, restore tissue architecture, and improve organ function, thereby underscoring their therapeutic potential (Fig. 3) [9▪▪,12,15▪,16▪,17,18,42▪▪]. Future research should aim to clarify the molecular mechanisms underlying TC-mediated antifibrotic effects, define their cell-to-cell and paracrine interactions with fibroblasts, immune cells and stem/progenitor cell niches, and explore novel strategies for their isolation, expansion, and delivery for therapeutic purposes. As tissue fibrosis remains a major unmet clinical challenge, TCs represent a new promising cellular target for the development of innovative antifibrotic therapies.

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Conflicts of interest

There are no conflicts of interest.

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Advances in the diagnosis and treatment of Sjögren disease

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Purpose of review
Sjögren disease (SjD) constitutes a diagnostic and therapeutic challenge due to its clinical heterogeneity and complex pathophysiology. This review synthesizes recent advances in diagnostics, disease stratification, and targeted therapies, highlighting their potential to optimize patient care .

Recent findings
Emerging diagnostic approaches include advanced salivary, lacrimal, and serum biomarkers, refinements of established diagnostic tools, role of specific autoantibodies, and AI-assisted histopathology, improving early detection and risk stratification, particularly for lymphoma-prone phenotypes. Novel immunological insights have enabled phenotype-based classification, guiding the development of targeted therapies against B-cell pathways, cytokines, and co-stimulatory molecules with several agents (e.g., belimumab, ianalumab, telitacicept) showing promise in reducing disease activity scores.

Summary
Recent advances provide a framework for precision medicine in SjD, integrating molecular and imaging biomarkers into patient selection and treatment monitoring. Clinically, this could enable earlier diagnosis, individualized risk assessment, and tailored therapy. Research priorities now include validating diagnostic innovations in diverse populations, elucidating phenotype-specific mechanisms, and conducting adequately powered, biomarker-driven trials to optimize therapeutic efficacy.

Keywords
autoimmunity, biomarkers, precision medicine, Sjögren disease, targeted therapy

INTRODUCTION

Sjogren disease (SjD), as recently renamed to reflect its systemic nature [1▪], is a prevalent autoimmune disease, classically presenting with mucosal dryness, fatigue and joint pain. Other systemic complications, including, among others, synovitis, small airway disease, interstitial lung disease, interstitial nephritis, peripheral neuropathies, cryoglobulinaemic vasculitis or lymphoma can also occur [2]. A female-to-male ratio of 14 : 1 is observed independent of geographical location, while higher disease activity scores and extraglandular involvement were identified in men at diagnosis. Mortality varies depending on the extent of systemic involvement, with cutaneous vasculitis, interstitial lung disease, and lymphoma showing poorer results. The still widely used term, primary Sjogren's syndrome (pSS), refers to Sjogren's syndrome which is not associated with other connective tissue diseases (CTDs) [3].

Regarding disease monitoring, the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) and EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) scoring systems are widely used to assess systemic disease activity and patient-reported symptoms, respectively. However, the newer Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) and candidate Sjögren's Tool for Assessing Response (STAR) are suggested as providing more holistic endpoints [4].

This review outlines current advances in diagnosing and managing the disease, covering clinical evaluation, laboratory testing, imaging, and histopathology,

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KEY POINTS

- Advances in salivary, lacrimal, and serum biomarkers, alongside artificial intelligence assisted histopathology, are enhancing early detection and risk stratification, particularly for lymphoma-prone phenotypes
- Targeted therapies show promise in reducing systemic disease activity, though large trials have yet to confirm consistent clinical benefit
- Most agents act on B-cell pathways, cytokines, or co-stimulatory molecules, but only a few have shown durable improvements in patient-reported outcomes
- Future work should validate diagnostic tools across diverse populations, clarify phenotype-specific mechanisms, and design biomarker-driven, adequately powered clinical trials to optimize therapeutic efficacy

and discussing treatments for glandular and extra-glandular manifestations targeting underlying disease mechanisms.

DIAGNOSTIC APPROACH

History and clinical examination

History-taking should be comprehensive, aiming to assess the extent of symptoms, evaluate disease burden, consider key differential diagnoses, and detect emerging complications. After documenting ocular and oral dryness (sicca symptoms) and systemic manifestations, clinicians should actively exclude alternative diagnoses such as Hashimoto's thyroiditis, sarcoidosis, amyloidosis, hepatitis C virus and HIV infection, IgG4-related disease, as well as head and neck radiation treatment. A thorough medication history including antidepressants, diuretics, checkpoint inhibitors [5,6▪], and combined oral contraceptive pill (COCP), among others, should be obtained [7]. Features associated with lymphoma development such as salivary gland enlargement or purpura should also be inquired [5]. Lastly, the psychological status of patients should be assessed. Apart from psychological stress being a known trigger for the onset of SjD [5], it has been recently demonstrated that patients with SjD had an elevated hazard ratio for attempted suicide after adjusting for demographics and coexisting conditions [8].

Exocrine gland assessment

Regarding assessment of objective ocular and oral dryness, Schirmer's test, determination of ocular surface scores (OSS) and unstimulated whole salivary flow (UWSF) are performed [5]. A recent study suggests that reducing the UWSF test time from 10 to 5 min does not compromise diagnostic accuracy, while recommending stimulated WSF testing in patients with 10-min UWSF rates of 0.1–0.2 ml/min [9]. Of note, a positive Schirmer's test has been shown to be a stronger predictor of a biopsy scoring more than 2 according to Chisholm and Mason, compared to ANA and anti-Ro/SSA positivity [10]. In-vivo confocal microscopy of the eye has demonstrated that specific changes in the corneal nerve, tear film, and at cellular level are significantly more indicative of SjD than of non-SjD conditions [11].

Laboratory investigations

Baseline laboratory investigations in patients suspected of having SjD should include full blood count, liver, kidney, and thyroid function tests, protein electrophoresis, antinuclear antibodies (ANA), anti-Ro/SS-A and anti-La/SS-B, rheumatoid factor, complement and vitamin D levels [5,6▪]. A chest X-ray should also be performed to exclude sarcoidosis. Notably, rheumatoid factor positivity, low complement levels, and monoclonal gammopathy have consistently been associated with an increased risk of lymphoma in Sjögren's disease [5]. Although all rheumatoid factor isotypes (IgA, IgG, and IgM) predict a more severe disease course, specifically IgA rheumatoid factor, was shown to act as an early potential poor prognostic factor for patients with SjD [12]. Additionally, the IgM- rheumatoid factor and IgA-RF profiles of patients with SjD-RA overlap closely with those of RA patients, while differing markedly from those of patients with SjD alone [13]. Other autoantibodies including anti-mitochondrial, anticitrullinated anti 21-hydroxylase and anticalponin-3 antibodies have been detected in sera of SjD patients [5]. Moreover, recent data highlight the rare occurrence as well as the lack of diagnostic and prognostic value of anti-La/SSB in isolation, observed over a period of 7 years [14].

Systemic sclerosis specific autoantibodies are frequently detected in patients with sicca symptoms and, at high titers, have been independently associated with minor salivary gland biopsy (MSGB) positivity [15]. In a recent report, anticentromere autoantibody positivity was linked to a distinct clinical phenotype characterized by greater systemic involvement, lower prevalence of anti-Ro/SSA, anti-La/SSB, and rheumatoid factor, and higher salivary gland ultrasound scores, particularly reflecting fibrotic changes and sialadenitis [16].

Biomarkers in tears, saliva, and serum

Technological advances have allowed the identification of innovative salivary, lacrimal and serological

biomarkers, revolutionizing the early diagnosis of SjD, offering a noninvasive potential alternative to traditional methods.

Recent studies have identified several promising noninvasive biomarkers for SjD. Tear lactoferrin levels, measured via photo-detection devices, were found to be significantly lower in SjD patients compared to controls [17]. Raman hyperspectroscopy, based on inelastic light scattering, combined with machine learning, has effectively distinguished SjD patients from healthy individuals and radiation-induced xerostomia patients by analyzing saliva's biochemical composition [18]. Additionally, a novel model incorporating salivary biomarkers – complement factor B (CFB), clusterin (CLU), calreticulin (CALR), neutrophil elastase – and serum autoantibodies offers a promising approach to differentiate primary SjD from non-SjD cases [19]. Altered mitochondrial RNA expression in saliva and plasma also discriminates SjD patients from healthy controls, with salivary expression correlating positively with disease activity [20].

Several novel autoantibodies, including IgG against CCL4, M5, TMPO, and OAS3, are more prevalent in SjD, with some (e.g., anti-TONSL, anti-IL6) linked to pulmonary involvement. Diagnostic models using these markers achieved up to 46% sensitivity and 95% specificity, effectively distinguishing SjD, particularly anti-Ro/SSA negative individuals-from controls [21]. Similarly, autoantibodies against D-aminoacyl-tRNA deacylase (DTD2) and retroelement silencing factor-1 peptides were shown to be associated with anti-SSA negative status as well as focus score (FS) positivity [22]. Moreover, elevated growth differentiation factor 15 (GDF15), a cytokine of the transforming growth factor-β (TGF-β) superfamily [23], and fibrinogen-like protein-1 (FGL-1), a hepatocyte-derived protein induced during acute inflammation that promotes T cell activation, show promise in improving disease discrimination [24▪▪].

In another study of 395 SjD patients three distinct phenotypes were identified via cluster analysis: B cell active with low symptoms (BALS), high systemic activity (HSA), and low systemic activity with high symptoms (LSAHS) [25▪▪]. The BALS and HSA clusters exhibited higher levels of CXCL13, IL-7, and TNF-RII compared to LSAHS, with a pronounced interferon (IFN) signature most prevalent in BALS. Although all lymphomas within the BALS group occurred in patients with a high IFN signature, this association was not statistically significant; notably, no lymphomas were observed in the LSAHS cluster [26]. Further, deep flow cytometry immunophenotyping of B and T cell compartments identified CD11c+ FcRL5+ tissue-like memory B cells and IFNγ+ TNFα+ conventional T cells as significantly associated with non-Hodgkin lymphoma in these patients [27].

Additionally, liquid chromatography-tandem mass spectrometry identified IFNγ-inducible biomarkers – kynurenines and neopterin – correlated with increased SjD risk, disease activity, glandular dysfunction, autoantibody presence, and immunological and inflammatory markers [28].

Imaging and histopathology

A recent systematic review showed that major salivary gland ultrasonography (SGUS) offers diagnostic accuracy comparable to MSGB for primary SjD, though MSGB remains more sensitive and specific [29]. Higher SGUS grades correlate with increased disease activity and greater prevalence of lymphoma-related risk factors and extraglandular manifestations [30]. However, the OMERACT ultrasound scoring system has yet to fully replace MSGB due to limited agreement [31].

While MSGB is not mandatory for diagnosing SjD, it offers important prognostic information for lymphoma development and systemic involvement. Biopsy is particularly indicated when SGUS is negative and anti-Ro/SSA antibodies are absent. Conversely, in anti-Ro/SSA seropositive patients, SGUS strongly correlates with biopsy findings [32]. An optimal sample size of five minor salivary glands (or four if large) has been proposed for accurate focus score evaluation [33]. Furthermore, assessing additional histopathological features beyond focus score – such as prelymphoepithelial and lymphoepithelial lesions, plasma cell shift, and germinal centers – significantly enhances diagnostic specificity [34]. Fiorentini *et al*. [35] highlighted differences between seropositive and seronegative patients: seropositive biopsies showed more intense periacinous and periductal lymphocytic infiltration with CD3+ and CD138+ cells, whereas seronegative biopsies exhibited milder infiltration with CD20+ and CD68+ cells, but greater fibrosis and fat replacement. Lymphocytic infiltration severity, fibrosis, and fat replacement increased with age, with fibrosis tending to be periglandular in younger patients [35].

Recent advances demonstrate the revolutionary role of artificial intelligence in SjD diagnostics. Artificial intelligence applied to labial gland biopsy whole-slide images has enabled identification of patients at high risk for extraglandular organ involvement [36]. Additionally, an artificial intelligence model accurately classified minor salivary gland biopsies by focus score ($\geq$1 vs. $<$1), achieving 87% sensitivity, 84% specificity, and 85.2% accuracy, effectively reducing underreporting and inter-observer variability [37].

A recent study found lacrimal gland ultrasound (LGUS) to have a sensitivity of 61.5% and specificity of 87.5% for SjD diagnosis, with positive and negative predictive values of 80.0 and 73.3%, outperforming major salivary gland ultrasound [38]. LGUS showed no significant association with Schirmer's test positivity but was strongly associated with anti-Ro/SSA [odds ratio (OR) 17.4] and anti-SSB antibodies (OR 23.0) [38].

Ultrasound elastography of the salivary glands has also emerged as a promising noninvasive diagnostic tool, with pooled sensitivity and specificity of 80% and 87%, respectively [39]. Specifically, lacrimal shear wave elastography demonstrated even higher accuracy, with 88% sensitivity and 94% specificity [40]. Additionally, FDG-PET/CT plays an important role in excluding pSS-associated lymphomas in patients without PET abnormalities, potentially reducing invasive biopsies, while also detecting systemic involvement and guiding biopsy site selection [41].

ADVANCES IN THERAPY

Since the development of biologic therapies, considerable advances have been made in the treatment of systemic autoimmune diseases. However, SjD management remains a challenging task, with numerous clinical trials on novel therapeutic agents, failing to demonstrate clinical benefits. As a result, therapeutic strategies primarily focus on symptomatic relief, with only limited progress recorded in systemic treatments. This is attributed to various factors, including the syndrome's uniquely complex pathogenic mechanisms, as well as its multiple phenotypes [42]. On this note, a study aimed at elucidating the underlying mechanisms of anti-TNF lack of efficacy in SjD patients revealed increased plasma levels of interferon-alpha (IFN-α) and B-cell activating factor (BAFF) in patients receiving etanercept, a recombinant TNF inhibitor [43]. Crucially, both IFN-α and BAFF are essential factors in SjD etiopathogenesis, hence it is

Table 1. Recommendation per disease manifestation

Disease manifestation	2020 EULAR recommendations	2024 BSR guidelines
Oral dryness	Mild: non–pharmacological (acidic lozenges, sugar–free gum) Moderate: secretagogues (pilocarpine, cevimeline); choleretic (anetholtrithione); mucolytic (bromhexine, N–acetylcysteine), electrostimulation Severe: saliva substitutes	Saliva substitutes for symptom relief Dental care – Oral hygiene Consider pilocarpine if systemic dryness
Ocular dryness	Artificial tears/gels Short-term topical NSAIDs or glucocorticoids Topical cyclosporine Serum eye drops Rescue treatment: plugs/oral secretagogues	Lifestyle measures Lubricating eye drops Serum eye drops Eyelid compresses Topical cyclosporin Consider pilocarpine if systemic dryness Short-term treatment with antibiotics in cases of meibomian gland dysfunction or blepharitis Punctal occlusion for selected cases
Pain and fatigue	Analgesics/pain-modifiers Hydroxychloroquine Glucocorticoids at minimal effective doses	Prioritize exercise for fatigue Hydroxychloroquine is first–line for musculoskeletal pain Escalate via methotrexate, sulfasalazine, leflunomide, azathioprine, low–dose steroids
Systemic/ extraglandular disease	Treat per ESSDAI severity First line: Symptomatic treatment, topical or low-dose systemic steroids Second line: conventional DMARDs Rescue: High dose steroids, cyclophosphamide, rituximab depending on the manifestation Specific considerations: plasma exchange and rituximab in cryoglobulinemic vasculitis, intravenous immunoglobulin in certain types of neuropathy and immune cytopenias, granulocyte colony-stimulating growth factor in severe neutropenia, eculizumab in neuromyelitis optica spectrum disorder, inhaled treatments for bronchial involvement, belimumab in refractory glandular enlargement, abatacept as rescue therapy for arthritis	Matches EULAR approach Systematic use of glucocorticoids, conventional DMARDs (methotrexate, azathioprine, mycophenolate) rituximab for severe organ involvement Concider colchicine for vasculitis, panniculitis, and pericarditis

hypothesized that their overexpression could justify anti-TNF agent treatment failure in SjD.

Current therapeutic decisions for SjD are largely based on clinical expertise and supporting data from various studies, as no evidence-driven guidelines have yet been established [44]. This is exemplified by rituximab, for which the literature provides only limited evidence for systemic treatment. However, specific disease manifestations show improvement following rituximab infusion, making it frequently used in refractory or life-threatening cases.

The 2020 EULAR and the 2024 British Society for Rheumatology Recommendations are among the most recent standardized SjD clinical instructions [6▪,45] (Table 1). Since then, emerging agents have enhanced the SjD treatment armamentarium with promising results.

Since SjD pathogenesis is remarkably complex, multiple molecular targets have been identified (Fig. 1). The implicated mechanisms include, among others, suppressing B-cell survival, proliferation and differentiation by attacking pertinent cytokines such as BAFF and APRIL, as well as their receptors, hindering B and T-cell interaction by inhibiting co-stimulatory molecules (CD40 and CD40 ligand, CD80/86), blocking intracellular signal transduction (JAK/STAT and BTK pathways), and reducing circulating pathogenic autoantibodies by preventing their recycling via FcRn. Combining anti-CD20 and anti-BAFF agents results in amplified B-cell depletion, probably due to the capacity of the former to induce B-cell depletion and of the latter to maintain it [6▪]. Several treatments failed to prove efficacy, while for others clinical testing was interrupted due to safety issues [46,47]. Some targeted therapies, however, demonstrated effectiveness in reducing systemic disease activity to preliminary study findings. Among these belimumab (BAFF inhibitor), ianalumab (BAFF receptor inhibitor), iscalimab (CD40 blocker), dazodalibep (CD40-ligand blocker), remibrutinib (BTK inhibitor), telitacicept (BAFF and APRIL blocker), and nipocalimab (FcRn blocker) reached the primary endpoints, yet larger, confirmatory trials are needed for drug efficacy validation [48–54]. Regarding the study outcomes, belimumab alone achieved a statistically significant reduction in the ESSDAI and ESSPRI scores from baseline at week 52 in the placebo-controlled BELISS study [48]. In addition, in

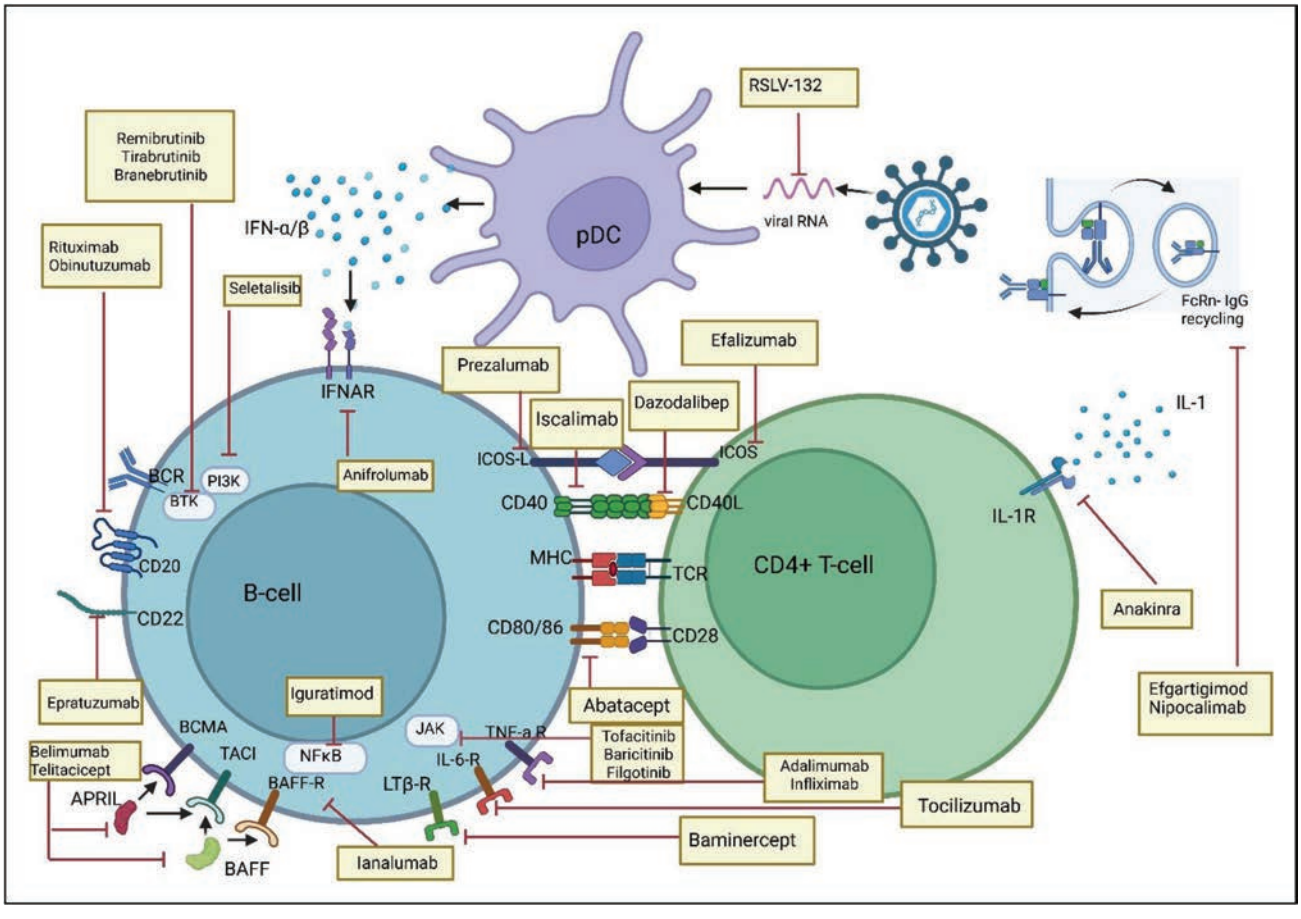

FIGURE 1. Current and prospective therapeutic targets [24▪▪]. Created in https://BioRender.com.

another randomized trial, sequential belimumab and rituximab administration resulted in great B-cell depletion in minor salivary glands and peripheral blood compared to placebo [55]. Ianalumab also achieved a significant dose-related reduction in ESSDAI over a 24-week period, likely due to its dual action of inhibiting B-cell maturation and inducing B-cell depletion [49]. Telitacicept was shown to be effective in reducing both ESSDAI and ESSPRI scores over a 24-week period, in a dose-dependent manner [52]. A randomized trial evaluating the efficacy of dazodalibep demonstrated a significant reduction in ESSDAI at week 24, in patients with moderate-to-severe disease activity, while a significant reduction in ESSPRI was observed in patients with a high symptom burden but limited organ involvement [54]. Intravenous but not subcutaneous administration of iscalimab also succeeded in significantly reducing the ESSDAI compared to placebo after 12 weeks [50]. Nipocalimab achieved the primary endpoint of the DAHLIAS study, which was a significant reduction in the clinically-assessed ESSDAI score at week 24, along with a notable decrease in circulating antibodies, a finding consistent with its mechanism of action [53]. Among BTK inhibitors, remibrutinib is the only one to show statistically significant results, demonstrating a reduction in ESSDAI but not in ESSPRI at week 24 [51]. Lastly, RSLV-132, which acts against viral RNA, that is a key activator of the innate immune response, and epratuzumab, which targets CD22, a B-cell marker, both demonstrated significant improvements in fatigue assessment scores [56,57].

CONCLUSION

Both the diagnostic assessment and therapeutic approach of SjD persist as a challenge. Current diagnostic strategies have improved the rigorous evaluation of SjD, minimizing the need for invasive procedures and aiding in the detection of high-risk disease subtypes. Regarding therapy, despite the emergence of targeted treatments, SjD management has not changed significantly recently, as only a few studies have demonstrated clinical improvement. Nonetheless, late insights into the disease's underlying pathophysiology have facilitated the development and selection of appropriate agents, not only providing symptom relief but also attenuating systemic disease activity.

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Conflicts of interest

There are no conflicts of interest.

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REVIEW

OPEN

Decoding VEXAS syndrome: emerging insights into pathogenesis and clinical management

Martina Fiumara[a,b,*], *Corrado Campochiaro*[b,c,*] *and Raffaella Molteni*[b,d]

Purpose of review
VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome is a newly discovered, adult-onset, hemato-inflammatory disease driven by clonal dominance of pro-inflammatory hematopoietic cells bearing a somatic mutation in the *UBA1* gene. This review aims to integrate and discuss the most recent insights into the evolving understanding of VEXAS pathogenesis and clinical management.

Recent findings
An interplay between inflammation and clonal dominance of UBA1 mutant hematopoietic clones underlies the pathogenesis of VEXAS syndrome. Mutant cells both generate and sustain a toxic inflammatory milieu that impairs wild-type hematopoiesis. Despite exhibiting dysfunctional differentiation, VEXAS cells activate pro-survival pathways that support their persistence and progressive dominance.
Recent international guidelines offer evidence-based recommendations to optimize therapy and manage both inflammatory and hematologic features of the disease.

Summary
This review dissects the key molecular mechanisms driving inflammation and clonal survival in UBA1 mutant cells, and outlines current therapeutic strategies proposed to counteract VEXAS progression and improve patient outcomes. The recent findings presented here, along with the deeper understanding that will be built upon them, not only advance the knowledge of the disease pathobiology, but also pave the way for more precise, mechanism-driven treatment approaches aimed at intercepting disease progression and improving long-term outcomes.

Keywords
Clonal dominance, hematopoiesis, inflammation, ubiquitylation, VEXAS

INTRODUCTION TO VEXAS SYNDROME

Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic (VEXAS) syndrome, first described in 2020, is a paradigmatic, severe acquired hemato-autoinflammatory disease caused by somatic mutations in the X-linked *UBA1* gene of hematopoietic stem and progenitor cells (HSPCs) [1]. The disease predominantly affects males over the age of 50, with an estimated prevalence of 1 in 4000 [2]. Female cases are rare and usually associated with Turner syndrome or altered X-chromosome inactivation [3]. The progression of VEXAS syndrome is driven by clonal dominance of proinflammatory hematopoietic cells harboring pathogenic *UBA1* mutations, ultimately leading to bone marrow (BM) failure. *UBA1* encodes the ubiquitin-activating enzyme 1 (E1), a key component of the ubiquitylation pathway, which is essential for protein degradation and regulation [4]. Clinically, VEXAS syndrome presents with steroid-dependent, myeloid-driven systemic inflammation coupled with hematologic abnormalities. Inflammatory features include recurrent high-grade fevers, unprovoked venous thrombosis, and multi-organ inflammation (e.g., pulmonary infiltrates, ear and nose chondritis, neutrophilic dermatosis, ocular

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KEY POINTS

- VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome is a recently discovered adult-onset hemato-inflammatory disorder driven by somatic *UBA1* mutations in hematopoietic progenitor cells.
- A vicious relationship between inflammation and clonal dominance underlies VEXAS pathogenesis.
- Current therapeutic strategies target inflammatory manifestations and pathogenic clones.
- Further dissection of VEXAS pathomechanisms will instruct novel therapeutic strategies against disease progression, improving prognosis and life expectancy.

inflammation, arthritis, and vasculitis) [5]. Hematologic manifestations commonly comprise macrocytic anemia, thrombocytopenia, monocytopenia, lymphopenia, and cytoplasmic vacuoles in myeloid and erythroid precursors. Approximately 35% of patients develop myelodysplastic syndrome (MDS) [6], while 10–20% progress to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) [7]. Additional clones bearing classical clonal hematopoiesis of indeterminate potential (CHIP) mutations are often detected [8], although overt hematologic malignancies remain relatively uncommon.

At the functional level, E1 is responsible for activating ubiquitin during ubiquitylation, a key post-translational modification that marks proteins for degradation and activity modulation, ultimately regulating multiple cellular processes such as cell survival and differentiation [9–12]. Indeed, protein ubiquitylation may trigger degradation by the ubiquitin-proteasome system (UPS), which governs numerous functions, including cell cycle, metabolism, homeostasis, inflammation, and stress adaptation [12–15]. In humans, two E1 enzymes are expressed, encoded by the *UBA1* and *UBA6* genes, exhibiting distinct substrate specificities and nonredundant functions [16,17]. Notably, *UBA1* is the most highly expressed E1 enzyme and initiates approximately 99% of ubiquitination events [18]. Two UBA1 isoforms have been characterized, nuclear (UBA1a) and cytoplasmic (UBA1b), which differ in their translation start site [4]. The most prevalent (94%) pathogenic *UBA1* mutations in VEXAS syndrome affect the methionine 41 (Met41) in exon 3, the starting codon of UBA1b. Substitution of Met41 with threonine (Thr), valine (Val), or leucine (Leu) results in reduced translation of UBA1b and expression of a shorter dysfunctional isoform, UBA1c, leading to impaired ubiquitylation, defective protein clearance, and accumulation of misfolded proteins [1,2,19]. Distinct *UBA1* mutations may selectively affect both the severity and the nature of pathogenic manifestations. Recent studies have linked specific *UBA1* variants to different dermatologic phenotypes. Indeed, the p.Met41Leu variant is frequently associated with Sweet syndrome–like neutrophilic eruptions, whereas the p.Met41Val variant has been correlated with vasculitic lesions characterized by mixed inflammatory cell infiltrates [20]. Moreover, the p.M41Val variant has been connected to kidney involvement, while the p.M41Thr mutation is associated with vein thrombosis and a reduced platelet count [21]. Overall, disease severity correlates with the extent of UBA1b functional loss: lower residual level of UBA1b drives higher expression of dysfunctional UBA1c and more severe clinical manifestations [19]. Similarly, mutations affecting the intron 2 splicing acceptor site (5% of VEXAS patients) reduce UBA1b translation and increase UBA1c production, resulting in a severe disease phenotype [22–24]. In contrast, noncanonical mutations occurring downstream of the UBA1b translational start site do not promote UBA1c translation but impair the enzymatic activity of both cytoplasmic and nuclear isoforms. These variants are generally associated with milder autoinflammatory phenotypes [25–28].

VEXAS PATHOGENESIS

Although the genetic basis of VEXAS syndrome is well characterized, the pathogenic mechanisms linking somatic *UBA1* mutations, inflammation, and clonal dominance of mutant cells remain elusive. Recent advances, however, have begun to unravel key aspects of VEXAS pathogenesis, providing new insights into how *UBA1* mutations drive the inflammatory state and clonal advantage (Fig. 1).

VEXAS-causing mutations arise in HSPCs, triggering inflammation and promoting progressive clonal dominance of mutant cells. Still, mutant clones are not uniformly distributed across hematopoietic lineages. While HSPCs and myeloid cells are predominantly mutated in individuals with VEXAS syndrome, lymphoid populations are almost exclusively wild-type, suggesting that pathogenic *UBA1* mutations are incompatible with lymphoid cell maturation or survival [1,29▪]. The natural killer (NK) cell compartment stands out as a remarkable exception, displaying a heterogeneous composition, with mutant clones coexisting alongside wild-type counterparts [29▪,30,31▪]. The erythroid compartment similarly emerges as a mosaic of mutant and wild-type cells. Notably, patients with high variant allele frequencies (VAF) of the VEXAS mutation exhibit defective erythroid maturation, suggesting that the *UBA1* mutation impairs terminal erythropoiesis, which potentially

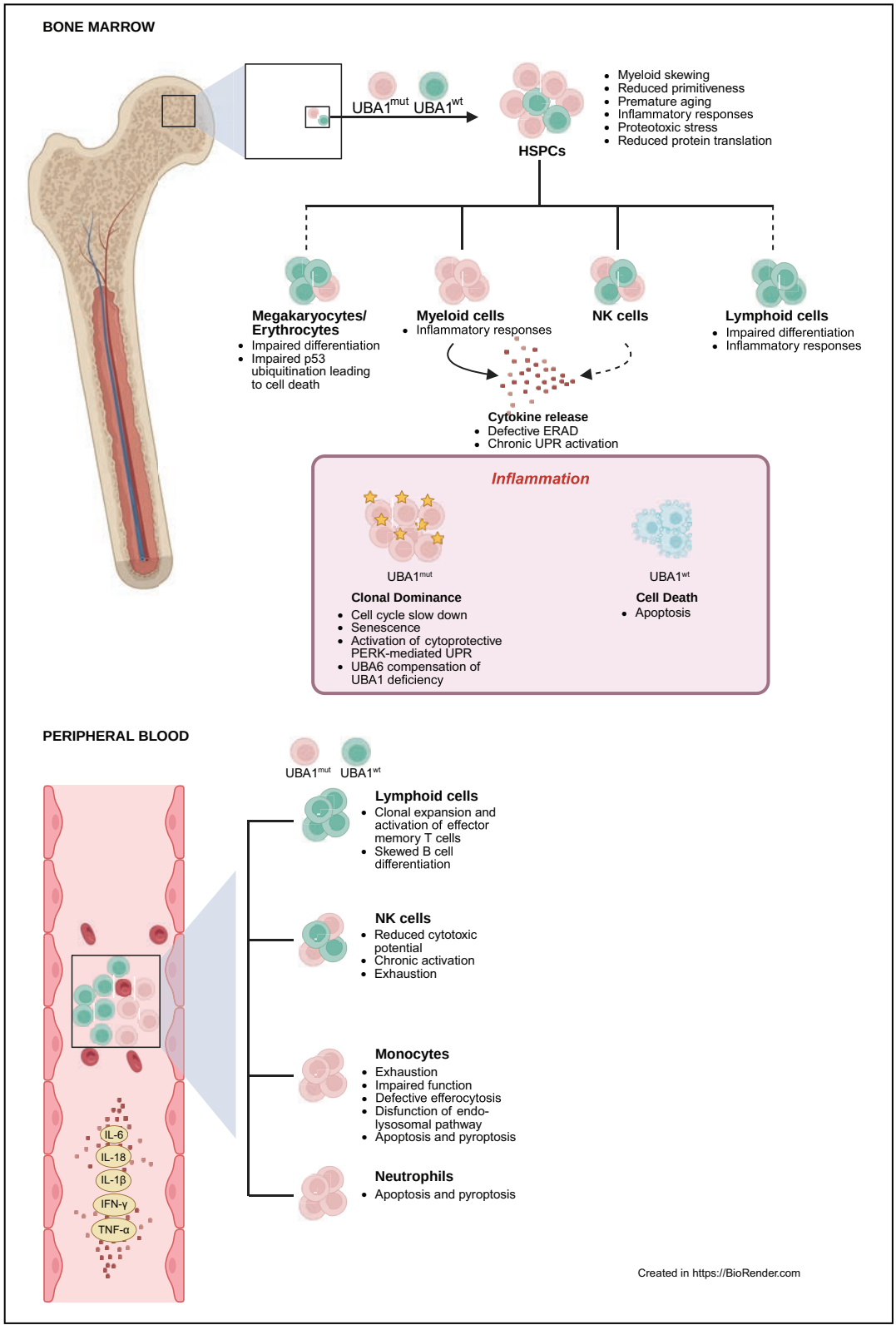

FIGURE 1. Pathogenesis of VEXAS syndrome. The pathogenic mechanisms linking *UBA1* mutations, inflammation, and clonal dominance of mutant cells involve cell intrinsic and extrinsic dynamics perturbing homeostasis within the BM and the peripheral blood niches. In the BM, UBA1 mutant cells, despite impaired differentiation properties, establish and maintain a detrimental inflammatory milieu to which they are intrinsically resistant and that disrupts normal hematopoiesis, thereby promoting their clonal dominance. In the peripheral circulation, increased levels of pro-inflammatory cytokines (IL-6, IL-18, IL1β, IFN-γ, TNF-α)

contributes to the anemia commonly observed in affected patients [32]. Single-cell transcriptomic analyses comparing VEXAS patients to age-matched controls confirm these lineage-specific biases, revealing an early shift toward myeloid differentiation of primary mutant HSCs, reduced primitiveness of mutant HSPC, and skewing towards myelopoiesis, along with early arrest in both lymphoid and erythroid differentiation trajectories [29▪,30,33▪▪]. These profound alterations of hematopoiesis are accompanied by activation of inflammatory programs in both mutant HSPCs and their differentiated progeny. Specifically, HSPCs from individuals with VEXAS syndrome display upregulation of gene categories associated with interferon gamma (IFN-γ), interferon alpha (IFN-α), and tumor necrosis factor-alpha (TNF-α) responses, along with a concurrent downregulation of cell cycle-related pathways. Direct comparison of mutant versus wild-type HSPCs within VEXAS patients shows in mutant clones stronger induction of inflammatory signatures, proteotoxic stress, activation of stress-adaptive strategies, including the unfolded protein response (UPR), and a global reduction of protein translation [30,33▪▪]. These features reflect the loss of UBA1b function and the resulting dysregulation of protein degradation, demonstrating that the mutant allele intrinsically drives inflammation and disrupts cellular protein homeostasis.

Novel insights into the mechanisms underlying inflammation and dominance of mutant clones in VEXAS syndrome have emerged from recent *in vitro* and *in vivo* disease models [29▪,34▪,35]. Genome engineering of wild-type HSPCs through base editing successfully installs the p.Met41Thr mutation in the *UBA1* gene, creating an *in vitro* model that faithfully recapitulates genotypic and phenotypic features observed in mutant HSPCs of VEXAS patients [29▪]. Xenograft mouse models, established by transplanting base-edited human HSPCs carrying the *UBA1* mutation, allow *in vivo* investigation of the hematopoietic abnormalities and clonal dynamics characteristic of VEXAS disease [29▪]. These disease models unveil the mechanisms of clonal dominance in VEXAS syndrome, providing evidence that healthy hematopoiesis is compromised by a detrimental inflammatory milieu, leading to dominance of inflammation-resilient UBA1 mutant clones and BM failure. UBA1 mutant HSPCs do not exhibit increased proliferative capacity compared to wild-type cells but display greater resilience to the inflammatory milieu, attributing their clonal dominance to an inflammation-driven survival advantage rather than a cell-intrinsic proliferative benefit. The absence of proliferative advantage and the somatic origin of the disease may suggest that the UBA1 mutant clone emerged early in life and gradually expanded over time until achieving clonal dominance. A slowdown in the cell cycle, accompanied by the adoption of a senescence-like state, may account for the persistence and pro-survival benefit of mutant HSPCs despite proteotoxic stress and dysfunctional differentiation properties [29▪]. In addition, activation of the PERK-mediated cytoprotective UPR may confer further survival advantage within the inflamed BM niche, thus sustaining clonal dominance [30]. Finally, a recent human cell line model of VEXAS syndrome suggests that partial functional compensation of UBA1 deficiency by UBA6 may also contribute to mutant cell fitness [36]. Collectively, these mechanisms identify potential therapeutic vulnerabilities that could be exploited to selectively target UBA1 mutant clones.

Clonal dominance of UBA1 mutant cells is sustained by an inflammatory milieu that they help to establish and maintain. Recent murine models, including conditional *UBA1* knockout in neutrophils and a patient-derived xenograft, recapitulate the autoinflammatory manifestations characteristic of VEXAS syndrome [34▪,35]. Across hematopoietic differentiation, all mature subsets exhibit activation of IFN-γ, IFN-α, and TNF-α signatures, associated with downregulation of cell cycle-related genes [29▪,31▪]. Notably, these inflammatory responses are not limited to the myeloid lineages, which are predominantly mutated, but also occur in lymphoid populations, almost exclusively wild-type, indicating that the inflammatory signals extend beyond mutant clones and act in trans on the wild-type hematopoiesis [29▪]. The activation of such transcriptional responses is mirrored by the detection of interleukin (IL)-6, IL-18, IFN-γ, IL-1β, and TNF in the plasma of individuals with VEXAS syndrome, reflecting inflammasome activation and myeloid cell dysregulation [31▪,37▪▪]. A key underlying pathogenic mechanism may involve the loss of cytoplasmic

FIGURE 1. Continued.

and dysfunctional immune cells are key hallmarks of the disease phenotype. Hematopoietic cells bearing wild-type UBA1 ($UBA1^{wt}$) and mutant UBA1 ($UBA1^{mut}$) are represented by green and red cells, respectively, with their proportions reflecting the genotypic analyses reported in recent literature. Dashed lines indicate impaired lineage differentiation, whereas dashed arrows signify a putative contribution that remains to be experimentally validated. BM, bone marrow.

ubiquitylation in mutant myeloid cells, which impairs the endoplasmic reticulum–associated degradation (ERAD) pathway and drives chronic UPR activation, leading to inflammation [38]. The combined effect of proteotoxic stress-triggered responses, cytokine release, and lack of negative selection of mutant myeloid cells fosters an inflammatory BM environment that progressively impairs normal hematopoiesis. Accordingly, recent evidence suggests that autoinflammatory symptoms precede hematologic abnormalities [39]. Moreover, at high VAF of mutant clones, monocytes appear functionally impaired, exhibiting exhaustion, defective efferocytosis, and dysfunction of the endo-lysosomal pathway [31▪,37▪▪,40]. I*n vitro* analyses further demonstrate increased apoptosis and pyroptosis in monocytes and neutrophils collected from the blood of VEXAS patients [41]. Granular analysis of the NK compartment reveals that in VEXAS patients NK cells are reduced in terms of absolute number, have a lower cytotoxic potential compared to controls, and display markers of chronic activation and exhaustion [42]. Hence, the reduced number of NK cells correlates with the risk of severe infections. In addition, lymphoid cells, predominantly wild-type, exhibit clonal expansion and activation of effector memory T cells as well as skewed B cell differentiation [31▪]. Finally, anemia, one of the hallmarks of VEXAS, results from massive cell death of erythroid cells during differentiation. Accordingly, patient-derived and gene-edited HSPCs fail to generate erythroid colonies *in vitro* [29▪]. Mechanistically, impaired regulation in p53 ubiquitylation during erythropoiesis has been recently implicated in this massive cell death [43]. Transcriptomic analyses from BM-derived samples further show robust enrichment of heme-metabolism in VEXAS patients compared to controls, suggesting a compensatory response to ineffective erythropoiesis [29▪]. Notably, these abnormalities were more pronounced in patients carrying the p.Met41Val mutation, highlighting a correlation between the genotype and the extent of the phenotype.

VEXAS CLINICAL MANAGEMENT

Therapeutic approaches for VEXAS syndrome are still largely empirical and rely on retrospective studies. Patients' prognosis and quality of life are unfortunately poor, with a five-year mortality rate of approximately 50% [1]. However, the recent publication of international treatment guidelines has marked a significant step toward the first standardization of VEXAS management [44▪▪]. These guidelines provide expert-based recommendations aiming at optimizing therapeutic strategies, improving clinical outcomes, and guiding treatment decisions for both inflammatory and hematologic manifestations of the disease.

First-line treatments for VEXAS syndrome focus on controlling inflammation and typically involve mid- to high-dose corticosteroids (prednisone 10–50 mg/day or higher). However, complete remission is rarely achieved, and the long-term toxicity associated with corticosteroids has prompted the use of corticosteroid-sparing agents, such as anticytokine therapies. Among them, anti-IL-1, anti-IL-6 agents, and anti-TNF show different degrees of efficacy. In detail, a retrospective study from the FRENVEX, with a median follow-up of 12 months, reports an overall response rate at 6 months of 26% for anti-IL-6, while anti-IL-1 and TNF inhibitors show lower efficacy [45]. Similarly, a retrospective study conducted across 126 Spanish hospitals demonstrates improvements with anti-IL-1 and anti-IL-6 treatments, while no benefit is observed with TNF inhibitor therapy [21]. Data from the AIDA Network VEXAS registry, with a median follow-up of 3 months for anti-IL-1 or 4.5 months for anti-IL-6, demonstrated that 23% of patients on IL-1 and 15% of patients on anti-IL-6 achieved complete efficacy, while partial efficacy was seen in 46% and 77%, respectively [46]. The concomitant use of cyclosporine was also found to be effective in our experience when combined with anti-IL-1 agents [47]. In contrast, 55.5% of patients treated with TNF inhibitors failed to respond, indicating that this class is the least effective. A retrospective study from the UK VEXAS cohort shows similar efficacy at 6 months with both anti-IL-1 and anti-IL-6 [48]. Notably high discontinuation rates due to severe injection site reactions were registered for anti-IL-1 treatment, in particular for anakinra. More recently, an Italian–French multicenter study has evaluated the effectiveness and safety of anti-IL-1 agents in VEXAS syndrome and found that canakinumab was superior to anakinra [49].

Janus kinase inhibitors (JAKis) offer a promising approach by targeting multiple disease-relevant cytokines, including type I and type II interferons, as well as IL-6. Several retrospective and prospective studies suggest a superior benefit of the JAKi compared to individual anticytokine inhibitors [46,48]. Notably, the efficacy of JAKis varies depending on the specific type of JAKi used, with Ruxolitinib demonstrating a higher response rate compared to other JAKis [21,45,48,50,51]. Furthermore, a recent report highlights that JAK2 is highly expressed in VEXAS patients' cells, marking it as a key target in the management of inflammatory symptoms [52]. However, JAKi's are associated with side effects such as worsening cytopenia and increased risk of serious infections, often leading to treatment discontinuation [53,54]. Although anticytokine therapies may control autoinflammatory symptoms, they are less effective in addressing the hematologic

manifestations of the disease, which often progress to BM failure [48,55,56]. As such, cytotoxic treatments targeting pathogenic clones, including the hypomethylating agent 5-azacitidine, are required to manage clonal dominance. Multiple studies have demonstrated partial or complete molecular remission of UBA1 mutant clones following repeated cycles of 5-azacitidine, alongside control of both inflammatory and hematological symptoms [45,57–59], with a reduction in steroid usage [60]. Interestingly, despite 5-azacitidine being routinely used to treat MDS patients, its efficacy also extends to patients without concomitant MDS [61]. While one retrospective study reported long-term clinical and molecular remission in a VEXAS patient after decades of 5-azacitidine treatment [62], follow-up after discontinuation in prospective studies remains limited due to the recent discovery of the disease. Some studies have reported genetic and clinical remission lasting up to 84 months following drug discontinuation [63], while others documented a high relapse rate [64], suggesting the need for further monitoring. Notably, 5-azacitidine treatment was also used as a bridge therapy before allogeneic hematopoietic stem cell transplantation (allo-HSCT) [65]. Despite its widespread use, the mechanism of action of 5-azacitidine remains unclear. Moreover, its potential damage to wild-type clones, as the drug predominantly targets VEXAS mutant clones, though not exclusively, is unknown. Furthermore, the need for repeated administration significantly impacts the patient's quality of life.

Another emerging approach in the management of hematological symptoms is the use of erythropoiesis-stimulating agents (ESAs) to treat moderate to severe anemia. A retrospective study involving 32 patients demonstrated the efficacy and safety of ESAs, highlighting the need for further investigation in prospective studies [66].

Currently, the only curative option for VEXAS patients is allo-HSCT, although it is burdened by substantial morbidity and mortality [67]. To date, 33 patients have undergone allo-HSCT, with 27 surviving, and 11 showing full eradication of VEXAS clones [68]. Occasionally, the VEXAS clinical phenotype remains controlled despite the presence of mixed chimerism. A phase II trial sponsored by the U.S. National Cancer Institute is ongoing to assess allogeneic HSCT in VEXAS syndrome and will help define which patients are most appropriate candidates for this approach (https://www.clinicaltrials.gov/study/NCT05027945).

The complexity of the disease necessitates a multidisciplinary approach, including continuous evaluation of treatment efficacy and proactive management of secondary complications.

CONCLUSION

Despite substantial progress has been made in understanding and managing VEXAS syndrome, further investigation is needed to identify key targetable mechanisms that sustain inflammatory circuits and afford pro-survival benefits to UBA1 mutant cells. Uncovering these pathways will be critical to instruct novel therapeutic strategies against VEXAS progression, enabling early intervention and ultimately improving prognosis and life expectancy. Notably, VEXAS syndrome may exemplify an extreme paradigm of acquired disorders in which mutant proinflammatory clones gain the capacity to partially shield themselves from the very hostile microenvironment they induce. Consequently, the mechanisms of clonal dominance underlying VEXAS syndrome may offer broader insights into disease evolution and resistance in clonal hematopoiesis, MDS, and other inflammation-associated hematologic malignancies.

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Conflicts of interest

There are no conflicts of interest.

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What have we learned about systemic sclerosis from the EUSTAR database?

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Purpose of review
This review provides a timely synthesis of key findings derived from the EUSTAR (European Scleroderma Trials and Research) database, the largest international registry dedicated to systemic sclerosis (SSc), now including over 27 000 patients worldwide. As interest grows in real-world data and precision medicine in rare diseases, EUSTAR offers a uniquely rich, longitudinal dataset built over two decades of global collaboration. With sustained growth, more than 1000 new patients enrolled annually, this registry continues to inform clinical practice and research with contemporary, diverse patient data.

Recent findings
Analyses from EUSTAR have clarified disease phenotypes and trajectories, identified predictors of organ involvement and mortality, and validated outcome measures including the EUSTAR Activity Index. Studies have also revealed heterogeneity in treatment patterns, supported the refinement of classification criteria, and highlighted regional disparities in care. The registry has been a foundation for innovative research approaches such as emulated clinical trials, comparative effectiveness analyses, and external control arms for interventional studies.

Summary
EUSTAR has become a reference model for collaborative research in rare diseases. Its findings have directly informed guidelines and routine management of SSc. Future directions include integrating digital tools, artificial intelligence, and expanding the registry's role in clinical trial design and personalized medicine.

Keywords
cohort, EUSTAR database, systemic sclerosis

INTRODUCTION

The EU Scleroderma Trials and Research (EUSTAR) database is the world's largest and most comprehensive international registry dedicated to systemic sclerosis (SSc). Initially launched as a European initiative, EUSTAR has evolved over the past two decades into a truly global consortium, with a database now including data from more than 27 000 patients across over 150 centres worldwide. This unique resource captures detailed longitudinal clinical, serological, and treatment data, enabling real-world insights into disease trajectories, prognostic factors, and therapeutic effectiveness.

EUSTAR's strength lies not only in its size, but in the consistent engagement of the international SSc community, with over 1000 new patients entered each year and continuous efforts to update and harmonize data collection. As a result, the EUSTAR cohort has become a cornerstone of SSc research, shaping both clinical understanding and trial design. In this review, we summarize the major contributions from the EUSTAR registry, highlighting findings that have influenced routine clinical practice,

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KEY POINTS

- The European Scleroderma Trials and Research (EUSTAR) registry now includes over 27 000 patients with systemic sclerosis worldwide, making it the largest international database for the disease.
- EUSTAR data confirmed that the extent of skin involvement and baseline DLCO are key predictors of progression in interstitial lung disease.
- Observational studies from EUSTAR have shown real-world effectiveness of tocilizumab in early diffuse cutaneous systemic sclerosis with elevated CRP.
- The registry provides a robust foundation for real-world comparative effectiveness studies and emulated clinical trials in systemic sclerosis.
- EUSTAR continues to serve as a model for collaborative data generation and personalized research in systemic sclerosis across continents.

often without clinicians realizing their origin from EUSTAR studies.

Interstitial lung disease

Interstitial lung disease (ILD) is the leading cause of death in SSc and a core focus of the EUSTAR research agenda. Leveraging longitudinal data from over 800 patients, EUSTAR investigators have shown that ILD progression is highly heterogeneous. In a landmark study, only one in four patients met progression criteria within a 12-month window, and just 8% followed a relentlessly progressive course over time, while the majority displayed intermittent decline or long periods of stability [1]. This variable trajectory has critical implications for monitoring and treatment timing. In parallel, data from over 1000 patients revealed that progressive skin fibrosis within 1 year was independently associated with subsequent FVC decline and increased mortality, reinforcing the link between fibrotic progression in skin and lung compartments [2]. These analyses were also confirmed more recently by Sobansky *et al.*, who showed that changes in lung function and skin fibrosis within 12 months are strong predictors of mortality [3▪]. Systemic inflammation was also identified as a key modifier: patients with persistently elevated CRP ($\geq$5 mg/l in $\geq$80% of visits) experienced faster FVC decline and over sixfold higher 5-year mortality, an effect mitigated by immunosuppressive treatment [4].

In addition, real-life cohorts from EUSTAR have highlighted the role of gastrointestinal manifestations. GERD, affecting over 80% of SSc-ILD patients, was associated with lower baseline lung function and higher risk of progression, particularly among women [5▪]. Conversely, male sex was independently associated with larger FVC decline and worse survival, suggesting sex-specific trajectories in SSc-ILD [6].

EUSTAR database has also been instrumental for evaluating in real-life the effectiveness of treatments for SSc-ILD patients. In a recent study by Yan *et al.*, the authors performed a posthoc comparison of tocilizumab, rituximab, mycophenolate mofetil and cyclophosphamide in SSc-ILD patients and found similar outcomes at a median follow-up time of 11 months [7▪▪]. Moreover, in an analysis of over 3700 patients with SSc-ILD, it was shown that while immunosuppressive treatments are widely used, no clear benefit of specific immunosuppressants could be confirmed due to confounding by indication, and glucocorticoids were associated with worse outcomes in patients with severely reduced FVC. The findings support personalized treatment strategies, favouring close monitoring in early disease and more aggressive therapy in moderate impairment, but caution against the liberal use of glucocorticoids [8]. Lastly, EUSTAR has enabled critical evaluation of enrichment strategies used in major SSc-ILD trials. Applying the inclusion criteria from focuSSced, SLS II, and SENSCIS to over 2200 real-life patients revealed major discrepancies in patient selection: only 1.6% met focuSSced criteria, 5.8% SLS II, and 31.2% SENSCIS, while most (67.7%) met none. Patients eligible for focuSSced showed greater lung function decline, but enrichment did not consistently predict progression. Moreover, restrictive criteria reduced recruitment feasibility. These findings show how EUSTAR can inform trial design, exposing gaps between eligibility criteria and real-world populations, and supporting more pragmatic approaches for future studies [9].

Vascular manifestations and PAH

The EUSTAR database has been crucial in characterizing the vascular burden in SSc, notably through its comprehensive analyses of digital ulcers (DUs) and their complications. A multicentre EUSTAR survey identified key clinical items for DU assessment and supported a novel categorization into episodic, recurrent, and chronic ulcers, which was considered more practical and informative than the traditional classification, potentially facilitating standardized evaluation in both practice and trials [10]. In a separate large-scale analysis, 9% of unselected SSc patients had experienced digital gangrene, with prior DUs and diffuse cutaneous disease identified as independent risk factors; interestingly, traditional cardiovascular risk factors were not associated with gangrene,

underscoring the disease-specific nature of SSc vasculopathy [11]. In a recent cross-sectional study of over 8000 SSc patients significant shifts in vascular treatment patterns from 2012 to 2022 were noted, with increased use of endothelin receptor antagonists, PDE5 inhibitors, calcium channel blockers, and antiplatelet agents, and a marked decline in iloprost use. These trends reflect a move toward more proactive and preventive vascular management in SSc and are highly informative for the design of future trials in SSc vasculopathy [12▪▪].

EUSTAR data have also contributed to redefining pulmonary arterial hypertension (PAH) risk stratification: a study applying the ESC/ERS risk score revealed that this classification has prognostic relevance in SSc-PAH and can guide therapeutic escalation strategies [13▪▪]. In addition, This EUSTAR study evaluated screening tools for identifying SSc patients with borderline pulmonary hypertension (mPAP 21–24 mmHg). Among available parameters, DLCO <80% predicted showed the highest sensitivity and negative predictive value, while TAPSE/sPAP <0.55 mm/mmHg had the highest specificity, positive predictive value, and accuracy [14▪].

Skin fibrosis and disease activity

Skin involvement remains a hallmark of SSc, with EUSTAR data providing pivotal insights into its progression and variability. While diffuse cutaneous SSc (dcSSc) has traditionally received most attention due to its higher early mortality and organ involvement, EUSTAR analyses have also highlighted the clinical burden of limited cutaneous SSc (lcSSc). In a EUSTAR study comparing over 12 000 patients found that skin involvement remains stable over time in most limited cutaneous SSc (LcSSc) patients, while lung function decline (FVC) and digital ulcers occur at similar rates in both LcSSc and diffuse SSc (DcSSc). These findings support including LcSSc patients in SSc-ILD trials and highlight the need for equal attention to digital ulcers in both subsets [15]. Importantly, EUSTAR data demonstrated that nearly 20% of patients can develop late skin fibrosis, defined as new worsening or failure to improve more than five years after disease onset, especially those with lower baseline mRSS and lcSSc phenotype, challenging the assumption that skin fibrosis is limited to early dcSSc [16].

Predictive models developed using EUSTAR data have better characterized how skin fibrosis in SSc follows distinct trajectories, with most progression occurring early in the disease course and often stabilizing or regressing thereafter. EUSTAR analyses [Skin 3, 4, and 5] have indeed clearly shown that in dcSSc patients, skin fibrosis typically peaks within the first year after the onset of Raynaud's phenomenon, with rapid progression particularly in patients with anti-RNA polymerase III or antitopoisomerase I antibodies. Predictors of future improvement include a high baseline modified Rodnan skin score (mRSS) and absence of tendon friction rubs, whereas progression is more likely in patients with short disease duration, joint synovitis, and lower baseline mRSS. These findings highlight the dynamic nature of skin involvement in SSc and underscore the importance of early stratification and timing in trial design, allowing for targeted recruitment of patients most likely to benefit from antifibrotic interventions [17–19].

EUSTAR data have also been used to validate tools to measure disease activity. Valentini *et al.* revised and validated the EUSTAR Activity Index as a weighted composite score that integrates clinical, laboratory, and functional parameters to identify patients with active disease (score $\geq$2.5), addressing limitations of previous indices and enabling more accurate tracking of disease fluctuations over time [20]. Fasano *et al.,* later demonstrated that this revised index had superior predictive power for short-term disease progression, particularly in skin, vascular, pulmonary, and cardiac domains [21].

Gastrointestinal and cardiac manifestations

EUSTAR data have helped define the clinical and prognostic burden of cardiac and gastrointestinal involvement in SSc, two domains often under-recognized in daily practice. In a recent EUSTAR analysis, Györfi *et al.* showed that the presence of primary heart involvement – defined as conduction abnormalities, arrhythmias, or cardiomyopathy in the absence of pulmonary arterial hypertension or other causes – was independently associated with poor survival [hazard ratio (HR) 2.34, 95% confidence interval (CI) 1.55–3.52] and often preceded other major organ damage [22▪]. The study emphasized the need for systematic screening, as a relevant proportion of cases were subclinical at presentation.

In the gastrointestinal domain, the EUSTAR registry supported a prospective 3-year follow-up study on Barrett's oesophagus (BE) in SSc. Among 50 patients with histologically confirmed BE, the risk of progression to high-grade dysplasia or adenocarcinoma was ~3% per year, with a marked increase in the subgroup with dysplasia at baseline (4% per year). Notably, 18% of BE patients were asymptomatic, underscoring the need for endoscopic surveillance even in the absence of reflux symptoms [23].

In the GI domain, data from the EUSTAR cohort confirmed that involvement of the gastrointestinal tract is nearly universal in SSc and is a major driver of

morbidity. While symptoms are highly prevalent, they do not reliably identify patients at risk for clinically significant nutritional decline. In an analysis of over 3600 patients, 438 were found to have lost $\geq$4.5 kg or $\geq$5% of body weight over a 5–12 month period. Significant weight loss was associated with shorter disease duration, elevated ESR and CK, pulmonary hypertension, diastolic dysfunction, and ILD, but not with GI symptoms themselves. These findings highlight the complexity of nutritional impairment in SSc and the limitations of symptom-based screening, calling for prospective studies to develop reliable clinical or biomarker-based prediction tools for early identification of at-risk patients [24].

Therapeutic strategy and real-life effectiveness

The EUSTAR registry has served as a powerful tool for evaluating the real-life use of immunosuppressants and biologics in SSc. A recent propensity score–matched study compared 93 patients receiving tocilizumab with over 3000 treated with standard care, showing no statistically significant difference in mRSS or FVC change at 12 months, yet consistently favouring tocilizumab across all predefined endpoints. These results generate hypotheses of effectiveness in a broader SSc population, beyond the highly selected trial cohorts [25]. Rituximab, analysed in 254 patients from the registry, demonstrated a favourable safety profile and a significant association with skin fibrosis improvement, though no benefit was seen on FVC or DLCO. Concomitant mycophenolate use appeared to enhance lung function stability [26]. Abatacept, primarily used in patients with joint involvement, was associated with improvement in joint symptoms, HAQ-DI, and morning stiffness. A modest benefit on skin score was also noted, while lung and GI manifestations remained unaffected [27]. In patients with refractory polyarthritis or myopathy, both tocilizumab and abatacept appeared safe and effective for joint disease, although no trends for improvement in fibrotic domains emerged, potentially due to short exposure or selection bias [28]. Collectively, these real-world data highlight the heterogeneity of drug response in SSc and emphasize the importance of tailoring therapy to individual manifestations. Importantly, findings from the EUSTAR cohort underscore the gap between trial and real-life populations: a significant proportion of patients initiating advanced therapies would not have qualified for recent pivotal RCTs, pointing to the role of registries in guiding inclusive therapeutic strategies [29]. The products described here are not labelled for the use under discussion.

Autoantibodies

In SSc, autoantibody profiling offers a robust stratification framework that can complement or even outperform traditional cutaneous subtypes in predicting disease course and organ involvement. A landmark EUSTAR study showed that an autoantibody-only stratification model outperformed cutaneous-only subsetting for predicting overall and progression-free survival, digital ulcers, and organ-specific outcomes such as renal crisis and restrictive lung disease [30]. The clinical heterogeneity associated with autoantibody specificities is exemplified by antitopoisomerase I antibodies (ATA), which occur more frequently in men and are associated with worse outcomes, including interstitial lung disease (ILD), diffuse cutaneous disease, and increased mortality. Notably, ATA-positive men had the highest 10-year mortality in two large European cohorts, highlighting a sex-specific risk profile [31]. Further granularity is offered by a study on ATA-positive patients with limited cutaneous SSc (lcSSc), who displayed high ILD risk comparable to ATA-diffuse cutaneous SSc (dcSSc), though with less severe pulmonary restriction. While ILD progression occurred in up to 58% of ATA-lcSSc patients, the overall mortality was lower than in ATA-dcSSc, emphasizing the need for ILD screening even in lcSSc subsets [32].

Other rarer antibodies also define distinct clinical subsets. Anti-PM/Scl-positive patients demonstrated a phenotype marked by muscle involvement, calcinosis, and cutaneous dermatomyositis-like changes, but had a relatively favourable ILD outcome. Neither scleroderma renal crisis (SRC) nor malignancies were significantly associated with this subgroup, and the presence of additional SSc-specific antibodies further enriched for typical SSc features [33]. Anti-Ku antibodies, though infrequent (2.2%), were linked to musculoskeletal manifestations such as myositis and arthritis, with a notable absence of vasculopathic features like digital ulcers, suggesting a myositis-prone clinical variant of SSc [34]. Similarly, anti-U1RNP antibodies were found in 5.4% of patients with SSc-ILD and associated with worse baseline lung function, higher joint and muscle involvement, and a predominance of lcSSc. Yet, longitudinal lung function decline and mortality were comparable to those without U1RNP, indicating no difference in disease trajectory despite worse starting lung function [35].

Lastly, NOR90 antibodies – present in approximately 3% of patients – were associated with milder skin disease (lower mRSS) and fewer gastrointestinal symptoms. This novel association further expands the serological landscape of SSc, suggesting that NOR90 defines a subset with a less severe phenotype [36]. Collectively, these findings reinforce the pivotal role of antibody profiling in refining clinical phenotypes and guiding risk assessment in SSc.

Methodology innovation and prognosis

The EUSTAR initiative has provided a pivotal platform for methodological innovation and prognostic research in SSc, allowing for advanced statistical modelling, deep phenotyping, and survival analysis in a uniquely large dataset of well characterized patients. One of the most significant recent contributions has been the shift away from traditional dichotomous classification into limited *vs.* diffuse cutaneous subsets, in favour of a more granular understanding based on cluster analyses. A data-driven approach using 24 clinical and serological variables from 6927 patients allowed the identification of six homogeneous clusters with distinct prognostic trajectories. While some mirrored classical cutaneous subsets, others revealed unique phenotypes, for example, lcSSc patients with antitopoisomerase I positivity and high rates of visceral damage, highlighting the limitations of relying solely on skin involvement for stratification and the prognostic weight of organ damage and autoantibody profiles [37].

In parallel, refinement of mortality risk prediction has been achieved through both multivariable modelling and validation of historical prognostic indices. A prospective study including 11 193 patients from EUSTAR identified cardiac and pulmonary complications as the leading causes of death, with a derived risk score showing excellent accuracy (AUC 0.82) for predicting 3-year mortality. Patients in the highest quartile of the risk score had a three-year survival of just 53% compared to 98% in the lowest quartile [38]. These findings were complemented by the successful external validation of an earlier five-item model – including age, gender, urine protein, ESR, and DLCO – demonstrating fair discrimination (AUC 0.78) for 5-year mortality in a European cohort of over 1000 patients [39].

Further methodological advancement is exemplified by a study aimed at identifying predictors of short-term disease progression in diffuse SSc. By employing multivariate imputation and LASSO regression, eight predictors, including age, active digital ulcers, lung fibrosis, muscle weakness, and elevated CRP, were shown to independently predict a composite endpoint of organ progression or death within 12 months. This model was validated through bootstrap resampling and offers an opportunity for cohort enrichment in clinical trials [40].

In terms of innovation in serological stratification, a comprehensive EUSTAR-led study on anti-RNA polymerase III antibodies (anti-RNAP3) revealed a significant association with cancer diagnosed around the time of SSc onset. A multicentre case-control analysis further confirmed that patients with anti-RNAP3 positivity were at markedly higher risk of synchronous malignancies (OR 7.38), especially older individuals and those with diffuse cutaneous disease. A Delphi consensus exercise involving 82 experts subsequently established the need for systematic cancer screening at SSc diagnosis and during early follow-up in this subset [41].

Collectively, these studies demonstrate how EUSTAR data have reshaped prognostic paradigms in SSc through methodological rigor, improved phenotypic resolution, and serological risk profiling. These insights support more personalized monitoring strategies and may enhance the design of future interventional trials.

Perspectives for EUSTAR

Strategic and global lessons

Harmonization of clinical practice through EUSTAR outputs: EUSTAR has played a key role in standardizing clinical evaluation in SSc through the development and validation of consensus definitions, disease activity indices, and outcome measures. Tools such as the EUSTAR Activity Index and updated definitions of organ involvement have promoted harmonized data capture and improved comparability across studies, while shaping guideline development and clinical decision-making.

Multinational collaboration lessons

The EUSTAR network has shown that large-scale, multinational collaboration in rare diseases is not only feasible but essential. Harmonized protocols, strong central coordination, and community-driven engagement have made it possible to achieve robust, high-quality data across highly diverse healthcare systems. EUSTAR's structure offers a successful model for global registries in other rare and complex diseases.

Use of EUSTAR as a platform for future intervention studies: Beyond observational insights, the EUSTAR registry offers a powerful platform for embedded trial methodologies and pragmatic study designs. Recent efforts have focused on emulating randomized trials using real-world data, developing robust external control arms, and identifying enriched subgroups for targeted interventions. EUSTAR's size and phenotypic diversity make it uniquely suited for adaptive designs and personalized medicine approaches.

CONCLUSION

Over the past two decades, the EUSTAR registry has generated key insights into SSc pathophysiology, prognosis, and therapeutic management. From redefining organ involvement trajectories to validating

biomarkers and stratification strategies, EUSTAR has profoundly shaped the way we understand and treat SSc.

Importantly, the registry has provided a roadmap for integrating real-world data into clinical trial design and has accelerated the transition toward personalized medicine. With the growing availability of digital health tools, artificial intelligence, and trial emulation techniques, the future of EUSTAR promises even deeper integration of patient-centred data and precision therapeutics. Continued support and innovation within this global collaboration will be essential to meet the evolving needs of the SSc community.

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Conflicts of interest

All authors are or have been members of the EUSTAR Executive Board. None of the authors declare any specific conflict of interest for this review.

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CAR T-cell therapy in systemic sclerosis: the next frontier in immune modulation

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Purpose of review
Cellular therapies such as CD19-targeting CAR T cells are a rapidly evolving field in an area of unmet clinical needs: autoimmune diseases including systemic sclerosis (SSc). The aim of this review is to summarize the available data on safety and efficacy of CAR T-cell therapy in SSc and to discuss upcoming developments and challenges for the near future.

Recent findings
Several case reports and series recently described the treatment of SSc patients with CD19-targeting CAR T cells, which resulted in profound B-cell depletion and downregulation of autoimmunity. Encouraging results on efficacy in several disease manifestations were reported including skin and organ fibrosis. Also, vascular phenomena including digital ulcerations improved. The safety profile showed mostly mild-to-moderate cytokine release syndrome (CRS) and low rates of neurotoxicity. Infectious complications ranged from mild upper airway infections to pneumonia. However, a case of herpes simplex reactivation with secondary lethal haemophagocytosis was also described.

Summary
Current evidence suggests very promising effects of CD19-CAR T-cell therapy on several SSc manifestations. Additional larger trials are needed. Current frontiers are patient selection, refining lymphodepletion protocols, and expanding target antigens beyond CD19.

Keywords
B-cell depletion, CD19-targeting CAR T-cell therapy, systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune disease (AID) that is based on vascular abnormalities, immune dysregulation and progressive fibrosis of the skin and inner organs [1–4]. Prognosis of SSc depends on the extent and severity of organ involvement [5]. Despite improvement in survival over recent decades due to improved screening techniques and the approval of first antifibrotic and immunomodulatory drugs, SSc remains the systemic rheumatic disease with the highest morbidity and mortality [6].

Autoantibody production occurs early in the course of SSc, often alongside or even before the onset of Raynaud's phenomenon, and typically precedes the development of progressive tissue fibrosis [1,6]. Herein, specific autoantibodies are associated with a disease phenotype and higher risk of defined organ involvements, for instance anti-Topoisomerase I and anti-RNAP III antibodies being associated with a higher risk of progressive skin and lung involvement and scleroderma renal crisis. Consistently, B-cell homeostasis is disrupted [7]. B-cells infiltrate the affected organs and exhibit an activated phenotype marked by the overexpression of CD19 [8–10]. Regulatory B cells are reduced and functionally impaired, with decreased IL-10 production correlating inversely with disease activity and autoantibody levels [11,12]. Within this framework, serum levels of B-cell trophic factors, including B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), are significantly elevated in SSc patients compared to healthy

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KEY POINTS

- CD19-targeting CAR T-cell therapy emerges as a promising investigational treatment, offering deep and sustained B-cell depletion that can potentially reset autoimmunity in SSc.
- Early clinical studies and case reports in patients with dcSSc show encouraging efficacy including improvement of skin, lung and cardiac involvement, reduction of organ fibrosis and decrease of autoantibody titres.
- CD19-targeting CAR T-cell therapy shows a favourable safety profile in most SSc patients, though mild immune-related toxicities such as CRS and LICATS and one case of HLH have been observed.
- Challenges remain to be encountered concerning optimal patient selection, lymphodepletion strategies and long-term outcomes. Ongoing research, including controlled trials are needed to further validate the application of CAR T-cell products and to strive for regulatory approval.

controls and correlate positively with the modified Rodnan skin score (mRSS) and interstitial lung disease (ILD) [13–15].

Accumulating evidence suggests that B cells are directly implicated in fibrotic tissue remodelling in SSc: B-cell depletion using CD20 monoclonal antibodies has shown to reduce skin fibrosis in both tight-skin [16] and bleomycin-induced mouse models of SSc [17]. Mechanistically, activated B cells promote fibrosis through multiple pathways [18], including the production of autoantibodies targeting fibroblast-associated antigens such as PDGF receptors [19–23]. Moreover, B-cell-derived cytokines such as IL-6 and TGF-β as well as direct interactions between B cells and fibroblasts appear to contribute to the profibrotic milieu characteristic of SSc [24,25].

In addition to their effects on fibroblasts, dysregulated B-cell activity can exacerbate vasculopathy and contribute to endothelial cell injury [26]. Anti-endothelial cell and antiangiotensin antibodies have been implicated in promoting endothelial activation and vascular pathology in SSc [26].

In this context, B cells represent a promising therapeutic target, offering potential for both immune modulation and potentially the consecutive attenuation of the fibrotic process [18]. This rationale is reinforced by clinical trials investigating B-cell depletion with rituximab (RTX) in SSc, which demonstrated clinical benefit in both cutaneous fibrosis and ILD [27–30]: the DESIRES study, a double-blind, randomized, placebo-controlled trial, demonstrated a significant improvement in the mRSS with RTX treatment compared to placebo [27,28]. In the RECITAL trial, a multicentre, randomized basket study that allowed inclusion of patients with ILD related to different connective tissue diseases including SSc, RTX was compared with cyclophosphamide (CYC) [30]. While the study did not meet its primary endpoint of demonstrating superiority of RTX over CYC in preserving FVC, both therapies showed comparable efficacy, with RTX exhibiting a more favourable safety and tolerability profile [30]. Consequently, RTX was recently included in the treatment recommendations of the SSc societies including the European Scleroderma Trials and Research Group Recommendations (EUSTAR) [31] and the ACR/Chest Guidelines [32].

Many patients continue to experience disease progression despite treatment with B-cell targeting monoclonal antibodies, highlighting the challenges in achieving full disease control with currently available therapies. The variable clinical efficacy of RTX may reflect insufficient depletion of pathogenic autoreactive B cells, residing in inflamed tissues or secondary lymphoid organs. The breadth of depletion across various B-cell maturation subsets may also be clinically relevant, as B-cell precursors, which are expanded in SSc, and plasmablasts/plasma cells, key contributors to autoantibody production, are not fully eliminated by CD20-targeting therapies. Notably, autologous stem-cell transplantation overcomes these limitations and is regarded as a disease-modifying option for refractory SSc, albeit with substantial treatment-related risk [33,34]. Recently, the adoptive transfer of chimeric antigen receptor (CAR)–modified T cells, genetically engineered to recognize CD19, demonstrated deep and broad B-cell depletion, positioning it as a promising, tolerable therapeutic modality for SSc [35,36–38,39,40,41,42▪] (Table 1).

MANUFACTURING OF CD19-TARGETING CAR T CELLS

Recently, CAR T cells have shown promising results in AIDs by targeting and eliminating autoreactive immune cells, potentially restoring immune tolerance and achieving long-term remission [36,43–51▪]. The cells are engineered to recognize a specific surface antigen such as CD19-CAR T cells are generated by introducing a synthetic transmembrane receptor into T cells using genetic engineering techniques, typically via retroviral or lentiviral vectors. Other alternative transduction methods such as lipid nanoparticles (LNPs) carrying mRNA coding the CAR or in-vivo CAR approaches are under development [52,53–55▪]. The CAR consists of the antigen recognition domain derived from a single-chain variable fragment of an immunoglobulin, a transmembrane

Table 1. Overview of published case reports and series of systemic sclerosis patients treated with CD19-targeting CAR T-cell therapy

Publication	CAR T product	Lymphodepletion	CAR T-cell dosage	Patient characteristics				Detectability of CAR T cells	Side effects
				Number	Sex	Organ involvement	Antibody profile		
Bergmann *et al.* [35], Müller *et al.*[36▪], Auth *et al.* [37▪]	Autologous, second generation	Fludarabine (25 mg/m^2 intravenously on days −5, −4, and −3) and cyclophosphamide (1 g/m^2 intravenously on day −3)	1 × 10^6 CAR T cells per kg bodyweight	6	4 Male, 2 female	6 Lung, 3 heart, 1 renal	5 Scl70, 1 RNA Pol III	Median 40 days (IQR 30–61) in patients after previous B-cell depletion therapy vs. 58 days (IQR 26–79) in patients without previous B-cell depletion	3 CRS grade 1, 1 CRS grade 2
Merkt *et al.* [38▪,39,40]	Autologous, 3rd generation	500 mg/m^2 cyclophosphamide + 30 mg/m^2 fludarabine on days −4 to −3, −2	400 × 10^6 (5 × 10^6/kg of body weight) CAR T cells	1	Female	Heart + lung	Scl70	still detectable after 24 months	CRS grade 1
Wang *et al.* [41▪]	Allogeneic	25 mg/day/m^2 Fludarabine (day−5 to −3) and 300 mg/day/m^2 cyclophosphamide (days −5 and −4)	1 x 10^6 CAR T cells per kg bodyweight	2	Male	Heart + lung	Scl70	Very low numbers after 2 months	None
Pecher *et al.* [42▪]	Autologous, second generation	fludarabine (25 mg/m^2, day 5 until 3) and cyclophosphamide (1000 mg/m^2, day 3)	1 × 10^6 CAR T cells per kg bodyweight	5	4 female, 1 male	5 lung, 2 heart, 2 renal	2 Scl70, 2 RNA Pol III, 1 nonspecific	At least until day 36, reappearance in one patient due to HLH	3 CRS grade 1, 1 fatal secondary HLH 2 months after therapy

CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; IQR, interquartile range; MMF, mycophenolate mofetil; RNA Pol III, RNA-polymerase III antibodies; Scl70, antitopoisomerase I antibodies.

domain and an intracellular domain responsible for target cell activation. The intracellular domain consists of a CD3ζ signalling chain of the T-cell receptor as well as a co-stimulatory domain. Second-generation CAR T-cell designs use a combination of the CD3ζ signalling chain and one co-stimulatory domain (CD28 or 4–1BB) for activation whereas third-generation CAR T cells typically incorporate two costimulatory domains, CD28 and 4–1BB [52▪,56]. Allogeneic CAR T cells are produced by genetically engineering healthy-donor-derived T cells. To prevent rejection and graft-versus-host disease (GVHD), different strategies such as gene editing with T-cell receptor deletion or knockout of HLA antigens have been described [41▪,57]. Here, the advantage of immediate availability without delay time from leukapheresis to CAR T-cell infusion is balanced against a more complex manufacturing process. CAR T cells are expanded *in vitro* and transferred to the patient at doses of around 1x107 cells in case of autologous CAR T cells and of around 1×10 cells in case of allogeneic CAR T cells. To allow homeostatic proliferation of CAR T cells *in vivo*, lymphodepletion therapy (usually a combination of CYC and fludarabine) is carried out before the CAR T cell are infused. For the treatment of SSc, the use of autologous second-generation and third-generation CD19-CAR T cells as and a first application of allogeneic CAR T cells has been reported [35,36–38,41,42▪].

SAFETY

CD19-targeting CAR T-cell therapy can be associated with a distinct toxicity profile including CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) [58,59]. While the majority of CRS cases are mild to moderate (grade 1–2), severe (grade $\geq$3) events can occur. Treatment of moderate to severe CRS includes tocilizumab or corticosteroids [56]. In a recent in-vitro study, Dingfelder *et al.* showed that CAR-mediated cytotoxicity is dependent on CD19 expression levels and that CAR T cells derived from patients with AIDs including SSc produce lower levels of inflammatory cytokines than healthy donor-derived CAR T cells in response to CD19+ B-cell targets [60]. ICANS can manifest with a spectrum of neurologic symptoms of encephalopathy and is thought to result from endothelial activation and disruption of the blood–brain barrier [61,62]. Furthermore, hematologic toxicities, such as prolonged cytopenia can occur upon CD19-targeting CAR T-cell therapy and patients are exposed to an increased risk of infections for a certain period of time [63]. Few cases of secondary malignancy (T-cell lymphoma) upon CD19-CAR T-cell therapy were described in patients with lymphoma. The secondary lymphoma was deduced to clonal T-cell receptor rearrangement of the CAR T-cell clone; however, secondary malignancies have not been reported in context of CAR T-cell therapy of AID [64].

Several case reports describe a favourable safety profile in SSc: in a series of six dcSSc patients treated with CD19-targeting CAR T cells, we reported CRS grade 1 in three patients and CRS grade 2 in one patient, who had to be treated with three doses of tocilizumab. None of the patients developed higher grade CRS or ICANS after CAR T-cell treatment. Regarding infections, we observed four cases of urinary tract infections and two cases of pneumonia (one influenza with bacterial superinfection). In addition, herpes zoster and cellulitis were reported [35,36▪,37▪]. Preliminary data of the first phase I/II study on the application of CD19-CAR T therapy in AIDs including SSc report a beneficial safety profile as described in published conference abstracts [65,66]. Consistently, other groups reported a mostly favourable safety profile: Merkt *et al.*[38▪] reported mild CRS grade 1 in a patient with progressive SSc after receiving third-generation CD19-targeting CAR T cells. Pecher *et al.* reported CRS grade 1 in four out of five patients, but no higher grade CRS. However, one SSc patient developed secondary hemophagocytic lymph histiocytosis (HLH) in conjunction with massive CAR T-cell expansion 74 days after therapy with lethal outcome. HLH was probably favoured by herpes simplex virus reactivation in this patient after stopping prophylactic acyclovir due an allergic reaction [42▪]. No signs of CRS or other side effects were described in a series of two patients with dcSSc within the 6-months follow-up period after treatment with allogeneic CD19-targeting CAR T cells [41▪].

Recently, a new form of toxicity was described in AIDs patients upon CD19-targeting CAR T-cell therapy: immune effector cell-associated toxicity syndrome (LICATS). It is characterized by local reactions in organs previously affected by the respective AID and likely based on the cleansing of B cells from the affected organs. In SSc patients with SSc receiving CD19-targeting CAR T-cell therapy, LICATS events related to the kidney, skin, muscle, heart, lung, gastrointestinal tract and joint were observed, mostly of mild intensity and resolved completely [67].

PRELIMINARY DATA ON EFFICACY

Accumulating evidence from case series shows beneficial effects of CD19-targeting CAR T-cell-mediated immunomodulation on various disease manifestations in SSc (Table 1): in an SSc patient with skin, heart, and joint involvement, we described the improvement of arthritis and skin fibrosis upon CD19-CAR T-cell therapy. Moreover, myocardial fibroblast activation as assessed by FAPI-PET/CT

reduced. Interestingly, clinical changes were accompanied by seroconversion of anti-RNA polymerase III autoantibodies, which persisted during the 6 months follow-up observation [35]. Similarly, short-term efficacy as assessed by mRSS and the EUSTAR activity index was described in a case series of patients with AIDs including four patients with dcSSc [36▪]. In a follow-up study, we described the effects CD19-CAR T-cell therapy on organ manifestations in SSc over a follow-up period of up to 18 months: here, no events as defined by progression of ILD, onset of congestive heart failure, onset of renal failure, onset of arterial hypertension, or initiation of new immunosuppressive or antifibrotic therapy occurred during the observational time. The probability of improvement assessed by ACR-CRISS increased to a median of 100%, and the EUSTAR activity index declined by a median of 2.1 points within the first months after therapy. The median mRSS decreased by 31% within 100 days. Regarding pulmonary involvement, ground glass opacification in CT scans and forced vital capacity tended to improve, while reticularization and honeycombing remained stable. Digital ulcer counts decreased and hand function improved. Antinuclear antibody titres decreased by a median of 10-fold within 3 months. Interestingly, antitopoisomerase I antibodies ($n=5$ patients) steadily decreased throughout the follow up period whereas RNA polymerase III antibodies ($n=1$ patient) were completely abrogated after therapy and reappeared 1.5 years later [37▪]. As of today, no re-initiation of immunosuppressants was necessary in any of the reported patients.

The first use of third-generation CD19-targeting CAR T cells was reported in a 38-year-old woman with dcSSc and rapid progressive ILD. Medication with mycophenolate and nintedanib was stopped before leukapheresis and reinitiated after therapy. Mycophenolate was finally stopped 7 months after CAR T-cell infusion. Six months after treatment, lung function parameters improved, and ground-glass opacities as well as ^{68}Ga-FAPI uptake in the lungs decreased. A decrease of ANA titres and disappearance of antitopoisomerase I antibodies 15 months after therapy was reported, and the mRSS score decreased by more than 10 points within the follow-up period [38▪,39]. Recently, the outcome data in this patient, 2 years after CAR T-cell therapy and upon continuation of nintedanib were reported with sustained absence of antitopoisomerase I autoantibodies, further reduction of pulmonary fibrosis on CT scans and stabilization of mRSS [40].

The use of autologous CD19-targeting CAR T cells in five patients with SSc who were not eligible for autologous stem cell transplantation were reported by Pecher *et al.* mRSS and lung function parameters improved in four patients after therapy. One patient passed away due to secondary HLH as already described in the section 'safety'. Autoantibodies declined in all patients with temporary negativity and reappearance in two patients [42▪].

The first application of allogeneic CD19-targeting CAR T cells in two patients with dcSSc was recently described: healthy donor-derived T cells were genetically engineered to improve immune compatibility using CRISPR CAS-mediated knockout of HLA antigens and enrichment of CD3-negative cells. The cell products were infused after lymphodepletion and stopping of immunosuppressants. Both patients showed a fast clinical improvement as assessed by ACR-CRISS score, and strong mRSS decreased within 6 months. Antitopoisomerase-I antibody titres decreased. Improvement of pulmonary involvement as documented by CT scan and lung function and amelioration of myocardial fibrosis as assessed by cardiac MRI scans was described [41▪].

Beyond the application of engineered T cells, the same group recently reported the first application of an iPSC-derived CD19/BCMA dual targeting chimeric antigen receptor natural killer cell (CAR-NK) product in a patient with severe dcSSc. In addition to strong depletion of B cells, beneficial effects on skin, lung and heart fibrosis at a favourable toxicity profile was reported [68▪].

IMMUNOLOGICAL EFFECTS OF CAR-T-CELL THERAPY IN SYSTEMIC SCLEROSIS

Unique attributes of CAR T cells are their dual capability for antigen recognition and cell killing; their good access to all organs and tissues; and their ability to act as 'serial killers', enabling them to effectively and thoroughly deplete B cells in the tissue [69,70▪]. Unlike RTX, CD19-targeting CAR T cells achieve complete elimination of CD19+ and CD20+ B cells in lymph nodes, reflecting superior efficacy in depleting tissue-resident and autoreactive B-cell clones [70▪].

First studies in AID convincingly showed disease remission despite full B-cell reconstitution upon CD19-targeting CAR T-cell therapy and thus suggest an immunological 'reset' [44]. Following extensive tissue depletion, reconstitution of the B-cell compartment post-CAR T-cell treatment is characterized by a predominance of naive B cells and a marked reduction in CD19+CD27+ memory B cells [36▪]. Analyses of the B-cell receptor repertoire in SLE patients showed that this shift corresponds with the loss of IgG- and IgA-expressing clones and a simultaneous expansion of IgM- and IgD-expressing populations, reflecting a more naive, antigen-inexperienced B-cell repertoire [71]. Notably, expanded

class-switched clones present prior to therapy are no longer detectable posttreatment, further supporting the concept of an extensive elimination of autoreactive memory B cells and a functional reset of the humoral immune system [71]. Interestingly, despite the predominance of naive B cells post-CD19-targeting CAR T-cell therapy, SARS-CoV-2 vaccination studies demonstrate that patients can still mount antigen-specific responses, indicating preserved capacity for de novo humoral immunity across different AID, including SSc [72].

Although the pathogenic relevance of anti-Scl70 autoantibodies in SSc remains to be defined, their dynamic titter changes following CD19-targeting CAR T-cell therapy suggests a profound immunological modulation [36▪]. Remarkably, anti-RNA polymerase III antibodies are rapidly eliminated after therapy [36▪], whereas antitopoisomerase I antibodies show a more gradual decline [73], which has not been reported in treatments other than SCT, where such reductions are observed in a subset of patients, for example, 10 out of 11 patients up to 24 months post-SCT [74].

Beyond reshaping the B-cell compartment, CD19-targeting CAR T-cell therapy might also interrupt the pathogenic feedback loop between adaptive autoimmunity and innate immune activation [73]. For instance, the broad and deep depletion of B cells and the resulting decline in autoantibody levels and immune complex formation appears to drive phenotypic changes in FcγRIIIA-expressing natural killer (NK) cells, which shift towards a less activated, more juvenile state following CD19-targeting CAR T-cell treatment [73].

CHALLENGES AND FUTURE CONSIDERATIONS

CAR T-cell therapy represents a promising frontier in the treatment of SSc. However, realizing the full therapeutic potential of this modality in SSc requires further investigations addressing several clinical, immunological and logistical challenges [1].

A central question is refining patient selection, as no standardized definition exists for 'refractory' disease across many autoimmune conditions. For SSc, an expert consensus outlines eligibility criteria for cellular therapies, including: age at least 18 years; diagnosis by ACR/EULAR 2013 criteria; disease duration 5 years or less; and either a mRSS >20 with elevated inflammation (ESR >25 mm/h or haemoglobin <11 g/dl), or mRSS greater than 15 with at least one major organ involvement such as ILD with reduced lung function (DLCO and/or FVC <80%), previous renal crisis or stage 2/3 chronic kidney disease, or cardiac complications including reversible congestive heart failure or arrhythmias [75]. Additionally, patients should have shown insufficient response to at least two immunosuppressive therapies over a minimum of 3 months [75]. Although CAR T cells are currently reserved for severe, treatment-resistant cases, it remains an open question whether earlier intervention, prior to irreversible organ damage [76], could yield better outcomes and prove more cost-effective. The development of biomarkers capable of predicting disease trajectories [77] could facilitate earlier application of CAR T-cell therapy in SSc, thereby enhancing therapeutic outcomes and optimizing the design of future clinical trials.

Lymphodepleting chemotherapy is critical for CAR T-cell engraftment and expansion, but the optimal regimen in AID is still under investigation [78]. Standard protocols (cyclophosphamide–fludarabine) pose risks such as infertility and secondary malignancies, which are especially concerning in young patients with AID. Moreover, fludarabine may impair immune tolerance by depleting regulatory T cells [79]. Alternatives like bendamustine might be promising but lack data in AID [80]. Thus, disease-tailored conditioning strategies are urgently needed.

Clinical data on CAR T-cell therapy in SSc mostly refer to a construct targeting CD19 with a 4-1BB costimulatory domain [56]. However, CD19-negative long-lived plasma cells may also be a source of pathogenic autoantibodies in a subset of patients. This is exemplified by the persistence of antinucleosome antibodies in individuals with SLE treated with CD19-directed CAR T cells [36▪], and is further supported by emerging evidence for the efficacy of CD38-targeting therapies in SLE, highlighting the potential value of incorporating plasma cell-directed strategies [81]. CAR T cells targeting CD38 or B-cell maturation antigen (BCMA), both expressed on plasmablasts and plasma cells, may offer a valuable strategy for further targeting of autoreactive plasma cells in SSc; however, potential trade-offs such as reduced titres of protective antibodies need further investigation [45].

While autologous CAR T-cell therapies show great promise, they are challenged by high costs, complex logistics, and the risk of manufacturing failure of personalized products [56]. LNPs delivering mRNA encoding CAR constructs or CRISPR–Cas9 gene-editing tools could be explored as a nonviral, in-vivo method to reprogram endogenous T cells. Preclinical studies have demonstrated proof-of-concept for LNP-mediated CAR delivery, suggesting a scalable, lower cost alternative with faster turnaround times [53,54]. In parallel, allogeneic 'off-the-shelf' CAR T-cell products are emerging as a promising alternative, with early evidence suggesting that multiplex genome-edited allogeneic CAR T cells derived from healthy

donors could induce deep and sustained B-cell depletion, along with marked clinical improvement in patients with refractory SSc [41▪]. Beyond cellular therapies and avoiding the fertility-damaging lymphodepleting preconditioning, the bispecific T- cell engagers directed against CD3 and a B-cell lineage antigen, such as CD19 or BCMA, have shown encouraging results in case reports in severe or relapsed SSc and may add our therapeutic armamentarium in selected patients [82,83].

CONCLUSION

In summary, the concept of deep B-cell depletion using CAR T-cell therapy holds promise to amend the existing treatment repertoire in a potentially life-threatening disease. However, controlled studies with extended follow-up are needed to further characterize this novel treatment option. So far, CAR T-cell products are in investigational use and not yet approved by FDA or EMA for application in AID.

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