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Editorial introduction

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 Editor for this issue.

SECTION EDITOR

Joerg Ermann

Dr Ermann is a rheumatologist at Brigham and Women's Hospital and Assistant Professor of Medicine at Harvard Medical School in Boston, MA. He is a native of Germany and received his MD from the University of Leipzig. After a postdoctoral fellowship in immunology at Stanford University and internal medicine residency at the University of Tennessee Memphis, he completed his subspecialty training in rheumatology at Brigham and Women's Hospital. His laboratory investigates disease mechanisms relevant to spondyloarthritis using mouse models and translational research approaches. He is the vice-chair of SPARTAN (Spondyloarthritis Research and Treatment Network), an organization of North American rheumatologists dedicated to research and education in the field of spondyloarthritis.

The challenge of bringing advances in sacroiliac joint imaging to the clinic

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Purpose of review
Recently reported criteria are more stringent for classification of axial spondyloarthritis (axSpA) in the absence of positive imaging. This places increased reliance on the accuracy of sacroiliac joint (SIJ) imaging. This review highlights some of the key challenges to bringing advances in SIJ imaging to clinical practice.

Recent findings
The first international consensus for an MRI acquisition protocol for sacroiliitis, published in 2024, defines how the sequences should be orientated, and which sequences are required to identify various lesions that may be seen in inflammatory sacroiliitis and degeneration. However, as anatomical and physiological variation and degeneration are very common in the SIJ, new techniques are not necessarily specific for sacroiliitis and may be more sensitive to changes in the SIJ regardless of cause. Artificial intelligence techniques are currently in use for improvement in image acquisition, but models used for enhancement of diagnostic ascertainment still need development and validation.

Summary
New techniques, especially adherence to a recommended MRI protocol, are essential for accurate assessment of sacroiliitis. However, the introduction of new techniques to clinical practice must be accompanied by the appropriate education to assist less experienced observers with appropriate interpretation of novel images.

Keywords
acquisition protocol, artificial intelligence, axial spondyloarthritis, MRI, sacroiliac joint

INTRODUCTION

In 1961, a group of world experts met in Rome to discuss 'The Epidemiology of Chronic Rheumatism' [1]. Chapter 23 of the proceedings of this meeting, discusses the first classification criteria for ankylosing spondylitis. In this chapter, the esteemed Jacques Forestier presents clinical, radiological and biological criteria, and the longest part of the chapter is devoted to 'Technique D'Examen Radiographique Des Articulations Sacro-Iliaques', with precise details on how to perform high-quality radiographs of the sacroiliac joints (SIJ). Some principles never change, and 65 years later, we face the same obstacles to the accurate diagnosis of axial spondyloarthritis (axSpA) – namely the accurate performance and interpretation of medical imaging of the SIJ.

Imaging of the SIJ has always been important in spondyloarthritis, but in recent years, it has become increasingly influential in the diagnosis, classification and management of axial spondyloarthritis (axSpA). The new Assessment of Spondyloarthritis International Society/Spondyloarthritis Research and Treatment Network (ASAS/SPARTAN) classification criteria place particular importance on imaging that is positive for the presence of sacroiliitis, and the new criteria are more stringent for classifying a patient as positive for axSpA in the absence of positive imaging [2▪]. The Classification in Axial Spondyloarthritis Inception Cohort (CLASSIC) study tested the 2009 ASAS classification criteria for axSpA in a worldwide inception cohort, targeting sensitivity of at least 75% and specificity of at least 90%. When these targets were not met, new proposed criteria reflected the fact that the highest association with axSpA was imaging evidence of sacroiliitis, especially MRI of the SIJ indicative of axSpA by global assessment of both active and structural lesions. The clinical arm (nonimaging

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KEY POINTS

- MRI is the best test for detection of sacroiliitis, and new classification criteria place increased reliance on accurate imaging of the sacroiliac joints (SIJ).
- A minimum 4-sequence MRI acquisition protocol is recommended and inclusion of a high-resolution erosion-specific sequence improves accuracy, because these sequences are consistently superior to conventional T1 spin echo for detection of erosion.
- Mimics of sacroiliitis and normal anatomical and physiological variation in the SIJ are very common, and the introduction of new techniques may create challenges for less experienced observers.
- Artificial intelligence techniques are currently in use for improvement in image acquisition, but models used for enhancement of diagnostic ascertainment still need development and validation in larger populations.
- Education is crucial for the successful implementation of new protocols or artificial intelligence techniques.

arm) of the 2009 classification criteria required HLA-B27 positivity plus any 2 of 11 SpA features for the patient to be classified positive for axSpA. By comparison, the number of available SpA features has been reduced to seven in the 2025 criteria, and positivity according to the clinical arm requires the patient to have HLA-B27 positivity, inflammatory back pain and any four of six other SpA features. These changes to the criteria make it substantially more difficult for patients to be classified positive for axSpA if the imaging results are negative, and one of the consequences of this is increased reliance of the classification criteria on accurate imaging of the SIJ.

This article discusses some recent advances in imaging the SIJ for the detection of sacroiliitis and the challenges that may be faced in the implementation of these techniques in clinical practice.

MRI

Without doubt, the most important development in imaging sacroiliitis has been MRI. This remarkable technique allows visualization of active inflammation in the form of osteitis/bone marrow oedema (BME) and structural damage in all its stages. From the outset, T1-weighted (T1) spin echo and sequences that are T2-weighted (T2) with one form or other of fat suppression have depicted active inflammation, erosion and ankylosis well. However, recent publications have emphasized that the normal SIJ is highly variable in appearance [3] with frequent anatomical variation [4,5▪], and that other conditions can look remarkably similar to inflammatory sacroiliitis [6]. Consequently, attention to detail is important in the creation of the images as well as in the interpretation of the findings.

The biggest challenge to bringing advanced MRI techniques to the clinic is education. Until recently, no universally agreed-upon protocol existed for SIJ MRI in clinical practice, but in 2024, ASAS-SPARTAN published an international consensus on a standardized image acquisition protocol (IAP) for diagnostic evaluation of the SIJ by MRI (Table 1) [7▪▪]. The protocol (Figs. 1 and 2) can be performed on any MRI scanner, is capable of detecting all the MRI findings commonly associated with both axSpA and its mimics and has been widely adopted [8].

This protocol established how the images should be orientated to the sacrum as opposed to the pelvis or lumbar spine. The precise orientation of sequences is important because high variations in sacroiliac anatomy makes images more difficult to interpret if they are not orthogonal to the sacrum. The IAP also establishes criteria for the minimum number of sequences required, and how different sequences should be acquired to address various pathological processes, including a high-resolution 3D sequence dedicated to the detection of erosion. Although the protocol is relatively straight forward, a major challenge to the implementation of these recommendations is large variations in current clinical practice, including a general resistance to change local protocols, which may have been in place for many years and, hitherto, would have been considered clinically adequate (Figs. 3 and 4).

Variations in the acquisition technique have been identified as potential problems [9▪]. Some centres have adapted MRI protocols designed to image peripheral joints, such as the knee, for use in the SIJ. But proton density (PD) and intermediate weighted (IW) sequences with fat saturation designed to image peripheral bone marrow and fibrocartilaginous structures are not suitable for BME detection in the spine and sacrum due to the high content of erythropoietic marrow present in the spine but absent in the extremities [10]. Ongoing education of MRI technologists and radiologists is essential so that they know not only how to acquire the images, but also why the scans should be done the recommended way so that technologists know how best to adapt protocols for difficult cases.

Education is also essential for improving the interpretation of the images. The new high-resolution 3D sequences, such as VIBE [11,12▪] (volumetric interpolated breath-hold examination) and ZTE (Zero Echo Time) [13], are very good for detecting articular erosion, which is important in early disease. It doesn't seem to matter which of the many

Table 1. A recommended four-sequence MRI protocol for diagnostic ascertainment of inflammatory sacroiliitis

Orientation	Sequence properties required	Recommended sequence	Target lesions
Semicoronal This plane is defined as: Parallel to the dorsal cortex of the S2 vertebral body (anterior border of sacral spinal canal)	Detect structural damage and bone marrow fat: Strong fat signal and low water signal 3–4 mm thick	T1-weighted Spin Echo	Fat lesion, erosion, sclerosis, backfill, ankylosis
	Detect active inflammation: Very strong water signal with suppressed fat signal 3–4 mm thick TE $\geq$55 ms	STIR, T2FS, T2-Dixon or equivalent	Osteitis/BME, capsulitis, enthesitis, inflammation in the joint space or erosion cavity
	Detect bone erosion and bone formation: Optimized contrast at the bone–cartilage interface T1-weighted with fat suppression suggested 1.0–1.5 mm thick High resolution, $\leq$1.0 mm voxel	3D Gradient Echo or equivalent	Erosion, alteration of joint space width (widening, narrowing, ankylosis) Other findings: Intraarticular gas, osteophyte, periarticular ankylosis, subchondral cyst
Semiaxial This plane is defined as: Perpendicular to the semicoronal plane	Detect active inflammation: Very strong water signal with suppressed fat signal 3–5 mm thick TE $\geq$ 55 ms	STIR, T2FS, T2-Dixon or equivalent	Osteitis/BME, capsulitis, enthesitis, inflammation in the joint space or erosion cavity
Suggested additions-incorporated into the above sequences	Detect active inflammation	Include whole pelvis in the axial T2-weighted sequence	Osteitis pubis, pelvic enthesitis, hip arthritis
	Detect bone erosion and bone formation in the semiaxial plane	Reconstruct high-resolution 3D gradient echo sequence	Erosion, alteration of joint space, other findings (as above)

A minimum four-sequence image acquisition protocol for diagnostic ascertainment of inflammatory sacroiliitis by MRI has been recommended [7▪▪]. Performing the sequences in semicoronal and semiaxial planes orthogonal to the sacrum, rather than orthogonal to the lumbar spine or pelvis, provides more consistent visualization of the SIJ, which are subject to very frequent anatomical variation. The recommended sequences are selected to optimally identify lesions that are commonly seen in axSpA and joint degeneration. The protocol can be applied to any MRI scanner with slice thickness and spatial resolution adapted to the age and configuration of the MRI unit. It is also suggested that the semiaxial sequence include the symphysis pubis and hip joints, and that the 3D sequence be reconstructed in the semiaxial plane. STIR, short tau inversion recovery; T2FS, T2-weighted with fat suppression; BME, bone marrow edema.

high-resolution 3D sequences available is used as long as the principles are adhered to (Table 1) [9▪]. However, these sequences also show anatomical variation in much more detail than we have previously seen. It has recently been shown that VIBE reveals 'nonerosion defects' in 95% of children, which may be indistinguishable from erosion unless the high-resolution sequence is carefully interpreted along with all the other sequences as part of a global interpretation [14]. At high resolution, normal 'defects' are also more frequently seen in adults (Figs. 5 and 6), and this illustrates that introduction of advanced techniques in MRI must be accompanied by comprehensive education about the benefits and limitations of any new protocol.

The next challenge to implementation of advanced MRI techniques is variation in both the hardware and software of MRI platforms, which is very considerable according to age and manufacturer. Older scanners may have difficulty doing 3D sequences with the required spatial resolution and contrast. Some sequences remain in the research domain, for example, Synthetic CT (sCT) is a new MRI sequence, which produces MRI images that appear almost identical to a CT scan [15,16]. This is a very exciting development, and if it proves to be reliable, it would be a great asset to be able to produce

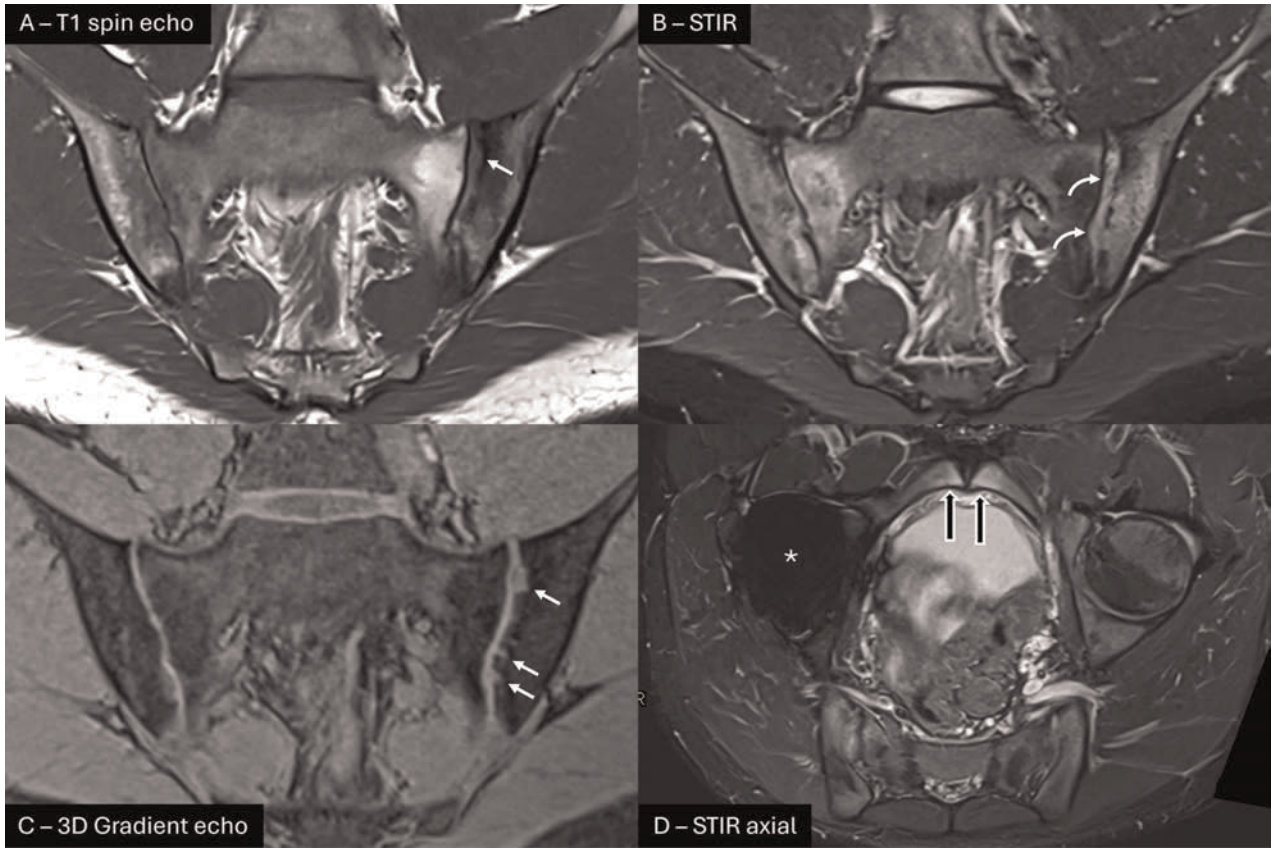

FIGURE 1. On semicoronal T1 spin echo (a), iliac erosion (arrow) with joint space widening and fat metaplasia in sacral subchondral bone are evident in the left sacroiliac joint. Subchondral bone marrow oedema (BME) is present in the right SIJ and left ilium with decreased signal on T1 and increased signal on STIR (b and d). Semicoronal STIR (b) also demonstrates 'inflammation in an erosion cavity' (curved arrows) with increased signal intensity in the usual location of the articular cartilage that is lower intensity than would be expected for joint effusion. There is no evidence of capsulitis. Semicoronal thin slice 3D gradient echo (c) enhances contrast at the bone/cartilage interface and reveals more erosion in the left SIJ (arrows) than is apparent on the T1 spin echo. A semiaxial T2-weighted sequence incorporating fat suppression (d – STIR), is performed perpendicular to the semicoronal sequences and completes the protocol. In this case, including the pubic symphysis demonstrates symphysitis with bilateral inflammation in the pubic bodies (arrows). A total arthroplasty of the right hip joint, performed for severe inflammatory arthropathy, causes signal loss in the right femoral head (asterisk). SIJ, sacroiliac joint.

CT-like images without any radiation. However, the software is proprietary and is not routinely available on any MRI scanner.

Finally, there is a general publication bias towards emphasizing the benefits of new techniques without thorough testing of the feasibility of the techniques in routine clinical practice. For example, it has been shown that diffusion weighted imaging (DWI) may provide superior detection of active inflammation in bone marrow and soft tissues related to enthesitis [17], but the application of the technique to the SIJ is more controversial where DWI may provide more objective data, but superiority of a global opinion compared to optimized standard sequences is less clear cut [18]. In summary, the challenges for widespread implementation of advances in MRI are:

(1) The need for education regarding recommended image acquisition protocols that can be applied to any MRI scanner, in the face of current widespread variation in clinical practice and resistance to change.
(2) The need for education regarding the many mimics of sacroiliitis and interpretation of new MRI techniques, including their advantages and disadvantages.
(3) Limitations in the capabilities of older MRI scanners that may restrict the application of the latest techniques.

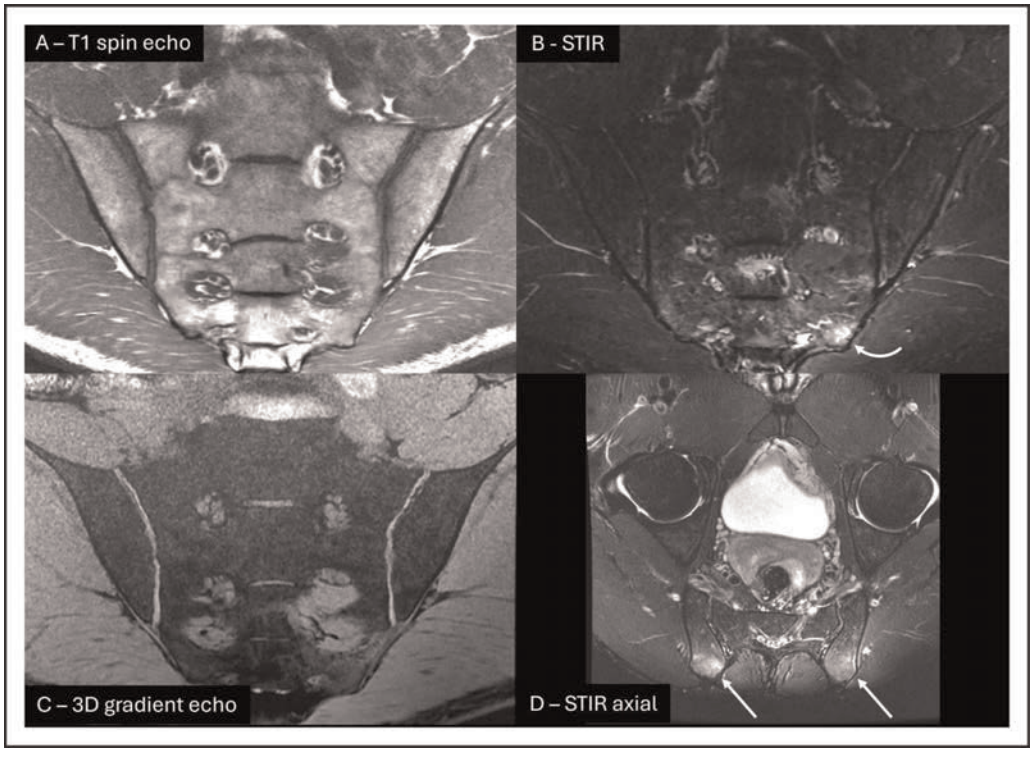

FIGURE 2. Slight irregularity in the contour of both sacroiliac joint is nonspecific with no definite evidence of erosion, BME, fat metaplasia or other feature of sacroiliitis. However, enthesopathy typical of axSpA is present with BME at the S4 level below the SIJ at the site of attachments of the left sacrotuberous/sacrospinous ligaments (curved arrow), and in the posterior ilium bilaterally posterior to the ligament compartments of the SIJ (straight arrows). axSPA, axial spondyloarthritis; BME, bone marrow oedema; SIJ, sacroiliac joint.

DIGITAL TOMOSYNTHESIS

Digital tomosynthesis (DTS) is an innovative radiographic technique that uses digital flat-panel detectors and linear movement of the x-ray source to generate a series of tomographic images in a primary plane. For the SIJ, they are coronal images (in the anterior–posterior projection). The technique produces x-ray images that are a few centimetres or millimetres thick in which the structures in front and behind each image are blurred, but the region of interest is well defined. The resulting images look similar to CT images on a bone window. In addition, if the acquired images are thin enough, DTS images can be reconstructed in orthogonal planes, for example, axial images can be created from coronals, but they are not as good as axial CT. Radiation dose varies with slice thickness. Exposure dose for DTS of the SIJ (~1 mSv) [19] is lower than standard CT (~4 mSv), and similar to low-dose CT (0.4–1 mSv) [20], but DTS radiation dose is several times higher than a single radiograph (XR) in the same plane (0.1–0.2 mSv).

DTS may be useful for evaluating fine bone detail and is superior to radiography for detecting erosive disease when skeletal anatomy is complex, and/or there are superimposed structures. Using CT as the gold standard for diagnosis of sacroiliitis, Wantz *et al.* [19] found that DTS was substantially more accurate (0.77) than radiography (0.44). However, DTS did misdiagnose several cases, and there was no significant difference in interobserver reliability between DTS and XR.

The challenges for widespread implementation of DTS are:

(1) Most radiography equipment is not DTS-capable, so it is less available.
(2) Accuracy for detection of structural damage changes is better than for XR but not as good as CT.
(3) Radiation dose is less than CT but is more than XR and is equivalent to low-dose CT.
(4) DTS cannot detect active inflammation.
(5) If other modalities are available, DTS is likely to be restricted to niche applications that relate to the particular circumstances of the local environment.

COMPUTED TOMOGRAPHY

CT uses a thin beam of x-rays to generate cross-sectional images with the primary plane of radiation

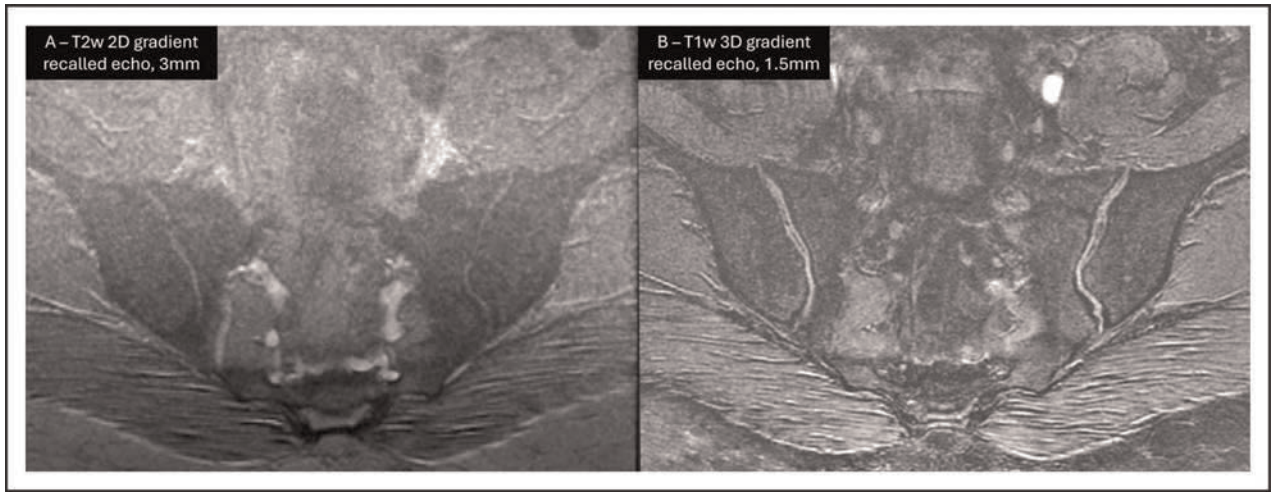

FIGURE 3. In the CLASSIC study, centres were required to scan the sacroiliac joint according to the new Assessment of Spondyloarthritis International Society/Spondyloarthritis Research and Treatment Network protocol. Centres occasionally provided examples of sequences that they had been previously using. This figure shows two gradient echo images from the same patient taken 20 min apart, illustrating the effects of optimizing sequence selection and image acquisition parameters. In (a), a 3 mm thick 2D gradient recalled echo sequence was performed with traditional T2 weighting (cropped and slightly magnified to match b). This sequence has been available for 30 years and is still in use in some centres. In (b), a 1.5 mm 3D gradient-recalled echo sequence was performed with T1 weighting. The SIJ articular surfaces are better visualized in (b) for many reasons, including (a) smaller field of view (220 mm), (b) thinner slice (1.5 mm), (c) higher in-plane resolution, and (d) T1 weighting (images provided with permission of SPARTAN). SPARTAN, Spondyloarthritis Research and Treatment Network protocol.

exposure being axial – hence the use of the term 'cross-sectional'. The images are intrinsically of high resolution and, most often, the data set is reconstructed in multiple 2D planes (sagittal, coronal, axial, oblique) without loss of resolution. CT is the ideal x-ray-based technique for creating thin-slice, high-resolution images of the SIJ and is easily reconstructed in semiaxial or semicoronal series to match the orientation of recommended MRI protocols. It is considered the gold standard for detection of most structural damage changes in bone due to its excellent calcium contrast such as erosion or bone formation – osteophyte, syndesmophyte, bone budding, and ankylosis [21]. Low-dose CT (ld-CT) techniques are easily performed and require no additional equipment or software. Ld-CT exposure doses are more than a single AP pelvis radiograph (~0.1 mSv) but are similar to radiography of the SIJ and are consistently less than 1 msV, (mean 0.4 mSv, SD 0.18 mSv; range, 0.14–0.83 mSv) [20]. The main disadvantages of CT are that it does not routinely provide any information regarding disease activity and is generally avoided in children, young women, and pregnant patients due to radiation exposure.

Dual-energy CT (DECT) differentiates materials based on differences in atomic number and can be used to identify the high-water content associated with BME as a sign of active inflammation superimposed on normal bone marrow that has a higher fat content. There are several limitations to DECT, however:

(1) Most CT scanners do not have the necessary specialized hardware or software, so DECT is less available than CT or ld-CT.
(2) It cannot be reliably performed at low dose, usually requiring a full-dose technique.
(3) Structural damage changes in the bone, especially sclerosis, interfere with BME detection, so it is less suitable for monitoring of follow-up of inflammatory changes.
(4) DECT is less reliable for BME detection than MRI [22].

NUCLEAR MEDICINE: PET

PET is most often performed using a radioactive analogue of glucose – [18F] fluorodeoxyglucose (FDG) – to detect metabolic activity. It is usually performed in combination with CT, which allows superior anatomical depiction and improved PET images through attenuation correction. The use of PET/CT for diagnosis, disease monitoring, and assessment of complicated cases has been studied in the inflammatory arthropathies [23]. However, it has not generally been adopted for routine use in the

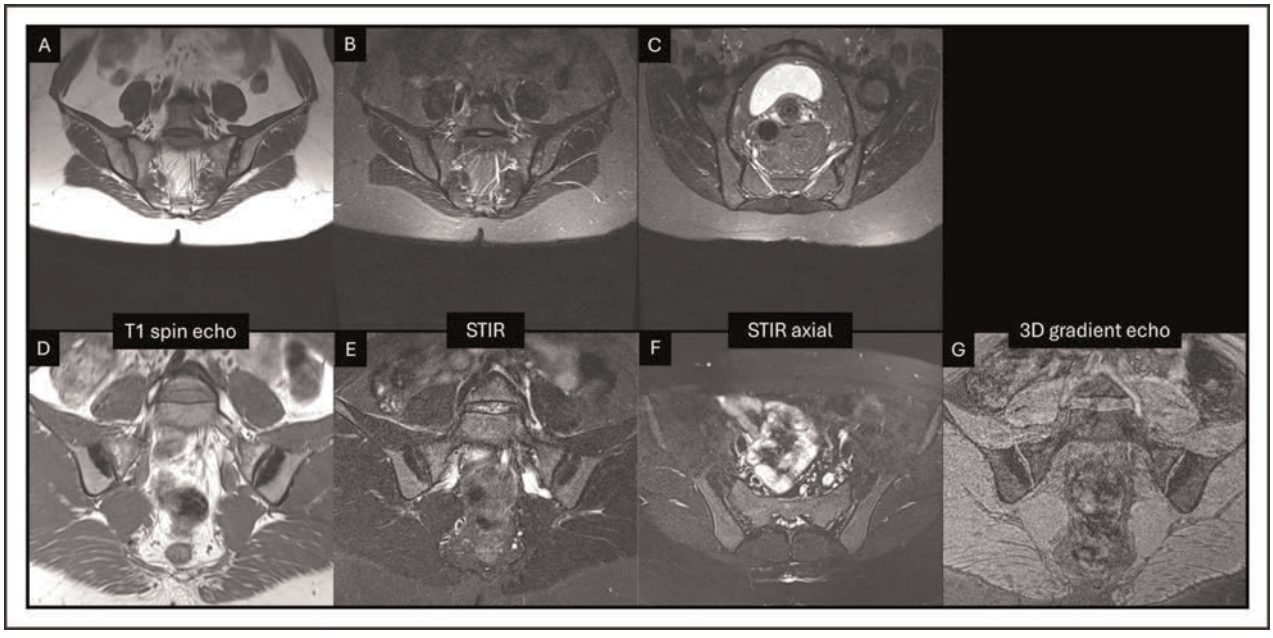

FIGURE 4. Two female patients with osteitis condensans ilii were scanned on the same type of 10-year-old Siemens 1.5 Tesla scanner. MRI images a–c were acquired in July 2025 in local clinical practice and represent a typical SIJ MRI protocol that has been in place for over 20 years. Images are generally adequate, but scanning at 300 mm fields of view provides limited spatial resolution, and the possibility of erosion in the left ilium is hard to interpret. MRI images d–g were acquired during the CLASSIC study according to the ASAS/SPARTAN protocol, which mandates the inclusion of a thin slice T1-weighted erosion-sensitive sequence. In this case, the semicoronal sequences are scanned at smaller fields of view (a –250 mm, b –280 mm, d – 220 mm) and the 1.5 mm thick 3D gradient echo sequence is reassuring that no significant erosion is present (images D-G provided with permission of SPARTAN). ASAS, Assessment of Spondyloarthritis International Society; SIJ, sacroiliac joint; SPARTAN, Spondyloarthritis Research and Treatment Network protocol.

management of arthritis with most authors recommending investigation by other means. The ACR Appropriateness Criteria consider FDG-PET/CT 'usually not appropriate' for investigating inflammatory back pain with known or suspected axial spondylarthritis [21]. PET naturally provides a whole-body assessment and can be very helpful for the investigation of complex cases. It can also be performed with a range of novel tracers than can target specific immunological processes, such as 11C-PK11195 for macrophages or 68Ga-DOTATATE for activated immune cells. While these complex techniques can provide unique information combining assessment of activity and structural damage, they are rarely available outside a research setting.

The challenges for bringing PET of the SIJ to routine clinical practice are primarily:

(1) High cost
(2) Highest radiation exposure
(3) Limited availability

ARTIFICIAL INTELLIGENCE

Artificial intelligence applications have emerged in medical imaging, with rapid growth in research publications and regulatory approval or clearance of commercial software. As of January 2026, there are over 1000 radiology-related devices on the United States FDA's 'AI-Enabled Medical Devices List' [24]. While a commercially available product for sacroiliac joint imaging assessment using artificial intelligence is not yet available, numerous experimental research studies have trained and tested artificial intelligence models targeted at the SIJ in axial spondylarthritis. For example, deep learning-based artificial intelligence algorithms have been shown to provide accurate detection of sacroiliitis on radiographs matching expert reader performance, in retrospective work [25,26]. Similarly, deep learning algorithms have successfully detected sacroiliac joint inflammation on MRI using the 2009 ASAS MRI definition [27], as well as inflammatory and structural changes on MRI [28,29▪]. Furthermore, specific spondylarthritis

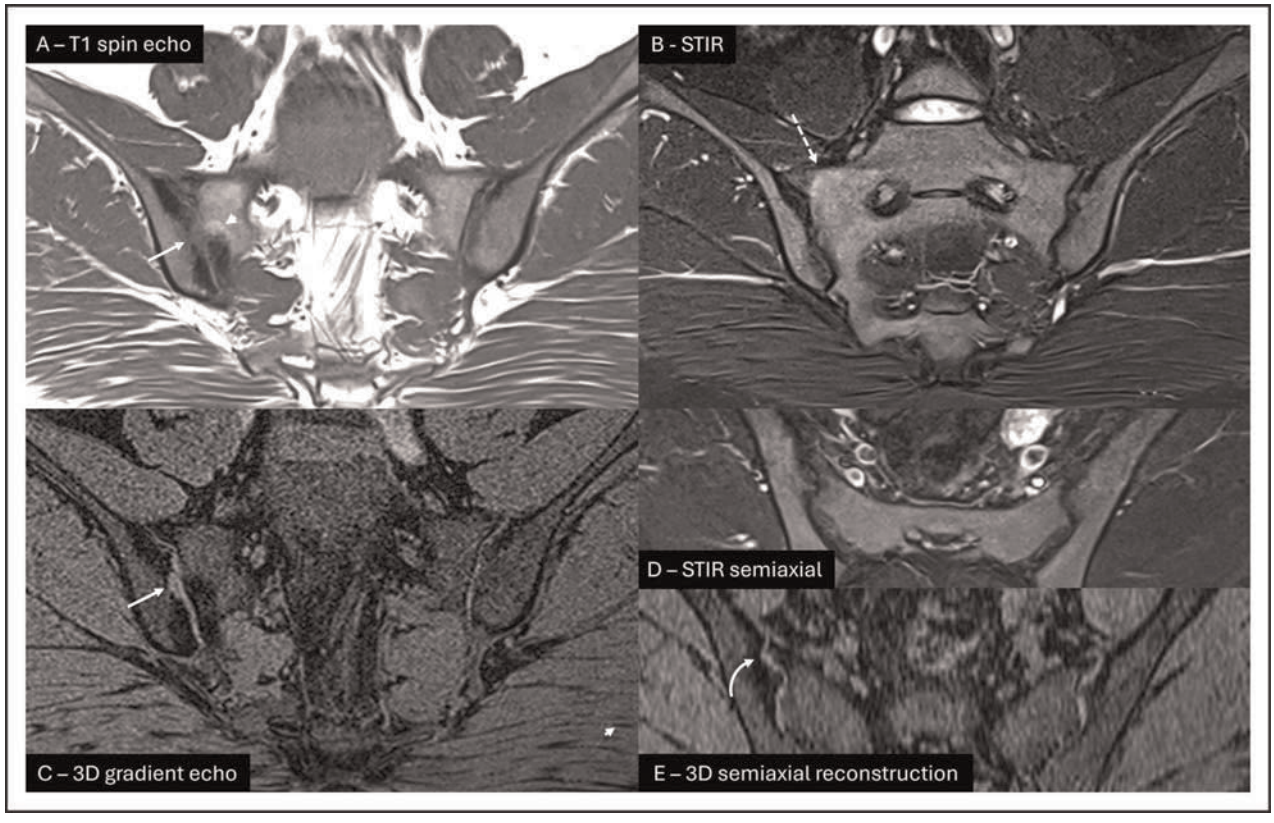

FIGURE 5. A 25-year-old woman presented with chronic low back pain with some symptoms suspicious for axial spondyloarthritis. The most prominent feature is right SIJ sclerosis best seen on the T1 spin echo (a) in the upper and lower ilium and lower sacrum, worst on anterior slices (not shown). Bilateral joint space narrowing is nonspecific. A small amount of BME in the right sacral ala (dashed arrow in b), and a thin rim of fat metaplasia surrounding the sacral sclerosis (arrowhead in a) are nonspecific findings. An apparent small defect in the right ilium (straight arrows in a and c) is easily mistaken for erosion. However, reconstruction of the semicoronal thin-slice high-resolution 3D gradient echo sequence (c) in the semiaxial plane (e) shows that an acute change in the contour of the joint (curved arrow in e) is the cause of the 'nonerosion defect' apparent in the ilium in the semicoronal plane (straight arrows in a and c). It should be noted that subchondral 'defects' that are seen on only a single slice (such as in this case) should be interpreted with caution. In clinical follow-up, the patient was HLA-B27-negative, acute-phase reactants were normal, and the final diagnosis was osteoarthritis with right osteitis condensans ilii.

grading systems, like the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system, have been automated using artificial intelligence techniques [30], and grading of CT images of SIJ has also been tested with artificial intelligence [31].

While not under the umbrella of artificial intelligence specifically, some studies have also used radiomics approaches, extracting quantitative imaging features using semi-automated computational methods, for sacroiliac joint imaging (e.g. detection of active sacroiliitis on MRI [32] and differentiation of inflammatory and degenerative changes on MRI [33]). However, there are ongoing concerns regarding the reproducibility of radiomics research due to methodological issues [34], which has hindered clinical translation of radiomics techniques. Deep learning-based artificial intelligence techniques, like those described earlier, may show greater generalizability, and show promise for future clinical use.

Because of the diagnostic challenge of sacroiliac joint imaging, the opportunity of such artificial intelligence applications is to increase access to subspecialty expertise. If high-performing artificial intelligence can provide an accurate interpretation or significantly improve the accuracy of nonsubspecialty interpretation, then a world class opinion could become available to any patient with sacroiliac joint imaging.

The challenges for implementation of artificial intelligence-based tools in clinical sacroiliac joint imaging include:

(1) Individual and institutional inertia related to adoption of artificial intelligence tools

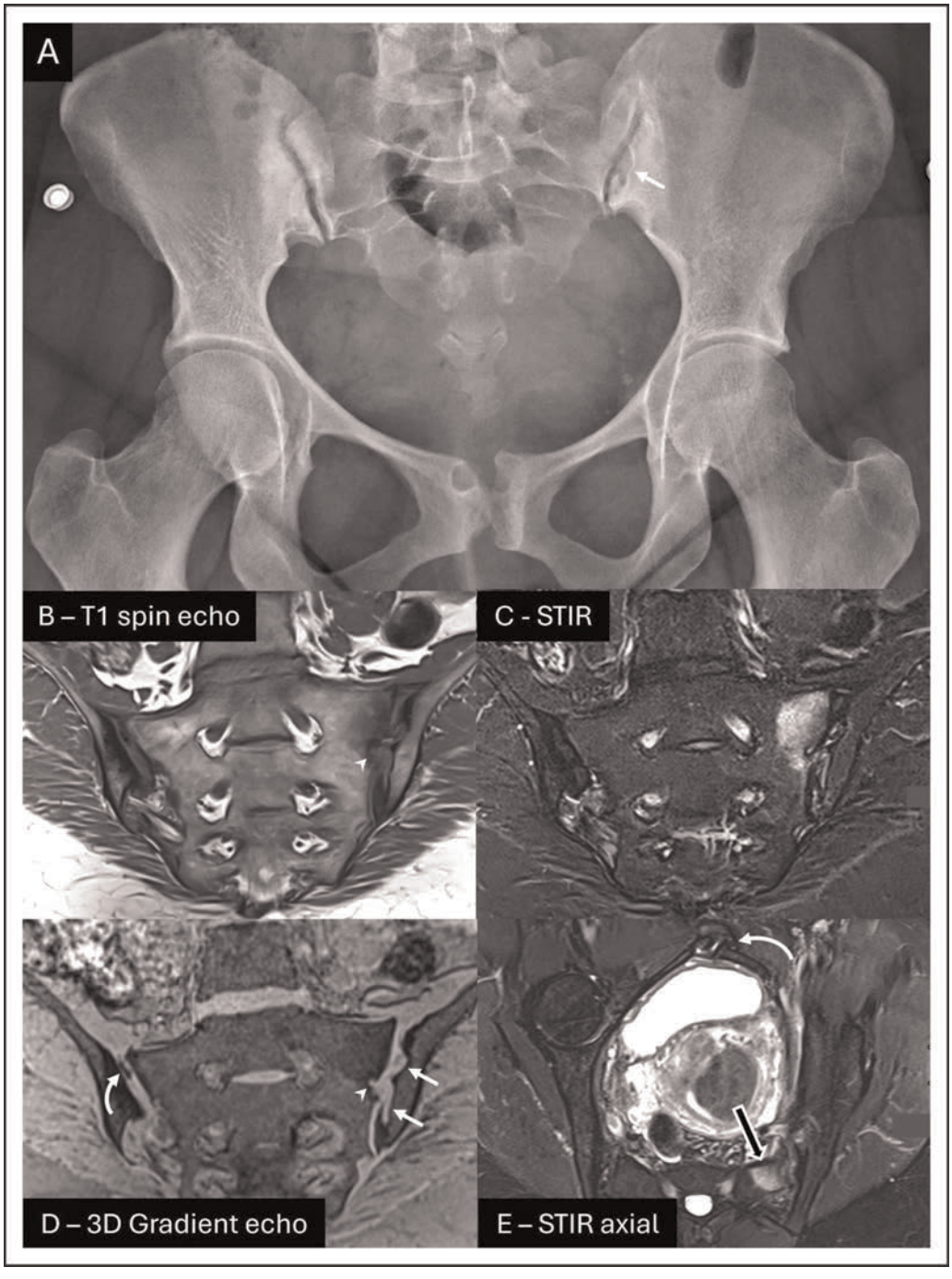

FIGURE 6. A 43-year-old woman with acute on chronic buttock pain was referred because of uncertain findings on pelvic radiography (a). The MRI scan confirmed bilateral osteitis condensans ilii (OCI) but a large area of BME and some irregularity of the left SIJ articular surface raised the possibility of coexistent axSpA. However, large defects in the left ilium relate to ligament insertions (straight arrows in a and d), and congenital asymmetry of the sacrum is present with a much smaller defect in the left sacrum (arrowheads in b and d) also related to a ligament insertion and not erosion. On the semiaxial STIR (e), the BME has the shape of a slice of pie with the apex of the lesion at the anterolateral corner of the left SIJ. The BME extends for an equal distance along the anterior nonarticular border of the sacrum (straight black arrow in e) and along the articular surface, and it is least intense at its apex due to the prominent sclerosis at this point. The shape and configuration of the BME lesion is typical for a mechanical cause. Osteitis pubis, also consistent with chronic strain, is much easier to detect on radiography (a) than it is to see on MRI (curved arrow in e) where the absence of active inflammation makes the distorted symphysis pubis hard to see. In clinical follow-up, the patient was HLA-B27-negative, acute-phase reactants were normal, there was a prior history of several term pregnancies, and the final diagnosis was osteitis condensans ilii with subacute stress reaction in the left SIJ exaggerated by anatomical asymmetry.

(2) Problems of generalizability of current artificial intelligence models
(3) Explainability and interpretability of artificial intelligence results
(4) Expense of artificial intelligence implementation and uncertainty of financial reimbursement

STRATEGIES FOR DISSEMINATION AND HARMONIZATION

The initial step in education of the those involved in the care of patients with or suspected of axSpA is promotion of awareness of recent advances in imaging, particularly MRI. This can be achieved by repeated highlighting of the existence of new criteria and protocols through lectures and publications. Radiology and rheumatology societies need to work together to emphasize the importance of these initiatives for axSpA patients through presenting at each other's meetings and publishing in the corresponding journals. Rheumatologists need to stress the importance of the new MRI protocol to radiologists, who in turn need to influence the MRI technologists or those clinically responsible for protocol implementation. Application specialists of the MRI manufacturers may be particularly helpful in this respect.

However, while presentations and publications help to educate, the experiential component of learning is frequently lacking, and this may be where the greatest opportunity lies. The development of online training modules could allow observers to access entire MRI scans in blinded fashion. If linked to online databases with interactive software, feedback to the learner can be provided in real time with progression from simple to complex cases determined by the progress of the learner. These modules are challenging to create, but initiatives could be advanced by collaboration with international societies and funding from industry.

Online training modules could also help to educate learners about several recent efforts to harmonize clinical practice in axSpA: clinical information required when ordering imaging tests [35▪], language that should be used when describing MRI features [36,37], and recommendations for the content and structure of MRI reports [38▪].

Finally, in locations where MRI is available, rheumatologists and radiologists need to work together to establish appropriate clinical access to the modality, including agreement on which cases take priority and the timeframe within which the service needs to be provided so it enhances patient care rather than hindering it through delay in access to imaging. Whether MRI is available or not, low-dose CT should be readily accessible for problem solving when radiographic results are indeterminate.

CONCLUSION

MRI is clearly the best method for imaging inflammatory sacroiliitis, although radiography will remain as a widely available and useful basic test. A clearly defined image acquisition protocol for MRI assessment of sacroiliitis has now been established, and the key remaining challenge to its widespread implementation is education of the healthcare personnel involved in ordering, acquiring and interpreting the MRI scans. Beyond that, incremental advances in the newest techniques may offer many exciting prospects but are not essential for the application of high-quality imaging of the SIJ in routine clinical practice.

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Conflicts of interest

R.G.W.L. has received consulting fees from AbbVie, CARE Arthritis and Image Analysis Group.

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- ▪ of special interest
- ▪▪ of outstanding interest

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This article provides guidance, to radiologists in particular, regarding the essential components that should be included in all SIJ radiology reports for suspected axSpA.

MRI sacroiliitis mimics

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Purpose of review
MRI of the sacroiliac joints (SIJ) is frequently performed in diagnostic workup of axial spondyloarthritis (axSpA), especially to detect not only early active inflammatory changes but also structural changes. The presence of subchondral bone marrow edema (BME) is an important early sign of sacroiliitis, but can also occur in many other conditions, whereas structural changes, especially erosions, are more specific axSpA features. The purpose of this review is to describe and illustrate MRI features of the most common conditions in adults that can mimic axSpA sacroiliitis.

Recent findings
These findings have focused on the frequently occurring anatomical SIJ variations, as their presence can be accompanied by non-inflammatory BME mimicking sacroiliitis. Studies of pregnancy-related changes, osteitis condensans ilii and other strain-related conditions have shown that non-inflammatory strain-related BME is most common in the anterior portion of the SIJ, whereas axSpA changes are more widespread. Awareness of data-driven MRI lesion thresholds with at least 95% specificity for axSpA may facilitate the differentiation between axSpA and the mimics with the exception of osteitis condensans ilii and postpartum changes.

Summary
Early accurate detection of axSpA is important for treatment in the clinic and for classification in research settings, and sacroiliitis misdiagnoses can result in inappropriate treatment.

Keywords
differential diagnosis, MRI, sacroiliac joint, sacroiliitis, spondyloarthritis

INTRODUCTION

Early detection of axial spondyloarthritis (axSpA) is important for initiating treatment to minimize or prevent irreversible changes. Imaging confirmation of early sacroiliitis is usually based on sacroiliac joint (SIJ) MRI, where subchondral bone marrow edema (BME) is indicative of active sacroiliitis [1,2]. MRI can also visualize other active inflammatory changes, such as enthesitis and capsulitis, and structural changes. However, changes mimicking axSpA sacroiliitis can occur in other conditions and lead to false-positive axSpA diagnoses [3], most importantly BME observed in healthy persons and in relation to load-related, degenerative, traumatic, infectious, metabolic, and other inflammatory conditions [3]. Structural changes consisting of erosion, sclerosis, subchondral fat metaplasia, backfill, and ankylosis are generally more specific axSpA features [4,5] and, if present, contribute enormously to an axSpA diagnosis [2]. However, somewhat similar structural changes in other conditions may mimic axSpA.

Careful interpretation of SIJ MRI and knowledge about changes mimicking axSpA sacroiliitis are important. The purpose of this review is therefore to describe and illustrate SIJ changes mimicking sacroiliitis in adults.

NORMAL SACROILIAC JOINT FINDINGS BY MRI

The SIJ anatomy is complex with two anatomically different compartments, an anterior/inferior cartilaginous and a posterior/superior ligamentous compartment [6,7]. There is considerable inter-individual variation in shape and contour of the joint surfaces with frequent occurrence of anatomical variation, especially in women, and intra-individual variation (left versus right) can also occur [6,8]. In addition to which the joints are subject to mechanical strain, as load between the body and the lower limbs is transmitted through the joints.

Adequate visualization of both joint compartments demands sequences in two perpendicular

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KEY POINTS

- Be aware of anatomical SIJ variations and how they can mimic sacroiliitis.
- Always consider the topographic location of MRI lesions keeping in mind that non-inflammatory strain-related BME is most frequent in the anterior portion of the SIJ.
- A contextual assessment of all SIJ MRI sequences is important, as a combination of active and structural changes are more axSpA-specific than single lesions.
- SIJ MRI findings should be interpreted in the appropriate clinical context, especially in young active individuals and post-partum women.

planes, semi-coronal and semi-axial, respectively, which can diminish false interpretation due to partial volume effects and facilitate a precise location of abnormalities (Fig. 1) [7,9,10▪]. Four standard sequences are recommended, STIR (Short Tau Inversion Recovery) or T2 fat saturated (FS) in two perpendicular planes (semi-coronal and semi-axial), a semi-coronal T1 and a cartilage sequence such as a gradient echo or T1FS sequence [10▪].

ANATOMICAL VARIATIONS

Anatomical SIJ variations are frequent morphological changes reportedly present in 57–85% of non-axSpA individuals with prevalence of up to 91% in healthy women and 37% in men [11–13,14▪▪]. Seven variations are well-described, and these variations may coexist within a single SIJ [11–13,14▪▪] (Figs. 2 and 3).

Only two variations, dysmorphic SIJ and unfused nuclei, are located in the cartilaginous SIJ compartment [4], but variations in the ligamentous compartment may change the joint load and exhibit subchondral BME in the cartilaginous compartment mimicking sacroiliitis.

Dysmorphic SIJ changes are frequent [11,13,15] and are occasionally accompanied by pain [3,11]. They are characterized by abnormal form of the cartilaginous joint facets with a focal prominence of the iliac or sacral joint facet and a corresponding groove in the opposite bone [11,15]. This may be associated with BME as well as irregular joint facets, which usually are focal, centered at the area of morphological changes, and often limited in extent (Fig. 2).

Unfused nuclei at the sacral wings appears as triangular osseous bodies mostly seen in young asymptomatic individuals [11,16].

Accessory SIJ is common [11–13,15–22] and is sometimes accompanied by pain [11,16,21]. It consists of an additional joint with congruent articular facets in the posterior part of the SIJ [21], sometimes with concomitant BME, sclerosis, and fat lesions which can mimic sacroiliitis on coronal slices, but the true location will appear on semi-axial MR-images (Fig. 3). However, a changed load on the SIJs can elicit BME in the cartilaginous compartment [11,15,22].

Iliosacral complex is also common [12,13] and may be accompanied by pain [19]. It consists of a focal osseous prominence of the iliac bone with a corresponding groove in the opposing sacral bone [11,12] (Figs. 2 and 3). There is no osseous contact and therefore no adjacent subcortical BME, but vessels in the reduced joint space may mimic enthesitis on coronal slices [15], and there may be concomitant subchondral BME in the cartilaginous compartment [11] and/or degenerative changes [18].

Bipartite iliac bony plate is frequent, especially in women [11–13,15–20,22], and is sometimes accompanied by pain [23]. The changes consist of a cleft-like appearance in the posterior part of the iliac bone, which is easily detected on semi-axial MR-images. Appearing on semi-coronal images as a channel parallel to the joint space filled with vessels, it can mimic BME and/or erosion (Fig. 4).

Crescent-like iliac bony plate and semicircular defects are relatively rare variations consisting of a concave configuration of the iliac bone with relatively congruent bulging of the opposite sacral bone [11,12,15–20,22] (Fig. 4) and focal rounded well-defined concave depressions in the sacral and/or iliac bone [12,13,15,17], respectively.

Anatomical variations involving the sacrum also include the frequently occurring lumbosacral transitional vertebrae [24,25], which may alter the load-related strain on the SIJ and elicit subchondral BME mimicking sacroiliitis, especially if there is lumbosacral asymmetry.

MRI FINDINGS IN HEALTHY INDIVIDUALS

Subchondral BME mimicking sacroiliitis can occur in healthy individuals [26▪▪,27,28], particularly in athletes and military recruits [5,9,27,29,30]. Areas of BME fulfilling the ASAS (Assessment of SpondyloArthritis international Society) MRI classification criteria (highly suggestive axSpA changes and $\geq$2 BME lesions on one slice or $\geq$1 BME on $\geq$2 slices [1,2]) were reported in 11.6–23.4% of healthy individuals aged below 50 years [27,28]. However, the extent of BME was usually limited, and BME exceeding a data-driven threshold with at least 95% specificity for axSpA (Table 1[31]) was present in only 2.5% [26▪▪]. The strain-related BME observed in healthy athletes and military recruits was somewhat similar although often more pronounced with 4.3–41% of the study participants fulfilling ASAS criteria [5,27,29,30].

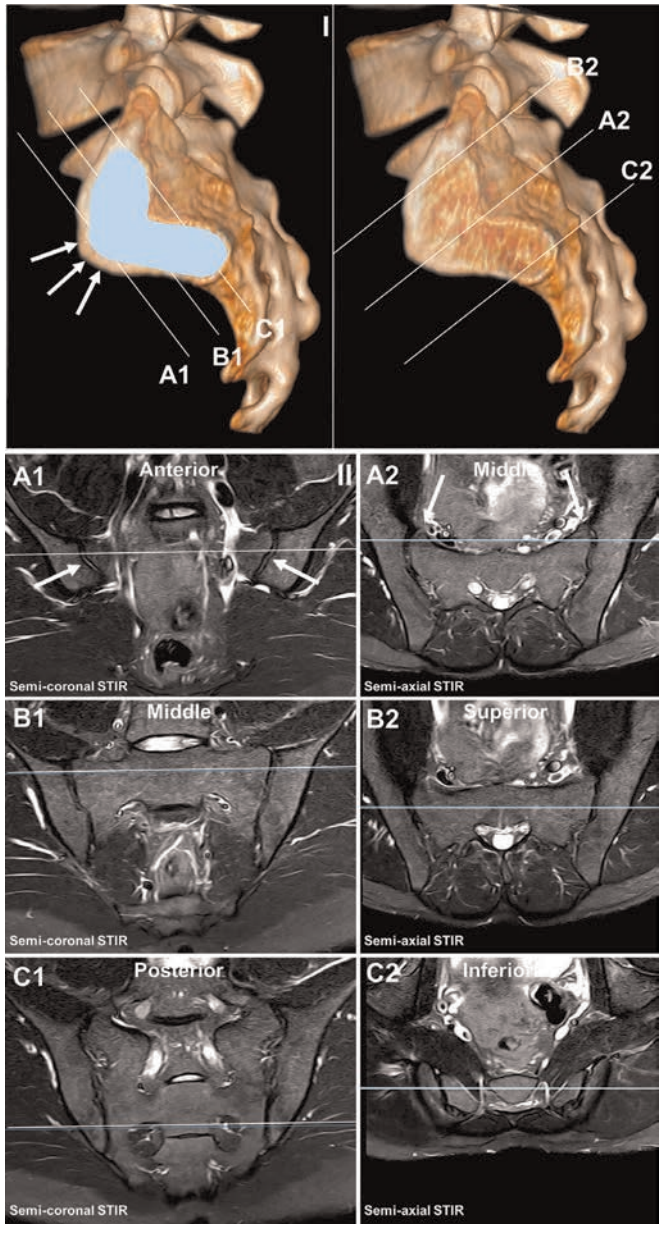

FIGURE 1. MRI slice orientations. (I) A lateral 3D CT-reconstruction of the sacral side of the sacroiliac joint with the light blue area on the left image delineating the cartilaginous covered joint surface. The slice orientation of semi-coronal (left) and semi-axial (right) scan planes are illustrated with the lines a1, b1, and c1 showing the location of anterior, middle, and posterior semi-coronal slices and a2, b2, and c2 the location of middle, superior, and inferior semi-axial slices, respectively. The arrows point to the most frequent location of load-related changes. (II) Corresponding MRI in a 31-year-old man with L4/L5 disk protrusion and no clinical or biochemical axial spondyloarthritis suspect changes; semi-coronal STIR in the anterior (a1), middle (b1), and posterior part of the joints with corresponding semi-axial slices. The computer-generated scout lines connecting the semi-coronal and semi-axial slices are shown and illustrate that the anterior semi-coronal slice (a1) correspond to a semi-axial slice in the middle portion of the joints (a2), the areas where load-related changes are most frequent (arrows on a1 and a2). The superior (b2) and inferior (c2) semi-axial slices are located on more posterior semi-coronal slice (b1 and c1, respectively). STIR, Short Tau Inversion Recovery.

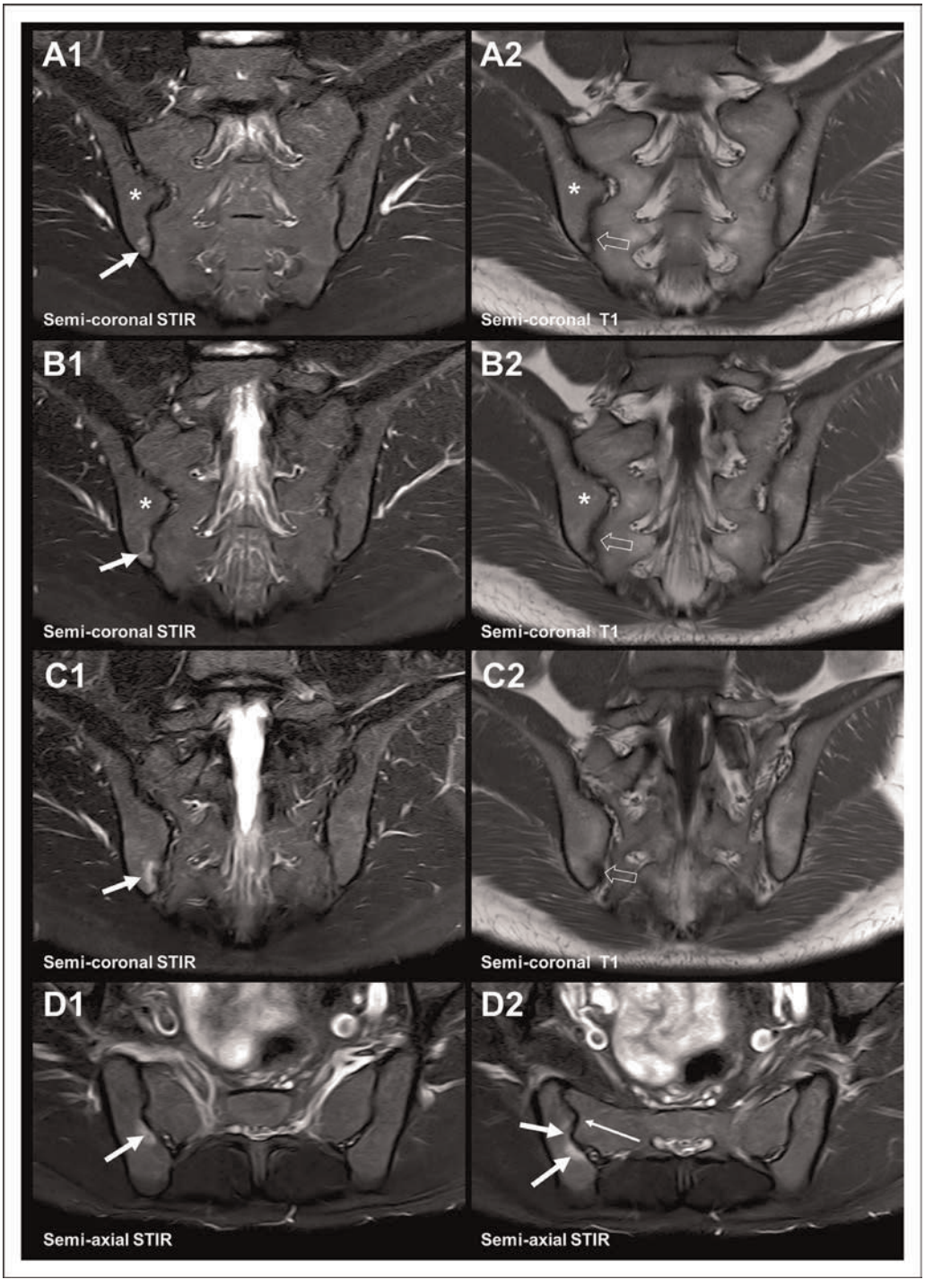

FIGURE 2. Dysmorphic joint changes and iliosacral complex with concomitant bone marrow edema. MRI in a 28-year-old man with recurrent low back pain for 2 years caused by L5/S1 disk degeneration with posterior disk protrusion; no clinical or biochemical findings suggesting sacroiliitis. Three consecutive semi-coronal STIR (a1, b1, c1) and corresponding T1-weighted images (a2, b2, c2) posteriorly in the SIJ with supplementary semi-axial STIR images at the lower part of the joints (d1 and d2). There is subchondral BME posterior/inferior in the right ileum on all semi-coronal STIR images (arrows on a1, b1, c1). The BME is related to dysmorphic joint changes visible on the semi-axial images as an iliac prominence into the middle of the sacral joint facet (long slim arrow on d2). There is also a right-sided iliosacral complex between the first and second sacral segment (asterisks on a1, a2, b1, b2). The BME causes decreased signal on T1-weighted images (open arrows on a2, b2, c2), but there are no erosions. BME, bone marrow edema; SIJ, sacroiliac joint; STIR, Short Tau Inversion Recovery.

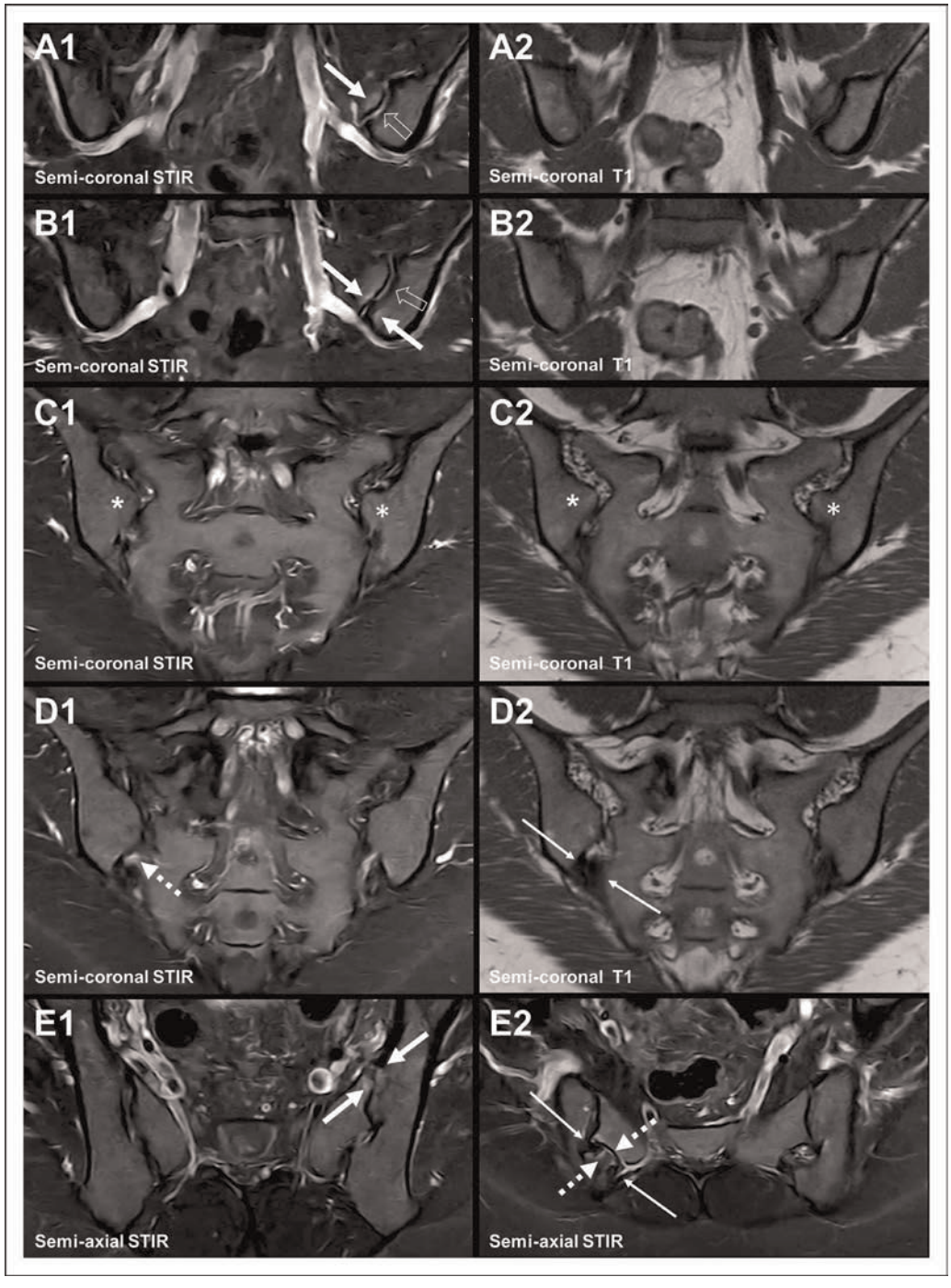

FIGURE 3. Accessory sacroiliac joint and iliosacral complex with concomitant bone marrow edema. MRI in a 27-year-old woman with pelvic pain due to a gynecological tumor. No clinical or biochemical findings suggesting sacroiliitis. Semi-coronal STIR (a1, b1, c1, d1) and corresponding T1-weighted images (a2, b2, c2, d2), two consecutive images anteriorly (a1/a2, b1/b2) and two consecutive images posteriorly (c1/c2, d1/d2) in the joint with supplementary semi-axial STIR images at the middle (e1) and lower part (e2) of the joints. There is bilateral iliosacral complex between the first and second sacral segment (asterisk on c1, c2) and a right-sided accessory joint (long slim arrows on d2, e2). There is concomitant subchondral BME anteriorly at the left SIJ (white arrows on a1, b1, e1) and joint fluid (open arrows on a1, b1). The accessory joint is seen on both the semi-coronal and semi-axial images (long slim arrows on d2, e2), but the exact location of adjacent BME (dashed arrows on d1, e2) is only visualized on the semi-axial image (e2). BME, bone marrow edema; SIJ, sacroiliac joint; STIR, Short Tau Inversion Recovery.

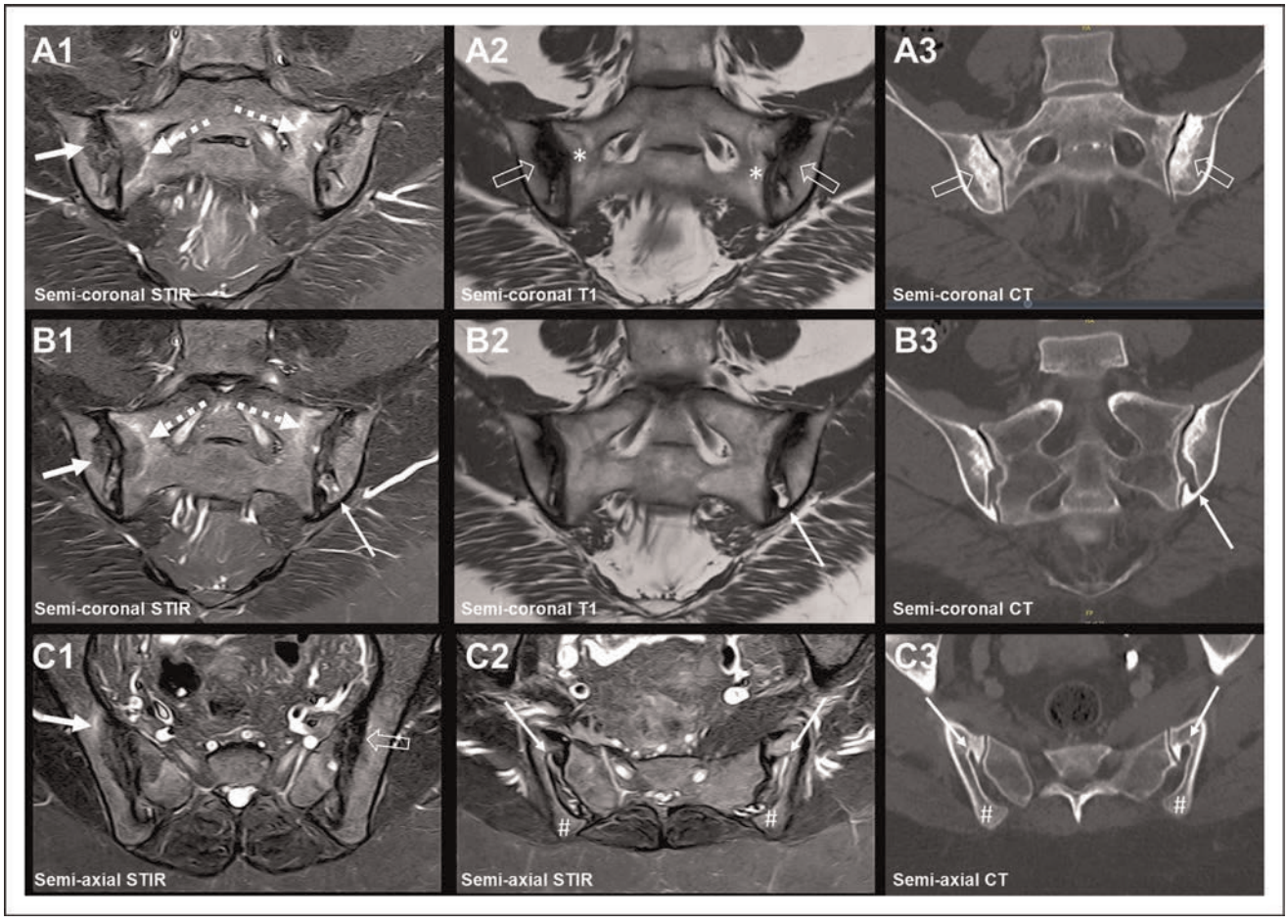

FIGURE 4. Bipartite and crescent-like iliac bony plate, and osteitis condensans ilii. MRI in a 44-year-old woman with buttock pain after her second pregnancy 2 years previously, but no clinical axial spondyloarthritis suspect changes; normal CRP and HLA-27 negative. Two semi-coronal STIR (a1, b1) and corresponding T1-weighted images (a2, b2) with supplementary semi-axial STIR images at the middle (c1) and lower part of the joints (c2) and CT images in the same slice orientations (a3, b3, c3). A bilateral bipartite variation is seen at the lower posterior part of the joints with fluid filled vessels surrounded by fat in the clefts (long slim arrows on b1, b2, b3, c2, c3), most pronounced on the left side. The semi-axial images show a concave configuration of the iliac bone (# on c2, c3) with relatively congruent bulging of the opposite sacral bone, consistent with crescent-like iliac bony plate, most pronounced on the right side. The osteitis condensans ilii changes consist of manifest bilateral iliac sclerosis anteriorly in the ilium (open arrows on a2, a3) with surrounding BME (arrows on a1, b1, c1) in addition to subchondral fat lesions in the sacrum (asterisks on a2) surrounded by BME (dashed arrows on a1, b1). BME, bone marrow edema; CRP, c-reactive protein; SIJ, sacroiliac joint; STIR, Short Tau Inversion Recovery.

Based on semi-coronal MR images, the most frequent location of BME in healthy individuals and athletes/military recruits was the superior portion of the sacrum and the inferior ilium [27,28,30]. However, the addition of semi-axial images reduced the prevalence of BME in the lower posterior ilium by showing that some 'BME' was actually related to vascular signals, deep ligament insertion containing vascular signals, or fluid-filled bone cysts giving the impression of BME on semi-coronal STIR images [9]. Two-plane assessment decreased the proportion of ASAS-positive individuals by 33–56%, and confirmed that the anterior sacrum was the most frequent site of strain-related BME [3] (Fig. 5).

Erosions and fat lesions have also been reported in healthy individuals and in athletes/military recruits. Prevalences of at least one erosion or erosions in at least one quadrant varied between 0 and 20%, whereas areas of fatty lesions occurred in 4–20% [5,26,28–30,32▪▪]. Erosions exceeding an at least 95% axSpA threshold was rare, but fat thresholds were exceeded in 2–7% of healthy individuals [5,26▪▪,28,32]. The occasional occurrence of irregular joint surface due to joint contour variation, strain, or degenerative changes and anatomical variations can mimic erosions [26▪▪], and physiological regression of erythropoietic bone marrow may mimic fat lesions. In addition, a contextual assessment of all

Table 1. Proposed cut-offs for sacroiliac joint MRI lesions with a specificity at least 95% for axial spondyloarthritis

ASAS group cut-offs [31]	Leiden cut-offs [32]
BME in ≥4 SIJ quadrants with BME at any location	
BME at the same location on ≥2 consecutive slices	
Erosions in ≥3 SIJ quadrants with erosion at any location	≥3 erosions[a]
Erosions on ≥2 consecutive slices	
Fat lesion in ≥5 quadrants with fat at any location	≥3 fatty lesions[a]
Fat lesion on ≥3 consecutive slices	
Fat lesion >1 cm in depth in ≥1 SIJ quadrants	≥5 erosions and/or fat lesions[a]

Data-driven cut-off values for single MRI lesions shown to have a specificity of at least 95% for axSpA based on the ASAS Classification Cohort [31], and a Dutch cohort of axSpA and control patients [32], respectively. ASAS, Assessment of SpondyloArthritis international Society; BME, bone marrow edema; SIJ, sacroiliac joint; quadrant, one SIJ area in an MRI slice where the joint is divided into four areas, upper and lower iliac and sacral areas, respectively. BME lesions in quadrants are usually assessed on six semi-coronal STIR images (48 per patients) and structural changes on five semi-coronal T1-weighted images (40 per patient) according to the SPARCC (Spondyloarthritis Research Consortium of Canada) scoring system.
[a]Each lesion seen on at least two consecutive slices.

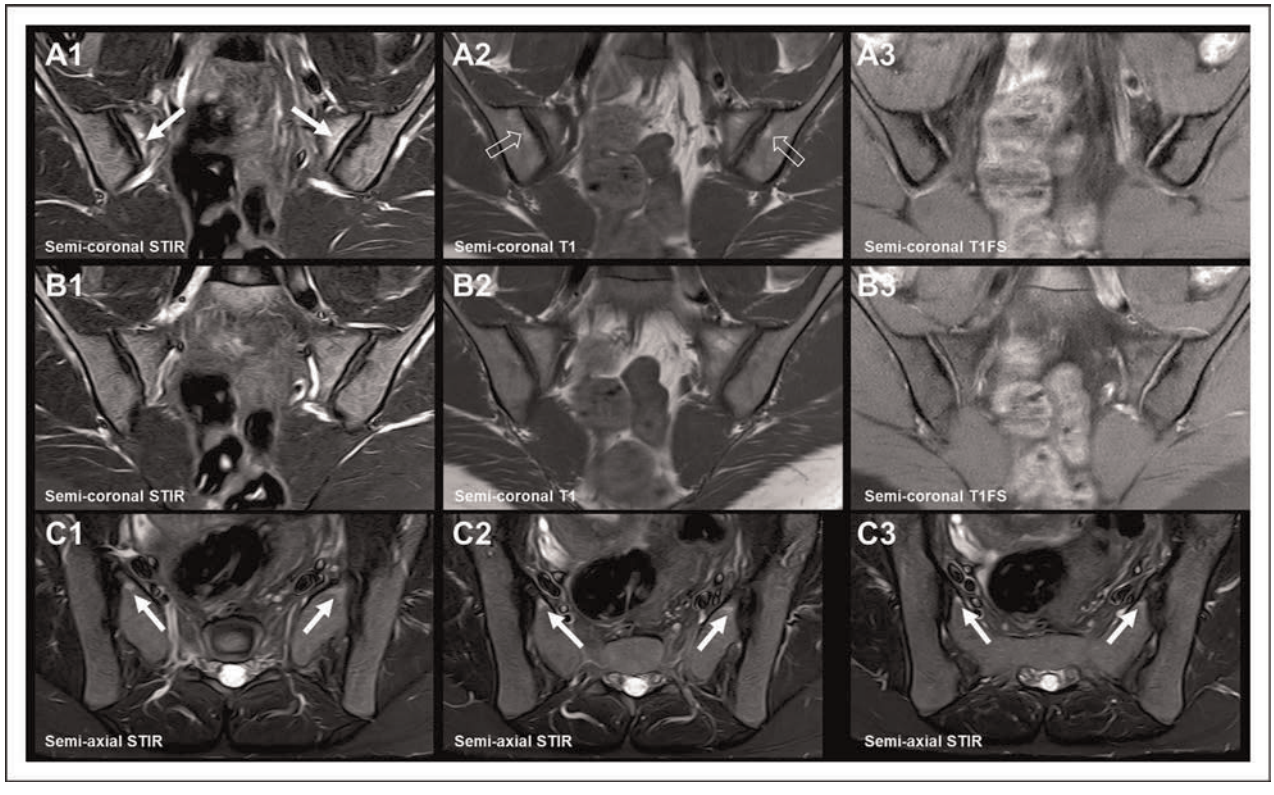

FIGURE 5. Load-related bone marrow edema and fat lesions. MRI in a 29-year-old woman with a BMI of 25 kg/m^2 and buttock pain starting after a twin pregnancy with delivery 18 months previously, but no clinical or biochemical findings suggesting sacroiliitis. Two consecutive semi-coronal STIR (a1, b1) and corresponding T1-weighted (a2, b2) and T1FS images (a3, b3) anteriorly in the joints and consecutive semi-axial STIR images at the upper and middle part of the joints (c1, c2, c3). There is symmetrical subchondral BME anteriorly in the sacrum on both sides (arrows on a1, c1, c2, c3) with concomitant fat lesions anterior/superior in the ilium (open arrows on a2), but no erosions (a3, b3). BME, bone marrow edema; SIJ, sacroiliac joint; STIR, Short Tau Inversion Recovery; T1FS, T1 fat suppressed.

sequences was rarely reported, although it is important as a combination of BME with erosions, and/or fat metaplasia has higher specificity in the diagnosis of axSpA sacroiliitis than one of these features on their own [33].

PREGNANCY-RELATED CHANGES

Pregnancy-related subchondral BME can be seen at any stage of pregnancy [34,35,36▪] and is frequent in postpartum women, occurring both with and without pain [5,27,34,35,37,38,39▪▪,40]. In a longitudinal study of 103 first-time mothers between gestational week 20 and 12 months postpartum, the prevalence of BME was found to be the highest at 3 months postpartum followed by a gradual decrease [34]. At 12 months postpartum, subchondral BME fulfilling the ASAS criteria occurred in 41% and 21% had BME exceeding an at least 95% axSpA threshold [34]. Other studies have confirmed a high prevalence of extensive BME in the early postpartum period [37,38] and a decrease during the first year postpartum, but persistence of considerable BME at 12 months postpartum [37,40]. The depth and intensity of BME may be as pronounced as in axSpA [5,27,34], which together with an extensive distribution may make it impossible to distinguish from inflammatory sacroiliitis, even at 12 months postpartum (Fig. 6). Fortunately, significant erosion is rare, which helps to differentiate between the conditions, although erosion-like lesions have been reported in up to 19% [5,34,37,38,40,41▪]. Postpartum, areas with BME may convert to areas with fat lesions or sclerosis [34,37,41▪], and subchondral sclerosis is especially frequent postpartum. It gradually increases during the first year, and a depth of at least 5 mm was reportedly present in 46% at 12 months postpartum, where 14% had a sclerosis depth of at least 8 mm, which may indicate the development of osteitis condensans ilii (OCI) [41▪].

Studies more than 1 year postpartum are rare, but the prevalence of BME fulfilling the ASAS criteria was reportedly present in 17% of women 2 years postpartum compared with 25% at 1 year postpartum [40]. In another study, 16% fulfilled the ASAS criteria 5 years postpartum compared with 15% at 6 months postpartum, but significant structural lesions suspicious for axSpA did not occur [39▪▪].

OSTEITIS CONDENSANS ILII

Characteristic OCI with manifest subchondral iliac sclerosis corresponding to the weight-bearing portion of the joint [42] can occur with or without pain [43▪]. It occurs predominantly in women, especially after pregnancy but is occasionally seen in men and nulliparous women [42,43▪,44,45], where it is often related to obesity or excessive load to the SIJ.

MRI findings consist of manifesting subchondral iliac sclerosis, located anteriorly and predominantly in the middle third of the joint with a reported depth of sclerosis varying between 11 and 13 mm continuously from the articular surface [44] (Fig. 4). Concomitant BME is frequent, observed in 48–93% of study participants and predominantly located at the anterior part of the SIJ [43▪,44,45]. The BME displays high signal intensity on STIR/T2FS images [43▪,44]. While it is reported that the depth of BME can be more than 10 mm, this is rare in the ilium where the BME is most often located peripheral to the subchondral sclerosis and usually seen as a thin continuous bright line [44] (Figs. 4 and 6), whereas iliac BME in sacroiliitis is subchondral and more widespread [45]. Sacral subchondral BME is frequent and is usually located at the strain-related areas anteriorly. Significant erosions are rare, but fat lesions are frequent, especially in the sacrum [43▪,45]. Despites these OCI characteristics, OCI MRI changes may be difficult to differentiate from sacroiliitis, and clinical findings such as previous childbirth and absence of clinical axSpA signs, HLA B27, and increased CRP has to be taken into account [45].

SACROILIAC JOINT CHANGES RELATED TO CHRONIC LOW BACK PAIN AND JOINT DEGENERATION

SIJ MRI findings are frequent in patients with chronic non-axSpA low back pain (LBP). In a study of 1037 patients aged 18–40 years with chronic LBP, BME fulfilling the ASAS MRI classification criteria occurred in 21.4% and fat lesions, sclerosis, and erosions in 14.5, 8, and 7.7% of the patients, respectively [46]. Only 2.4% of these patients turned out to have axSpA sacroiliitis at 3.5-year of follow-up [47]. The reported prevalences of SIJ MRI lesions in other groups of patients with non-axSpA LBP were rather similar with BME occurring in up to 20.7%, and erosions and fat lesions in 5.3–9 and 0–12.3% of the patients, respectively [26▪▪,27,32]. However, deep BME was not reported in non-axSpA patients, and erosions and fat lesions exceeding data-driven at least 95% axSpA thresholds were rare [26▪▪,27,32]. BME and erosions in non-axSpA LBP patients are most frequent at the load-related anterior joint portion, whereas they are more widespread in axSpA patients [23,48].

Degenerative SIJ changes are far more frequent than axSpA sacroiliitis [49]. They are common in middle-aged and elderly individuals but can occur already in the 20s [12]. If classical signs of

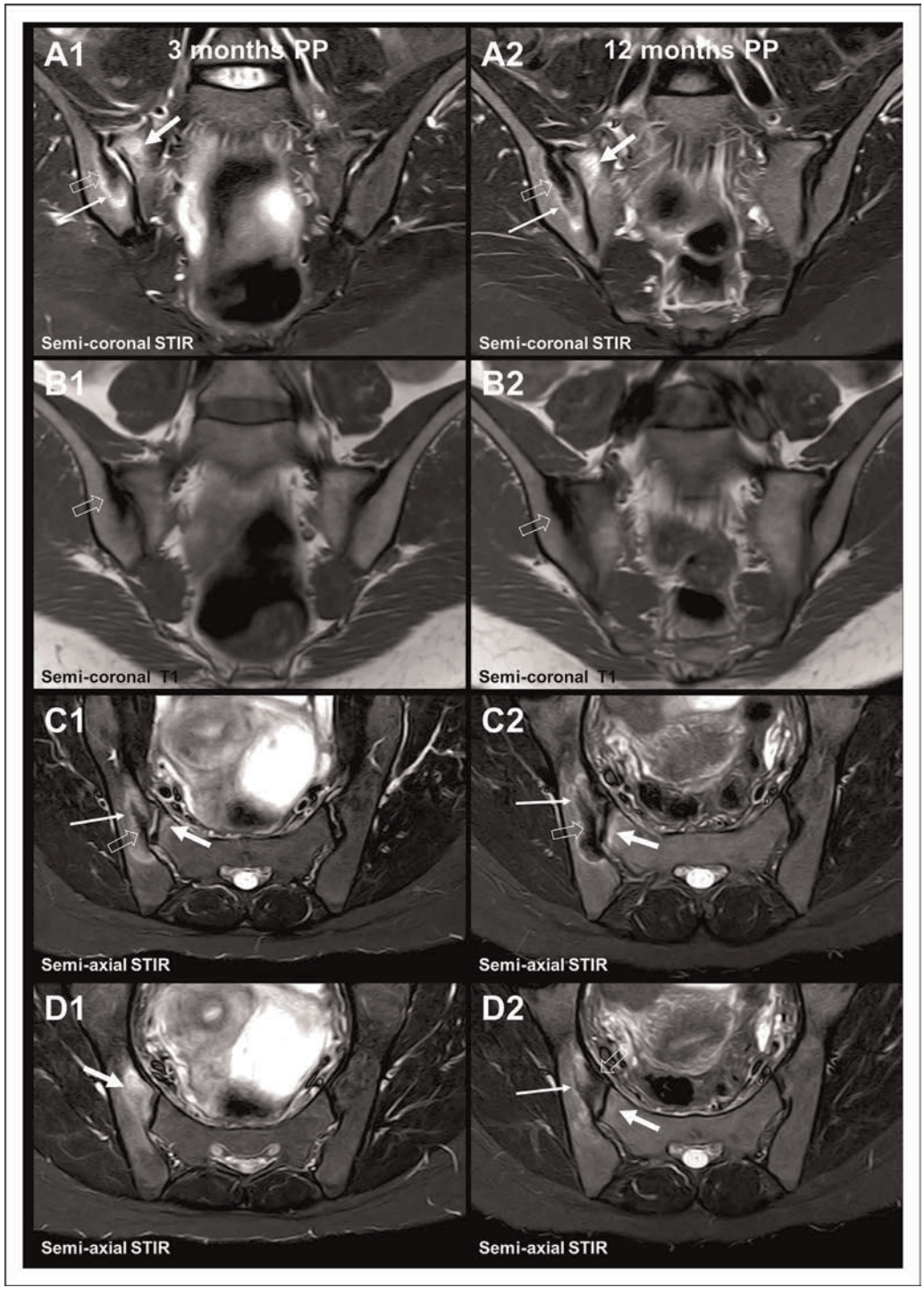

FIGURE 6. Postpartum changes. MRI in a 32-year-old volunteer woman without any back pain; normal CRP and HLA-27 negative. Semi-coronal STIR and corresponding T1-weighted images anteriorly in the joints and two semi-axial STIR images in the middle part of the joints at 3 months (a1, b1, c1, d1) and 12 months postpartum (a2, b2, c2, d2). Three months postpartum, there is pronounced subchondral BME in the ilium and sacrum at the right SIJ (arrows on a1, c1, d1) with additional subchondral sclerosis in the ilium (open arrows on a1, b1, c1) surrounded by a continuous rim of edema (slim arrows on a1, c1). At 12 months postpartum, the subchondral iliac BME is diminished, whereas the sclerosis has progressed (open arrows on a2, b2, c2, d2), and there is still a rim of edema at the periphery (slim arrows on a2, c2, d2). The sacral edema has increased in intensity as well as extent (arrows on a2, c2, d2). BME, bone marrow edema; CRP, c-reactive protein; PP, postpartum; SIJ, sacroiliac joint; STIR, Short Tau Inversion Recovery.

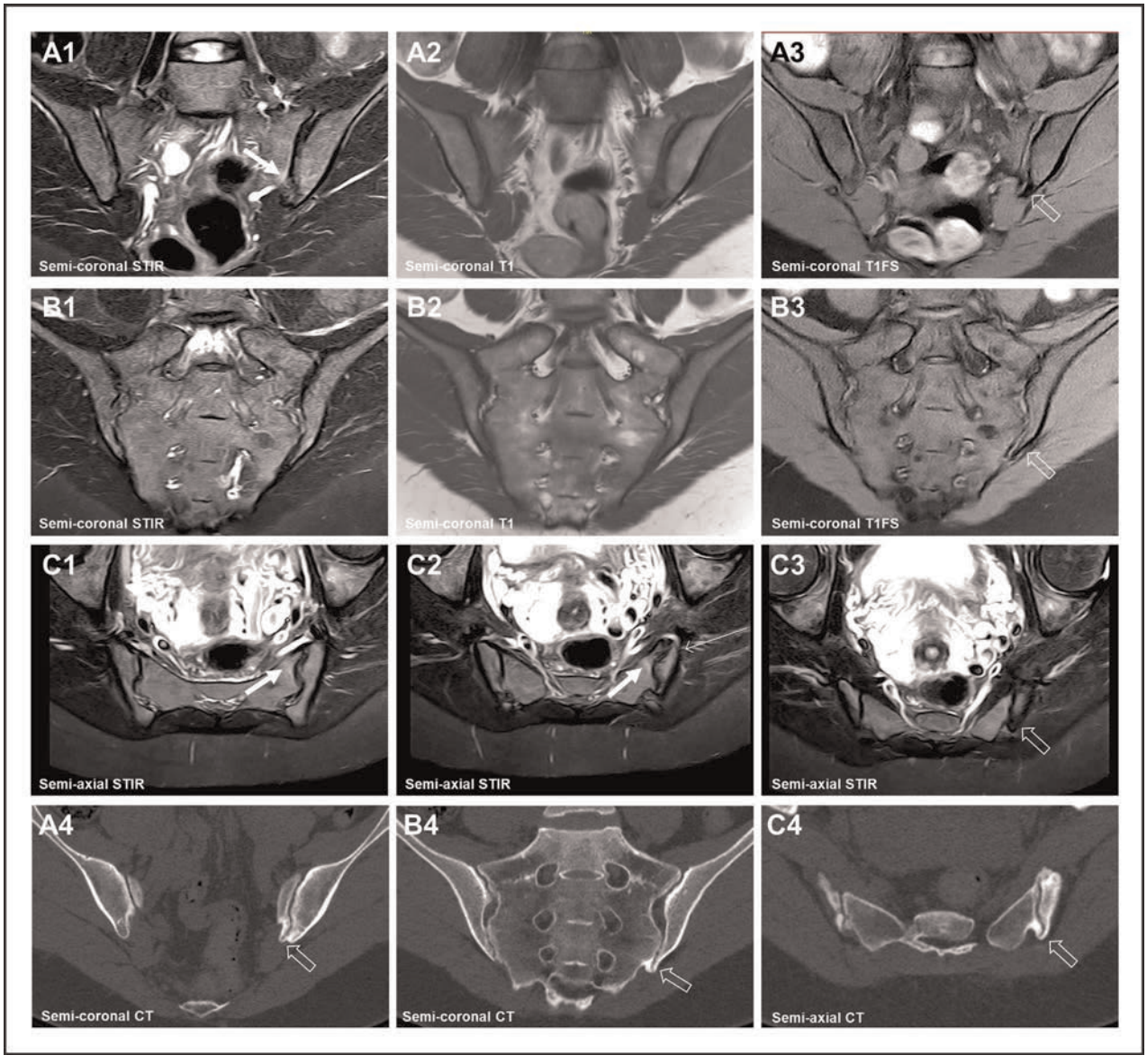

FIGURE 7. Degenerative changes. MRI in a 35-year-old woman with low back pain, but no clinical or biochemical axial spondyloarthritis suspect changes. Semi-coronal STIR and corresponding T1-weighted and T1FS images anteriorly (a1, a2, a3) and posteriorly (b1, b2, b3) in the joints with concomitant semi-axial STIR images at the middle (c1) and lower part of the joints (c2, c3), and CT images in the same slice orientations (a4 corresponding to a1–a3, b4 to b1–b3 and c4 to c3). There is slight subchondral BME anteriorly in the sacrum on the left side (arrows on a1, c1) and slightly irregular joint facets without erosion, but the T1FS images show osteophyte formation anteriorly and posterior/inferior at the left SIJ (open arrows on a3, b3). The manifest osteophyte formation seen on the CT images (open arrows on d2, d3) are very difficult to detect on T1 and STIR images, and on T1FS the osteophyte formation posterior/inferior is seen only as a signal void mass (open arrow on c3) and is more difficult to appreciate compared to the osteophytes that are obvious on CT. BME, bone marrow edema; SIJ, sacroiliac joint; STIR, Short Tau Inversion Recovery; T1FS, T1 fat suppressed.

degenerative changes (joint space narrowing, osteophytes, sclerosis, and subchondral cysts [8,20]) are not detected, the MRI findings can mimic sacroiliitis. It may be difficult to detect specific degenerative features by MRI due to a relatively poor visualization of minor osseous changes such as osteophytes. The use of a sequence designed for visualizing the bone–cartilage interface (Fig. 7) or sequences producing CT-like images [synthetic computed tomography (sCT)] can facilitate the assessment. Using sCT it has been shown that only 55% of osteophytes seen by sCT were visible by MRI [50].

DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS

Diffuse idiopathic skeletal hyperostosis (DISH) can involve the SIJ [51] and may be accompanied by back pain and stiffness [52]. SIJ MRI changes usually consist of extra-articular ossified bridges related to the SIJ ligaments and capsule, sometimes accompanied by partial fusion in the upper part of the SIJ, but the lower two-thirds of the joint space is usually spared [53]. There may be concomitant BME at the base of bone bridges and fat lesions, but significant erosions are rare [52].

INFECTIOUS SACROILIITIS

Infectious sacroiliitis is a relatively rare condition with variable clinical signs, but usually more acute symptoms than in axSpA [54]. MRI changes are typically unilateral with extensive BME, often with a sacral predominance or an even distribution and not an iliac predominance as in axSpA [54,55,56▪]. There is usually concomitant joint fluid accumulation, distended inflamed capsule, and periarticular edema including muscle edema with or without periarticular abscess formation [54,56▪], whereas axSpA changes are limited to the bone and intra-articular space. Erosions usually supervene and joint space narrowing, bone bridging, fat lesions, and ankylosis may develop when the infection is chronic or after treatment [55].

SACRAL FRACTURES

Sacral stress fractures seen in healthy young adults [57,58] or insufficiency fractures occurring in weakened bone after minimal or unrecognized trauma [59–61] will present on MRI with sacral BME, which can mimic sacroiliitis if involving the peripheral subchondral areas. However, the BME is usually most pronounced around fracture lines, which are best visualized on T1-weighted or T2-weighted images, presenting as black lines, which together with the lack of erosions can be used to differentiate the changes from sacroiliitis [3].

OTHER CONDITIONS

Whipple's disease can cause sacroiliitis indistinguishable from axSpA [62]. Crystalline arthropathies occasionally affect the SIJ, usually with a non-specific appearance. Findings in gout [63] include a mixture of intraarticular joint fluid, erosions filled with a material of intermediate-to-low signal intensity on all sequences and accompanying subchondral BME [3,64]. Subchondral BME may be profound in patients with acute attacks of calcium pyrophosphate dihydrate (CPPD) deposition [3,65]. Chronic non-bacterial osteitis (CNO) may present with osseous inflammation [3,66], but SIJ changes are typically unilateral and in early stages confined to one bone, with BME often accompanied by articular erosion [3]. However, osseous hyperostosis and sclerosis with concomitant fat metaplasia usually supervene, and there is often CNO lesions in other skeletal regions. In hyperparathyroidism, subchondral bone resorption is bilateral and symmetrical on the iliac side, and gross erosion-like lesions may cause pseudo-widening of the joint [3,67,68]. There may be concomitant subchondral BME [3], but joint space narrowing or bone bridging/ankylosis and sacral-sided erosions are not seen [67].

CONCLUSION

The most frequent conditions that mimic active sacroiliitis on MRI are anatomical variations and pregnancy-related or other strain-related conditions. The topographic location of BME lesions should always be considered, and the findings should be interpreted in the appropriate clinical context, especially in young active individuals and post-partum women. A contextual assessment of all MRI sequences is important. BME is not only the most sensitive finding but also lacks specificity in certain settings, whereas erosions are more specific findings for axSpA. In patients with extensive erosion, there are only a few relevant differentials such as infection, other inflammatory conditions, and metabolic disorders.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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What's next in psoriatic arthritis therapy? A look at the pipeline

Enrique R. Soriano

Purpose of review
Psoriatic arthritis (PsA) outcomes have improved, yet many patients do not achieve sustained control, and a meaningful proportion develop difficult-to-treat disease. This review summarizes relevant new therapies in the PsA pipeline and highlights emerging strategies likely to shape near-term care, including interception, metabolic targeting, combination/sequence approaches, and early precision-medicine efforts.

Recent findings
Pipeline innovation clusters in three areas: interleukin (IL)-17 pathway advances, including dual IL-17A/IL-17F blockade and engineered formats (nanobodies/small scaffolds) that may alter tissue pharmacology; selective tyrosine kinase 2 inhibition (allosteric and highly selective catalytic-site inhibitors) expanding oral options; and oral IL-23 receptor antagonism progressing from strong psoriasis efficacy into phase 3 PsA development. Beyond new molecules, strategies are evolving. Exploratory evidence supports further evaluation of dual-targeted approaches for highly refractory PsA, while metabolic targeting with incretin-based therapy is being tested as an adjunct to immunomodulation to address obesity-linked inflammatory amplification and cardiometabolic risk. EULAR transition frameworks, prodromal musculoskeletal symptoms and imaging abnormalities support a plausible interception window in at risk psoriasis.

Summary
The next wave in PsA will be defined by both new agents and smarter strategies: more oral/selective therapies, testing interception in risk-enriched psoriasis, integrating metabolic approaches, and evaluating optimized sequencing and selected combination therapy while precision tools mature.

Keywords
disease interception, interleukin-17A/interleukin-17F blockade, interleukin-23 receptor antagonism, psoriatic arthritis, therapeutic pipeline, tyrosine kinase 2 inhibition

INTRODUCTION

Psoriatic arthritis is a heterogeneous inflammatory disease affecting peripheral joints, entheses, digits, spine, skin, and nails [1]. Despite several approved therapeutic classes, a meaningful proportion of patients do not achieve treat-to-target states such as minimal disease activity (MDA) or low disease activity, and drug survival in routine practice is limited by partial response, adverse events, and access barriers [2]. An increasing subset meets contemporary concepts of difficult-to-treat (D2T) psoriatic arthritis (PsA), reflecting persistent symptoms and/or inflammation despite appropriate use of multiple therapies, often compounded by comorbidities and contextual factors [3,4]. Unlike psoriasis (PsO), where, with modern biologics and targeted therapies, complete or near-complete skin clearance is now a realistic therapeutic target, PsA remains harder to control across its multiple domains [2,5].

Fortunately, the PsA therapeutic pipeline remains highly active, with multiple agents and platforms under development to improve efficacy across domains and expand convenient oral options. Two trends stand out. First is increasing precision: greater pathway selectivity [e.g., selective tyrosine kinase 2 (TYK2) inhibition], broader cytokine neutralization within a pathway [e.g., interleukin (IL)-17A/IL-17F], and engineered molecular formats that may modify pharmacology at inflamed tissues (nanobodies and small protein scaffolds), often coupled with a shift toward orally administered targeted therapies. Second is moving earlier: risk-based intervention in psoriasis patients at high risk of

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KEY POINTS

- Novel interleukin (IL)-17 approaches (including dual IL-17A/F blockade and smaller engineered formats) may raise the ceiling of multidomain response in psoriatic arthritis (PsA).
- Selective tyrosine kinase 2 inhibition and oral IL-23R antagonism are expanding the prospect of biologic-like pathway targeting in oral formulations.
- Imaging abnormalities and nonspecific musculoskeletal symptoms in psoriasis define a plausible interception window for preventing clinically classifiable PsA.
- Combination and sequential biologic strategies are emerging for difficult-to-treat PsA but require stronger efficacy–safety evidence before broader use.
- Metabolic targeting (GLP-1/dual incretin therapy) may complement immunomodulation by addressing obesity-linked inflammatory amplification and cardiometabolic risk.

developing PsA, and in symptomatic psoriasis patients with subclinical inflammation, to delay or prevent progression to clinically classifiable PsA.

In parallel, therapeutic strategy is evolving – toward more deliberate sequencing informed by emerging precision-medicine approaches (clinical phenotype, imaging and biomarkers to predict response), and, in selected difficult-to-treat cases, exploratory combination or dual-targeted strategies to address persistent multidomain disease.

PREVENTION AND INTERCEPTION

Risk enrichment and candidate populations

Only around 30–40% of patients with psoriasis develop PsA. Epidemiologic studies have identified modifiable risk factors, including obesity and weight gain, while clinical features such as nail disease, higher psoriasis severity, and musculoskeletal symptoms (particularly arthralgia) enrich risk [6–9]. A staged concept of transition from PsO to PsA, ranging from PsO at higher risk, through a subclinical phase, to clinically overt PsA, is increasingly used to frame prevention and interception strategies [10,11]. In this framework, nonspecific arthralgia/musculoskeletal symptoms and imaging abnormalities are complementary but distinct indicators of progression: arthralgia can mark a symptomatic prodrome, whereas ultrasound power Doppler enthesitis and MRI inflammatory lesions support a subclinical inflammatory phase, together suggesting an interception window at the skin-to-joint transition [9,10,12]. These observations justify enriched cohort designs in which symptomatic psoriasis patients undergo targeted imaging and longitudinal follow-up [13] (Table 1).

Do psoriasis therapies modify future psoriatic arthritis risk?

Observational studies examining whether systemic psoriasis therapy modifies future PsA risk have yielded mixed results, largely due to confounding by indication and protopathic/channeling bias [13,14]. Nonetheless, several cohorts suggest a possible reduction in incident PsA with biologic therapy [including tumor necrosis factor (TNF) inhibition], with hazard ratios in propensity-matched analyses around 0.3 in some datasets [15–19].

Additional real-world datasets suggest class-dependent differences, with several analyses reporting lower rates of incident inflammatory arthritis among patients treated with IL-23/IL-12/23 inhibitors compared with TNF inhibitors and, in some studies, IL-17 inhibitors, although residual confounding remains difficult to exclude because biologic choice is strongly influenced by skin vs. musculoskeletal phenotype at baseline [18,20–23].

Taken together, current evidence supports biological plausibility and consistent observational signals that systemic therapy, particularly when initiated early, may delay or reduce PsA onset in selected psoriasis populations, but prospective, risk-enriched trials are required to establish causality. The PAMPA trial, enrolling psoriasis patients at increased risk/with early musculoskeletal symptoms, is expected to provide more definitive evidence on whether targeted intervention in psoriasis can prevent or delay progression to clinically classifiable PsA [24].

LATE-STAGE AND PRACTICE-RELEVANT PIPELINE THERAPIES

Interleukin-17 pathway innovation

IL-17 biology integrates cutaneous and musculoskeletal inflammation and remains central to PsA, particularly for patients with prominent skin disease, nail involvement, enthesitis and axial symptoms. Pipeline innovation is occurring through broader cytokine neutralization within the IL-17A-F pathway and through novel molecular formats intended to optimize distribution and target engagement (Table 2).

Dual interleukin-17A/interleukin-17F blockade: bimekizumab

Bimekizumab neutralizes IL-17A and IL-17F. Long-term extension data from pivotal PsA programs

Table 1. Observational evidence on whether systemic psoriasis therapies may modify future PsA risk

Study	Population/setting	Exposure vs. comparator	Outcome definition	Effect estimate/direction (as reported)	Key caveats
Biologic class comparisons (within biologics/targeted therapy)					
Strober *et al.* 2024 (USA) [57]	Biologic-naïve PsO patients initiating IL-23, IL-12/23, IL-17A or TNF inhibitors	Exposure: Biologic-naïve PsO patients initiating IL-23, IL-12/23, IL-17A or TNF inhibitors; Ref: IL-23 inhibitors	Incident inflammatory arthritis (including PsA) based on ICD codes	7144 PsO pts in Optum Clinformatics (2007–2023). Incidence rates per 100 PY: 4.99 (IL-23i), 7.29 (IL-17Ai), 6.06 (IL-12/23i), 9.39 (TNFi). Adjusted HRs vs. IL-23i: IL-17Ai HR 1.44 ($P=0.0294$) and TNFi HR 1.90 ($P<0.0001$); IL-12/23i not significantly different.	Optum Clinformatics Data Mart; retrospective cohort of biologic initiators; Multivariable Cox models using IL-23 as reference; adjusted for demographics, comorbidities and treatment history
Singla *et al.* 2023 (multicountry, USA-centred) [23]	New users of TNFi, IL-17Ai, IL-23i, IL-12/23i for PsO	Exposure: New users of TNFi, IL-17Ai, IL-23i, IL-12/23i for PsO; Ref: TNFi	Incident inflammatory arthritis (PsA or other IA) based on diagnostic codes after biologic start	Mean follow-up ≈2.4 years. IL-12/23 and IL-23 inhibitors showed significantly lower risk of incident IA than TNFi; IL-17Ai showed no significant difference vs. TNFi.	TriNetX US EHR network; retrospective cohort (~15 500 PsO pts); Weighted Cox proportional hazards with extensive covariate adjustment and propensity methods
Cho *et al.* 2025 (South Korea) [20]	New users of IL-23i, IL-17Ai, IL-12/23i, TNFi for PsO	Exposure: New users of IL-23i, IL-17Ai, IL-12/23i, TNFi for PsO; Ref: TNFi	Incident PsA (claims-based definition)	9499 PsO pts; 3.0% developed PsA over 23 275 PY. Any IL inhibitor vs. TNFi: HR 0.40 (0.25–0.62). IL-23i HR 0.22 (0.13–0.37); IL-17Ai HR 0.47 (0.28–0.80); IL-12/23i HR 0.46 (0.29–0.74). All IL-targeted classes associated with lower PsA risk than TNFi, greatest reduction with IL-23i	Korean nationwide health-insurance claims; retrospective cohort; Multinomial overlap weighting across classes; weighted Cox models; robust adjustment for demographics, comorbidities and psoriasis severity proxies
Yu *et al.* 2025 (USA) [58]	IL-23i users ($n\approx2273$) vs. IL-17Ai users ($n\approx2307$) with PsO	Exposure: IL-23i users ($n\approx2273$) vs. IL-17Ai users ($n\approx2307$) with PsO; Ref: IL-17Ai	Incident PsA (ICD-coded)	In TriNetX U.S. Collaborative Network, IL-23i were associated with lower PsA incidence vs. IL-17Ai: HR ≈0.60 (95% CI ~0.44–0.82).	TriNetX US Collaborative Network; retrospective cohort across multiple health systems; Cox regression with propensity adjustment; subgroup and sensitivity analyses (age, sex, ethnicity, reference TNFi)
Lin *et al.* 2025 (Taiwan) [59]	IL-23i vs. IL-17Ai (class-level and individual agents) in PsO	Exposure: IL-23i vs. IL-17Ai (class-level and individual agents) in PsO; Ref: Anti-IL-17Ai (class)	Incident PsA (claims-based)	In Taiwanese national claims, class-level IL-23i exposure was associated with significantly lower PsA risk than IL-17Ai	National Health Insurance database; retrospective cohort of biologic initiators; Propensity-score weighting and Cox models; analyses by biologic class and by individual drugs
Gisondi *et al.* 2025 (Italy) [21]	Biologic-naïve plaque PsO patients initiating TNFi, IL-17Ai or IL-23i	Exposure: Biologic-naïve plaque PsO patients initiating TNFi, IL-17Ai or IL-23i; Ref: TNFi	Incident PsA (rheumatologist-confirmed; clinical PsA)	Single-centre cohort of 622 PsO pts After IPTW, HR for PsA vs. TNFi: IL-17Ai 0.63 (95% CI 0.38–1.05); IL-23i 0.57 (0.34–0.96).	Verona bionaïve biologic cohort; retrospective observational study; Inverse-probability-of-treatment-weighted Cox regression comparing three biologic classes; careful balance of baseline covariates

Table 1 (*Continued*)

Study	Population/setting	Exposure vs. comparator	Outcome definition	Effect estimate/direction (as reported)	Key caveats
Floris *et al.* 2025 (Italy, DIAPSON cohort) [60]	TNFi, IL-17Ai, IL-23/12-23i vs. never-biologic	Exposure: TNFi, IL-17Ai, IL-23/12–23i vs. never-biologic; Ref: Never-biologic PsO patients	Prevalent PsA (peripheral ± axial), CASPAR	In 303 PsO pts with systematic rheumatology assessment, all biologic classes associated with lower odds of having PsA vs. never-biologic	DIAPSON monocentric PsO cohort; Multivariable logistic regression adjusted for PsA risk factors and PsO duration/ severity
Biologics vs. conventional systemic therapy (e.g., MTX)					
Watad *et al.* (Israel) [18]	PsO patients in Meuhedet HMO electronic database	Biologic/systemic vs. Methotrexate; topical-only therapy	Incident PsA (ICD codes)	Biologics vs. methotrexate: decreased risk HR 0.46 (0.35–0.62). Biologics vs. topical therapy only: increased risk HR 2.16 (1.44–3.24)	HMO electronic database; Cox proportional hazards model, adjusted; extensive confounder control
Biologics vs. topical/no systemic therapy					
Acosta Felquer *et al.* (Argentina) [15]	PsO patients in large health-care system	Biologic/systemic vs. Topicals/no systemic therapy	Incident PsA based on charts review (CASPAR)	Decreased risk with biologics vs. nonbiologic/no systemic therapy: HR 0.19 (0.05–0.81)	Health-care service EHR, manual review; Cox proportional hazards model with propensity-score matching
Floris *et al.* (Italy) [60]	DIAPSON monocentric cohort of PsO patients	Biologic/systemic vs. Nonbiologic systemic / topical therapy	Incident PsA, based on rheumatologists' assessment	Lower odds of having PsA in biologic-treated vs. never-biologic: OR 0.23 (0.15–0.36)	Prospective clinical cohort with rheumatologic assessment; Multivariable logistic regression adjusted for major PsA risk factors
Biologics/systemic therapy vs. phototherapy					
Gisondi *et al.* (Italy) [17]	Moderate–severe chronic plaque PsO, dermatology clinic	Biologic/systemic vs. nb-UVB phototherapy (and topical therapy in secondary analyses)	Incident PsA based on rheumatologists' assessment (CASPAR)	Decreased risk with bDMARDs vs. nb-UVB phototherapy: HR 0.5 (0.3–0.9). No clear association vs. topical therapy: HR 2.07 (0.87–4.93)	Manual review of EHR; Cox proportional hazards model with propensity-score matching
Rosenthal *et al.* (Israel) [61]	PsO patients treated within a health-care service	Biologic/systemic vs. ≥2 systemic drugs or ≥1 systemic + phototherapy	Incidente PsA (ICD codes)	Decreased risk with biologics: HR 0.66 (0.51–0.84)	Health-care service EHR; nested case–control; Cox proportional hazards model with propensity-score matching
Piaserico *et al.* (Italy) [62]	PsO patients in combined derm/rheum clinic	Biologic/systemic vs. nb-UVB phototherapy	Incident PsA based on rheumatologist assessment	Decreased risk with biologics vs. nb-UVB phototherapy: HR 0.32	Prospective clinical collection; Cox proportional hazards model with propensity-score matching
Meer *et al.* (USA) [19]	Large US PsO cohort from OptumInsights	Biologic/systemic vs. Nonbiologic systemic oral therapy or phototherapy	Incident PsA (ICD codes)	Increased risk among biologic-treated vs. nonbiologic systemic / phototherapy: HR 4.5 (4.2–4.7)	Optum EHR database; Cox proportional hazards model with propensity-score matching; outcome = any inflammatory arthritis, not only PsA

Table 1 (*Continued*)

Study	Population/setting	Exposure vs. comparator	Outcome definition	Effect estimate/direction (as reported)	Key caveats
Bar *et al.* (Israel) [16]	Newly diagnosed PsO patients; tertiary-care cohort	Biologic/systemic vs. No systemic DMARD (topical ± phototherapy)	Incident PsA based on ICD codes + clinical confirmation	Early MTX vs. no DMARD: early MTX associated with significantly lower PsA incidence (adjusted HR < 1; protective); late MTX less protective.	Retrospective cohort from rheum/derm clinic; Cox proportional hazards model adjusted for demographics, PsO duration and severity, and comorbidities
Miao *et al.* (USA) [22]	Adults with moderate–severe PsO receiving phototherapy, then either continuing phototherapy or switching to biologics	Biologic/systemic vs. Continued phototherapy (no biologic)	Incident PsA (ICD codes for PsO and PsA)	Biologic initiation vs. continued phototherapy: HR 0.66 (0.53–0.83)	Optum Clinformatics Data Mart, population-based claims; Multivariable Cox proportional hazards model adjusted for demographics, comorbidities, insurance, and oral systemic therapy

Grouped by type of comparison; effect estimates are as reported in the original studies/analyses.
ACR, American College of Rheumatology; bDMARD, biologic disease-modifying antirheumatic drug; CASPAR, Classification Criteria for Psoriatic Arthritis; CI, confidence interval; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; EHR, electronic health record; HR, hazard ratio; IA, inflammatory arthritis; ICD, International Classification of Diseases; IL, interleukin; IL-12/23i, IL-12/23 inhibitor; IL-17Ai, IL-17A inhibitor; IL-23i, IL-23 inhibitor; MTX, methotrexate; nb-UVB, narrow-band ultraviolet B; OR, odds ratio; PsA, psoriatic arthritis; PsO, psoriasis; TNF, tumor necrosis factor; TNFi, TNF inhibitor.
Observational studies cannot establish causality; confounding by indication, channeling, and outcome misclassification may influence estimates of risk modification.

report sustained improvements across joint and skin outcomes through approximately two years in both biologic-naïve and TNF inhibitor inadequate responder populations [25▪]. In plaque psoriasis, dual IL-17A/F blockade may offer incremental skin efficacy than IL-17A inhibition alone, supporting the biological relevance of IL-17F in cutaneous inflammation [26]. In PsA, however, a clear incremental benefit for arthritis outcomes over IL-17A-only inhibition has not been established, and available data primarily support durable multidomain efficacy rather than superiority vs. IL-17A-only agents. Safety is consistent with IL-17A pathway inhibition, with mucocutaneous candidiasis as an anticipated adverse event requiring clinical vigilance [25▪].

Nanobody-based interleukin-17A/interleukin-17F inhibition: sonelokimab

Sonelokimab is an IL-17A/IL-17F–targeting nanobody engineered with an albumin-binding domain to extend half-life and potentially enhance delivery to inflamed tissues. In the phase 2 ARGO trial, the primary endpoint (ACR50 at week 12) was met: 46.3–46.5% with sonelokimab (60–120 mg with induction) vs. 20.0% with placebo; key secondary endpoints were also positive [27▪▪]. Responses continued to improve through week 24, with high-threshold outcomes such as minimal disease activity achieved by a substantial proportion of participants. The smaller size of nanobodies compared with conventional monoclonal antibodies is hypothesized to improve tissue penetration and target engagement [28], although whether this translates into superior clinical performance in enthesitis or axial domains will require confirmation in larger studies.

Small-protein interleukin-17A inhibition: izokibep

Izokibep is an IL-17A-targeting agent in a small protein scaffold format, which may influence tissue distribution and pharmacology [28]. In a randomized, double-blind phase 2 study in active PsA, the primary endpoint (ACR50 at week 16) was met: 52% with izokibep 80 mg every 2 weeks vs. 13% with placebo ($P = 0.0006$). Minimal disease activity was also more frequent with izokibep (39–42% across 80 mg and 40 mg arms) vs. 5% with placebo [29▪▪]. Treatment-emergent adverse events were generally similar across groups, with injection-site reactions reported more often with active therapy [29▪▪]. Small-protein scaffolds aim to preserve high-affinity cytokine neutralization while potentially optimizing distribution to inflamed tissues.

Table 2. Late-stage and practice-relevant pipeline/strategy candidates in PsA (selected)

Agent	Mechanism/target	Route	Primary outcome (selected key result)
Bimekizumab [25▪]	Dual IL-17A/IL-17F monoclonal antibody	SC	Phase 3 PsA: ACR20 at wk16 met (see pivotal trials); sustained responses to ~2 years in extensions.
Sonelokimab [27▪▪]	Nanobody targeting IL-17A/IL-17F (albumin-binding)	SC	ARGO phase 2: ACR50 wk12 46.3–46.5% vs. 20.0% placebo.
Izokibep [29▪▪]	Small protein scaffold targeting IL-17A	SC	Phase 2: ACR50 wk16 52% vs. 13% placebo.
Deucravacitinib [30]	Allosteric TYK2 inhibitor	Oral	POETYK PsA-1: ACR20 wk16 54.2% vs. 34.1% placebo.
Zasocitinib (TAK-279) [34▪▪]	Catalytic-site TYK2 inhibitor (highly selective)	Oral	Phase 2b: ACR20 wk12 53.3–54.2% vs. 29.2% placebo.
Brepocitinib [35]	Dual TYK2/JAK1 inhibitor	Oral	Phase 2b: met primary endpoint vs. placebo (ACR20 at wk16; see trial).
Icotrokinra (JNJ-77242113) [36]	Oral IL-23 receptor antagonist peptide	Oral	PsA phase 3 ongoing; psoriasis proof-of-concept with high PASI responses.
Ixekizumab + tirzepatide (TOGETHER-PsA) [46][a]	IL-17A blockade + dual GIP/GLP-1 agonism (metabolic adjunct)	SC + SC	Composite at wk36 (ACR50 + ≥10% weight loss): 31.7% vs. 0.8% ixekizumab alone.
Guselkumab + golimumab (AFFINITY) [51][a]	IL-23p19 + TNF inhibition (dual targeted strategy)	SC + SC	MDA wk24: 28.8% vs. 21.9% guselkumab alone (primary not met).

ACR, American College of Rheumatology; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; IL, interleukin; JAK1, Janus kinase 1; MDA, minimal disease activity; PsA, psoriatic arthritis; SC, subcutaneous; TNF, tumor necrosis factor; TYK2, tyrosine kinase 2; wk, week.
[a]Unpublished data: presented as press-release.

Selective tyrosine kinase 2 inhibition

TYK2 mediates signaling downstream of IL-12 and IL-23 and contributes to type I interferon pathways. Selective TYK2 inhibition is a major pipeline development because it could expand oral options with pathway selectivity conceptually closer to IL-23/IL-12 modulation than to broad Janus kinase (JAK) inhibition.

Allosteric tyrosine kinase 2 inhibition: deucravacitinib

Deucravacitinib is an allosteric TYK2 inhibitor approved for moderate-to-severe plaque psoriasis and now in phase 3 PsA development. In POETYK PsA-1, the primary endpoint (ACR20 at week 16) was met (54.2% with deucravacitinib vs. 34.1% with placebo), with higher rates of key secondary endpoints including PASI75 (40.9% vs. 15.4%) and MDA (25.6% vs. 14.7%) [30]. In POETYK PsA-2, benefits were sustained through week 52, supporting durability [31]. Across analyses, improvements were also observed in enthesitis and dactylitis [31]. Deucravacitinib was generally well tolerated, with a safety profile consistent with prior experience [32]. Herpes zoster events were reported in psoriasis trials and long-term extension studies [32,33], but were uncommon, and none were observed in the PsA trials reported to date [30,31].

Highly selective catalytic-site tyrosine kinase 2 inhibition: zasocitinib (TAK-279)

Zasocitinib (TAK-279) is a highly selective oral TYK2 inhibitor designed for strong selectivity at the catalytic site. In a randomized phase 2b PsA study, the primary endpoint (ACR20 at week 12) was achieved by 53.3–54.2% with zasocitinib 15–30 mg once daily vs. 29.2% with placebo ($P=0.002$). ACR50 responses at week 12 were 26.4–26.7% vs. 9.7% with placebo, and MDA was numerically higher at the 30 mg dose (29.2% vs. 12.5%) [34▪▪]. Longer-term follow-up and phase 3 development will define durability, safety, and performance across domains such as enthesitis and dactylitis.

Dual tyrosine kinase 2/Janus kinase 1 inhibition: brepocitinib

Brepocitinib inhibits TYK2 and JAK1, broadening its cytokine signaling footprint. In a randomized phase 2b PsA study, brepocitinib improved clinical outcomes compared with placebo [35]. Broader pathway inhibition may offer incremental efficacy in some phenotypes but could also increase safety and monitoring considerations compared with more selective TYK2 approaches. Its eventual positioning will depend on the balance between incremental efficacy and long-term safety as the TYK2 landscape matures.

Inyerleukin-23 axis evolution: oral interleukin-23 receptor antagonism

IL-23 is upstream of IL-17 biology and is highly effective in psoriasis; IL-23 monoclonal antibodies also improve peripheral PsA. A potentially disruptive development is oral antagonism of the IL-23 receptor (IL-23R), aiming to combine pathway specificity with oral convenience.

Icotrokinra (JNJ-77242113; formerly JNJ-2113)

Icotrokinra is an oral peptide that antagonizes IL-23R. In plaque psoriasis, it produced robust efficacy and an acceptable safety profile, providing proof-of-concept for oral IL-23R blockade [36]. Importantly, it has entered phase 3 PsA programs in both biologic-naïve and biologic-experienced populations [37,38]. If joint, enthesitis and dactylitis efficacy is confirmed alongside strong skin responses, oral IL-23R antagonism could reshape early sequencing by offering pathway-specific oral therapy with biologic-like performance.

BEYOND THE MAINSTREAM AND ADJUNCTIVE STRATEGIES

In addition to new biologics and targeted synthetic DMARDs, attention is shifting toward upstream modifiers of psoriatic disease biology. Cardiometabolic dysfunction and obesity are strongly linked to inflammation and may influence both disease severity and treatment response, supporting interest in weight-centric and metabolic interventions alongside immunomodulation. Microbiome alterations have also been reported in PsA, and dietary and microbiome-directed approaches are under investigation; however, current evidence remains preliminary and these strategies should be considered adjunctive rather than disease-modifying at present.

Metabolic targeting: glucagon-like peptide-1 receptor agonists and dual incretin approaches

Obesity and insulin resistance are common in psoriatic disease and are linked to poorer PsA outcomes, including a lower likelihood of achieving MDA and higher discontinuation rates [39,40]. Weight loss is associated with improved PsA activity and may reduce progression risk across the psoriasis–PsA continuum [41]. In this context, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have attracted interest as potential metabolic–anti-inflammatory adjuncts.

Clinical evidence remains limited, but a first-in-kind randomized program has now reported topline data in PsA. In psoriasis, prospective cohorts and small trials (mostly with liraglutide) have reported improvements in PASI and quality of life in some obese patients with type 2 diabetes, although results have been inconsistent in glucose-tolerant populations [42–44]. In PsA, early observational data in obese patients suggest potential improvements in MDA and skin activity alongside expected metabolic benefits [41], but controlled trials have been scarce and one liraglutide PsA study was withdrawn due to recruitment challenges [45]. In the phase 3b TOGETHER-PsA trial (open-label with blinded assessor), concomitant ixekizumab plus tirzepatide met the primary composite endpoint at week 36 (ACR50 plus $\geq$10% weight reduction: 31.7% vs. 0.8% with ixekizumab alone; $P \leq 0.001$) and improved ACR50 as a key secondary endpoint (33.5% vs. 20.4%). Serious adverse events were less frequent with the combination (3.6% vs. 7.6%), while gastrointestinal adverse events and discontinuations were somewhat more common with concomitant tirzepatide [46].

At present, GLP-1RAs should be viewed primarily as comorbidity-targeted therapy in patients with obesity and/or diabetes, with possible secondary benefits on inflammation, cardiovascular risk, and treatment responsiveness. More randomized trials, ideally fully published and powered for musculoskeletal and structural outcomes, are needed before these agents can be recommended as disease-modifying therapy for PsA.

Dual biologic therapy

Dual targeted therapy is not part of the conventional pipeline in a regulatory sense, but it is an emerging strategy for highly refractory, multidomain PsA.

Observational data provide initial context for the feasibility and safety of combination targeted therapy in PsA. In a multicenter U.S. electronic health record study, combination targeted therapy was uncommon and was not associated with a higher risk of serious or opportunistic infection compared with standard targeted monotherapy, although residual confounding and limited event counts remain important limitations [47▪▪]. Complementary real-world series in refractory PsA and spondyloarthritis, typically motivated by persistent arthritis/enthesitis or concomitant extra-musculoskeletal disease, suggest potential clinical benefit in selected individuals but highlight heterogeneous combinations and the need for systematic safety surveillance [48]. Additional case-series data (including bDMARD plus tsDMARD combinations) have been reported in conference abstracts, reflecting growing real-world uptake in difficult-to-treat disease [49]. Across immune-mediated inflammatory diseases, systematic reviews similarly conclude that evidence is low certainty and that infection risk is a key

concern, supporting prospective evaluation and registry-based pharmacovigilance [50].

In the phase 2a AFFINITY trial in patients with active PsA and inadequate response to prior TNF inhibition, guselkumab plus golimumab did not meet the primary endpoint of MDA at week 24 [28.8% vs. 21.9% with guselkumab alone; odds ratio (OR) 1.4, 90% confidence interval (CI) 0.6–3.3; $P=0.557$] [51]. However, several secondary outcomes numerically favored combination therapy, including ACR50 at week 24 (44.1% vs. 21.9%) and MDA at week 16 (32.2% vs. 12.5%), with similar enthesitis resolution rates (48.6% vs. 52.4%) [51]. Whether the incremental efficacy of dual biologic therapy is greater in patients with a higher systemic inflammatory burden remains uncertain. Notably, AFFINITY was designed to enroll a population enriched for inflammation [the initial intended population included participants with C-reactive protein (CRP) ≥ 0.3 mg/dl], reflecting the hypothesis that higher systemic inflammation could amplify the incremental value of dual cytokine blockade. Safety interpretation is limited by sample size, but serious adverse events occurred in 6.8% on combination therapy vs. none on guselkumab alone, underscoring the need for larger trials powered for both efficacy and safety.

Sequential IL-17/IL-23 inhibition has also been proposed as a pragmatic strategy for a small subset of treatment-refractory PsA, aiming to address residual activity across domains by alternating upstream (IL-23) and downstream (IL-17A-F) pathway blockade [52]. Evidence remains limited to case-based experience and expert opinion, and should be viewed as hypothesis-generating, pending prospective evaluation of patient selection, durability, and safety [53].

Precision medicine and response prediction

Alongside new drugs and formats, there is growing interest in whether treatment selection can be individualized in PsA. To date, potential predictors are mostly clinical and context-dependent (dominant skin vs. musculoskeletal phenotype, enthesitis/axial symptoms, comorbidities such as obesity or central sensitization, and baseline inflammatory burden such as CRP), and real-world effectiveness signals are frequently confounded by treatment channeling.

Biomarker studies provide proof-of-concept: Chandran *et al.* reported associations between baseline and early changes in serum MMP-3 and COMP and response to TNF inhibitors [54] and have highlighted PsA as a model for precision medicine that integrates phenotype with validated biomarkers [55]. However, reviews conclude that few candidates replicate consistently and that prospective stratified testing and pragmatic assay standardization remain key gaps [56].

CONCLUSION

The next wave of PsA therapeutics will be defined not only by new agents, but also by new strategies. Near-term pipeline additions most likely to influence practice include IL-17 pathway innovation (dual IL-17A/F blockade and novel molecular formats), selective TYK2 inhibitors expanding oral options, and oral IL-23R antagonism progressing through phase 3 PsA programs. At the same time, the field is moving toward smarter use of existing and emerging mechanisms, including biomarker- and phenotype-informed sequencing (precision medicine) and, for selected difficult-to-treat patients, exploratory dual-targeted approaches that require larger, safety-informed evaluation. Metabolic interventions, particularly GLP-1-based agents, are also entering the conversation as adjuncts with cardiometabolic benefits and possible disease-impact effects but require additional randomized evidence before being considered disease-modifying therapy for PsA. Finally, prevention and interception strategies are increasingly plausible and should be evaluated prospectively in risk-enriched psoriasis populations using pragmatic endpoints within integrated dermatology–rheumatology care pathways.

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Choosing NSAID treatment in axial spondyloarthritis: factors guiding clinical decision-making

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Purpose of review
Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy for axial spondyloarthritis (axSpA), improving pain, function, and disease activity. This review evaluates evidence for NSAID efficacy, potential disease modification, and safety considerations in patients with axSpA, particularly those with inflammatory bowel disease (IBD) or elevated cardiovascular risk.

Recent findings
Evidence for NSAID-mediated disease modification remains inconsistent. In patients with IBD, contemporary data suggest variable risk of disease exacerbation depending on NSAID selectivity and exposure patterns. Established gastrointestinal toxicities persist outside the IBD context, though risk-mitigation strategies are available. While general-population studies demonstrate increased cardiovascular risk with certain NSAIDs, emerging axSpA-specific observational data suggest a smaller excess risk of major adverse cardiovascular events, potentially reflecting the counterbalancing effect of inflammation control. Pharmacogenomic data increasingly support CYP2C9 variation as a determinant of NSAID exposure and toxicity.

Summary
NSAIDs remain foundational in axSpA management, but long-term use requires individualized assessment of gastrointestinal, cardiovascular, and IBD-related risks. Pharmacogenomic considerations may further refine patient selection and dosing strategies.

Keywords
axial spondyloarthritis, cardiovascular, gastrointestinal, inflammatory bowel disease, nonsteroidal anti-inflammatory drugs, pharmacogenomics

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory arthritis marked by inflammatory back pain, sacroiliitis, spondylitis, and extra-musculoskeletal manifestations including uveitis, psoriasis, and inflammatory bowel disease (IBD). Cardiovascular comorbidity is common. Nonsteroidal anti-inflammatory drugs (NSAIDs) remain first-line therapy for active axSpA across radiographic (r-axSpA/ankylosing spondylitis) and nonradiographic (nr-axSpA) disease. Ongoing questions include whether continuous NSAID use modifies structural progression, how best to prescribe NSAIDs with coexisting IBD, and how to mitigate gastrointestinal (GI), cardiovascular, renal, and other toxicities amid evolving comorbidities. Finally, pharmacogenomic data (notably CYP2C9) can influence NSAID exposure and may guide individualized dosing when results and guidelines are available. This review integrates these domains to support risk-stratified NSAID use in axSpA.

EFFICACY OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN AXIAL SPONDYLOARTHRITIS

NSAIDs are recommended as first line pharmacologic therapy in active axSpA [1,2]. An outstanding question, is whether NSAIDs are effective beyond symptom control? Specifically, it remains unclear whether NSAIDs should be considered disease-modifying agents (slowing radiographic progression).

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KEY POINTS

- Nonsteroidal anti-inflammatory drugs (NSAIDs) remain foundational therapy in axial spondyloarthritis (axSpA), with selection individualized by comorbidities, and patient preference.
- Cardiovascular risk signals with NSAIDs in axSpA may differ from the general population, potentially reflecting inflammation control.
- Toxicity risk varies by NSAID class and specific agent (gastrointestinal, renal, cardiovascular), supporting risk mitigation strategies (i.e. gastroprotection when indicated) and ongoing monitoring.
- Pharmacogenomics (i.e. CYP2C9) may help guide NSAID dosing/selection in select settings, though implementation is not yet routine.

SYMPTOM CONTROL

There is strong evidence that NSAIDs improve symptoms in axSpA. Multiple randomized controlled trials (RCTs) show improvement in pain, function, and disease activity compared to placebo [3,4]. Pooled data show that NSAIDs reduce overall pain scores by approximately 16.5 points on a 100 mm visual analogue scale (VAS) compared to placebo (95% CI: –20.8 to –12.2), with a number needed to treat (NNT) of 4 (95% CI: 3–6) [4,5]. A 2016 systematic review found a mean reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of 17.5 points on a 100-point scale (NNT 3, 95% CI: 2–4) and a mean reduction in the Bath Ankylosing Spondylitis Functional Index (BASFI) of 9.1 points on a 100-point scale (NNT 5, 95% CI: 3–8) [3]. While there is a role for NSAIDs in the treatment of patients with active axSpA, there are numerous agents to choose from, including nonselective and COX-2 selective NSAIDs. NSAIDs range from short-acting (e.g., ibuprofen half-life = 2 h) to long-acting (e.g., meloxicam half-life = 15–20 h). NSAID choice is individualized and should be based on efficacy, tolerability, dosing regimen, and comorbidities in each patient. In a 2016 network meta-analysis evaluating the efficacy of 20 NSAIDs in patients with r-axSpA inter-drug comparisons did not show superiority of any particular NSAID aside from one trial which found etoricoxib to be superior for pain reduction compared to celecoxib, ketoprofen and tenoxicam [4]; etoricoxib, however, is not available in all regions. A 2025 double-blind, randomized crossover N-of-1 trial program compared celecoxib, meloxicam, and naproxen in patients with axSpA and found that while responses varied across individuals, most patients had a clearly preferred NSAID, supporting individualized selection [6].

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AS DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Evidence for NSAIDs as disease-modifying antirheumatic drugs (DMARDs) in axSpA is mixed, and most studies focus on spinal radiographic progression in r-axSpA. A 2005 RCT comparing continuous vs. on-demand celecoxib over two years reported less radiographic progression (mSASSS) with continuous use, particularly among patients with elevated CRP and baseline syndesmophytes. Interestingly, celecoxib doses were similar between groups (201 ± 93 mg/day on-demand vs. 243 ± 59 mg/day continuous) [7,8]. In contrast, the 2016 ENRADAS RCT found no significant difference in progression between continuous and on-demand diclofenac (mean mSASSS change 1.28 vs. 0.79; $P = 0.39$); in subgroups with elevated CRP or syndesmophytes, progression was numerically higher with continuous diclofenac, though not statistically significant [9] Observational data from the German Spondyloarthritis Inception Cohort (GESPIC) over 10 years showed higher NSAID intake (per 10-point NSAID index increase) was associated with a modest reduction in progression in r-axSpA (β –0.077 [95% CI –0.152, –0.003]) but not in nr-axSpA (β -0.014 [95% CI -0.042, 0.014]) [10▪▪]. The randomized CONSUL trial evaluated adding continuous celecoxib to golimumab (vs. golimumab alone) in radiographic axSpA patients enriched for progression risk (elevated CRP and/or syndesmophytes) and found no statistically significant reduction in 2-year spinal radiographic progression (mSASSS), although there was a numerical trend toward fewer new syndesmophytes with combination therapy [11].

Meta-analyses show inconsistent and modest effects at best. A 2020 study found no significant difference in 2-year progression with NSAIDs vs. controls (pooled mSASSS difference –0.30, 95% CI –2.62 to 1.31) and noted heterogeneity [12]. Another review found no significant benefit of continuous NSAIDs in three of four studies (two RCTs, two retrospective cohorts) [13]. A 2016 Cochrane review concluded individual studies suggest a modest potential for continuous NSAIDs to slow progression in select subgroups (e.g., elevated CRP) [3]. Overall, larger prospective studies with standardized methods are needed given heterogeneity in definitions and study design

NSAID USE IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Understanding the domains of disease involvement is critical in approaching NSAID use in patients with axSpA, particularly in those with comorbid IBD. NSAIDs are first-line therapy for multiple

spondyloarthritis (SpA) manifestations (e.g., enthesitis, axial disease) that commonly occur in patients with IBD [14,15]. However, the use of NSAIDs in patients with IBD is controversial. Beyond the known gastrointestinal toxicities associated with NSAID use [16], there is additional concern that NSAID exposure may precipitate IBD intestinal disease flares. Small single-center studies from the 1990s and early 2000s reported increased risks of IBD flare ranging from mild disease relapse to hospital admission [17–19]. These initial studies have bred a lingering concern surrounding NSAID use in patients with IBD and led to the 2018/2019 American College of Gastroenterology IBD treatment guidelines strong recommendation against NSAID use in this population [20,21]. Without the option of NSAIDs for individuals with IBD, the question of safe analgesic alternatives remains. A large administrative claims study of over 360 000 patients with IBD spanning 22 years found opioid use to be consistently twice as common as NSAID use [22▪▪], highlighting the gap in effective and safe analgesia in this population.

Despite the association of NSAIDs and IBD flares reported in early studies, it has been challenging to draw definitive conclusions for several reasons. First, there has been significant heterogeneity in exposure and outcome definitions amongst studies examining NSAID safety in this population. Second, a recent pivotal pharmacoepidemiology study has raised concerns that prior attribution of IBD flare risk to NSAID exposure may have been at least partially due to methodologic issues with reverse causality and residual confounding [23]. Finally, the literature has been mixed with several studies not observing any increase in risk of IBD disease flare associated with NSAID use [24,25]. In a summary of the evidence to date, a 2018 systematic review and meta-analysis did not find a significantly increased risk of IBD flares in pooled risk estimates [relative risk (RR) 1.29, 95% CI 0.92–1.80] [26].

A more careful examination of the literature suggests that a more nuanced approach to NSAID use in those with IBD is likely warranted. Specifically, differential risk across subtypes of IBD and NSAID mechanism of action (MOA; i.e. nonselective vs. COX-2 selective) needs to be considered. With respect to IBD subtype, the risk associated with NSAIDs seems most apparent in patients with Crohn's disease (CD) while no consistent risk has been identified in individuals with ulcerative colitis (UC). In a sensitivity analysis of studies at low risk of bias in the aforementioned meta-analysis, a significantly increased risk of flare was exclusively noted in the CD subgroup (RR 1.53, 95% CI 1.08–2.16) [26]. A propensity score-weighted retrospective cohort study using administrative claims data from 269 304 patients with IBD found an association between prescription NSAID exposure and IBD-related hospitalization only in those with the CD subtype [hazard ratio (HR) 1.16, 95% CI 1.11–1.21] but not UC (HR 0.96, 95% CI 0.91–1.01) [27]. Beyond the potential risk conferred by the Crohn's subtype, NSAID dose may be an important interacting factor. In a large cohort study of patients with IBD in remission, a 50% increased risk of active disease at follow-up was found in patients with CD taking at least five NSAID doses per month whereas increased risk was not identified in those with lesser intake [28]. In another large single-center prospective cohort study, only those patients with CD with higher doses of recent NSAID use had significantly higher IBD disease activity scores [29].

NSAID risk likely further differs depending on the drug MOA. Many of the known gastrointestinal side effects of NSAIDs relate to intestinal hypermotility and reduced intestinal mucosal integrity from cyclo-oxygenase-1 (COX-1) enzyme inhibition [16]. COX-2 selective NSAIDs were developed in the late 1990s to minimize these adverse intestinal effects [30], and there is evidence that this drug class may be more tolerable in patients with IBD. Two randomized placebo-controlled trials of etoricoxib [31] ($n=159$) and celecoxib [32] ($n=222$) did not show any significantly increased short-term risk of IBD exacerbation associated with COX-2 NSAID exposure. Whether the safety data for pure COX-2 selective inhibitors can be extrapolated to NSAIDs that preferentially, but not exclusively, block the COX-2 enzyme (e.g., meloxicam) is unclear.

It is thus apparent that generalized statements on NSAID safety in patients with IBD, without consideration of IBD subtype or NSAID MOA, may be inappropriate. Accordingly, the 2024 European Crohn's and Colitis Organization guidelines on extraintestinal manifestations of IBD acknowledge the lower risk profiles of COX-2 selective NSAIDs and the UC subtype and recommend that NSAIDs can be considered for musculoskeletal symptom management on a case-by-case basis [33]. It is similarly the author's practice to judiciously use COX-2 selective NSAIDs at the lowest effective dose for short periods of time (i.e., 1–2 weeks) in patients with IBD and musculoskeletal complaints, particularly in those with quiescent UC.

OTHER GASTROINTESTINAL NSAID EFFECTS

Finally, it is important to consider the potential for common and well established non-IBD-related gastrointestinal toxicities associated with NSAID use, including peptic ulcer disease (PUD) and gastrointestinal bleeding [34]. Risks are accentuated in elderly

patients, with one Veterans Affairs study showing a three-fold higher risk of mortality from upper gastrointestinal events associated with NSAID use in patients over 65 years old [35]. Accordingly, national gastroenterological guidelines and experts have recommended to ensure NSAID use is appropriate in a given patient, test for/eradicate *Helicobacter pylori* in patients initiating long-term NSAIDs and/or those with risk factors (history of PUD, age ≥65, concomitant use of antiplatelet, anticoagulant, or steroid agents), and consider starting aproton pump inhibitor and preferentially using COX-2 selective NSAIDs, if not contraindicated, in those with risk factors [36–38].

CARDIOVASCULAR DISEASE RISK IN AXIAL SPONDYLOARTHRITIS

Patients with axSpA have higher prevalence of cardiovascular risk factors and cardiovascular disease (CVD) than the general population. Pooled prevalence estimates are 23% for hypertension, 17% for hyperlipidemia, and 14% for obesity, each higher than matched controls [39]. Heart failure odds are nearly doubled (odds ratio, OR 1.84), and greater comorbidity burden correlates with higher disease activity, worse function, and increased mortality [39–42]. Subclinical atherosclerosis is also more common, with increased carotid intima-media thickness (cIMT) and carotid plaques that correlate with traditional risk factors and disease features such as elevated acute phase reactants [42] Persistent inflammation (particularly C-reactive protein, CRP) and sustained high disease activity predict cardiovascular events. Each 1% increase in visits with elevated CRP is associated with a 3% higher hazard of cardiovascular events (HR 1.03, 95% CI 1.015–1.045).43 Higher ASDAS and BASDAI scores are also independently associated with increased risk [43].

Standard cardiovascular risk assessment tools underestimate actual risk in axSpA because they do not account for the impact of chronic inflammation and disease activity [43]. EULAR recommends cardiovascular risk screening in inflammatory arthritis, though not specifically in axSpA [44]. There is a recognized need for axSpA-specific cardiovascular risk models that incorporate disease activity and inflammation to improve risk stratification [45].

IMPACT OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS ON CARDIOVASCULAR RISK IN AXIAL SPONDYLOARTHRITIS

In the general population, NSAIDs are associated with increased risk of major adverse cardiovascular events (MACE), including myocardial infarction and stroke, with the risk being dose-dependent [46,47]. High-dose coxibs (COX-2 selective NSAIDs) raise MACE by 37% (RR 1.37, 95% CI 1.14–1.66), and high-dose ibuprofen increases major coronary events by 122% (RR 2.22, 95% CI 1.10–4.48) [46]. In axSpA, however, several large studies and meta-analyses suggest NSAID use is not associated with higher MACE risk and may even be protective, potentially via NSAID's modulation of chronic inflammation [45,48,49]. However, confounding by indication may still exist – particularly if NSAIDs are preferentially prescribed to patients who are healthier at baseline and therefore intrinsically at lower cardiovascular risk.

In axSpA-specific populations, cardiovascular safety appears comparable between celecoxib and traditional NSAIDs. A Korean nationwide cohort study of 6094 patients found no significant difference in composite CVD events between celecoxib and nonselective NSAIDs (HR 1.17, $P=0.499$) [50]. Similarly, a Swedish national cohort study of 21 872 SpA patients found no major risk differences for MACE among etoricoxib, celecoxib, and nonselective NSAIDs [51].

A nationwide French cohort study of 22 929 patients with AS found that NSAID use was associated with a significantly lower risk of MACE over eight years [subhazard ratio (SHR) 0.39, 95% CI 0.32–0.50], and anti-TNF therapy also conferred a protective effect (SHR 0.61, 95% CI 0.46–0.80) [48]. Similarly, a Korean cohort study found that long-term NSAID use (>365 cumulative defined daily doses) did not increase the CVD risk in patients with AS (adjusted hazard ratio [aHR] 1.06, 95% CI 0.94–1.20), in contrast to non-AS controls where the risk was significantly increased (aHR 1.64, 95% CI 1.48–1.82) [52]. A Taiwanese case-control study found that frequent COX-2 inhibitor use (medication possession rate ≥80%) was associated with a tenfold lower risk of CVD at 24 months (OR 0.08, 95% CI 0.01–0.92). However, higher NSAID doses were associated with a modestly increased risk of CVD in axSpA, with each dose increment increasing risk by 10% (aHR 1.10, 95% CI 1.08–1.13) [53].

The impact of NSAIDs on traditional cardiovascular risk factors, such as blood pressure, is modest and similar across agents, but should be monitored, especially in patients with preexisting hypertension [46]. In a study of 628 r-axSpA patients without baseline hypertension, continuous NSAID use was associated with a 12% increased risk of developing incident hypertension (aHR 1.12, 95% CI 1.04–1.20) compared to noncontinuous or no NSAID use [54].

Comparative safety in high-risk populations

The PRECISION trial, a large RCT of 24 081 patients with osteoarthritis or rheumatoid arthritis and

elevated cardiovascular risk, found that moderate-dose celecoxib (mean 209 mg/day) was noninferior to ibuprofen (mean 2045 mg/day) and naproxen (mean 852 mg/day) for the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke over a mean 34-month follow-up [55]. Hazard ratios for celecoxib vs. naproxen and ibuprofen were 0.93 (95% CI 0.76–1.13) and 0.85 (95% CI 0.70–1.04), indicating similar cardiovascular risk at these doses. Celecoxib was associated with fewer GI and renal adverse events than ibuprofen or naproxen [55–57].

CYP2C9 PHARMACOGENOMICS AND NSAID THERAPY

Cytochrome P450 2C9 (CYP2C9) is a key hepatic enzyme involved in the metabolism of several NSAIDs, including celecoxib, ibuprofen, meloxicam, and piroxicam [58–66]. Decreased-function CYP2C9 variants, most notably *2 and *3, occur at meaningful frequencies across populations and reduce metabolic clearance, increasing systemic NSAID exposure [65,67,68▪▪]. Homozygous CYP2C9*3 (*3/*3) markedly reduces enzyme activity and clearance, increasing systemic exposure. Celecoxib levels are ~3–7-fold higher vs. wild-type with reduced clearance and prolonged half-life; meloxicam, piroxicam and ibuprofen show similar effects, with AUC increases up to ~eightfold and ~sixfold, respectively [58–61,63,64]. Consistent with this, the FDA label for celecoxib recommends a 50% dose reduction in known CYP2C9 poor metabolizers [69].

These pharmacokinetic changes matter clinically because higher NSAID exposure increases dose-dependent adverse events, including GI bleeding [65,70–72]. The FDA label for celecoxib recommends a 50% dose reduction in known CYP2C9 poor metabolizers [69]. Meta-analyses further support a clinically meaningful gene–dose relationship between CYP2C9 reduced-function alleles (especially *3) and NSAID-associated GI bleeding risk, with odds ratios approaching ~1.9 in poor metabolizers [71,73].

Clinical utility and cost-effectiveness of testing

Routine CYP2C9 pharmacogenomic testing for NSAID prescribing in the general population is not currently supported by evidence of cost-effectiveness or clinical impact. Approximately 18% of the global population are predicted to be intermediate or poor metabolizers for CYP2C9, with the prevalence rising to 35% in European populations [68▪▪]. Most patients with CYP2C9 variants do not experience adverse events [74]. Economic evaluations indicate that pharmacogenetic testing is most cost-effective when targeted to high-risk drugs and populations, and when the cost of genetic testing is minimized [75–77]. Panel-based pharmacogenetic testing strategies, which include CYP2C9s, have shown promise in reducing adverse drug reactions and healthcare costs, but these benefits are most pronounced in populations with polypharmacy and high baseline risk [77,78]. The barriers to routine CYP2C9 testing include insurance coverage, lack of prospective outcome data, and need for clinical decision support systems to integrate genetic information into prescribing workflows [79,80]. Given that patients with axSpA often require high-dose NSAIDs for prolonged periods), axSpA may represent a higher-risk group in whom CYP2C9-inclusive testing could be more clinically and economically justified than the general population, though these data are currently lacking. Additionally, because CYP2C9 variation can meaningfully alter exposure, it is likely therapeutic concentrations may be met at lower concentrations in poor or intermediate metabolizers and efficacy may be attenuated in rapid metabolizers, supporting a role for genotype-informed dose selection and/or agent choice.

CONCLUSION

NSAIDs remain central to axSpA management overall, improving pain, function, and disease activity. Evidence that continuous NSAID use slows radiographic progression is inconsistent and modest; dosing should be individualized and risk-informed. With comorbid IBD, choose NSAIDs by subtype, dose intensity, and COX selectivity, favoring COX-2 inhibitors when needed. Mitigate GI and cardiovascular risks with established protective strategies, noting axSpA data may differ from general-population estimates. CYP2C9 pharmacogenomics influences exposure and toxicity substantially; routine testing is not currently recommended, though using prior results and targeted testing in high-risk patients may improve safety.

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There are no conflicts of interest.

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OPEN

Evidence-based follow-up in axial spondyloarthritis: how much is (not) enough?

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Purpose of review
Present follow-up strategies for axial spondyloarthritis (axSpA) entail frequent preplanned in-person outpatient visits. Capacity constraints make this approach increasingly difficult, and it is plausible that regular follow-up in axSpA is not necessary for all patients. The purpose of this review is to discuss emerging alternative follow-up strategies to improve care efficiency in axSpA, and the challenges of applying these solutions in clinical practice.

Recent findings
Patient-initiated follow-up (PIFU) and remote monitoring have been investigated in axSpA in two recent trials. These strategies demonstrated meaningful reductions in the number of outpatient visits and associated healthcare costs in patients with stable (ax)SpA, without negatively affecting health outcomes. Qualitative studies have additionally shown widespread acceptability of PIFU and remote monitoring from the perspective of both patients and healthcare providers, and their ability to enhance self-efficacy of patients. Loss to follow-up, delayed care, and logistical limitations are associated concerns requiring further consideration.

Summary
PIFU and remote monitoring hold potential as effective, efficient, and safe strategies for the follow-up of patients with axSpA. For successful implementation in practice, their inherent challenges must be addressed, including the careful selection and training of patients, and ensuring the necessary infrastructure.

Keywords
axial spondyloarthritis, patient-initiated care, remote monitoring

INTRODUCTION

The chronic nature of axial spondyloarthritis (axSpA) often requires a lifelong approach to follow-up. As such, recommendations for disease management highlight the importance of regular monitoring, with the goal of attaining and retaining an inactive disease (ID), or at minimum, low disease activity (LDA) state [1,2]. Currently, this entails frequent preplanned in-person follow-up at the outpatient clinic, through the application of patient-reported outcomes (PROs), clinical findings, laboratory tests, and imaging [1].

However, many clinics face capacity constraints in providing care for patients with axSpA and other rheumatic and musculoskeletal disorders due to rising healthcare expenditures, shortage of rheumatologists, and a gap between workforce supply and demand, that is expected to widen in coming years [3,4]. It is plausible that not all patients with axSpA require regular preplanned follow-up. Scheduled visits for a condition like axSpA, with an unpredictable disease course, are unlikely to coincide with disease flare-ups, raising questions about the usefulness of this follow-up strategy. Alternative approaches may be feasible, particularly in patients with stable disease. In this review, we discuss an evidence-based appraisal of emerging solutions and the key challenges of applying these solutions in the follow-up of patients with axSpA.

CURRENT SITUATION AND EMERGING SOLUTIONS

The consequences of capacity constraints in rheumatology care are manifold. Prominently, this has led to extensive waiting lists for new patients and reduced ability to provide rapid access to patients during flares or when experiencing side effects, which may

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KEY POINTS

- In axial spondyloarthritis (axSpA), patient-initiated follow-up (PIFU) and remote monitoring result in significant and clinically meaningful reductions in rheumatology outpatient visits without compromising health outcomes.
- PIFU and remote monitoring may lead to enhanced self-efficacy and autonomy of patients and is highly acceptable to patients and healthcare providers.
- Careful selection and training of patients before offering PIFU and remote monitoring is likely warranted.

compromise quality of care [5–8]. Additional efforts, such as improving care efficiency, are therefore needed to ensure timely patient access to the clinic and manage the workloads of healthcare providers (HCPs).

The traditional follow-up of patients with axSpA is typically physician-initiated, with outpatient visits scheduled every 3–6 months. However, this strategy represents a suboptimal use of time and resources. An observational study in clinical practice showed that approximately one-third of routine outpatient visits of patients with SpA were considered unnecessary in retrospect by rheumatologists [9]. During these visits, antirheumatic therapy remained unchanged in 87% of cases, and 77% of these visits did not lead to any clinical actions. Visits were more likely to be considered unnecessary when disease activity was low and patient satisfaction [based on patient global assessment of disease activity (PtGA)] was high.

Alternative care models, such as patient-initiated follow-up (PIFU) and remote monitoring, may provide solutions to the inefficiencies of traditional follow-up strategies. PIFU enables patients to schedule appointments according to their needs, rather than following a fixed schedule. This approach may empower patients, avoid unnecessary visits, and offer capacity for new and urgent appointments [10]. However, it also carries risks in loss to follow-up and delayed care [11]. Therefore, digital solutions, including telemedicine (TM) and mobile health applications to remotely monitor patients, are increasingly being introduced to support PIFU, either in a synchronous form (involving real-time virtual interactions between patients and HCPs) or asynchronous form (without real-time interactions).

EVIDENCE FOR PATIENT-INITIATED FOLLOW-UP AND REMOTE MONITORING IN AXIAL SPONDYLOARTHRITIS

PIFU and remote monitoring have recently been studied in (ax)SpA in two randomized controlled trials (RCTs) (Figure 1). The first, the TeleSpA trial, was a multicentre, pragmatic, open-label RCT, which investigated the clinical and cost-effectiveness of PIFU supported by asynchronous telemedicine (PIFU/TM) for patients with SpA compared to usual care (UC) [12▪▪,13]. Patients with axSpA (36%), peripheral SpA (54%, including psoriatic arthritis), or combined axial and peripheral SpA (10%) were eligible if they had stable disease (acceptable symptom state according to patient and treating rheumatologist, with no treatment changes expected in the next 3 months). Patients were randomly assigned to either the PIFU/TM or UC group. All patients visited the outpatient clinic at baseline and after 1 year. In the PIFU/TM group, no additional preplanned visits were scheduled, with remote monitoring via TM at 6 months instead. In the UC group, additional visits in-between were scheduled at the discretion of the treating rheumatologist. Extra visits could be scheduled on-demand at any time by patients in both groups. The primary outcome was the between-group difference in number of rheumatology outpatient visits (in-person, telephone, and video) after 1 year. Secondary outcomes were noninferiority of PIFU/TM compared with UC regarding several health outcomes of interest (related to disease activity) and overall experience with care, as well as cost-effectiveness of PIFU/TM. Adverse events were recorded and assessed on seriousness and relatedness to the intervention.

For the primary outcome, the mean number of rheumatology visits was 1.9 (SD 1.5) in the PIFU/TM group and 2.6 (SD 1.3) in the UC group after 1 year (mean difference –0.7 [95% CI –1.0 to –0.3]; 25.4% reduction). At the 6-month TM assessment, 74 of 94 (79%) patients from the PIFU/TM group indicated that no visit or contact was needed, 16 (17%) requested a telephone call, and 4 (4%) an outpatient visit. Regarding secondary outcomes, noninferiority was shown for all outcomes of interest. PIFU/TM was cost-effective from a healthcare perspective, saving costs (–€180 [95% CI –921 to 560]) without a loss in quality-adjusted life years (+0.004 [95% CI -0.022 to 0.030]). Seven nontrial-related adverse events occurred in the PIFU/TM group and eight (including one death) occurred in the UC group.

The second RCT, the Remote Monitoring in Axial Spondyloarthritis (ReMonit) trial, was a single-centre, three-armed, parallel-group, open-label RCT, comparing remote monitoring (comparable to asynchronous TM), PIFU, and UC [14▪▪]. Patients with axSpA were eligible if they were in an LDA state [Axial Spondyloarthritis Disease Activity Score (ASDAS) < 2.1] at time of inclusion and had been on stable treatment with a TNF inhibitor for ≥ 6 months. All participants were assessed at baseline

TeleSpA (Hermans et al, 2024)	ReMonit (Berg et al, 2025)
Design	
Multicentre, pragmatic, open-label RCT in the Netherlands	Single-centre, three-armed, parallel-group, open-label RCT in Norway
Eligibility criteria	
≥18 years, clinical diagnosis of SpA, disease duration ≥2 years, stable disease (acceptable symptom state according to patient and rheumatologist, no treatment changes expected in the next 3 months)	≥18 years, diagnosis of axial SpA according to ASAS criteria, stable disease (stable dose of TNFi for the past 6 months and ID/LDA according to ASDAS <2.1)
Primary outcome	
Number of rheumatology outpatient visits (physical, telephone and video consultations) within a 1-year period	Mean probability of ASDAS <2.1 at 6, 12 and 18 months
Intervention	
PIFU/TM: • Scheduled outpatient visit at baseline and after 1 year • Remote monitoring at 6 months via online registry (SpA-Net) • Additional visits only if requested by patient or rheumatologist	*Remote monitoring:* • Scheduled outpatient visit at baseline and after 18 months • Monthly reporting of PROs via mobile health application (MyDignio) • Rheumatology nurse contacted patient if BASDAI ≥4 *Patient-initiated care:* • Scheduled outpatient visit at baseline and after 18 months • Self-monitoring of symptoms by patients • Patients contacted rheumatology nurse when necessary
Control (UC)	
Follow-up at discretion of the treating rheumatologist	In-person visits every 6 months

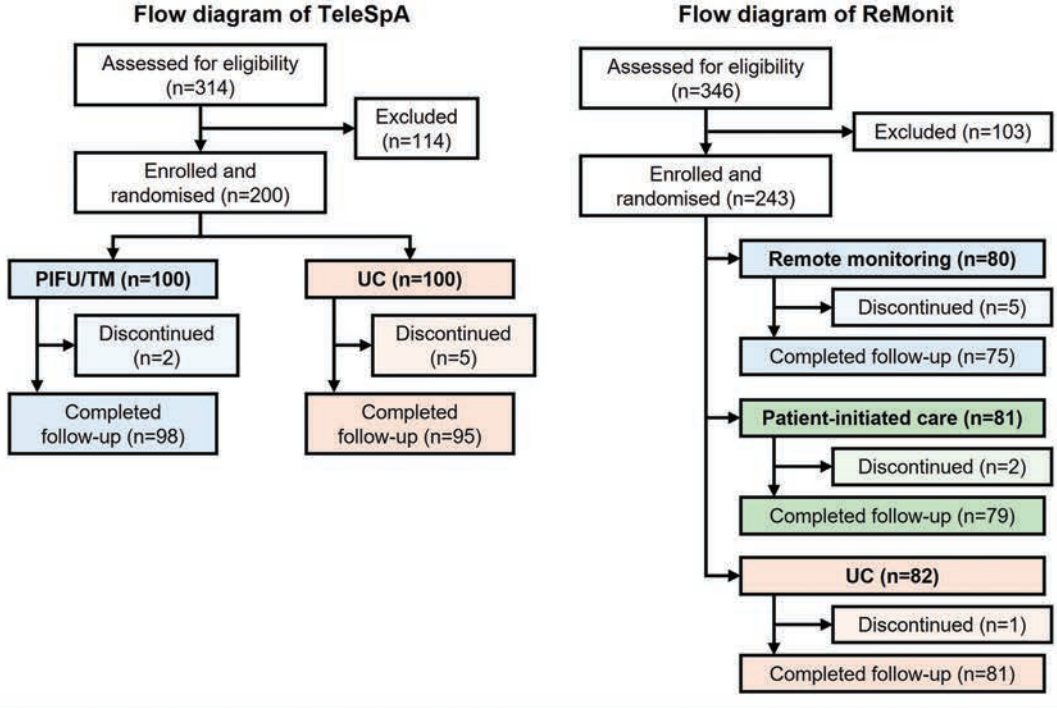

FIGURE 1. Overview of the TeleSpA and Remote Monitoring in Axial Spondyloarthritis (ReMonit) studies. ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Axial Spondyloarthritis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ID, inactive disease; LDA, low disease activity; PIFU, patient-initiated follow-up; PRO, patient-reported outcome; RCT, randomized controlled trial; SpA, spondyloarthritis; TM, telemedicine; TNFi, tumour necrosis factor inhibitor; UC, usual care.

and after 18 months. In the UC group, follow-up visits with a rheumatology nurse (supervised by a rheumatologist) were planned every 6 months in-between. In the remote monitoring and PIFU groups, no preplanned visits were scheduled during follow-up. Instead, in the remote monitoring group, participants completed PROs every month [PtGA, flare question, and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) if PtGA was ≥ 3 or a flare was suspected]. A BASDAI ≥ 4 alerted the rheumatology nurse to contact the patient and assess the need for a visit. In the PIFU group, patients self-monitored their symptoms and could contact the rheumatology nurse when necessary (e.g. symptom worsening or adverse event). The primary outcome was noninferiority of remote monitoring or PIFU compared to UC for maintaining disease control (ASDAS < 2.1; 15% noninferiority margin) at 6, 12, and 18 months. Secondary outcomes included disease activity, pain, physical function, and satisfaction with care, among others. Number of visits (in-person and telephone), HCP contacts, and adverse events were also recorded.

In all three groups, $\geq$90% of patients were in an LDA state at 6, 12, and 18 months. For the primary outcome, noninferiority for disease control was demonstrated in both intervention groups, with between-group differences in probability of maintaining LDA of –4.1% (97.5% CI –9.9% to 1.8%) for UC versus remote monitoring, and –1.1% (97.5% CI –7.2% to 4.9%) for UC versus PIFU. Furthermore, PIFU was noninferior to remote monitoring regarding disease control. Secondary outcomes were also similar between groups. Both remote monitoring and PIFU led to a reduction in the total number of visits compared to UC, and the number of unscheduled visits in the three groups was comparable. Of note, when brief telephone contacts were also considered, these were substantially higher in the remote monitoring group (by design of this intervention, where the nurse contacted the patient if BASDAI ≥ 4).

Overall, these two trials demonstrate that PIFU can be an effective, efficient, and safe way to reduce the number of outpatient visits in patients with axSpA. The results from ReMonit suggest that remote monitoring might not always be required for safe PIFU, although it should be noted that this was a single-centre study with strict eligibility criteria, possibly limiting generalizability of results.

PERSPECTIVE OF PATIENTS AND HEALTHCARE PROVIDERS ON PIFU AND REMOTE MONITORING

Qualitative studies on PIFU and remote monitoring in (ax)SpA have additionally provided insight into the experiences of patients and HCPs with this new care approach. Patients in the intervention arms of both the TeleSpA (PIFU/TM) and ReMonit (remote monitoring and PIFU) trials reported positive experiences in semi-structured interviews, highlighting appreciation for the ability of PIFU and remote monitoring to reduce unnecessary visits during flare-free periods, thereby reducing waiting and travel times [15▪,16▪]. Additionally, improvements in disease insight, patient empowerment, autonomy, and shared decision-making were expressed. These improvements were attributed to a greater sense of independence promoted by PIFU and access to personal health data through using remote monitoring tools. Altogether, HCP-patient relationships and communication were not negatively affected. A third related study, the TeleSpactive mixed methods study, further reinforced these benefits [17▪]. In this study, patients with stable axSpA used a mobile health application and C-reactive protein (CRP) self-testing for 6 months to monitor disease activity, with an optional in-person visit at 3 months if considered necessary through shared decision-making via telephone. Patients indicated widespread satisfaction with all components of this care approach. However, several concerns raised by patients should be acknowledged. Loss of a 'safety net' and emotional support due to reduced face-to-face contact with HCPs, as well as feelings of insecurity and potential exclusion of vulnerable populations arising from increased reliance on technology, were the primary disadvantages voiced [15▪,16▪]. Even so, predominantly positive experiences were reflected, with all TeleSpA participants indicating willingness to continue receiving care through PIFU/TM and recommend this approach to others [15▪]. Similarly, 96% of the ReMonit cohort reported willingness to use remote care in an ancillary survey [16▪,18▪].

Comparable experiences with PIFU and remote monitoring were expressed by HCPs in the TeleSpA trial. Illustratively, 12 of 13 (92%) surveyed HCPs were satisfied with the PIFU/TM intervention, and one was indifferent [15▪]. When interviewed, the vast majority considered PIFU/TM acceptable, safe, and able to facilitate good quality of care. While HCPs experienced little difference in terms of workload and time investment at the outpatient clinic, a noteworthy advantage was the increased flexibility in daily planning afforded by a reduced number of preplanned in-person appointments. This, in turn, contributed to improvements in workflow and allowed HCPs to allocate additional time to patients in greater need of consultation (e.g. those experiencing a flare). Several prerequisites for the implementation of PIFU/TM were nonetheless emphasized, including the integration of remote monitoring modalities with existing hospital systems to reduce

administrative burden, and the availability of a supporting infrastructure that allows ad-hoc diagnostic testing and provides accessible logistical and technical support. Given the fulfilment of these conditions, all interviewed HCPs involved in the TeleSpA trial found providing care through PIFU/TM agreeable.

CHALLENGES OF IMPLEMENTING PIFU AND REMOTE MONITORING IN PRACTICE

The merit of PIFU combined with remote monitoring is evident. However, in addition to the practical challenges with this approach encountered in trial settings, further recognized concerns warrant attention before implementation in practice. While remote monitoring can help mitigate some of these risks – including loss to follow-up, delayed care due to patient reluctance or inability to access services, and diagnostic delays when conditions are asymptomatic or patients fail to recognize the need for medical review – continuous vigilance is essential [19]. Particularly, remote monitoring of PROs, alongside laboratory tests (e.g. CRP, renal and liver function) conducted at the convenience of the patient in their own environment or via a home test, should be incorporated. This enables continuous assessment of disease activity through both subjective and objective measures, including recommended composite indices that require laboratory testing (e.g. ASDAS), and ensures adequate surveillance of medication safety [1]. It is also necessary to carefully select the right patient for PIFU and remote monitoring, and facilitate direct-access appointments through several means. Patients may further benefit from training and support on how to recognize, monitor, and self-manage their symptoms, as well as a hybrid approach combining PIFU with both remote monitoring and preplanned appointments once every (other) year, providing a 'safety net' and allowing for continued care planning [10,13].

The ideal patient for PIFU combined with remote monitoring is someone with stable disease (i.e. acceptable disease state and no changes in medication expected), who is digital and health literate, as well as motivated and compliant [15▪]. In patients that do not (initially) meet these prerequisites, PIFU could still be an option with additional support from HCPs. Patients with higher disease activity states, as measured by the ASDAS, may also be suitable, provided that both the patient and rheumatologist consider the disease state acceptable, with no changes in medication expected on the short term [12▪▪]. It is important to note that disease state in axSpA is largely assessed via PROs within the ASDAS, which may be influenced by concomitant diseases (e.g. osteoarthritis) not requiring treatment (changes), potentially resulting in an overestimation of disease activity scores [12▪▪]. Simultaneously, it should also be recognized that not every patient is a suitable candidate for PIFU and remote monitoring. If, despite extra guidance and consideration, disease-related or contextual prerequisites cannot be met, 'traditional' follow-up with preplanned visits should always remain an option [15▪].

A final consideration is the (very) low number of HCP-patient contacts that might result from PIFU and remote monitoring, which has several consequences. Firstly, medication tapering could become less frequent, eventually leading to overtreatment. It may therefore be advantageous for patients considering tapering to not participate in this follow-up approach. Secondly, lower contact frequencies could necessitate the use of mobile health applications for remote monitoring through electronic PRO measures. Employing these applications has the potential to enhance efficiency of care and aid decisions on whether to postpone a visit or conduct it remotely, especially for patients in an ID/LDA state [20]. Conversely, a serious threat when applying mobile health applications is poor adherence and high attrition rates [21]. Adherence is often achievable during the foreseeable timeframe of trial settings. For example, in the ReMonit trial, adherence was >80% over 18 months, albeit declining over time, with no specific patient characteristics significantly associated with adherence to PRO reporting [18▪]. In practice, however, sustained engagement with monitoring is required, and there is no guarantee that this behaviour will persist, as patients may eventually no longer find it useful or relevant to record their symptoms, particularly when their disease is inactive [22,23]. Consequently, patient education on the importance of remote monitoring when implementing PIFU is pivotal, and for patients that have been in an acceptable disease state for prolonged periods, the frequency and intensity of remote monitoring could possibly be minimized. Lastly, replacing frequent HCP-patient contacts with remote monitoring introduces logistical challenges, requiring a smoothly operating back office with a well-integrated digital infrastructure to manage large patient populations, as well as process electronically captured health data and (externally collected) laboratory results [15▪]. This may not be feasible in all healthcare settings, and could call for collaboration with an interprofessional team. Logistical feasibility is also linked to financial considerations, whereby the arrangement of adequate reimbursement for asynchronous remote follow-up (i.e. checking remotely-collected questionnaires and laboratory results) is necessary. As reimbursement pathways have been established for e-consultations in many countries, these could potentially also be used for this purpose. Altogether,

these concerns represent important factors that still require careful consideration when adopting PIFU and remote monitoring.

CONCLUSION

As an alternative to current practice, PIFU combined with remote monitoring results in significant and meaningful reductions in rheumatology visits, without significant changes in health outcomes (particularly disease activity). This approach also leads to healthcare cost savings. While implementation of PIFU and remote monitoring for axSpA in clinical practice holds potential, their inherent challenges must be addressed, for example through patient training and support on symptom recognition, monitoring, and self-management.

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Cholinergic anti-inflammatory pathway and vagus nerve stimulation in rheumatoid arthritis

Marcos Renato de Assis and Izabela Guimarães

Purpose of review
To integrate mechanistic and clinical evidence on vagal regulation of immunity via the cholinergic anti-inflammatory pathway, linking neural and inflammatory signaling in rheumatoid arthritis (RA). It highlights how reduced vagal tone contributes to disease onset and progression and frames neuromodulation as a rationale for adjunctive therapeutic strategies.

Recent findings
Preclinical and clinical data demonstrate that vagal efferent activity modulates immune responses through noradrenergic circuits and activation of α7-nicotinic-acetylcholine-receptors on immune cells, inhibiting NF-κB nuclear translocation and reducing pro-inflammatory cytokines. This neuroimmune axis interacts with the hypothalamic–pituitary–adrenal axis and the microbiome, supporting an integrated model of inflammation. Vagus nerve stimulation (VNS) has been associated with reductions in inflammatory markers and clinically meaningful improvements in patients with RA. Implantable VNS has demonstrated efficacy and has received regulatory approval for moderate-to-severe RA refractory to disease-modifying antirheumatic drugs; however, the available evidence remains limited and requires confirmation in larger and more diverse populations. Noninvasive approaches show favorable safety profiles but heterogeneous efficacy and currently lack regulatory approval for immune-mediated diseases.

Summary
VNS represents a promising adjunct to conventional immunosuppressive therapy for RA. Further well–designed trials are needed to standardize stimulation protocols, and define optimal strategies for clinical implementation.

Keywords
cholinergic anti-inflammatory pathway, neuroimmune modulation, neuromodulation., rheumatoid arthritis, vagus nerve stimulation

INTRODUCTION

The vagus nerve is the longest cranial nerve – a characteristic that is well reflected in its name, which derives from the Latin word "vagus", meaning "wandering" – extending into the thorax and abdomen, where it regulates parasympathetic activity. It also modulates immune function through its afferent and efferent arms, forming what is known as the cholinergic anti-inflammatory pathway (CAP) or "inflammatory reflex."

As classically described, the neuroimmune interaction is mediated by norepinephrine (noradrenaline, NE) signaling and macrophage modulation via the α7 nicotinic acetylcholine receptor (α7-AChR) expressed on splenic macrophages. More recently, another simplified model proposes a direct inhibition of immune cells through stimulation of β2-adrenergic receptors by the NE released by the splenic nerve [1,2].

The afferent arc of the inflammatory reflex was identified in the 1990s, when sensory activity in the vagus nerve was shown to increase markedly after intraperitoneal injection of interleukin-1β (IL-1β), provided that the nerve remained intact. A few years later, the efferent arm of the reflex was demonstrated in animal models of inflammation. In these experiments, mitogen-activated protein kinase (MAPK) inhibitors administered intracerebroventricularly suppressed peripheral edema at doses far lower than those required to achieve the same effect through systemic administration. This potent anti-

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KEY POINTS

- The vagus nerve regulates immune responses through the cholinergic anti-inflammatory pathway, integrating neural and inflammatory signaling.
- Experimental and clinical evidence supports a role for reduced vagal tone in the development and progression of rheumatoid arthritis (RA).
- Vagus nerve stimulation (VNS) reduces pro-inflammatory cytokines and improves disease activity, particularly in refractory RA.
- Implantable VNS has demonstrated clinically meaningful efficacy, while noninvasive approaches show promising safety but require further validation.
- Neuroimmune modulation represents a novel therapeutic paradigm that complements conventional immunosuppressive strategies in RA.

inflammatory effect disappeared after bilateral vagotomy. Moreover, electrical stimulation of the distal end of the transected vagus nerve increased survival in experimental sepsis by reducing tumor necrosis factor (TNF) production by splenic macrophages [3,4]. Commonly, the autonomic nervous system is portrayed as a balance between antagonistic sympathetic and parasympathetic influences. In reality, however, its physiological roles are far broader, and in many settings these two components act in a coordinated and synergistic manner rather than in strict opposition [4].

The CAP involves the vagus and the splenic nerve as the efferent arm of the inflammatory reflex. The vagus nerve is the tenth cranial nerve originating from the medulla oblongata of the brainstem and gathers its main fibers from four nuclei: dorsal motor nucleus of the vagus, nucleus ambiguus, nucleus tractus solitarius, and spinal trigeminal nucleus. The nerve exits the skull through the jugular foramen and descends through the neck parallel to the carotid artery, carrying approximately 80% afferent fibers and 20% efferent fibers which have the crucial role of autonomic regulation, especially heart rate variability (HRV) and gastrointestinal motility, as well as in the inflammatory reflex, through the release of acetylcholine (ACh).

Vagal afferent fibers detect peripheral cytokines and relay signals to the medulla and hypothalamus. This signaling triggers the hypothalamic–pituitary–adrenal (HPA) axis to release cortisol [5]. Ascending signals are processed in the nucleus tractus solitarius, which coordinates an efferent response to inhibit TNF-α – a mechanism shown to be crucial in sepsis and abolished by vagotomy [3]. To resolve inflammation, cortisol downregulates pro-inflammatory pathways such as nuclear factor (NF)-αB and enhances anti-inflammatory proteins such as annexin A1, while adrenaline promotes immune resolution via β-adrenergic receptors [6▪]. Therefore, the vagus nerve is the main effector of the parasympathetic response. It does not directly innervate the spleen but it influences this organ through its connection with the coeliac ganglion.

The splenic nerve is a sympathetic (adrenergic) nerve that carries fibers from preganglionic sympathetic neurons located in the intermediolateral cell column of the thoracic spinal cord between T6 and T9 levels. These fibers constitute the greater splanchnic nerve that projects to the celiac ganglion where it synapses to postganglionic sympathetic fibers. These postganglionic fibers travel along the splenic artery as the splenic nerve connecting the central autonomic system to the spleen. It innervates the white pulp, especially near T-cell zones, the marginal zone, and the splenic vasculature acting through the release of norepinephrine, which binds to β2-adrenergic receptors on macrophages and modulates cytokine production, particularly TNF. This mechanism not only preserves immune homeostasis but also mitigates the risk of tissue damage from excessive inflammation [6▪] (Fig. 1).

Together, these findings provided a mechanistic framework for the long-suspected dialogue between the nervous and immune systems. The conceptual shift was so striking that it invites a playful reformulation of a familiar slogan: "What happens in the vagus does not stay in the vagus."

Rheumatoid arthritis (RA) is an autoimmune disease characterized by synovial hyperplasia, cartilage destruction, and persistently elevated proinflammatory cytokines [7▪▪]. Despite the availability of numerous conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biological or targeted synthetic DMARDs (bDMARDs or tsDMARDs) with distinct mechanisms of action, treatment failure remains a challenge for many patients due to lack of initial response. Up to 50% of patients discontinue their therapy after two years due to lack of efficacy, toxicity, or poor compliance [7▪▪,8▪▪,9].

Historical observations of improvement in RA symptoms on the hemiplegic side of patients following stroke suggested a connection between the nervous and immune systems [10▪]. The Danish cohort analysis further reinforced this link by demonstrating an increased incidence of RA in individuals who had undergone truncal vagotomy compared with controls, pointing to a loss of the CAP [11]. Additional evidence indicates that reduced vagal tone may precede disease onset, whereas dominant

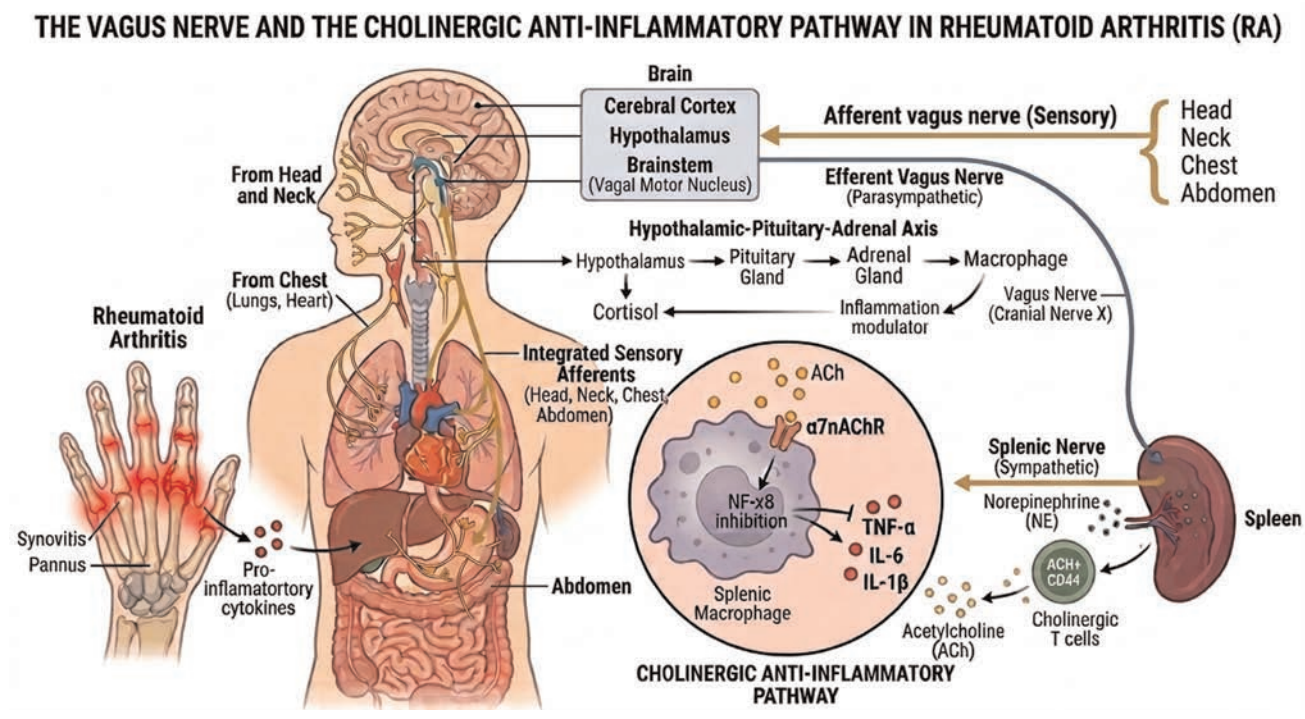

FIGURE 1. The cholinergic anti-inflammatory pathway (CAP) in rheumatoid arthritis (RA). The diagram illustrates the bidirectional communication between the central nervous system and the immune system. Pro-inflammatory cytokines released from synovial tissue in RA are detected by afferent vagus nerve fibers, signaling the brain's hypothalamus and vagal motor nucleus. This triggers two primary regulatory responses: the activation of the HPA axis, leading to cortisol release, and the stimulation of the efferent vagus nerve. The efferent signal travels to the spleen, where the splenic nerve releases NE, prompting $CD4^+$ T cells to secrete ACh. This neurotransmitter binds to α7nAChR on splenic macrophages, inhibiting NF-⊠B translocation and subsequently suppressing the production of systemic pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β). α7nAChR, alpha-7 nicotinic acetylcholine receptor; ACh, acetylcholine; $CD4^+$, cluster of differentiation 4 (T helper cells); HPA axis, hypothalamic–pituitary–adrenal axis; IL-1β/ IL-6, interleukin 1 beta/interleukin 6; NE, norepinephrine; NF-αB, nuclear factor kappa-light-chain-enhancer of activated B cells; RA, rheumatoid arthritis; TNFα, tumor necrosis factor alpha. This image was generated with the assistance of the Gemini 3 Flash/Nano Banana 2 artificial intelligence tool, based on the prompt provided by the authors.

parasympathetic activity in patients with RA, as measured by heart rate variability (HRV), predicts a favorable response to anti-TNF therapy [12,13].

Based on the concept of autonomic imbalance between sympathetic and parasympathetic activity in RA, VNS has been investigated as a potential therapeutic strategy.

Several studies in animals and humans have demonstrated that VNS activates brain regions with connectivity to the vagus nerve and its projections such as the nucleus of the tractus solitarius, locus ceruleus, and dorsal raphe nucleus [14]. VNS, either directly or via T-cell–mediated ACh release, inhibits pro-inflammatory pathways, reducing the production of cytokines such as TNF and interleukin-6 (IL-6) by approximately 30–70%, and decreasing NF-κB activity [15▪].

Transcutaneous vagus nerve stimulation (tVNS) has demonstrated clinical efficacy in reducing fatigue in patients with Sjögren's disease and systemic lupus erythematosus [16,17]. VNS has also shown evidence of effectiveness in relieving symptoms of inflammatory bowel disease (IBD). Clinical studies have demonstrated reductions in inflammatory biomarkers, intestinal mucosal inflammation, severity of intestinal lesions, intestinal pain, and sympathetic dominance. Notably, VNS has not been associated with long-term adverse effects [18]. Therefore, interactions between the CAP and biological pathways – including those involving the gut microbiota and endocrine signaling – highlight its extensive regulatory influence on metabolic balance and energy homeostasis [6▪].

The literature contains multiple abbreviations that contribute to terminological inconsistency, and no universal standard has yet been established. For example, the term ABVN that stands for auricular branch of the vagus nerve stimulation (VNS) has

been used synonymously with taVNS. However, following the introduction of tVNS, the use of ABVN has become less precise, as it does not clearly distinguish between auricular and cervical approaches. Additionally, the term percutaneous stimulation – where "percutaneous" refers to stimulation delivered via needle puncture – has been used to describe auricular stimulation techniques that are noninvasive or minimally invasive [19]. In this article, we will use the terms VNS, noninvasive VNS (nVNS), transcutaneous VNS (tcVNS), transauricular VNS (taVNS) and invasive VNS (iVNS) as defined above. This distinction extends beyond nomenclature, as the physiological mechanisms and the clinical effects may differ substantially among the various VNS modalities (Fig. 2).

VNS was first approved in Europe for drug-resistant epilepsy in 1994 and subsequently by the U.S. Food and Drug Administration (FDA) in 1997; in 2005, the FDA extended its approval to include treatment-resistant depression [17,20]. tVNS has also received FDA approval for the treatment of migraine and cluster headache. A significant milestone in the field occurred on July 31, 2025, when the FDA approved the SetPoint iVNS System for the treatment of RA, representing the first VNS-based therapy authorized for an immune-mediated inflammatory disease. While nVNS has demonstrated reductions in inflammatory markers in clinical studies of RA, it has not yet received regulatory approval for this indication. In parallel, another neuromodulation milestone was reached on December 8, 2025, with the first FDA premarket approval of a home-use tDCS device (Flow Neuroscience) for the treatment of major depressive disorder [21]. However, tDCS has not been approved for immune-mediated conditions [22].

In the context of RA, the first human evidence supporting VNS was reported in 2016 in patients with epilepsy carrying an implanted stimulator, in whom device activation reduced TNF production and was accompanied by improvement in arthritis symptoms. Subsequently, 18 patients with active RA and inadequate response to methotrexate, including some refractory to biologics, received VNS through an implanted device. Stimulation was safe and

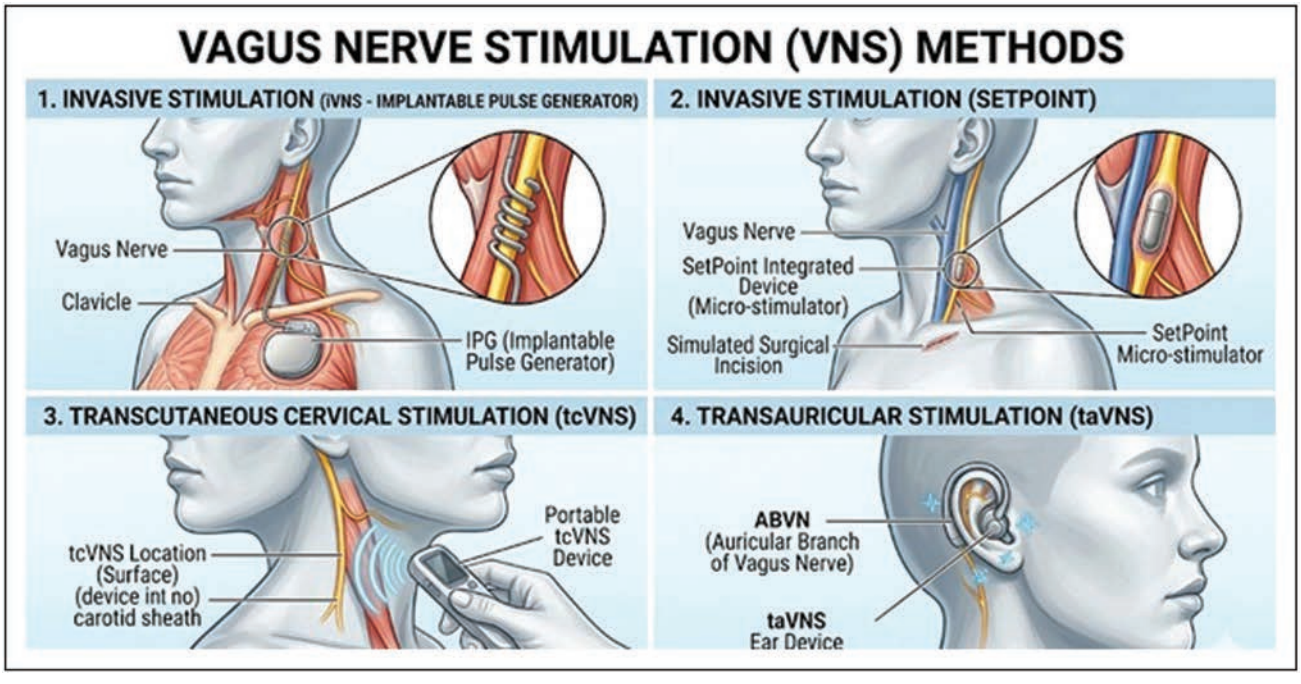

FIGURE 2. Modalities of vagus nerve stimulation (VNS). The figure illustrates the primary methods for stimulating the vagus nerve, categorized by invasiveness and anatomical targets. (1) Invasive VNS (iVNS) involves the surgical implantation of an IPG in the chest with leads wrapped around the cervical vagus nerve. (2) Micro-stimulator VNS represents a miniaturized invasive approach (e.g., SetPoint Medical) where a single integrated device is placed directly on the nerve via a smaller incision. (3) Transcutaneous cervical VNS (tcVNS) is a noninvasive method using a portable device to deliver electrical impulses through the skin to the carotid sheath. (4) Transauricular VNS (taVNS) targets the ABVN using an ear-mounted electrode to provide noninvasive neuromodulation. ABVN, auricular branch of the vagus nerve; IPG, implantable pulse generator; iVNS, invasive vagus nerve stimulation; taVNS, transauricular vagus nerve stimulation; tcVNS, transcutaneous cervical vagus nerve stimulation; VNS, vagus nerve stimulation. This image was generated with the assistance of the Gemini 3 Flash/Nano Banana 2 artificial intelligence tool, based on the prompt provided by the authors.

reduced TNF levels and disease activity measured by DAS28-CRP. Disease activity increased when stimulation was stopped and improved again when it was restarted. Several patients achieved ACR20, ACR50, and ACR70 responses, and some reached EULAR remission. Decreased IL-6 levels were associated with treatment response [12].

nVNS offers a promising surgery-free alternative to the vagal implants, particularly through taVNS of the cymba concha of the ear, which has been reported to be almost completely innervated by the auricular branch of the vagus nerve. However, the innervation of the concha is complicated by multiple neural communications of partly somatogenic and branchiogenic origin. Although neuroimaging studies suggest that this method activates brain regions and inflammatory reflexes similar to those activated by iVNS, its clinical efficacy in RA remains uncertain. Regarding the safety of taVNS, a systematic review and meta-analysis of 177 studies involving 6322 patients demonstrated that the incidence of adverse events, in general, was 12.84/100 000 person-minutes-days of stimulation, with ear pain, headache, and tingling being the most frequently reported symptoms [23].

taVNS has been increasingly explored as a noninvasive neuromodulatory approach in immune-mediated and pain-related conditions. However, the current body of evidence is predominantly derived from proof-of-concept and observational studies, with a limited number of randomized controlled trials. Regarding RA, no published randomized controlled trials (RCTs) have yet demonstrated taVNS effects on RA disease activity, including clinical outcomes or serum inflammatory biomarkers [9,24▪,25]. An open-label, proof-of-concept study, conducted across six centers evaluated RA patients nonresponsive to conventional DMARDs. The authors reported favorable safety and suggested clinical benefit after 12 weeks of daily stimulation, with a mean DAS28-CRP reduction of 1.4 points; more than half of participants achieved an ACR20 response and clinically meaningful improvement in HAQ-DI. The device was well tolerated, with no serious adverse events reported. Notably, these clinical improvements occurred without significant changes in CRP or cytokine levels, raising questions about whether the observed effects are primarily mediated by systemic anti-inflammatory mechanisms or, instead, involve pathways related to non-inflammatory or nociplastic components of disease expression [26]. While these early findings suggest potential biological and clinical effects, the heterogeneity in study design, stimulation parameters, and outcome measures precludes definitive conclusions concerning efficacy.

It has been hypothesized that the response to tVNS could predict the therapeutic response to implantable VNS. Nevertheless, there is currently no clinical evidence supporting this assumption in patients with RA. Reported side effects include redness and skin irritation at the stimulation site in some individuals [9]. In addition, effective delivery of tcVNS presents anatomical challenges. In some individuals the vagus nerve may lie more than 4 cm beneath the skin surface, which may limit the consistency and depth of stimulation [27].

In contrast, VNS using an implantable device has recently been approved for the treatment of moderate to severe RA [17,28]. The safety profile of VNS has been established over decades of use in hundreds of thousands of patients with refractory epilepsy, with no significant infection risks reported. The procedure was well tolerated, with low rates of adverse events such as dysphonia and vocal cord paresis [29].

Optimal VNS parameters vary significantly depending on the intended therapeutic mechanism. For epilepsy and depression, classical protocols rely on high-intensity stimulation to modulate ascending pathways [30▪]. In contrast, anti-inflammatory effects are preferentially triggered by low-frequency stimulation, which activates the CAP pathway via vagal efferents. Regarding taVNS, while parameters are still being standardized, current research suggests that lower intensities and specific pulse widths are necessary to target the auricular branch without recruiting neighboring somatosensory fibers [9,31,32] (Table 1).

The FDA-approved SetPoint system consists of a small oblong pulse generator connected to a lead with electrodes encased in silicone and is projected to have a lifespan exceeding 10 years. The implantation procedure requires approximately 60–90 min and is performed by an experienced neurosurgeon, who places the neurostimulator below the left clavicle and positions the electrodes adjacent to the left vagus nerve [29]. The device is externally programmed to deliver a fixed daily electrical stimulus lasting only 60 s and must be recharged using external equipment for approximately 5–10 min once per week [33▪].

In the RESET-RA trial, patients with inadequate responses to biologic or targeted synthetic DMARDs underwent VNS using the implanted device. The treatment group demonstrated clinically significant improvements in ACR20, ACR50, and ACR70 responses, as well as in disease activity scores (CDAI and DAS28-CRP), at 3 and 6 months compared with controls. The procedure was well tolerated, with low rates of adverse events. Approximately 82% of patients continued treatment without the addition of biologic agents or JAK inhibitors [34].

VNS is a slow-acting therapy since its benefits increase over time [9]. Unlike pharmacological

Table 1. Comparison of vagus nerve stimulation parameters

Parameter	iVNS – high intensity	iVNS for immune-mediated diseases	tcVNS	taVNS
Clinical focus	Epilepsy, treatment-resistant depression	Rheumatoid arthritis	Migraine, cluster headache, inflammation	Inflammation, pain, depression
Primary target	Cervical vagus trunk (left)	Implanted cervical vagus stimulator (SetPoint Medical)	Cervical vagus (via carotid sheath)	Auricular branch (cymba concha/tragus)
Current intensity	0.25–3.75 mA	0.25–2.0 mA (lower titration)	0.5–1.5 mA	0.13–5.0 mA (often set to perceptual threshold)
Frequency	20–30 Hz (standard)	10 Hz (optimized for CAP)	25 Hz (typical)	10–25 Hz (CAP ~15 Hz)
Pulse width	250–500 μs	250 μs	100–250 μs	100–500 μs
Duty cycle	30 s ON/5 min OFF (standard)	Once daily (1 min)	2-min sessions or 30 s ON/OFF cycles	Variable (30 s ON/OFF or continuous)

CAP, cholinergic anti-inflammatory pathway; iVNS, invasive VNS; taVNS, transcutaneous auricular VNS; tcVNS, transcutaneous cervical VNS; VNS, vagus nerve stimulation.

treatments, nVNS requires active patient participation, which typically involves daily or on-demand use of the device. One limitation of using tVNS devices is the treatment adherence, which does not occur with the use of implantable devices [9]. Ensuring adherence to prescribed treatment regimens is vital for achieving optimal outcomes, yet it presents a significant challenge without proper education and support. Incorporating nVNS into comprehensive care plans that include regular follow-ups, monitoring, and feedback can significantly boost patient engagement and compliance [6▪].

From a clinical perspective, patient selection remains an important consideration for VNS-based therapies. Current evidence for implantable VNS (iVNS) is largely derived from studies involving patients with moderate to severe RA who are refractory to one or more biologic DMARDs, a population characterized by persistent inflammatory activity despite optimized pharmacological treatment. While one might hypothesize that earlier-stage disease could be more amenable to neuromodulatory interventions, this assumption cannot be confirmed, as underlying mechanisms may differ, particularly in patients with prominent nociplastic features. Therefore, it remains uncertain whether patients with predominantly noninflammatory or nociplastic features – such as persistent pain, fatigue, or functional impairment disproportionate to inflammatory markers – may derive similar benefit. This distinction may be particularly relevant for noninvasive VNS approaches, for which clinical effects are not consistently associated with measurable changes in systemic inflammation. Therefore, it remains important to clarify which patient subgroups are most likely to benefit and how to guide appropriate clinical implementation.

Collectively, these findings support a role for neuroimmune modulation as a complementary therapeutic strategy in RA, particularly in patients with refractory disease, with potential to expand treatment options in selected patients, although existing trials were not designed to assess sustained remission in the absence of pharmacologic therapy.

VNS offers a mechanism distinct from conventional immunosuppression by engaging endogenous regulatory pathways, with potential effects extending beyond inflammation to domains such as pain, fatigue, and mood. However, variability in study design, patient populations, and stimulation protocols limits the generalizability of current findings. The extent to which these effects are mediated through specific neuroimmune pathways, including potential indirect involvement of the vagus nerve, remains to be clarified [6▪].

Within the clinical presentation of RA, recent attention has focused on noninflammatory refractory RA (NIRRA), a persistent pain state, likely mediated by nociplastic mechanisms involving peripheral alterations and localized brain inflammation. A recent Brazilian clinical trial (in print) demonstrated that transcranial direct current stimulation (tDCS) improved pain scores and reduced circulating BDNF levels in RA patients. These findings suggest that brain regions beyond the vagal nuclei contribute significantly to symptom regulation, highlighting the need to better characterize the contribution of central and peripheral pathways to disease expression [35▪,36].

Increasing recognition of noninflammatory and nociplastic components in RA underscores the need for therapeutic strategies beyond cytokine modulation. Emerging evidence suggests that neuromodulation techniques, including VNS and tDCS, may influence symptom domains such as pain and fatigue through central and neuroimmune mechanisms. While these approaches remain under investigation, they offer a potential framework for more individualized treatment strategies targeting both inflammatory and noninflammatory dimensions of disease [16,36–38].

The presence of neuroinflammatory changes in the central nervous system, along with dysregulation of the hypothalamic–pituitary–adrenal axis in central sensitization conditions such as fibromyalgia, reinforces the hypothesis that neuromodulation techniques – such as VNS and tDCS – exert their effects, at least in part, through modulation of anti-inflammatory pathways [3,4,6▪,7▪▪]

Several studies indicate a reduction in the inflammatory process in patients resistant to conventional therapy, as well as significant improvements in fatigue, chronic pain resulting from central sensitization, and concomitant mood disorders – factors that directly impact the assessment of disease activity [16,36–38]. Consequently, advancing this field will depend on a better understanding of underlying mechanisms and on refining stimulation protocols, particularly in light of interindividual variability in clinical response.

CONCLUSION

Neuroimmune modulation represents a potential therapeutic strategy that activates endogenous anti-inflammatory pathways rather than directly targeting specific cytokines. The recent approval of implantable VNS introduces a new option for patients with RA refractory to conventional therapies. However, despite encouraging early findings, the current evidence base remains limited. Additional well designed clinical studies will be essential to confirm efficacy, define target patient populations, clarify the role of VNS in clinical practice, and guide its appropriate implementation.

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Conflicts of interest

There are no conflicts of interest.

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Selective immunoglobulin E deficiency: an overlooked hypogammaglobulinemia and its association with rheumatoid arthritis

Benedict K. Tiong and Tamara Dahhan

Purpose of review
As part of current rheumatoid arthritis management, immunosuppressive treatments with disease-modifying antirheumatic drugs can potentially result in needing to manage immunodeficiency in our patient population. The purpose of this review is to evaluate one specific type of hypogammaglobulinemia, selective immunoglobulin E deficiency, and examine the association with rheumatoid arthritis.

Recent findings
In patients with hypogammaglobulinemia, there is consensus that autoimmunity is more prevalent, though there is heterogeneity among specific immunodeficiency disorders.

Summary
Given the potential for high-risk complications associated with immunosuppressive therapies in rheumatoid arthritis and other systemic autoimmune diseases, including the risk for severe infections, furthering our understanding of the association between immunodeficiency and autoimmune disease will only allow for more thorough care of these patients.

Keywords
hypogammaglobulinemia, immunoglobulin E, rheumatoid arthritis

INTRODUCTION

The association between autoimmune diseases and common variable immunodeficiency (CVID) has been previously described [1], including higher incidence of rheumatologic disease in patients with CVID [2,3]. There are other types of hypogammaglobulinemia, such as selective IgA deficiency (sIgAD), which is the most common primary immunodeficiency [4], and one with a high incidence of autoimmune disease. Selective immunoglobulin E deficiency (sIgED) is another form of hypogammaglobulinemia which we will discuss. Our aim will be to review the association between sIgED and rheumatoid arthritis (RA).

As part of long-term treatment for RA, disease-modifying antirheumatic drugs (DMARDs), most notably rituximab, have the potential to cause secondary hypogammaglobulinemia [5,6]. Diagnosis of hypogammaglobulinemia in RA and other connective tissue disease can potentially be delayed or challenging due to concurrent use of immunosuppressive medications [7]. There are instances when it may be difficult to determine if the hypogammaglobulinemia was present prior to initiation of therapy, or if it was there to begin with [8].

AN OVERVIEW OF IMMUNOGLOBULIN E

This antibody was recognized by the WHO International Reference Centre for Immunoglobulins in 1968 [9]. Consisting of two identical heavy chains and two identical light chains with a molecular weight of 190 000 Daltons, IgE takes part in the allergic response through signal responses, including binding to the Fc Epsilon Receptor I, Fc Epsilon Receptor II, and galactin-3 [10]. This leads to degranulation of mast cells and release of proteases, cytokines, chemokines, and growth factors [10]. While IgE is best known for its role in allergic responses [9], it also has additional immune functions, including participation in host defense against parasitic infections [11]. Antibody class-switch recombination (CSR) converts immunoglobulin M (IgM) to different

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KEY POINTS

- Selective IgE deficiency has association with autoimmunity and autoimmune diseases.
- Further investigation is needed to determine if there is a higher incidence of rheumatoid arthritis in patients with selective IgE deficiency.
- With frequent use of immunosuppressive DMARDs in the treatment of rheumatoid arthritis, there should be a low threshold to screen for hypogammaglobulinemia, including with serum IgE.

immunoglobulins, including IgE. Regulation of IgE involves intracellular transcription factors, DOCK8 and STAT3, taking part in differentiation, as well as IL-13 and IL-21 cytokines participating in production [12]. IgE is also believed to play a role in expelling environmental toxins, irritants, and venoms [13,14]. Factors leading to variability of IgE levels include environment, season, age, genetics, and ethnicity, including higher levels in African–Americans and Filipinos [10]. Th2 cells can enhance IgE synthesis or class switching, while Th1 cells can inhibit [10]. The stability of IgE levels may also vary according to age, including the possibility of stabilization occurring after the age of 15 [11]. There have been reports evaluating low serum IgE in children, suggesting higher incidence of autoimmunity and malignancy [15▪]. On the other end of the spectrum when there are elevated levels of IgE, there can also be association with autoimmunity and autoimmune disease [13]. The concept of IgE hypergammaglobulinemia is utilized in anti-IgE therapies such as omalizumab, as part of treatment of hyper IgE related disorders [16].

SELECTIVE IgE DEFICIENCY

The laboratory criteria used to define selective IgE deficiency include serum IgE levels less than or equal to 2.5 international units per milliliter (IU/ml) with normal levels of other immunoglobulins, including IgA, IgG, and IgM [17▪▪,18,19]. Similarly, total serum IgE levels of less than 2 kIU/l have also been used as a cut off to define severe IgE deficiency [10]. The mechanism for isolated IgE deficiency has not been elucidated. Genetic polymorphisms in the activation-induced cytidine deaminase (*AICDA*) gene, which takes part in CSR in the generation of IgE, have been reported [20]. Familial IgE deficiency has been discussed in the literature, including association with sinopulmonary disease, however some family members in this study had other concomitant immunoglobulin deficiencies as well [21]. The prevalence of selective IgE deficiency is not known, but prior studies of IgE hypogammaglobulinemia show prevalence of 1.95–2.4% [18,22], depending on the population studied. While a low IgE can be a part of CVID [23], the clinical significance of sIgED is not clearly established [17▪▪]. Currently, sIgED is not accepted as a primary immunodeficiency disorder [18]. Patients with sIgED may be asymptomatic. Although large-scale studies are lacking, several smaller studies suggest higher rates of autoimmune disease among patients with sIgED [11,24▪▪], the most commonly associated were thyroid autoimmune diseases, including Hashimoto's thyroiditis and Grave's disease. Associated clinical manifestations include chronic fatigue and arthralgias [10,11]. Studies of low IgE in adults and children have also demonstrated higher incidence of malignancy [18,25]. As far as infections in patients with IgE deficiency, higher prevalence of *Helicobacter pylori* has been reported [26]. Selective IgE deficiency and cardiovascular disease has been studied, showing significantly more arterial hypertension in patients with sIgED than control groups [27].

SELECTIVE IgE DEFICIENCY AND RHEUMATOID ARTHRITIS

In reviewing the literature evaluating sIgED in RA patients, four studies will be highlighted below. One study [25] involved 226 patients with sIgED, with 158 of these patients over the age of 12. Among patients with sIgED, two individuals (1.3%) were diagnosed with RA. The control group from the study consisted of 600 patients, including three patients with RA, or 0.5%, with a *P*-value of 0.279 [25]. Exclusion criteria included other hypogammaglobulinemia and use of immunosuppressive therapies 4 weeks prior to the date of when the serum IgE laboratory measurement was done, including use of corticosteroid therapies. A second study [24▪▪] from 2025 with 3692 patients had 1203 patients with sIgED compared to 2489 patients in the control group. From this study [24▪▪], there were 22 patients with RA, or 1.8%, compared to 52 patients with RA in the control group, or 2.2%. The P-value from this study was 0.494. Another study [22] included 134 patients with sIgED. From this study, a total of eight patients were found to have RA, or 6%. In 2021, another study by Picado *et al*. [28] evaluated 52 patients with sIgED, identifying one patient with RA, or 1.9%, and four patients with undifferentiated arthritis.

The next two studies did not include patients with sIgED only, but included patients with IgE deficiency broadly. The first study [11] included

420 patients, 44 of these with IgE deficiency compared to 376 in the control group. Among the patients with IgE deficiency from this group, there were five patients with RA, or 0.5%. In the second study by Zhang *et al*. [29] with 62 997 patients, of the 223 patients with IgE deficiency, only one patient was found to have RA, or 0.45%.

In a study by Smith *et al*. [30], 45 patients with RA were evaluated and IgE deficiency was found to be more prevalent compared to other types of hypogammaglobulinemia, including IgG subclass deficiency. In this study, IgE deficiency was defined as serum IgE less than 4 IU/ml. These RA patients with IgE deficiency were also more likely to have multiple immunoglobulin deficiencies [30].

DISCUSSION

Several potential mechanisms theorize how sIgED can lead to autoimmunity. One theory evaluates the breakdown of the mucosal barrier leading to increased antigen exposure in the mucosa and eventual lymphocyte stimulation through processes such as molecular mimicry, and immune complex formation [10]. Another theory is the possibility of decreased mast cell function and survival, thereby leading to a shift in balance between Th1-mediated lymphocyte and Th2-mediated lymphocyte activity, with predominance of Th1 favoring autoimmune diseases such as RA [10,24▪▪,25]. Further, disruption of regulatory T cells (Tregs) through interaction with mast cells is another potential mechanism [1,24▪▪]. The potential mechanisms for selective immunoglobulin A deficiency leading to autoimmunity has also been evaluated and compared to sIgED leading to autoimmunity, including mucosal barrier breakdown and exposure to antigens [31]. Theories about how genetics contributes as it relates to IgE deficiency and development of autoimmunity have also been proposed [10,11,17▪▪].

While the available studies support an association between sIgED and autoimmunity, it remains unclear whether this translates into higher clinical incidence of RA. Given the limitations, while CVID and sIgAD may have a higher incidence of autoimmunity and autoimmune diseases, we may not be able to make the same conclusion for sIgED, or other forms of hypogammaglobulinemia. There remains a need for more investigation in the field. There were studies that included evaluating sIgED in other autoimmune inflammatory arthritis etiologies, such as psoriatic arthritis, or undifferentiated inflammatory arthritis, but these were not included as the aim was to focus specifically on RA. While we recognize that there is a scarcity in the number of studies that examined the subject being reviewed, there are limitations in the studies that were presented. This includes the potential for biases, such as selection bias [25], as patients in the studies were primarily from allergy and immunology clinics. Further, the limited studies were derived primarily from retrospective studies. Among the studies examining patients with RA, there was no differentiation between seronegative or seropositive RA. The RA disease activity was not detailed, nor the extent of RA disease manifestations, such as erosive deformities or extra-articular disease.

In general, it is usually not commonplace for rheumatology clinics to routinely check quantitative immunoglobulins, including IgE, unless there is another reason, including further investigation for a primary or secondary immunodeficiency. Additionally, the exclusion criteria from prior studies used relevant to patients with RA, such as exclusion of patients with recent immunosuppressive medication use, or rituximab use [24▪▪], can further impact the number of sIgED patients overall. Our hope is that expanding the understanding of comorbid conditions, such as sIgED, will translate into broader clinical application for RA patients in the future.

CONCLUSION

Further investigation is needed to determine whether patients with sIgED truly have a higher incidence of RA. Given the use of DMARDs such as rituximab, and the potential for immunosuppressive side effects such as hypogammaglobulinemia, there can be utility in checking quantitative immunoglobulins, both pretreatment and posttreatment, including serum IgE levels.

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B.T. has consulted for Amgen, Exagen Inc. The remaining author has no conflicts of interest.

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Glucagon-like peptide-1 receptor agonists in rheumatoid arthritis

Ryan Massay, Angela Malani and Aaron Stubbs

Purpose of review
This article synthesizes current preclinical and clinical literature regarding glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in rheumatoid arthritis (RA), highlights mechanistic hypotheses and explores potential clinical roles and limitations of their use.

Recent findings
GLP-1 RAs are established therapies for type 2 diabetes mellitus and obesity, with demonstrated benefits on glycemic control and cardiovascular risk reduction. Emerging evidence suggests that GLP-1 RAs may exert anti-inflammatory and immunomodulatory effects relevant to RA.

Summary
Present evidence is insufficient to recommend GLP-1 RAs as standard RA therapy. Well designed randomized controlled trials are needed to establish their efficacy and optimal role.

Keywords
glucagon-like peptide-1 receptor agonists, rheumatoid arthritis

INTRODUCTION

First identified in the 1980s as a potent insulin-stimulating hormone, glucagon-like peptide-1 (GLP-1) is an incretin hormone vital in maintaining glucose homeostasis. It facilitates insulin secretion, inhibits glucagon release and delays gastric emptying thereby helping post prandial blood sugar control [1]. The discovery of exendin-4, a naturally occurring GLP-1 mimetic extracted the saliva of the Gila monster (Heloderma suspectum), was a turning point, which led to the development of exenatide, the first Food and Drug Administration (FDA) approved GLP-1 RA in 2005 [1,2].

GLP-1 RAs have since shown benefit in a variety of conditions, including major cardiovascular events, heart failure with preserved ejection fraction, diabetes prevention, obstructive sleep apnea, peripheral artery disease, renal disease, metabolic dysfunction–associated steatohepatitis and neurodegenerative diseases [3]. As of October 2025, 12 GLP-1 therapies have been FDA approved for indications in type 2 diabetes, obesity, cardiovascular risk reduction and obstructive sleep apnea while over 40 agents are in active development across various indications and with different formulations [3].

Rheumatoid arthritis (RA) is characterized by persistent synovial inflammation, systemic immune dysregulation, joint destruction and increased cardiovascular morbidity and mortality. Given the beneficial effects of GLP-1 receptor agonists on metabolic disease through enhanced incretin signaling, there is growing interest in their potential influence on inflammatory pathways, immune function and possible utility in RA.

Currently however, there are no published randomized controlled trials specifically evaluating GLP-1 RAs as a disease-modifying treatment for RA. The existing evidence consists entirely of preclinical and retrospective observational studies that have yielded conflicting findings regarding RA risk and outcomes in patients using GLP-1 RAs.

MECHANISTIC RATIONALE AND PRECLINICAL EVIDENCE

GLP-1 RAs show potential disease-modifying effects in RA through anti-inflammatory and immunomodulatory mechanisms.

In an in-vitro study of tumor necrosis factor alpha (TNF α) stimulated RA fibroblast-like synoviocytes (RA-FLS), dulaglutide decreased levels of pro-

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KEY POINTS

- GLP-1 RAs are multifaceted medications which have found use in a variety of medical conditions.
- Mechanistically GLP-1 RAs may also be beneficial in RA.
- Larger and more rigorous data is necessary to fully elucidate the role and impact (either positive or negative) of GLP-1 RAs in patients with RA.

inflammatory cytokines interleukin-1β (IL-1β), interleukin 6 (IL-6) and the matrix metalloproteinase 13 signaling protein (MMP-13) [1,4].

In another TNF α stimulated model [5], exenatide similarly reduced expression of MMP-3 and MMP-13, IL-1β, IL-6, monocyte chemoattractant protein-1 and high-mobility group protein 1. It ameliorated the activation of the p38 mitogen-activated protein kinase (p38/MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) proinflammatory signaling pathways which are implicated in RA pathogenesis.

Lixisenatide downregulated TNF-α, IL-6 and interleukin-8 (IL-8); inhibited MMPs and blocked c-Jun N-terminal kinase (JNK), activator protein 1 (AP-1) and NF-κB cellular signaling pathways in IL-1β-stimulated RA-FLSs [6]. It improved oxidative stress, rescued mitochondrial membrane potential and prevented cell death in fibroblast-like synoviocytes [6].

These findings suggest that GLP-1 receptor agonists may exert chondroprotective effects by reducing synovial inflammation, preserving cartilage integrity and potentially limiting joint destruction [1].

CLINICAL IMPLICATIONS

Risk of developing rheumatoid arthritis

Population-based data is conflicting with respect to the effect of GLP-1 RAs on the risk of developing RA. Observational studies of patients with type 2 diabetes mellitus (T2DM) have reported that GLP-1 RAs may increase [7,8], decrease [9] or not significantly alter the risk of developing RA [10–12] when compared to other hypoglycemic agents.

Impact on disease activity

GLP-1 RAs show some promise in reducing disease activity in RA. This maybe indirectly mediated through weight loss and metabolic improvements rather than direct disease-modifying effects [1].

A 24-week observational cohort study of 15 patients T2DM with active inflammatory arthritis (11 with RA, 4 with psoriatic arthritis, DAS-28 > 4.0) was conducted. All patients received liraglutide (1.2 mg/day) while remaining on stable disease-modifying antirheumatic drug (DMARD) therapy. DAS-28 scores improved significantly in nine out of 15 patients (60%), with reductions in swollen joint counts, C-reactive protein (CRP) levels and HbA1c values. Significant weight loss was seen in DAS28 responders (94 + 5 pre, 90.6 + 5.2 kg, $P=0.008$) [13].

A 6-month prospective observational cohort study involving 30 RA patients with T2DM receiving GLP-1 RA was conducted in 2024 [14]. The patients were naive to steroids or DMARDs throughout the study period and only received GLP-1 RAs. The assessed outcomes included weight loss, duration of morning stiffness, pain levels and inflammatory markers (CRP, ESR). The results showed a 10% reduction in body weight and significant decreases in ESR and CRP levels, correlating with improvements in arthritis symptoms.

A subsequent larger single-center retrospective observational study examined the effects of semaglutide and tirzepatide on disease activity and cardiovascular risk profile in RA patients who were overweight or obese [15]. All patients simultaneously took DMARDs, and the treatment group (those prescribed and who took GLP-1RAs, $n=173$) had a higher prevalence of hypertension and diabetes (statistically significant, 0.04 and < 0.01 respectively), higher mean glycosylated hemoglobin (HbA1c) and serum triglyceride values than the control group (those prescribed but did not take the GLP-1 RAs, $n=42$). The measured outcomes included RA disease activity, cardiovascular risk markers and patient-reported outcomes. The treatment group experienced significantly greater reductions in disease activity, pain, body weight, total cholesterol and glycosylated hemoglobin than control patients. Within the treatment group, there were also significant reductions in ESR, CRP, low-density lipoprotein cholesterol values, and triglyceride values ($P<0.05$). Interestingly, there was no significant correlation between weight loss and reduction in visual analogue scale (VAS) pain score ($r=0.09$, $P=0.08$) or acute phase reactants. The presence of diabetes did not meaningfully affect these results. There was a significantly higher proportion of white patients in the treatment group than in the control group (71 versus 47%, $P=0.01$) which raises questions of the generalizability of these findings.

Evaluating the TriNetX Database, Stipho *et al.* [16] sought to assess the risk of RA flare-ups in patients with RA who were prescribed semaglutide. Through propensity score matching, they found that RA patients with a semaglutide prescription had statistically lower risks of RA flare-ups such as synovitis, stiffness, swelling and joint pain at the studied

time points of 30 days, 90 days and 1 year when compared to RA patients without a semaglutide prescription.

Conversely, in a retrospective cohort study conducted by Sakthivel *et al.* [17], comparing the association between SGLT2 inhibitors or GLP-1 RAs and RA flare outcomes in DMARD-treated patients revealed that flare proxies [intravenous (i.v.) steroids, injections and inflammatory marker elevations] were more frequent in the GLP-1 RA group. These findings suggest a possible association between GLP-1 RA use and higher flare burden in patients with RA.

Obesity reduction

It has previously been shown that obesity is linked to higher disease activity, diminished responses to DMARDs, lower remission rates [18,19] and an increased risk of cardiovascular disease in RA [15]. Cardiovascular disease remains the leading cause of death in this population [15].

Excess adipose tissue promotes chronic inflammation by releasing adipokines (leptin, resistin, visfatin) and cytokines (TNF-α, IL-6, IL-1β), exacerbating disease activity and worsening clinical outcomes [20].

GLP-1 receptors are expressed in synoviocytes and chondrocytes [12], where its activation suppresses pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and matrix metalloproteinases (MMPs), particularly MMP-3 and MMP-13, which are associated with cartilage degradation [1]. GLP-1 receptor signaling upregulates the synthesis of aggrecan and collagen type II, essential components of the extracellular matrix, thereby helping to preserve cartilage integrity. Therefore, GLP-1 receptor activation may potentially reduce synovial hyperplasia and pannus formation which are integral parts of RA pathogenesis, by inhibiting fibroblast proliferation and the release of inflammatory mediators in synovial fibroblasts [1].

Reducing thromboembolic risk

Patients with RA have approximately a two-fold increased risk of venous thromboembolism (VTE) compared to the general population. VTE incidence rates range between 3.8 and 5.9 per 1000 person-years in RA patients versus 2.4–2.8 per 1000 person-years in matched controls [18]. A meta-analysis of 12 studies including 272 884 RA patients found elevated risks for deep vein thrombosis (odds ratio 2.25), pulmonary embolism (2.15) and overall VTE (2.23) [22].

A retrospective cohort study using TriNetX database conducted between January 1, 2006, and December 1, 2024, showed that when compared to DPP-4 inhibitors, GLP-1 RAs use in diabetic RA patients was associated with a 24% lower risk of all thromboembolic events (hazard ratio 0.76, 95% CI 0.70–0.83) and reduced all-cause mortality [23].

Gastrointestinal considerations

Gastrointestinal adverse events are the most common side effect of GLP-1 RAs with 40–70% of patients reporting nausea, vomiting, diarrhea and constipation [24]. While these symptoms are generally transient, this can affect treatment adherence and lead to therapy discontinuation. Additionally, gastroparesis, gastritis and bowel obstruction can occur less commonly but remain clinically important [25].

For RA patients specifically, the combination of NSAIDs and DMARDs with risk of gastrointestinal complications (sulfasalazine, methotrexate, leflunomide and IL-6 inhibitors) with GLP-1 RAs warrants careful consideration. This theoretical compounded risk has yet to be studied.

Sarcopenia implications

Independent of age, RA patients are at risk for sarcopenia due to chronic inflammation, effects of long-term glucocorticoid use and reduced capacity for physical activity due to joint pain [1]. Sarcopenia in RA is a particular concern, as it has the potential to reduce functional status, increase risk of falls and impair quality of life. Patients receiving GLP-1 receptor agonists may experience significant weight loss; however, approximately 20–30% of this loss may consist of lean body mass [26]. Longitudinal studies have shown that prolonged semaglutide use reduces handgrip strength and may accelerate sarcopenia in older individuals [27].

Taken together, this raises concerns for compounded muscle deterioration in this population if GLP-1RAs are added. Ensuring that RA patients increase resistance training and consume adequate amounts of protein while taking GLP-1 RAs may be an important mitigation strategy. Monitoring functional status during appointments may become necessary [28]. Further research is needed to better understand and characterize risks across all rheumatic diseases.

Mortality benefit

A large-scale population-based cohort study evaluated the impact of GLP-1 RAs on all-cause mortality and major adverse cardiovascular events (MACE) in RA patients compared to those using dipeptidyl peptidase-4 (DPP-4) inhibitors. This study included 1367

RA patients receiving GLP-1 RAs and 2913 RA patients receiving DPP-4 inhibitors. It reported that GLP-1 RAs were associated with a 45% reduction in all-cause mortality [29].

A retrospective cohort study conducted by Loizidis *et al.* [30] utilized the TriNetX platform, selecting obese (BMI $\geq$30 kg/m^2) nondiabetic adults ($\geq$18 years) with RA to determine the impact of GLP-1 RA treatment on all-cause mortality and MACE. Patients initiating GLP-1 RA treatment (semaglutide, liraglutide, tirzepatide) were propensity score matched (1 : 1) with RA controls not receiving GLP-1 RA therapy, balancing demographics, BMI categories, cardiovascular comorbidities, immunosuppressive therapies and cardiometabolic medications. GLP-1 RA therapy was associated with significantly reduced one-year all-cause mortality (0.37 versus 0.93%; hazard ratio, 0.14; 95% CI, 0.04–0.47; P=0.0002) and MACE incidence (1.09 versus 2.19%; hazard ratio, 0.60; 95% CI, 0.38–0.95; P=0.026) compared to matched controls. The latter was driven by fewer heart failure events (0.74 versus 1.71%; hazard ratio, 0.52; 95% CI, 0.31–0.90; P=0.017). Myocardial infarction and cerebrovascular events were not significantly different between the groups.

CONCLUSION

While the small body of evidence is encouraging, it is currently insufficient to recommend GLP-1 RAs as standard RA therapy. Well designed randomized controlled trials are needed to establish their efficacy and optimal role, whether as adjunctive therapy in difficult-to-manage cases or in high-risk populations such as obese patients with inflammatory arthritis.

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Synovial lymphatic system structure and function in rheumatoid arthritis: lymphatic phases, telocytes, and therapeutic modulation through Eexercise

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Purpose of review
Lymphatic changes are associated with rheumatoid arthritis (RA), commencing with lymphangiogenesis in the "expanding phase", which transitions to the "collapsed phase" with dysfunction and advanced disease. Here, we review our understanding of the synovial lymphatic system (SLS) during joint homeostasis and arthritis, and the potential of exercise therapy.

Recent findings
How collecting lymphatic vessels (cLV) responsible for joint drainage sense effusion is unknown. Recently, murine models identified peri-cLV telocytes (interstitial mesenchymal cells involved in tissue maintenance and the regulation of muscle contraction). These telocytes were found buried within the rich extracellular matrix (ECM) of the cLV, and in networks extending from the synovium to the joint-draining cLV. *In vivo* telocyte depletion studies demonstrated decreased lymphatic drainage and exacerbated synovitis and bone erosions during zymosan-induced arthritis. Gene expression studies demonstrated that *Efhd1, Dpp4,* and *Pi16* are specific markers of human and murine synovial telocytes, which are absent in RA synovium and mice with inflammatory arthritis. Preliminary studies demonstrate that ad libitum exercise increases the number of synovial telocytes in mice.

Summary
Telocytes maintain the ECM of the SLS and may transmit signals to joint-draining cLV. Telocyte loss is associated with arthritic progression, which may be abated with exercise.

Keywords
exercise, lymphatics, rheumatoid arthritis, telocytes

INTRODUCTION

Although morning stiffness precedes the development of rheumatoid arthritis (RA) and is associated with systemic and subclinical joint inflammation [1], and lymphadenopathy occurs in 41–82% of RA patients [2], the cause-and-effect relationship between these factors and joint disease remains poorly understood. As background, it is critical to note that while some lymph migrates passively through unidirectional bicuspid valves in lymphatic vessels secondary to interstitial fluid pressure and passive compression by adjacent tissue movement [3], the majority is transported by the contractile activity of collecting lymphatic vessels (cLV) [4–6]. While there have been major advances in our understanding of intrinsic cLV contractions by lymphatic muscle cells (LMC) in response to intraluminal pressure and shear forces [7,8▪▪,9▪,10▪], how joint draining cLV sense acute edema in distal tissue to activate LMC, and how cLV contractions are lost in lymphedema, remain unknown [11,12]. To reconcile this physiology with our understanding of lymphatic dysfunction during arthritic flares and progression [13,14], we proposed the existence of the synovial lymphatic system (SLS), which comprises open-ended capillaries in the synovium that connect to the cLV [15]. The primary function of the SLS is to

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KEY POINTS

- Lymphatics are increased during early rheumatoid arthritis (RA) and become damaged and dysfunctional in advanced joint disease.
- Telocytes and mast cells are integral to the synovial lymphatic system (SLS), which maintains joint homeostasis.
- Moderate exercise enhances the SLS, which may help ameliorate RA signs and symptoms.

maintain joint homeostasis through the steady-state flow of synovial fluid and lymph, a process that has been comprehensively reviewed [16,17,18▪▪].

Our most recent investigations of the SLS revealed two previously unknown cell populations: mast cells embedded within the cLV cellular architecture [19] and telocytes [20▪]. To put these discoveries into context, here we review changes in the SLS during the early versus advanced stages of inflammatory-erosive arthritis in animal models and RA patients, the structure and potential function of the telocyte network, and the potential of exercise to maintain the SLS in the setting of arthritis.

The expanding and collapsed lymphatic phases in rheumatoid arthritis progression

Our interest in lymphatics in RA commenced with studies of osteoclast precursors in the tumor necrosis factor-transgenic (TNF-tg) mouse model [21], and the serendipitous finding of increased expression of the lymphangiogenic factor vascular endothelial growth factor-C (VEGF-C) in monocytes and osteoclasts, together with lymphangiogenesis in inflamed joints [22,23]. Subsequent functional studies demonstrated that loss of VEGF-C signaling, together with decreased lymphangiogenesis, exacerbates inflammatory-erosive arthritis [24], while VEGF-C therapy ameliorates inflammatory arthritis by increasing lymphangiogenesis [25]. Longitudinal MRI [26–28], power Doppler ultrasound (PDUS) [29,30], and near-infrared (NIR) imaging of injected indocyanine green (ICG) dye [31–33] identified two distinct structural and functional lymphatic patterns during arthritic progression in our murine models. The early "Expanding" phase is characterized by enlarged joint-draining lymph nodes due to increased blood and lymphatic flow, and by the accumulation of $CD23^{+}/CD21^{hi}$ B cells in inflamed lymph nodes (B-in cells) [28,34]. The "Collapsed" phase that occurs with advanced disease is associated with three distinct mechanisms of lymphatic dysfunction [13]: release of local vasodilators (e.g., nitric oxide) from inflammatory cells that contribute to reduced lymphatic flow [13,35]; translocation of B-in cells into the sinuses of joint-draining lymph nodes, obstructing passive lymphatic flow [28,32,36]; and loss of cLV contractions [30,32]. In support of the translational relevance of these findings are data demonstrating that RA patients display similar B-in cell accumulation and translocation in joint draining lymph nodes, lymphatic dysfunction, including reduced cLV contractility, and lymphatic clearance compared to healthy controls [34,37–39].

Mast cells and telocytes within the synovial lymphatic system

Mast cells are recognized as effective regulators of LMC contractility due to their anatomical proximity and ability to produce, store, and release various inflammatory and vasoactive mediators [40–42]. Additionally, mast cells are positioned throughout the RA synovial sublining, where they comprise 5% or more of the expanded synovial cell population, and microanatomic clusters of mast cells are present in pannus tissue proximal to cartilage and bone erosion [43]. Based on these findings and evidence from preclinical and clinical studies supporting pro-inflammatory and catabolic roles for mast cells in RA [43–45], we investigated the effects of mast cells on joint-draining lymphatics and inflammatory-erosive arthritis in TNF-tg mice and their wild-type (WT) littermates. We found that popliteal lymphatic vessels (PLVs) are surrounded by an expanded frequency of $MCT^{+}/MCPT1^{+}/MCPT4^{+}$ mast cells in TNF-tg mice, and the percentage of peri-PLV degranulating mast cells was inversely correlated with lymphatic clearance [19]. We also identified a unique population of $MCT^{+}/MCPT1^{-}/MCPT4^{-}$ mast cells embedded within the PLV cellular architecture; however, the function of these cells remains unknown [19]. Genetic and pharmacologic mast cell loss-of-function experiments in TNF-tg mice demonstrated severe lymphatic defects, which were associated with exacerbated inflammatory-erosive arthritis [19]. Collectively, these findings led us to surmise that while $MCT^{+}/MCPT1^{+}/MCPT4^{+}$ mast cells have a well established role in inflammation, particular mast cell subtypes are also required for normal lymphatic function, proposed to be mediated by $MCT^{+}/MCPT1^{-}/MCPT4^{-}$ mast cells embedded within PLVs. However, the anatomy and physiology of mast cell integration into the SLS [16,46], and the mechanisms that facilitate increased contraction frequency during the Expanding phase of RA, remain to be elucidated.

Our discovery of telocytes within the SLS was initiated by a single-cell RNA sequencing (scRNAseq) analysis of murine PLV, aimed at identifying genes specifically expressed in LMC but not in blood vessels. This analysis identified *Efhd1, Myoc,* and *Pla1a* as candidate genes [47], and we generated three knock-in mouse lines in which a *CreER*^{T2} cassette was inserted into these genes [20▪]. The resulting mice were crossed to Ai9 reporter mice to assess tamoxifen-induced in vivo gene targeting via ex vivo whole-mount immunofluorescent microscopy (WMIFM), which revealed the presence of elongated tdT^{+} cells around PLVs in two of these lines (*Efhd1*-CreER$^{+/-}$ × Ai9$^{+/-}$ and *Myoc*-CreER$^{+/-}$ × Ai9$^{+/-}$ mice) [20▪]. Two distinct tdT^{+} populations of fibroblastic cells were observed that contained very long dendritic processes, phenotypically consistent with telocytes [48]. One population extended longitudinally along the PLV, while the other existed in telocyte arrays within the adipose tissue adjacent to the PLVs. Initial findings with the WMIFM approach identified tdT^{+} telocyte networks that parallel lymphatic vessels from the ankle synovium to the PLV [20▪]; formal studies to confirm the existence of this contiguous telocyte network are ongoing.

We also performed transmission electron microscopy (TEM) studies on PLVs from these transgenic mice, which revealed elongated cells with telocyte morphology (i.e. spindle-shaped polygonal cells with a large single nucleus, scant cytoplasm filled

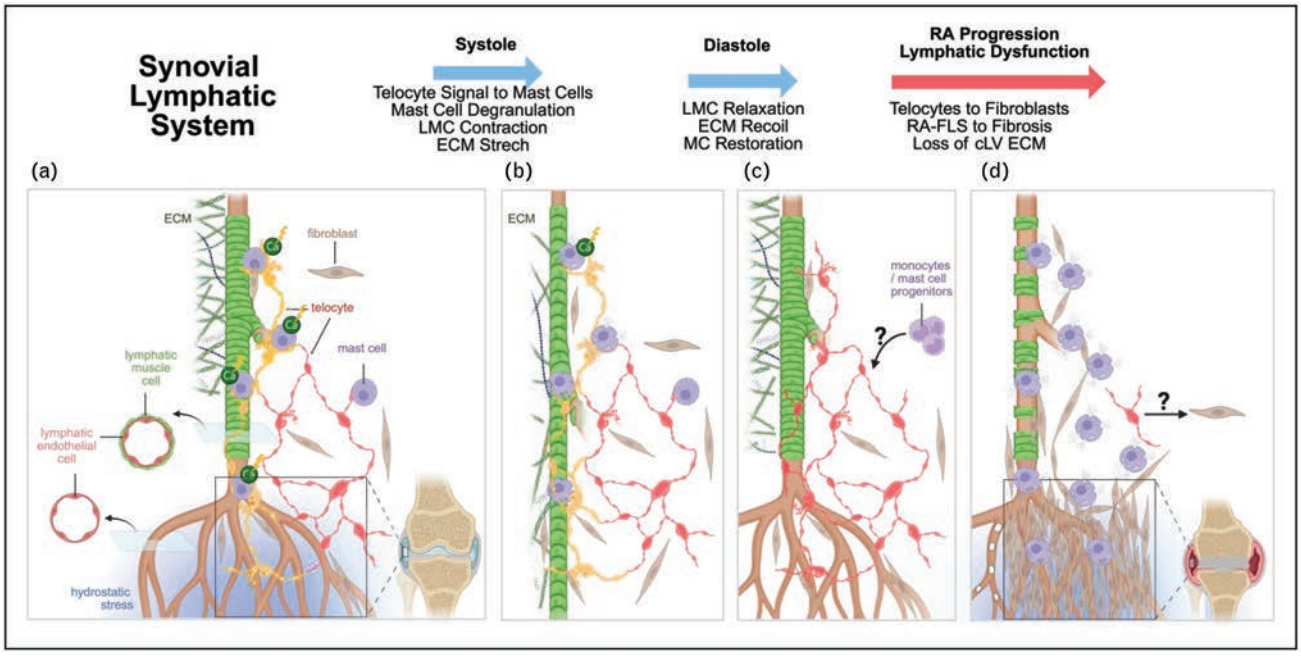

FIGURE 1. Anatomy and function of the synovial lymphatic system (SLS) in health and end-stage rheumatoid arthritis (RA). Schematic model of the SLS modified from Cao *et al.*[16] to include telocytes, fibroblasts, and mast cells. Anatomically, the SLS originates from open-ended lymphatic capillaries in the synovium (box), which collect excess interstitial fluid, proteins, waste, and immune cells within the joint. These branched capillaries are composed solely of lymphatic endothelial cells and feed lymph into collecting lymphatic vessels (cLV), which have lymphatic muscle cells (LMC) wrapped around the endothelium. Recently, we found that telocyte networks, integrated by their interconnecting telopodes, parallel the lymphatic vessel from the synovium to cLV, where they are physically integrated into mast cells. Adventitial fibroblasts also exist in the synovium and in the peri-cLV tissue that may function as extracellular matrix (ECM) producing cells to hold the SLS together and cover the cLV [20▪]. Once a hydrostatic threshold from interstitial fluid in the joint is achieved, synovial telocytes commence a Ca^{2+} mediated signal through the telocyte network to peri-cLV mast cells, which triggers their degranulation and release of factors (i.e., histamine, cytokines) to initiate LMC contraction and stretching of the ECM in resting cLV (systole). Diastole follows mast cell depletion with LMC relaxation and EMC tensile force-mediated reformation of the cLV. Subsequently, intrinsic cLV contractions in response to intraluminal shear force from draining lymph are perpetuated until the excess interstitial joint fluid is removed from the joint. Although the SLS is enlarged from lymphangiogenesis and synovial hyperplasia during early RA, the physiologic functions of the SLS are unchanged during this "expansion" phase of the disease. The "collapsed" phase of disease at end-stage RA involves several SLS changes, including: disintegration of lymphatic capillaries and the telocyte network, synovial telocyte differentiation into RA-fibroblast-like synoviocytes (FLS), and loss of cLV LMC and ECM. These changes result in lymphatic dysfunction and fibrosis.

with mitochondria, and thinly attenuated cytoplasmic extensions known as telopodes) consistent with the tdT^{+} telocytes identified by WMIFM [20▪]. Remarkably, these peri-PLV telocytes exhibited intimate contacts with mast cells via specialized junctional structures at their plasma membrane interfaces, suggesting active intercellular communication. These observations were validated using 3D immunofluorescent confocal microscopy [20▪], which demonstrated that the spatial distribution and interaction patterns observed by 3D confocal microscopy matched those observed by WMIFM and TEM. Altogether, these findings suggest a previously unrecognized cellular partnership between telocytes and mast cells along lymphatic vessels, potentially representing a novel signaling axis in SLS regulation (Fig. 1). In this model, synovial telocytes sense the hydrostatic pressure of the joint, and when it exceeds a threshold, these cells transmit a signal through the telocyte network into peri-cLV mast cells that triggers their degranulation and release of vasoactive factors to initiate resting cLV contractions, followed by intrinsic cLV contractions until the excess interstitial fluid in the joint is drained. This model also predicts that chronic inflammation degrades the ECM and joint-draining cLV cells together with the telocyte network, resulting in the lymphatic dysfunction observed in the Collapsed phase of inflammatory-erosive arthritis. It also predicts that synovial telocytes are lost during RA pathogenesis, which is consistent with immunohistochemistry studies [49].

This model also posits two features of the SLS for which no evidence exists, and which are now areas of active investigation. The first is that peri-cLV mast

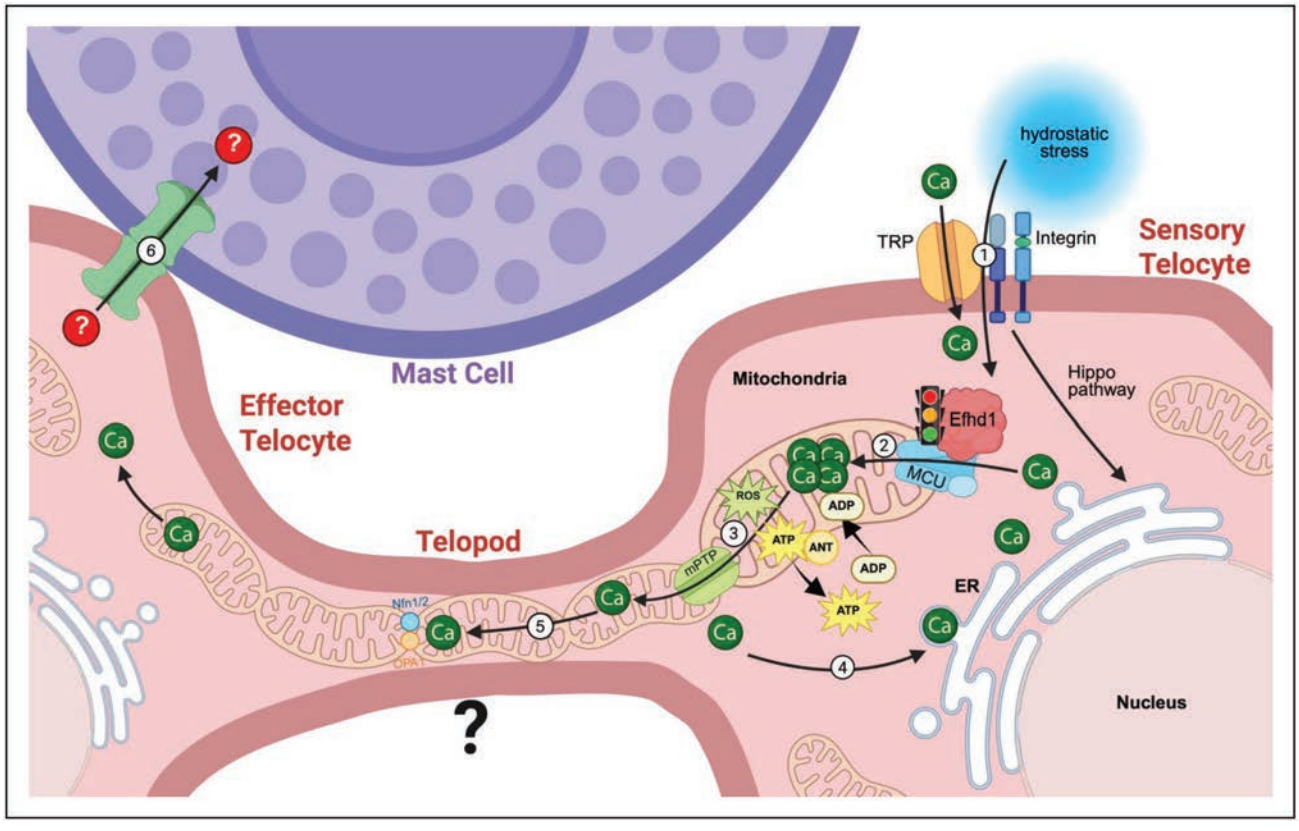

FIGURE 2. Long-range physical cell-to-cell Ca^{2+} signaling via mitochondria inside membrane nanotubes (telopodes) through the telocyte network and into peri-cLV mast cells. Schematic model illustrating how a synovial "sensory" telocyte (right) responds to hydrostatic pressure (1) via integrin receptors (i.e. $\alpha2\beta1$ and $\alpha2\beta5$) and transient receptor potential (TRP) ion channels (i.e. PC1 and PC2), which leads to increased cytosolic Ca^{2+} directly via channels and release of Ca^{2+} from the endoplasmic reticulum (ER). (2) This cytosolic Ca^{2+} enters mitochondria via Efhd1 regulation of the mitochondria calcium uniporter (MCU), and (3) is utilized for ATP and O_2^- production. (4) This ATP is exchanged with cytosolic ADP via the adenine nucleotide translocator (ANT) and is utilized to restore ER Ca^{2+}. Simultaneously, Ca^{2+} released from the mitochondrial permeability transition pore (mPTP) is transferred through intercellular mitochondrial networks held together by Nfm1/2 and OPA1 in nanotubes (telopodes) between telocytes via a hypothesized but unknown mechanism (?). This cascade continues through the telocyte network (5), terminating with Ca^{2+} transfer from an "effector" telocyte via an unknown mechanism (?) through gap junctions (i.e., connexin 43) into mast cells adjacent to collecting lymphatic vessels (6) to induce their degranulation and release of vasoactive factors.

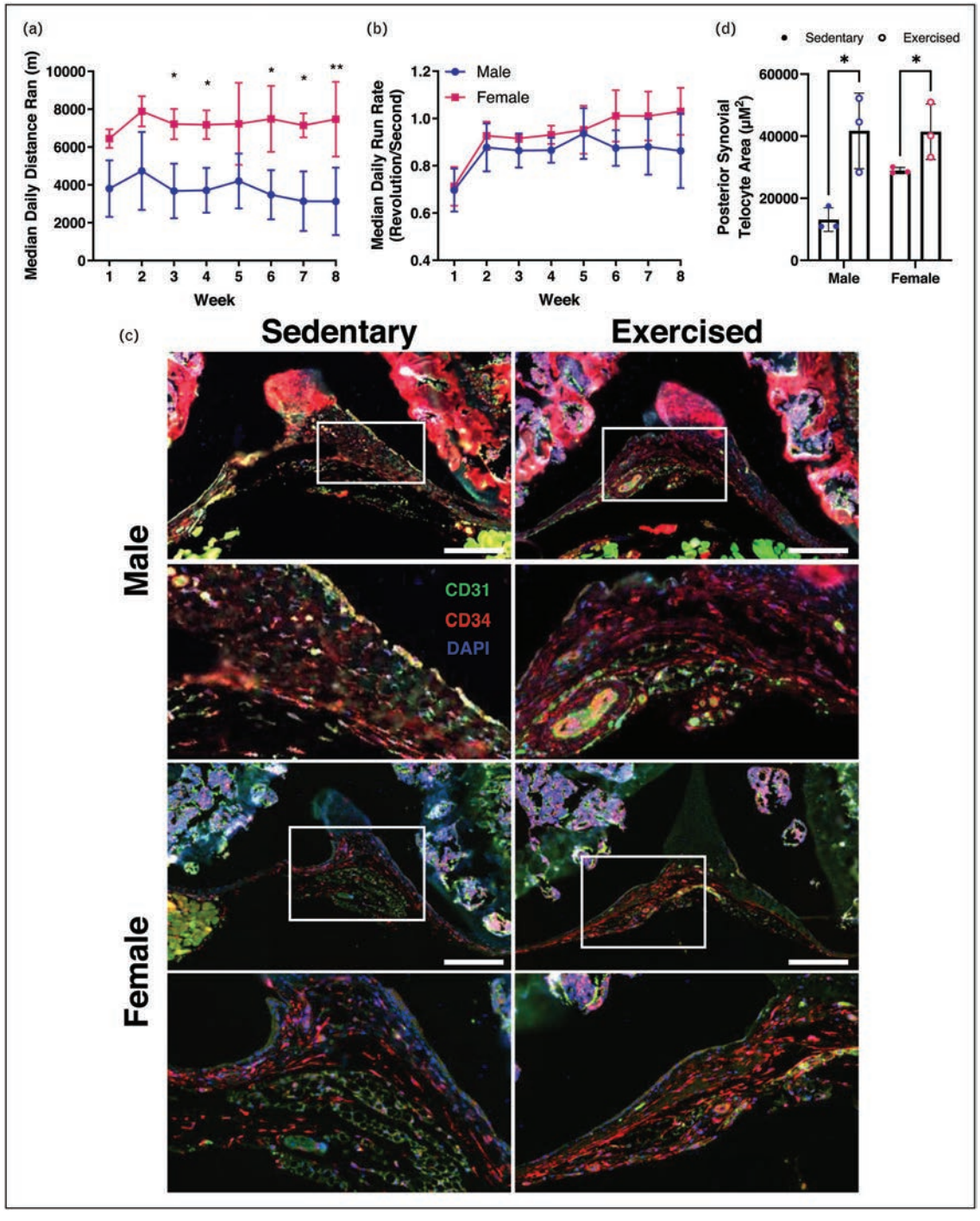

FIGURE 3. Voluntary wheel running increases the synovial telocyte area in the knee of mice. Animal research was performed on IACUC-approved protocols in which 6-week-old WT male and female C57B6 mice (n = 3) were individually housed in cages with locked (sedentary) or unlocked (exercised) running wheels for 8 weeks as previously described [63]. Plots of (a) daily median distance run in meters (m), and (b) daily median running rate (revolutions/second) per week in male and female mice are presented as the mean ± SD (*$P < 0.05$, **$P < 0.01$ via 2-way repeated measures ANOVA with Tukey's multiple-comparison test). (c) Mice were euthanized, and their knees were processed for formalin-fixed paraffin-embedded immunohistochemistry using labeled antibodies specific for CD31 and CD34, and DAPI counterstain as previously described [49]. Representative 10x fluorescent micrographs are shown (bar = 200 μm) with a magnified region of interest (box) highlighting the red, spindle-shaped telocytes in the synovium. (d) Quantification of the total $CD34^+/CD31-$ telocyte area within the posterior synovium in sedentary and exercised male and female mice are graphed with the mean ± SD (*$P < 0.05$. Two-way ANOVA with Tukey's multiple-comparison test).

cells are lost following lytic degranulation and must be replaced by the recruitment and differentiation of hematopoietic progenitors, driven by factors from adventitial cells. The other is the telocyte network intercellular signaling mechanism. We believe that Ca^{2+} signaling through mitochondria is critically involved, based on EFHD-1's only known functions, which are the regulation of the mitochondria calcium uniporter (MCU) [50] and mitoflash [51], and our findings that SLS telocytes are filled with mitochondria and display mitochondrial Ca^{2+} signals in response to osmotic shock in vitro [20▪]. Taken together, we hypothesize that the SLS telocyte network signals via long-range physical cell-to-cell Ca^{2+} signaling via mitochondria within membrane nanotubes [52], initiating with "sensory" telocytes within the synovium, and terminating with "effector" telocyte signaling to peri-cLV mast cells (Fig. 2).

Effects of exercise on telocytes and the synovial lymphatic system

Exercise is a well established therapeutic modality that mitigates disease-related chronic inflammation [53]. The American College of Rheumatology (ACR) recently released its first guidelines recommending exercise, rehabilitation, diet, and related interventions alongside disease-modifying antirheumatic drugs (DMARDs) as part of an integrative approach for managing RA [54]. Exercise improves lymphatic function by stimulating repetitive LMC and skeletal muscle contractions that act as a "lymphatic pump", promoting lymph flow, enhancing drainage, reducing swelling, and supporting overall immune health [55,56▪▪]. In addition to enhancing systemic lymphatic flow, exercise has recently been shown to increase local cardiac lymphangiogenesis and vessel density following 8 weeks of voluntary wheel running in aged mice [56▪▪]. Thus, gentle activities suitable for RA patients, including walking, light-to-moderate aerobic and resistance exercise, Pilates, yoga, and traditional Chinese exercise, which improve several RA symptoms [57▪], may also enhance lymphatic drainage in inflamed arthritic joints. However, further investigation is needed to uncover the potential benefits of exercise on lymphatic drainage and function in RA symptom relief.

As a follow-up to our clinical studies demonstrating lymphatic defects in RA patients with symptomatic hand disease [37], we conducted a pilot study to assess the effects of hand exercise on lymphatic flow in RA patients [58]. Three subjects completed both hand strength assessments and lymphatic studies before and after 6 weeks of standardized hand exercises by an occupational therapist. Although anecdotal, exercise improved grip strength at 19 of 36 sites (53%) and increased lymphatic flow at 14 of 30 sites (47%). These findings demonstrate the need for prospective clinical studies to formally establish the effects of hand exercise on RA signs and symptoms and on lymphatic drainage.

Both endurance and resistance exercise expand telocyte abundance in skeletal and cardiac muscle, where telocyte activity has been linked to stem cell activation and tissue regeneration [59–61]. Recently, we demonstrated that ad libitum running improves interstitial lung disease in TNF-tg mice compared to sedentary controls [62]. Based on these beneficial findings of exercise, we conducted a pilot study to determine whether voluntary wheel running increases synovial telocyte area in the knees of WT male and female mice (Fig. 3). Consistent with our prior work [52], female mice ran approximately double the distance of male mice at a similar pace. Interestingly, sedentary female mice exhibited an approximately twofold greater synovial telocyte area than males. Despite this sex difference at baseline, 8 weeks of ad libitum wheel running significantly increased synovial telocyte area in both sexes, resulting in a similar final telocyte synovial area in male and female mice. While these early findings demonstrate the beneficial effects of exercise on synovial telocyte expansion, the role of this expansion in supporting the SLS in an arthritic setting remains unclear. Thus, these preliminary findings warrant further investigation into how exercise-induced changes in synovial telocyte expansion and function may influence RA symptom management.

CONCLUSION

Lymphatic changes during RA pathogenesis can be defined in phases, in which the initial Expansion phase is associated with compensatory lymphangiogenesis to increase drainage of inflamed joints, and the Collapsed phase, in which lymphatic dysfunction is associated with flare and advanced disease. Joint homeostasis is maintained by the SLS, which contains telocyte networks that parallel lymphatic vessels from capillaries to mast cells adjacent to cLVs. The SLS breaks down during RA progression, which might be abated by moderate exercise.

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Conflicts of interest

There are no conflicts of interest.

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REVIEW

OPEN

Digital monitoring in rheumatoid arthritis: remote assessment, wearables, and data-driven disease management

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Purpose of review
This review examines the emerging role of digital monitoring technologies in rheumatoid arthritis (RA) management, including electronic patient-reported outcome measures (ePROMs), wearable sensors, and data-driven approaches. The aim is to evaluate how these tools support continuous disease monitoring, timely flare detection, and patient self-management, aligning with treat-to-target principles.

Recent findings
Recent evidence suggests increasing digital health monitoring feasibility through the use of smartphone applications, wearables, and analysis of the multisource data collection. However, barriers such as digital literacy from both patients and healthcare professionals, accuracy of the data collected, correct interpretation still need to be addressed. While digital health has overall shown benefits in terms of appointment distribution, waiting time reduction, continuous monitoring of disease activity, and psychological outcomes, the safe shift to digital monitoring without compromising safety and individuals personal preferences should remain a priority

Summary
Digital monitoring technologies represent a novel shift in RA management, offering continuous assessment beyond traditional clinic visits. While patient acceptance is generally high, implementation challenges include clinician awareness, software integration, and ensuring equitable access. Future directions involve refining predictive algorithms, establishing standardized digital biomarkers, and integrating multimodal data streams for personalized disease management

Keywords
digital health, patient-reported outcomes, rheumatoid arthritis, telemedicine, wearable devices

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease, carrying a high disease burden, and often characterized by unpredictable disease course [1]. In current practice, the predominant method of assessment remains in-hospital outpatient clinic visits, with a usual frequency of a couple of months [2], likely limiting the opportunity of closer disease monitoring. Thus, the emerging role of digital monitoring has come to surface, aligning with the treat-to- target principles proposed by EULAR guidelines [3▪▪]. Digital monitoring encompasses smartphone applications, wearable sensors, electronic patient-reported outcome measures (ePROMs), teleconsultation platforms, and data analysis of collected metrics. These promising tools aim to offer continuous management, including timely detection of disease flares, while simultaneously promoting self-management. In this review we discuss the following topics: remote assessment tools including ePROMs, wearable devices and sensor-based monitoring, and data-driven approaches.

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KEY POINTS

- Digital monitoring (ePROMs, wearables, and apps) enables continuous assessment of rheumatoid arthritis, improving flare detection and supporting self-management beyond clinic visits.
- Combining multiple data sources (patient-reported outcomes, sensor data, and clinical inputs) provides more accurate disease tracking than any single method alone.
- Benefits include reduced clinic burden, improved monitoring, and better psychological outcomes, but challenges remain in data accuracy, interpretation, and digital literacy.
- Sustained patient and clinician engagement is a key limitation, with participation often declining over time without integrated, human-supported care models.
- Future progress depends on validating digital biomarkers, developing predictive algorithms, and safely integrating these tools into routine, personalized care.

REMOTE ASSESSMENT IN RHEUMATOID ARTHRITIS

Remote assessment in rheumatoid arthritis brings together multiple digital tools that enable continuous monitoring and more responsive, patient-centered care, including ePROMs, use of smartphone applications, and tools effective in measuring disease activity in teleconsultation, while in parallel highlighting the need for multisource assessment for optimal management.

Electronic patient-reported outcome measures

Patient-reported outcome measures are routinely used to determine the patient's view regarding their experience with their disease. Examples of measurement instruments include Rheumatoid Arthritis Disease Activity Index (RADAI), 36-Item Short Form Survey (SF-36), Routine Assessment of Patient Index Data 3 (RAPID3), and Health Assessment Questionnaire (HAQ) among others [4]. Although historically, PROMs are completed in clinic consultations, new evidence suggests that electronic PROM (e-PROM) use has demonstrated significant positive outcomes in completion over the years, frequency of follow-up appointments and subsequent clinic time and wait time savings in patients with RA [4]. Despite high rates of patient satisfaction with this system, it is still important to not undermine the less than 9% of patients expressing neutrality or dissatisfaction [4]. Interestingly, a greater proportion of clinicians expressed satisfaction compared to the patients; however, both cohorts exhibited a predominantly positive response to their experiences [4]. On the other hand, Krushe *et al.*, revealed barriers in the rheumatologists' engagement with ePROMs, highlighting unawareness of suitable software solutions, as the main barrier to implementation [5]. Moreover, it has been suggested that clinicians have concerns about disease-related anxiety being increased due to self-reported measures, while high satisfaction with usual management approaches, poor motivation due to lack of symptoms and the system acting as a disease reminder. Nonetheless, both stakeholders found remoting interventions useful; however, it is important to note that evidence of noninferiority of remote health management in terms of RA disease activity and remission rates was conflicting among studies [6▪▪].

Of note, PROMs are advised not to be used as a substitute to disease activity as determined by clinical and laboratory measurements [7], while their cumulative use rather than the sole use of one PROM has been found useful [8▪▪]. More specifically, a combination of Visual Analogue Scale (VAS) general health/patient global assessment, Health Assessment Questionnaire- Disability Index, quality of life (EQ-5D) and pain, could be used as a remote screening tool for active RA [8▪▪]. However, this combination of multiple dichotomized PROMs resulted in a moderate diagnostic accuracy [area under the receiver operating characteristic curve (AUC-ROC) of 0.76] for distinguishing active from well controlled disease [8▪▪]. Further research on this model, identified that the sum of specific PROM items as well as demographic metrics enabled for more accurate discrimination of disease activity [9▪▪]. Compared to the model above, this one uses a combination of age, sex, disease duration, visual analogue scale (VAS) general health, 7 Health Assessment Questionnaire-Disability Index items, and VAS pain for the differentiation between well controlled and active disease; An AUC-ROC of 0.89 was shown in the development set, which maintained excellent discriminating ability (AUC-ROC 0.82) in the external validation set [9▪▪]. These findings align with previous data which show that wearable-integrated and app-based PROM collection has shown promise in capturing disease fluctuations and improving sensitivity to change compared with static clinic-based assessments [10▪].

The RAPID-3 also demonstrates a good discriminating ability, albeit based on both patient and physician assessment. This digital disease activity score (DAS) aligns with DAS-defined disease states which are commonly used in daily practice [9▪▪]. RAPID-3 was also used to determine treatment outcomes in patients initiating upadacitinib [11].

Similarly, a case-series evaluated the possibility of using electronic patient-generated pain scores to monitor response to corticosteroid treatment [12]. Therefore, these initiatives hold promising results both in aiding the stratification of the patients to be seen in clinic, but also in treatment monitoring. Nonetheless, this should not override patient and clinical concerns.

Regarding the long-term sustainability of ePROMs in the real-word, the engagement with ePROMs was evaluated in patients with inflammatory arthritis, including RA, through the use of an application. Patient engagement decreased overtime with half of the patients having dropped out by 14.8 months [13▪]. The rate of the app downloads was markedly increased during the COVID-19 pandemic, highlighting the need to assess the influence of environmental circumstances in digital health. In contrast, another feasibility study introducing the IMIDoc platform encompasses a broader, more integrated digital intervention, including monitoring with medication management, educational content, bidirectional communication between patients and clinicians, in addition to ePROMs [14]. While this study demonstrated good usability and acceptability, it has not yet detected long-term engagement in routine care. Collectively, these findings highlight a key gap between platform capability and sustained participation in clinical practice.

Teleconsultation and virtual triage

While teleconsultation compared to face-to-face consultations can entail challenges, it can be a viable and approach for patients, provided there is a safe framework. The RAID score was shown to be strongly correlated with DAS28-CRP score, while a score of <2 reflected good disease control in a teleconsultation setting [15▪]. However, this study did not evaluate the triggers to elicit a face-to-face visit, and as mentioned above these scoring systems should always be used along with clinical judgement. As recognized above, the issue of engagement emerges. A mixed methods study evaluated the uptake and views of an online RAID questionnaire, revealing that despite optimal patient engagement, this was not true for the healthcare providers [6▪▪], underpinning that efficiency of the digital approach necessitates mutual involvement.

With regards to psychological support for patients with RA, digital cognitive behavioral therapy (CBT) in the form of an application, demonstrated sustained improvements in SF-36 mental (MCS) scores compared to active controls, together with improvements in depression, anxiety, fatigue and social functioning. However, there were no changes in the physical component of SF-36, pain, and disability scores [16]. Overall, this study provides reassurance regarding the safeguarding of the mental health of patients, even from afar.

Interestingly, another feasibility study assessed the significance of digital health measures in patients at-risk of RA [17]. A multimodal digital self-monitoring program was trialed, including a general RA education video, a joint self-examination video, and REMOTRA, a monitoring decision support-system. None of the patients with REMOTRA scores <10 developed RA, yielding a negative predictive value and sensitivity of 100%. However, this should be further refined to ensure diagnostic accuracy is not compromised. Overall, the program was well received, however again engagement declined overtime [17].

Focusing on the reinforcement of self-monitoring via digital methods, the On-demand Program to EmpoweR Active Self-management (OPERAS) app, coupled with a Fitbit′ and physiotherapist counselling sessions, demonstrated significantly improved Patient Activation Measure (PAM-13) scores [18], sustained after 27 weeks. This reflects the benefits of multifaceted care, as well as the crucial beneficial role of physiotherapists in remote care. On the contrary, another randomized controlled trial, using an application alone, showed no improvement of Arthritis Self-Efficacy Scale (ASES) scores compared to controls [19▪]. This further stresses the importance of the human factor, and the benefits of blended care, as opposed to use of an application alone. Of note, this study reported no increased in pain catastrophizing as a measure to alleviate concerns about the psychological impact of digital monitoring [19▪].

WEARABLES

The use of wearable devices now gives the opportunity for continuous data gathering and utilization. Sharma *et al.* identified patterns in heart rate collected from the wearables, with the capability of distinguishing periods of symptomatic and inflammatory flares, enabling the identification of physiological changes before the onset of clinical disease. However, one of the limitations of this study was the approximate definition of an inflammatory flare as ± 7 days of each CRP measurement as part of routine care, underpinning the need for more frequent, scheduled biomarker measurement collection [20]. As alluded to above, the question of adherence to the device use remains, with comfort and digital literacy being potential contributing factors [20]. The need of a 'trigger" system now comes into question, to determine at which point should each patient need a more thorough review [20]. A feasibility study for wearable accelerometery, demonstrated that this

device for use in RA is feasible, has near-perfect adherence by the patients, with reported minimal impact on their daily life, and high willingness for long-term use [21]. Wearables therefore seem to have a practical advantage over the use of a smartphone application. However, this is something to be assessed on an individual basis. Moreover, Creagh *et al.* [22▪] expanded on the utility of wearables, by investigating physical activity (PA) metrics of daily-life, using machine learning to characterize symptoms of disease in people with RA compared to healthy controls.

Following the multisource approach, this study proposed that detection of RA severity levels could be improved by augmenting standard patient reported outcomes with sensor-based features as opposed to using PRO assessments alone [22▪]. Stradford *et al.* agree that PROMs, wearable data, or clinical measures in isolation are incomplete. In this study they used Fitbit devices to continuously monitor steps, heart rate, sleep patterns, and activity intensity in 150 patients with RA over a 12-week period [23]. The devices demonstrated excellent wear compliance (>90% of days) and successfully captured meaningful variations in activity patterns associated with disease activity changes [23]. The accessibility and affordability of consumer wearables make them attractive for large-scale implementation, though questions remain regarding measurement accuracy and clinical validation.

DATA-DRIVEN DISEASE MANAGEMENT

With the development of all the aforementioned new technologies used for efficient and monitoring, the transition of this data to meaningful management strategies is imperative. As mentioned above, combining wearable-derived sensor data with patient-reported outcomes has been shown to improve disease classification and severity estimation compared to PROMs alone [22▪], which in turn triggers the initiation of management.

Also, the aforementioned emerging digital monitoring systems are extending beyond disease tracking towards prediction and early detection, demonstrating high sensitivity for identifying individuals at risk of developing RA [17]. Although Sharma *et al.* did present that a combination of physiological deviations from baseline may act as early digital trigger signals for disease flares [20], further studies are warranted to establish how these signals are communicated and actioned by the patients and healthcare professionals. Nonetheless, integration into clinical workflows remains a major challenge, with healthcare professionals highlighting concerns regarding data interpretation, validation, and increased workload [24▪▪].

PRINCIPLES OF REGULATION OF REMOTE HEALTH

The development of these new technologies warrant careful frameworks for their implementation into practice, to offer appropriate and safe management. EULAR established points to consider (PtC) for the evaluation and implementation of apps for self-management of rheumatic and musculoskeletal diseases (RMDs) [25▪▪]. Key principles, include data protection, the emotional and physical safety of the applications, inclusiveness and consideration of individual user needs, and promotion of communication with healthcare professionals [25▪▪]. Expanding on these points, more recent PtC regarding remote care in RMDs overall also highlight some specific points, such as the diagnosis need to the established in a face-to-face visit, as well as the initiation of disease-modifying agents [26].

CONCLUSION

Digital monitoring in RA is shifting care from intermittent, clinic-based assessment towards a more continuous and data-driven approach. Electronic patient-reported outcomes, wearable devices, and teleconsultation each provide valuable but distinct information, all contributing to identifying changes in disease activity. As shown in this review, these modalities are most effective when used together, rather than in isolation, allowing for a more comprehensive assessment.

An important emerging concept is the move from simple monitoring to actionable disease management. Early evidence suggests that changes in physiological and behavioral data may precede clinical flares, raising the possibility of digital "trigger systems" to prompt timely reassessment. In parallel, predictive models are beginning to support risk stratification and earlier detection of disease. However, there is still a lack of clearly defined thresholds to guide clinical action, and uncertainty remains around how these data should be integrated into routine care.

Sustained patient engagement and clinician involvement are key to the success of digital approaches, as the presence of communication has been shown to improve outcomes,

Overall, digital health technologies offer significant potential to support more personalized and responsive management of RA. Future studies should focus on validating digital signals, defining actionable triggers, and ensuring that increasing data availability translates into meaningful improvements in patient care.

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Conflicts of interest

There are no conflicts of interest.

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Food additives, emulsifiers, microplastics, and ultra-processed foods in rheumatic disease pathogenesis

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Purpose of review
Dietary patterns have changed significantly over time, with ultra-processed foods now comprising a large proportion of daily energy intake in many countries. Ultra-processed foods (UPFs) contain numerous additives and may also increase exposure to processing- and packaging-related contaminants that could influence immune function. This review summarizes why UPFs have drawn growing attention and evaluates their potential relevance to autoimmune inflammation, with a focus on rheumatoid arthritis (RA) and related disorders.

Recent findings
Population studies suggest that higher UPF intake is associated with an increased risk of RA after adjustment for obesity and lifestyle factors. Experimental and translational studies suggest that components common in UPF-rich diets (e.g., emulsifiers, thickeners, synthetic colorants, added sugars, excess sodium, and some nonnutritive sweeteners), as well as microplastic exposures, may disrupt gut barrier integrity, remodel the microbiome, and promote low-grade inflammation. These mechanisms overlap with pathways implicated in RA and systemic inflammation, including dysregulation of Treg/Th17 balance, loss of mucosal tolerance, endotoxemia, and innate immune activation.

Summary
Overall, evidence supports biologically plausible mechanisms and epidemiologic associations linking UPF-rich dietary patterns to immune dysregulation relevant to rheumatic disease, but direct RA-specific interventional and mechanistic clinical data remain limited. Dietary exposures may represent modifiable risks; however, stronger longitudinal studies with validated RA phenotyping and pragmatic dietary interventions are needed before firm clinical recommendations can be made.

Keywords
autoimmunity, emulsifiers, food additives, rheumatoid arthritis, ultra-processed foods

INTRODUCTION

Rheumatoid arthritis is an autoimmune disease characterized by symmetric inflammatory polyarthritis with chronic synovitis and potential extra-articular complications. Diet has long been regarded as a modifiable influence on systemic inflammation and cardiometabolic risk, and emerging evidence suggests potential relevance to autoimmunity.

Ultra-processed foods (UPFs) are commonly defined using the NOVA classification as industrial formulations (NOVA Group 4) composed largely of refined ingredients and multiple additives, typically packaged and designed for palatability and convenience. They are widely consumed and represent a substantial proportion of daily dietary intake in many industrialized countries.

Epidemiologic studies suggest that higher UPF consumption, even after adjustment for obesity and lifestyle factors, is associated with higher rheumatoid arthritis risk and greater prevalence of arthritis [1▪,2▪]. Parallel experimental studies suggest that specific additive classes – including emulsifiers, carrageenan and other thickeners, synthetic dyes, excess sodium, added sugars, monosodium glutamate (MSG), and nonnutritive sweeteners – as well as environmental contaminants

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KEY POINTS

- Ultra-processed foods (NOVA Group 4) bundle multiple nutritional and nonnutritional exposures and have been associated with higher odds of arthritis and higher risk of incident rheumatoid arthritis (RA) in observational studies.
- Experimental and translational evidence suggests that components common in ultra-processed food-rich diets (e.g., emulsifiers, excess sodium, added sugars, some sweeteners, and certain colorants), as well as microplastic exposures, may impair gut barrier integrity and promote immune dysregulation relevant to autoimmunity.
- RA-specific longitudinal studies with validated phenotyping and pragmatic dietary interventions are needed to clarify causality, quantify effect sizes, and guide clinical recommendations.

such as microplastics, may impair gut barrier function, remodel the microbiome, and amplify pro-inflammatory immune pathways [6▪,7▪▪,8–11▪,12▪▪,13▪,14▪▪,15▪,16,17,18,19▪,20,21,22▪,23▪▪,24,25▪,26,27▪,28,29,30,31▪,32▪▪,33–37▪,38▪▪].

UPFs serve as a pragmatic exposure proxy that bundles multiple nutritional and nonnutritional factors. The following sections discuss specific additive classes and contaminants as candidate mechanistic mediators, recognizing that isolating individual effects in human populations remains challenging due to co-exposure and confounding.

This review focuses on UPFs as a dietary pattern and on key additive classes and contaminants as candidate mechanistic mediators, emphasizing gut barrier dysfunction, microbiome remodeling, T-cell polarization, and innate immune activation as plausible links between dietary exposure and synovial inflammation.

FOOD ADDITIVES, CONTAMINANTS, AND ULTRA-PROCESSED FOODS IN RHEUMATIC DISEASE PATHOGENESIS

Ultra-processed foods as a framework for additive exposure

UPFs are industrial formulations composed of refined starches, added sugars, industrial fats, and multiple cosmetic additives (emulsifiers, colorants, sweeteners, thickeners, flavor enhancers) [3▪,4▪]. In a large cohort analysis, higher UPF intake was associated with higher risk of incident rheumatoid arthritis (RA) after adjustment for BMI and covariates [e.g., UK Biobank: highest vs. lowest quintile adjusted hazard ratio (HR) 1.17; 95% confidence interval (CI), 1.01–1.36; per SD increase HR 1.06; 95% CI, 1.01–1.11] [1▪].

In cross-sectional NHANES analyses (2001–2018), higher UPF intake was associated with higher odds of self-reported arthritis after adjustment for covariates [2▪]. However, interpretation is limited by cross-sectional design, potential reverse causation, and phenotype misclassification. Residual confounding and dietary pattern clustering (e.g., socioeconomic factors, physical activity, smoking, overall diet quality) remain important limitations in observational studies.

UPF intake has also been associated with higher systemic inflammatory markers such as hs-CRP and pro-inflammatory cytokine profiles in some populations (e.g., adolescents) [5▪], though these associations are similarly vulnerable to residual confounding. Mechanistically, UPF-rich diets have been linked to intestinal dysbiosis, reduced short-chain fatty acid (SCFA) production, impaired mucus layer integrity, and increased gut permeability [4▪,10▪] – changes that may favor translocation of microbial products (e.g., lipopolysaccharide), activation of innate immune receptors, and skewing toward Th17-dominant responses that are also implicated in RA immunopathology [15▪].

UPFs serve as a pragmatic exposure proxy that bundles multiple nutritional and nonnutritional factors (e.g., energy density, glycemic load, fatty acid profile, sodium load, palatability, and packaging-related exposures). The following sections discuss specific additive classes and contaminants as candidate mechanistic mediators, recognizing that isolating single-additive effects in human populations remains challenging due to co-exposure and confounding. The relative strength of evidence across these exposure categories, including human data and key limitations, is summarized in Table 1.

Rheumatoid arthritis-specific research need: Prospective cohorts with validated RA phenotyping and repeated dietary assessments, plus pragmatic interventions that reduce UPF intake while tracking inflammatory biomarkers and RA outcomes.

Trans fats and industrial lipids

Although regulatory actions have reduced industrial trans-fat content in many settings, residual exposure persists through some UPFs and restaurant foods. Reviews of UPF components highlight industrial fats and interesterified oils as contributors to low-grade inflammation, endothelial dysfunction, and altered lipid handling [10▪]. Trans-fat- and saturated-fat-rich diets can activate innate immune pathways (e.g., TLR4 signaling, NLRP3 inflammasome activation)

Table 1. Summary of dietary exposures and evidence strength

Exposure	Type of human evidence	Main findings	Key limitations
Ultra-processed foods (dietary pattern)	Prospective cohorts; cross-sectional studies	Associated with higher RA risk and inflammatory markers	Confounding, diet clustering, self-reported arthritis
Emulsifiers	Short-term feeding trial; experimental studies	Increased gut permeability and microbiome changes	Short duration; mixture exposures
Added sugars / sweetened beverages	Large observational cohorts	Linked to metabolic and systemic inflammation	Limited RA-specific outcomes
Excess sodium	Human mechanistic and immunology studies	Promotes Th17 responses; impairs Treg function	Few RA-specific trials
Artificial sweeteners	Reviews and mixed human studies	Microbiome disruption; inflammatory signals	Heterogeneous exposure and confounding
Artificial food dyes	Preclinical and microbiome studies	Dysbiosis and intestinal inflammation in models	Limited human clinical data
Thickeners (carrageenan, xanthan, guar)	Preclinical and ex vivo studies	Mixed inflammatory and microbiome effects	Context-dependent; limited human data
Microplastics/nanoplastics	Emerging observational and experimental data	Barrier dysfunction and immune activation	Exposure measurement; causality unproven

RA, rheumatoid arthritis.

and promote macrophage infiltration in adipose tissue – mechanisms overlapping with RA-associated cardiometabolic inflammation [10▪]. While rheumatology-specific interventional data are limited, reducing industrial fats and UPF-derived lipids is biologically plausible given their links to innate immune activation and cardiometabolic inflammation.

RA-specific research need: Dietary trials testing replacement of UPF-derived industrial fats with minimally processed unsaturated fat sources, assessing clinical disease activity and cardiometabolic inflammation.

Sodium

High-salt environments can drive immune dysregulation across multiple cell types. Excess sodium enhances pathogenic Th17 and Th1 polarization, impairs regulatory T-cell (Treg) function, and activates inflammatory signaling pathways in antigen-presenting cells and macrophages [13▪,14▪▪]. High-salt diets exacerbate disease in experimental autoimmune models by amplifying SGK1-dependent Th17 differentiation and interleukin (IL)-17A production while impairing Treg function [13▪,14▪▪]. Dietary sodium reduction – and in some models SCFA supplementation – can partially restore Treg stability and blunt Th17 polarization, attenuating inflammatory cytokine production [13▪,14▪▪].

Human RA data remain limited, but sodium intake is strongly linked to hypertension and cardiovascular risk, which are clinically important comorbidities in RA. Because UPFs contribute disproportionately to dietary sodium, sodium reduction within an overall UPF-reduction strategy may be a low-risk target while awaiting RA-specific trials.

RA-specific research need: Randomized sodium-reduction interventions in RA (ideally embedded in a broader diet pattern trial) with mechanistic endpoints (Th17/Treg markers, microbiome, permeability) and clinical outcomes (DAS28, flares).

Added sugars and high-fructose corn syrup

Experimental work links high fructose intake to gut barrier injury and systemic inflammation. High-fructose diets can increase intestinal permeability and endotoxemia by altering tight-junction proteins and microbial composition, promoting hepatic and systemic inflammatory signaling [16,18▪]. Stress and high-fructose exposure may act synergistically to compromise mucosal immunity in preclinical models [17]. Epidemiologic studies associate sugar-sweetened beverages (SSBs) with metabolic syndrome, type 2 diabetes, cardiovascular disease, and increased mortality [19▪], and more recent cohorts link higher sugar/SSB intake to incident inflammatory bowel disease and worse outcomes in established disease [20]. Collectively, these data suggest that high added

sugar intake – particularly via SSBs and UPFs – may promote mucosal and systemic inflammation through microbiome shifts, oxidative stress, and metabolic endotoxemia.

RA-specific research need: Trials reducing added sugar within an anti-inflammatory dietary pattern, with microbiome/permeability biomarkers and RA clinical outcomes; observational studies distinguishing sugar sources (SSBs vs. solid foods) in relation to RA onset and activity.

Monosodium glutamate

Monosodium glutamate (MSG) is a widely used flavor enhancer in UPFs. Recent human studies have begun to clarify MSG's impact on the gut ecosystem. In 2024, a cross-sectional study reported that higher MSG intake was associated with shifts in gut microbial composition, including dose-related differences in taxa linked to inflammation and metabolic dysfunction [25▪]. A 2023 mechanistic review summarized animal and in vitro findings of MSG-associated oxidative stress, mitochondrial dysfunction, and altered cytokine profiles [26]. Combined exposures (e.g., MSG plus certain synthetic dyes) have also been reported to influence oxidative stress and neuroimmune signaling in experimental models [27▪]. While direct clinical evidence in RA is lacking, MSG may act as a potential co-factor in susceptible hosts, particularly when consumed as part of UPF-rich dietary patterns.

RA-specific research need: Controlled feeding studies varying MSG exposure within otherwise similar diets, measuring microbiome composition, gut permeability markers, and short-term inflammatory readouts in people with inflammatory arthritis.

Artificial sweeteners (nonnutritive sweeteners)

Nonnutritive sweeteners (NNS) such as aspartame, sucralose, saccharin, acesulfame K, and stevia derivatives are common in diet beverages and "sugar-free" UPFs. A 2025 narrative review described potential trade-offs: reduced caloric sugar intake but possible disruption of gut microbiota and SCFA-producing taxa in some animal and human studies [21▪]. Mechanistic work has suggested that certain agents (e.g., neotame) may impair epithelial integrity and alter commensal profiles in experimental models [22▪]. A 2025 systematic review reported associations between certain NNS (e.g., aspartame, sucralose) and inflammatory biomarkers, though causality remains uncertain due to heterogeneity, exposure misclassification, and confounding [23▪▪]. In RA, chronic NNS exposure may plausibly influence disease activity through microbiome-mediated pathways, but direct RA-specific clinical evidence is limited.

RA-specific research need: Prospective RA cohorts with quantified NNS exposure and trials comparing NNS-containing vs. NNS-free dietary patterns with microbiome and inflammatory endpoints.

Emulsifiers

Dietary emulsifiers such as polysorbate-80, carboxymethylcellulose, lecithin, mono- and diglycerides, and certain gums are key texturizing agents in UPFs. Experimental studies suggest that some synthetic emulsifiers can erode the mucus layer, increase bacterial encroachment, and disrupt tight-junction integrity, contributing to increased intestinal permeability and low-grade inflammation [6▪,7▪▪,8▪,9▪]. A 2025 placebo-controlled randomized feeding trial in humans reported that short-term consumption of a mixture of commonly used emulsifiers increased intestinal permeability and altered gut microbiota and inflammatory biomarkers, supporting potential causality for gut barrier effects in humans [7▪▪]. Carrageenan, used as a thickener and emulsifier, can amplify pro-inflammatory signaling in intestinal models, particularly under inflammatory conditions [11▪,12▪▪].

Although no trials have examined emulsifier restriction in RA, these data support studying emulsifier-reduced dietary patterns as potential adjunctive strategies in rheumatic disease management.

RA-specific research need: Interventions reducing emulsifier exposure (or switching to minimally processed alternatives) with validated RA outcomes and mechanistic biomarkers (permeability, endotoxemia, microbiome).

Artificial food dyes

Synthetic azo dyes (e.g., tartrazine, sunset yellow, Allura Red/Red 40) are used in beverages, candies, and snack foods. Microbiology studies show that many gut bacteria can reduce azo dyes, generating metabolites with potential genotoxic or immunomodulatory effects [28]. In experimental models, Red 40 exposure has been associated with dysbiosis and colonic inflammation, and microbiota transfer experiments suggest that dye-altered communities can worsen colitis in recipient animals [29] These findings suggest that certain colorants may aggravate intestinal inflammation and dysbiosis in experimental models. Clinical links to RA remain unproven, and dye exposures in humans co-occur with broader dietary pattern factors.

RA-specific research need: Observational studies quantifying dye exposure (including medication

sources) and short-term feeding studies assessing microbiome and inflammatory biomarkers in inflammatory arthritis.

Thickeners and stabilizers (carrageenan, xanthan, guar)

Thickeners such as carrageenan, xanthan gum, and guar gum are widely used in dairy products, plant-based milks, sauces, and processed meats. Reviews highlight carrageenan as a potential amplifier of intestinal inflammation, particularly in individuals with existing IBD [11▪,31▪]. In vitro and ex vivo studies show dose-dependent epithelial inflammatory responses following carrageenan exposure, although permeability effects may be context-dependent [12▪▪,32▪▪]. Data on xanthan and guar gums remain limited and require further study; effects may vary by dose, food matrix, and host factors [30▪]. In patients with established systemic inflammation, limiting diets heavily enriched in thickener-containing UPFs may be reasonable, although RA-specific evidence remains limited and stronger studies are needed before firm recommendations.

RA-specific research need: Feeding studies comparing thickener-containing vs. thickener-free versions of common foods, with permeability, symptom, and inflammatory outcomes; longer trials in RA are needed to assess clinical relevance.

Microplastics and nanoplastics

Microplastics and nanoplastics have been detected in food and water and in human biospecimens, raising interest in their potential biologic effects. Experimental studies suggest that microplastic exposure can impair gut barrier function, induce oxidative stress, alter microbiota composition, reduce SCFA-producing taxa, and activate inflammatory signaling pathways (e.g., NF-κB; cGAS–STING) [31▪,32▪▪, 33▪,34▪]. In a 2023 experimental study, polystyrene microplastics aggravated disease severity in an RA model, with enhanced synovial inflammation and joint destruction linked to gut barrier disruption and immune activation [35▪]. These data provide preliminary mechanistic evidence linking microplastic exposure to pathways relevant to rheumatic disease pathophysiology, highlighting microplastics as emerging environmental exposures of potential rheumatologic relevance. Given that UPFs may increase exposure to plastics via processing and packaging, this intersection warrants further study, particularly to clarify dose–response relationships, exposure measurement, and clinical relevance in rheumatic disease.

RA-specific research need: Human studies with standardized exposure assessment (dietary, water, and biomarkers) and prospective RA outcomes; mechanistic studies evaluating whether UPF reduction also reduces plastic-associated biomarkers.

CONCLUSION

Recent evidence suggests that ultra-processed foods and their associated additives may influence rheumatic disease risk through effects on gut barrier integrity, alterations in the intestinal microbiome, and downstream immune dysregulation. Epidemiologic studies suggest associations between higher UPF intake and RA risk, while experimental models provide biologically plausible mechanisms involving endotoxemia, innate immune activation, and dysregulation of Treg/Th17 balance. However, direct RA-specific interventional and mechanistic clinical data remain limited. Diet may represent a modifiable exposure, but stronger studies are needed before definitive clinical recommendations can be made.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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Rheumatoid arthritis contributes to comorbidity burden through systemic inflammation and autoimmunity: examples of atherosclerotic cardiovascular disease, interstitial lung disease, and depression

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Purpose of review
To summarize the recent literature investigating systemic impact of rheumatoid arthritis (RA) on comorbidity burden, using atherosclerotic cardiovascular disease (ASCVD), interstitial lung disease (ILD), and depression as examples.

Recent findings
People with RA have consistently higher rates of comorbidities compared to the general population that include ASCVD, ILD, and depression. In addition to enrichment of traditional risk factors such as smoking and obesity, people with RA have unique factors related to inflammation, autoimmunity, and medications that contribute to excess comorbidities across diverse organ systems. Specific inflammatory pathways contribute to excess ASCVD in RA perhaps through dysregulated lipid metabolism. Trials for ASCVD prevention have been performed or underway for several RA medications. Seropositivity and high articular disease activity are associated with RA-ILD that may lead to lung fibrosis/inflammation. Several antifibrotic medications show utility in RA-ILD, and the contribution of specific anti-inflammatory medications is being investigated. Pain from uncontrolled inflammation and autoimmunity may impact mental health, leading to higher risk of depression in people with RA.

Summary
RA contributes directly and indirectly to comorbidity burden across diverse organ systems through systemic inflammation and autoimmunity. While further work is needed, controlling RA disease activity through specific RA medications may mitigate excess risk for comorbidities such as ASCVD, ILD, and depression risk.

Keywords
cardiovascular disease, comorbidity, depression, interstitial lung disease, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) affects up to 1% of the population and is characterized by inflammatory arthritis, typically of the small joints of the hands and feet [1]. RA is a systemic inflammatory autoimmune disease and can affect organs besides the joints, such as the lungs. RA has been associated with increased risk for many types of comorbidities [2]. This excess comorbidity risk in RA may be due to varying mechanisms. For example, risk factors for RA may also contribute to risk of other diseases. The best-known example is smoking, which is strongly associated with RA and many other comorbidities [3–7]. Chronic systemic inflammation may cause organ damage indirectly. The RA disease process and autoimmunity itself may directly affect organs. Medications used to treat RA, such as glucocorticoids, can cause side effects that result in comorbidities. Finally,

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KEY POINTS

- Rheumatoid arthritis (RA) is associated with increased risk of many diverse comorbidities, perhaps through systemic inflammation and autoimmunity.
- RA has higher risk of atherosclerotic cardiovascular disease (ASCVD) through excess traditional risk factors (such as smoking and sedentary lifestyle), dyslipidemia, inflammation, and autoimmunity.
- Trials have investigated whether specific RA medications may prevent ASCVD.
- RA has higher risk of interstitial lung disease characterized by fibrosis and/or inflammation.
- RA has higher risk of depression perhaps due to chronic pain from articular inflammation and damage.

chronic pain from articular inflammation and damage may affect sleep, mood, and lifestyle that results in comorbidities. This narrative review describes recent literature investigating RA and its comorbidity burden using three examples: atherosclerotic cardiovascular disease (ASCVD), interstitial lung disease (ILD), and depression.

Rheumatoid arthritis and atherosclerotic cardiovascular disease

Rates of cardiovascular disease (CVD) continue to increase and remain the leading cause of death globally [8▪,9]. ASCVD arises from the intersection of lifestyle and nonlifestyle factors including older age, male sex, obesity, smoking, genetics/family history and hyperlipidemia [8▪]. CVD mortality rates are greatly influenced by age due to vascular disease [10]. Across biological sexes, men develop CVD at a younger age than women likely due to differences in hormonal and endothelial function, and greater engagement in CVD risk behaviors [11▪]. Obesity causes pathophysiologic cardiovascular changes that increase risk for CVD [12]. Cigarette smoking has been associated with increased risk of CVD with the level of risk correlating to number of pack years and exposure [13]. Physiologically, smoking alters the lipid profile and induces chronic inflammation of the vascular wall [13,14]. Lastly, hyperlipidemia, high LDL-cholesterol levels, increases risk of ASCVD [15]. ASCVD risk scores developed for the general population do not adequately capture the risk for patients with RA [16].

Individuals with RA are disproportionately affected by ASCVD, with a 1.5-fold higher risk [17▪]. RA and CVD share similar risk factors such as smoking, diet, and sedentary lifestyle [18▪,19,20]. Patients with RA have a greater frequency of traditional CVD risk factors, especially older age, hypertension, smoking, and diabetes mellitus [18▪]. Importantly, smoking has been found to increase RA disease activity, which increases risk of ASCVD [21]. In regard to sex, RA disproportionately affects women [21]. However, men with RA experience higher rates of CVD creating a gender paradox in the association of RA and ASCVD [21]. Beyond shared risk factors, a greater risk is observed in patients with longer disease duration, seropositivity, and additional systemic manifestations [17▪].

Inflammation is an important mediator for risk of ASCVD in RA [22]. RA and ASCVD share common inflammatory pathways, most notably interleukin (IL)-6, a pro-inflammatory cytokine, that drives the progression of both conditions [23]. Furthermore, persistent inflammation in RA, especially with high disease activity and frequency of inflammatory flares, has been shown to accelerate atherosclerosis [24,25▪▪]. This may promote plaque rupture, thrombosis, and vessel occlusion [22]. Ultimately, inflammation in RA leads to subclinical ASCVD, which includes carotid plaques, vascular resistance and hypertension, predictors of cardiovascular (CV) events [21,26▪]. These changes are mediated by cytokines, immune complexes, and endothelial dysfunction [26▪].

Immune and inflammatory-mediated CV disease have been observed across various studies. A 2024 study evaluated the relationship between the complement system and subclinical ASCVD in patients with RA [26▪]. Elevated levels of complement were observed in patients with RA associated with both increased carotid intima-media thickness (cIMT) and carotid plaque burden, markers of ASCVD [26▪]. This suggests that complement activation may contribute to ASCVD in RA [26▪]. Another longitudinal study in 2024, observed that chronic inflammation, measured by higher erythrocyte sedimentation rate (ESR) levels, in patients with RA had increased arterial stiffness, an established causal factor of CVD [25▪▪]. These studies, among others, demonstrate the role of the immune system and inflammation in the progression of ASCVD in the context of RA.

A "lipid paradox" has been observed that may mask the true risk of ASCVD in patients with RA [16]. In the general population, high LDL cholesterol levels are an indicator of high risk of CVD, as they induce a proatherogenic dyslipidemic state [16]. However, in patients with RA, inflammation may lower LDL levels but qualitatively still at high risk, making the patient appear paradoxically at low risk [16]. Thus, inflamed patients with RA may have relatively low LDL levels despite being at high risk

for ASVCD risk, calling for the development of new biomarkers for ASCVD risk prediction in patients with RA and other inflammatory conditions.

A trial in 2024 found multiple candidate biomarkers, such as serum amyloid A (SAA), high-sensitivity c-reactive protein (CRP), soluble TNF receptor 1 (sTNFR1), adiponectin, YKL-40, and osteoprotegerin (OPG) associated with both RA activity and arterial inflammation as measured by an FDG PET/CT scan [27▪▪]. Simultaneously, suppression of SAA leads to reduced atherogenesis [27▪▪]. This dual role makes SAA a promising target to improve detection and reduce CVD mortality in patients with RA.

A study in 2025 evaluated the role of detectable high-sensitivity cardiac troponin T (hs-cTnT) levels for CV risk stratification in patients with RA [28▪]. Traditionally, hs-cTnT is released in response to heart muscle damage allowing physicians to predict future cardiac events [28▪]. The study found that 29% of patients presumed low risk for CVD had evidence of subclinical myocardial injury, suggesting that hs-cTnT has the ability to predict risk in patients with RA [28▪]. Another recent bioinformatic analysis found six immune related hub genes (such as *NFIL3*, *EED*, *GRK2*, *MAP3K11*, *RMI1*, and *TPST1*) that have the potential to act as diagnostic genes for ASCVD in patients with RA [22]. To highlight, GRK2 is a receptor that plays a significant role in the progression of AS and has a high expression level in the synovial tissues of RA patients [22]. The related functionality of *GRK2* makes it a promising marker for identifying patients with RA at risk for CVD [22].

Several clinical trials have investigated the impact of specific RA treatments on ASCVD risk. Oral Surveillance, a 2022 clinical trial, evaluated cardiovascular risk attributable to Tofacitinib, a Janus kinase inhibitor, compared to tumor necrosis factor inhibitors (TNFi) [29]. Tofacitinib was found to be not noninferior to TNFi for risk of major cardiovascular adverse events [29]. Another trial evaluated the cardiovascular safety of tocilizumab (TCZ), an IL-6 antagonist, versus etanercept, a TNFi [30]. TCZ and etanercept had similar risk for CVD, with a hazard ratio of 1.05, despite observed increase in lipid levels in TCZ [30].

Many clinical trials have investigated the efficacy of rheumatic medications in the treatment of CVD. The CANTOS trial stemmed from the inflammatory hypothesis of atherothrombosis evaluating the potential of Canakinumab, a monoclonal antibody targeting IL-1β, to reduce IL-6 levels and consequently reduce AS [31]. Canakinumab successfully reduced the inflammatory marker CRP without reducing LDL cholesterol levels, effectively reducing CV events compared to the placebo group [31]. This highlights the role of inflammation in CVD risk [31].

A similar trial CIRT evaluated the ability of Methotrexate, a widely used anti-inflammatory treatment for RA, to prevent secondary atherosclerotic events [32]. Methotrexate was not found to have beneficial effects on the reduction of cardiovascular events demonstrating the complexity of inflammatory pathways [32]. Another trial investigating the impact of methotrexate with either a TNFi, or with both sulfasalazine and hydroxychloroquine found a reduction in arterial inflammation, decrease in CVR, in both treatment groups [33].

Rheumatoid arthritis and interstitial lung disease

Interstitial lung disease (ILD) is a serious and common extra-articular complication of RA [34▪,35▪]. While the pathogenesis is still being elucidated, it is thought to be a direct manifestation of the RA disease process, rather than indirectly related from inflammation, treatment, and symptoms. The exact prevalence of RA associated interstitial lung disease (RA-ILD) is unclear as the case definition is dependent on criteria used to define the disease and the study population [36]. Although the prevalence reported in various studies ranged from 2% to 60%, a large recent meta-analysis estimated that clinically apparent RA-ILD is present in about 11% of patients with RA [37▪,38].

There are various factors that put individuals with RA at a higher risk for developing RA-ILD. Epidemiological risk factors described for RA-ILD such as older age and male sex, are identified in several studies [34▪,39,40▪▪]. ILD is most common among male individuals who are older than 60 years of age [36,40▪▪,41▪▪,42,43,44▪]. Although RA is common in females, the increased occurrence of RA-ILD in males has resulted in this phenomenon being described as the "sex paradox" [34▪,37▪,42,43,45]. Cigarette smoking has also been identified as an independent risk factor in various epidemiological studies [34▪,41▪▪,42]. Smoking triggers an immune response in the lungs that leads to inflammation and injury of epithelial cells, promoting the formation of citrullinated proteins and the subsequent production of circulating autoantibodies. This process contributes to the development of RA-ILD [39]. In addition to cigarette smoking, several environmental factors have been implicated in the development of RA and RA-ILD. Environmental pollutants, such as fire smoke have been linked to RA-ILD development [46]. This was shown in a case-control study conducted using VA data from 2009 to 2018 that found that exposure to fire smoke was associated with almost 2 fold higher risk of RA-ILD [47▪▪].

A recent area of interest has been the association of the *MUC5B* promoter variant and leukocyte telomere length with RA-ILD [48,49▪]. The *MUC5B* promoter variant has been identified as the strongest known genetic risk factor associated with RA-ILD and this has been replicated in various international cohorts [50▪,51,52]. This variant has been identified as a risk factor in patients with idiopathic pulmonary fibrosis (IPF) and due to the significant overlap between IPF and RA-ILD [52]. This biomarker appears to be specific to RA-ILD with a usual interstitial pneumonia (UIP) pattern and does not seem to be linked with ILD that is associated with other autoimmune diseases [50▪,53▪]. Although the mechanisms of its contribution to the pathogenesis is unclear, it is hypothesized that over-expression of this gene leads to excessive mucin production and interferes with mucociliary clearance and repair mechanism in the distal airways ultimately resulting in fibrosis [50▪].

Another emerging area of interest is telomere length shortening. Prospective studies have shown that mutations that result in shorter peripheral blood leukocyte telomere length is associated with an increased risk of RA-ILD and IPF, as well as with disease progression [49▪,54▪]. Telomeres are repetitive DNA sequences found at the end of chromosomes serving as protective "caps" that prevent activation of DNA damage response and apoptosis [55]. These shorten with age, but in RA-ILD, individuals with this genetic risk factor have impaired alveolar repair mechanisms and increased release of inflammatory and fibrotic pathways [55].

Several risk factors for RA-ILD are closely related to their underlying disease and its treatments. The role of commonly prescribed medications such as methotrexate (MTX) and tumor necrosis factor inhibitors (TNFi), in the development and progression in various population groups has been debated [56▪,57▪]. MTX has been implicated as a causative agent in fibrotic lung diseases, but recent studies have even found it to be protective [35▪,56▪]. A recent study done in mice showed that MTX treatment increases pulmonary inflammation by inducing pneumonitis and increasing activation of Th17 cells leading to increased myofibroblasts expression and subsequent fibrosis [58▪,59▪]. In contrast, in mice that were treated with TNFi, the features of pulmonary inflammation and leukocyte infiltration were alleviated. Similarly, a matched retrospective cohort study of participants with RA-ILD found that TNFis did not significantly increase risk of respiratory hospitalization or all-cause mortality [60▪▪,61]. Consistent results were reported in a recent systematic review investigating the association between incident RA-ILD in patients using DMARDs where there was no increased risk found in those using TNFis [57▪]. However, this study reported a protective effect which was observed in those on MTX [57▪].

Anticyclic citrullinated peptide (CCP) antibody is an autoantibody routinely used in clinical practice for the diagnosis of RA [62]. This antibody has also been associated with an increased risk of RA-ILD and progression in various studies, including a recent meta-analysis [63,64▪▪,65]. These studies have found increased expression of these antibodies in patients with RA-ILD when compared to RA patients without ILD [39]. Notably, these autoantibodies can be present in patients with RA long before any clinical manifestation of the disease [39,66]. Articular disease activity has also been strongly associated with incident and prevalent RA-ILD [37▪,40▪▪,51,67,68].

RA-ILD arises from a complex interplay of genetic and environmental factors [69]. The exact mechanism by which RA-ILD occurs is not fully understood, however, pulmonary inflammation and autoimmunity are thought to be the main drivers of the disease [39,70,71]. Chronic inflammation resulting from infection, smoking or other mucosal injuries leads to airway and alveolar epithelial damage, triggering immune cell activation and the release of pro-fibrotic cytokines [71]. These mediators promote the deposition of extracellular matrix components such as fibronectin that ultimately leads to fibrosis [69]. In genetically susceptible individuals, auto antibodies against citrullinated proteins, which are expressed at a higher level in the patients with RA-ILD, contribute to disease development by recruiting immune cells that drive inflammation [72]. Similarly, smoking damages the epithelial linings of airways producing citrullinated protein resulting in autoimmunity to these peptides. This initiates a cascade of pro-inflammatory cytokines that result in fibrotic tissue deposition in the lungs [39,72].

Currently, there is no FDA approved therapy specifically indicated for RA-ILD, but several guidelines were recently released [37▪,41▪▪,73▪,74▪▪,75▪▪]. Treatment relies on controlling articular RA disease activity, antiinflammatories, and antifibrotics. Antifibrotic medications approved for IPF such as pirfenidone and nintedanib are agents commonly used for treatment of RA-ILD [71]. Nintedenib works by inhibiting multiple tyrosine kinase receptors that contribute to fibrosis. In the INBUILD trial, which enrolled patients with fibrosing ILD, a subgroup of patients with RA-ILD showed a significant slowed decline in their forced vital capacity (FVC) when compared to placebo group [76]. Pirfenidone suppresses growth factor β1 (TGF-β1), which is a key driver of fibrosis, and reduces fibroblast proliferation and differentiation [71]. Pirfenidone was shown to reduce the decline in FVC in two phase 2 trials, the

RELIEF and TRAIL-1 [77,78]. However, since the RA-ILD is a systemic autoimmune disease, there are underlying immune mechanisms that should be targeted [71]. Immunosuppressive agents like cyclophosphamide, rituximab, and azathioprine have shown benefits in patients with RA-ILD where patients showed stabilization or improvements of their lung function [71,79]. Recent trials continue to refine treatment options for fibrotic lung diseases. New trials such as FIBRONEER-IPF and FIBRONEER-PPF evaluated the use of nerandomilast, a phosphodiesterase-4B (PDE4B) inhibitor that targets both inflammation and fibroblast activation [80▪▪,81▪▪]. These trials on IPF and PPF have shown promising results with the medication now being FDA approved for both indications. There are ongoing trials investigating the use of this medication on patients diagnosed with systemic autoimmune rheumatic disease-associated ILD, including RA-ILD.

Rheumatoid arthritis and depression

RA may increase risk of depression and other mental health disorders through chronic pain and fatigue due to systemic and articular inflammation and damage [82▪]. This may lead to limitations in functionality and mobility that lead to disability and impact activities of daily life. There are also contributions from disturbed sleep that results in increased central sensitization and lower mood [83▪]. In addition, chronic glucocorticoid use may disturb the hypothalamus-pituitary-adrenal axis, leading to increased inflammation and adrenal insufficiency [84]. Finally, RA and its treatment may contribute to sedentary lifestyle, resulting in weight gain, lower function, and lower dietary quality [85,86]. Thus, RA contributes to increased depression risk in a myriad of ways, some directly related to RA disease processes and some indirect consequences. The prevalence of depression is up to threefold higher in people with RA compared to the general population [87].

Control of RA disease activity seems to be associated with lower depression risk. For example, a study found improvements in depression rates of calendar time that were correlated with improvements in disease activity [88]. Depression is also an impediment to reaching remission. A pooled analysis of randomized trials showed that depression, but not anxiety, was associated with less frequent remission [89]. This finding held even when only considering swollen joints rather than tender joints or patient global assessment [89]. Another large observational study also showed that depression was associated with lower rate of remission in RA [90]. Finally, depression has also been associated with increased risk of incident RA, specifically the seronegative phenotype [91]. This may be mediated by other lifestyle risk factors for RA that include low quality diet [92▪,93,94], sedentary lifestyle [19,95], and obesity [20,96–98]. There is likely a complex relationship, bidirectional relationship between RA and depression mediated by many factors.

CONCLUSION

We described several examples of how RA contributes to comorbidities through a variety of different mechanisms through systemic inflammation and autoimmunity. RA contributes to excess ASCVD indirectly through shared risk factors and disease specific processes such as dyslipidemia. Specific RA medications may lower this excess ASCVD risk. RA contributes to ILD risk as a direct manifestation of the RA disease process through systemic inflammation and autoimmunity that can result in inflammatory and/or fibrotic lung disease. RA-ILD may be treated with antifibrotics. Specific RA anti-inflammatory medications may also treat RA-ILD. RA may increase depression risk indirectly related to symptoms such as pain, poor sleep, and fatigue that result in low mood. Also, RA may increase risk for lifestyle factors such as obesity, low quality diet, and sedentary lifestyle that all may contribute to depression risk. This illustrates the complexity of how RA contributes to comorbidities and, in part, explains the myriad of excess comorbidities that people with RA may experience. Controlling disease activity seems to lower comorbidity risk, emphasizing the importance of treating RA to remission.

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Conflicts of interest

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Pathogenesis-directed lupus therapeutics

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Purpose of review
Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized, posing significant challenges to effective management. This review summarizes current United States Food and Drug Administration –approved therapies and management guidelines of the American College of Rheumatology.

Recent findings
Contemporary SLE management is guided by organ systems involvement and disease severity. Discoveries of molecular mechanisms underlying disease pathogenesis have driven the development of targeted biologic therapies, including natural and engineered antibodies, chimeric antigen receptor–guided cell therapies, and T-cell engagers, transforming the therapeutic landscape of lupus. In addition to traditional B-cell and plasma cell surface targets, emerging molecular targets include transmembrane signaling molecules such as CD40L and intracellular organelles such as endosomes and mitochondria.

Summary
While antibody and cell-based biologic therapies target pathogenesis-driving molecules, they suppress key immune pathways and thus infection remains a leading cause of morbidity and mortality. Accordingly, this review also addresses nonpharmacologic strategies – such as dietary modifications – that may confer therapeutic benefit without increasing susceptibility to infection. With a rapidly expanding portfolio of mechanistically driven clinical trials, the future of SLE management appears increasingly promising.

Keywords
antibody-directed therapies, cell therapies, diet, environmental factors, genetics, immunopathogenesis, metabolism, systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex, multisystem autoimmune disease, with multifaceted pathogenesis and varied presentation [1].

Since its earlier descriptions in 1800s as a limited cutaneous disease, our understanding of SLE has significantly evolved to what we currently view as a complex systemic disease [2]. The management of SLE is challenging due to its variable presentation and organ involvement.

The therapeutic options for the management of Systemic lupus erythematosus have greatly evolved since the last guidelines from American College of Rheumatology in 1999. The ACR has published new guidelines in 2025 which encompasses these multiple therapies [3▪].

New therapies with targeted molecular treatments have changed the landscape of lupus management. Following the success of cell therapies in oncology, these approaches bring a promising future in the treatment of lupus [4▪,5].

The purpose of this article is to obtain brief overview of these therapeutic options included in the guidelines as well as to look into emerging medications and therapies.

This review has grouped lupus therapeutics into three categories comprising of medications approved by the United States Food and Drug Administration (FDA) for the treatment of SLE (Table 1), indications other than lupus (Table 2), and new treatment approaches under development (Table 3).

PHARMACOLOGICAL THERAPIES

Antimalarials: hydroxychloroquine, chloroquine, and quinacrine

Hydroxychloroquine and chloroquine are 4–amino quinolones with a basic side chain and exert their

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KEY POINTS

- Complex multisystem involvement of lupus renders a challenge for management of patients.
- Understanding of molecular pathogenesis of lupus has paved way to more targeted therapies including biologics and cell therapies.
- With multiple trials ongoing targeting different molecules in the pathogenesis of systemic lupus erythematosus, the therapeutic options for lupus looks promising.

effects by accumulation in acidic compartments specially lysosomes. By increasing the pH, lysosomal enzymatic activity is prevented and thus leads to prevention of autoantigen presentation. These medications also inhibit toll-like receptor (TLR 7) and TLR 9 signaling, which inhibits further cell activation and production of inflammatory cytokines [6].

The ACR recommends hydroxychloroquine for all patients with SLE (Table 1) unless contraindicated, with baseline and periodic monitoring of CBC, renal and liver function, and EKG if indicated [3▪].

Hydroxychloroquine and chloroquine are associated with retinopathy; thus, it is recommended to get ophthalmologic screening with visual field testing and optical coherence tomography at baseline then annually not later than 5 years of initiation of hydroxychloroquine; and baseline then 4–6 monthly for chloroquine [2,3▪,6,7].

The ACR recommends addition of quinacrine to hydroxychloroquine if persistent mild cutaneous lupus despite topical therapies. Therapy with quinacrine may be challenging given availability through compounding pharmacies and cost barrier [3▪].

Antimetabolites: mycophenolate mofetil and azathioprine

Mycophenolate mofetil is a prodrug of mycophenolic acid (Table 2). Mycophenolic acid inhibits inosine monophosphate dehydrogenase, thus inhibiting the formation of guanine nucleotides, thereby inhibiting lymphocyte proliferation [8].

Mycophenolate is used for multiple organ manifestations in SLE including moderate to severe cutaneous manifestations, arthritis, recurrent pleuropericarditis, neuropsychiatric lupus, vasculitis, carditis, nephritis and thrombocytopenia [3▪]. It is recommended to monitor blood counts at baseline then in 2 weeks and then regularly once stable dosage obtained. Urine pregnancy test is recommended when on this medication at baseline, 8–10 days then on follow-ups [3▪].

Azathioprine is a prodrug of 6-mercaptopurine which can be converted to toxic thioguanosine nucleotides; and thus exhibits its immunosuppressive effects by eventually inhibiting the synthesis of DNA and cell proliferation [8].

Similar to mycophenolate, azathioprine is indicated in multiple SLE manifestations such as bullous lupus, arthritis, recurrent pleuropericarditis, vasculitis, and thrombocytopenia [3▪].

Calcineurin inhibitors: cyclosporine, tacrolimus, voclosporin

Tacrolimus, cyclosporine and voclosporin are calcineurin inhibitors. When T cells are activated, calcium calmodulin upregulates calcineurin activity resulting in activation of nuclear factor of activated T-cell pathway and thus resulting in transcription of interleukin (IL)-2. Calcineurin inhibitors inhibit this activation and thus decrease proinflammatory cytokine production [8].

Calcineurin inhibitors are indicated for treatment for lupus nephritis and thrombocytopenia in SLE [3▪,9]. When using tacrolimus or cyclosporine, It has been recommended to monitor complete blood count and liver function monthly for three months after initiation and then every three months, Lipid panel should be checked every 6 months, Creatinine, magnesium and potassium should be checked every two weeks for 3 months after initiation followed by monthly, Blood pressure should be monitored regularly [3▪]. If voclosporin is initiated then eGFR should be monitored biweekly for the first month followed by monthly thereafter, blood pressure should also be measured biweekly for the first month but after that monitoring should be done as needed [10].

B cell targeted therapies

Belimumab

Belimumab is a monoclonal antibody against B lymphocyte stimulator (BlyS). BlyS plays a role in differentiation of B lymphocytes to antibody producing plasma cells [11,12] (Fig. 2).

Belimumab is indicated for treatment of multiple manifestations of SLE such as cutaneous, musculoskeletal, serositis, hematologic, vasculitis and nephritis [3▪].

As a result of BLISS-LN study, it has been approved for lupus nephritis and is part of triple therapy for management of lupus nephritis (Table 1) [9,13].

Table 1. Current FDA approved therapies for systemic lupus erythematosus

Drug name	Organ system	Mechanism of action	Target molecule	Target cell	Current FDA indications	References
HCQ	All patients with SLE unless contraindicated	Increase pH in lysosome, affect antigen presentation Inhibition of TLR7 and TLR9 signaling	Multiple targets: Toll like receptors, lysosomes	Dendritic cells, T cells, B cells	-Lupus erythematosus -Malaria -Rheumatoid arthritis	[3▪,6,7]
Voclosporin	Nephritis Thrombocytopenia	Inhibit activation of nuclear factor of activated T-cell pathway → decrease transcription of IL-2→ decrease proinflammatory cytokine production.	Calcineurin	T cells	Lupus nephritis	[3▪,10]
Anifrolumab	-cutaneous -arthritis -vasculitis -recurrent pleuropericarditis	monoclonal antibody against type I interferon receptor→ decrease inflammation and immune response	Type I interferon receptor (IFNAR)	Multiple immune cells	Moderate to severe Systemic lupus erythematosus	[3▪,10,18]
Belimumab	-cutaneous -musculoskeletal -serositis -hematologic -vasculitis -nephritis	monoclonal antibody against B lymphocyte stimulator (BlyS→ interferes with differentiation of B lymphocytes to antibody producing plasma cells	Cytokine B-cell-activating factor (BAFF/BLyS)	B cells [12]	- Systemic lupus erythematosus -lupus nephritis	[9,10,12]
Obinutuzumab	-cutaneous (severe bullous lupus) - vasculitis -hemolytic anemia -thrombocytopenia - neuropsychiatric - carditis	B cell depletion - direct cell death -antibody-dependent cell-mediated cytotoxicity - antibody-dependent cellular phagocytosis -complement-dependent cytotoxicity	CD20	B cells	-Chronic lymphocytic leukemia -Follicular lymphoma -Active lupus nephritis	[3▪,10,15]
Glucocorticoids	For organ or life-threatening manifestations / acute control of inflammation: however shortest duration and lowest dose	Bind intracellular glucocorticoid receptor→ formation of complex which act on DNA sequences / Glucocorticoid response elements→enhance transcription of anti-inflammatory genes; suppress transcription of proinflammatory genes. Block transcription factors and affect stability of mRNA→ decrease production of inflammatory cytokines.	Intracellular glucocorticoid receptor	All cells	Multiple multisystem indications including rheumatological, endocrine etc.	[3▪,10,24]
Aspirin	Cardiovascular and thrombotic risk reduction in SLE	Acetylates and inhibits Cycloxygenase-1(COX-1), thus inhibits production of Thomboxane A2 in platelets→ inhibits platelet aggregation	COX-1 and at high doses COX-2	Primarily platelets, also megakaryocytes and other cells.	Arthritis, Carotid endarterectomy, Atherosclerotic cardiovascular disease, pain, fever	[10,25]

Table 2. FDA-approved for indications other than SLE

Drug name	Organ system	Mechanism of action	Target molecule	Target cell	Current FDA indications	References
Chloroquine	Mild ongoing cutaneous lupus despite HCQ	Increase pH in lysosome, affect antigen presentation Inhibition of TLR7 and TLR9 signaling Increase pH in lysosome, affect antigen presentation Inhibition of TLR7 and TLR9 signaling	Multiple targets: Toll like receptors, lysosomes	Dendritic cells, T cells, B cells	-Treatment and prophylaxis of malaria -Extraintestinal amebiasis	[3▪,6,10]
Quinacrine					N/A (compounded)	
Mycophenolate mofetil/ mycophenolic acid	-cutaneous -arthritis -recurrent pleuropericarditis -neuropsychiatric lupus -vasculitis -carditis, -nephritis -thrombocytopenia.	Inhibition of inosine monophosphate dehydrogenase→ inhibits the formation of guanine nucleotides → inhibits lymphocyte proliferation	Inosine monophosphate dehydrogenase	Lymphocytes	Maintenance immunosuppression for Solid organ transplantation	[3▪,8,10]
Azathioprine	-bullous lupus -arthritis, -Recurrent pleuropericarditis -Vasculitis -Thrombocytopenia	Azathioprine → 6-mercaptopurine → converted to toxic thioguanosine nucleotides→ eventually inhibits the synthesis of DNA and cell proliferation → immunosuppression	Purine synthesis pathway	Lymphocytes	-Renal transplant -rheumatoid arthritis	[3▪,8,10]
Tacrolimus	-Nephritis -Thrombocytopenia	Inhibit activation of nuclear factor of activated T-cell pathway → decrease transcription of IL-2→ decrease proinflammatory cytokine production.	Calcineurin	T cells	-Renal, Liver and heart transplant	[3▪,10]
Cyclosporine					-Renal, Liver and heart transplant -Rheumatoid Arthritis -Psoriasis	
Anakinra	-Recurrent pleuropericarditis	Antagonist of IL-1 receptor → prevents binding of IL1R to IL-1α and IL-1β	IL-1 type I receptor (IL-1RI)	Cells expressing IL-1RI	-Rheumatoid arthritis -Cryopyrin associated periodic syndromes (CAPS) -Deficiency of Interleukin-1 Receptor Antagonist (DIRA)	[3▪,10]
Canakinumab		Binds IL-1β and prevents binding of IL-1βwith IL1R	Cytokine IL-1β	IL-1β producing and responsive cells	-Cryopyrin-associated periodic syndromes (CAPS) -Familial Mediterranean fever (FMF) - hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) - tumor necrosis factor receptor–associated periodic syndrome (TRAPS) -Active Still's Disease -Gout flare	

Table 2 (*Continued*)

Drug name	Organ system	Mechanism of action	Target molecule	Target cell	Current FDA indications	References
Rilonacept		Dimeric fusion protein→binds IL-1α and IL-1β →prevents their binding to IL1 R	Cytokines IL-1α and IL-1β	IL-1 responsive cells	-Cryopyrin-associated periodic syndromes -Deficiency of interleukin-1 receptor antagonist (DIRA); remission maintenance -Recurrent pericarditis.	
Cyclophosphamide	-neuro psychiatric lupus - vasculitis -nephritis	Activated by hepatic metabolism→ cross links DNA→interferes with DNA synthesis and cell proliferation	DNA (alkylating agent)	Lymphocytes	-Malignant lymphomas, multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, Retinoblastoma, breast carcinoma.	
Rituximab	-cutaneous (severe bullous lupus) - vasculitis -hemolytic anemia -thrombocytopenia - neuropsychiatric - carditis	B cell depletion via multiple mechanism -antibody dependent cell mediated and/or complement-mediated cytotoxicity - Promoting apoptosis and inhibiting cell proliferation	CD20	B lymphocyte	- Chronic lymphocytic leukemia -Non-Hodgkins Lymphoma -Rheumatoid arthritis -Granulomatosis with polyangiitis -Microscopic polyangiitis -Pemphigus vulgaris	[3▪,10,14]
Colchicine	-Leukocytoclastic vasculitis -Pleuropericarditis	inhibits microtubule polymerization→ interferes with neutrophil activation, migration, degranulation→decrease neutrophil mediated inflammation	β-tubulin	Neutrophils Monocytes	-Familial Mediterranean fever -Gout flares -Atherosclerotic cardiovascular disease, risk reduction	[3▪,10,27]
Dapsone	Cutaneous (mild bullous lupus) - Leukocytoclastic vasculitis	-decreases production of superoxide and elastases; decreases adhesion and chemotaxis of neutrophils	Myeloperoxidase	Neutrophils	- Dermatitis herpetiformis - Leprosy - Acne vulgaris	[3▪,10,28]
IVIG	-Pleuropericarditis -thrombocytopenia hemolytic anemia -myocarditis	Multiple mechanism such as Fc receptor blockade, reduction of complement system mediated damage, FcRn blockade, B cell and T cell regulation	Fc gamma receptor, neonatal Fc receptors, complement components, cytokine receptors	Multiple immune cells	-Primary Humoral Immunodeficiency - Immune thrombocytopenia - Chronic inflammatory demyelinating polyneuropathy -Dermatomyositis - Multifocal motor neuropathy	[10,29]
Methotrexate	-Cutaneous -Arthritis	Inhibit DHFR→ decrease production of tetrahydrofolate→ decrease de novo DNA synthesis, cell proliferation Other: - Adenosine Release: - T-Cell Apoptosis/Nitric Oxide Synthase (NOS) Uncoupling NF–κB Inhibition	Dihydrofolate reductase	Rapidly dividing cells, immune cells, others	- acute lymphoblastic leukemia (ALL) - mycosis fungoides - non-Hodgkin lymphoma - meningeal leukemia - osteosarcoma - breast cancer - squamous cell carcinoma of the head and neck -gestational trophoblastic neoplasia -rheumatoid arthritis - polyarticular juvenile idiopathic arthritis (pJIA) - severe psoriasis	[3▪,10,30]
Leflunomide	-Arthritis: alternative	Inhibits Dihydroorate dehydrogenase → interfere with de novo pyrimidine synthesis→ inhibit DNA synthesis. At higher doses, also affect tyrosine kinase involved in T/B cell signaling.	Dihydroorate dehydrogenase	Activated T and B lymphocytes	- Rheumatoid arthritis	[3▪,10]

Table 2 (*Continued*)

Drug name	Organ system	Mechanism of action	Target molecule	Target cell	Current FDA indications	References
Lenalidomide	Refractory Cutaneous	Inhibits proinflammatory cytokines, enhances cell mediated immunity.	Cereblon	T cells, NK cells	- Multiple myeloma -Myelodysplastic syndrome - Mantle cell lymphoma - Follicular lymphoma - Marginal zone lymphoma	[3▪,10]
NSAIDs	-multiple	Anti-inflammatory effects through COX inhibition	Cycloxygenase enzyme	Most cells	multiple	
Sirolimus	Renal and Non renal SLE	Binds with FKBP-12→ complex inhibits mTOR→ prevents T cell activation	FK-binding protein 12	T cells	-Chordoma -Kidney Transplant rejection prophylaxis -Lymphangioleiomyomatosis	[10,48,49]
N-acetyl cysteine	Systemic SLE manifestations including neuro psychiatric, hepatic.	Precursor for glutathione synthesis→Reverse oxidative stress, inhibit mTOR activation, decrease mitochondrial ETC activation	Glutathione	T cells and other immune cells	-Acetaminophen overdose -Adjuvant in respiratory conditions	[10,55,63]
GLP-1 Receptor Agonist	-possible favorable outcomes in cardiovascular and renal manifestations	Enhances glucose dependent insulin secretion; affect GI motility. Possibly has immunomodulatory effects	Glucagon like peptide 1-receptor	Multiple cells including pancreatic, GI, cardiovascular, immune cells.	-Type 2 Diabetes mellitus -Obesity -MASH	[10,31,32]
SGLT-2 inhibitors	Possible renal and cardiovascular benefit Especially reduction in AKI, CKD, heart failure	Inhibit proximal tubular glucose reabsorption→ glycosuria	Sodium–glucose co-transporter 2	Proximal renal tubular cells	-Type 2 Diabetes mellitus -Chronic Kidney Disease -Heart Failure	[10,34]
Metformin	-Potential benefit in nephritis, decreasing cardiovascular events	Decreases hepatic production of glucose. Additionally, works on AMP kinase dependent and independent pathways to exert anti-inflammatory and immunomodulatory effects.		Multiple including hepatocytes, intestinal cells, tissue resident immune cells	-Type 2 Diabetes mellitus.	[10,33,35]

Table 3. Emerging therapies for SLE

Drug name	Target	Target cell	MOA	Indication/study phase	References
Iscalimab	CD40	B cells, monocytes, macrophages, dendritic cells	Anti CD40 monoclonal antibody	II proliferative LN	[68]
Mosunetuzumab	CD20, CD3	B and T lymphocyte	humanized IgG1 CD20xCD3 bispecific antibody → binds CD3 on T cells and CD20 on B cell → T cell mediated cytotoxicity	Phase 1	[88]
Felzartamab	CD38	NK cells, plasma cells	anti-CD38 monoclonal antibody → binds CD38 on NK/plasma cells→ antibody dependent cellular cytotoxicity/ antibody dependent phagocytosis	Phase 1,2	[71]
Daratumumab	CD38	Plasma cells, plasmablasts, immune regulator cells	anti-CD38 monoclonal antibody → binds CD38 highly expressed on plasma cells and plasmablasts → antibody dependent cellular cytotoxicity/ antibody dependent phagocytosis/ direct cell death and complement mediated cytotoxicity→ depletes plasma cells	Phase 2 for lupus nephritis	[72] [73]
Xeligekimab	IL17A	T cells, B cells, other cells	recombinant human interleukin (IL)-17A-neutralizing monoclonal antibody → block binding of IL17A and IL17AR→prevent downstream inflammation		[81]
DS-7011a	TLR7	Plasmacytoid dendritic cells, B cells, monocytes/macrophages.	Monoclonal antibody against TLR7→ inhibits TLR7 signaling → decrease production of interferon, B cell activation.	Completed phase 1b/2	[74]
Ianalumab	BAFF-R	B cells	Afucosylated monoclonal AB against BAFF-R. dual mechanism: -B cell depletion by enhanced antibody-dependent cellular cytotoxicity (ADCC -blocks BAFF:BAFF-R mediated signaling	Phase 3	[79,80]
Frexalimab (SAR441344)	CD40L	T cells	anti-CD40L monoclonal antibody→ inhibits binding of CD40L to CD 40→ deceased T cell mediated immune response	Phase 2	[69]
Nipocalimab	Neonatal Fc receptor	Immune cells, endothelial and hematopoietic cells	Monoclonal antibody binds and block IgG binding site Neonatal Fc receptor> prevents binding of Fcrn to IgG → decrease circulating IgG	Phase 2	[82]
Dapirolizumab	CD40L	T cells	Fab which binds CD40L→blocks CD40-CD40L binding→ inhibits CD40 activation	Phase 3	[70]
Litifilimab	Blood dendritic cell antigen 2 (BDCA2) on plasmacytoid dendritic cells,	Plasmacytoid dendritic cells	a humanized monoclonal antibody against BDCA2; is a receptor that is exclusively expressed in PDCs →suppress type I Interferon production	-Phase 3 SLE -CLE	[83–85]
Upadacitinib	JAK		JAK inhibitor	Completed phase 2; Phase 3 ongoing	[89] [90]
Zanubrutinib	BTK	B cells	Targets Bruton tyrosine kinase which is important for B cell development and function	Phase 2 in China	[91] [92]
Iptacopan	complement	Cells involved in alternate complement pathway	Complement inhibitor→inhibit activation of alternate pathway	Phase 2	[93]
Envudeucitinib	TyK2	T cells, dendritic cells, APCs, other immune cells	Selective TyK2 inhibitor→blocks signaling through cytokine receptor that use TyK2 (IL-12 and IL23R, type I interferon receptors, IL10 family)	Phase 2	[86]
Deucravacitinib	TyK2	T cells, dendritic cells, APCs	TyK2 inhibitor→ inhibit downstream, activation of STATs	Phase 3 current	[87]
VENT-03	cGAS	Multiple cells	cGAS inhibitor→inhibits cGAS mediated production of cGAMP→ decrease expression of IFN and NFKB proinflammatory cytokines	Completed phase 1	[99,100]
CAR-T and CAR-NK cell therapy	CD19/CD19-BCMA/CD20-BCMA	B cell/plasma cells	Activates genetically engineered T cells to target antigen of interest → CD19/BCMA in B cells/plasma cells →B cell depletion	Phases 1,2,3	[4▪,5]

Table 3 (*Continued*)

Drug name	Target	Target cell	MOA	Indication/study phase	References
Low dose IL-2	IL-2 receptor	Regulatory T cells (Tregs)	Activates STAT5 → enhances anti-inflammatory effect →Treg/TH17 balance	Phases 2,3	[94]
Enpatoran	TLR7 and TLR8	Plasmacytoid dendritic cells and other innate immune cells	Inhibits TLR 7/8→ ultimately inhibits expression of type 1 interferons		[75,78]
E6742	TLR7 and TLR8	Plasmacytoid dendritic cells and mononuclear cells	Inhibits TLR 7/8→ ultimately inhibits expression of type 1 interferons		[76,78]
MHV370	TLR7 and TLR8	plasmacytoid dendritic cell and other immune cells	Inhibits TLR 7/8→ ultimately inhibits expression of type 1 interferons		[77,78]
Mizoribine	inosine-5-monophosphate dehydrogenase	T cells, B cells,	Inhibition of inosine monophosphate dehydrogenase→ inhibits the formation of guanine nucleotides → inhibits lymphocyte proliferation.	Completed phase 3. Approved for Lupus nephritis in Japan.	[95]
Atacicept	BAFF and APRIL	B cells	BAFF is required for B cell maturation, function and proliferation. APRIL(a proliferation-inducing ligand) affects B cell maturation and function. Atacicept and Telitacicept bind both BAFF and APRIL and prevent them from interacting with receptors on B cells.	Phase 2,3	[96,97]
Telitacicept	BAFF and APRIL	B cells		Approved for SLE in China	[98]

Anti-CD20 monoclonal antibodies

Obinutuzumab and rituximab are monoclonal antibodies against CD20 (Fig. 2). Rituximab is a type I chimeric anti-CD20 monoclonal antibody whereas obinutuzumab is glycoengineered type II chimeric anti-CD20 monoclonal antibody [14]. Obinutuzumab provides enhanced antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis along with better tissue B cell depletion compared to rituximab [15,16].

Anti-CD-20 agents are indicated for refractory lupus nephritis [9]. They are also indicated for severe bullous lupus, severe vasculitis, hemolytic anemia, thrombocytopenia, neuropsychiatric manifestations, carditis in lupus [3▪].

When using CD20 monoclonal antibodies, it is recommended to monitor blood counts at 3 months then 6 months, and immunoglobulin levels every 6 months [3▪].

Drugs targeting cytokine signaling

Anifrolumab

Anifrolumab is a monoclonal antibody against type I interferon receptor [17,18] (Fig. 2). It is indicated for moderate to severe cutaneous manifestations, arthritis, vasculitis, recurrent pleuropericarditis in SLE [3▪]. Currently, anifrolumab is also being studied for treatment of lupus nephritis [19].

In long-term placebo-controlled extension study of anifrolumab, it was found to be generally well tolerated with lower glucocorticoid use and improvement in SLEDAI in anifrolumab group [20].

Recombinant varicella zoster vaccine is recommended for all adults, in addition to routine vaccination, prior to starting therapy with anifrolumab [3▪].

Interleukin-1 blockade

IL-1 antagonists are indicated in management of recurrent pleuropericarditis in SLE, this is mostly from indirect evidence in studies done for non SLE pleuropericarditis [3▪].

Anakinra (IL-1 receptor antagonist) and rilonacept (IL1 alpha and beta cytokine trap) have been shown to be efficacious in the management of recurrent pericarditis [21–23].

Glucocorticoids

Glucocorticoids are recommended for organ or life-threatening manifestations/acute control of inflammation, however at shortest duration and lowest dose [3▪]. Glucocorticoids bind intracellular glucocorticoid receptor thus forming a complex which act

on DNA sequences/glucocorticoid response elements to enhance transcription of anti-inflammatory genes and suppress transcription of proinflammatory genes [24].

Aspirin

Aspirin is recommended for cardiovascular and thrombotic risk reduction in SLE.

It acetylates and inhibits COX1 thereby inhibiting TXA2 and inhibiting platelet aggregation [25].

Alkylating agent: cyclophosphamide

The use of alkylating agent cyclophosphamide in lupus has decreased with the approval of less toxic therapies. It is still indicated in SLE in neuropsychiatric lupus, vasculitis, nephritis [3▪]. Given its adverse effect profile, it is recommended to monitor blood counts and creatinine weekly for 1 month then monthly. Urinalysis should be performed with every infusion and 6 monthly after therapy [3▪]. Urine pregnancy test should be monitored before every infusion, and consideration should be given to fertility preservation for patients requiring cyclophosphamide therapy [3▪,26]. Other alkylating agents such as chlorambucil have been studied in the past for SLE, however are not part of current therapy due to significant adverse effect profile outweighing benefits. Given significant carcinogenic effects of chlorambucil, its use is limited only for treatment of chronic lymphoid leukemias and malignant lymphomas [10].

Other medications

Several medications that are not yet approved for treatment of SLE by the FDA, however used off label and are included in the ACR 2025 guidelines, are briefly discussed in this section and their specifics have been summarized in the Table 2.

Colchicine

Colchicine can be used for pleuropericarditis and leukocytoclastic vasculitis in SLE. Given metabolism by CYP3A4, multiple drug interactions exist and must be considered [3▪,27].

Dapsone

Dapsone can be used for management of mild bullous lupus [28]. Careful consideration should be given to check G6PD deficiency prior to its use. Blood counts and liver function should be monitored weekly for a month, then monthly for three months then quarterly [3▪].

IVIG

Intravenous immunoglobilin (IVIG) can be used for multiple presentations in SLE, such as pleuropericarditis, myocarditis, thrombocytopenia and hemolytic anemia [3▪]. IVIG acts by multiple mechanisms such as Fc receptor blockade, reduction of complement system mediated damage, FcRn blockade, B cell and T cell regulation [29]. Complete blood count and chemistries including liver function is recommended prior to treatment and CBC should be monitored monthly to evaluate hemolysis [3▪].

Methotrexate

Methotrexate is used for inflammatory arthritis in SLE [3▪]. Methotrexate inhibits DHFR thus decreasing production of tetrahydrofolate and decrease de novo DNA synthesis, cell proliferation [30].

When on Methotrexate, blood counts liver and renal function should be monitored monthly for three months then quarterly [3▪].

Leflunomide

Leflunomide can be used as alternative for arthritis in SLE. Blood counts liver and renal function should be monitored monthly for three months then quarterly [3▪].

Lenalidomide

For severe refractory cutaneous lupus, lenalidomide can be used if multiple therapies do not prove effective. However, given potential of teratogenicity urine pregnancy testing is recommended 24 h prior to initiating therapy, weekly during the first month followed by 2–4 weekly [3▪].

Metformin, SGLT2 inhibitors, GLP1 agonists confer potential benefits for cardiovascular and renal outcomes in lupus and are currently being studied [31–35].

Bispecific T cell engagers

Bispecific T cell engagers (BiTEs) are molecules that bind B cell and T cells leading to T cell engagement which eventually leads to release of perforin from T cell resulting in apoptosis of B cell [36].

BiTEs consist of two single-chain variable fragments, which concurrently binds CD3ε on T cells and target on B cell (CD19/BCMA) thus forming a synapse and leading to T-cell-mediated B cell destruction [16].

BiTEs have been successfully used in acute lymphoblastic leukemias and have recently shown benefit in refractory rheumatoid arthritis [36]. BiTEs can be effective therapy for autoimmunity in lupus.

Chimeric antigen receptor-T cell therapy

Chimeric antigen receptors (CARs) are fusion proteins made up of multiple components: T cell activating domain, co stimulatory domain, transmembrane domain, hinge region and extracellular domain which contains antibody variable fragment which targets molecule of interest (CD19/BCMA) [37] (Fig. 1). Following the success of CAR-T therapy in treatment of B cell malignancies, this has emerged as a potential revolutionary treatment of lupus given the fundamental role of B cells in the pathogenesis of SLE [4▪,5]. Currently, investigations are ongoing to study CD20/BCMA CAR-T cell therapy for management of lupus by targeting antibody producing plasma cells as well as B cell precursors [38].

Regulatory T cells have been engineered to target immunogenic fragment of smith autoantigen subsequently reducing renal dysfunction in lupus nephritis [39].

Multiple studies using CD19/CD19-BCMA have shown promising results in SLE management with significant reduction in SLEDAI scores as well as serological markers [4▪].

A recent study assessed safety and efficacy of CD19 CAR-T cells for refractory SLE, systemic sclerosis (SSc), and idiopathic inflammatory myositis (IIM), and showed promising results regarding safety and efficacy of this therapy. In SLE patients, DORIS remission was reached, progression of ILD was halted in SSc and moderate/major response was achieved in IIM patients [40]. Prior studies have shown similar improvement for refractory SLE with CD19 CAR T cell therapy [41].

Targeted lipid nanoparticle technology to deliver mRNA for in vivo generation of CAR T cells are being studied for SLE with encouraging results [42,43]. Avoiding the need for lymphodepletion and providing immune reset in refractory autoimmune disease would be the eventual goal of these therapies [42,43].

Short-lived (SLPCs) and long-lived plasma cells (LLPCs) are distinct subsets of plasma cells in SLE. SLPCs are generated from activation of extrafollicular

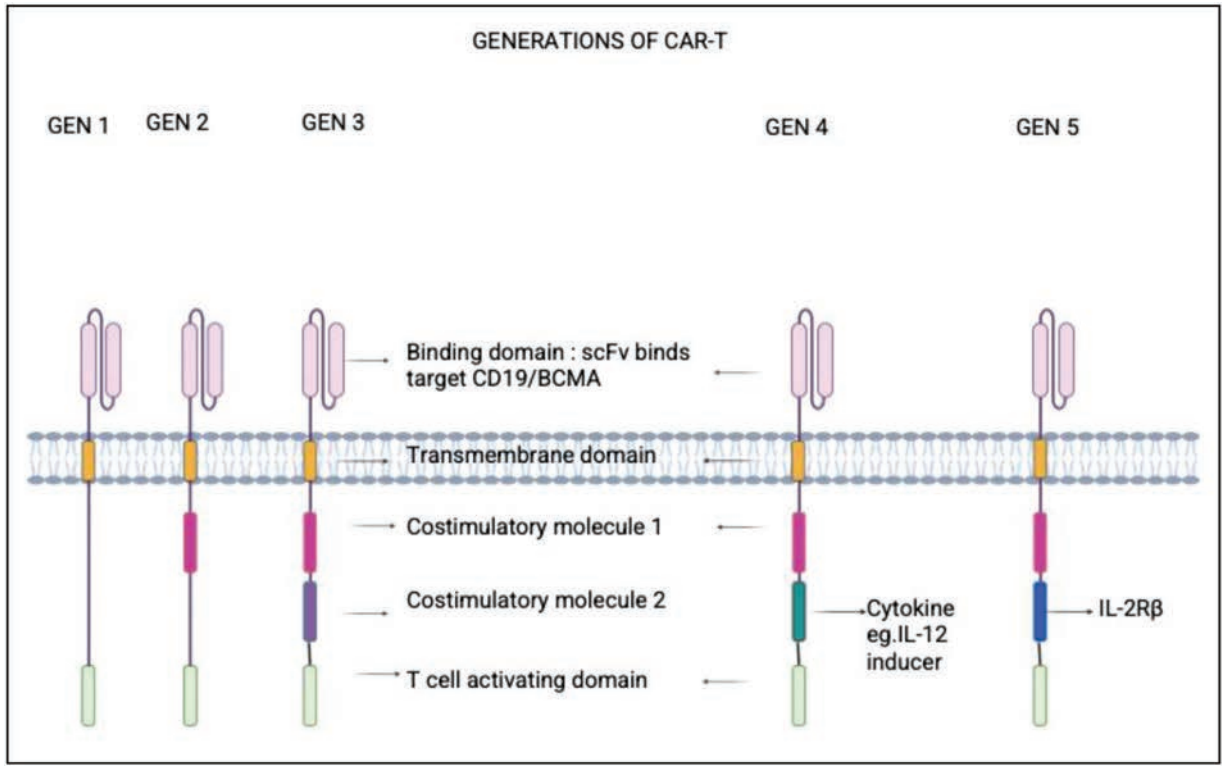

FIGURE 1. Structure of different generations of chimeric antigen receptor (CAR) T cell. Diagram representing basic structure of CAR with T cell activating domain, co stimulatory domain, transmembrane domain, hinge region and extracellular domain which contains antibody variable fragment which targets molecule of interest (CD19/BCMA). First-generation CAR consist of Extracellular domain with antigen recognition domain which is a single-chain fragment variant (scFV), transmembrane domain and intracellular domain (which consist of ITAM or immunoreceptor tyrosine-based activation motifs.). In addition to this, second generation CARs have 1 costimulatory molecule, and third generation CARs have 2 costimulatory molecules. The fourth and fifth generations are based on second generation CARs, with addition of inducible chemokine such as IL-12 in fourth generation, and addition of intracellular domains of cytokine receptors (e.g. IL-2Rβ chain fragment) in fifth generation.

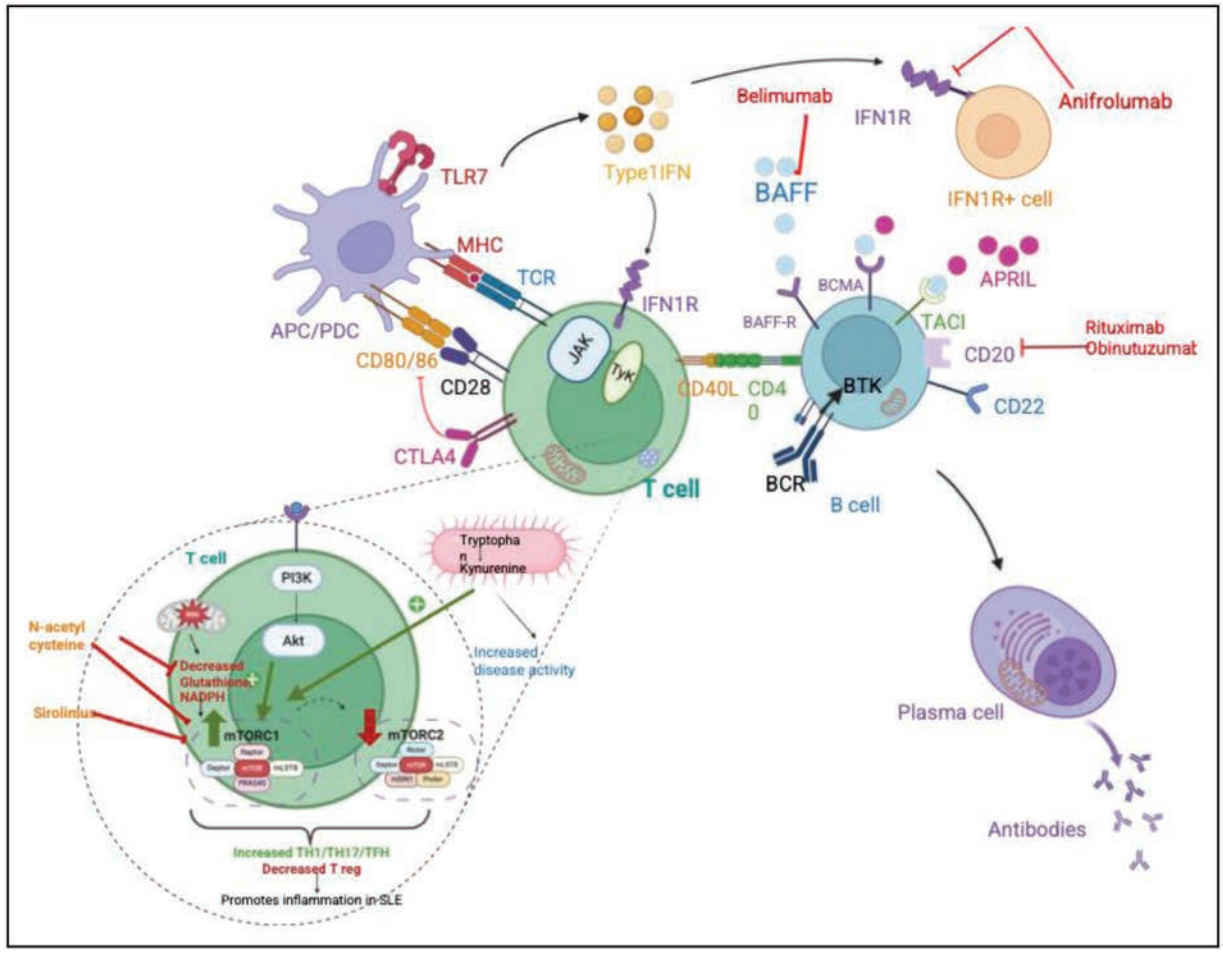

FIGURE 2. Immunopathogenesis and current treatment targets in SLE. FDA approved and off label therapies currently in use. A schematic diagram showing immunopathogenesis in SLE and targets of therapies currently in use. Hydroxychloroquine acts by increasing pH of lysosomes and inhibits TLR7 and 9. Plasmacytoid dendritic cells produce type I interferon which acts on interferon receptors which is blocked by anifrolumab. Rituximab and obinutuzumab act on CD20 on B cells and lead to B cell depletion by antibody or complement mediated cytotoxicity, and additionally direct cell death with obinutuzumab. Sirolimus inhibits mTORC1 activation thus leading to decreased TH1/TH17/TFH response and maintaining T reg balance. N-acetylcysteine replenishes glutathione and inhibits mTORC1.

B cells and produce dsDNA antibodies and are typically responsive to therapy. LLPCs on the other hand are present in the bone marrow, are CD19 negative and do not respond to immunosuppression including B cell depletion or CAR T therapies [44].

Drugs affecting mitochondrial dysfunction in lupus T cells

Blocking mTOR activation: sirolimus

mTORC1 activation has been demonstrated in lupus nephritis and is associated with disease activity [45].

Sirolimus maintains mitochondrial transmembrane potential and calcium flux, leading to reduction in disease activity in murine models [46]. Multiple studies have shown that Sirolimus is effective in the patients with SLE [47–49].

An open label prospective cohort study in China showed comparable efficacy of sirolimus to mycophenolate in lupus nephritis, along with beneficial effect in sirolimus group in improved complement levels [50]. Sirolimus has shown benefit in clinical and serological outcomes in renal and nonrenal lupus [51].

IL-21 driven mTORC1 and C2 activation in T reg results in T reg dysfunction, which was successfully reversed upon administration of sirolimus [52].

Replenishing glutathione: *N*-acetylcysteine

Lupus T cells unlike normal cells show mitochondrial hyperpolarization which leads to decreased ATP production, increased reactive oxygen species (ROS)

production and consumptions of reduced glutathione (GSH); thus leading to oxidative stress which activate mechanistic target of rapamycin (mTOR) in SLE [53].

Oxidative stress along with reduction in protective mechanisms has been linked to autoimmunity in lupus. Antioxidant effect of glutathione which is replenished by NAC, decreases oxidative stress and can be an effective therapy in SLE [54,55].

As newly discovered, SLE patients preferentially produce phosphatidylserine antibodies [56], which block immune complex phagocytosis by macrophages [57]. NAC treatment not only blocks mTOR [58–60] but also restores phagocytic function of macrophages in mice and patients with SLE [57].

Studies have shown benefit of NAC on manifestations of SLE including neuropsychiatric and hepatic complications of SLE [61–63].

NON-PHARMACOLOGICAL CONSIDERATIONS

In addition to pharmacological therapies, there is evidence to suggest that nonpharmacological therapies may have a role in SLE pathogenesis and management.

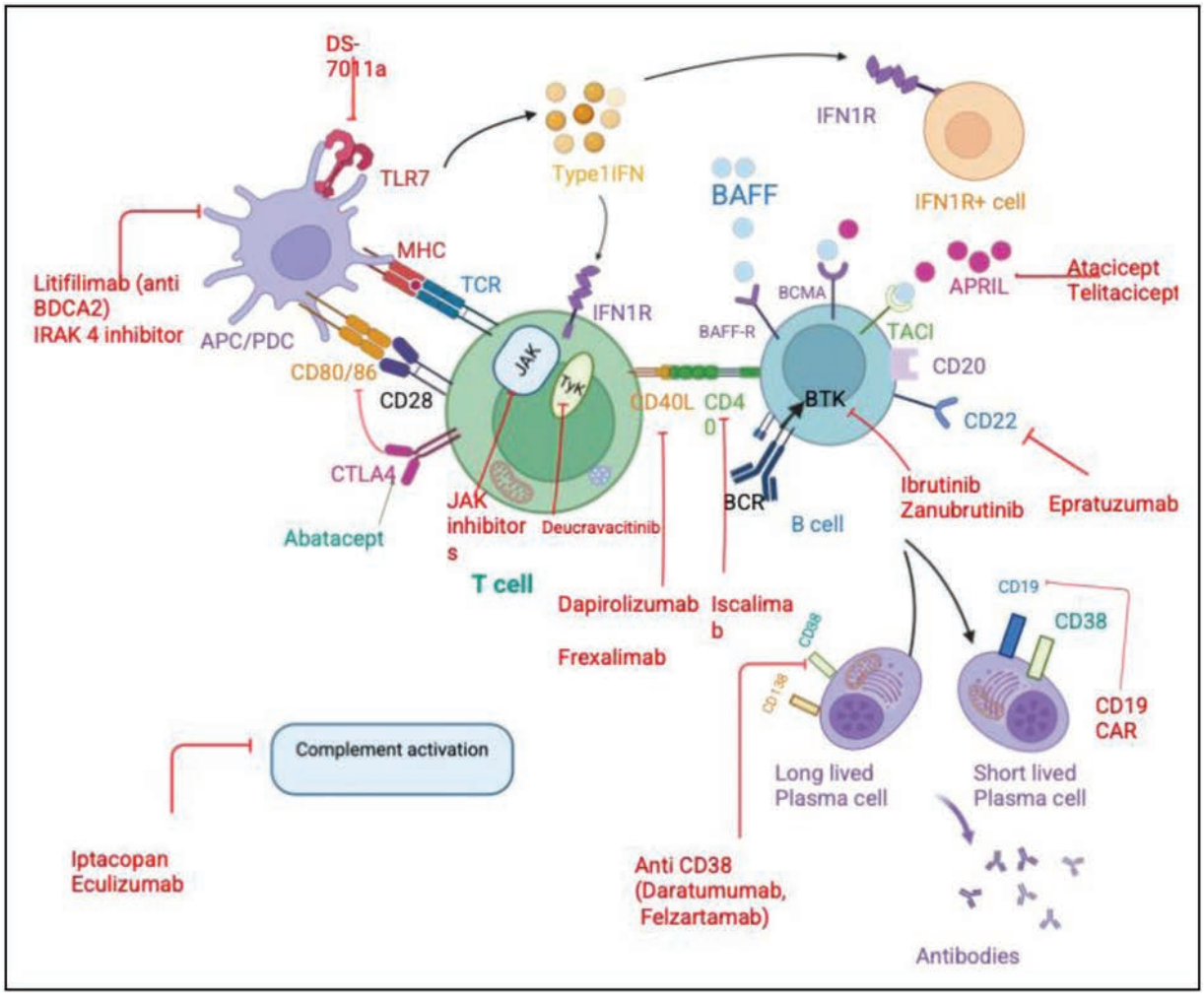

FIGURE 3. Immunopathogenesis and emerging treatment targets in SLE. A schematic diagram showing immunopathogenesis in SLE and targets of emerging therapies. DS-7011a inhibits TLR7. Litifilimab acts on BDCA2 and inhibits interferon production from PDCs. Therapies targeting CD40 on B cells (iscalimab) and CD40L on T cells (dapirolizumab, frexalimab) inhibit the interaction of CD40-CD40L thus inhibiting T cell mediated immune response. BAFF is a cytokine that activates B cell through BAFF-R, TACI and BCMA. Ianalumab blocks BAFF-R. APRIL cytokine acts on TACI and BCMA. Atacicept and telitacicept inhibit APRIL and BAFF which are required for B cell maturation and function. Complement inhibitors such as iptacopan and eculizumab are being studied for SLE. Daratumumab blocks CD38 in plasma cells. Therapies such as CD19 CAR T cell therapy act on CD19 in short lived plasma cells. JAK inhibitors and Tyk inhibitors block downstream STAT signaling in T cells. Therapies that target CD38 on plasma cells and CD19 on short lived plasma cells are being studied.

Interventions such as photoprotection, smoking cessation and exercise (aerobic and resistance training) have shown benefit and are recommended for patients with SLE [64,65].

In SLE, Gut microbiota dysbiosis leads to metabolism of tryptophan to produce kynurenine, which activates mTOR in T cells [53,66]. Reduction in dietary tryptophan resulted in lower rate of autoimmunity in mice [66].

Emerging therapies

Several medications are currently being studied for different manifestations of SLE [67] (Fig. 3).

Some of the important emerging therapies have been summarized in Table 3.

Iscalimab is a monoclonal antibody targeting CD40 on B cells, which is currently being studied for lupus nephritis [68]. Frexalimab and dapirolizumab conversely act on CD40 ligand on T cells and are in phase 2 and phase 3 respectively for SLE [69,70]. Anti-CD38 monoclonal antibodies such as felzartamab and daratumumab are being studied for lupus and lupus nephritis [71–73]. DS 7011a is a monoclonal antibody against Toll like receptor 7 which inhibits TLR7 signaling and decreases the production of interferon and subsequent B-cell activation [74]. Enpatoran, E6742 and MHV370 inhibit TLR7/8 and ultimately inhibit the expression of Type I interferons [75–78]. Ianalumab is an afucosylated monoclonal antibody against BAFF receptor which acts by dual mechanism, one by antibody dependent cellular cytotoxicity and the other by blocking BAFF: BAFF receptor mediated signaling [79,80]. Xeligekimab is IL-17 a neutralizing monoclonal antibody which is currently being studied for lupus [81]. Nipocalimab is a monoclonal antibody that binds in blocks immunoglobulin G (IgG) binding site neonatal Fc receptor and prevents binding of FCR and to IgG and thus decreases the circulating IgG and is currently being studied for lupus [82]. Litifilimab is a monoclonal antibody against BDCA2 expressed exclusively on plasmacytoid dendritic cells that suppresses type on interferon production and is being studied for systemic as well as cutaneous lupus erythematosus [83–85]. envudeucitinib and deucravacitinib are selective TyK2 inhibitors that block downstream activation of STAT and are being studied as therapies for SLE [86,87]. Mosunetuzumab is a humanized IgG1 CD20 and CD3 bispecific antibody which binds CD3 on T cells and CD20 on B-cell and is currently being studied for lupus [88]. Upadacitinib is a JAK inhibitor and is being studied for lupus [89,90]. Zanubrutinib targets Bruton kinase which is important for B-cell development and function and is undergoing trials for management of lupus [91,92]. Iptacopan is a complement inhibitor which inhibits activation of alternate complement pathway [93]. Low-dose IL-2 therapy activates STAT 5 and enhances anti-inflammatory effect and is currently in phase 2 and 3 lupus trials [94]. Mizoribine is an inosine 5 monophosphate dehydrogenase inhibitor which inhibits the formation of guanine nucleotides thus inhibiting lymphocyte proliferation [95]. It has completed phase 3 trials for lupus nephritis and is approved for lupus nephritis management in Japan. Atacicept and telitacicept are inhibitors of BAFF and APRIL and are being studied for SLE management [96,97]. Both drugs bind BAFF and APRIL and prevent them from interacting with receptors on B cells. These cytokines are required for B-cell maturation and function. Telitacicept is currently approved for SLE in China [96,98]. Inhibition of cGAS mediated production of cGAMP leads to decreased expression of IFN and NFKB proinflammatory cytokines, cGAS inhibitors are being studied for SLE [99,100].

CONCLUSION

With all the recent advancements in understanding the pathogenesis and treatment targets for SLE and the advent of cell therapies, there seems to be a hope and promise of cure on the horizon.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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Contraception in systemic lupus erythematosus and antiphospholipid antibody syndrome

Lauren He and Wendy Marder

Purpose of review
Family planning and contraception are central to disease management in people with rheumatic musculoskeletal diseases (RMD), particularly systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS), in whom unplanned pregnancy can carry substantial maternal and fetal risk. This review summarizes current evidence and guideline-based recommendations regarding contraceptive choices in women with SLE and APS, with a focus on thrombotic risk, bone health, and cardiovascular considerations.

Recent findings
Estrogen-containing hormonal contraception is well established as a pro-thrombotic risk and should be avoided in those with APS, antiphospholipid antibodies (aPL), lupus nephritis, or at least moderately active SLE. Emerging data also suggest an association of certain higher dose progestins such as norethindrone acetate, and injectable preparations such as depot medroxyprogesterone acetate (DMPA), with increased venous thromboembolism (VTE) risk. Regarding bone health, oral contraceptive pills (OCPs) and combined hormonal contraception (CHC) may slow the rate of bone mass acquisition in adolescents with uncertain long-term effects on fracture risk, whereas use in adult women is associated with modestly higher bone mineral density and lower osteoporotic risk. While awareness of the importance of contraception in the rheumatology community is improving, real-world practice reveals that implementation of reproductive health guidelines is lagging.

Summary
For women with SLE and APS, contraception selection must account for thrombotic risk, bone health, and cardiovascular comorbidities. Long-acting reversible contraceptives, particularly progestin-only intrauterine devices (IUDs) and subdermal implants, remain highly effective and well tolerated for those with SLE and APS. Ongoing efforts to improve guideline implementation, shared decision-making, and patient and provider education are essential to reduce unplanned pregnancies and optimize reproductive outcomes in this population.

Keywords
antiphospholipid syndrome, contraception, systemic lupus erythematosus

INTRODUCTION

Pregnancy planning is an important part of disease management for people with rheumatic musculoskeletal disease (RMD), and is made possible in large part through access to safe contraception. Planning for pregnancy after 6 months of good disease control on pregnancy-compatible medications has been shown to improve maternal and fetal health outcomes by reducing adverse pregnancy outcomes [1–3]. The 2020 American College of Rheumatology (ACR) Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases and the EULAR updated 'points to consider' recommend that all RMD patients ((both men and women) should get early and regular counselling about reproductive health, including family planning [1,2]. In this review, we highlight the most recent literature concerning the safety and efficacy of hormonal contraception in RMD patients at the highest risk of adverse events related to hormonal contraceptive therapies: those with active systemic lupus erythematosus (SLE), in particular with lupus nephritis, and those with antiphospholipid antibodies (aPL) or antiphospholipid antibody syndrome (APS). We address major categories of concern when recommending a contraceptive method for patients in these risk

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KEY POINTS

- IUDs and subdermal implants remain safe choices and are preferred for contraception in patients with SLE and APS.
- Estrogen-containing contraception and some OCPs containing higher dose progestins (including norethindrone acetate and medroxyprogesterone acetate) and injectable DMPA are recommended against use in those with elevated thrombotic risk, including those with APS, positive antiphospholipid antibodies, and moderate-high lupus disease activity and in particular those with lupus nephritis and nephrotic syndrome.
- DMPA should be avoided in those with elevated risk of developing osteoporosis, and may decrease bone formation (likely reversibly) when used in critical adolescent years.
- Efforts to understand and improve the low rates of highly effective contraception use in RMD populations are ongoing.

categories, including the heightened risk of venous thromboembolism, the potentially deleterious effects on bone health, and cardiovascular risk. We also provide a review of the implementation of ACR Reproductive Health Guideline statements on contraception in general rheumatology practice in the 5 years after its publication.

CONTRACEPTION METHODS CURRENTLY AVAILABLE

Currently available contraception options and their risk profiles are listed in Table 1. [1,4,5]. Importantly, the most effective forms of contraception, including intrauterine devices (IUD) and the subdermal implant, have no absolute contraindications related to the RMD itself and are safe for use in RMD patients, including those with SLE and APS. The progestin-only IUDs or subdermal implants may be favored for those on anticoagulation given the propensity for copper IUDs to cause heavier bleeding during menses. Oral contraception pills (OCPs) discussed below include both combined hormonal contraceptive pills (CHCs), containing progestin and estrogen, and progestin-only pills. Special consideration is required for patients using mycophenolate mofetil (MMF), which may decrease plasma concentrations of levonorgestrel and other progestins [1]. FDA and ACR guidelines recommend that women on MMF and hormonal contraception should consider dual methods (adding barrier protection) or preferentially using IUDs or implants to ensure efficacy. Dual contraception for those on MMF is considered standard of care, but this recommendation is conditional due to lack of published reports of contraception failure in this population. Other considerations exist for progestin-only OCPs, including taking at a consistent time of the day due to the effects on cervical mucus for optimal efficacy, which should be discussed with each patient. Depot medroxyprogesterone acetate (DMPA) is a progestin-only injectable contraceptive that provides 3 months of reversible contraception with special considerations discussed below. Less effective contraceptive methods including barrier protection (male condom), the contraceptive sponge, and rhythm/withdrawal methods are not recommended as first-line choices for patients with RMD, although may still serve a role in reproductive health (e.g. use of barrier protection to decrease risk of infection due to sexually transmitted diseases).

RISKS ASSOCIATED WITH COMBINED HORMONAL CONTRACEPTION IN HIGH-RISK RHEUMATIC MUSCULOSKELETAL DISEASE POPULATIONS

Venous thromboembolism risk in systemic lupus erythematosus and antiphospholipid antibody syndrome

The 2020 ACR Reproductive Health Guideline recommends avoiding estrogen containing contraception in populations with elevated thrombotic risk, including those with APS, positive aPL without history of thrombosis, lupus nephritis, or least moderately active SLE [1,6]. The relative risk of developing venous thromboembolism (VTE) in the general population while on estrogen-containing contraception is 3.5-fold increased risk compared with nonuse, with an overall incidence rate of 5–15 per 10 000 person-years [7]. Estrogen, particularly ethinyl estradiol, which is commonly used in CHCs, stimulates clotting factors II, VII, IX, X, reduces anticoagulant proteins, including antithrombin and protein S, and increases tissue plasminogen activator [8]. The risk of VTE is highest within the first year of starting estrogen-containing contraception, but can persist.

While the prothrombotic effect of estrogen is well recognized, there is increasing interest in the impact of different forms and potencies of progestin-containing contraception on VTE risk. A recent case-controlled study involving over 120 000 women revealed the use of higher dose progestins such as norethindrone acetate and medroxyprogesterone acetate significantly increased the odds of VTE [9]. Norethindrone acetate, when used at standard or high doses (>2.5 mg/day), was associated with an adjusted odds ratio (aOR) of 3 [99% confidence

Table 1. Overview of methods of contraception including efficacy and considerations for use in patients with rheumatic musculoskeletal diseases

Contraception method		Mechanism of Action	Efficacy (number of pregnancies per 100 females in 1 year)	Common side effects	Considerations for use in rheumatic disease
Intrauterine device (IUD)	Nonhormonal (copper)	Impairs sperm motility	Most effective (<1)	Irregular bleeding Heavy menstrual bleeding (copper) Amenorrhea (progestin-only)	Safe for all women with RMD No clear association of procedural complications
	Progestin-only	Thickens cervical mucus to block sperm, prevents ovulation			
Subdermal implant		Releases etonogestrel: prevents ovulation and thickens cervical mucus	Most effective (<1)	Changes in menstrual bleeding pattern (irregular, frequent, or absent bleeding)	Likely safe for all women with RMD based on limited studies in this specific population May be associated with decreased bone mineral density in the radius over 3 years of use
Depot medroxyprogesterone acetate (DMPA)		Prevents ovulation	Effective (4–7)	Irregular bleeding (menstrual spotting, amenorrhea)	Avoid in elevated clot risk (+aPLs, active SLE) Avoid in elevated osteoporosis risk
Oral contraceptive pill (OCP)	Progestin-only	Thickens cervical mucus to block sperm, prevents ovulation (inconsistently)	Effective (4–7)	Irregular bleeding, amenorrhea	
	Estrogen + progestin	Prevents ovulation	Effective (4–7)	Nausea Irregular bleeding, amenorrhea	Avoid in elevated clot risk (+aPLs, active SLE)
Vaginal ring	Estrogen + etonogestrel	Thickens cervical mucus, prevents ovulation	Effective (4–7)	Irregular bleeding, discomfort	Avoid in elevated clot risk (+aPLs, active SLE)
Patch	Estrogen + norelgestromin	Inhibits ovulation, thickens cervical mucus	Effective (4–7)	Cramping, application site irritation, breast tenderness	Avoid in elevated clot risk (+aPLs, active SLE)
Male condom		Barrier	Less effective (>13)	Discomfort, mechanical breaking	

aPL, antiphospholipid antibodies; RMD, rheumatic musculoskeletal disease; SLE, systemic lupus erythematosus.

interval (CI) 1.96–4.59] for developing VTE when compared to nonuse. Furthermore, the use of medroxyprogesterone acetate depo preparation (DMPA) was associated with aOR for VTE of 2.37 (99% CI 1.95–2.88), and oral medroxyprogesterone acetate with increased aOR of 1.98 (99% CI 1.41–2.80). Interestingly, levonorgestrel-releasing IUD, etonogestrel implant, and other oral progestins, including low-dose norethindrone (used in progestin only pills), were not associated with increased VTE risk. There are multiple theories regarding why certain forms of progestin confer greater clotting risk. When used in CHCs, it is thought to be due to the balance of estrogen strength vs. strength of progestin's antiestrogen effect, which varies based on type and dose of progestin used [7]. The hypercoagulable

risk of medroxyprogesterone acetate could also be due to its known ability to upregulate thrombin receptor expression [9]. Progestin-only containing oral contraception, which typically contains first or second generation (lower dose) progestins, confers lower risk in observational data from the general population [10].

The Opill, or Over-the-Counter Oral Birth Control Pill, is the first FDA-approved nonprescription oral contraceptive pill available in the United States. This is a progestin-only pill whose active ingredient is norgestrel, considered a low-to-moderate-dose progestin. No studies have compared VTE risk of Opill in the general population, but given that it is a lower moderate-dose progestin, it is considered low thrombotic risk. Emergency contraception is also available over the counter: the progestin-only pill (levonorgestrel) and ulipristal acetate pill are safe for use even in those at increased VTE risk, and there are no absolute contraindications for emergency contraception for patients with RMDs.

The recommendation to avoid estrogen-containing contraception and DMPA extend to those with active lupus nephritis and nephrotic syndrome of any cause. VTE risk is elevated at any stage of disease for patients with nephritis: a recent prospective observational study involving 324 patients revealed that 9.3% ($n=30$) developed VTE with a median first time to event of 4.4 years [11]. Elevated SLEDAI-2K score and proteinuria were associated with increased risk, indicating more active disease is associated with higher risk. The use of combined OCPs in those with treated, inactive lupus nephritis should be considered on a case-by-case basis given this persistent risk. While patients with nephrotic syndrome have been excluded from research studies due to the hypercoagulability associated with this condition, updated recommendations by the US Medical Eligibility Criteria (MEC) for contraception note that the risks of estrogen-containing contraception, drosperinone (due to elevated risk of hyperkalemia), and DMPA in those with nephrotic syndrome outweigh their advantages [12,13]. The US MEC included important updates for the RMD population in 2024, updating their 2016 guidance by supporting the use of IUD, implant, and progestin-only oral contraceptives in this population, stating that the benefits likely outweigh the theoretical risk of use [13]. Importantly, a recent analysis of Medicaid population found that despite having higher rates of lupus nephritis, African American women with SLE had significantly lower odds of receiving highly effective contraception (LARC or sterilization) compared to White women (OR 0.71, 95% CI 0.56–0.89), highlighting an important opportunity for improving contraception counselling in the lupus nephritis population [14].

Bone health considerations in systemic lupus erythematosus, antiphospholipid antibody syndrome, and other rheumatic musculoskeletal diseases

An important aspect in the care of patients with RMD is preservation of bone health, given that both inflammatory diseases and exogenous glucocorticoid exposure increase the risks of osteoporosis and osteoporotic fractures [15]. Whether hormonal contraception contributes to or protects against loss of bone mineral density (BMD) in women with RMD is not a straightforward question. Both estrogen and progesterone are involved in modulating bone turnover. Estrogen plays an important role in inhibiting bone resorption by blocking synthesis of interleukin-6 (IL-6) by osteoclasts and regulating mediators of bone turnover, including TNF-α and the osteoprotegerin/RANKL/RANK system [16]. Levels of circulating bone stimulatory mediators, including growth hormone and insulin growth factor-1 (IGF-1), rise with estrogen levels during the menstrual cycle. Progesterone is involved in bone modulation by stimulating new osteoblasts to be made from mesenchymal stem cells and by stimulating osteoblasts to create more bone matrix [17,18]. By modulating estrogen and progesterone levels, hormonal contraception can affect BMD. The extent of this effect depends on the specific contraceptive used and the individual's age, with adolescents and young women at potentially greatest risk because they have not yet reached their peak bone mass [19].

CHCs have been shown to inhibit the bone-stimulatory molecule IGF-1, with the effect lessening as women age and with transdermal therapy [20]. Given this observation, recommendations for use of CHCs among adolescent and young women have advised caution. A recent systematic review focusing on CHC in adolescent girls found that CHCs may slow BMD accrual, especially at lower estrogen doses, during a critical period for skeletal development [21]. However, the authors concede that there are limited long-term data on this subject, making it difficult to determine the lasting impacts, if any, of CHCs on peak bone mass. In one of the more recent studies included in the review, Orsolini *et al.* enrolled 168 adolescents and randomized them to 20 μg Ethinylestradiol (EE)/150 μg Desogestrel or 30 μg EE/3 mg Drospirenone for 2 years, and compared them to a control group of adolescent non-CHC users [22]. The results revealed that bone mass was greater in the group of adolescents who did not use CHC compared to the two other groups who did, with a respective increase of 2.15 g and loss of 0.43 g in lumbar bone mineral content ($P=0.001$). The authors concluded that bone mass acquisition in adolescents using CHC was compromised when compared to controls, with

the most pronounced negative effect among those taking the higher estrogen preparation (30 μg EE), however, it is not known if long-term fracture risk is increased.

DMPA has also been associated with reductions in BMD, especially with use longer than 2 years, due to its suppression of estrogen production [23]. The most worrisome group again is adolescent girls who have not yet reached peak bone mass, as well as longer term users. The FDA recommends using DMPA for more than 2 years only if other methods are inadequate, and to ensure adequate calcium and vitamin D intake [24]. While fracture data are mixed and limited, multiple studies of premenopausal women and adolescents treated with DMPA for up to 5 years show that bone loss seems to be largely reversible after cessation of the drug; however, long-term impact on ultimate peak bone mass remains an area of limited study [25,26].

In mature women there appears to be a more favorable effect of hormonal contraception and BMD. A recent study from the United Kingdom examined the effect of oral contraception on BMD in a population-based cohort including more than 500,000 residents aged 37–72 years, who were recruited between 2006 and 2010. They examined the effect of oral contraception use on BMD using self-reported exposures to OCPs among 257,185 women, including the date of initiation and duration of exposure [27]. Based on their birth years (1936–1970), it is most likely that this cohort used CHCs, which were the dominant type of OCP formulation for many years. The authors found that BMD *T*-scores were higher among those with previous OCP use. Ever having used OCPs was associated with a 0.052 increase in BMD *T*-score at enrollment (95% CI: 0.038–0.067, $P = 2.1 \times 10^{-12}$). Long-term OCP use was more strongly associated with higher BMD, whereas short-term use (0–1 years) showed no significant effect. For those who used OCPs for 2–5 years, the estimate increased to 0.046 (95% CI 0.027–0.065, $P = 2.2 \times 10^{-6}$), for 6–10 years of use, to 0.062 (95% CI 0.043–0.080, $P = 2.2 \times 10^{-6}$). Those who used OCPs for 16 years or more showed the largest estimated increase in BMD *T* score at 0.064 (95% CI 0.044–0.083, $P = 1.2 \times 10^{-10}$), although most of the BMD benefit appeared after 6–10 years of use. The authors concluded that OCP use is associated with higher BMD and reduced risk of osteoporosis later in life, with the strongest effects observed in postmenopausal women. No significant association was detected in premenopausal women, suggesting that OCP use may reduce osteoporotic risk primarily in older populations.

Finally, progestin-only pills and IUDs seem to have no significant impact on bone density as they do not suppress estrogen to the same degree [28]. This is also true for other nonestrogen-containing contraceptive options including copper IUDs.

Cardiovascular risk and contraceptive choice in systemic lupus erythematosus and antiphospholipid antibody syndrome

Contraindications to CHCs, as identified by the Centers for Disease Control and Prevention (CDC) and WHO, are listed in Table 2[4,29]. Many of these contraindications are more prevalent in RMD populations, in particular increased risks of hypertension, hypercoagulable states, history of of ischemic heart disease or stroke, and complicated valvular heart disease [30]. Real-world risks of stroke and myocardial infarction (MI) associated with hormonal contraception were recently evaluated in a large Danish prospective cohort of women aged 15–49 years, without prior history of conditions that could influence cardiovascular risk [31]. In their cohort of over 2 million women and over 22 million person-years of follow-up, CHC approximately doubled the risk of both ischemic stroke and MI compared with nonuse, corresponding to approximately 21 excess strokes and 10 excess MIs per 100,000 person-years. Progestin-only pills were associated with smaller but still measurable events, resulting in approximately 15 excess strokes and 4 excess MIs per 100,000 person-years, and increased risks were also observed with vaginal rings, patches, and progestin implants. Acknowledging that these absolute risks remain low in the general population, they may be clinically

Table 2. List of contraindications for use of combined hormonal contraceptive pills based on Centers for Disease Control and Prevention and WHO

Contraindications for CHC
Age ≥35 years and smoking ≥15 cigarettes per day
Two or more risk factors for arterial cardiovascular disease Older age, tobacco use, diabetes, hypertension
Hypertension Systolic ≥140 mmHg or diastolic ≥90 mmHg (CDC) Systolic ≥160 mmHg or diastolic ≥100 mmHg (WHO)
History of venous thromboembolism not on current anticoagulation
Acute venous thromboembolism
Known thrombogenic mutation
History of ischemic heart disease or stroke
Complicated valvular heart disease (pulmonary hypertension, risk for atrial fibrillation, history of subacute bacterial endocarditis)
Breast cancer
Hepatocellular adenoma or malignant hepatoma
Cirrhosis
Migraine with aura

CHC, combined hormonal contraceptive pills.

significant in those with RMD whose baseline risk of CVD is higher. Notably, progestin-only IUDs showed no increased risk of ischemic stroke or MI, with event rates comparable to nonusers.

RATES OF CONTRACEPTION USE AFTER PUBLICATION OF THE 2020 REPRODUCTIVE HEALTH GUIDELINE

Following the publication of the 2020 ACR Reproductive Health Guideline, there has been focus on ascertaining how well the recommendations related to contraception are being implemented by rheumatologists. For comparison, a 2018 study examining the rate of contraception documentation in the medical record in the Rheumatology Informatics System Effectiveness (RISE) registry was only 9.1% [32]. Documentation was higher for rheumatoid arthritis (RA) patients on teratogenic medications than on nonteratogenic medications, but in contrast, documentation did not differ between SLE patients on teratogenic versus nonteratogenic medications. A subsequent 2023 review of contraception discussion and documentation in RISE registry revealed similarly low rates (8.1% in pre-COVID pandemic 2019, and 8.5% through mid-pandemic 2022) with higher rates for participants who were white, young, or had multiple visits [33]. Patients with higher risk for thrombosis were less likely to be prescribed estrogen-containing contraception, but estrogen-containing contraception was still reported in up to 26% of those with elevated thrombotic risk, and 53% with a history of lupus nephritis. Implementing Electronic Meical Record-driven quality improvement initiatives including patient-driven questionnaires, educational sessions, and clinical scripting for providers has been successful in improving contraception documentation at single institutions [34,35].

Although documentation rates of contraception discussions are slowly improving, ongoing low rates of highly effective contraception use in RMD patients continue. One large, single-center study found only 32% of patients with RMD were using prescription contraception, even though over 70% were prescribed one or more teratogenic medications during the 2-year study time period [36]. Another cross-sectional study identified that most women with SLE were using some form of contraception, but a minority (37%) were using highly effective forms [37]. Concerningly, 28% of participants in this study had a possible contraindication for the form of contraception they were using.

Efforts to understand the relatively low rates of contraceptive use in RMD patients are underway. One qualitative study seeking to understand the decision-making process behind contraception use conducted semi-structured telephone interviews with 30 reproductive-aged women with RMD and categorized themes including disease perception, healthcare providers' influence, and patient and providers expectations as major contributors to decision-making around contraception [38]. Key areas of improvement identified were continuing education initiatives to fill knowledge gaps for patients and providers, and augmenting shared decision-making practices. A theme in this study was patients' perception that contraception was unsafe in the context of their RMD or medications, when in fact, contraception prevents unplanned pregnancies, which pose greater health risks, highlighting opportunities to address knowledge gaps and barriers to safe contraception.

CONCLUSION

Counseling patients about reproductive health is an important component for the care of RMD patients and is the responsibility of the rheumatologist. Current data confirm that highly effective contraceptives, particularly IUDs and implants, are safe for most patients with RMD, even after accounting for thrombotic, bone, and cardiovascular risks. Despite these findings, the use of highly effective contraception remains suboptimal in women with RMDs even 5 years after the publication of the 2020 ACR Reproductive Health Guideline. Rheumatologists should continue efforts to make family planning discussions a regular part of clinical care. Through consistent counseling, documentation, and shared decision-making, rheumatology providers can directly influence and improve the reproductive health outcomes of our patients.

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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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