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The apprehension of seronegative rheumatoid arthritis

Iqra Javed & Cynthia S. Crowson

Seronegative rheumatoid arthritis (RA) is often misunderstood and underrecognized, and this leads to delays in diagnosis and treatment. Emerging studies highlight distinct features and unmet needs of seronegative RA, calling for increased awareness of the challenges faced by patients and the need for tailored therapeutic approaches to improve outcomes.

Apprehension can mean two different things — either anxiety and hesitation, or grasp and capture. Seronegative rheumatoid arthritis (RA) embodies both meanings as many rheumatology experts approach it with hesitation and scepticism, whereas others work to grasp an understanding of it. Seronegative RA is a subclassification of RA that — unlike seropositive RA, which is characterized by the presence of rheumatoid factor or anti-citrullinated protein antibodies (ACPAs) — is defined by the absence of known autoantibodies[1]. Seronegative RA presents persistent challenges in both diagnosis and management owing to disease heterogeneity and the skewed focus of research on seropositive RA[2].

Epidemiological evidence from the Olmsted County cohort study in the USA has indicated a rising incidence of seronegative RA and a concurrent decline in seropositive RA from 1995 to 2014 in this population[2]. In this study, RA was defined based on fulfilment of at least four criteria from the 1987 ACR recommendations with no alternative diagnosis, reducing the risk of bias from provider variability, although misclassification cannot be excluded. Similarly, data from the Leiden Early Arthritis Clinic in the Netherlands demonstrated a steady increase in ACPA-negative RA from 1993 to 2016, whereas the incidence of ACPA-positive RA remained stable[3].

By contrast, two studies from Denmark and Finland have reported declining trends in the incidence of seronegative RA[4,5]. However, these studies relied on ICD-10 codes, which might have low positive predictive value for seronegative RA, thus raising concerns about potential misclassification and underestimation of true incidence[4]. Furthermore, epidemiological trends based on the use of ICD codes might be influenced by variability related to inconsistencies in clinical judgment and the evolving awareness of RA. Implementation of the 2010 ACR–EULAR classification criteria might have influenced diagnosis of seronegative RA in these studies. Fewer seronegative patients meet the 2010 criteria compared with the 1987 criteria, and this might contribute to more patients being diagnosed with undifferentiated arthritis after 2010.

Notably, multiple demographic and environmental factors might contribute to the rising incidence of seronegative RA incidence in some populations. Population ageing is a key driver, as late-onset RA is more often seronegative than seropositive, possibly owing to dysregulation of inflammation among older individuals[1,3]. Declining smoking rates over the past few decades might also contribute to the changing epidemiology of RA subtypes, given the strong association of smoking with ACPA-positive RA[2]. Concurrently, rising obesity rates, particularly among women, have been linked to increased risk for ACPA-negative RA[2]. Additional factors, such as alterations in the gut microbiome, crystalline silica exposure, periodontitis, vitamin D deficiency, breastfeeding and oral contraceptive use have all been implicated in RA pathogenesis, though their association with seronegative versus seropositive RA remains poorly understood[2]. Improved access to care and increased clinical awareness aided by expanded use of imaging modalities are likely to result in enhanced detection of seronegative RA.

Diagnostic ambiguity complicates not only the epidemiological analysis but also longitudinal classification of seronegative RA (Fig. 1). In a Finnish national study of 9,784 patients initially diagnosed with seronegative RA, 8.8% of the diagnoses were reclassified as spondyloarthritis over 15 years of follow-up[6], whereas in a second cohort of 435 patients analysed by the same group, only 32% of patients were not reclassified over 10 years, with most patients evolving to updated diagnoses of polymyalgia rheumatica, crystal arthropathies or spondyloarthritis[7]. Based on these observations, it was concluded that "it may not be reasonable to study seronegative arthritis patients as a homogenous entity".

Seronegative RA has been previously assumed to represent a mild phenotype of seropositive RA, but it now emerges as a distinct clinical and immunological entity. Genetically, seronegative RA has been associated with variants in *HLA-B08* and *DRB103* alleles, or in non-HLA genes such as *ANKRD55* and *CLYBL*, whereas seropositive RA has been strongly linked with variants of the *HLA-DRB104/*10* genes or polymorphisms in the JAK–STAT pathway[1]. These genetic associations implicate greater involvement of innate immunity in seronegative RA than in seropositive RA, which seems to involve mainly adaptive immune responses[1]. Immunological features also differ between the two types with synovial monocytes, synovial macrophages and plasma cells more common in seronegative RA and synovial $CD4^+$ T cells, vessel $CD31^+$ cells and $CD68^+$ cells in the synovial lining more common in seropositive RA[1]. Clinically, seronegative RA has been observed in contexts of immune dysregulation, including immune checkpoint inhibitor therapy and blocking both IL-4 and IL-13 signalling[1].

Whereas seronegative RA is commonly thought to be milder than seropositive RA, data from patients of the Canadian Early Arthritis Cohort (CATCH) show that seronegative RA often involves higher disease activity and greater radiographic damage at baseline compared with seropositive RA[8]. Concordantly, in the 2005–2014 period in the Olmsted County cohort, erosion rates in seronegative RA had reached parity with seropositive RA[2]. The 2010 ACR–EULAR classification criteria may be intensifying the average disease severity of patients with seronegative RA as more extensive joint involvement is required to fulfil the criteria in the absence of serological markers. Patients with mild disease activity might no longer be diagnosed with seronegative RA.

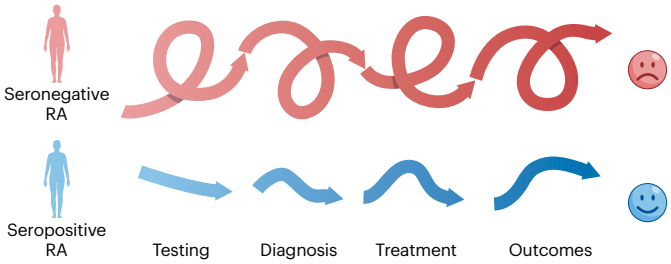

Fig. 1 | The long journey through apprehension and uncertainty for patients with seronegative RA compared to the less complicated path for patients with seropositive RA. Delays and uncertainties affect each step of the path for seronegative rheumatoid arthritis (RA), including additional autoantibody testing, uncertain diagnosis, inadequate treatment and poor outcomes.

Therapeutically, seronegative RA seems to be less responsive to treatment strategies, as most of those strategies have been optimized for seropositive RA. A 25-year longitudinal cohort study demonstrated that although aggressive early treatment reduced disease activity in both seronegative RA and seropositive RA in the short term, it achieved long-term improvements in mortality, physical function and rates of sustained DMARD-free remission only in patients with seropositive RA[9]. These findings suggest a need for therapeutic approaches tailored specifically to seronegative RA. Moreover, diagnostic delays are more common in seronegative RA than seropositive RA, increasing the risk of missing the therapeutic window for early intervention[2,10].

In summary, the continued controversies surrounding diagnosis of seronegative RA have a negative impact on patients and long-term outcomes. Diagnostic uncertainty and the persisting viewpoint that seronegative RA is milder than seropositive RA might exacerbate diagnostic delays and associate with less aggressive treatment strategies. Research on seronegative RA is limited and despite standardized approaches to defining seronegative RA using classification criteria, research on seronegative RA might be hampered by scepticism, as some rheumatologists still doubt that seronegative RA is a separate disease entity. Classification criteria were designed to identify homogeneous groups for research, but there is still a lack of acceptance of seronegative RA, even when these criteria are applied to classify patients. Enhanced biomarkers for seronegative RA would provide an optimal solution. In their absence, initiatives aimed at fostering consensus on seronegative RA within the rheumatology community may aid in reducing the existing shortcomings faced by patients with seronegative RA.

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Competing interests

The authors declare no competing interests.

Rheumatoid arthritis

Two subsets of T_{PH} cells with distinct functions in RA

T peripheral helper (T_{PH}) cells support B cell responses and autoantibody production in rheumatoid arthritis (RA). Although T_{PH} cell numbers have been associated with disease activity and severity, their trajectories and functional profiles in the inflamed joint have remained unclear.

Hideki Ueno and Hiroyuki Yoshitomi, co-corresponding authors of a new study on T_{PH} cells in RA, indicate that their work "elucidates the ecosystem of T_{PH} cells within synovial tissue at high resolution". Ueno, Yoshitomi and colleagues report the presence of two distinct subsets of T_{PH} cells in the synovial tissues of individuals with RA: a stem cell-like subset (S-T_{PH} cells) and an effector-like subset (E-T_{PH} cells). S-T_{PH} cells expressed the chemokine receptor CCR7 and the stemness-associated transcription factors TCF1 and LEF1. By contrast, E-T_{PH} cells were characterized by high expression of CXCR6 and molecules associated with effector function such as LAG3, granzyme A and IFNγ. Analysis of chromatin accessibility profiles indicated stemness-associated transcription factor activity in S-T_{PH} cells and interferon regulatory factor-associated transcriptional activity in E-T_{PH} cells.

In line with the transcriptional and epigenetic profiles, $CCR7^{+}CXCR6^{-}$ S-T_{PH} cells isolated from the synovial fluid of individuals with RA had increased proliferative potential in vitro and were able to differentiate into $CCR7^{-}CXCR6^{+}$ E-T_{PH} cells upon stimulation. Moreover, analysis of selected T cell receptor genes indicated that S-T_{PH} and E-T_{PH} cells share some clonotypes, which undergo expansion in the E-T_{PH} subset, suggesting that E-T_{PH} cells proliferate in the synovium upon their differentiation from S-T_{PH} cells.

Next, the authors asked whether both T_{PH} cell subsets support B cell responses within the tertiary lymphoid structures (TLSs) that are formed in the RA synovium. In in vitro co-culture assays, S-T_{PH} cells but not E-T_{PH} cells were able to support antibody production by B cells. Moreover, spatial transcriptomic analyses showed that S-T_{PH} cells co-localize with B cells at the centre of synovial TLSs in RA. According to these analyses, S-T_{PH} cells or their precursors are potentially recruited from the circulation to the TLSs by perivascular fibroblast-like synoviocytes that secrete the CCR7 ligands CCL19 and CCL21. By contrast, E-T_{PH} cells were localized partly at the margin of TLSs and mostly outside the TLSs and close to pro-inflammatory macrophages and $CD8^{+}$ T cells.

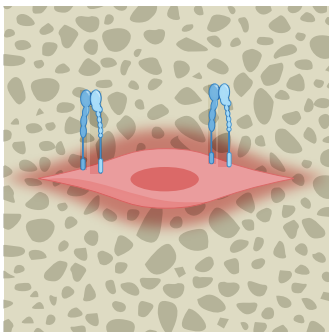
Based on these findings, Ueno and Yoshitomi note that "although T_{PH} cells are generally considered to be B helpers, our study shows that B helper function is mainly performed by S-T_{PH} cells". Considering that S-T_{PH} cells also give rise to E-T_{PH} cells, which disseminate inflammation in the tissue, Yoshitomi concludes that "S-T_{PH} cells contain villains, which should be targeted for the therapy. How? I don't know right now. But we would like to elucidate further the molecular mechanisms underlying the self-renewal of S-T_{PH} cells in TLSs".

Maria Papatriantafyllou

Original article: Masuo, Y. et al. Stem-like and effector peripheral helper T cells comprise distinct subsets in rheumatoid arthritis. *Sci. Immunol.* **10**, eadt3955 (2025)

Rheumatoid arthritis

Integrin α11 on fibroblast-like synoviocytes promotes joint damage in arthritis



Integrin expression on fibroblast-like synoviocytes (FLS) has been implicated in the pathogenesis of rheumatoid arthritis (RA). In cancer, the role of the collagen-binding integrin α11β1 on cancer-associated fibroblasts is well established, but the role of integrin α11 (the alpha subunit of integrin α11β1) in arthritis is unclear. Findings now indicate that integrin α11 might be a therapeutic target for RA. When discussing what prompted this research, corresponding author Adelheid Korb-Pap remarks "we hypothesized that similar mechanisms to those described in cancer could operate in inflammatory joint diseases, such as RA, which are characterized by extensive phenotypic transformation and activation of FLS that drive joint damage".

The authors report increased expression of integrin α11 in synovial tissue and FLS from individuals with RA and in the *hTNFtg* mouse model of RA, compared with individuals with osteoarthritis and wild-type mice, respectively. Expression of integrin α11 on FLS was particularly high at sites of adhesion and on sublining FLS. In a 3D co-culture system of cartilage and FLS from *hTNFtg* mice, integrin α11 expression in FLS was higher than in control cultures and localized to areas of invasiveness and at sites where FLS were in close contact with the cartilage extracellular matrix.

The *Itga11* gene encodes integrin α11. The authors crossed *Itga11*$^{-/-}$ and *hTNFtg* mice, creating a model of RA in which integrin α11 is absent. Using this model, the researchers assessed the role of integrin α11 in disease progression; integrin α11 mice on the *hTNFtg* background exhibited reduced histological scores for joint destruction, FLS attachment and bone loss compared with wild-type mice. In addition, in vitro analysis revealed that FLS from mice that lack integrin α11 have altered morphology and function. Korb-Pap comments that "our findings demonstrate a previously unrecognized and disease-relevant role for integrin α11 in cartilage degradation and joint pathology".

"We aim to further dissect the molecular mechanisms by which integrin α11 regulates fibroblast activation and matrix degradation in arthritic joints. This knowledge could help identify whether targeting this integrin offers a promising therapeutic strategy", notes Korb-Pap.

Holly Webster

Original article: De Giuseppe, A. et al. Collagen-binding integrin α11β1 contributes to joint destruction in arthritic hTNFtg mice. *Ann. Rheum. Dis.* https://doi.org/10.1016/j.ard.2025.07.011 (2025)

Clinical guidelines

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Guided management of familial Mediterranean fever

Hatem El-Shanti

Familial Mediterranean fever (FMF) is a monogenic autoinflammatory disorder with high prevalence in Mediterranean populations. Considerable advances in the management of FMF have been made in the past decade, with respect to the use of biologic drugs and understanding colchicine resistance. The 2024 updated FMF management recommendations are timely and reflect these advances.

Refers to Ozen, S. et al. EULAR/PReS endorsed recommendations for the management of familial Mediterranean fever (FMF): 2024 update. *Ann. Rheum. Dis.* **84**, 899–909 (2025).

Autoinflammatory diseases are a group of disorders marked by dysregulation of the innate immune system, sometimes with secondary activation of the adaptive immune system, which results in inappropriate inflammation[1]. Familial Mediterranean fever (FMF), the most common autoinflammatory disease, has considerably high prevalence in specific eastern Mediterranean ethnic groups but is rare in other regions of the world[2]; increasing the global awareness of this disease is key. In line with this need, recommendations for the management of FMF were developed in 2016 by a group of experts with the aim of providing physicians and patients with evidence-based practices[3]. The accumulation of new data and evidence published in the ensuing 8 years, the low evidence level for some of the 2016 recommendations, the emergence of new definitions and the expanding role of new therapeutic options necessitated the development of an updated set of recommendations[4].

The main characteristics of FMF are fever and polyserositis that present as recurrent short-lived episodes of fever that usually start and end abruptly (lasting 1–3 days) and are often accompanied by pain owing to peritonitis, pleuritis or acute synovitis of large joints. Onset of this lifelong illness usually occurs in adolescence and attack frequency varies considerably. During attacks, there is neutrophilia and a quick acute-phase response; between attacks, patients feel well, although biochemical evidence of inflammation might persist. The most substantial complication of FMF is renal amyloidosis (which manifests as proteinuria and renal failure) and, in rare instances, might be the presenting symptom without prior disease attacks. Daily oral colchicine is the mainstay treatment for FMF and often results in the prevention or considerable reduction in the frequency and severity of the attacks in patients who adhere to treatment. Importantly, this continuous prophylactic treatment inhibits the development of amyloidosis, even for the minority group of patients who adhere to treatment but whose symptoms do not improve. Overwhelming evidence suggests that FMF is an autosomal recessive disorder caused by biallelic pathogenic variants of the *MEFV* gene; however, the pathogenicity of the described variants might not always be clearly defined, and carriers can have signs and symptoms of disease, both of which contribute to the genetic complexity of FMF.

Because FMF is rare in most regions of the world[5] and not frequently encountered in healthcare practices, the development of recommendations that are based on evidence and expert experience are invaluable. In 2016, Ozen et al.[3] published a set of widely accepted recommendations for the management of FMF and in 2024 provided a timely update[4]. The updated recommendations address published evidence from the past 8 years that focus on patients with colchicine resistance, the new definitions of colchicine resistance and tolerance[6] and the increasing use of biologic agents for the treatment of FMF, particularly in patients with colchicine resistance. A few of the 2016 recommendations, which were based on publications with relatively low evidence levels, are also reviewed in these updated recommendations. In the 2024 update, Ozen et al.[4] outline four overarching principles and 12 recommendations with a high level of agreement (>9, on a 0–10 scale with 10 meaning full agreement) and with a much-improved level of evidence. Several of the 2016 recommendations were transformed into overarching principles. Ozen et al.[4] did not identify any studies that investigated the quality of life of patients with FMF, non-pharmacological interventions or the barriers to colchicine adherence but used indirect evidence to address these points.

The overarching principles state the clinical and genetic complexity of FMF, emphasize that diagnosis and management require expertise and recommend the use of the detailed French protocol for the diagnosis of FMF[7]. These overarching principles set the treatment goals, which are to achieve minimal or no clinical activity of the disease and to provide total control of subclinical inflammation between attacks. The overarching principles also state that FMF requires lifelong management including long-term amyloidosis prophylaxis with colchicine and that patient-centred management is essential for good quality of life. Seven of the 12 recommendations address treatment with colchicine: when to start treatment; daily dosing; frequency of administration; safely increasing the daily dose to control symptoms; monitoring for toxicity and overdosing; use during conception, pregnancy, and lactation; and recommended continuation during attacks and during treatment with biologic agents. The authors reiterate that adherence to colchicine treatment is the cornerstone of FMF management. Three of the 12 recommendations address treatment with biologic agents, including indications, the optimization of dosing and tapering and discontinuation for patients who are in remission. Biologic agents are recommended for patients who adhere to colchicine treatment but who have inadequate response to the maximum tolerated colchicine dose. FMF-related chronic inflammatory joint disease can require additional treatment, usually with DMARDs, as colchicine and the biologic agents

typically used to treat FMF, such as canakinumab and anakinra, might not effectively treat this disease manifestation. FMF-related protracted febrile myalgia is complex and serious and might need to be treated with systemic glucocorticoids. One recommendation states that the aim of AA amyloidosis treatment is to obtain complete and sustained control of biochemical inflammation (as measured by serum amyloid A, for example).

The set of recommendations put forward by Ozen et al.[4] is endorsed by both the adult and paediatric European rheumatology societies (EULAR and the Paediatric Rheumatology European Society), which, together with the strong evidence base used, substantially strengthen the recommendations. The article outlines barriers to the implementation of the recommendations and suggests strategies to overcome them, such as developing educational material for patients and families with information on colchicine treatment to overcome the lack of adequate information about the drug, which often leads to non-adherence. One limitation is that there is a lack of input from experts from other parts of the world, particularly in areas where FMF is considerably prevalent. Although this point does not diminish the value of these recommendations for FMF healthcare provision, it might limit their use globally. Addressing these dissemination and implementation strategies will enable the translation of these recommendations into practice in different geographic settings. The recommendations provide a comprehensive approach that brings people with FMF and their healthcare providers together, with the aim of successful management of symptoms and possible complications, and outline unanswered research questions about the pathophysiology of FMF that need to be scientifically addressed.

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Competing interests

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Review article

Check for updates

Global epidemiology of spondyloarthritis

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Abstract

The worldwide epidemiology of axial spondyloarthritis (axSpA), psoriatic arthritis (PsA) and peripheral spondyloarthritis, as well as of *HLA-B27* and other MHC and non-MHC genes in these diseases, is reviewed herein. The frequency of axSpA is highest in circumpolar groups (such as Sami people and certain Indigenous American groups) and lowest in those of Japanese and African ancestry. The same pattern holds for PsA, although the overall prevalence of PsA seems much lower in East Asia, where it is less frequent than axSpA. The prevalence of PsA in people with psoriasis is increased where rheumatological assessment was carried out and seems to be increasing over time. *HLA-B27* remains the most important genetic factor in axSpA susceptibility, although its frequency is lower in African American, South American and Middle Eastern populations than in others. The presence of *HLA-B27* and other HLA alleles seems to be important in discerning clinical subsets of SpA and PsA, particularly those characterized by acute anterior uveitis or by axSpA with psoriasis, although these *HLA-B27* and other MHC and non-MHC associations are derived from genome-wide association studies and other chip-based studies in large populations. These studies have been carried out mainly in populations of European and East Asian ancestry, and similar data from Latin America, sub-Saharan Africa and South Asia are lacking. This under-representation is an unmet need in applying genetic factors to understand the pathogenesis, diagnosis and classification of SpA and PsA.

Sections

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Key points

- The prevalence of radiographic axial spondyloarthritis (r-axSpA) varies worldwide, being highest in Indigenous people of the circumpolar north and lowest in people of African and Japanese descent.
- The prevalence of psoriatic arthritis (PsA) follows similar trends, although it seems to be lower in East Asia than in Western countries; PsA prevalence seems to be increasing over time.
- Variation across epidemiological studies of axSpA and PsA is attributable in part to differences in study design, the classification or diagnostic criteria used, and the populations studied.
- HLA-B27 remains the most important genetic factor in r-axSpA susceptibility, although its population frequency varies considerably in different regions and between groups in the same region.
- Numerous other MHC and non-MHC genes are associated with susceptibility to r-axSpA, PsA and/or psoriasis; knowledge of the genetic basis of these diseases could improve diagnosis, classification and treatment.
- Epidemiological and genetic studies of r-axSpA and PsA are limited by under-representation of some populations, as most studies have been carried out in Europe, East Asia and North America.

Introduction

Spondyloarthritis (SpA) is a heterogeneous group of diseases with axial SpA (axSpA) and/or peripheral SpA (pSpA) and enthesitis, as well as an overlapping spectrum of extra-musculoskeletal features, including uveitis, psoriasis and inflammatory bowel disease. These diseases exhibit strong familial aggregation, and genetic factors are dominant in pathogenesis, especially genes of the MHC, most notably *HLA-B27*.

Inflammatory back pain (IBP) is a cardinal feature of axSpA. Criteria for this phenomenon were first described in 1977 (ref. 1), revised by the European Spondyloarthropathy Study Group classification criteria for SpA in 1991 (ref. 2), further revised by Rudwaleit et al. in 2006 (ref. 3) and finally as part of the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axSpA in 2009 (ref. 4). Generally, IBP is characterized by insidious onset, morning stiffness, improvement with activity and not with rest, awakening in the second half of the night and alternating buttock pain[1–4]. Depending on the criteria used, in studies from the USA and the UK chronic IBP occurs in up to one-third of those with chronic back pain, especially younger people[5,6]. However, a 2022 systematic review found the concept of IBP to be largely restricted to rheumatologists[7]. In fact, among surgeons and radiologists, the concept of 'inflammatory spinal disease' relates to a spinal MRI finding known as Modic changes, the clinical relevance of which is controversial[8] and has not been found to be associated with axSpA[9,10].

In this Review, we examine the descriptive epidemiology of SpA, especially in its three most common forms: axSpA (including non-radiographic axSpA (nr-axSpA) and radiographic axSpA (r-axSpA), the latter classically referred to as ankylosing spondylitis (AS)), psoriatic arthritis (PsA) and pSpA. The concept of nr-axSpA came from studies showing that up to 40% of patients with IBP and other features of axSpA had not developed radiographic sacroiliitis 10 years after symptom onset[11], as well as from refinements in MRI technology whereby patients had MRI results suggestive of sacroiliitis (that is, bone marrow oedema on either side of the sacroiliac joints) but without the radiographic (plain X-ray) changes required for a diagnosis of r-axSpA[12]. Generally, r-axSpA and AS are equivalent terms in that both depend on the presence of radiographic sacroiliitis, although a classification of r-axSpA can be made on the basis of a broader group of SpA imaging and clinical features[13].

We also examine the genetic epidemiology of both axSpA and PsA, including the worldwide epidemiology of the *HLA-B27* gene and other MHC and non-MHC genes in these diseases. We do not review reactive arthritis or enteropathic arthritis individually, as per ASAS classification criteria these conditions are included under the terminology axSpA and pSpA[12–14], are less well characterized epidemiologically and genetically and show extensive overlap of pSpA and axSpA; however, because of the extensive epidemiological and genetic data available for PsA, this condition is included. To carry out this Review, a literature search was conducted on PubMed using the terms "spondylitis, epidemiology", "spondyloarthritis, epidemiology", "axial spondyloarthritis, epidemiology", "peripheral spondyloarthritis, epidemiology", "HLA-B27, epidemiology", "spondylitis, genetics", "spondyloarthritis, genetics" and "psoriatic arthritis, genetics"; any other articles that any of the co-authors felt were relevant to the topics covered here were also considered.

The worldwide epidemiology of axial spondylarthritis

The earliest studies of the epidemiology of axSpA predated classification criteria and were usually based on pelvic radiographs, which were carried out in large population studies (which would be considered unethical today)[15] (reviewed in Dean et al., Stolwijk et al. and Kellgren et al.[16–18]) or were based on clinical assessments[18–20]. Studies of Native American people found an increased prevalence of radiographic sacroiliitis and r-axSpA, up to 9.5% in Haida people in the Pacific Northwest[21]. To our knowledge, the first study to examine r-axSpA prevalence in the USA was published in 1967, reporting a population frequency of 0.4% in male individuals and 0.05% in female individuals[19]. The National Health and Nutrition Examination Survey (NHANES I) was a nationally representative study conducted between 1971 and 1975 at 100 locations in the USA. Among 6,913 participants between the ages of 25 and 74, pelvic radiographs were obtained in all but 2,010 of these individuals (the latter mostly women under the age of 50 years). The prevalence of moderate-to-severe sacroiliitis was 0.52% (ref. 15); this radiographic severity would correspond to grade 3–4 sacroiliitis in the original or the modified New York criteria for AS (now known as r-axSpA)[22,23] and would not capture less-severely affected people. It should be noted, however, that radiographic sacroiliitis does not by itself equate to a diagnosis of r-axSpA, as noted in the modified New York criteria[23].

Diagnostic criteria for r-axSpA (AS) were first introduced in 1963 (the Rome criteria)[18] and were updated in 1966 (the original New York criteria)[22] (Supplementary Fig. 1). The New York criteria were further modified in 1984 to change chronic back pain to chronic IBP[23] (Fig. 1), and these modified criteria are still used to this day. However, with the discovery of the association of HLA-B27 with r-axSpA and related diseases, with the concept of SpA representing a disease spectrum encompassing not only axial but also peripheral musculoskeletal involvement (arthritis, enthesitis), as well as other mucocutaneous, ocular, cardiovascular, gastrointestinal and pulmonary manifestations,

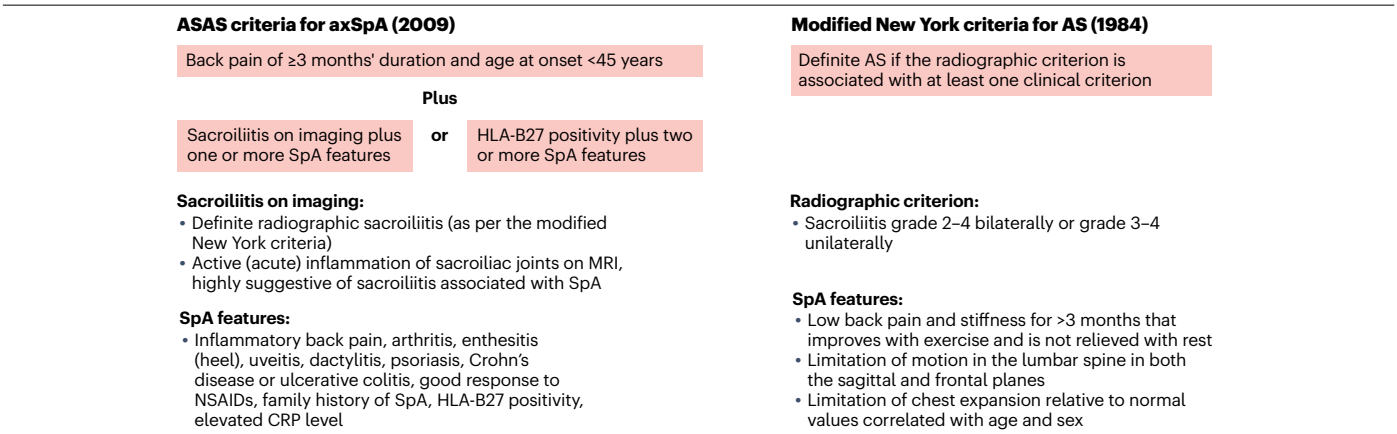

Fig. 1 | Current classification criteria for axial spondyloarthritis. Classification criteria developed by the Assessment of SpondyloArthritis international Society (ASAS) identify patients with a broad spectrum of axial spondyloarthritis (axSpA), including both radiographic axSpA and non-radiographic axSpA[13]. Patients with back pain for at least 3 months and age at onset <45 years can fulfil the criteria for axSpA through either a 'clinical' arm or an 'imaging' arm. The modified New York criteria for classification of axSpA (ankylosing spondylitis (AS)) identify patients as having 'probable' or 'definite' axSpA, depending on fulfilment of clinical and radiographic criteria[23].

two further sets of classification (but not diagnostic) criteria for SpA were proposed: one set by Bernard Amor[24], which listed a differential weighting for each manifestation and included HLA-B27, and the other by the European Spondyloarthropathy Study Group, which included both SpA and axSpA[3] (Supplementary Fig. 2). The latter criteria did not include a requirement for radiographs and have therefore been widely used in population studies (Table 1). With improvements in imaging technology, specifically MRI, as well as with the more widespread use of HLA-B27 testing, newer classification criteria were developed and tested by ASAS for both axSpA (including those with negative sacroiliac radiographs, nr-axSpA)[13] and pSpA (including peripheral arthritis, enthesitis and dactylitis)[14]. The spectrum covered by the ASAS criteria not only includes r-axSpA and nr-axSpA, but also encompasses reactive arthritis, juvenile-onset SpA, PsA, enteropathic arthritis and undifferentiated SpA[14]. The inclusion of imaging in the ASAS classification criteria has made these criteria non-feasible for population studies. Moreover, concern regarding lack of specificity, particularly of the 'clinical arm' (which requires HLA-B27 positivity plus two clinical features for axSpA classification) has led to these criteria currently being re-evaluated and revised[25,26]. Of note, however, a study from a French early SpA cohort that included 262 people who met the ASAS clinical criteria and 173 who met the ASAS imaging criteria found no major differences between the two groups, except that those in the imaging arm were more likely to be younger, male and have higher concentrations of C-reactive protein[27].

The prevalence of r-axSpA varies widely[16–21,28–80] (Table 1) and largely correlates with that of HLA-B27, with the frequency of r-axSpA being highest in populations in which HLA-B27 is most frequent (in circumpolar groups such as Indigenous Chukotka (Siberia), Northwestern Americans, Inuit and Finnish Sami people[21,29,42,69]) and is least common in populations in which HLA-B27 is rare (people of African and Japanese descent)[32,70]. Generally, the prevalence of axSpA tended to be higher in population-based epidemiology studies and surveys[15–19,30–33,35–37,41–56,67–78] than in national or insurance registries using International Classification of Diseases (ICD) coding or patient referrals[38–40,57–65,79,80], probably because population-based studies include undiagnosed patients or those not in the medical care system. Therefore, when comparing occurrence estimates from different studies, it is crucial to consider methodological differences such as study design, demographics (age and sex) of the source population, modes of case ascertainment and the classification criteria used. Additionally, genetic and environmental variations across different countries could also contribute to these discrepancies. Cross-sectional, population-based studies offer a more comprehensive view of prevalence by capturing undiagnosed cases, albeit demanding more time and resources. Conversely, diagnostic prevalence studies using large electronic health care databases are more feasible to conduct but might underestimate true occurrence rates owing to reliance on diagnostic codes with low sensitivity or unvalidated sensitivity, as well as to potential omissions or misinterpretations within health care documentation systems[81,82]. Although many studies from Asia and South America employ the Community Oriented Program for Control of Rheumatic Diseases (COPCORD) study design, a lack of uniform standardization in protocols has led to variations in core questionnaires, methods, diagnostic and classification approaches, time frames and response rates; these differences can substantially affect prevalence estimates[83].

The worldwide epidemiology of psoriatic arthritis

In PsA, 'criteria' proposed in 1973 by Moll and Wright[84] were used in early studies, although once the CASPAR classification criteria were adopted in 2006 (ref. 85) most studies thereafter utilized them in classifications (Table 2 and Fig. 2). As most patients with PsA also have psoriasis, the prevalence of this condition mirrors the geographic prevalence of psoriasis. The population prevalence of psoriasis in adults ranges from 0.91% (USA) to 8.5% (Norway), being higher in countries more distant from the equator and lower in East Asian and South Asian countries (China (mainland), Taiwan and Sri Lanka)[86]. The frequency of PsA in Western countries varies between 0.002% and 0.67% (refs. 43,48,49,51,52,65,87–117) (Table 2), being highest in Scandinavia[46,105], and it is least frequent in East Asia[70–72,118–122]. Only one study addressed the issue of PsA prevalence in First Peoples of Australia[123] and population-based studies on the prevalence and incidence of PsA in African countries are lacking[124].

The variation in the estimated prevalence of PsA across studies can be partially explained by methodological differences in case

Table 1 | Worldwide incidence and prevalence of axial spondyloarthritis

Year	Country	Mode of ascertainment	Criteria used[a]	Incidence (per 100,000 person-years)	Prevalence (%)	Refs.
Systematic reviews and meta-analyses						
2014	Global	Systematic review including 36 eligible studies	Varied	NR	0.238 Europe; 0.167 Asia; 0.319 North America; 0.102 Latin America; 0.074 Africa	16
2015	Global	Systematic review and meta-regression analysis of 84 studies	Varied	NR	SpA/r-axSpA 1.61/0.35 Arctic; 0.54/0.25 Europe; 0.79/0.16 East Asia; 0.22/0.06 South Asia; 0.20/0.07 Southeast Asia; 1.35/0.20 North America; 0.52/0.14 Latin America; 0.32/0.11 Middle East and North Africa; 0.02 Sub-Saharan Africa (SpA and r-axSpA combined)	17
Americas: questionnaire, medical record, clinical evaluation						
1979	USA	NHANES	Sacroiliac radiography	NR	0.52 'moderate-to-severe' sacroiliitis	15
1979	USA	Mayo Clinic databases	Clinical evaluation	NR	0.129 (r-axSpA)	20
1992	USA	Mayo Clinic databases	mNY	7.3	NR	28
1994	USA (Alaska Native)	Clinical databases	ESSG	NR	2.5 SpA	29
2009	Cuba	COPCORD questionnaire	Clinical evaluation	NR	0.1 r-axSpA	30
2012, 2013	USA	NHANES national survey	Previous physician diagnosis, ESSG, Amor	NR	0.57 r-axSpA; 0.9 axSpA (Amor); 1.4 SpA (ESSG)	31,32
2013	Mexico	COPCORD survey followed by physician evaluation	ESSG	NR	0.1 r-axSpA; 0.6 axSpA	33
2013	USA	Review of medical records from 101 US practices	ASAS	NR	0.35 r-axSpA; 0.35 nr-axSpA	34
2016	Venezuela (Indigenous tribes)	COPCORD interview	mNY	NR	0.4 r-axSpA	35
2016	Mexico (Indigenous tribe)	COPCORD interview	mNY	NR	0.8 r-axSpA	36
2018	Colombia (Indigenous tribe)	COPCORD interview	Clinical evaluation	NR	0.11–0.18-axSpA	37
Americas: national database or registry reviews						
2016	USA	Kaiser Permanente Northern California Database	ICD-9 code 720	NR	0.107 r-axSpA; 0.226 axSpA	38
2023	USA	Military Health System Data Repository	ICD-9 codes (720.0, 720.9), ICD-10 codes (M45.xx)	27.22	NR	30
2024	Colombia	National Health Registry (SISPRO) database	ICD-10 codes	NR	0.03–0.2 axSpA	40
Europe: questionnaires, medical records, clinical evaluations						
1985	Norway	Questionnaire, assessment by rheumatologist	NY	NR	1.1–1.5 r-axSpA	41
1992	Norway (Sami people)	Questionnaire, medical assessment	NY	NR	1.8% r-axSpA	42
1998	Germany	Questionnaire, clinical evaluation	ESSG	NR	1.73 SpA; 0.55 r-axSpA	43,44
2002	Azores	Hospital records review, assessment by rheumatologist	mNY, ESSG	NR	1.6 SpA; 1.2 r-axSpA	45
2003	Finland	Inpatient and outpatient rheumatological referral, clinical assessment, questionnaire	Back pain, imaging	7 r-axSpA 13 USpA	N/A	46
2005	France	Telephone interview, assessment by rheumatologist	Rheumatologist diagnosis	NR	0.3 SpA	47

Table 1 (continued) | Worldwide incidence and prevalence of axial spondyloarthritis

Year	Country	Mode of ascertainment	Criteria used[a]	Incidence (per 100,000 person-years)	Prevalence (%)	Refs.
Europe: questionnaires, medical records, clinical evaluations (continued)						
2005	Greece	Questionnaire, rheumatological assessment	mNY, ESSG	NR	0.24 r-axSpA; 0.49 SpA	48
2007	Italy	Questionnaire, assessment by rheumatologist	mNY, ESSG	NR	0.37 r-axSpA; 1.06 SpA	49
2008	Lithuania	Telephone interview, assessment by rheumatologist	ESSG	NR	0.84 SpA	50
2010	Greece	Mailed questionnaire, assessment by rheumatologist	ESSG	NR	0.29 r-axSpA	51
2010	Czech Republic	Patients referred to rheumatologists	mNY	6.4 r-axSpA	0.094 r-axSpA	52
2010	Iceland	Medical record review	mNY	NR	0.13 r-axSpA	53
2015	Serbia	Random selection of telephone list, follow-up call and assessment by rheumatologist	ESSG	NR	0.32 SpA; 0.08 r-axSpA	54
2015	UK	Questionnaire, clinical evaluation, MRI	ASAS, ESSG, mNY	NR	0.15 r-axSpA; 0.3 AxSpA ASAS; 1.2 AxSpA ESSG	55
2020	Spain	Telephone survey with follow-up	mNY	NR	0.26 r-axSpA	56
Europe: national database/registry						
1997	Finland	National medication re-imbursement database	Clinical diagnosis	6.9 r-axSpA	0.15 r-axSpA	57
2011	Sweden	Skåne Health Care Register	ICD-10 codes	NR	0.45 SpA; 0.096 r-axSpA	58
2014	Norway	HUNT national registry	ICD-9 codes, ICD-10 codes	27.0	NR	59
2015	Poland	National Health Fund registry	ICD-10 codes	NR	0.0748 r-axSpA	60
2015	Sweden	Swedish National Patient Register	ICD codes	NR	0.18 r-axSpA	61
2016	Scotland	PCCIUR electronic primary care database	Clinical diagnosis	NR	0.134 r-axSpA	62
2020	Denmark	Danish National Patient Registry	ICD-10 codes (M45, M46)	axSpA: 476 r-axSpA (2000–2004): 660 r-axSpA/SpA (2010–2013): 707	NR	63
2020	Poland	National Health Fund registry	ICD-10 codes	NR	0.083 r-axSpA	64
2023	Norway	Norwegian Patient Registry	ICD-10 codes (M45, M46.0, M46.1, M46.8 and M46.9)	NR	0.51	65
Asia: systematic review/meta-analysis						
2020	China	Meta-analysis	Varied	NR	0.29 r-axSpA	66
Asia: questionnaire/clinical evaluation						
1994	Taiwan	Questionnaire, assessment by rheumatologist	mNY	NR	0.19–0.54 r-axSpA	67
1994	China	Questionnaire, physician assessment	Clinical and radiological evaluation	NR	0.26 r-axSpA	68
1994	Chutkota Siberians	Interviews, medical examinations	Expert evaluation	NR	1.3 r-axSpA; 2.5 SpA	69

Table 1 (continued) | Worldwide incidence and prevalence of axial spondyloarthritis

Year	Country	Mode of ascertainment	Criteria used[a]	Incidence (per 100,000 person-years)	Prevalence (%)	Refs.
Asia: questionnaire/clinical evaluation (continued)						
2001	Japan	Physician questionnaire, medical record review	mNY, ESSG, Amor	0.48	0.0065 r-axSpA; 0.0095 SpA	70
2008	China	Pooled surveys	NY, mNY, Amor, ESSG	NR	0.2-0.54 r-axSpA; 0.6-1.2 USpA	71
2008	Turkey	Telephone interview, assessment by rheumatologist	mNY, ESSG	NR	0.49 r-axSpA; 1.05 SpA	72
2009	China	Questionnaire, assessment by rheumatologist	mNY, ESSG	NR	0.253 r-axSpA; 0.782 AxSpA	73
2012	Turkey	Physician household visit	Rome, ESSG	NR	0.12 r-axSpA	74
2015	Turkey	Interview of university employees	ASAS, mNY	NR	0.5 r-axSpA; 1.3 axSpA (ASAS)	75
2018	Japan	Nationwide survey in 2,221 randomly selected facilities	mNY	NR	0.0026 r-axSpA; 0.0006 nr-axSpA	76
2018	South China	University students	ASAS	NR	0.34 axSpA	77
2021	Pakistan	Door-to-door nurse COPCORD survey followed by physician evaluation	ASAS	NR	1.0 r-axSpA	78
Asia: National Database/Registry						
2018	South Korea	Health Insurance Review Agency database	mNY	6.34	0.0316 r-axSpA (2010); 0.0523 r-axSpA (2015)	79
2024	Thailand	Thailand Database Ministry of Public Health	ICD-10 codes (M45)	10.4	0.0204 r-axSpA (2017)	80

[a]Criteria used: NY, 1966 New York criteria for ankylosing spondylitis (1966)[22]; mNY, modified New York Diagnostic Criteria for ankylosing spondylitis (1984)[23]; Amor, Amor Classification Criteria for Spondyloarthritis[24]; ESSG, European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy (1991)[2]; ASAS, Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (2009)[13]; Rome, Rome Diagnostic Criteria for Ankylosing Spondylitis (1963)[18]. NHANES, National Health and Nutrition Examination Survey; NR, not reported; SpA, spondyloarthritis; r-axSpA. radiographic axial spondyloarthritis; COPCORD, Community Oriented Program for Control of Rheumatic Diseases; nr-axSpA, non-radiographic axial spondyloarthritis; ICD-10, International Classification of Diseases 10; USpA, undifferentiated spondyloarthritis; PCCIUR, Primary Care Clinical Informatics Unit Research.

ascertainment, as studies that relied on self-reported diagnosis tend to report higher rates and those using administrative databases or medical records report lower rates. However, differences in genetic and environmental factors are also important. PsA commonly affects people in their fourth decade of life, with age at onset in women often lagging behind that in men[90,103]. PsA is typically considered to affect male and female patients equally. However, recent studies describe a change in the trend with an increasing number of female individuals being diagnosed with PsA compared with male individuals[125].

Generally speaking, the frequency of PsA in people with psoriasis varies widely, ranging from 5.8% in studies from China to 41% in Canada[98,100,104,108,109,111–113,122,123,126–154], depending on when and where the assessments were done, what type of observer did the assessment and which criteria were used (Table 3). In most series, the prevalence ranged between 15% and 30%, with the highest rates in Europe and Canada and the lowest in Asia and Africa. The prevalence of PsA tended to be higher when patients attending dermatology clinics were screened by a rheumatologist[127–129,133,135,140–142,149], and lower when health care databases were screened using ICD-9 and ICD-10 codes (Table 3). This variability could be explained by the fact that patients attending dermatology clinics typically have more severe psoriasis, which is a risk factor for PsA, or by the inclusion of false-negative diagnoses in health care databases[115]. Thus, the higher rates of PsA in a dermatology setting probably reflect the enrichment of populations with risk factors for PsA; however, underdiagnosis of PsA in general practice is another explanation.

Studies examining specific populations over time have shown the prevalence of PsA to be rising[111,116,117,119,120]. The pattern of joint involvement likewise varies, with polyarthritis being the most common manifestation in Europe and Japan and oligoarthritis most commonly seen in Africa, China and South America[128,131,154]. However, the classification of oligoarthritis versus polyarthritis depends on at what point in time the diagnosis of PsA is made, as without treatment many people who initially present with oligoarthritis can later develop polyarthritis; thus, older studies or those involving populations with reduced access to medications might have reported polyarthritis as a more common pattern. The frequency of axial involvement in PsA also varied widely[98,100,128–130,142,147,148,152,154].

The worldwide epidemiology of peripheral spondyloarthritis

Data on the prevalence of pSpA in the general population are scarce, probably because before classification criteria for pSpA were proposed in 2011 (ref. 14) this term was often referred to by various disease categories that it encompasses, such as reactive arthritis (previously known as Reiter's syndrome), PsA, enteropathic arthritis and undifferentiated SpA. Also, in many patients, the transient nature of some of these diseases (such as reactive arthritis) has complicated epidemiological studies. As noted

Table 2 | Worldwide incidence and prevalence of psoriatic arthritis

Year	Country	Mode of ascertainment	Criteria[a]	Incidence (per 100,000 person-years)	Prevalence (%)	Refs.
Systematic reviews and meta-analyses						
2013	Multiple	Meta-analysis	Varied	83	0.13	87
2024	Multiple	Meta-analysis	Varied	NR	0.11	88
America: questionnaire/medical record/clinical evaluation						
2005	USA	27,220 telephone interviews	Report of physician diagnosis	NR	0.25	89
2021	USA (Olmstead County)	Medical records of health care providers	CASPAR	8.5	0.182	90
America: nationwide database/registry						
2000	USA (Olmstead County)	Rochester Epidemiology Project computerized medical record system	Inflammatory arthritis associated with psoriasis	6.59	0.1	91
2009	USA (Olmstead County)	Rochester Epidemiology Project computerized medical record system	CASPAR	7.2	0.16	92
2011	Argentina	Computerized HMO records, rheumatologist databases	CASPAR	8.3	0.074	93
2013	USA (north CA)	Computerized databases	ICD-9 codes	NR	0.068	94
2019	Canada	Ontario health administrative data	ICD-9, ICD-10 codes	15.5	0.17	95
Europe: questionnaire/medical record/clinical evaluation						
1998	Germany	Questionnaires mailed to 348 blood donors	Self-report	NR	0.29	43
2000	Finland	Patients referred to University Hospital and clinics, medical record review by rheumatologists	RF-negative arthritis with psoriasis, excluding axSpA	23.1	NR	46
2002	Sweden	Patients referred to rheumatologists	Psoriasis with RF-negative arthritis	8	NR	96
2003	Greece	Patients referred to rheumatologists	ESSG	3.02	0.057	97
2005	Greece	Rheumatologist home visits	ESSG with skin and/or nail involvement	NR	0.17	48
2005	Norway	Chart reviews from rheumatology centres for 442,000 participants	Psoriasis and arthritis without rheumatoid nodules	NR	0.195	98
2007	Italy	3,664 questionnaires with physician assessment	ESSG	NR	0.42	49
2007	Iceland	157 participants interviewed and examined	Clinical assessment	NR	0.14	99
2009	Norway	Patients seen over 19 years at one rheumatology department	ICD-9 codes	6.9	0.13	100
2010	Czech Republic	Patients referred to rheumatologists	Vasey and Espinoza criteria	3.6	0.05	52
2010	Greece	Mailed questionnaire, rheumatological assessment	CASPAR	NR	0.35	51
Europe: medical record/database/registry						
1996	Finland	Nationwide sickness insurance scheme	Medical record review	6.0	NR	101
2009–2012	Germany	National SHI Database	ICD-10 codes	16.01 (2009); 17.31 (2012)	NR	102
2013	UK	Population-based medical records database	Medical diagnosis by primary care practitioner	NR	0.19	103
2014	Sweden	Skåne Healthcare Register	ICD-10 codes	NR	0.21	104
2015	Central Norway	Nord-Trøndelag health study databases	CASPAR	41.3	0.67	105
2016	Poland	National Health Fund database	ICD codes (M07 and L40.5)	NR	0.032	106
2017	Denmark	Nationwide registry data	ICD-10 codes (M07.0–3 and M09.0)	7.3 (1993); 27.3 (2010)	0.22	107
2019	Germany	National SHI data	ICD codes	NR	0.0018–0.0021 (men); 0.0021–0.0025 (women)	108

Table 2 (continued) | Worldwide incidence and prevalence of psoriatic arthritis

Year	Country	Mode of ascertainment	Criteria[a]	Incidence (per 100,000 person-years)	Prevalence (%)	Refs.
Europe: medical record/database/registry (continued)						
2020	Sweden	Four secondary administrative registries	ICD-10 codes (L40.5, M07.0–M07.3 or M09.0)	1.69	NR	109
2021	France	Four secondary administrative registries	ICD-10 code (M07)	8.4	0.1	110
2021	Poland	National Health Fund database	ICD-10 codes (L40.5, M07)	NR	0.038 (2008); 0.073 (2018)	111
2021, 2023	Germany	German health insurance databases	ICD-10 codes	NR	0.29–0.31	112–114
2022	UK	The Health Improvement Network database	Physician report	5.4		115
2023	Norway	Norwegian Patient Registry	ICD-10 codes (L40.5, M07.0–M07.3)	NR	0.46	65
Asia: questionnaire/medical record/clinical evaluation						
1994	Siberia	Medical examinations and interviews	Clinical diagnosis	NR	0.3	69
2001	Japan	Medical record review	Clinical and radiographic features	NR	0.0012	70
2008	China	38 COPCORD surveys	CASPAR	NR	0.01–0.1	71
2012	Turkey	Physician household visit	ESSG	NR	0.05	72
2012	China	Screening questionnaire in 14,642 individuals	CASPAR	NR	0.02	118
Asia: nationwide database/registry						
2016	Taiwan	National Health Insurance Research Database	ICD-9 code (696.0)	NR	0.005 (2003); 0.013 (2013)	119
2018	South Korea	Korean National Health Insurance Claims Database	ICD-10 code (M07.3)	NR	0.04 (2006); 0.23 (2013)	120
2018	Israel	Clalit Health Services database	ICD-5 code (696.0)	10.9	0.073 (2006); 0.153 (2015); 0.221 (2022)	116,117
2018	Taiwan	Taiwan National Health Insurance research database	ICD-5 (696.0)	3.64 (2000); 6.91 (2013)	0.011 (2000); 0.038 (2013)	121
2022	Taiwan	Taiwan National Health Insurance claim database	ICD-9 code (696.0), ICD-10 codes (L40.5, L40.51, L40.52, L40.53, L40.54, L40.59)	5.0	77	122
Australia: questionnaire/medical record/clinical evaluation						
2004	First Peoples of Australia	House-to-house visit with COPCORD Core Questionnaire	Clinical diagnosis	NR	0.5	123

[a]Criteria used: 2006 CASPAR criteria[85], European Spondylarthropathy Study Group (ESSG) 1991 preliminary criteria for the classification of spondylarthropathy[2]. COPCORD, Community Oriented Program for Control of Rheumatic Diseases; ICD, International Classification of Diseases; NR, not reported; RF, rheumatoid factor; HMO, health maintenance organization; SHI, Statutory Health Insurance.

above, we did not review reactive arthritis or enteropathic arthritis for this Review. Nevertheless, the relative proportion of pSpA among the whole SpA population can be retrieved from SpA cohorts in studies since 2011.

In the international ASAS-PerSpA cohort, which included 4,465 consecutive patients with any subtype of SpA, peripheral joint disease was reported in 57% of the cases, enthesitis in 44% and dactylitis in 15% (ref. 155). However, pSpA was considered the main SpA diagnosis in only 10.3% of the cases. Of those cases with pSpA as the main diagnosis, 62% were considered 'pure' pSpA (that is, without associated axSpA or PsA), corresponding to 6.4% of the whole SpA population[156].

In another international cohort study led by the ASAS group, Comorbidities in SpA (COMOSPA), which included 3,985 patients with SpA, pSpA was identified in 14% of the cohort as per the ASAS classification criteria[157].

In other, smaller cohorts, allowing overlaps between SpA entities, namely the Belgian Be-Giant early SpA cohort, the Spanish Esperanza SpA cohort, the Dutch SpA cohort and the French GAZEL cohort, the reported proportion of pSpA ranged from 22.8% to 28.5% of the whole SpA population[158–161].

The worldwide epidemiology of HLA-B27 and other MHC genes

HLA-B27 positivity worldwide, its relevance and its association with axial spondyloarthritis

*HLA-B*27:05*, which is regarded as the 'parent' HLA-B27 allele, almost certainly originated before *Homo sapiens* left Africa 50,000–80,000 years ago, as this allele is the most common HLA-B27 subtype in all populations examined. As ancient man migrated to the rest of the world, the major HLA-B27 subtypes evolved, including *HLA-B*27:03* in West Africa, which was found to be the most common HLA-B27 subtype there[162], although it is not associated with r-axSpA there or elsewhere[163,164], as well as

*HLA-B*27:02* in the Mediterranean and throughout Europe, *HLA-B*27:07* in South Asia, and *HLA-B*27:04* in East Asia, all of which are associated with r-axSpA[164] (Table 4). Two other subtypes have evolved that are relatively common in their respective locations but are not associated with r-axSpA, namely *HLA-B*27:06* in Southeast Asia[164,165], which is presumably derived from *HLA-B*27:04*, and *HLA-B*27:09*, which is found most frequently in Sardinia and is derived from *HLA-B*27:05* (refs. 164,166). Thus far, more than 294 protein subtypes of HLA-B27 have been described[167], most of which are too uncommon to have disease associations established.

The frequency of HLA-B27 worldwide is lowest in areas around the equator[162,168–172] and highest in circumpolar regions, being lowest in Africa and highest in Inuit and other Indigenous groups residing in northern climates[69,173,174] (Fig. 3). Population-based studies, such as NHANES in the USA, have defined different prevalences of HLA-B27 in white, Black and Mexican American people[172]; the NHANES study also suggested a decreased prevalence of HLA-B27 with increased age[172], a trend that was also seen in France[161] but not confirmed in other studies from New Zealand[175] and the UK[176]. In the USA, in a study in US Veterans Administration Hospitals, HLA-B27 positivity was associated with increased mortality in Walsh et al.[177]. This study, though, had incomplete genetic profiling of the cohort, potentially influencing the results. A large study of the UK Biobank found that in the absence of axSpA there was no association between HLA-B27 carriage and mortality[176]. Elsewhere, the difference in HLA-B27 frequencies has been attributed to environmental pressures such as malaria and other infections[178]. There is suggestive data that HLA-B27 confers resistance to certain viral diseases, such as HIV[179], hepatitis C[180] and influenza[181], although apparently not COVID-19 (ref. 182). Conversely, the presence of HLA-B27 might confer decreased resistance to diseases caused by intracellular pathogens[178], such as malaria, which is most frequently encountered in equatorial climates. The reason for this link between malaria and HLA-B27 is unclear, and it is not certain whether the finding of gene–gene interaction between HLA-B27 and *ERAP1* (encoding endoplasmic reticulum aminopeptidase 1 (ERAP1))[183–188], resulting in aberrant peptide processing in the endoplasmic reticulum, might influence susceptibility to intracellular micro-organisms[178].

The prevalence of HLA-B27 in most populations of people with r-axSpA ranges between 80% and 95%, with the lowest frequencies found in those of African American ethnicity[189,190], among whom HLA-B27 prevalence is approximately 60%, and in populations in sub-Saharan Africa, where the prevalence is even lower[191]. Perhaps because of environmental pressures[168], HLA-B27 is distinctly uncommon in sub-Saharan Africa, as is r-axSpA[192,193]. Among people with SpA in sub-Saharan Africa, HLA-B27 is rare, with the overwhelming majority being HLA-B27 negative[191–194]. Instead, an association was reported between r-axSpA and HLA-B14 in a study of West African people living in Togo, with HLA-B14 being found in 62.5% of the participants with r-axSpA but only 2% of the healthy participants, and specifically the *HLA-B*14:03* allele being the predominant allele in those with r-axSpA[194].

In the Middle East the overall population frequency of HLA-B27 has been reported to be as low as 0.3% in Oman and up to 6.8% in Turkey[171], and in North Africa the population prevalence of HLA-B27 ranges from 3% to 6% (ref. 171). However, in people with r-axSpA in the Middle East the frequency of HLA-B27 varies widely, being highest in such countries as Egypt (59.6%), Jordan (72.2%), Morocco (45.3–58.7%), Qatar (74%), Tunisia (61.7%), Turkey (71%) and Iran (69–74%)[171,195–201] and lowest in Lebanon (41.1%)[171,196]. In certain Native American and Indigenous Siberian groups, the population frequency of HLA-B27 is as high as 50% (refs. 69,173,174). Compared with the general population, the strength of the association between HLA-B27 positivity and r-axSpA is strongest in East Asian populations (China (mainland), Taiwan and Korea) (Table 4). *HLA-B*27:05* seems to confer the strongest association in most populations, except in East Asia; in China, the greatest risk of r-axSpA is conferred by *HLA-B*27:04* (refs. 189,202,203) (Table 4), although in Korea *HLA-B*27:05* is the most strongly disease-associated HLA-B27 allele[204]. Of note, HLA-B27 subtyping has not been reported in Japanese patients with axSpA, despite the odds ratios for HLA-B27 and axSpA being among the highest reported from Asia[205]. Generally speaking, *HLA-B*27:02*, *HLA-B*27:07* and *HLA-B*27:15* are disease-associated alleles, although not as much as *HLA-B*27:04* and *HLA-B*27:05* (ref. 189).

Moll & Wright criteria (1973)

Inflammatory arthritis (peripheral arthritis and/or sacroillitls or spondylitis)
+ Presence of psorlasis
+ Negative test for rheumatold factor
+ One of the following five subsets:

- Oligoarthritic (<5 involved joints) asymmetric
- Polyarticular (often symmetric)
- Distal interphalangeal predominant
- Spondylitis predominant
- Arthritis mutilans

CASPAR diagnostic criteria (2006)

Inflammatory musculoskeletal disease (joint, spine or entheseal) with three or more of the following:

1. Psoriasis	a. Current: psoriatic skin or scalp disease present today, diagnosed by a rheumatologist or dermatologist (+2) b. Personal history of psoriasis c. Family history of psoriasis: psoriasis in a first- or second-degree relative
2. Nail changes	Typical psoriatic nail dystrophy: onycholysis, pitting and hyperkeratosis on exam
3. Negative RF	Any method except latex; ELISA or nephelometry preferred, according to local laboratory reference range
4. Dactylitis	a. Current: swelling of an entire digit b. History of dactylitis recorded by a rheumatologist
5. Radiographic evidence of juxta-articular new bone formation	Ill-defined ossification near joint margins excluding osteophyte formation

Fig. 2 | Classification and diagnostic criteria for psoriatic arthritis. The widely used criteria for psoriatic arthritis (PsA) proposed by Moll and Wright in 1973 define the condition as inflammatory arthritis co-occurring with psoriasis, usually with a negative serological test for rheumatoid factor[84]. They also describe five clinical presentations of the disease. With the 2006 CASPAR criteria, patients with inflammatory musculoskeletal disease are considered to have PsA if they have a score of at least 3 points from a list of clinical and imaging features; all of the features are assigned a score of 1 point, except for 'current psoriasis', which is assigned a score of 2 points[85]. RF, rheumatoid factor.

Table 3 | Prevalence of psoriatic arthritis in people with psoriasis

Year	Country	Mode of ascertainment	PsA prevalence (%)	Prevalence of PsA manifestations (%)	Ref.
Multinational					
2013	7 European and North American countries	Dermatology clinics, assessment by a rheumatologist	30	NR	127
2019	Worldwide	Varied (systematic review and meta-analysis)	22.7 Europe; 21.5 South America; 19.5 North America; 15.5 Africa; 14.0 Asia	NR	131
Americas					
2012	Canada	Dermatology clinic, questionnaire	36.4–40.9	NR	126
2014	Argentina	Dermatology clinics, assessment by rheumatologist	17	Polyarthritis: 47.1; oligoarthritis: 52.9; axial SpA: 5–6	128
2015	Brazil	Dermatology clinics, assessment by rheumatologist	33	Axial SpA: 28	129
2016	Canada	Dermatology and phototherapy centres, CASPAR criteria	12.9	Mutilans, polyarthritis, oligoarthritis or DIP: 81.4; axial SpA: 33.3	130
2021	USA	Health Care Database, ICD-9, ICD-10 codes	12	NR	132
Europe					
1995	Italy	Dermatology clinic, assessment by rheumatologist	36	NR	133
2005	Norway	Rheumatology clinic	NR	Polyarthritis: 68.6; oligoarthritis: 28.7; axial SpA: 2.7	98
2005	Italy	Patients hospitalized for psoriasis, assessment by dermatologist	7.7	NR	134
2009	Germany	Dermatology clinic, assessment by rheumatologist	20.6	Mutilans: 4.9; polyarthritis: 58.7; oligoarthritis: 31.6; DIP: 41.0	135
2009	Norway	Rheumatology clinic	NR	Mutilans: 2; polyarthritis: 32; oligoarthritis: 48; DIP: 2; axial SpA: 9	100
2009	Germany	Assessment by dermatologist	19.0	NR	136
2009	UK	GP database, questionnaire	13.8	NR	137
2010	UK, Italy, France, Spain	Dermatology clinics, questionnaire	20.5 after 30 years since psoriasis diagnosis	NR	138
2010	Italy	National health care database	8	NR	139
2014	Germany	Dermatology clinic, assessment by rheumatologist	20.2	NR	140
2014	Sweden	National Health Care Database, ICD-10 codes	18.5	NR	104
2015	Spain	Dermatology clinic, assessment by rheumatologist	22.9	NR	141
2016	Greece	Dermatology clinic, assessment by rheumatologist	30	Polyarthritis: 51; oligoarthritis: 12; axial SpA: 8	142
2019	Germany	National statutory health insurance data	31	Polyarthritis (in men): 1.8–2.1	108
2021	Germany	National health care database, ICD-10 codes	10	NR	112
2021	Poland	National health care database, ICD-10 codes	8.3 (2008); 17.5 (2018)	NR	111
2021	Germany	National health care database, ICD-10 codes	14	NR	113
2021	Denmark	National e-based survey, questionnaire	19	NR	143
2023	Italy	PsoReal and PsoCare registries	22.6	NR	144
2024	UK	Clinical assessment, assessment by rheumatologist	4.3	NR	145
Asia					
2008	Iran	Dermatology clinic	9.1	NR	146
2011	China	Dermatology clinic	5.8	Polyarthritis: 19.6 Oligoarthritis: 48.2 DIP: 5.4 Axial SpA: 26.8	147

Table 3 (continued) | Prevalence of psoriatic arthritis in people with psoriasis

Year	Country	Mode of ascertainment	PsA prevalence (%)	Prevalence of PsA manifestations (%)	Ref.
Asia (continued)					
2014	India	Dermatology clinic, assessment by rheumatologist	8.7	Mutilans: 1; polyarthritis: 58; oligoarthritis: 21; DIP: 3; axial SpA: 49	148
2015	Japan	Dermatology clinic, assessment by rheumatologist	14.3	NR	149
2016	Taiwan	National health care database, ICD-9 codes	6.3 (2003); 12.7 (2013)	NR	119
2016	Japan	Dermatology clinic, questionnaire	10.5	Polyarthritis: 36; oligoarthritis: 22; DIP: 26	151
2018	Israel	National HMO database, ICD-9 codes	15.3	NR	116
2022	Japan	Psoriasis Epidemiology Screening Tool of 764 patients with PsA	6.5	NR	151
2023	Malaysia	Single-center, cross-sectional study	29.7	Polyarthritis: 46.8; oligoarthritis: 22.4; DIP: 2.8; axial SpA: 5.6	152
2024	S. Korea	Health Insurance Review and Assessment Service Data	6.17 (2008) 19.0 (2020)	NR	153
Africa					
2018	Nigeria	Rheumatology clinic	5.6	Mutilans: 8.3; polyarthritis: 41.7; oligoarthritis: 58.3; DIP: 16.7; axial SpA: 33.3	154

DIP, distal interphalangeal joint spondyloarthritis; ICD, International Classification of Diseases; NR, not reported; SpA, spondyloarthritis.

In countries not in North America, Europe or Asia, HLA-B27 is less frequent. In Brazil, the frequency of HLA-B27 in white people with SpA (predominantly descendants of Portuguese, Spanish, Italian and German immigrants) has been reported to be as high as 73.4% and in non-white counterparts 50% (refs. 206,207), whereas the overall population frequency was 4.35% (4.85% in white people, 2.92% in Black people and 3.18–3.95% in other (including mixed ancestry and Indigenous) populations)[169]. In patients from Colombia, primarily from the Andean region, the frequency of HLA-B27 in those referred for testing because of clinical signs and symptoms suggestive of SpA was as low as 12%, although it was much higher (64%) in patients referred for testing by a rheumatologist[170]. Given that these populations represented patients with both axSpA and pSpA, these lower frequencies are less surprising. Of note is that *HLA-B*15* has been associated with peripheral manifestations of SpA, even in the setting of r-axSpA, in Latin America and in the USA[208–210], even though *HLA-B*15* is negatively associated with r-axSpA overall[186,189]. In a study of 2,269 patients with axSpA in the ASAS-PerSpA cohort, which included participants from 24 countries, HLA-B27 positivity was associated with uveitis, a positive family history of axSpA and younger age at symptom onset and diagnosis, and HLA-B27 negativity was associated with enthesitis, psoriasis and inflammatory bowel disease[211], replicating previous studies in r-axSpA. Another study from the Brazilian Registry on Spondyloarthritis included 1,096 patients with axSpA, 73.4% of whom were HLA-B27 positive. In this study HLA-B27 positivity was associated with male sex, earlier age at disease onset and diagnosis, uveitis and a positive family history of SpA. On the other hand, those lacking HLA-B27 were more likely to have psoriasis, a higher frequency of peripheral joint disease, greater disease activity and a worse quality of life[207].

HLA genes other than HLA-B27 in axial spondyloarthritis susceptibility

A number of studies have examined associations between axSpA and HLA genes other than *HLA-B27*. The most consistently implicated gene has been *HLA-B*40* (also known as *HLA-B*60* by older allosteric typing), which has been described in patients of European ancestry[184–186,189,212–214], Taiwanese and Han Chinese patients[189,215], and in African American patients[189]; however, for non-HLA-B alleles, linkage disequilibrium with HLA-B27 has confounded the significance of many of the previous reports. Similar to what was described for gene–gene interaction between HLA-B27 and *ERAP1* (refs. 183–186), evidence was reported of an interaction between *HLA-B*40:01* and *ERAP1* in HLA-B27-negative individuals that affects axSpA susceptibility[186]. Three studies examined MHC genes in large numbers of people of European and Asian ancestry. Two of the studies used imputation from the Illumina Immunochip study, the first of which included 9,069 r-axSpA cases and 13,578 controls of European ancestry[184,186] and the second of which examined 1,637 Chinese, Taiwanese and Korean r-axSpA cases meeting the modified New York criteria for r-axSpA and 1,589 ethnically matched controls[188]; the third study utilized direct HLA typing in 1,948 r-axSpA patients of European ancestry and 567 controls, and included HLA-A, HLA-C, HLA-DRB1, HLA-DQB1 and HLA-DPB1 typing for 668 of the patients with r-axSpA[189]. The larger, European imputation study[186] found that the associations of r-axSpA with HLA-B alleles, including HLA-B27, was best explained by amino acids around position 97 of the HLA-B molecule, and also implicated *HLA-B*13:01*, *HLA-B*47:01* and *HLA-B*51:01* in r-axSpA susceptibility, as well as *HLA-A*02:01* (refs. 184,186). The imputation study in Korean, Chinese and Taiwanese patients found the primary amino acid associations to be with lysine at position 70 and asparagine at position 97 of the HLA-B molecule, as well as demonstrating a highly significant association of *HLA-C*15* with r-axSpA, even after controlling for the presence of HLA-B27 (ref. 188). The study using direct HLA typing found negative associations of r-axSpA with *HLA-B*07* and *HLA-B*35* in white (of European descent), Han Chinese and African American individuals, after correction for the presence of HLA-B27 (ref. 189). In addition, MHC class II genes have been implicated in axSpA susceptibility in these studies. At HLA-DRB1, the strongest association with an amino acid was

observed with aspartic acid at position 70 (ref. 186), with *HLA-DRB1:15:01* being negatively associated with r-axSpA per se, even after correction for the presence of HLA-B27 by both imputation[186] and direct HLA typing[189]. Of particular note was the subsequent finding of an association of HLA-DRB1*15:01 with acute anterior uveitis (AAU) in the setting of r-axSpA in both an international imputation study of 2,752 white people with r-axSpA with AAU and 3,836 people with r-axSpA without AAU[216], which was also found in the study that used direct HLA typing[189]. The HLA-DP locus has also been implicated in r-axSpA susceptibility[17,189,217], with single nucleotide polymorphisms (SNPs) correlated with the presence of leucine at position 11 of the DPB1 molecule[186], which, on direct HLA typing, correlated with the presence of *HLA-DPB1*03* (ref. 189) in HLA-B27-positive and HLA-B27-negative people with r-axSpA.

HLA genes in psoriasis and psoriatic arthritis susceptibility

Psoriasis has most consistently been associated with *HLA-C*06:02* in populations of European descent[218]; in fact, interaction between *HLA-C*06:02* and *ERAP1* has been shown in the context of psoriasis susceptibility[219]. In PsA, there is also an association with HLA-B27, with approximately 25% of people with PsA being HLA-B27 positive, and is much stronger in those with axial disease, especially symmetric sacroiliitis, and with other features of SpA, such as dactylitis and enthesitis[220–225]. Aside from HLA-B27, the HLA alleles *HLA-B*08*, *HLA-B*18*, *HLA- B*37, HLA-B*38* and *HLA-B*39* have been associated with the greatest increased risk of PsA, and *HLA-C*06* has been associated with a decreased risk of PsA (that is, a PsA-protective effect) when compared with people with psoriasis without arthritis[223–225], despite it being more common in people with psoriasis overall than in healthy individuals[223,225]. *HLA-C*06* has also been associated with earlier age at onset of psoriasis and delayed onset of PsA and with a milder phenotype of peripheral arthritis. However, the prevalence of HLA-B27 in people with axSpA occurring in the setting of psoriasis tends to be much lower than that found in r-axSpA, reported to be around 40% (refs. 220,224,225). HLA-B27 is also a marker of PsA severity and is associated with the development of peripheral joint damage and with requirement for joint surgeries[226,227]. It has also been associated with earlier onset of PsA, often prior to the onset of the skin disease[225]. The presence of glutamic acid at position 45 is a common feature of HLA-B27, HLA-B38 and HLA-B39 and has been associated with an increased risk of PsA compared with psoriasis alone (odds ratio 1.46) in a genome-wide association study (GWAS)[218].

Examining the prevalence of HLA-B27 in people with axial psoriatic spondyloarthritis (axPsA) has been complicated by the lack of widespread recognition of nr-axSpA prior to the adoption of the ASAS classification criteria for axSpA (2009)[13] and for pSpA (2011)[14]. Earlier cohorts often used the modified New York criteria to distinguish r-axSpA from pSpA, and cohorts after the adoption of the ASAS criteria often included patients with IBP or PsA. Reviewing cohorts with 'pure' pSpA (that is, excluding axSpA and PsA) has revealed a lower prevalence of HLA-B27 in pSpA than in axSpA, with a frequency of 64.9% in 211 people with 'pure pSpA' from the ASAS-PerSpA cohort (compared with a frequency of 8.2% in 345 people with 'pure PsA' and 82. 6% in people with 'pure axSpA')[156] and a frequency of 32.6% in 86 patients from the Esperanza cohort from Spain (which included individuals with PsA) compared with a frequency of 75.3% in 291 people with axSpA (likewise including individuals with psoriasis and axSpA)[163]. Among 178 Colombian people with SpA, none of 13 individuals with 'isolated' pSpA were HLA-B27 positive, compared with 100% of those with 'isolated' axSpA (the rest having 'mixed' pSpA and axSpA manifestations)[209].

Non-MHC genes in genome-wide association studies

Non-MHC genes and axial spondyloarthritis in genome-wide association studies

The initial GWASs examining SNPs associated with r-axSpA susceptibility were carried out in UK, US and Australian populations, and identified and verified associations with SNPs in and around *ERAP1* and

Table 4 | Odds ratios of HLA-B27 positivity worldwide in people with axial spondyloarthritis versus the general population

Study year	Country (population)	HLA-B27 overall	Specific HLA-B27 alleles	Refs.
1997	USA (Alaska Native)	210	NR	174
2002	Mexico	41.4	NR	208
2010	China	137.5	B*27:04: 87.9* B*27:05: 13.5*	202
2010	China	152.3[a]	B*27:04: 100.9* B*27:05: 6.57*	203
2011	Tunisia	53.6	NR	200
2012	Egypt	59.6[a]	NR	199
2013	Netherlands	81.4	NR	185
2015	Morocco	16.8	NR	201
2015	Multinational (European ancestry)		B*27:02: 43.4 B*27:05: 62.4	186
2018	Iran	48.2	B*27:04: 21.3 B*27:05: 57.5 B*27:07: 15.8	171,198
2018, 2019	Turkey	29.8	B*27:02: 44.9 B*27:04: 15.9 B*27:05: 34.3	171,198
2019	North America and Australia (European ancestry)	NR	B*27:02: 10.9 B*27:05: 36.5	189
2019	Han Chinese	NR	B*27:04: 22.6 B*27:05: 9.20	189
2019	USA (African American)	NR	B*27:05: 41.3	189
2019	Algeria	54.1	NR	171
2019	Jordan, Qatar	104.9	NR	171
2019	Kuwait	8.21	NR	171
2019	Lebanon	24.5	NR	171
2019	Syria	105.6	NR	171
2020	China (mainland), Taiwan, Korea	205.3	B*27:04: 1,637 B*27:07: 1,589	188
2021	North Africa	NR	B*27:04: 60 B*27:07: 4	195
2023	Japan	1,146	NR	205

[a]Odds ratio was not provided in the cited publication but has been calculated on the basis of data provided. NR, not reported.

ERAP2 and the gene encoding IL-23 receptor (*IL23R*)[183,228,229] (Table 5), as well as two 'gene deserts' (regions of the genome thought to be devoid of protein-coding genes) at chromosomes 2p15 and 21q22 (refs. 183,229). It should be noted that GWASs constitute collections of SNPs relatively evenly spaced throughout the genome, enabling not only coverage of the entire genome but also imputation analyses, whereby the identity of SNPs in nearby genes can be predicted by prior GWASs or by whole-genome sequencing studies. These GWASs of white populations with r-axSpA[183,229], as well as the international Immunochip study[184] and a subsequent study of combined Immunochip genotype data from people with r-axSpA, ulcerative colitis, Crohn's disease, psoriasis and primary sclerosis cholangitis[230,231], have further identified up to 116 genes implicated in r-axSpA susceptibility. The 116 genes include those involved in key immune functions, such as IL-17-mediated immunity (*TYK2*, *IL6R*, *IL1R2*, *IL12B*, *TNFAIP3*, *IL10*, *IL19*), those involved in $CD8^+$ T cell function (*RUNX3*, *EOMES*, *IL7R*, *ICOSLG*), those functioning in peptide presentation (MHC, *ERAP1*, *ERAP2*, *LNPEP*, *UBE2E3*, *NPEPPS*) and others engaged in microbial sensing (*CARD9*, *CARD15*, *NOS2*, *NFKB1*, *NFKBIA*, *NOD2*, *TLR4*). In addition, genes important in a variety of other immune functions have been identified, including *ZMIZ1*, *FCGR2A*, *KIF21B*, *SH2B3*, *ANTXR2*, the *LTBR–TNFRSF1A* gene complex, *GPR65*, the *IL27–SULT1A1* gene complex, *GPR35*, *BACH2*, *NKX2-3*, *HHAT*, *FUT2*, *JAK2*, *PTGER4* and *TBKBP1*, among others[230,231].

In studies of groups of non-European ancestry, a study of 1,164 Korean people with r-axSpA and 752 healthy people confirmed the associations of *ERAP1* and the chromosome 2p15 gene desert[232], and a GWAS of 1,837 Han Chinese people with r-axSpA and 4,231 healthy individuals likewise confirmed the association of the two gene deserts at chromosomes 2p15 and 21q22, as well as the association of r-axSpA with *ERAP1* and *IL12B*[233] (Table 5). The latter study also implicated new susceptibility loci: one located between *EDIL3* and *HAPLN1* at chromosome 5q14.3 and another within *ANO6* at chromosome 12q12. These two additional susceptibility loci in a Han Chinese population were not, however, confirmed in the Immunochip study, neither in patients of European nor in those of East Asian ancestry[184]. The Immunochip study confirmed the association of r-axSpA with *IL23R* in Han Chinese, Korean and Taiwanese groups, interestingly with a different SNP from the association seen in the r-axSpA population of European descent, owing to differences in population allele frequencies[234]. The Immunochip study also implicated in both the European and Asian cohorts SNPs near *RUNX3*, *HHAT*. *UBE2E3*, *ZMIZ1*, *GPR35*, *IL27-SULT1A1*, *NOS2*, *NPEPPS–TBKBP1–TBX21*, *TYK2* and *ICOSLG*[184], associations that were confirmed in subsequent studies in the Chinese population[184,235,236]. Additional GWASs in cohorts from Turkey (1,001 people with r-axSpA and 1,011 without) and Iran (479 people with r-axSpA and 830 without)[198] found genome-wide significant and suggestive associations of r-axSpA with the previously described gene desert at chromosome 2p15, *ERAP1* and *USP8*, as well as multiple other novel or replicative suggestive associations (*P* values between 1×10^{-5} and 5×10^{-8}). Of particular interest was the finding of an association of genome-wide significance in the Turkish r-axSpA cohort (also seen in the Iranian r-axSpA cohort) with the *MEFV* gene, which encodes pyrin, mutations in which are a cause of familial Mediterranean fever and lead to dysregulated inflammasome function and excessive IL-1β production. This association was especially strong in HLA-B27-negative patients, and was also seen in HLA-B51-negative patients (HLA-B51 being positively associated with r-axSpA[186], as it

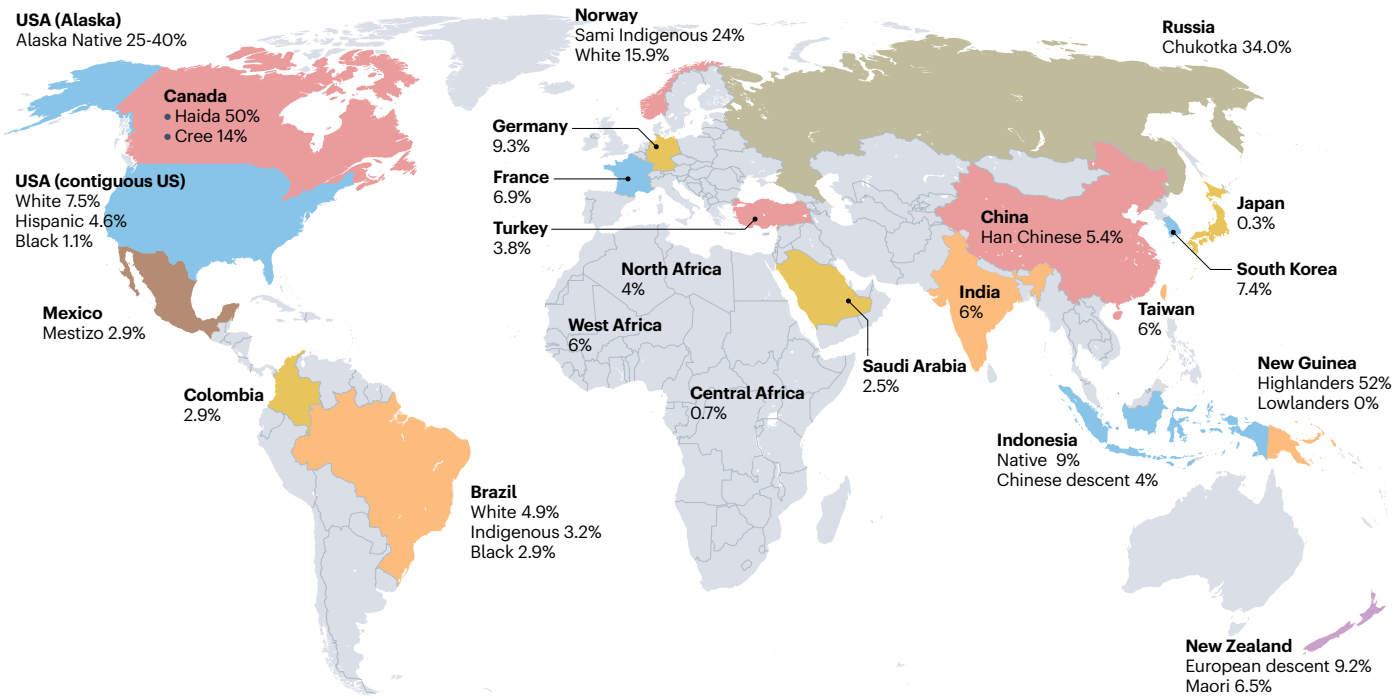

Fig. 3 | Population frequency of HLA-B27 worldwide. HLA-B27 is strongly associated with axial spondyloarthritis (axSpA). The frequency of this genetic marker in the general population varies worldwide, being lowest in areas around the equator[163–168] and highest in northern regions[69,169,170]. HLA-B27 frequency also varies between populations within the same region. *Nature Reviews Rheumatology* remains neutral with regard to jurisdictional claims in published maps.

is with Behcet disease). The functional relevance of these genes cannot be over-emphasized, including IL-17-mediated immunity, $CD8^+$ T cell function, peptide presentation, microbial sensing and other immune-mediated functions.

Non-MHC genes and psoriatic arthritis in genome-wide association studies

The genetic basis of psoriasis has been extensively dissected in the past 15 years. Thus far, nearly 50 genetic loci have been implicated in psoriasis susceptibility[219,237–242] (Fig. 4), many of which are shared with r-axSpA and PsA. The associated loci harbour genes are involved in epidermal differentiation and innate and adaptive immunity, as well as antigen presentation and processing. However, a much smaller number of genes have been implicated in PsA (as compared with psoriasis). In addition to MHC genes, studies from European populations have implicated in PsA susceptibility genes also involved in r-axSpA susceptibility, including *RUNX3*, *IL23R*, *TNFAIP3, TYK2* and *NOS2*, as well as other genes not associated with axSpA, including *IFIH1*, *SLC22A5*, *TNIP1*, *IL12B, TRAF3IP2*, *STAT2* and *CCDC116* (refs. 240,241 (Fig. 4). PsA has been less extensively studied in populations in East Asia, although a replication study of 36 non-MHC loci previously associated with PsA susceptibility in people of European ancestry implicated *RUNX3, IL12B, ERAP1* and *LCE3A/3B* in PsA susceptibility in Han Chinese people, as well as providing nominal associations for *ZBPB2* and *TNIP1* (ref. 242).

Table 5 | Worldwide genome-wide association studies of radiographic axial spondyloarthritis

Year	Country	SNPs associated with radiographic axial spondyloarthritis	Refs.
2010	USA, UK, Australia	IL23R, 2p15, ERAP1	229
2011	USA, UK, Australia	RUXN3, IL23R, 2p15, ERAP1	183
2011	Han Chinese	2p15, ERAP1	233
2013	Multinational, European ancestry	RUNX3, IL23R, 2p15, UBE2E3, GPR35, ERAP1, IL27–SULT1A1, NOS2, NPEPPS, TYK2	184
2013	China (mainland), Taiwan, Korea	IL23R[a], 2p15, UBE2E3, PTGER4, ERAP1, IL27–SULT1A1, NOS2, NPEPPS, TYK2	184,235
2016	Multinational, European ancestry (combined datasets)	IL23R, 2p15, UBE2E3, GPR35, ERAP1, NPEPPS	230
2018	Turkey	2p15, NOS2, MEFV	198
2018	Iran	2p15, ERAP1, NOS2, MEFV	198
2020	China	RUNX3, 2p15, UBE2E3, GPR35, ERAP1, NOS2, NPEPPS	187

[a]Associated with a different SNP within *ERAP1*.

Potential use of genotyping data in the diagnosis of axial spondyloarthritis and psoriatic arthritis

With the availability of extensive genotyping data in both SpA and healthy populations, whether these data can be used to assist in diagnosis can be assessed. HLA-B27 typing has been used as a diagnostic tool by clinicians since the 1970s. However, the moderately high frequency of HLA-B27 in the general population, and its much lower frequency in groups with axSpA of certain ancestries (South American, African and some Middle Eastern populations), as well as in certain axSpA disease states (axPsA, enteropathic SpA), limit the usefulness of HLA-B27 typing. Polygenic risk scores (PRSs) use large numbers of genetic factors to predict the genetic risk of developing disease. PRSs are especially helpful in the diagnosis of less-common diseases in which heritability plays a dominant role, such as in axSpA[243]. PRSs for r-axSpA for people of European and East Asian ancestries were recently developed utilizing GWAS data from 15,585 r-axSpA cases and 20,452 controls[244]. In both populations, these PRSs were found to perform better than HLA-B27 status alone, C-reactive protein testing or sacroiliac joint MRI. These PRSs were also found to perform nearly as well in individuals with r-axSpA of Iranian and Turkish origin. However, important gender differences were found in applying the PRSs to nr-axSpA. Women with nr-axSpA had a lower mean PRS and lower HLA-B27 prevalence than men or patients with r-axSpA, and although PRS was successful in distinguishing men with nr-axSpA from healthy male first-degree relatives, this discriminatory capacity was not seen in women[245]. This observation confirms the findings of previous studies, which demonstrated that patients with nr-axSpA as defined by ASAS classification criteria have limited genetic similarity to patients with r-axSpA, and are only moderately distinguished from the general population when considering genetic risk scores that are strongly discriminatory for r-axSpA, particularly amongst women[26].

As has been done for axSpA, with the availability of several genotyped datasets, genetic profiling for PsA risk has also been carried out. In a study using data from six cohorts with over 7,000 genotyped patients with PsA and psoriasis, nine new loci associated with psoriasis conditions were identified, and genetic profiling using 200 genetic markers achieved an area under the receiver operator curve of 0.82 for distinguishing PsA from psoriasis, with >90% precision and specificity approaching 100% (ref. 239). Despite the fact that in this analysis the MHC was the only locus of genome-wide significance in comparing PsA with psoriasis, this method performed more effectively than just considering MHC genes alone.

Current advances and future directions

Studies of the genetics of axSpA and PsA are currently underway and are utilizing whole-exome or whole-genome sequencing to further elucidate the hereditary basis of these diseases. Although GWASs have been effective in finding genes with common SNPs (>5% frequency), ascertaining the contributions of rare genetic variants would not be possible using the GWAS approach. Moreover, how these genes actually influence disease predisposition remains to be elucidated, and functional studies are underway to determine their contribution. This knowledge is crucial, as novel treatments for SpA and PsA have already successfully targeted genes implicated in disease predisposition. Moreover, most genetic studies have involved patient populations of European or East Asian ancestry. Examining the genetic basis of SpA and PsA in other populations, such as those of South Asian or sub-Saharan African ancestry, are lacking. These studies will also be important in biomarker discovery, as well-performing biomarkers of disease predisposition, disease activity, and disease prognosis and outcome are simply lacking. Whether the use of PRSs in clinical practice will enable earlier diagnosis and intervention remains to be clarified.

The same limitation affects epidemiological studies. As is apparent from Tables 1–3, the bulk of the studies of r-axSpA and PsA have been carried out in Europe, East Asia and North America. Such studies are

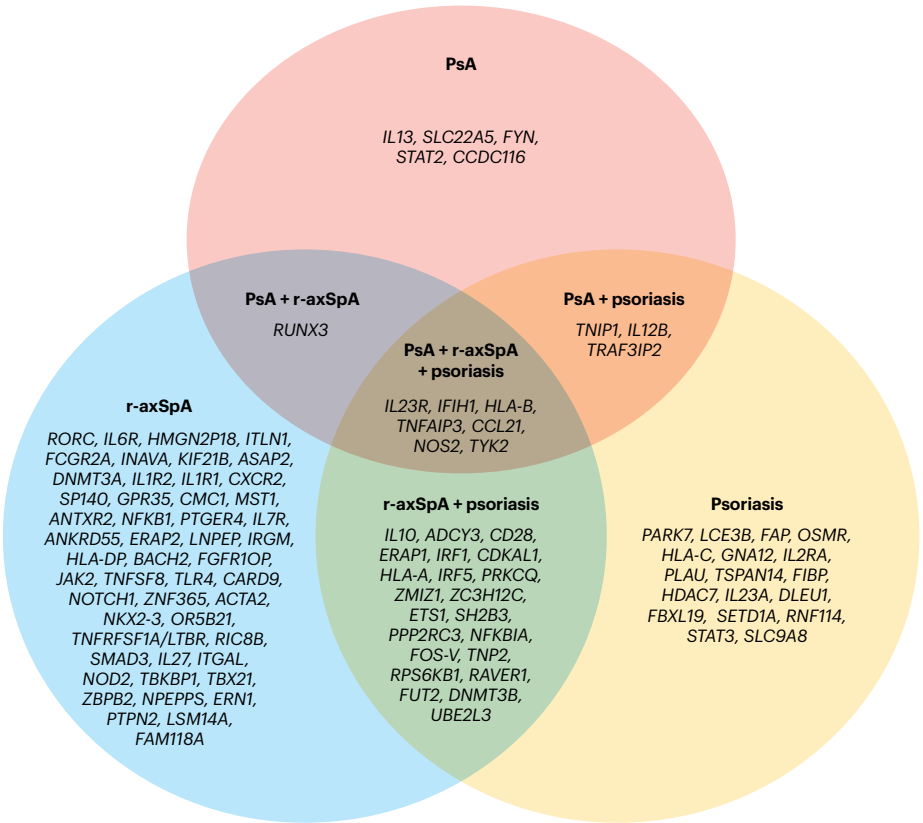

Fig. 4 | Genes shared by or specific to psoriasis, psoriatic arthritis and radiographic axial spondyloarthritis in populations of European descent. Many genetic loci have been implicated in susceptibility for radiographic axial spondyloarthritis (r-axSpA), psoriasis and psoriatic arthritis (PsA), with some being associated with more than one of these diseases. Genes within each group are listed in the order in which they are located on specific chromosomes (locations mapped at NCBI Gene). The full names of the genes and their locations are listed in Supplementary Table 1.

needed in sub-Saharan Africa, South Asia and Latin America. With the revision of the ASAS criteria for axSpA currently underway, how this will impact epidemiological studies remains to be seen. Another consideration is how innovations in treatment will affect the progression of nr-axSpA to r-axSpA, or the prevalence of PsA in patients receiving novel treatments for psoriasis.

Conclusions

In conclusion, the epidemiology of axSpA and PsA varies considerably by the mode of epidemiological ascertainment, the classification or diagnostic criteria used, and the ethnic group studied. Overall, the frequency of axSpA seems to be higher in population-based surveys than in studies using ICD coding or in national registries and is particularly high in Indigenous people of the circumpolar north (Sami, Inuit and certain other Native American groups) and lowest in groups with Japanese or African ancestry. The same trend holds for PsA, although overall its frequency seems much lower in East Asia than in Western countries. The prevalence of PsA in patients with psoriasis is higher when rheumatological assessment has been carried out and seems to be increasing over time. HLA-B27 remains the most important genetic factor in axSpA susceptibility; its frequency is highest in those of East Asian ancestry and lowest in African American, South American (particularly Brazilian) and Middle East populations and in those with PsA (as well as in women with nr-axSpA). The presence of HLA-B27 and other HLA alleles seems to be important in discerning clinical subsets of SpA and PsA, particularly those with acute anterior uveitis and patients with psoriasis and axSpA. A number of GWASs and other chip-based studies completed in large populations of patients have augmented knowledge of the pathogenesis of SpA and PsA, and, despite including limited data from Asia, show important similar and different genetic factors. The knowledge obtained from these studies has also enabled the development of instruments (such as PRSs) that might ultimately serve to improve the diagnosis and classification of patients with SpA and PsA.

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Author contributions

J.D.R., L.E., N.Z., P.D.S.B., N.A. and M.A.B. researched data for the article and wrote the article. All authors contributed substantially to discussion of the content reviewed and/or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

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Parathyroid hormone receptor agonists in the management of osteoporosis

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Abstract

Parathyroid hormone (PTH) regulates bone homeostasis. Intermittent exposure to PTH results in bone formation being greater than bone resorption, and this effect has been harnessed through the development of agonists of the PTH and PTH-related protein type 1 receptor (PTH1R) to treat osteoporosis. Teriparatide, an analogue of the first 34 amino acids of PTH, and abaloparatide, which resembles PTH-related protein (PTHrP) in structure, are PTH1R agonists currently in clinical use. Both medications have been shown to increase bone mineral density at the lumbar spine, femoral neck and total hip. Randomized controlled trials with teriparatide or abaloparatide have also provided evidence of reduction in vertebral and non-vertebral fractures. The ACTIVE trial suggested slightly greater efficacy for major osteoporotic fractures (as an exploratory end point) for abaloparatide than for teriparatide. A similar potential superiority was suggested for hip fracture in a real-world, observational study. Side effects of these medications are usually transient, and although a risk of osteosarcoma was suggested by studies using murine models, no such risk has been observed in extensive human studies. Overall, both teriparatide and abaloparatide have demonstrated convincing clinical effectiveness and cost-effectiveness, with a reassuring safety profile. Potential differences in their effects on bone mineral density and their antifracture effects offer avenues for differentiation but require further validation in appropriately designed studies.

Sections

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Key points

- Parathyroid hormone type 1 receptor (PTH1R) agonists stimulate bone formation and effectively reduce the risk of vertebral and non-vertebral fractures.
- The PTH1R agonists teriparatide and abaloparatide act via intermittent PTH1R stimulation, as opposed to the constant PTH1R stimulation seen in hyperparathyroidism.
- The safety profiles of teriparatide and abaloparatide are favourable, with previous concerns regarding osteosarcoma in murine models not born out in humans, and with cardiovascular safety having been consistently demonstrated.
- Exploratory analysis of data from the ACTIVE trial suggests that abaloparatide might have greater efficacy in reducing the risk of major osteoporotic fractures than teriparatide.

Introduction

Osteoporosis is defined in terms of low bone mineral density (BMD) and constitutes a major risk factor for fracture. Such fractures are common, affecting half of women and a fifth of men over the age of 50 years, and are responsible for an estimated US$19 billion of costs per year in the USA alone.

Anti-osteoporosis medications are roughly divided into antiresorptive and bone-forming (or anabolic) therapies. Antiresorptives prevent bone breakdown, largely through effects on osteoclasts. This class of drugs includes bisphosphonates such as alendronate, risedronate and zoledronate — which all inhibit farnesyl pyrophosphate synthase[1] — denosumab, which inhibits receptor activator of NF-κB ligand (RANKL)[2], selective oestrogen-receptor modulators (SERMs)[3] that mimic oestrogenic effects on bone during hormone replacement therapy[4], and the sclerostin inhibitor romosozumab. Bone-forming therapies involve agonism of parathyroid hormone receptors (PTHR).

Parathyroid hormone (PTH) and PTH-related protein (PTHrP) have vital roles in bone homeostasis[5], and agonists of their receptor, PTH1R, have thus been evaluated as therapeutic interventions in osteoporosis. Teriparatide (previously referred to as PTH (1–34)) is an analogue of the first 34 amino acids of PTH, whereas abaloparatide resembles PTHrP in structure. Both PTH1R agonists have a well-established mechanism of action, and substantial clinical trial and real-world data support their use in the treatment of osteoporosis[6–8]. This has led to the incorporation of both agents into treatment algorithms for osteoporosis[9,10].

In October 2024, the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) convened a working group consisting of rheumatologists, endocrinologists, orthopaedic surgeons, researchers, regulatory experts and health economic specialists. The purpose of this working group was to analyse the latest literature and leverage expert opinion in order to collate expert insights on PTH1R agonists in the management of osteoporosis. These insights fed into the current Review, which explores the functions of PTH and PTHrP in bone physiology, and discusses the efficacy, safety, health economic status and deployment of teriparatide and abaloparatide in clinical practice.

Parathyroid hormones in bone physiology

PTH is mainly released from the parathyroid glands and is a primary controller of calcium–phosphate homeostasis. As such, PTH maintains serum calcium levels within a tight, functional window and is released in response to hypocalcaemia[11] (Fig. 1). PTH has a triple effect on the kidney: increasing tubular reabsorption of calcium; increasing urinary phosphate excretion by inhibiting phosphate reabsorption in the proximal tubule; and promoting the conversion — via 1α-hydroxylase CYP27B1 — of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (also known as calcitriol), which leads to increased intestinal absorption of calcium and phosphate. PTH also increases calcium levels in the serum via effects on the bone that are discussed below; when released continuously PTH acts on the bone to increase bone resorption so that calcium stored in the bone is released in the circulation[12]. PTHrP is an important regulator of calcium balance during pregnancy and lactation[13], but is also released by many other tissues and manifests a paracrine action on the brain, smooth muscle, skin, cartilage and fetal tissues[13]. Both PTH and PTHrP act predominantly via the PTH1R receptor, which is expressed on osteoblasts. However, PTH, as well as tuberoinfundibular protein 39 (TIP39), also activates PTHR2 (ref. 14).

The *PTH* gene is found on chromosome 11 and the *PTHLH* gene (which encodes PTHrP) is located on chromosome 12 (ref. 15). Although they are encoded by different chromosomes, PTH and PTHrP share substantial homology at their N termini (62%)[16]. The C-terminal portions of the molecules share no homology.

PTH1R is a G-protein-coupled receptor and has two different conformations: R^0 and R^G. Both conformations lead to cAMP release, but the R^0 conformation causes a prolonged release of cAMP that is associated with a catabolic (resorptive) downstream effect, whereas the R^G conformation leads to a tightly regulated and short release of cAMP that is linked to anabolic actions[17].

As briefly mentioned above, intermittent (once-daily or once-weekly) and continuous stimulation of PTH receptors have distinct effects. Continuous stimulation (for example, in primary hyperparathyroidism) is associated with increased levels of RANK ligand, a decrease in osteoprotegerin, downstream activation of osteoclasts, and subsequent increased bone resorption and increased serum calcium (one of the clinical hallmarks of primary hyperparathyroidism)[18,19]. The catabolic effects are largely observed in cortical sites such as the middle third of the radius with relative preservation of the trabecular compartment[20,21]. By contrast, when PTH receptors are stimulated only once daily, their activation prolongs the survival of the osteoblast population by reducing apoptosis via inhibition of the WNT signalling inhibitors dickkopf-related protein 1 (DKK1) and sclerostin, and promotes pre-osteoblasts via CBFA1-mediated transcription, thus enhancing bone formation and bone strength[18,19] (Fig. 1). The increase in bone mass and structure downstream of PTH receptor stimulation are evident via the imaging of bone microarchitecture and of iliac crest biopsies[22,23].

Synthetic ligands of parathyroid hormone receptors

Synthetic ligands that operate via PTH1R have been used as treatments to optimize bone health in individuals with osteoporosis. Full-length PTH has 84 amino acids and the synthetic ligand teriparatide contains just 34, these 34 being identical to the first 34 N-terminal amino acids in PTH. Abaloparatide is identical to the first 21 N-terminal amino acids of PTHrP and shows 76% homology with PTHrP (PTHrP amino acids 1–34) and 41% homology with PTH (PTH amino acids 1–34)[24]. Abaloparatide

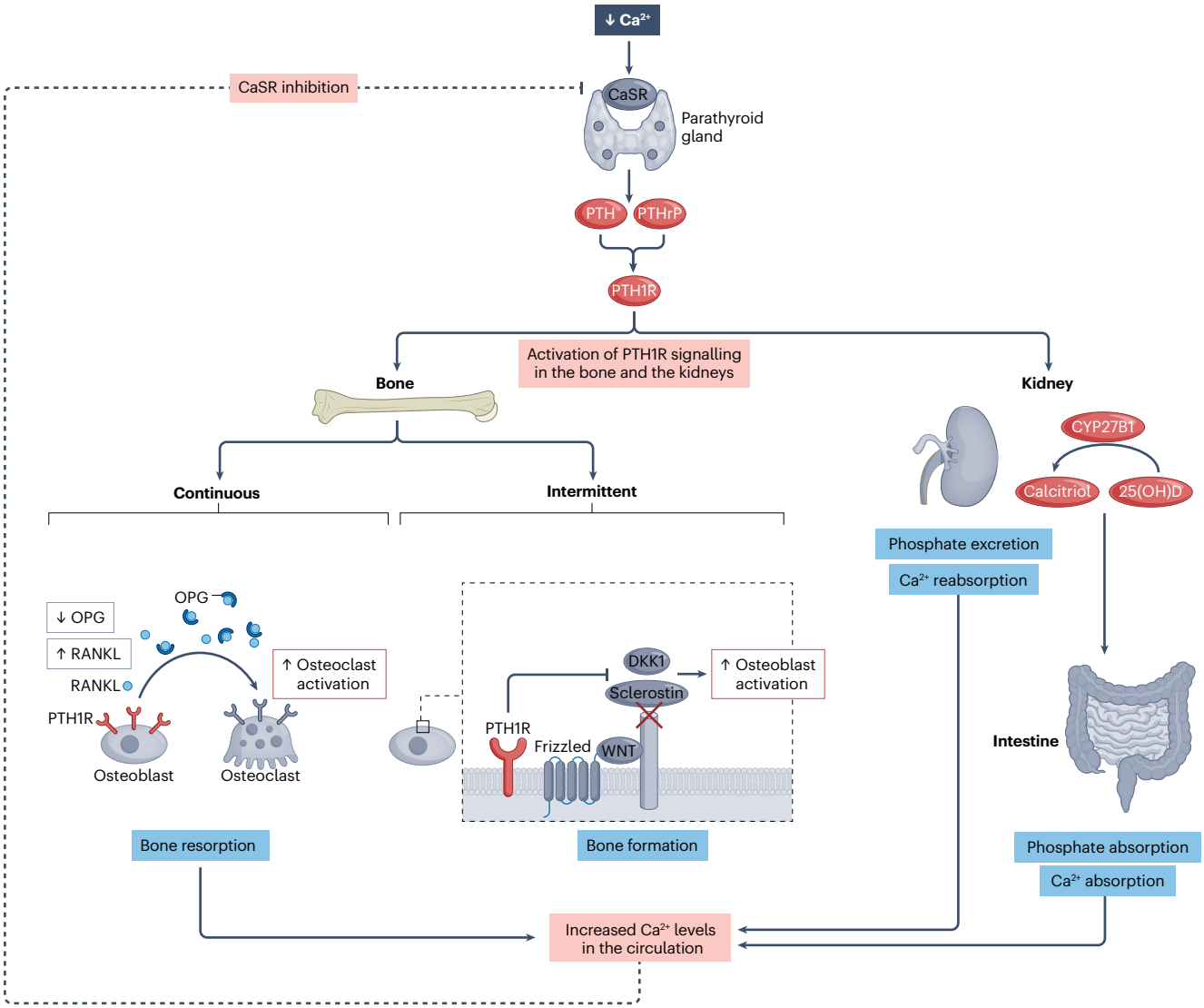

Fig. 1 | PTH and PTHrP signalling via PTH1R. Continuous activation and intermittent activation of PTH type 1 receptor (PTH1R) have distinct effects on bone biology. Continuous release of parathyroid hormone (PTH) from the parathyroid gland, as seen in hyperparathyroidism, results in increased expression of receptor activator of NF-κB ligand (RANKL) and downregulation of osteoprotegerin (OPG) in osteoclasts, leading to osteoclast activation, and resultant bone resorption. Intermittent release of PTH or PTH-related protein (PTHrP), as simulated via once daily dosing of teriparatide and abaloparatide, leads to inhibition of dickkopf-related protein 1 (DKK1)-mediated and sclerostin-mediated WNT signalling via the Frizzled receptor. WNT signalling inhibition results in activation of osteoblasts, supporting bone formation. PTH1R signalling also regulates calcium (Ca^{2+}) levels in the circulation, and thereby parathyroid gland function, via its effects in the kidneys and intestine. PTH1R signalling in the kidneys promotes phosphate excretion and Ca^{2+} reabsorption, leading to increased Ca^{2+} levels in the circulation, while also promoting calcitriol conversion from 25-hydroxyvitamin D (25(OH)D) via the enzyme CYP27B1. Calcitriol in turn increases absorption of phosphate and Ca^{2+} in the intestine. CaSR, calcium-sensing receptor.

leads to more potent cAMP release downstream of PTH1R activation[25] and has a shorter duration of cAMP stimulation compared with teriparatide, with reduced stimulation of resorption being a potential benefit of the former[26]. The affinity of both teriparatide and abaloparatide is greater for R^G than for R^0, thus favouring the anabolic PTH1R conformation. Nevertheless, the affinities of the two agonists for PTH1R differ substantially, with affinity ratios (R^G/R^0) of 3:1 for teriparatide and 1,600:1 for abaloparatide[17,19].

Teriparatide has a half-life of approximately 1 h when delivered subcutaneously, and is eliminated by hepatic and extrahepatic clearance[27]. It requires refrigeration, and a cold chain must be organized for patients needing to travel. Teriparatide has an EMA indication for the treatment of osteoporosis in postmenopausal women and in men at high risk of fracture. Recommended treatment duration is up to 24 months, increased from the original maximum of 18 months[27]. As efficacy data for this class of drugs are not yet available for beyond a 24-month period,

the opinion of our expert working group is that continued use or re-use should be based on an individualized risk profile assessment.

Micro-computed tomography (Micro-CT) has been used to map the microarchitectural effects of treatment with teriparatide, with benefits including an anabolic action on cortical bone, without contemporaneous increases in cortical porosity, and improvements in cancellous bone microarchitecture[22]. The histomorphometric effects of teriparatide as observed via bone biopsy studies include: modelling-based bone formation with smooth cement lines; remodelling-based bone formation with filling of resorption pits, and with scalloped cement lines; and remodelling at quiescent sites[19,23]. This process is particularly observed in cancellous bone and at the endocortical surface with increases in endocortical wall width and reductions in the eroded perimeter[23].

Abaloparatide also has a half-life of 1 h and is delivered subcutaneously, but is eliminated via non-specific proteolytic degradation with subsequent renal clearance. Refrigeration is only required before the first dose of abaloparatide, but after that point it can be stored at ambient temperatures. Abaloparatide has an EMA indication for the treatment of osteoporosis in postmenopausal women who have an increased risk of fracture, and the maximum duration of therapy with abaloparatide is 18 months[28].

The relative anabolic and resorptive effects of teriparatide and abaloparatide have been documented using bone turnover markers, namely procollagen type I N-terminal propeptide (PINP) as a marker of bone formation and β-isomerized C-terminal telopeptide of type I collagen (β-CTX) as a marker of bone resorption. Notably, in the ACTIVE trial both medications were associated with an initial rapid rise in PINP, reaching a greater peak for teriparatide than for abaloparatide[6] (Fig. 2). Compared with teriparatide, abaloparatide increased β-CTX levels more gradually than teriparatide over the first 3 months of treatment, and was associated with a lower peak and a subsequently faster decline in β-CTX levels[6]. These differences have been interpreted as demonstrating a more positive bone balance with abaloparatide than with teriparatide; although this notion awaits direct empirical confirmation, it would be consistent with observed differences in efficacy in improving BMD and reducing fracture risk[11].

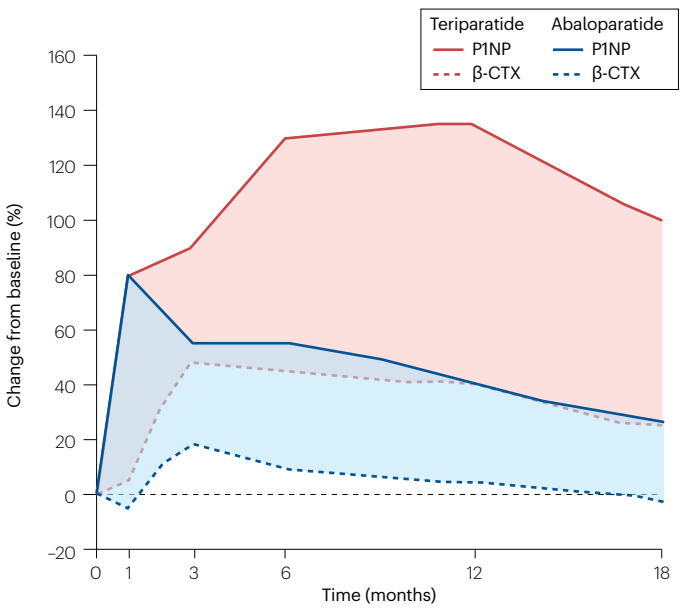

Fig. 2 | Bone turnover marker profiles and anabolic windows of teriparatide and abaloparatide. Percentage changes in bone turnover markers shown over time from baseline (in months). The relative levels of the bone formation marker procollagen type 1 N-terminal propeptide (P1NP) and the bone resorption marker β-isomerized C-terminal telopeptide of type I collagen (β-CTX) might provide information on the timing of the maximal anabolic effect, a concept which has been termed the 'anabolic window'. The graph is based on data from the ACTIVE trial[6].

Efficacy of PTH1R agonists in osteoporosis

The efficacy of PTH1R agonists in increasing BMD and reducing fracture risk is supported by clear evidence from randomized controlled trials, real-world studies and meta-analyses. PTH1R agonists are not administered in isolation, and the effect of combined and sequential therapy has been investigated.

Teriparatide

The 2021 seminal Fracture Prevention Trial (FPT) studied the efficacy of teriparatide in 1,637 postmenopausal women divided approximately equally between daily 20 µg teriparatide, daily 40 µg teriparatide and daily placebo arms for a period of approximately 18 months. The FPT demonstrated a reduction in new vertebral and non-vertebral fractures in the teriparatide arms after treatment for around 18 months. Although the study was not powered to investigate the effect of teriparatide on hip fracture, relative risks for vertebral fracture were 0.35 (95% confidence interval (CI) 0.22–0.55) for 20 µg teriparatide and 0.31 (95% CI 0.19–0.50) for 40 µg teriparatide compared with placebo[7]. A post hoc analysis of this study investigated the effect in a population of adults older than 75 years, demonstrating similar protection against vertebral fracture for this age group, although, again, the study was insufficiently powered to draw conclusions on the effect on non-vertebral or hip fractures[29]. Further analysis demonstrated that the fracture risk reductions for non-vertebral and morphometric vertebral fractures were unaffected by baseline 10-year fracture probability in those taking teriparatide[30].

The FPT participants were invited to take part in an extension, with >90% participant uptake, for a period of another 30 months after the initial trial completion[31]. During this time, about half of the participants in each arm were started on bisphosphonates (after completion of teriparatide), with about 10% receiving SERMs and approximately 5% receiving hormone replacement therapy. Of the 1,262 participants, non-vertebral fragility fractures occurred in 55 (13.3%) of those initially receiving placebo, 37 (8.5%) of those who had received 20 µg teriparatide and 30 (7.3%) of those who received 40 µg teriparatide (20 µg teriparatide hazard ratio (HR) 0.62, 95% CI 0.41–0.93 ($P = 0.022$); 40 µg teriparatide HR 0.52, 95% CI 0.34–0.82 ($P = 0.004$); combined teriparatide doses (20 µg and 40 µg) HR 0.57, 95% CI 0.40–0.82 ($P = 0.002$)) for the duration of the FPT and the trial extension. If the extension alone was considered, a statistically significant protection against non-vertebral fractures was not seen for the 20 µg teriparatide dose (HR 0.73, 95% CI 0.45–1.18 ($P = 0.204$)), but was observed for the 40 µg teriparatide dose (HR 0.54, 95% CI 0.32–0.92; teriparatide ($P = 0.022$)) and the amalgamation of both teriparatide doses (HR 0.64, 95% CI 0.42–0.97 ($P = 0.035$))[31]. During the extension period of the study, both total hip and femoral neck BMD decreased in study participants who had been treated with teriparatide and received no other anti-osteoporosis medication; by contrast, BMD plateaued or even increased in participants who received bisphosphonate therapy following teriparatide[31], providing an early indication of the benefits of sequential antiresorptive therapy.

The Vertebral Fracture Treatment Comparisons in Osteoporotic Women (VERO) study aimed to compare the antifracture efficacy of daily 20 µg teriparatide with weekly 35 mg risedronate and, as such, represents a head-to-head comparison of teriparatide and a bisphosphonate[32]. The study population comprised postmenopausal women with at least two moderate vertebral fractures or one severe vertebral fracture, and with osteopenia or osteoporosis, as evidenced by dual-energy X-ray absorptiometry (DXA). Over the course of 2 years, the study used comprehensive placebo-treated controls, with one arm receiving subcutaneous teriparatide with oral placebo (n = 680) and the other arm receiving a subcutaneous placebo and oral risedronate (n = 680). The primary outcome was incident vertebral fracture, which occurred in 28 (5.4%) participants in the teriparatide group and 64 (12.0%) participants in the risedronate group (risk ratio (RR) 0.44; 95% CI 0.29–0.68; P < 0.0001). The results for clinical fracture were similar (HR 0.48, 95% CI 0.32–0.74; P = 0.0009) although non-significant for non-vertebral fracture (HR 0.66, 95% CI 0.39–1.10; P = 0.10)[32].

A 2019 systematic review of 23 randomized controlled trials, 19 studies with an active-controlled arm and 11 double-blind studies — all representing data from 8,644 individuals with osteoporosis, 3,893 of whom had been treated with teriparatide — demonstrated an odds ratio (OR) for hip fractures of 0.44 (95% CI 0.22–0.87; P = 0.019) in individuals treated with teriparatide compared with individuals treated with placebo (four studies) or at least one active comparator (19 studies), evaluating in total 34 incident events. There was no difference in the risk of fractures of the humerus (OR 1.02, 95% CI 0.50– 2.08), forearm (OR 0.53, 95% CI 0.26–1.08) or wrist (OR 1.21, 95% CI 0.72– 2.04)[33].

Murine studies have highlighted the fact that long-term bisphosphonate exposure blunts the bone-forming response to teriparatide, possibly owing to the exposure of osteoblasts to bisphosphonates[34]. Indeed, the Parathyroid Hormone and Alendronate (PaTH) study, a randomized, 12-month trial in a population of postmenopausal women with DXA-measured osteoporosis or with a T score of <−2.0 and an additional risk factor for osteoporosis (n = 238), investigated the potential for a synergistic relationship between full-length PTH and alendronate in three arms: PTH alone, alendronate alone, or both agents concurrently[35]. Rather than demonstrating a benefit from the combined effects of PTH and alendronate on bone formation and antiresorption, respectively, the increase in trabecular volumetric BMD (as measured by quantitative CT) in the group receiving PTH was twofold higher than that in the combination therapy group, and serum markers of bone formation only increased significantly in the group receiving PTH alone. These findings suggest that the dual use of alendronate with PTH is not synergistic but, in fact, restricts some bone forming effects of PTH.

To investigate whether this apparent deleterious effect of combination therapy was due to the relatively frequent (weekly) administration of oral alendronate, a study was undertaken in postmenopausal women with osteoporosis (n = 412) randomized to 12-months of subcutaneous teriparatide at a dose of 20 µg, a yearly intravenous administration of zoledronate, or combination therapy with both[36]. The greatest gains in lumbar spine BMD were observed in the combination therapy group and the group receiving teriparatide alone, whereas the greatest gains in total hip BMD were observed in the combination group and the group receiving zoledronate alone. These results might reflect the superior ability of teriparatide to improve BMD at trabecular sites via bone formation.

Combination therapy with teriparatide and denosumab was similarly investigated in the Denosumab and Teriparatide Administration (DATA) study over a duration of 24 months[37]. The combination therapy provided greater gains in BMD at the lumbar spine (9.1% (s.d. 3.9)) compared with teriparatide alone (6.2% (s.d. 4.6); P = 0.0139) or denosumab alone (5.5% (s.d. 3.3); P = 0.0005), with similar findings at the total hip (4.9% (s.d. 2.9) with the combination; 0.7% (s.d. 2.7) with teriparatide alone (P < 0.0001); 2.5% (s.d. 2.6) with denosumab alone (P = 0.0011))[37]. However, the bone turnover profile of the combination therapy group was more similar to that of the denosumab-alone group (antiresorptive) rather than the teriparatide group (bone-forming), demonstrating that combination therapy blunts the bone-forming effect of teriparatide.

A blunted bone-forming effect of teriparatide in combination therapy was also demonstrated in a study in postmenopausal women taking either alendronate or raloxifene (for at least 18 months) who were then either prescribed additional teriparatide or switched to teriparatide alone[38]. In this setting, gains in BMD after a period of at least 18 months of treatment were greater in the combination group than in the sequential therapy group, although dual administration of antiresorptive and bone-forming agents decreased the levels of bone turnover markers[38].

The DATA-Switch study, which included 77 postmenopausal women and was an extension of the DATA study, assessed 4-year lumbar spine BMD in three arms: denosumab followed by 24 months of teriparatide; teriparatide followed by 24 months of denosumab; and combination therapy followed by 24 months of denosumab. At 4 years, increases in spinal BMD were observed in all groups with no significant differences between them. At the femoral neck and the hip, increases in BMD and volumetric BMD were greatest in the arm of combination treatment followed by denosumab. Switching from denosumab to teriparatide led to transient reductions in lumbar spine and hip BMD, increases in bone turnover and large losses in BMD at the distal radius in both total and cortical volumetric BMD[39,40]. These results highlighted that the sequence of treatment matters, with teriparatide potentially being more beneficial in terms of BMD gain in individuals who are naive to antiresorptive therapy compared with those who have previously received antiresorptive medication[41,42].

Further real-world evidence was provided by the European Forsteo Observational Study (EFOS), which analysed the efficacy of 18 months of treatment with teriparatide followed by an 18-month period during which most participants (postmenopausal women) were treated with alendronate. There was a persistent reduction in fracture rate following discontinuation of teriparatide with reductions observed for all fractures, both vertebral and non-vertebral[43]. At 36 months, there were 258 fractures (from a total of 1,576 participants), of which 34% were clinical vertebral fractures and 66% were non-vertebral fractures. The risk of fracture was significantly lower between 30 and 36 months after treatment initiation than during the initial period of treatment with teriparatide, with a 74% decrease in the adjusted odds of fracture compared with the first 6 months of treatment (P < 0.001)[44]. This emphasizes the efficacy of teriparatide and the persisting fracture risk reduction after completing the course of treatment.

Meta-analysis of six randomized controlled trials comparing teriparatide with alendronate in postmenopausal women (n = 618 patients) demonstrated that teriparatide leads to significantly greater increases in BMD than alendronate at the lumbar spine (weighted mean difference (WMD) 3.46, 95% CI 2.15–4.77; P < 0.00001) with a smaller apparent benefit at the femoral neck (WMD 1.50, 95% CI 0.04–2.95; P = 0.04)[45]. This same meta-analysis investigated fracture risk, but was limited by the number of fracture events (23 in the teriparatide group versus 27

in the alendronate group), and showed no differences in fracture rates between the two treatments (OR −0.03, 95% CI −0.12–0.07; $P = 0.52$)[45].

In conclusion, the above evidence underscores the efficacy of teriparatide in reducing vertebral risk and, to a lesser extent, non-vertebral and hip fracture risks, particularly in postmenopausal women with osteoporosis (Table 1). The bone-accruing benefits are most pronounced when commenced in antiresorptive-naive individuals and then used in sequence with bisphosphonates or denosumab. However, combination with antiresorptive therapies in those already receiving denosumab might still help to optimize BMD outcomes, albeit with potential attenuation of bone formation markers.

Abaloparatide

Randomized controlled trials have, in some cases, included teriparatide as a comparator to abaloparatide, providing the opportunity to compare these two PTH1R agonists head-to-head.

The Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) study examined the efficacy of abaloparatide (80 µg daily) compared with placebo and open-label teriparatide (20 µg daily) over 18 months in a group of postmenopausal women ($n = 2{,}463$)[6]. The inclusion criteria were that participants had to have a previous radiographic vertebral fracture, or recent non-vertebral fracture with either DXA-proven osteoporosis if aged ≤65 years or a T score of ≤−2.0 if aged <65 years. Participants were also included if they had no prior fracture but very low BMD ($T \leq -3.0$) and were aged >65 years. The main outcomes of the ACTIVE trial were vertebral, non-vertebral, clinical and major osteoporotic fractures, DXA-measured BMD and bone turnover markers[6].

New vertebral fractures were significantly reduced by abaloparatide (RR 0.14, 95% CI 0.05–0.39; $P < 0.001$) and teriparatide (RR 0.20, 95% CI 0.08–0.47; $P < 0.001$). Abaloparatide significantly reduced non-vertebral fractures (HR 0.57, 95% CI 0.32–1.00; $P = 0.049$), whereas teriparatide non-significantly lowered the risk of non-vertebral fractures (HR 0.72, 95% CI 0.42–1.22; $P = 0.22$). Major osteoporotic fracture constituted an exploratory end point, for which evidence supported a greater risk reduction for abaloparatide than for teriparatide (HR 0.45, 95% CI 0.21–0.95; $P = 0.03$). In this study, the risk reductions with open-label teriparatide compared with placebo did not reach formal statistical significance for non-vertebral, clinical or major fracture outcomes. However, the absolute differences in risk reduction between the two PTH1R agonists were small, as were the number of events, and the licensed dose of teriparatide is lower than that tested for abaloparatide. In terms of BMD, both teriparatide and abaloparatide were associated with significantly greater gains than placebo at all time points (6, 12 and 18 months) and at all sites (lumbar spine, femoral neck and total hip). Compared with teriparatide, abaloparatide was associated with greater gains in BMD at all sites and at all time points, except for 18-month follow-up at the lumbar spine. Bone turnover marker profiles differed between the PTH1R agonists. Teriparatide induced an initial peak with subsequent plateaus for both PINP and β-CTX. By contrast, abaloparatide induced an initial peak for PINP and then gradual declined over 18 months, while slightly increasing the levels of β-CTX, which, however, remained consistently lower than those observed in individuals receiving teriparatide throughout the study.

A post hoc analysis of the ACTIVE study examined the relationship between baseline fracture risk and the efficacy of abaloparatide[46]. In the trial, the mean baseline major osteoporotic fracture risk was 13.2%. Abaloparatide was associated with a 69% reduction in major osteoporotic fracture risk and 43% reduction in any clinical fracture risk versus placebo. There was no significant interaction between efficacy of abaloparatide and baseline fracture risk, indicating that the efficacy of abaloparatide observed in the ACTIVE trial was independent of the baseline fracture risk of the participants[46]. Using a random subset of the ACTIVE trial ($n = 250$ per arm), bone microarchitectural changes, derived from 3D active shape modelling within DXA images, showed differential effects on the cortical and trabecular compartments between abaloparatide and teriparatide[47]. Compared with placebo, both anabolic agents increased trabecular volumetric BMD (9% gain; $P < 0.001$) and cortical thickness (1.5% gain; $P < 0.001$). However, cortical hip volumetric BMD was increased with abaloparatide (1.3% gain; $P < 0.001$) but not with teriparatide. The degree of increase in cortical volumetric BMD at the hip was inversely correlated with levels of β-CTX, indicating that a higher bone turnover might have attenuated cortical gains[47].

The ACTIVExtend study included 1,139 (92%) of the original ACTIVE participants and extended the abaloparatide and placebo arms with 24 months of oral alendronate[48]. Lumbar spine and femoral neck BMD continued to increase after abaloparatide treatment in participants taking the oral bisphosphonate, with suppression of PINP and β-CTX being similar in both groups. In terms of fractures, 0.9% of women in the abaloparatide group and 5.6% of women in the placebo group sustained a new radiographic vertebral fracture, indicating a relative risk reduction of 84% ($P < 0.001$) with abaloparatide[48]. The reduction in vertebral fracture risk observed during the 18 months treatment with abaloparatide persisted during the 24 months therapy with alendronate. A further post hoc analysis of ACTIVExtend examined the efficacy of abaloparatide followed by alendronate in the oldest participants of the study (in this case ≥80 years of age). This included 46 participants with a mean age of 83.3 years, and abaloparatide was well tolerated and effective for the gain in BMD versus placebo in this subgroup[49].

A transdermal formulation of abaloparatide was trialled in an open-label study against the subcutaneous form in 511 postmenopausal women[50]. The results for the primary outcome at 12 months demonstrated inferiority of the 'microstructured transdermal system' compared with the subcutaneous version, with significantly lower percentage gain in lumbar spine BMD (transdermal 7.14% (s.e.m. 0.46%), subcutaneous 10.86% (s.e.m. 0.48%)). No placebo group was included in this study. A 24-week dose-ranging trial of abaloparatide at doses of 20 µg, 40 µg and 80 µg was performed with two other arms including 20 µg teriparatide and placebo[51]. This randomized controlled trial on 222 postmenopausal women revealed a significantly greater BMD increase at the lumbar spine for abaloparatide doses of 40 µg and 80 µg compared with placebo, and greater gains in total hip BMD for these two doses (40 µg and 80 µg) compared with teriparatide. Trabecular bone score, a measure of bone microarchitecture, was significantly higher in the 80 µg abaloparatide arm than in the teriparatide arm, and greater than placebo at all doses[51]. Given the short duration of the study, it might not represent a true comparison of abaloparatide and teriparatide. Further clinical studies have investigated the differences between these two PTH1R agonists.

An analysis of health insurance claims data from the USA provides real-world evidence of the benefits of abaloparatide over teriparatide with regard to fracture prevention[8]. In a propensity score-matched investigation that monitored over 20,000 patients in each group for 18 months, abaloparatide was associated with a lower risk of fracture compared with teriparatide; reduced risk was determined for hip fracture (HR 0.83, 95% CI 0.70–0.98; $P = 0.027$) and non-vertebral fracture (HR 0.88, 95% CI 0.80–0.96; $P = 0.003$). Similarly, significantly lower

Table 1 | Key clinical trials of teriparatide

Study	Study participants (*n*)	Duration (months)	Study arms	Key outcomes for teriparatide
FPT[7]	Postmenopausal women with prior vertebral fracture (*n* = 1,637)	21	Teriparatide 20 µg Teriparatide 40 µg Placebo	Reduced vertebral fractures (RR 0.35, 95% CI 0.22–0.55, with 20 µg; RR 0.31, 95% CI 0.19–0.50, with 40 µg) and non-vertebral fractures (RR 0.47, 95% CI 0.25–0.88, with 20 µg; RR 0.46, 95% CI 0.25–0.861, with 40 µg)
FPT, subgroup analysis[29]	Postmenopausal women with prior vertebral fracture age <75 years (*n* = 841) and age ≥75 years (*n* = 244)	19	Participants aged ≥75 years receiving teriparatide Participants aged <75 years receiving teriparatide	No difference in efficacy and safety of teriparatide in those aged ≥75 years
FPT, post hoc analysis[30]	Postmenopausal women with prior vertebral fracture (*n* = 1,637)	21	Teriparatide combined (20+40 µg) Placebo	Non-vertebral fractures: RRR 37% (95% CI 10–56%) Low-energy non-vertebral fractures: RRR 56% (95% CI 24–75%) Morphometric vertebral fractures: RRR 66% (95% CI 50–77%) Fracture risk reduction was consistent across all baseline fracture probabilities, as assessed by FRAX with or without BMD (no significant interaction, *P* > 0.30)
FPT extension[31]	Postmenopausal women with prior vertebral fracture (*n* = 1,262)	50	Teriparatide combined doses (20+40 µg) Placebo	Hazard ratio for non-vertebral fragility fractures (combined teriparatide group vs placebo): 0.57 (*P* = 0.002) for over 50 months Significant fracture risk reduction persisted up to 30 months after discontinuation of teriparatide BMD declined in teriparatide-treated patients with no follow-up treatment BMD stabilized or increased in those who received bisphosphonates after teriparatide
VERO study[32]	Postmenopausal women with two or more moderate or one or more severe vertebral fracture+BMD T score ≤−1.5 (*n* = 1,360)	24	Teriparatide 20 µg Risedronate	Incident vertebral fracture (RR 0.44, 95% CI 0.29–0.68) Clinical fractures (HR 0.48, 95% CI 0.32–0.74) Non-vertebral fragility fractures (HR 0.66, 95% CI 0.39–1.10)
PaTH trial[35]	Postmenopausal women with T score ≤−2.5 at hip or spine, or ≤−2.0 with additional risk factors (*n* = 238)	12	PTH (1–84) 100 µg Alendronate Combination therapy	Lumbar spine BMD increased in lumbar spine by 6.3% with PTH, 4.6% with alendronate, and 6.1% with combination therapy Trabecular spine volumetric BMD increased by 25.5% with PTH, 10.5% with alendronate, and 12.9% with combination therapy
Zoledronate combination study[36]	Postmenopausal women with T score ≤−2.5 at hip or spine, or ≤−2.0 with fracture history (*n* = 412)	12	Teriparatide 20 µg Zoledronate Combination therapy	Lumbar spine BMD increase at 52 weeks: 7.0% with teriparatide, 4.4% with zoledronic acid, 7.5% with combination therapy; early greater gains with combination therapy at 13 and 26 weeks (*P* < 0.001) Total hip BMD at 52 weeks: 1.1% with teriparatide, 2.2% with zoledronic acid, 2.3% with combination therapy; significantly higher with combination therapy vs teriparatide at all time points (*P* ≤ 0.02) Clinical fracture incidence: 8 (5.8%) with teriparatide, 13 (9.5%) with zoledronic acid, 4 (2.9%) with combination therapy; significantly lower with combination therapy vs zoledronic acid (*P* = 0.04)
DATA study[37]	Postmenopausal women with T scores ≤−2.5 or ≤−2.0 with risk factors (*n* = 100)	24	Teriparatide 20 µg Denosumab Combination therapy	Lumbar spine BMD increased by 9.5% with teriparatide (*P* = 0.01 vs combination therapy), 8.3% with denosumab (*P* = 0.008 vs combination therapy), and 12.9% with combination therapy (24 months) Femoral neck BMD increased by 2.8% with teriparatide (*P* = 0.003 vs combination therapy), 4.1% with denosumab (*P* = 0.008 vs combination therapy), and 6.8% with combination therapy Total hip BMD increased by 2% with teriparatide, 3.2% with denosumab, and 6.3% with combination therapy (*P* < 0.001 for the combination vs both)
DATA-Switch[39]	Postmenopausal women (*n* = 83)	28	Teriparatide 20 µg to denosumab Denosumab to teriparatide Combination therapy to denosumab	Lumbar spine BMD increased by 18.3% with teriparatide to denosumab, 14% with denosumab to teriparatide, and 16% with combination therapy to denosumab Femoral neck BMD increased by 8.3% with teriparatide to denosumab, 4.9% with denosumab to teriparatide, and 9.1% with combination therapy to denosumab Total hip BMD increased by 6.6% with teriparatide to denosumab, 2.8% with denosumab to teriparatide, and 8.6% with combination therapy to denosumab
EFOS[44]	Postmenopausal women with severe osteoporosis in routine clinical practice (*n* = 1,649)	36	Teriparatide (observational study)	208 patients (13.2%) sustained 258 fractures over 36 months 74% decrease in adjusted odds of fracture for the months 30–36 vs the months 0–6 (OR 0.265; *P* < 0.001)

BMD, bone mineral density; DATA study, Denosumab and Teriparatide Administration study; EFOS, European Forsteo Observational Study; FPT, Fracture Prevention Trial; PaTH trial, Parathyroid Hormone and Alendronate trial; PTH, parathyroid hormone; RR, relative risk; RRR, relative risk reduction; VERO study, Vertebral Fracture Treatment Comparisons in Osteoporotic Women study.

risks of both hip and non-vertebral fractures were observed as early as 6 months after commencing treatment[8]. Although this analysis used state-of-the-art epidemiological methods, it still should be viewed as hypothesis-generating rather than definitive evidence equivalent to that from a randomized controlled trial.

Meta-analyses have further compared available data, including data from the trials discussed above, in terms of abaloparatide and teriparatide efficacy[51]. One of these studies showed significant benefits of abaloparatide over teriparatide in terms of gain in BMD at the femoral neck (mean difference 1.58, 95% CI 0.52–2.63) and total hip (mean difference 1.46, 95% CI 0.59–2.32)[52]. However, this meta-analysis only included group comparisons from dose-ranging studies and might therefore show limited generalizability. In a Bayesian network meta-analysis including 17 studies — 11 randomized controlled trials and six studies incorporating real-world evidence[53] — both abaloparatide and teriparatide were effective for the prevention of vertebral and non-vertebral fractures compared with placebo. This analysis also demonstrated that abaloparatide was more protective than teriparatide for non-vertebral fracture (OR 0.87, 95% CI 0.80–0.95) and hip fracture (OR 0.81, 95% CI 0.71–0.93). Moreover, teriparatide and abaloparatide were found to be superior to placebo, raloxifene and calcitonin for the prevention of vertebral fracture, teriparatide was superior to denosumab and risedronate for the prevention of vertebral fracture, and abaloparatide was superior to all other interventions for the prevention of non-vertebral fracture. No differences between interventions was observed for hip fracture. These data from meta-analyses demonstrate the substantial antifracture efficacy of the PTH1R agonists.

In summary, abaloparatide has demonstrated robust efficacy in reducing fracture risk and improving BMD across multiple studies (Table 2), including head-to-head comparisons with teriparatide. The consistency of effect across age groups, baseline fracture risk levels, and in real-world data supports abaloparatide as a valuable therapeutic option in the management of women with postmenopausal osteoporosis.

Osteoporosis in men

Given the higher incidence of osteoporosis in women, most studies evaluating PTH1R agonists have focused on women and, particularly, on postmenopausal women. However, osteoporosis is also a substantial burden in men[10].

Teriparatide has been shown to be effective in men in increasing lumbar spine BMD and femoral neck BMD compared with placebo[54–56], similar to the observations in postmenopausal women[7]. Sequential antiresorptive therapy has demonstrated similar benefits in men and women[57]. In a study in men with low BMD, 83 men were treated with alendronate, or alendronate and PTH in combination or sequentially over 30 months[58]. Among 73 men analysed (mean age 58 years), the combination and sequential treatments led to greater gains in BMD than alendronate alone in the lumbar spine (18.1% sequential, 14.8% combination, 7.9% alendronate alone), in the femoral neck (9.7% sequential, 6.2% combination, 3.2% alendronate alone) and in spinal trabecular bone (measured by quantitative CT; 48% sequential, 17% combination, 3% alendronate alone).

The Abaloparatide-SC for the Treatment of Men with Osteoporosis (ATOM) study randomized osteoporotic or hypogonadal men to 80 µg abaloparatide subcutaneously (n = 149) or placebo (n = 79) and demonstrated increases in BMD at all sites with abaloparatide compared with placebo[59], similar to the findings of the ACTIVE study[6]. Significant and more rapid improvements were observed at 3, 6 and 12 months with >3% increases in BMD at all measured sites (lumbar spine, total hip and femoral neck). Although a greater body of evidence supports the use of PTH1R agonists in postmenopausal women than in men, these studies do support the use of PTH1R agonists as anti-osteoporosis medications in men.

Safety

The efficacy of PTH1R agonists should be balanced against the safety profile of these medications. In gaining a holistic view of the safety profile, particularly for the oldest patients (>75 years) who are more

Table 2 | Key clinical trials of abaloparatide

Study	Study participants (n)	Duration (months)	Study arms	Key outcomes for abaloparatide
ACTIVE[6]	Postmenopausal women with osteoporosis, with or without previous vertebral or low-trauma nonvertebral fractures (n = 2,463)	18	Abaloparatide 80 µg (blinded) Placebo (blinded) Teriparatide 20 µg (open-label)	Vertebral fracture: RR 0.14, 95% CI 0.05–0.39 (P < 0.001, abaloparatide vs placebo) Non-vertebral fracture: HR 0.57, 95% CI 0.32–1.00 (P = 0.049, abaloparatide vs placebo)
ACTIVE trial, subgroup analysis[46]	Postmenopausal women with osteoporosis, with or without previous vertebral or low-trauma non-vertebral fractures (n = 1,645)	18	Abaloparatide 80 µg (blinded) Placebo daily subcutaneously (blinded)	Major osteoporotic fracture: RRR 69%, 95% CI 38–85% Clinical fracture: RRR 43%, 95% CI 9–64%
ACTIVExtend[48]	Postmenopausal women with osteoporosis, with or without previous vertebral or low-trauma nonvertebral fractures (92% of eligible women from the ACTIVE trial) (n = 1,139)	43	Placebo switched to alendronate Abaloparatide switched to alendronate	Vertebral fracture: RRR 84% (P < 0.001) Major osteoporotic fracture, clinical fracture and non-vertebral fracture significantly lower in abaloparatide switched to alendronate vs placebo switched to alendronate group
ACTIVExtend, subgroup analysis[49]	Postmenopausal women aged ≥80 years with osteoporosis and high fracture risk (n = 56)	43	Placebo switched to aldosterone Abaloparatide switched to aldosterone	Significant gains in BMD vs placebo at all sites, particularly at the spine (abaloparatide +17.2% vs placebo +8.6%, P < 0.0001)

ACTIVE, Abaloparatide Comparator Trial in Vertebral Endpoints; BMD, bone mineral density; RR, relative risk; RRR, relative risk reduction.

susceptible to adverse effects via comorbidity and polypharmacy, adverse events in the intervention and control arms of randomized controlled trials of PTH1R agonists can be compared. As previously mentioned, PTH1R receptors are expressed on smooth muscle cells including those of the vessels, bladder, gallbladder, uterus and myocardium. Receptor activation in cardiomyocytes might lead to potential reductions in blood pressure through relaxation of smooth muscle and to increases in heart rate via chronotropic effects on the myocardium[60].

Data from the VERO trial provide a perspective on the comparison of adverse effects for teriparatide and risedronate[32]. Adverse effects that were significantly more common in participants taking teriparatide included dizziness (4.4% with teriparatide vs 1.8% with risedronate; $P = 0.007$) and arthralgia (5.4% with teriparatide vs 2.6% with risedronate; $P = 0.013$). Despite the potential of teriparatide to target the cardiovascular system, it was not associated with excessive risk of cardiovascular events. The cardiovascular risks of bisphosphonates and teriparatide were further compared using data from VigiBase[61], the World Health Organization (WHO) global database for adverse event reporting for medicines and vaccines. Meta-analysis of the adverse events from over 130 countries indicated that teriparatide and bisphosphonates are comparable in terms of clinical manifestations of cardiac disease including angina, myocardial infarction and stroke[62].

Data from the FPT were used to further assess the risks of adverse events in the oldest participants receiving teriparatide: data from a population of individuals aged ≥75 years were compared with data from a population of patients aged <75 years[29]. The adverse events that significantly differed between teriparatide and placebo included constipation ($P = 0.04$), cataracts ($P = 0.003$), deafness ($P = 0.006$), weight loss ($P = 0.03$) and pruritus ($P = 0.02$), but all occurred significantly more commonly in the placebo arm[29]. Even in this high-risk population of women (>75 years), no increased cardiovascular risks were observed. Thus, evidence from extensive pre-market and post-market studies demonstrate no increase in the cardiovascular risk of teriparatide, including in high-risk groups such as participants >75 years.

An increased risk of osteosarcoma has been reported in rats treated with teriparatide from weaning and over the course of 24 months[63]. Rat skeletons continue to grow throughout their life course, and 2 years of treatment covers a high percentage of a rat's lifespan, which might explain the reported increased risk in osteosarcoma in this particular study. Moreover, in these studies, teriparatide was administered at doses that were three times higher than the dose given to humans[64]. Data from clinical trials and extensive post-marketing surveillance studies using cancer registers in the USA have convincingly demonstrated no increased risk of osteosarcoma over the course of 15 years, from 2003 to 2016 (ref. 65). A further systematic review found only 3 patients with osteosarcoma among 253,704 patients taking teriparatide in North America, Europe and Asia[66]. These findings justified the removal of the box warning and the extension of the duration of treatment from 18 to 24 months in 2020 in the USA. Similar concerns for abaloparatide were derived from murine models[63] but have not been borne out in real-world analyses of large cohorts ($n = 44{,}728$) investigating the rate of primary bone malignancy in high-risk patients. This rate was 5.96% for the anabolic-exposed patients versus 8.13% for non-exposed patients[67].

Regarding other adverse effects of abaloparatide, the ACTIVE trial found dizziness in 10.0% of participants taking abaloparatide, but this proportion was not significantly different from the 6.1% of participants taking placebo and 7.3% of participants taking teriparatide. Moreover, the proportions of individuals developing nausea were 8.3% for abaloparatide, 3.0% for placebo and 5.1% for teriparatide (differences not statistically significant). The proportions of individuals developing palpitations was 5.1% for abaloparatide, compared with 0.4% for placebo and 1.6% for teriparatide (differences not statistically significant)[6]. No excessive risk of myocardial infarction, falls or syncope were observed in this study among participants in the abaloparatide arm. Abaloparatide is associated with a transient increase in heart rate and a small reduction in blood pressure, which might account for the dizziness experienced by some individuals, but did not translate to an increase in major adverse cardiovascular events (MACE) or heart failure in a cohort of postmenopausal women[68].

The low cardiovascular risk profile of both PTH1R agonists is supported by real-world evidence from a US database of administrative claims that showed no difference in the risk of myocardial infarction, stroke and heart failure between abaloparatide and teriparatide. The data also indicate equivalent rates of MACE (3.0% for abaloparatide and 3.1% for teriparatide[69]) and comparable risks of new events (HR 1.00, 95% CI 0.84–1.20; $P = 0.97$)[8,69]. A Bayesian network meta-analysis of data from 75 studies testing anti-osteoporosis medications in postmenopausal women, of which one investigated abaloparatide, found that abaloparatide was protective against MACE-4, which includes myocardial infarction, stroke, cardiovascular death and heart failure (OR 0.28, 95% CI 0.06–0.88). No significant association was found between teriparatide and MACE-4 (OR 0.68, 95% CI 0.34–1.31)[70]. A meta-analysis of the data from four studies indicated a non-significant increase in the odds of hypercalcaemia with teriparatide versus abaloparatide (OR 0.49, 95% CI 0.18–1.35; $P = 0.117$). The same meta-analysis showed a non-significant odds of hypercalcaemia with abaloparatide versus placebo (OR 1.30, 95% CI 0.58–2.91)[52]. Incidentally, the same study found increased odds of nausea (OR 2.61, 95% CI 1.73–3.95; $P < 0.00001$) and palpitations (OR 12.54, 95% CI 4.50–34.93; $P < 0.00001$) for those taking abaloparatide compared with placebo[52].

To summarize the safety data, although dizziness and nausea are likely to be more common with PTH1R agonists than with placebo, there is no evidence of meaningful cardiovascular risk. Osteosarcoma is not an issue in humans, and there is little evidence that any potentially increased propensity to hypercalcaemia or hypercalciuria result in any clinically apparent manifestations.

Health economics

PTH1R agonists are effective and safe options for fracture prevention but are more expensive than oral bisphosphonates. Health economic analyses are therefore crucial to understand the positioning of these drugs in the treatment algorithm for osteoporosis and are certainly of understandable interest for reimbursement decisions. Cost-effectiveness is assessed via the incremental cost-effectiveness ratio (ICER), in which the difference in total societal and health-care costs between the intervention of interest and a control intervention are divided by the difference in the quality-adjusted life years (QALYs) between the two interventions. The lower the ICER, the more cost-effective the intervention of interest.

Initial health economic analyses focused on cost-effectiveness of teriparatide as a sole intervention, without sequential therapy (with an antiresorptive agent). In this context, in studies in Iran[71] and Sweden[72], teriparatide was found to be cost-effective for the treatment of postmenopausal women when compared with no treatment. However, when compared with antiresorptives, the cost-effectiveness of teriparatide was heterogeneous. In a study in Sweden, teriparatide was more cost-effective than oral

bisphosphonates for the treatment of postmenopausal osteoporosis and glucocorticoid-induced osteoporosis[73]; by contrast, in a study in Iran, oral risedronate was more cost-effective than teriparatide for the treatment of severe postmenopausal osteoporosis[74]. In a study in the USA, denosumab was also found to be more cost-effective than teriparatide in the treatment of osteoporosis in men[75]. However, these findings might not be clinically relevant, as it is unusual for teriparatide to be used in isolation in current clinical practice.

In studies of sequential therapy versus antiresorptive monotherapy, teriparatide (for 2 years) succeeded by alendronate (for 8 years) was not as cost-effective as 10 years of alendronate alone in a population of community-dwelling women in Japan with a history of vertebral fracture (except at the age of 80 years)[76]. Similar findings (except without the cost-effectiveness for the oldest participants) were found for the cheaper biosimilar formulations of teriparatide in a Japanese population[77]. Abaloparatide was cost-effective when used for 18 months followed by 3 years of alendronate, compared with 5 years of alendronate alone, in a US population of women ≥60 years of age[78]. Indeed, dominance of abaloparatide sequential therapy was demonstrated in those with T scores ≤−3.5 and those with T scores from −2.5 to −3.5 and a history of one or more osteoporotic fractures[78].

In a systematic review of ten studies published up to 2022 investigating the cost-effectiveness of sequential therapies for the treatment of osteoporosis, 75% of studies showed that sequential therapy was at least cost-effective, if not dominant (that is, less cost for more QALYs), compared with other sole antiresorptive therapy[79]. Thus, cost-effectiveness differs between abaloparatide and teriparatide, with more favourable cost-effectiveness observed for abaloparatide. In direct head-to-head comparisons of cost-effectiveness in a population based in the USA, sequential therapy with abaloparatide followed by alendronate was more effective than teriparatide followed by alendronate in women with postmenopausal osteoporosis aged <65 years, in those aged ≥65 years with a prior vertebral fracture over a 10-year time horizon, and in those aged ≥65 years with a prior vertebral fracture over a lifetime horizon[80]. Similarly, in another study, abaloparatide–alendronate was more effective than teriparatide–alendronate sequential therapy in those with T scores ≤−3.5 and in those with T scores from −2.5 to −3.5 and a history of one or more osteoporotic fractures from a US payer perspective[81]. Not only was abaloparatide shown to be more effective than teriparatide when each was combined with alendronate for sequential therapy, but also abaloparatide–alendronate sequential therapy was more cost-effective than alendronate monotherapy in men aged ≥50 years with any type of fracture, in women aged ≥65 years with any fracture, and women aged ≥55 years with a history of hip or vertebral fracture[82].

The limitations of the current health economic literature include the scarcity of evidence available for European countries (except Sweden[83] and the UK for teriparatide only) and other countries, and the limited transferability of cost-effectiveness findings and comparisons of medications between health systems, given the regional differences in drug costs and fracture costs.

Clinical deployment

Although in the ideal world the most effective drugs would be available to use freely in all patients, in many health-care systems, anabolic therapies for osteoporosis are reserved for those with the highest fracture risk of or as second-line agents[84,85]. Recommendations from the ESCEO have set out how baseline risk assessment may be used to target therapy according to fracture risk, with anabolic medications used first in those with the highest fracture risk[85,86]. These include using the fracture risk assessment tool FRAX to assess fracture risk and as a gateway to the assessment of BMD in borderline cases. In this way, 10-year fracture risk is used to classify individuals into low-risk, high-risk or very high-risk categories using a nomogram, with those at very high risk being most appropriate to target with bone-forming therapies.

Although definitive data are awaited, exploratory outcomes from the ACTIVE trial, findings from real-world evidence, and potential implications from patterns of bone turnover markers, all suggest that abaloparatide might have broader antifracture efficacy than teriparatide, with a consistent health economic picture in some settings[53,79,87]. A practical advantage of abaloparatide is the lack of requirement for ongoing refrigeration after first use, and this might be helpful, for example, in patients required to travel. Beyond these considerations, the choice of PTH1R agonist may be dictated by availability and local policy as much as by any clinical imperatives.

For many patients, a tangible benefit of PTH1R agonists compared with bisphosphonates is the lack of concern regarding the rare, but important adverse effects of osteonecrosis of the jaw or atypical femoral shaft fractures. Although transient dizziness and potentially transient hypotension are potential adverse effects of PTH1R agonists, they rarely limit treatment, and cardiovascular safety has been conclusively demonstrated. Human studies have provided no evidence of osteosarcoma[88,86], but the contraindication to use in individuals with previous bone malignancy, skeletal radiation or Paget disease of course remains.

Research priorities

There is substantial and excellent research in the area of PTH1R agonists for the treatment of osteoporosis. However, particular areas of research need to be expanded as the field moves forwards. These include further health economic analyses and the development of bodies of real-world evidence.

Owing to the availability of large databases of health-care claims in the USA, health economics analyses have so far focused on the US population and health-care system. Further research is required to take account of the individual nuances of costs and reimbursement in the European, African, Australasian, Asian and South American contexts. Similarly, most real-world evidence on the use of PTH1R agonists has been accrued in the North American geographic region. Work focused on other regions is required to ensure that the use of PTH1R agonists is based on robust, real-world research and alleviates rather than reinforces health inequalities.

Conclusions

In conclusion, there is excellent evidence for the use of PTH1R agonists in the treatment of osteoporosis. In the absence of definitive head-to-head findings, taken as a whole, data from clinical trials, real-world evidence and meta-analysis suggest possible superiority of abaloparatide compared with teriparatide for BMD, health economic and non-vertebral fracture outcomes. These medications seem to show better efficacy than antiresorptives (with slightly differing clinical profiles), and there is clinical and economic evidence to support the use of sequential antiresorptive treatment following the anabolic agents. Future research should expand the reach of the current real-world data and health economic analyses.

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Review article

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Emerging therapies for the treatment of systemic sclerosis

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Abstract

Systemic sclerosis (SSc) is an autoimmune disease in which fibrotic, vascular, autoimmune and fibrotic mechanisms synergize to promote disease progression. SSc is associated with high morbidity and mortality, primarily owing to fibrotic tissue remodelling and subsequent organ failure. Despite progress with the approval of novel therapies, mortality remains high; approximately half of the people diagnosed with SSc will succumb to disease. This statistic highlights the considerable need for novel, effective therapies. Indeed, SSc has become a disease with very active drug development. Numerous drugs with different modes of actions are currently evaluated in or are about to enter clinical trials in SSc. These clinical trials provide hope for effectively slowing or even halting the progression of fibrosis and thereby further improving outcomes for patients with SSc.

Sections

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Key points

- Currently available drugs for systemic sclerosis (SSc) might slow down disease progression, but do not halt it, generating a great medical need for novel, more effective therapies.
- These drug candidates have a broad-spectrum of distinct anti-inflammatory and/or anti-fibrotic modes of action relevant to the pathogenesis of SSc.
- A large number of drug candidates and cellular therapies with different molecular modes of actions are currently under investigation or about to enter clinical trials in SSc.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease that is histopathologically characterized by vasculopathy, autoimmunity and fibrotic tissue remodelling[1]. Approximately 50% of people diagnosed with SSc will eventually die as a direct consequence of disease, which represents the highest disease-related mortality of all autoimmune rheumatic diseases[2]. Thus, novel, effective therapies for the treatment of SSc are required. Owing to this need, the development of therapies to treat SSc has become an active area of research. The interest of pharmaceutical companies in SSc has also been stimulated by several positive randomized controlled trials (RCTs) with nintedanib, tocilizumab and rituximab, which have been published within the past 5 years (Table 1). These new drugs greatly augment the evidence-based therapeutic arsenal for the treatment of the fibrotic manifestations of SSc, which were previously limited to mycophenolate mofetil, cyclophosphamide, haematopoietic stem cell transplantation (HSCT) after high-dose chemotherapy and, eventually, methotrexate (for skin fibrosis only).

However, despite this progress, the need for more effective therapies for the treatment of SSc remains high. Treatments that are currently available, perhaps with the exception of HSCT after high-dose chemotherapy, only slow down progression of fibrotic tissue remodelling, but do not halt it or even induce regression of fibrotic damage for most patients[3]. Moreover, most of the primary outcomes of previous and ongoing clinical trials mainly focus on interstitial lung disease (ILD) and, to a lesser extent, on skin fibrosis. There is a lack of evidence from RCTs on how to treat other common and life-threatening fibrotic manifestations of SSc, such as primary myocardial involvement or intestinal involvement.

In this Review, we provide an overview of the drugs and cellular therapies that are currently being evaluated in clinical trials for the treatment of SSc (Table 2). We discuss their mode-of-action and the preclinical data for each approach.

Fibroblast targeting approaches

Fibroblasts are key effector cells involved in fibrotic remodelling. They are not only the main source of extracellular matrix deposition in fibrotic tissues but may also modulate inflammatory processes and vascular remodelling.

Targeting hedgehog signalling

Numerous studies show that hedgehog signalling is implicated in fibrotic tissue remodelling in a variety of fibrotic disorders, including SSc[4–12]. Hedgehog signalling is essential to organ development. During homeostasis, the activity of this signalling pathway is very low in the majority of cells and tissues, except for stem cells, in which hedgehog signalling has an important role in the regulation of behaviour and function. Nevertheless, during fibrotic tissue remodelling, hedgehog signalling is activated and has pathogenic effects[12–14]. The expression of sonic hedgehog (SHH, which is a key hedgehog ligand in the context of skin fibrosis) and of GLI1 and GLI2 (hedgehog signalling-associated transcription factors) are upregulated in the skin of patients with SSc[6,15]. In addition, the SHH levels in the serum of patients with SSc are increased compared with healthy individuals and correlate with fibrotic burden[16]. Hedgehog signalling is highly interlinked with other pathways that are implicated in fibrotic tissue remodelling; for example, the activation of hedgehog signalling in SSc is caused, in part, by TGFβ, which not only induces the expression of SHH but also activates the promoter of *GLI2* to upregulate GLI2 expression in fibroblasts[6]. Hedgehog signalling also stimulates fibroblasts to differentiate into myofibroblasts and induces skin fibrosis[6]. Pharmacological or genetic inactivation of hedgehog signalling ameliorates fibrosis in a wide variety of mouse models of fibrosis and in many different organs[17–20].

The inhibition of hedgehog signalling is currently being evaluated for its anti-fibrotic effects in pulmonary fibrosis. Current pharmacological efforts to target hedgehog signalling focus on small molecule inhibitors of Smoothend (SMO). SMO is a G protein coupled receptor that activates GLI transcription factors in response to hedgehog ligand–receptor binding (these ligands include SHH, Indian hedgehog and desert hedgehog). Two SMO inhibitors, sonidegib and vismodegib, have been approved by the FDA for the treatment of basal cell carcinoma[21]. In a phase IIa RCT of patients with idiopathic pulmonary fibrosis (IPF), individuals receiving the SMO inhibitor ENV-101 (200 mg daily) were found to have a significantly higher predicted FVC mean change from baseline after 12 weeks than those receiving placebo (1.9% increase in the ENV-101 arm versus 1.3% decrease in the placebo arm)[22]. Although further studies with more patients and longer follow-up are required to confirm these results, the increase in FVC upon ENV-101 treatment might be indicative of anti-fibrotic remodelling induced by SMO inhibition. Indeed, preclinical findings demonstrate that inhibition of hedgehog signalling can deactivate myofibroblasts and induce re-differentiation into resting fibroblasts[4]. A confirmatory phase IIb trial of ENV-101 in IPF is currently recruiting (NCT06422884).

Targeting LPAR1 signalling

Fipaxalparant is a small molecule inhibitor that inhibits lysophosphatidic acid receptor 1 (LPAR1). This inhibitor blocks the effects of phospholipid lysophosphatidic acid (LPA)[23]. LPA is a small molecule mediator that is released during enzymatic breakdown of lipid membranes by the enzyme autotaxin. LPA is part of the tissue injury response that can promote inflammation and scarring and evidence suggests that LPA is a mediator of bleomycin-induced lung fibrosis[24]. LPA signals through a family of receptors (LPAR1–LPAR6), which are expressed on a variety of cells that contribute to the pathogenesis of SSc. LPAR1 is considered the dominant LPA receptor in the pathogenesis of fibrotic tissue remodelling. Clinical trials of LPAR antagonists in IPF have shown positive results[25]. A small phase IIa trial of an LPAR1 antagonist in diffuse cutaneous SSc (dcSSc) demonstrated that treatment with this antagonist attenuated LPA-regulated target genes in vivo and showed a beneficial trend in modified Rodnan Skin Score (mRSS) over 12 weeks compared with placebo[26]. This trial led to a larger randomized controlled phase IIb study (BEACON), which did not reach its primary end point of changes in FVC (NCT04781543).

Table 1 | Clinical trials with positive primary or secondary outcomes that changed the management of SSc

Drug	Molecular target	Clinical trial	Target population	Clinical trial design	Primary outcome	Key secondary outcomes
Nintedanib	Multiple tyrosine kinases	SENCSIS[184]	SSc-ILD	Phase III placebo-controlled RCT	Adjusted annual rate of change in FVC	Change in mRSS at 52 weeks
Nintedanib	Multiple tyrosine kinases	INBUILD[185]	PPF including SSc	Phase III placebo-controlled umbrella RCT	Adjusted annual rate of change in FVC	Change in total score on K-BILD questionnaire at 52 weeks
Tocilizumab	IL-6 receptor	faSScinate[186]	Early inflammatory dcSSc	Phase II placebo-controlled RCT	Change in mRSS at 24 weeks	Change in FVC at 48 weeks
Tocilizumab	IL-6 receptor	FocuSSed[187]	Early inflammatory dcSSc	Phase III placebo-controlled RCT	Change in mRSS at 48 weeks	Change in FVC at 48 weeks
Rituximab	CD20	DESIRES[188]	SSc	Investigator-initiated phase II placebo-controlled RCT	Change in mRSS at 24 weeks	Change in FVC at 24 weeks
Rituximab	CD20	RECITAL[189]	Severe or progressive CTD including SSc	Phase IIb, double-blind, double-dummy RCT	Change in FVC at 24 weeks	Change in FVC at 48 weeks

CTD, connective tissue disease; dcSSc, diffuse-cutaneous SSc; FVC, forced vital capacity; ILD, interstitial lung disease; K-BILD questionnaire, King's Brief Interstitial Lung Disease questionnaire; mRSS, modified Rodnan Skin Score; PPF, progressive pulmonary fibrosis; RCT, randomized control trial; SSc, systemic sclerosis.

Other approaches that target LPA signalling, such as autotaxin inhibition, have also been investigated. Ziritaxestat, an autotaxin inhibitor, was evaluated in IPF and in SSc with positive results for mRSS in a small phase IIa study[27]. However, parallel trials in IPF reported safety concerns and a lack of efficacy, and increased mortality was reported in the group receiving the highest dose in the ISABELA trials[28], which led to the clinical development of ziritaxestat being discontinued. Based on these results, targeting LPA signalling in SSc is currently considered challenging.

Anti-TGFβ3 antibodies

The regulation of tissue repair and development pathways by members of the TGFβ family is well established. TGFβ has three major isoforms (TGFβ1, TGFβ2 and TGFβ3) that signal through the same receptor complex[29]. Although the downstream canonical and non-canonical signalling pathways are shared, these isoforms differ in their bioavailability, accessory protein binding and cell and tissue-specific expression patterns[30]. TGFβ ligands are generally complexed to latent TGFβ binding proteins and are released from sequestered, inactive forms bound to matricellular proteins in response to conformational changes of integrins[31]. All three TGFβ isoforms seem to be profibrotic in preclinical models and findings suggest that attenuating TGFβ signalling can prevent or even reverse fibrosis in preclinical models[1,32]. Ample evidence indicates that TGFβ pathways are upregulated in many fibrotic diseases, including SSc. The first study of TGFβ inhibition in SSc evaluated the monoclonal antibody CAT-192 (metelimumab), which binds to TGFβ1 (ref. 33). Although this phase I–II trial showed some positive dose-dependent changes in mRSS at 6 months, these changes did not reach statistical significance. In addition, biomarker studies in this trial were limited and it remains unclear if in vivo antagonism of TGFβ signalling pathways occurred[33].

Other approaches involve targeting TGFβ ligands. An uncontrolled trial of fresolimumab in SSc showed encouraging molecular benefits; the target genes *COMP* and *TSP1* were downregulated and a two-gene score, proposed as a biomarker for the progression of skin fibrosis, improved[34]. However, there were concerns about toxicity including gastrointestinal tract effects, vascular lesions and a possible increase in the incidence of proliferative lesions of the skin (keratoacanthomas). The TGFβ1/3 ligand trap, AVID200, has been evaluated in SSc and in myelofibrosis[35]; however, these studies were too small and/or lacked placebo arms to definitively test the hypothesis of blocking TGFβ ligands as an anti-fibrotic approach in SSc. Determining lack of efficacy or unacceptable toxicity is crucial as the TGFβ pathway remains one of the most relevant targets for SSc owing to extensive preclinical evidence. The emergence of the activin signalling inhibitor, sotatercept, as an approved therapy for pulmonary arterial hypertension (PAH), including PAH associated with connective tissue disease, with remarkable benefit in clinical trials, confirms the feasibility of targeting TGFβ superfamily members and serves as a reminder that these pathways are closely interdependent and so targeting one member might affect signalling by others[36].

Currently, there is an ongoing phase Ib dose ranging trial of RG-6315 (RO-7303509), a human monoclonal antibody that targets TGFβ3, in SSc (NCT05462522)[37]. RG-6315 is administered via subcutaneous or intravenous routes and is a novel molecular entity. It is hypothesized that TGFβ3 might be an important profibrotic mediator and that neutralization could have fewer adverse effects than targeting all TGFβ ligands, TGFβ1 or TGFβ2 (ref. 32). Conversely, historical literature supports TGFβ3 having anti-fibrotic effects based on evidence from non-scarring fetal wound healing in animal models[38]. This finding was not substantiated in clinical trials and thus clinical development of recombinant TGFβ3 as a potential anti-fibrotic therapy has ceased.

Dual targeting of fibroblasts and immune cells

Several emerging therapeutic approaches target fibroblasts directly and indirectly by modulating inflammatory immune responses.

Targeting phosphodiesterase 4b

Phosphodiesterases (PDEs) are a large group of enzymes comprising 11 subfamilies with diverse functions. Members of the PDE4 subfamily (PDE4A, PDE4B, PDE4C and PDE4D) are the major subfamily of PDEs expressed in immune cells[39]. PDE4s regulate cytokine synthesis and other pro-inflammatory pathways in leukocytes via hydrolysis of cyclic AMP[40]. Indeed, non-selective PDE4 inhibitors are in clinical use for the treatment of inflammatory diseases; apremilast is approved for plaque psoriasis, psoriatic arthritis and Behçet syndrome, and

Table 2 | Therapies currently in or about to enter clinical trials in SSc

Therapy	Entity	Molecular target(s)	Predominantly targeted mechanism(s)	Predominant target cell(s)	Developmental stage
ENV-101	Small molecule	Smoothend	Hedgehog signalling	Fibroblast activation	Phase II trial, recruiting
Fipaxalparant	Small molecule	LPAR1	LPA signalling	Fibroblast activation	Phase IIb trial, completed
Ziritaxestat	Small molecule	Autotaxin	LPA signalling	Fibroblast activation	Phase II trial, terminated
RG6315 (RO-7303509)	Antibody	TGFβ3	TGFβ signalling	Fibroblast activation	Phase II trial, active
Nerandomilast	Small molecule	PDE4B	cAMP signalling	Immune cell and fibroblast activation	Phase III trial in progressive pulmonary fibrosis, completed; phase IIb trial in SSc, in preparation
CAN10	Antibody	IL1RAP	IL-1, IL-33 and IL-36 signalling	Immune cell and fibroblast activation	Clinical trial in preparation
Dersimelagon (MT-7117)	Small molecule	MC1R	αMSH–MC1R signalling	Immune cell and fibroblast activation	Phase II trial, completed
Asengeprast	Small molecule	GPR68	GPR68 signalling	Immune cell and fibroblast activation	Phase IIa trial completed; phase IIb trial, in preparation
CAL101	Antibody	S100A4	S100A4 signalling	Immune cell and fibroblast activation	Clinical trial in preparation
Itacitinib	Small molecule	JAK1	JAK1–STAT signalling	Immune cell and fibroblast activation	Phase II investigator-initiated trial, ongoing
Vixarelimab	Antibody	OSM	OSM signalling	Immune cell and fibroblast activation	Phase II trial, recruiting
Nemolizumab	Antibody	IL-31RA	IL-31 signalling	Immune cell and fibroblast activation	Phase II trial, completed
Efgartigimod	Antibody	Neonatal Fc receptor	Reduction of autoantibody titres	Autoantibodies	Phase II trial, recruiting
Belimumab	Antibody	BAFF	BAFF signalling	B cells	Phase II–III trial, recruiting
Ianalumab	Antibody	BAFF receptor	BAFF signalling	B cells	Phase II trial, recruiting
Telitacicept	Decoy receptor	BAFF	BAFF signalling	B cells	Phase II IIT trial, recruiting
Inebilizumab	Antibody	CD19	B cell depletion	B cells	Phase IIa trial, completed
Anti-CD19 CAR T cells	CAR T cell	CD19	Deep depletion of B cells	B cells	Several phase II trials recruiting or in preparation
Anti-BCMA CAR T cells	CAR T cell	BCMA	Deep depletion of B cells including plasma cells	B cells and plasma cells	Phase II trials, in preparation
CD19xCD3, CD20xCD3 and BCMAxCD3 BiTEs	BiTEs	CD19, CD20 and BCMA	Deep depletion of B cells including plasma cells	B cells and plasma cells	Several phase I and phase IIa trials, in preparation
Amlitelimab	Antibody	OX40 ligand	T cell proliferation, survival, and context-dependent T_H1, T_H2, and T_H9 cell skewing, T_{FH} cell development and B cell help	T cells and B cells	Phase II trial, recruiting
Tulisokibart	Antibody	TL1A	TL1A–DR3 signalling	T cells and ILCs	Phase II trial, recruiting
Brodalumab	Antibody	IL-17A	IL-17 signalling	T_H17 cells	Phase II trial, completed (results withdrawn)
Guselkumab	Antibody	p19	IL-23 signalling	T_H17 cells	Phase II trial, completed
Tibulizumab	Bispecific antibody	IL-17A and BAFF	IL-17 and BAFF signalling	T_H17 cells and B cells	Phase II trial, recruiting

Table 2 (continued) | Therapies currently in or about to enter clinical trials in SSc

Therapy	Entity	Molecular target(s)	Predominantly targeted mechanism(s)	Predominant target cell(s)	Developmental stage
Anifrolumab	Antibody	IFNAR1	Type I interferon signalling	Multiple target cells	Phase III trial, recruiting
Efzofitimod	HARS–IgG fusion protein	Neuropilin-2	HARS–neuropilin-2 signalling	Macrophages and other immune cells	Phase II trial, recruiting
Avenciguat	Small molecule	sGC	cGMP signalling	Broad spectrum including fibroblasts, vascular cells and possibly immune cells	Phase II trial, recruiting
Ifetroban	Small molecule	TPR	Thromboxane–prostanoid signalling	Broad spectrum including fibroblasts and vascular cells	Phase II trial, recruiting

αMSH, α-melanocyte-stimulating hormone; BAFF, B cell activating factor; BCMA, B cell maturation antigen; BiTEs, bispecific T cell engagers; cAMP, cyclic adenosine monophosphate; CAR, chimeric antigen receptors; cGMP, cyclic guanosine monophosphate; DR3, death receptor 3; HARS, histidyl-tRNA synthetase 1; IFNAR1, interferon-α/β receptor subunit 1; IL-31RA, IL-31 receptor A; IL1RAP, IL-1 receptor associated protein 1; ILCs, innate lymphoid cells; JAK1, Janus kinase 1; LPA, lysophosphatidic acid; LPAR1, lysophosphatidic acid receptor 1; MC1R, melanocortin receptor 1; OSM, oncostatin M; PDE4B, phosphodiesterase 4B; sGC, soluble guanylate cyclase; SSc, systemic sclerosis; STAT, signal transducer and activator of transcription; T_{FH} cell, T follicular helper cell; T_H cell, T helper cell; TL1A, TNF-like ligand 1A; TPR, thromboxane prostanoid receptor.

roflumilast is approved for chronic obstructive pulmonary disease. However, the systemic adverse effects, particularly gastrointestinal effects, of inhibiting PDE4 limit its use[41,42], particularly the use of higher doses that provide a more effective inhibition of PDE4 activity. The PDE4B subtype exhibits variant-specific expression patterns with high levels of expression in immune cells and tissue-resident cells in the lungs, but lower levels in the intestinal tissues[43]. Thus, selective inhibition of the PDE4B subtype might reduce the risk of gastrointestinal adverse events and enable higher doses to be used for more effective targeting of PDE4B activity. Nerandomilast is a PDE4 inhibitor that preferentially inhibits PDE4B with a 9-fold selectivity over other PDE4 subtypes[44]. In vitro, nerandomilast skews the balance from a pro-inflammatory to an anti-inflammatory cytokine profile, inhibits fibroblast proliferation and reduces myofibroblast differentiation and collagen synthesis[44]. Moreover, nerandomilast ameliorates experimental bleomycin-induced dermal and pulmonary fibrosis[45]. Of particular interest, nerandomilast prevented the decline of FVC over 12 weeks compared with placebo in a proof-of-concept phase II trial in patients with IPF[46]. A follow-up phase III RCT of nerandomilast in patients with progressive pulmonary fibrosis other than IPF met its primary end point of reduced decline in FVC and also showed reduced mortality in the nerandomilast arm compared with standard of care[47]. However, in this trial, patients were not treated according to current rheumatology standards; patients received less background therapy than would be expected for progressive disease. Nerandomilast is currently being evaluated in SSc in a phase IIb platform trial using the CONQUEST platform[48]. CONQUEST is the first platform clinical trial in the field of rheumatology, in which multiple investigational drugs can be evaluated in parallel with a shared placebo group. In this trial, changes in FVC are the primary end points and changes in mRSS are amongst the secondary endpoints.

Anti-IL1RAP antibodies

IL-1, IL-33 and IL-36 are pro-inflammatory cytokines that are linked to the aetiology of fibrotic tissue remodelling[49]. The protein levels of IL-1β, IL-33 and IL-36γ are upregulated in the skin of patients with SSc compared with healthy donors, expression of the respective receptors for these cytokines were also upregulated on relevant target cells such as fibroblasts, endothelial cells and leukocytes[50]. Bioinformatic modelling using gene expression datasets from mice that lack each of these individual cytokines and SSc skin provided evidence that all three cytokines can regulate specific, and only partially overlapping, sets of genes that are differentially expressed in SSc skin[50], which provides evidence that IL-1, IL-33 and IL-36 synergistically drive the pathogenesis of SSc. All three cytokines might be blocked simultaneously by targeting the IL-1 receptor accessory protein (IL1RAP). IL1RAP is an essential co-receptor for the IL-1 receptor, the IL-33 receptor (also known as ST2) and the IL-36 receptor and is required for downstream signalling of these cytokine receptors[51]. IL1RAP is overexpressed in SSc skin compared with healthy skin and the messenger RNA (mRNA) levels of several molecules associated with IL1RAP signalling are increased in SSc skin[50]. Blocking IL1RAP with a monoclonal antibody (mCAN10) in mice interfered with the activation of a transcriptional regulatory network of genes that are implicated in inflammation and fibrosis and also ameliorated experimental dermal and pulmonary fibrosis in three different mouse models of SSc[50]. A first-in-human phase I clinical study of a humanized anti-IL1RAP antibody (CAN10) demonstrated good tolerability and successful target engagement (NCT0614337)[50]; a phase II study in SSc is currently in preparation.

Activation of MC1R signalling

The melanocortin receptors (MCRs) are a family of G protein-coupled receptors that consists of five members with different functions. MC1R is not only expressed on melanocytes, but also on other cell types such as fibroblasts, monocytes, endothelial cells and keratinocytes, with comparable expression patterns in SSc and healthy skin[52].

Although MC1R is best known for its involvement in melanin production in melanocytes via α-melanocyte-stimulating hormone (αMSH) binding, activation of MC1R also mediates anti-inflammatory effects that include inhibition of nuclear factor-κB (NF-κB) and shifts in the balance from pro-inflammatory to anti-inflammatory mediators with suppression; MC1R suppresses TNF, IL-1, IL-6, IL-8, prostaglandin E2, IFNγ and adhesion molecules and induces the expression of IL-10 (ref. 53).

The first direct evidence of a role for MC1R in fibrotic tissue remodelling was that αMSH, the MC1R ligand, suppresses bleomycin-induced skin fibrosis in mice; mice that lack MC1R signalling have exacerbated skin fibrosis[54]. Treatment with dersimelagon phosphoric acid

(MT-7117), an orally bioavailable agonist for MC1R that is selective for MC1R over other MCRs, also ameliorated bleomycin-induced inflammation and fibrosis of the skin. Incubating human dermal fibroblasts with MT-7117 inhibited TGFβ-induced *ACTA2* expression, which demonstrates a direct effect on fibroblasts in addition to anti-inflammatory effects[52]. Activation of MC1R by αMSH binding also ameliorates vascular dysfunction in lipopolysaccharide-induced cutaneous vasculitis[55] and ischaemia–reperfusion models[56]; however, whether these findings are relevant for SSc-associated vasculopathy remains to be studied in relevant models.

A randomized, placebo-controlled phase II clinical trial of MT-7117 in patients with dcSSc, with a change in American College of Rheumatology (ACR)–Composite Response Index in Systemic Sclerosis (CRISS) at 52 weeks being the primary end point, showed no difference between patients treated with MT-7117 and placebo[57].

GPR68 inhibition

GPR68 is a proton-sensing G protein coupled receptor that is widely expressed on many cell types[58]. It has emerged as a sensor of the pH in the cellular microenvironment that is activated by the release of protons at sites of tissue damage. GPR68 is implicated in tumour growth regulation and was identified in a variety of tumours as a suppressor of progression and metastasis[59]. The drug asengeprast (FT011) was developed as a derivative of tranilast and preclinical assays indicate that this drug could be an anti-fibrotic agent[60]. In a small phase IIa clinical trial of FT011 in SSc, treatment was associated with an improved ACR–CRISS score (NCT04647890). Treatment with asengeprast for 12 weeks (but not placebo) demonstrated inhibitory effects on a marker gene set linked to renal fibrosis that is also enriched in SSc skin; however, this trial was limited by the imbalanced background immunosuppression across treatment arms, the short duration of the study and the small number of participants. Previous studies have shown similar beneficial effects for potential therapies at phase II that were not observed in phase III trials (such as lenabasum)[61]. A further phase IIb study of asengeprast in SSc is planned.

Targeting S100A4

As previously discussed, targeting damage response signalling is emerging as a novel approach for the treatment of SSc and other inflammatory and fibrotic diseases. A strategy that has considerable preclinical support but has not yet been tested in human disease is targeting the damage-associated molecular pattern (DAMP) protein S100A4. The S100 proteins are a large family defined by solubility characteristics. S100A4 is released by damaged cells and can function both intracellularly and extracellularly to promote inflammation and fibrosis[62]. Notably, S100A4 has been identified as the fibroblast marker FSP-1, which was first identified in cells undergoing epithelial-mesenchymal transition[63]. Evidence indicates that functional interaction occurs between S100A4 and TGFβ pathways[64], and that this protein can activate cells directly through engagement of cell-surface receptors including Toll-like receptor 4 (ref. 65) and the receptor for advanced glycation end products[66]. Mice lacking S100A4 are protected from experimental dermal and pulmonary fibrosis[64]. In addition, neutralizing antibodies against S100A4 can attenuate pre-established bleomycin-induced skin fibrosis and induce its regression in mice[67]. In humans, S100A4 is increased in the serum of people with SSc compared with healthy individuals, with highest levels found in those with severe disease and lung fibrosis[68]. Treating cultured SSc fibroblasts or precision cut skin slices from people with SSc with the neutralizing anti-S100A4 antibody CAL101 reduced SSc-specific transcriptional signatures[68,69]. A phase I clinical trial of this antibody was completed in 2024 and was well tolerated, with no serious adverse events reported across all tested doses (J.H.W.D., unpublished observations). Future studies to evaluate the therapeutic potential, safety and pharmacokinetics of CAL101 in fibrotic diseases such as SSc are currently in preparation.

Targeting JAK–STAT3 signalling

Growing evidence supports aberrant activation of Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signalling in SSc. JAK1 and JAK2 are increasingly phosphorylated and thereby activated in the skin of patients with SSc and accumulate in immune cells and fibroblasts[70–75]. JAKs synergize with other kinases such as SMAD3, JNK, SRC and c-ABL to activate STAT3 (ref. 72). In addition to STAT3, a genetic polymorphism of the *STAT4* gene was found to be associated with dcSSc and might promote fibrotic tissue remodelling in mice[76,77]. Pharmacological or genetic inactivation of JAK1, JAK2 or STAT3 inhibited fibroblast-to-myofibroblast differentiation and experimental dermal and pulmonary fibrosis[70–75]. These findings prompted an investigator-initiated clinical trial with the selective JAK1 inhibitor itacitinib in France, which is currently recruiting (NCT04789850).

Anti-OSM and IL-31RA antibodies

The oncostatin M receptor (OSMR, also known as oncostatin M-specific receptor subunit β) is a member of the type I cytokine receptor family. OSMR heterodimerizes with gp130 (also known as interleukin 6 signal transducer) to form the type II OSMR with the IL-31 receptor A (IL-31RA) to form the IL-31 receptor. OSMR thus transduces oncostatin M (OSM) and IL-31-induced signalling events. Two different antibodies that target these signalling cascades have entered clinical trials in SSc, vixarelimab and nemolizumab. Vixarelimab is a recombinant human monoclonal antibody that targets OSMR and has shown efficacy in a phase IIa clinical trial in the skin condition prurigo nodularis[78]. Nemolizumab is a recombinant humanized monoclonal antibody that targets IL-31RA and has also shown efficacy in a phase III clinical trial in prurigo nodularis[79]. These findings are in keeping with the known role of IL-31 in pruritus[80]. IL-31 has also been identified as a potential mediator in SSc; IL-31 expression is upregulated in the skin of patients with SSc and is found in dermal blister fluid[81]. Moreover, IL-31 directly promotes collagen production in dermal fibroblasts and indirectly by enhancing T helper 2 (T_H2) immune responses[82]. The levels of OSM are also increased in the blood of patients with SSc[83,84]; however, a 2022 phase I study of an anti-OSM monoclonal antibody (GSK2330811) in SSc showed no differences between treatment and placebo groups and no favourable clinical or biomarker outcomes[85]. Importantly, there was also a clear signal of toxicity with anaemia and thrombocytopenia. These adverse effects probably reflect 'on target' toxicity related to the role of OSM in haematopoiesis. These findings make OSM an unlikely target for future clinical development in SSc; however, there is plausible evidence supporting the potential role of OSM in the pathogenesis of SSc[86] and so if vixarelimab can achieve inhibition without toxicity and have additional anti-fibrotic benefits via its action on IL-31 pathways these effects might justify further evaluation of targeting OSM in SSc. This rationale underlies the ongoing evaluation of vixarelimab in a two-cohort, phase II, multicentre, randomized, double-blind, placebo-controlled study in patients with IPF and in patients with SSc-associated ILD (SSc-ILD) (NCT05785624). In addition, a phase II, open-label clinical trial of nemolizumab was conducted in patients with SSc, but the results remain unpublished (NCT05214794).

Targeting B cells and autoantibodies

Emerging evidence suggests that B cells are key effector cells in SSc. Thus, several approaches to targeting B cells or B cell-related mechanisms are currently being evaluated for the treatment of SSc.

Fc receptor blockade

Studies in mice indicate that the neonatal Fc receptor (FcRn) transports IgG from the milk of nursing dams to pups[87] and regulates IgG turnover in adult mice[88]. FcRn extends the half-life of IgG by reducing its lysosomal degradation[89–91]. IgG and other serum proteins are continuously internalized into cells through pinocytosis with subsequent lysosomal degradation. FcRn binds IgG (and other serum proteins) at the acidic pH within early endosomes, and releases it back into the circulation, as FcRn cannot bind IgG at the neutral pH of the extracellular environment[92,93]. Of interest for the pathogenesis of SSc, the expression of FcRn is regulated by pro-inflammatory cytokines; TNF induces the expression of FcRn, whereas IFNγ downregulates FcRn expression[94].

The antibody fragment efgartigimod alfa is a first-in-class drug that interferes with FcRn-induced recycling of IgG. Treatment with efgartigimod alfa decreases the level of circulating IgG by up to 75%, with maximal effects observed within 4 weeks, with corresponding decreases in autoantibody levels in humans[95]. In addition, the simultaneous inhibition of albumin recycling did not lead to significant changes in serum albumin levels[95]. Efgartigimod alfa demonstrated efficacy for the treatment of myasthenia gravis and is approved for the treatment of generalized anti-acetylcholine receptor antibody-positive myasthenia gravis by the FDA and EMA. Based on its mode of action, efgartigimod alfa is currently under investigation for a variety of different autoimmune diseases, including SSc. A multicentre, randomized, placebo-controlled, double-blinded, phase II trial with a 2:1 randomization of efgartigimod versus placebo and changes in mRSS after 48 weeks as the primary outcome is currently recruiting (NCT06655155).

BAFF inhibition

B cell activating factor (BAFF, also known as B lymphocyte stimulator) is a crucial cytokine in B cell homeostasis, survival and differentiation. Dysregulation of BAFF has been implicated in various autoimmune diseases, including SSc. Considerable experimental evidence indicates that BAFF has a profibrotic role. Culturing dermal fibroblasts with peripheral blood B cells from patients with SSc demonstrated that BAFF stimulates cell-contact-induced release of profibrotic mediators, such as IL-6, CCL2 and TGFβ1, as well as collagen gene expression from fibroblasts[96]. Moreover, genetic ablation of BAFF or BAFF neutralization attenuated fibrotic tissue remodelling in the Tsk/$^{+}$ mouse model of skin fibrosis and in a bleomycin-induced lung fibrosis mouse model[97,98]. In people with SSc, *BAFF* gene expression levels correlate with the upregulation of a type I interferon signature and serum type III procollagen N-terminal propeptide levels, which suggests a potential link between innate and adaptive immune responses via BAFF[99]. Finally, BAFF promotes the survival and activation of autoreactive B cells, which leads to autoantibody production. As BAFF has a crucial role in B cell hyperactivation, autoimmunity and fibrosis in SSc, agents that block BAFF are being explored as potential therapeutic strategies for SSc.

Two antibodies, belimumab and ianalumab, which target aberrant BAFF signalling are currently being evaluated in clinical trials in SSc. Belimumab is a fully human monoclonal antibody that neutralizes BAFF and is approved for the treatment of moderate-to-severe systemic lupus erythematosus (SLE) and lupus nephritis. The efficacy and safety of belimumab in patients with dcSSc and ILD is currently being investigated in a phase II–III, randomized, double-blind, placebo-controlled trial (NCT05878717). Ianalumab (VAY-736) is a fully human monoclonal antibody that targets the BAFF receptor and has a dual mechanism of action as it not only blocks BAFF–BAFF receptor interactions but also depletes B cells by antibody-dependent cellular cytotoxicity. Ianalumab has shown favourable safety and encouraging efficacy in SLE and Sjögren disease, and is being evaluated in an ongoing phase II, randomized, double-blind, placebo-controlled trial in patients with SSc (NCT06470048).

Telitacicept is a fully human fusion protein composed of the transmembrane activator and CAML interactor (TACI; also known as TNFRSF13B) and IgG1. Telitacicept is a soluble decoy receptor for BAFF and APRIL that can inhibit the maturation of immature B cells and the differentiation of mature B cells into plasma cells by blocking BAFF and APRIL, respectively[100]. An investigator-initiated trial of telitacicept in SSc is currently recruiting in China (NCT06546540).

Novel B cell-targeted approaches

Several novel approaches that target antigens on specific B cell populations are currently under investigation. The target antigens CD19, CD20 and B cell maturation antigen (BCMA) are expressed during different stages of B cell development. CD20 is induced in pre-B cells and expressed on immature, naive, germinal centre and memory B cells and on a subset of plasmablasts, whereas plasma cells do not express CD20. CD19 is expressed throughout B cell development from pro-B cells to fully differentiated B cells; however, only a subset of plasma cells expresses CD19 and the plasma cell compartment is thus only partially targeted by therapeutics that target CD19. BCMA is expressed at the later stages of B cell development with induction on germinal centre B cells, and expression on all memory B cells, plasmablasts and plasma cells; BCMA thus offers the opportunity to target all antibody-producing B cells[101].

Despite most of the evidence thus far being from case reports and case series from single centres, autologous anti-CD19 chimeric antigen receptor (CAR) T cells show clinical efficacy and relative safety in the treatment of SSc and other autoimmune diseases[102–104]. The available data provide evidence of major efficacy in a population of patients with progressive SSc previously refractory to multiple treatments. Reported beneficial effects include regression or at least stabilization of fibrotic manifestations (such as dermal, pulmonary and cardiac fibrosis), rapid regression of inflammatory manifestations (such as arthritis or myositis) and improved microcirculation with reduced frequency and intensity of Raynaud attacks and lower incidence of fingertip ulcers[105]. Early evidence suggests that treatment with anti-CD19 CAR T cells might be better tolerated than high-dose chemotherapy followed by autologous HSCT and that this treatment is safe and effective in patients with SSc and advanced pulmonary or cardiac involvement, who are no longer eligible for HSCT (J.H.W.D., unpublished observations). Additional unpublished evidence indicates that anti-CD19 CAT T cell therapy, but not the anti-CD20 antibody rituximab, can restore the papillae in the upper dermis, which are typically flattened in SSc (J.H.W.D., unpublished observations). Although further histological studies and molecular analyses are required to support these initial findings, they indicate that anti-CD19 CAR T cell therapies not only halt disease progression but can also induce, at least to some extent, the regeneration of fibrotic skin, which could possibly extend to fibrosis in other organs. CD19-positive cells are rapidly depleted in peripheral blood, but also in lymph nodes following anti-CD19 CAR T cell therapy,

which is associated with strongly decreased levels or even complete loss of disease-associated autoantibodies[106]. The persistence of CAR T cells varies depending on the CAR T construct but is often limited to a few months after second-generation CAR T cells[103]. However, the clinical benefits of anti-CD19 CAR T cell therapy persist beyond the presence of CAR T cells in the peripheral circulation; clinical benefits have been reported 3 years post-treatment. Despite its promise, careful longitudinal studies are needed to confirm these findings, optimize the treatment protocols and patient selection criteria, study the duration of the therapeutic effects and explore the molecular mechanisms underlying the effects on the different histopathological changes in SSc. Thus far, several clinical trials of autologous anti-CD19 CAR T cells in SSc from different companies are recruiting. In addition to autologous anti-CD19 CAR T cells, clinical trials of allogenic anti-CD19 CAR T cells are currently in preparation for SSc and other autoimmune diseases based on first reports of efficacy and safety in three patients with autoimmune rheumatic diseases, including two patients with dcSSc[107].

In addition to anti-CD19 CAR T cells, CAR T cells that target BCMA$^+$ B cells are currently being evaluated for the treatment of autoimmune diseases[108]. Although the initial results from case series are encouraging, further studies with additional patients and long-term follow-up are required. Moreover, high costs as well as complex organization might make widespread use outside of specialized centres challenging.

Case reports from the past year indicate the efficacy of bispecific T cell engagers (BiTEs) for the treatment of severe, refractory SSc[109,110]. These bispecific antibodies direct T cell-mediated cytotoxic activity against cells that express target antigens. BiTEs are fusion proteins consisting of two single-chain variable fragments of different antibodies. One of the single-chain variable fragments binds to and activates CD3 on T cells, and the other single-chain variable fragment binds to antigens on the target cell such as CD19. Binding of bispecific antibodies thus induces the formation of an immunological synapse between T cells and target cells, which causes T cells to exert cytotoxic activity on target cells by releasing perforin and granzymes, independently of the presence of other co-stimulatory molecules or MHC I[111]. One case report describes the successful treatment of a patient with severe, progressive SSc with blinatumomab (a CD19xCD3 BiTE)[109]. Three different case series demonstrate the efficacy of teclistamab (a BCMAxCD3 BiTE) in people with advanced, previously treatment-refractory SSc, although the total number of patients in these studies was less than ten[110] (and J.H.W.D., unpublished observations).

Anti-CD19 antibodies

Inebilizumab is a depleting, affinity-optimized, afucosylated humanized monoclonal anti-CD19 antibody that is approved for the treatment of neuromyelitis optica spectrum disorder in adult patients who are anti-aquaporin-4 antibody positive. Inebilizumab demonstrated good safety and tolerability in a phase I, randomized, placebo-controlled, escalating single-dose study in people with SSc[112]. Inebilizumab treatment at doses of 0.1–10.0 mg/kg led to dose-dependent depletion of circulating B cells and plasma cells in 24 people with SSc compared with 4 people who received placebo[112]. Interestingly, patients with a plasma-cell mRNA signature in biopsy-obtained skin samples at baseline showed greater improvement in mRSS following treatment with inebilizumab than patients with a low plasma-cell mRNA signature, which suggests that patient enrichment prior to therapy might be beneficial[113].

T cell-targeted approaches

In addition to the numerous approaches that target B cells, several therapies that alter T cell activation are being evaluated for the treatment of SSc.

OX40 ligand blockade

OX40 ligand (OX40L, also known as TNFSF4) is upregulated on activated antigen-presenting cells and interacts with OX40 on T cells, which promotes T cell proliferation, survival and context-dependent T_H1, T_H2 and T_H9 skewing and cytokine release. Moreover, OX40–OX40L signalling promotes germinal centre formation and humoral immunity by promoting T follicular helper cell development and supporting B cell responses[114]. In SSc, polymorphisms in *OX40L* are linked to disease susceptibility[115]. OX40L expression is increased in the fibrotic skin of patients with early, diffuse SSc at the protein and transcript levels[116,117]. Interestingly, OX40L is not only expressed in immune cells but also in dermal fibroblasts[116,117]. In a preclinical study, OX40L knockout or neutralizing OX40L antibodies abrogated fibrosis and the infiltration of macrophages and T cells, B cells and NK cells in the bleomycin-induced dermal fibrosis mouse model[116]. Similarly, neutralizing OX40L antibodies decreased pulmonary fibrosis in the Fra2 transgenic mouse model[116]. Amlitelimab is a fully human, non-depleting, non-cytotoxic anti-OX40 ligand monoclonal antibody that has shown promising efficacy and safety results for the treatment of atopic dermatitis in a phase IIa double-blind placebo-controlled study[118]. Amlitelimab will be examined for the treatment of SSc-ILD in the ongoing CONQUEST clinical trial platform[48] with the primary end point being FVC change from baseline after 52 weeks[48].

TL1A blockade

TNF-like cytokine 1A (TL1A – also known as TNFSF15) is a pro-inflammatory cytokine that belongs to the TNF superfamily. TL1A is expressed by immune cells during inflammation and exerts its functions via interactions with cell-surface death domain receptor 3 (DR3). Preclinical studies indicate that injection of TL1A into the airways of wild type mice induces a fibrotic response via interactions with DR3 in a T cell- and/or innate lymphoid cell-independent manner[119]. Moreover, genetic deletion of *DR3* attenuated increases in collagen deposition in the bleomycin-induced pulmonary fibrosis mouse model[119]. Serum TL1A levels were elevated in patients with SSc with late diffuse cutaneous involvement (disease duration >5 years) but not in those with early cutaneous involvement (disease duration <2 years) compared with matched healthy individuals[120]. Moreover, bulk RNA sequencing analysis revealed that *TL1A* gene expression was increased in SSc-ILD compared with healthy individuals[120]. Tulisokibart is a humanized monoclonal antibody that binds to the membrane-bound and soluble forms of TL1A, which prevents its interaction with DR3. In a phase II randomized, double-blind clinical trial, tulisokibart was effective at inducing clinical remission in patients with moderately to severely active ulcerative colitis and had an adequate safety profile[121]. Building on the aforementioned data, an ongoing phase II, randomized, placebo-controlled clinical trial is investigating the safety and efficacy of intravenous tulisokibart in SSc-ILD, with the primary outcome being FVC change from baseline after 50 weeks (NCT05270668).

Targeting IL-17 signalling

IL-17 comprises a family of cytokines, including IL-17A, IL-17B, IL-17C, IL-17D (also known as IL-27), IL-17E (also known as IL-25) and IL-17F. IL-17A and IL-17F form homodimers and/or heterodimers, both of

which interact with the same heterodimeric receptor, composed of the ubiquitously expressed IL-17 receptor A (IL-17RA) chain and the inducible IL-17 receptor C chain[122]. IL-17A is a pro-inflammatory cytokine mainly produced by T_H17 cells and has a key role in host defence against opportunistic pathogens such as *Candida albicans*[123]. This cytokine is also implicated in the pathogenesis of various inflammatory diseases, and might have a role in fibrotic tissue remodelling as suggested by experimental evidence from studies on fibrotic disease of the lungs, kidneys, heart and skin[124]. However, there are conflicting reports regarding the role of IL-17A in pathogenesis of SSc and its precise contribution to SSc pathogenesis remains unclear[125]. For instance, several studies report elevated circulating IL-17A levels in patients with SSc, whereas others have found no significant difference or even lower IL-17A levels[126–131]. $IL\text{-}17A^+$ cells are increased in the dermis of SSc skin, whereas $IL\text{-}17F^+$ cells do not increase. Functionally, IL-17A can stimulate the proliferation of SSc fibroblasts in vitro, but the direct stimulatory effects of this cytokine on collagen and extracellular matrix protein synthesis in fibroblasts seem to be minimal under standard cell-culture conditions[126,127,129]. Results from another study indicate that IL-17A might even inhibit collagen synthesis in vitro[127]. More pronounced effects of IL-17A on fibroblasts have been reported in 3D cultures[127]. In contrast to the limited effects on cultured fibroblasts, IL-17 blockade potently reduced fibrosis severity in various mouse models of skin fibrosis, including the bleomycin-induced fibrosis model, mice with chronic graft-versus-host disease and $TSK/^+$ mice[132]. The more pronounced effects of IL-17 blockade in mouse models might, in part, be explained by the effects of IL-17 on immune-cell recruitment, which is a critical pathophysiological feature in the bleomycin-induced fibrosis and chronic graft-versus-host disease mouse models.

Beyond fibrosis, IL-17A might also contribute to the vascular pathogenesis of SSc. IL-17A induces endothelial cells to release cytokines and chemokines, which promotes neutrophil infiltration via the ERK1–2 signalling pathway, but also triggers endothelial apoptosis, which exacerbates endothelial dysfunction[133]. Several biologic therapies that target IL-17A, IL-17F, both IL-17A and IL-17F, and IL-17RA are already approved for psoriasis, psoriatic arthritis, spondyloarthritis and inflammatory bowel disease. Notably, a phase III RCT with brodalumab, an IL-17RA antagonist that inhibits multiple IL-17 family members, in patients with SSc, was completed in Japan; however, the sponsor ultimately withdrew from publication of the results, leaving the potential of this therapeutic for SSc unresolved.

Targeting IL-23

IL-23 has a crucial role in the differentiation and maintenance of T_H17 cells, promoting the production of IL-17A and IL-22. IL-12 is composed of the IL-23-specific p19 subunit and the common p40 subunit, the latter of which is shared with IL-12. Monoclonal antibodies that target the p19 subunit, such as guselkumab and risankizumab, are approved for the treatment of psoriasis and psoriatic arthritis. Beyond its role in T_H17 cell expansion and IL-17A production, IL-23 also enhances B cell survival and autoantibody production. Although IL-23 is primarily regarded as pro-inflammatory, some studies suggest that it might also exhibit immune regulatory effects under certain conditions[134]. Further research is needed to clarify the precise role of IL-23 in SSc pathogenesis. Despite these uncertainties, a phase IIa, multicentre, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of guselkumab in patients with SSc has been completed (NCT04683029).

Other inflammation-modulating approaches

Combined inhibition of IL-17A and BAFF

Tibulizumab is a humanized tetravalent bispecific dual-antagonist antibody engineered to neutralize both BAFF and IL-17A[135]. By targeting these two pro-inflammatory cytokines, tibulizumab is aimed at modulating immune responses. As outlined previously, BAFF and IL-17A are both implicated in the pathogenesis of SSc. Potential synergistic effects between these two cytokines have been reported in a mouse model of bleomycin-induced lung fibrosis[114]. Specifically, the induction of BAFF expression was IL-17A dependent and BAFF in turn promoted IL-17A-driven fibrosis by stimulating IL-17A production by T cells. Tibulizumab is currently being investigated in a phase II, double-blind, placebo-controlled trial in early dcSSc (NCT06843239).

Type I interferon receptor blockade

There are several lines of evidence that indicate that interferon activation is involved in the pathogenesis of SSc. Several genes in the interferon pathways are associated with susceptibility to SSc[136]. Moreover, an interferon activation signature is the most prominent gene expression profile in peripheral blood cells from patients with SSc[137]. Prominent interferon signatures are found in affected end-organs such as the skin and lung[117,138]. Moreover, the levels of interferon-inducible chemokines in plasma are associated with SSc disease severity[139]. Last, evidence of the pathogenic role of type I interferon comes from an RCT of IFNα in patients with early diffuse SSc. In this trial, treatment with IFNα exacerbated rather than improved skin and lung fibrosis[140], although it was initially hypothesized that this treatment would improve fibrosis owing to observed inhibitory effects of IFNα on collagen synthesis in fibroblasts in vitro[141]. Anifrolumab is a fully human, monoclonal antibody that targets the type I interferon receptor α subunit 1 (IFNAR1). As all interferon α and β subtypes signal via IFNAR, this therapy can effectively block downstream type I interferon signalling. Anifrolumab is approved for the treatment of moderate-to-severe SLE; interferon signatures similar to those in SSc are observed in SLE. Anifrolumab demonstrated adequate safety and tolerability in a phase I trial in patients with SSc[134,142]. In this trial, anifrolumab suppressed the type I interferon gene expression signature in whole blood and skin, demonstrating adequate target engagement. Analysis of serial skin samples collected prior to treatment initiation and 28 days post-treatment revealed that blocking IFNAR1 blockade was also associated with suppression of extracellular matrix-related transcripts, including type I collagen[143,144]. A multinational, randomized, placebo-controlled, double-blind phase III clinical trial has been launched to determine the efficacy of subcutaneous anifrolumab in SSc. This trial permits background immunosuppression and the primary efficacy end point is a revised CRISS-25 response at 52 weeks (NCT05925803).

Neuropilin-2 modulation

Histidyl-tRNA synthetase (HARS) is one of several aminoacyl tRNA synthetase enzymes that catalyse the esterification of tRNA to its corresponding amino acid based on its base sequence. These enzymes are essential for the translation of mRNAs to an accurate amino acid sequence. Specifically, HARS is responsible for the incorporation of histidine into a growing peptide. Although this process occurs intracellularly, fragments and splice variants of tRNA synthetase are also present extracellularly[145]. The gene encoding HARS gives rise to several splice variants. One HARS splice variant, which only contains the N-terminal domain (HARS amino acids 1–60), is enriched in human lung tissue, and its expression is increased following stimulation with

pro-inflammatory cytokines, such as interferon and TNF[146]. Notably, the N-terminal domain of HARS is targeted by the anti-Jo-1 antibody, which is the most common antibody associated with anti-synthetase syndrome, a systemic autoimmune disease that frequently leads to ILD[147]. Detectable circulating free HARS can be identified in sera from healthy people but not in sera from patients with anti-Jo-1 antibody-positive anti-synthetase syndrome[148]. Moreover, recombinant HARS decreases T cell activation and cytokine release[148]. Cumulatively, these data support the hypothesis that sequestration of HARS through anti-Jo-1 antibodies leads to disruption of immune homeostasis. HARS has a short half-life, but the therapeutic drug efzofitimod contains a HARS amino acid sequence (amino acid 2–60) that is fused with the Fc portion of human IGg1, which extends its half-life. In a follow-up experiment, Neuropilin-2 (NRP2) was identified as the sole binding partner for efzofitimod[146,149]. NRP2 is a cell-surface receptor that is expressed on several immune cells, such as macrophages, and has a role in myeloid-cell biology, including cell differentiation. NRP2 is highly expressed on macrophage populations within the granulomas of patients with sarcoidosis[150]. Efzofitimod decreased immune-cell counts in the lung tissue and bronchoalveolar lavage in a lipopolysaccharide acute lung inflammation mouse model[146]. Building on these preclinical findings, the safety and efficacy of efzofitimod were investigated in a randomized, double-blind, placebo-controlled phase II–III clinical trial in patients with pulmonary sarcoidosis[151]. Efzofitimod was generally well tolerated and showed non-significant trends towards improved FVC and glucocorticoid reduction. Building on the aforementioned results, a double-blind, randomized, placebo-controlled phase II study has been launched to evaluate the safety and efficacy of efzofitimod in SSc-ILD. The primary outcome of this ongoing trial is the absolute change from baseline in FVC (NCT05892614).

Anti-fibrotic approaches with vascular effects

Vascular manifestations of SSc are a leading cause of morbidity and contribute to overall mortality. Moreover, vascular manifestations might promote fibroblast activation and tissue fibrosis directly via endothelial-to-mesenchymal transition[152,153], release of profibrotic mediators from endothelial cells[154], platelet activation at the damaged endothelium[155] or indirectly by vasculopathy-induced hypoxia[154]. Therapeutics that interfere with vascular and fibrotic features of SSc might thus exert additive effects on fibrotic tissue remodelling and simultaneously address two key medical needs in SSc.

Activators of soluble guanylate cyclase

Soluble guanylate cyclase (sGC) is an enzyme that catalyses the conversion of GTP to cyclic guanosine monophosphate (cGMP), when nitric oxide is bound to a prosthetic haem group on sGC[156,157]. cGMP is an anti-fibrotic mediator that limits TGFβ-induced ERK phosphorylation and fibroblast activation[157]. Preliminary evidence indicates that cGMP might also reduce the release of profibrotic mediators from cultured endothelial cells and limit type I interferon signalling in bleomycin-induced fibrosis in mice[158]. cGMP transmits its anti-fibrotic effects in part via protein kinase G (PKG1 and PKG2); however, chronic exposure of fibroblasts to TGFβ downregulates the expression of PKGs[159], thereby partially desensitizing fibroblasts to the anti-fibrotic effects of cGMP. Another mechanism that might contribute to inhibition of sGC–cGMP signalling in SSc is oxidative stress, which leads to the formation of an oxidized, haem-free form of sGC that is unresponsive to nitric oxide. Two different types of drugs have been developed to activate sGC signalling. sGC stimulators require haem-bound sGC and enhance sGC sensitivity to nitric oxide, whereas sGC activators bind directly to haem-free sGC and can activate the enzyme independently of nitric oxide. sGC stimulators and sGC activators both show anti-fibrotic effects in vitro and in mouse models of SSc[156,158,160].

In a phase II RCT of the sGC stimulator riociguat in patients with dcSSc, treatment showed a beneficial trend for mRSS as the primary outcome, and for several secondary readouts including FVC, but did not reach statistical significance[161]. Based on these findings and the hypothesis that sGC activators might be more effective in upregulating cGMP levels than sGC stimulators in a disease with high levels of oxidative stress and accumulation of oxidized, haem-free sGC, a placebo-controlled, double-blind, parallel-group phase II clinical trial of the sGC activator avenciguat in patients with SSc-ILD is currently recruiting, with the primary outcome being changes in FVC after 48 weeks (NCT05559580).

Targeting the thromboxane prostanoid receptors

The thromboxane prostanoid receptor (TPR, encoded by *TBXA2R*) is activated by thromboxane and prostanoids and induces constriction of vascular smooth muscle cells, promotes platelet aggregation and induces pro-inflammatory responses in endothelial cells. Moreover, aberrant TPR signalling might be implicated in the pathogenesis of fibrotic remodelling of the lungs and heart and of pulmonary arterial hypertension[162–164].

Lung fibroblasts upregulate TPR expression during fibrosis, with increased expression levels in patients with IPF and in mice with experimental fibrosis[162]. Genetic deletion of *Tbxa2r* protected mice from bleomycin-induced lung fibrosis, suggesting the functional role of TPR signalling in fibrotic tissue remodelling[162]. TPR activation does not predominantly occur via thromboxanes in this model, as inhibition of thromboxane synthase did not ameliorate fibrosis. F2-isoprostanes, which are non-enzymatic products of arachidonic acid induced by reactive oxygen species, might account for the activation of TPR. F2-isoprostanes are elevated during experimental fibrosis and can activate TPR signalling in fibroblasts and induce fibroblast-to-myofibroblast transition in vitro. Pharmaceutical inhibition by the selective, orally bioavailable TPR antagonist ifetroban ameliorated bleomycin-induced fibrosis and radiation-induced experimental fibrosis and reduced fibrotic remodelling in a mouse model of Hermansky–Pudlak syndrome[162].

Preclinical studies also provide evidence of the use of TPR antagonists to treat PAH and associated right heart failure. In a rat model of monocrotaline-induced PAH, treatment with the TPR antagonist NTP42 also alleviated pulmonary vascular remodelling, inflammation and fibrosis in monocrotaline-challenged rats[163]. These histological changes were associated with improved clinical readouts of PAH with reduction in mean pulmonary arterial pressure and right systolic ventricular pressure in rats treated with NTP42 (ref. 163). These beneficial effects of the TPR antagonist might be mediated by a combination of anti-fibrotic, anti-inflammatory, anti-proliferative and vasodilative effects in combination with inhibitory effects on platelet aggregation. TBXA2R inhibition also ameliorated fibrotic remodelling of the right ventricle and TGFβ signalling in a mouse model of right heart failure induced by pulmonary artery banding[164], a common model of PAH-induced right heart failure.

The safety and efficacy of the TPR antagonist ifetroban is currently being investigated in a randomized, double-blind and placebo-controlled phase II clinical study in people with diffuse dcSSc or SSc-associated pulmonary arterial hypertension (NCT02682511).

The future of drug development in systemic sclerosis

Despite progress with the approval of novel medications and major increases in the number of clinical trials in SSc compared with previous decades, several potential targets for therapeutic intervention with promising preclinical data have not yet been translated from bench to bedside.

Targeting epigenetic modifications in SSc might have therapeutic potential but this approach has not yet been used in clinical practice. Various epigenetic modifications, such as DNA methylation, and different histone methylation and acetylation markers are altered in SSc[70,165–177]. These epigenetic changes are thought to maintain an SSc-specific, activated cellular phenotype particularly in less inflammatory stages of disease and might thus promote disease progression in later stages of SSc. Targeted modification of these epigenetic alterations with genetic and pharmacological approaches in cultured cells from patients with SSc and in mouse models of fibrosis show therapeutic effects in preclinical assays with amelioration of the SSc-specific cellular phenotype and reduced fibrotic remodelling[70,175,177–179]. Although several epigenetic drugs such as DNA-methyltransferase inhibitors or histone-deacetylase inhibitors are in clinical use in oncology, these findings have not been investigated in interventional clinical trials in SSc.

Aberrant cellular senescence is also emerging as a central pathomechanism in SSc and in other fibrotic diseases[180,181]. Accumulating evidence demonstrates that immunosenescence might promote disease progression by directly altering cell functions or indirectly by defective immune surveillance[180,181]. First proof-of-concept studies with senotherapeutics showed encouraging results in other fibrotic diseases; however, these compounds are currently not specific to senescence and can have broader effects[180].

Another emerging area is targeting individual cell subpopulations that are relevant to disease pathogenesis rather than broad, unselective targeting of entire cell types. Advances in single-cell omics technologies have facilitated the identification of phenotypically and functionally distinct subpopulations of cells in health and disease. These studies demonstrate shifts in the proportion of individual subpopulations rather than general changes in cell phenotype in chronic diseases such as SSc. For example, even in affected skin from patients with highly active, progressive SSc, not all fibroblasts display an activated, profibrotic phenotype, but profibrotic and pro-inflammatory fibroblast subpopulations such as $CCL19^+$ fibroblasts, $SFRP4^+SFRP2^+$ fibroblasts, $ADAM12^+GLI1^+$ fibroblasts or $S1PR^+$ fibroblasts expand, whereas the number of homeostatic cell subpopulations such as $PI16^+$ fibroblasts and $TFAM^{high}$ fibroblasts decrease[182,183]. Selectively targeting these disease-promoting subpopulations of cells rather than broader cell populations might minimize treatment-related adverse events; however, specifically targeting these defined cell subpopulations can be challenging, as most are defined by combinations of several different markers rather than by specific individual markers. However, surrogate markers can be defined for many of these subpopulations, which enables preferential, but not entirely specific, targeting of disease-relevant cell subpopulations.

Another emerging area for the treatment of SSc is precision medicine. Although precision medicine with a specific treatment regimen for individual patients is common in oncology, precision medicine approaches to rheumatic diseases are scarce. However, precision-medicine approaches with upfront selection of effective therapies would be particularly important in fibrotic diseases, in which responses to therapies can be assessed only after prolonged follow-up of often 6 or even 12 months, thus leading to potentially long periods on suboptimal or even insufficient therapies. Emerging approaches to precision medicine in SSc include upfront evaluation of molecular responses to treatments in ex vivo cultures of precision-cut slices of skin from patients with subsequent omics-based profiling of molecular responses to individual treatments. Initial results indicate that molecular responses might be predictive of clinical responses to the respective drugs; thus, drug selection for individual patients could potentially be based on molecular responses in skin samples from people with SSc (J.H.W.D., unpublished observations). However, these approaches require confirmation in larger cohorts with longer follow-up. Such an approach would require upfront biopsies, generation of precision-cut slices, standardized exposure to test drugs and standardized evaluation of molecular responses, which would need to be established across different centres before broader use.

Conclusions

SSc has become a major focus of active and expanding drug development, with successful approval of novel targeted therapies over the past 5 years and promising ongoing clinical trials targeting different molecular and cellular entities. These clinical trials might yield additional therapeutic approaches to further reduce the high morbidity and mortality associated with SSc. With the approval of additional treatments, personalized medicine strategies for the selection of optimal treatments for each patient need to be developed to avoid prolonged periods of suboptimal or even ineffective treatment.

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Author contributions

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Review article

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Pain in systemic lupus erythematosus: emerging insights and paradigms

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by protean clinical manifestations that are associated with immune system dysregulation. Of these manifestations, pain and pain-related symptoms such as fatigue, mood disturbance and cognitive impairment are the most common features reported by patients and represent important determinants of quality of life. Nevertheless, the relationship of these symptoms to underlying immune mechanisms is unclear. To advance scientific study and patient-centric care, this Review will consider the origin of pain in SLE and the clinical ramifications. Although many of the inflammatory aspects of SLE, including arthritis, serositis and skin disease, can be associated with nociceptive pain, patients frequently report pain that seems out of proportion to the degree of inflammation. In many of these patients, pain might reflect central and peripheral nervous system sensitization that mediates nociplasticity, a change in brain processing; with nociplasticity, changes in neuronal function and brain connections can amplify the experience of pain and pain-related symptoms. The close interplay between the immune and the nervous systems means that widespread pain and the associated symptoms can be considered as essential features of SLE; these features might share pathogenic mechanisms with other autoimmune diseases and nociplastic pain syndromes such as fibromyalgia.

Sections

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Key points

- Symptoms of systemic lupus erythematosus (SLE) are protean but differ in their relationship to inflammation and autoreactivity as determined by current biomarkers.
- Pain and pain-associated symptoms such as fatigue, mood changes and cognitive impairment are important determinants of quality of life in patients with SLE.
- Many aspects of the patient response to disease, including interoception, sickness behaviour and nociplasticity, complicate the assessment of pain in patients with SLE.
- Pain and pain-associated symptoms might reflect immune-mediated peripheral and central nervous system sensitization that results in nociplasticity.
- The term lupus-associated nociplasticity might help to explain many of the symptoms identified as most concerning by patients living with SLE.
- Managing pain in SLE requires a multimodal approach that uses pharmacological and non-pharmacological interventions directed at both pain and inflammation.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a wide array of clinical manifestations that result from inflammation and autoreactivity[1]. SLE primarily affects young women in their childbearing years and is more severe in certain populations; for example, in the USA, people of African descent have a worse overall prognosis. Among individual patients, SLE varies markedly in severity, clinical manifestations and pattern of disease activity[2,3]. Furthermore, in the same patient, disease activity can fluctuate over time, with flares often occurring abruptly and unexpectedly, altering the clinical course of disease[4]. Along with disease manifestations that can be assessed objectively by laboratory, biopsy or imaging studies, SLE is characterized by prominent subjective manifestations that can dominate the clinical picture and dramatically impair quality of life[5]. These symptoms include widespread pain, fatigue, cognitive impairment (also known as brain fog) and mood disturbances (such as depression); as a group, these symptoms can be difficult to evaluate because of their subjective and non-specific nature. For many patients, however, these symptoms constitute their 'lupus'. As these symptoms might not respond to conventional anti-inflammatory and immunosuppressive agents, understanding their relationship to immune mechanisms is essential.

To provide a framework for elucidating SLE symptomatology, a model for the symptoms of SLE has been proposed and includes two main categories (type 1 and type 2 SLE)[6]. Type 1 manifestations are the classic manifestations of inflammation such as arthritis, nephritis and serositis. By contrast, type 2 manifestations include widespread pain, fatigue and mood disturbances; how these features are linked to inflammation remain unclear. In this proposed framework, type 2 manifestations are essential features of SLE and can result from immune system dysregulation that can perturb pain processing via central nervous system sensitization and peripheral nervous system sensitization. As such, this model links the immune and nervous systems; although these systems might function beneficially together in the host response to trauma and infection, they can be harmful in autoimmune diseases such as SLE.

At present, advances in immunology and biotechnology have led to new and exciting therapeutic strategies for SLE that could have unprecedented levels of efficacy. Using novel antibody and cellular platforms, these treatments target immune cells such as B cells, T cells, macrophages and other myeloid cells and are designed to achieve either greater elimination of specific immune-cell populations or more profound inhibition of their function than previously possible[7]. As immune mediators are key to both the nervous system and the immune system, these emerging treatments might ameliorate both type 1 and type 2 symptoms.

At a time of great interest generated by the prospects of new treatments, we think that incorporating considerations of pain (and the related type 2 symptoms) into studies of new therapies is essential to understand how these therapies affect the full gamut of SLE symptomatology, regardless of whether the symptom is caused by the immune system or the nervous system. In this Review, we consider the determinants of pain in SLE and provide a framework to guide both research and clinical care to improve patient outcomes.

Mechanisms of pain in systemic lupus erythematosus

This section reviews the immunopathogenesis of SLE and the mechanisms of pain generation and transmission. As inflammatory mediators can affect cells of the nervous system, both central and peripheral sensitization can occur during inflammatory disease, which intensifies pain.

Immunopathogenesis of systemic lupus erythematosus

The current model for SLE pathogenesis focuses primarily on the induction of tissue inflammation as mediated by the actions of antinuclear antibodies (ANAs)[8] and their cognate nuclear antigens. ANAs are the serological hallmark of disease and essential biomarkers for clinical and research purposes[8]. In SLE, autoantibody-mediated pathogenicity results from immune complex deposits in the tissue, especially the kidneys, which can activate complement during flares and heighten disease activity; in this setting, a decrease in the level of complement components (such as C3 and C4) can correlate with elevations of anti-DNA antibodies[9–11].

Immune complexes have important roles in SLE pathogenesis because of the intrinsic immunological activity of the cargo nuclear antigens[12,13]. Whether of endogenous or exogenous origin, DNA and RNA can function as molecular patterns and stimulate intracellular nucleic-acid sensors; in this scenario, immune complexes promote the uptake of nucleic acids into innate immune cells. These nucleic acid sensors include both Toll-like receptors (TLRs) and non-TLRs (such as cGAS–STING) and are part of an internal host defence system that stimulates the production of pro-inflammatory cytokines, most prominently type I interferon[14]. Cytokines in turn can drive downstream inflammation and other systemic effects[12]. Thus, the current model of SLE pathogenesis highlights three key factors that drive local and systemic inflammation: ANA immune complexes, immunostimulatory nucleic acids and pro-inflammatory cytokines.

Although the current model of SLE is very useful, there are limitations related to uncertainty about the mechanisms of manifestations other than nephritis and the frequent lack of correlation of active

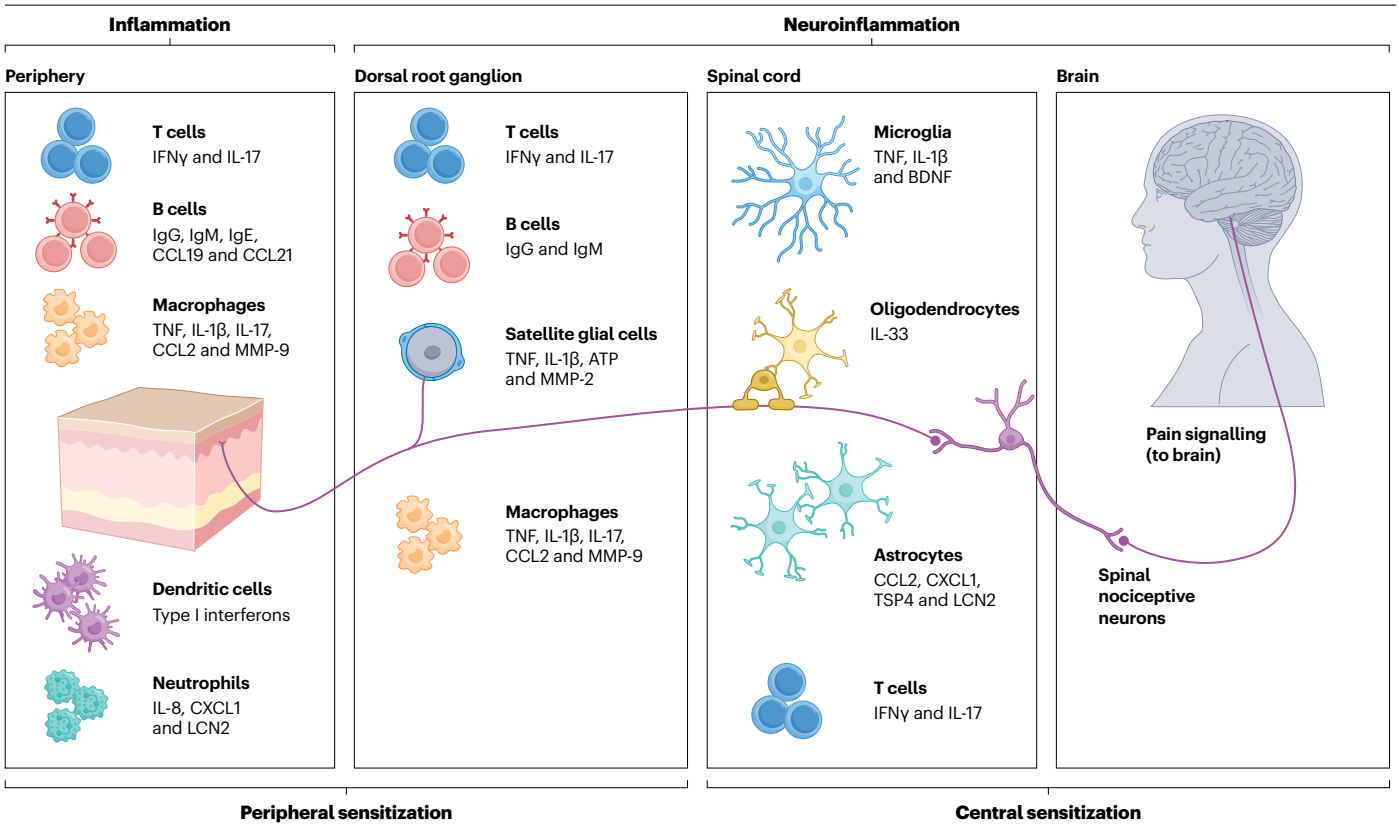

Fig. 1 | Neuroinflammation, central sensitization and neuroimmune interactions in systemic lupus erythematosus and chronic pain. In systemic lupus erythematosus (SLE), tissue inflammation can drive neuroinflammation in the peripheral nervous system, dorsal root ganglia (DRG) and central nervous system (spinal cord, brainstem and brain), which contributes to chronic pain. This figure illustrates the distinct locations of inflammation, neuroinflammation, peripheral sensitization and central sensitization and would pertain to tissues involved in SLE such as the skin (as shown here) or joint. It also highlights the various immune cells that can mediate these processes. These cells include T cells, B cells, macrophages, neutrophils and dendritic cells; in addition, glial cells, including satellite glial cells in the DRG, and microglia, astrocytes and oligodendrocytes in the spinal cord dorsal horn can participate in this process. Notably, pro-inflammatory mediators released by non-neuronal immune cells and glial cells can directly activate nociceptive neurons, which promotes pain via neuroimmune interactions. The DRGs are not protected by the blood–brain barrier and therefore can be exposed to pro-inflammatory and pro-nociceptor mediators in the blood, including antibodies; these features make DRGs potentially important sites of pain generation by neuroimmune mechanisms in SLE and other nociplastic pain conditions[150]. BDNF, brain-derived neurotrophic factor; LCN2, lipocalin 2; MMP, matrix metalloproteinases; TSP4, thrombospondin 4. Adapted with permission from ref. 151, AAAS.

disease with current biomarkers, especially the levels of anti-DNA antibodies and complement[15,16]. In addition, the current model lacks consideration of prominent and debilitating symptoms such as widespread pain and fatigue that afflict many patients. Furthermore, many studies report discordance between patients and health care providers in their assessment of disease activity and severity; patients with SLE might report what they consider disease activity in the apparent absence of demonstrable inflammation or serological activity[17–19]. These findings challenge both routine care and clinical trials, and also prompt consideration for the origin of pain in SLE and how pain relates to autoreactivity.

Pathways of nociception

For certain manifestations of SLE, pain can result from classic mechanisms of nociception. Arthritis is a prime example; in the inflamed joint, nociceptive primary afferent neurons, including fast-conducting Aδ fibres and slow-conducting C fibres, can detect noxious stimuli such as heat, cold and mechanical pressure above a certain threshold. These fibres can also respond to inflammatory mediators to generate information for transmission to the central nervous system[20]. The cell bodies of nociceptive neurons reside in the dorsal root ganglia (DRG), outside of the spinal cord, are not protected by the blood–brain barrier and project into dorsal horn regions of the spinal cord. In the spinal cord, these neurons form synapses with spinal cord neurons to relay the information to the brainstem and brain[21] (Fig. 1).

Once signals generated peripherally reach the thalamus, multiple brain regions interpret and modulate the nociceptive information into the experience of 'pain'. Pain modulation also involves the interplay of other influences such as cognition, affect, experience and emotion. Furthermore, facilitation or inhibition of nociceptive signals by brainstem processes can effectively 'dial-up' or 'dial-down' the signals across multiple levels of the nervous system[22–26].

Although local inflammation can initiate pain, chronic pain can ensue and involve sensitization of primary afferent nociceptive

fibres (such as nociceptors) resulting from increased sensory and/or nociceptive input at the affected site (such as a joint). In this process, pro-inflammatory mediators (such as prostaglandins, nerve growth factor, cytokines and chemokines) can influence neuronal excitability and sensitivity[27]; other triggers such as pathogen and danger-associated molecular patterns (PAMPs and DAMPs, such as RNAs and DNAs released from damaged cells) can also mediate these interactions[28].

As factors such as DNA and RNA can alter both immune cells and neuronal cells, peripheral sensitization can occur through transcriptional, translational and post-translational changes[29,30]; these changes can modulate gene expression and the function of key receptors and transduction and conduction molecules[27] (Fig. 2). Furthermore, peripheral sensitization can enhance neurotransmitter release in the spinal cord and brain, promoting central sensitization, which underlies the transition from acute to chronic pain. Central sensitization is sustained by neuroinflammation (Fig. 1) and can lead to widespread pain, thus linking the nervous system and immune system in autoimmune disease[31] (Box 1).

Sources of pain in systemic lupus erythematosus

As SLE is a systemic disease, symptomatology is highly diverse and depends on the specific organs or tissues that are affected in individual patients, the intensity of disease activity and the ensuing damage, whether caused by the disease itself or the associated treatment[32]. For each symptom, attribution is essential, with a detailed clinical and laboratory evaluation often necessary to determine the source of each manifestation (that is, SLE or another source such as an infection or adverse effects of medication).

Musculoskeletal pain in systemic lupus erythematosus

Of sources of pain in SLE, lupus arthritis is often the presenting manifestation. Lupus arthritis is a polyarticular disease that predominantly affects the small joints of the hand; large-joint involvement is less common and could indicate another cause (such as osteoarthritis or avascular necrosis)[33,34]. Classically, pain in lupus arthritis is disproportionate to the level of swelling; this finding distinguishes lupus arthritis from

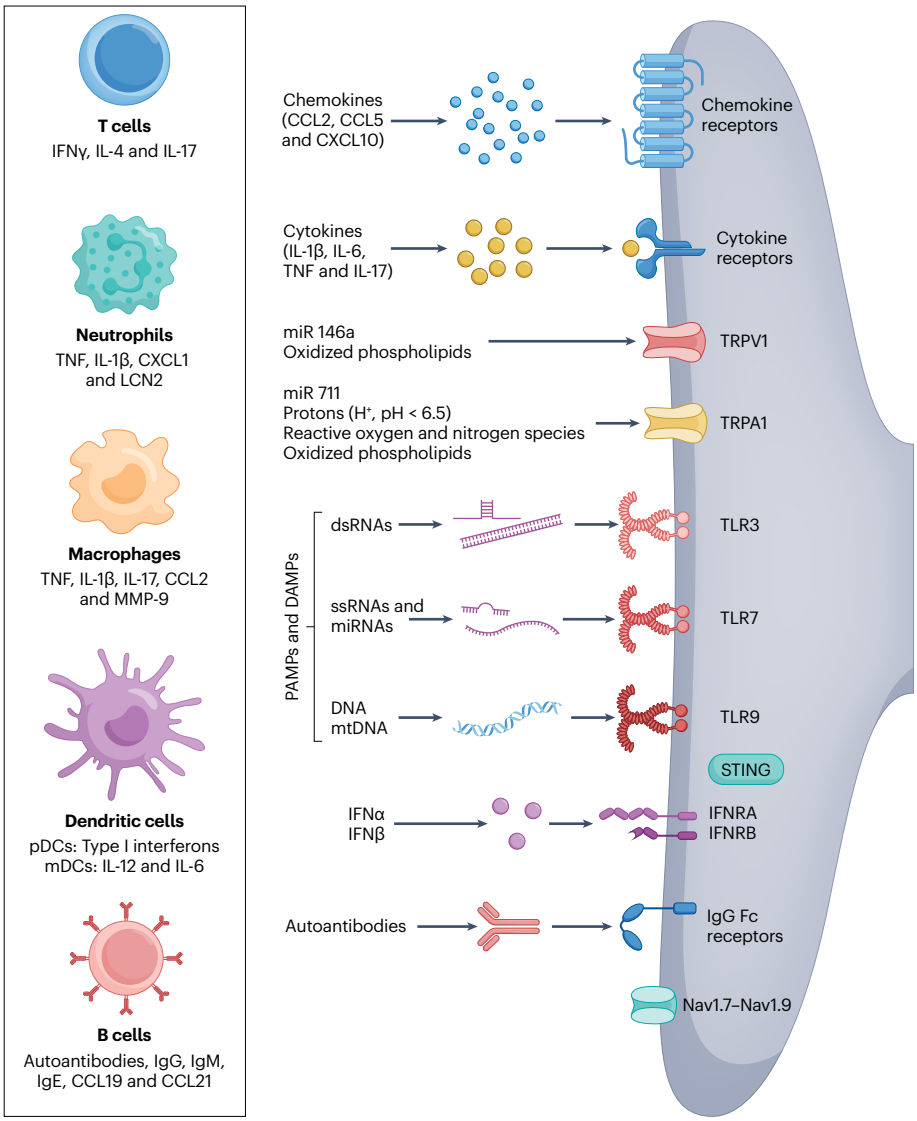

Fig. 2 | Immune system interactions with nociceptive neurons that underly pain in systemic lupus erythematosus. Pro-inflammatory mediators have a role in activating nociceptive neurons, including peripheral terminals, cell bodies and central terminals via interactions with cytokine receptors and chemokine receptors (such as G protein coupled receptors)[151]. Dendritic cells (DCs) consist of plasmacytoid DCs (pDCs), which produce type I interferons (IFNα and IFNβ) and myeloid DCs (mDCs), which also secrete cytokines. Type I IFN receptors (IFNRA and IFNRB) are highly expressed on primary sensory neurons, with their activation modulating physiological and pathological pain. Autoantibodies can form immune complexes that can localize to neurons, immune cells and satellite glial cells in the dorsal root ganglion (DRG), which activates sensory neurons via Fc receptors. RNA and DNA can serve as pathogen and danger-associated molecular patterns (PAMPs and DAMPs) that activate receptors (such as Toll-like receptors (TLRs) and the cGAS–STING pathway) on sensory neurons and immune cells. DAMPs can arise from various cell types and can be released or secreted from cells during processes that include inflammation, activation and cell death[152,153]. These activation events are linked to transient receptor potential (TRP) ion channels (TRPV1 and TRPA1), which transduce pain. TRPA1 and TRPV1 are also activated by reactive oxygen species, phospholipids and microRNAs (miRNAs). Voltage-gated sodium channels (including Nav1.7, Nav1.8 and Nav1.9) on nociceptive neurons regulate action potential conduction in axons and pain transmission. In peripheral sensitization, the activity of TRPA1, TRPV1 and Nav1.7–Nav1.9 is modulated by pro-inflammatory mediators. Itch (pruritus) occurs in SLE, resulting from the activation of itch receptors on sensory neurons (pruriceptors). dsRNAs, double-stranded RNA; LCN2, lipocalin 2; MMP, matrix metalloproteinases; mtDNA, mitochondrial DNA; ssRNAs, single-stranded RNA; STING, stimulator of interferon genes.

rheumatoid arthritis (RA), in which synovial proliferation (referred to as pannus) can be easily visible and palpable. In lupus arthritis, swelling is more subtle but nevertheless can be visualized using ultrasonography or MRI[34–36].

Although lupus arthritis and RA are both very painful, clinical and laboratory features of these conditions differ. Thus, lupus arthritis does not usually cause radiographic bone erosions although it can lead to deformity that results from damage to peri-articular structures[33]. Another difference between these two conditions relates to serological findings. In patients with lupus arthritis, rheumatoid factor is not usually detected. Rheumatoid factor is typically an IgM antibody that targets sites on IgG molecules, usually the Fc portion[37]. As rheumatoid factor probably arises in response to IgG immune complexes, the infrequent expression of rheumatoid factor in SLE is notable given the important role of immune complexes in SLE pathogenesis.

Lupus arthritis and RA also differ in the expression of antibodies that target post-translational modifications of proteins, of which citrullination is the most characteristic[38]. Citrullinated proteins can arise during inflammation and citrullinated histones are present in neutrophil extracellular traps (NETs). NETs, which are large aggregates of nuclear material, including DNA and proteins from neutrophil granules, are generated during cell death in a process known as NETosis[39]. With the exception of an overlapping condition called 'rhupus', anti-citrullinated protein antibodies (ACPAs) are usually not present in lupus arthritis, a curious finding because citrullinated histones, a target antigen of ACPAs, are nuclear molecules[40,41].

An important feature of RA that might be relevant to lupus arthritis is the role of autoantibodies in mediating pain. Transferring monoclonal ACPAs or ACPAs isolated from patients with seropositive RA (that is, people who are ACPA-positive) into mice can induce pain, even in the absence of overt inflammation[42,43]. Monoclonal ACPAs can also exert pro-nociceptive effects by inducing tenosynovitis, and activating osteoclasts to produce cytokines. Interestingly, individual ACPAs can differ in their effects on disease severity in animal models[44–46]. The effects of ACPAs and other autoantibodies might involve immune complexes that can interact with Fc receptors on neurons and subsequently modulate excitability, which links the nervous system and immune system in symptomatology[47]. As SLE is characterized by abundant immune complexes, a similar mechanism might occur in lupus arthritis, albeit involving different autoantibodies.

Along with inflammation and the direct action of autoantibodies and immune complexes on neuronal function, pain in RA might involve changes in synovial innervation, as indicated by the development of sensory nerve growth in regions of synovial hypertrophy[48,49]. In lupus arthritis, the source of pain remains unclear, partly owing to the lack of detailed histopathological studies and phenotypic analyses of cell populations in the synovium. Studies of gene expression in the RA synovium have documented distinct phenotypes characterized by lymphoid, myeloid and fibroblastic elements; the few studies of gene expression in lupus arthritis show a predominance of macrophages and cells of the myeloid lineage and a strong interferon gene signature[50,51]. Owing to the close proximity of cells of the immune system and nervous system, macrophages and other myeloid cells might intensify arthritis pain via the production of cytokines and other mediators that can alter pain processing.

Two other common sources of musculoskeletal pain are avascular necrosis (AVN) and degenerative arthritis[52]. AVN is an occlusive vasculopathy that leads to bone-cell death and extreme pain, perhaps related to structural bone collapse. This condition can arise from the pro-coagulant activities of anti-phospholipid antibodies that create a pro-thrombotic environment[53,54]. AVN is also an adverse effect of glucocorticoid therapy in SLE; glucocorticoids can increase marrow fat, which can elevate bone pressure and promote bone-cell death[55]. In SLE, AVN can occur in both small and large joints.

Fibromyalgia

Pain associated with fibromyalgia occurs frequently in the setting of inflammatory and non-inflammatory joint disease, can have a substantial effect on patient well-being and thus can influence reports of pain and other symptoms, necessitating its consideration in the assessment of pain in SLE[56]. In current terminology, fibromyalgia is a form of nociplastic pain and can be distinguished from nociceptive pain and neuropathic pain by underlying neural mechanisms[56,57]. Two key findings in fibromyalgia are hyperalgesia and allodynia. These symptoms arise from central and peripheral sensitization, which amplify pain[31,58]. In the musculoskeletal system, depending on the clinical condition, nociplastic pain can occur along with either nociceptive or neuropathic pain or both; for example, a patient with RA might have pain from joint inflammation (nociceptive pain) and fibromyalgia (nociplastic pain)[59]. Furthermore, central sensitization might influence the response to other, non-painful auditory, visual and tactile stimuli[60,61], which suggests that neural changes extend beyond nociception and represent a more general heightened state of responsiveness[62] (Box 1).

Data from studies using validated measures indicate that fibromyalgia can occur in as many as 30% of patients with SLE[63–65]. This frequency is higher than that of the general population, which suggests a close mechanistic relationship between fibromyalgia and SLE. Fibromyalgia can also occur in other autoimmune and inflammatory diseases and is often characterized as refractory, difficult-to-treat or treatment-resistant disease; the frequency of fibromyalgia in these conditions (such as RA) might be lower than in SLE[66].

Box 1 | Mechanisms of central sensitization

Numerous cellular mechanisms within the dorsal horn synapse contribute to the development of central sensitization[154]. These events include receptor phosphorylation, increased receptor trafficking to the synaptic membrane and enhanced activation of G-coupled receptors and calcitonin gene-related peptide receptors. Sensitization can also involve transcriptional changes that impart long-lasting strengthening of the synapses. Although these synaptic changes can enhance responses within nociceptive pathways, they also lead to synaptic changes that cause non-nociceptive peripheral neurons to contribute to the activation of pain circuits. In addition to the peripheral–central synapse-related mechanisms of central sensitization, more general changes to the function and structure of regions in the brain, brainstem and spinal cord can occur. These changes include altered functional relationships between regions of the central nervous system, altered structure of grey matter and white matter and changes in the levels and function of neurotransmitters, including glutamate, glycine, opioid, dopamine and serotoninergic systems. These changes can be observed through neuroimaging studies, which show changes that might contribute to chronic pain, fatigue and other comorbid symptoms, even in the absence of observed peripheral neuropathology[155].

The association of fibromyalgia with a variety of inflammatory and musculoskeletal diseases raises important questions about directionality. Thus, inflammatory joint disease might promote central sensitization; correspondingly, central sensitization might exacerbate symptomatology from joint inflammation. In this regard, an inflammatory or musculoskeletal disease can develop in a patient with pre-existing fibromyalgia (referred to as 'top down' sensitization) or other manifestations of chronic overlapping pain syndrome (including fibromyalgia, temporomandibular joint disorder, headache, low back pain and irritable bowel syndrome, all of which commonly coexist)[67]. Correspondingly, inflammation can lead to sensitization, which is referred to as 'bottom up' sensitization[68–70].

Interoception, a process that relates to the internal perception of the self and awareness of physiological processes such as heart rate and respiratory rate, is associated with fibromyalgia[71,72]. Interoception contrasts with exteroception, which involves sensations outside the body[73]. Disrupted interoception can cause aberrant sensing of bodily states; for example, fatigue might be perceived as more intense, and mood can be distorted[72]. A disturbed sense of self might, therefore, exacerbate symptomatology in fibromyalgia and in other related conditions[74].

In considering pain in SLE, the presence of fibromyalgia can complicate clinical assessments, as symptoms associated with lupus arthritis might be amplified by central sensitization. Furthermore, even in the absence of objective arthritis, patients with SLE and fibromyalgia might report musculoskeletal pain. Pain from fibromyalgia, however, is usually denoted as widespread as opposed to articular[56]. Alone or in combination with arthritis, fibromyalgia in SLE can lead to a high symptom burden, confound assessment of disease activity and complicate treatment decisions. In this regard, fibromyalgia can occur in association with other conditions known as chronic overlapping pain syndromes[67,75].

Although pain is a major symptom of fibromyalgia, the accompanying features of fatigue, mood disturbance and cognitive impairment are integral to the diagnosis of nociplastic pain[57]. Consistent with this relationship, a considerable percentage of all patients with SLE will have symptomatology that can impair quality of life as well as lead to the conclusion that their disease is inadequately treated and out of control.

Small-fibre neuropathy

In SLE, small-fibre neuropathy (SFN) can contribute to pain as it affects small-diameter myelinated Aδ fibres and unmyelinated C fibres. Although peripheral neuropathy is included as a manifestation of neuropsychiatric SLE in the ACR classification system, SFN is not[76]. The prevalence of SFN in SLE is similar to that of peripheral neuropathy in SLE, ranging from 13–38% and 5–32%, respectively[77–79].

In general, pain in SFN is often characterized as dysesthesia, with burning, prickling or itching. Allodynia, alterations in temperature sensation and autonomic dysfunction can also occur. As nerve conduction and electromyography studies are often normal in SFN, diagnosis usually requires analyses of skin biopsies to demonstrate a decreased density of epidermal nerve fibres[80]. Corneal confocal microscopy can serve as a non-invasive approach[81].

As highlighted in a 2019 meta-analysis, SFN is present in approximately 50% of patients with fibromyalgia, depending on the measure used for ascertainment[82]. The relationship between SFN and fibromyalgia is unclear. Although some studies have indicated an association of SFN with central sensitization and neuropathic pain[83], other studies have indicated that SFN and fibromyalgia differ in terms of the location of pain, pain characteristics and coexistent conditions[84,85]. Elucidating a relationship between SFN and pain in SLE will probably entail detailed clinical, neuropsychological and pathological studies.

Sickness behaviour

SLE is a state of heightened immune activity that itself can cause diverse symptomatology beyond local inflammation. This state is called 'sickness' and reflects the profound effects of immune system activation on the body, including the nervous system. Indeed, so-called 'sickness behaviour' is a common feature of many immune-mediated diseases, including SLE, and can involve symptoms such as fatigue, lassitude and mood change[86,87]. Sickness behaviour is also a well-recognized consequence of viral infection and can manifest as arthralgias, myalgias and tiredness. Therapeutic administration of cytokines can also lead to sickness behaviour; for example, administration of interferon for the treatment of hepatitis or multiple sclerosis causes adverse events such as fatigue and mood changes[88].

Sickness behaviour might also have a metabolic component that is related to energy shifts in the immune system during host defence. Inflammation requires energy and is associated with fluxes in both lymphoid and non-lymphoid populations, with decreased physical activity conserving energy. Thus, given the array of neuropsychological features (such as fatigue and mood change) that occur because of immune system activation, sickness behaviour can influence the expression of other signs and symptoms in SLE, implying that many symptoms could be influenced by immune system activation, although the precise mechanisms have not been fully delineated.

Other sources of pain in systemic lupus erythematosus

Pain characterizes other manifestations of SLE that can be considered as evidence of disease activity despite difficulty in obtaining objective evidence of inflammation. Indeed, the presence of these conditions is often based on patient reports as opposed to laboratory findings or imaging.

Serositis. Serositis or serosal inflammation can present as chest pain and can be accompanied by other symptoms such as fever. Two main forms of serositis are pleuritis and pericarditis[89]. In some patients, these conditions can be reliably diagnosed by imaging, but, not infrequently, serositis is diagnosed on the basis of the location and characteristics of the pain; for example, pleuritic pain is exacerbated by breathing.

Another site for serositis is the abdomen; serositis attributed to SLE might be considered the cause of peritoneal signs and symptoms after exclusion of other painful abdominal conditions (of which there are many), especially those that would require prompt surgical intervention; acute abdominal pain can also signal enteritis or vasculitis in SLE[90].

Headache. Headache is another painful condition that occurs commonly in SLE, although, depending on the type of headache, the frequency might not be greater than that of the general population. Studies, including meta-analyses, indicate that approximately 30% of patients with SLE might experience headaches, although the severity can vary[91]. So-called 'lupus headache' is considered evidence of disease activity in SLE. The characteristics of 'lupus headache' are not well defined, although headache attributable to SLE is usually considered severe and persistent, migrainous and poorly responsive to opioid therapy[91]. Imaging is usually unrevealing. Data from one study suggest that 'lupus headache' is rare and affects approximately 1.5% of patients with SLE[92].

Skin disease. Along with joint disease, skin disease is among the most common manifestations of SLE. Although descriptions of cutaneous lupus might not emphasize symptomatology, cutaneous lupus can cause severe pain and itching[93]. Unlike other manifestations of SLE, cutaneous disease can be objectively assessed, with analysis of biopsy-obtained skin samples showing immune-cell infiltration and immune deposits[94]. Similar to that in other inflammatory skin diseases, pain and itching can result from pro-inflammatory mediators such as IL-31, which can affect local neuronal cells[95,96]. In general, itching is mild in most patients with cutaneous lupus. The increased recognition of the frequency of pain and itching in cutaneous lupus is notable and suggests that assessing symptom burden can depend on asking patients the appropriate questions and their inclusion in patient-reported outcome measures.

Categorizing pain in systemic lupus erythematosus

This section discusses the categorization of pain in SLE according to a proposed model that divides symptoms according to their putative relationship to autoreactivity and inflammation. The importance of changes in nervous-system function will also be considered as these changes can influence the pain experience.

The type 1 and type 2 model of systemic lupus erythematosus

As this discussion indicates, pain is one of the most common and prominent manifestations of SLE and can be attributed to immune activation even in the absence of evidence of tissue inflammation from biopsies or traditional markers of disease activity. Furthermore, many patients with SLE have a clinical profile consistent with fibromyalgia, a condition that, as discussed previously, can produce a high symptom burden and intensify symptoms of other painful conditions. Complicating this situation further is the uncertainty in the diagnosis and treatment of widespread pain. Indeed, there is even controversy as to whether the diagnosis of fibromyalgia is a useful construct in the clinical arena as opposed to a spectrum of 'fibromyalgianess'[97,98].

The type 1 and type 2 model of SLE was proposed to help elucidate SLE symptomatology, improve patient assessment and foster better therapy by dividing the symptoms of SLE based on their putative relationship to inflammation and autoreactivity[5]. As such, this model represents a more encompassing view of symptomatology, which incorporates both objective measures and patient reports to improve communication between the patient and their health care provider and reduce the discordancy that can affect many clinical encounters. In short, the model divides manifestations of SLE into two broad categories: type 1 and type 2 SLE[5].

Type 1 manifestations

Type 1 SLE includes the major clinical manifestations that are represented in the criteria for classification and/or disease activity and are manifestations of classic immune-mediated inflammation. These manifestations include nephritis, arthritis, cutaneous disease, pleuritis and/or pericarditis and haematological manifestations[5]. Of these conditions, nephritis can be delineated most reliably and objectively, especially with renal histopathology. For other type 1 manifestations, additional clinical information might be needed to establish the relationship with inflammation and/or autoreactivity. For type 1 manifestations, currently available biomarkers and findings from physical examinations provide valuable adjunctive data for attribution, with levels of anti-DNA antibodies and complement serving as the main laboratory assessments for type 1 disease activity.

Type 2 manifestations

Type 2 manifestations differ from type 1 manifestations because, as symptoms, they are subjective and are based on patient reports (at least at present). Pain, fatigue, mood disturbance and cognitive impairment are the most notable type 2 manifestations, with pain a defining feature of this group[5]. These symptoms can resemble those of fibromyalgia and nociplastic pain, with measures of fibromyalgia providing a useful approach to diagnosing type 2 SLE[99]. Although overlap of type 2 symptoms is common (such as pain and fatigue), in individual patients, any can be the most bothersome and debilitating. Importantly, type 2 symptoms can occur in the presence or absence of classic signs of immune-mediated inflammation[100].

The type 1 and type 2 model of SLE is meant to categorize disease activity of patients with SLE and, therefore, is applicable only to patients who meet the ACR–EULAR or SLICC criteria for SLE. The model does not provide a basis for classification or diagnosis and is not intended to be used to diagnose SLE or lupus-like disease in a patient with fibromyalgia who is ANA positive, for example. The model does not extend the boundaries of SLE but rather works within existing boundaries.

Second, the model considers the full gamut of symptoms of SLE as at least potentially attributable to SLE. This aspect of attribution has the greatest importance with respect to nociplastic pain and related symptoms in the type 2 category. Although fibromyalgia can arise from different factors and can occur in isolation, in SLE, the type 1 and type 2 model posits that nociplastic pain and related symptoms can be characterized as a manifestation of SLE because of the prominence and frequent occurrence of fibromyalgia. This approach differs from current practice that would consider fibromyalgia-like symptoms in a patient with SLE as either secondary to SLE or an intercurrent process that might result from other mechanisms. As a group, similar to fibromyalgia, type 2 symptoms can be intensified by disturbances in interoception[71,72]. Type 2 SLE disease activity can be measured using various methods (Box 2).

Nociplasticity

As noted, current terminology in the field of pain medicine divides pain into three main types: nociceptive, neuropathic and nociplastic pain. Although pain is the cardinal feature of each type of pain, for nociplastic pain, the associated symptoms (such as fatigue) are defining features for diagnosis. The high frequency of type 2 symptoms in SLE (such as fatigue and cognitive impairment), prompted consideration of a new terminology, lupus-associated nociplasticity[6]. For this terminology, nociplasticity, rather than nociplastic pain, has been proposed to encompass a broader set of symptoms beyond just pain; the term also affirms the close link of fatigue and related symptoms to pain in this conceptualization. The term nociplasticity also echoes the term neuroplasticity in emphasizing nervous-system changes[6]. In this framework, the term nociplasticity provides a broader and more unified categorization of symptomatology than nociplastic pain and enables overlapping symptoms (such as pain, fatigue and mood changes) to be considered together as manifestations of neuronal change. The term nociplasticity also allows more parsimonious investigation of patient symptomatology by looking at common aetiologies of overlapping symptoms.

To date, the term nociplasticity has appeared in only a few places in the scientific literature[101], but its application to SLE symptomatology has value both practically and heuristically. Importantly, it enables one term to describe symptoms beyond just pain, thereby

Box 2 | Measures for assessing type 2 systemic lupus erythematosus

In the evaluation of pain in the clinical setting, both patient-reported and physician-reported measures can provide valuable information to determine the extent of type 2 system lupus erythematosus (SLE) disease activity. These measures can be used to assess the burden of type 2 SLE symptoms at a single clinic visit; they can also be used longitudinally to assess changes of symptoms over time as well as the response to therapy. For research purposes, these measures can identify those patients with low or high type 2 SLE disease activity cross-sectionally and longitudinally, enabling the characteristics and risk factors for type 2 SLE symptoms to be determined. Some of the most useful measures are described here.

The Polysymptomatic Distress Scale

The Polysymptomatic Distress Scale is a patient-reported outcome measure that includes the widespread pain index (WPI) and symptom severity score (SSS)[156,157]. The WPI is the sum of the scores of 19 areas of the body for which patients indicate pain in the past month. The SSS (which ranges from 0 to 12) asks patients to report the extent of fatigue, cognitive symptoms and waking unrefreshed over the past month according to the following scale: (0) no symptoms, (1) mild, (2) moderate and (3) severe. Additionally, patients can report headaches, pain or cramps in the lower abdomen or depression in the past 6 months. The total Polysymptomatic Distress Scale score combines the WPI and SSS (ranges from 0 to 31); a score ≥8 indicates moderate-to-severe polysymptomatic distress. A threshold of ≥8 has also been used to indicate high type 2 SLE disease activity[17,158].

PROMIS-29 profile

The PROMIS-29 short forms include four-item scales in the following domains: pain interference, physical function, social function, fatigue, sleep disturbance, depression and anxiety[159]. Raw scores can be uploaded to the HealthMeasures Scoring Service to obtain T-scores. A T-score of 50 is the reference population mean, with a standard deviation of 10. A 5-point difference (half standard deviation) is considered to be a clinically significant difference[158–160]. PROMIS-29 can be used to quantify the burden and effect of type 2 SLE symptoms. As studies have shown, patients with high type 2 SLE activity, with or without high type 1 SLE activity, have increased levels of pain interference and fatigue scores and reduced social and physical functioning scores compared with the general population[158].

36-item Short-Form Health Survey

The 36-item Short-Form Health Survey is a patient-reported outcome measure that quantifies health-related quality of life across eight domains: physical functioning, social functioning, physical role limitations, emotion role limitations, pain, mental health, vitality and general health perceptions. The 36-item Short-Form Health Survey has been used in a research study to identify type 2 SLE disease activity, which involved selecting 17 of the 36 items to measure widespread pain, fatigue and depression; for this analysis, a total score of ≥14 of these 17 items was used to indicate high type 2 SLE disease activity[161].

Type 2 Physician Global Assessment

The Type 2 Physician Global Assessment (PGA) was developed by rheumatologists at Duke University as a physician-reported measure of type 2 SLE activity[149]. The Type 2 PGA is scored on a scale ranging from 0, indicating no type 2 SLE activity, to 3, indicating severe type 2 SLE activity. Evaluation of the performance characteristics of the Type 2 PGA by rheumatologists indicated that the inter-rater and intra-rater reliability of the Type 2 PGA score was strong; the Type 2 PGA correlated positively with patient-reported outcome measures of polysymptomatic distress, fatigue, cognitive dysfunction, waking unrefreshed and forgetfulness. A Type 2 PGA score ≥1 is considered evidence of high type 2 SLE disease activity[162]. Similar to the PGA for type 1 SLE disease activity[163,164], a score of ≥1.5 indicates that a change in treatment or other recommendations should be considered.

Pain maps

Pain maps can also be a useful approach in evaluating pain as the number and location of regions with pain can help to delineate the presence of widespread pain[144,165]. In general, pain maps provide the image of a person with regions of posterior and anterior pain illustrated. Using manual or electronic means, the patient can indicate the regions that are painful. The number of regions that are assessed varies among pain maps; for example, the WPI includes 19 areas as the original use of this map was for fibromyalgia. Maps for other measures are more extensive and are especially useful for the evaluation of patients, such as chronic overlapping pain conditions[157,166,167].

avoiding a piece-meal approach to closely associated symptoms. As nociplastic pain can be a feature of other inflammatory conditions (such as RA and psoriatic arthritis), the term nociplasticity can be customized in a disease-specific manner[102]. Nevertheless, it is possible that nociplasticity might have more profound effects on patients with SLE than on those with other diseases because of the nature and confluence of the underlying immune dysregulation, which affects the nervous system.

Lessons from the type 1 and type 2 systemic lupus erythematosus model

Studies using the type 1 and 2 model of SLE have produced notable findings that have direct implications for understanding pain in SLE. First, patients with SLE are heterogenous with respect to the presence of type 1 and type 2 features and the activity of both can vary over time[99]. The patients at the extremes are of great interest (that is, individuals with predominant or exclusive type 1 or type 2 manifestations). A clinical profile of type 1 but not type 2 manifestations suggests that active autoimmune and/or inflammatory disease might not necessarily lead to substantial patient symptomatology and so-called 'sickness behaviour'[86,87]. Conversely, the type 2-predominant phenotype indicates that considerable nociplastic pain can be present even in the absence of obvious classic inflammatory disease. In this regard, type 2 symptoms can arise from damage (which might contribute to nociplastic pain), even when classic inflammatory disease is in remission[103].

The fact that some patients have a mixed type 1 and type 2 phenotype suggests that manifestations of one type might influence

expression of the other. Thus, patients with SLE who have mixed type 1 and type 2 disease activity might have painful inflammation (such as arthritis)[99]; however, because of coexistent type 2 disease, patient reports of the magnitude and intensity of these symptoms might be increased, which suggests even greater inflammatory activity[104]. This scenario could account for the classical observation that, in lupus arthritis, the extent of pain reported by patients can seem disproportionate to the physical findings. The mixed phenotype can also lead to an apparent lack of response to treatment with immunosuppressive and inflammatory agents since the nociplastic component might persist, even though the inflammatory manifestations have been reduced.

Finally, a concept that brings the type 1 and 2 model of SLE and nociplasticity together might simplify communication between patients and their physicians and reduce discordancy between how patients and physicians view disease activity, especially flare[105]. As shown in provocative studies, health care providers consider fibromyalgia to have low prestige and a low priority for treatment[106,107]. By contrast, SLE as well as other autoimmune and inflammatory diseases, have high prestige because of their potential to cause severe and permanent organ damage, sometimes rapidly. For patients with SLE, pain and related type 2 and nociplastic manifestations can be a top priority and should be viewed as having the same prestige as other manifestations marked by tissue inflammation and damage.

An integrated approach to pain in systemic lupus erythematosus

Many exciting developments in the science of pain have not yet been fully applied to SLE. A few examples of how the application of new developments in the understanding of pain could address unresolved issues in SLE will serve to highlight relevant considerations, especially those that could lead to substantial improvements in patient outcomes.

Neuroinflammation

Neuroinflammation defines the interplay between the immune system and nervous system and highlights the effects of pro-inflammatory mediators such as cytokines, PAMPS and DAMPs on the many cells of the nervous system, including neurons, glial cells and astrocytes[108,109]. These interactions can occur in both the central and peripheral nervous systems and have probably evolved as part of the host defence system to protect against foreign threats, for which the coordination between the nervous and immune systems is essential. In neuroinflammation, the classical signs of inflammation, such as cell infiltration, might not be apparent, despite the many downstream effects of inflammatory mediators on neuronal function[28,31].

As an alternative to the term neuroinflammation, the term neuroimmune dysfunction has been suggested, in view of the differences from canonical inflammation and neuroinflammation[6]. This term also emphasizes that immune mediators (such as cytokines) can cause nerve-cell dysfunction without obvious signs of inflammation. Whichever term is used, this concept is relevant to the symptomatology of SLE, as it highlights the many ways in which the immune system can alter the nervous system. Certainly, there is a large body of literature on the role of IL-1, IL-6, TNF and type I interferon in nervous-system processes, especially with regard to influences on mood[110,111]. As these cytokines, along with nucleic acid DAMPs, are elevated in SLE, the concept of neuroimmune dysfunction provides a way of unifying type 1 and type 2 manifestations as potentially related to immune activity, albeit by somewhat diverse mechanisms.

Disease classification and categorization

Nosology is an important aspect of scientific inquiry that enables the organization and interpretation of data for the development of diagnostic and classification categories or measures of disease activity. This type of categorization can help to explain disease to patients, guide treatment to include agents and approaches that are directed at pain and inflammation, and can also be used to highlight commonalities among diseases. For example, symptoms that have been identified as type 2 manifestations in SLE can also be observed in other inflammatory diseases. Although arthritis has been a focus of attention in RA, studies also indicate that patients have increased frequency of fatigue, mood disturbance and even cognitive impairment compared with the general population[112,113].

The term nociplasticity is a term that can encompass all of the symptoms experienced by the patient, without excluding the role of other aetiologies; each patient can experience differences in the magnitude of each of these symptoms and their associated effects[6]. As research on SLE moves forward, it seems reasonable that studies on pain would include more quantitative measures of the other symptoms; the same approach would be true for fatigue. The use of the term nociplasticity could also be of value in the clinic to promote communication with patients and establish the full range of type 2 symptoms as a treatment goal.

Depending on further study and the development of criteria for its determination, the term nociplasticity might be used as a descriptor for symptoms in patients with SLE and potentially other immune-mediated conditions. This term might also provide a framework for mechanistic studies to underpin the search for biomarkers.

Antibody-mediated pain

Studies of other diseases over the past few years have provided convincing evidence of the role of autoantibodies in pain modulation. The role of antibody-mediated pain was first productively explored in the setting of neuropathic pain, whereby nerve injury in both male and female mice could induce the production of pro-nociceptive IgG[47]. The IgG accumulates in the lumbar region, including within the DRG. The pro-nociceptive properties of IgG are further supported by findings that interventions aimed at reducing IgG production or accumulation, such as B cell depletion or blocking the neonatal Fc receptor, attenuate hypersensitivity following nerve injury[47,114–116].

Evidence indicates that a substantial proportion of patients with severe fibromyalgia have autoantibodies that can elicit pain-like responses (such as mechanical and thermal hypersensitivity) when transferred into mice[117,118]. In addition, in these studies, sensory nerve fibres, including C fibres and Aδ fibres, showed increased responsiveness to mechanical stimuli; small nerve fibre density in the skin was also reduced. Antibodies from patients with fibromyalgia can also bind to stellate glial cells in tissue sections of mouse and human DRG, with binding intensity correlating with pain severity reported by the patient[119–121].

Although the molecular targets of these antibodies have not yet been identified, their presence in the blood of patients with fibromyalgia suggests a novel pathway by which pain could arise in autoimmunity. Importantly, serum antibodies from patients with fibromyalgia can also transfer fatigue-like behaviour to mice[96]. As discussed, administration of monoclonal ACPAs to patients can elicit pain, suggesting that pain-inducing antibodies might vary in their activity depending on antibody specificity as well as formation of immune complexes. The presence of pain-inducing antibodies has not yet been identified in

Glossary

Allodynia
A condition in which ordinarily non-painful stimuli (such as touch) elicit pain.

Central nervous system sensitization
A key feature of nociplastic pain. This form of sensitization involves changes in the processing of pain information at multiple levels in the nervous system and leads to pain amplification.

Dysesthesia
An unusual sensation that is elicited by touch and can be experienced as unpleasant or strange. Dysesthesia can be described as burning, tingling or pins and needles among other sensations.

Fibromyalgia
A form of nociplastic pain characterized by widespread pain in association with symptoms such as fatigue, mood disturbances and cognitive impairment. Fibromyalgia can occur alone or in association with nociceptive and/or neuropathic pain from another disease process. Fibromyalgia involves pain amplification that arises from central nervous system sensitization.

Hyperalgesia
A manifestation of pain amplification in which a stimulus elicits more pain than expected from the intensity of the stimulus.

Lupus-associated nociplasticity
A condition in which central sensitization leads to amplification of pain and other symptoms, most prominently fatigue, mood disturbance and cognitive impairment. The term builds upon the terminology of nociplastic pain but is not confined only to pain.

Neuropathic pain
A form of pain that results from nerve injury or dysfunction.

Neuropsychiatric SLE
An array of neurological and psychological manifestations that can affect all levels of the nervous system in patients with systemic lupus erythematosus (ranging from mood disturbance to transverse myelitis). Determining the cause of these manifestations is key and often involves testing to determine whether the condition can be explained by another process (such as adverse effects of medication).

Nociceptive pain
A form of pain that results from stimulation of nociceptors by noxious stimuli. Nociceptive pain has a protective function.

Nociplastic pain
A form of pain that occurs in the absence of inflammation or other evidence of tissue injury. Nociplastic pain arises from changes in pain processing at various levels, is chronic and lacks an apparent protective function.

Nosology
A branch of medical science involved with the classification of disease. This classification can be based on cause, pathogenesis or symptoms.

Peripheral nervous system sensitization
This form of sensitization alters the sensitivity of the peripheral nervous system to noxious stimuli. This process involves changes in the activation threshold of nociceptive neurons and therefore increased signalling.

Peripheral neuropathy
Damage or injury to peripheral nerves (that is, nerves outside of the CNS) that can arise from a wide variety of causes including inflammatory, metabolic and degenerative processes. Symptoms depend on the nerves affected and can involve disturbances of sensory and motor function and autonomic dysfunction.

Serositis
Inflammation of serosal surfaces such as the pleura or pericardium. Serositis can be experienced as painful and can occur in association with symptoms such as fever. Serositis can be visualized using imaging (such as radiography or ultrasonography), although it can be inferred from characteristic symptoms.

Sickness behaviour
An array of symptoms such as weakness, fatigue and malaise that can arise in response to infection, systemic inflammation or the administration of cytokine therapies. Sickness behaviour might promote host defence by influencing energy fluxes and expenditure necessary to mount an immune response.

Small-fibre neuropathy
A form of peripheral neuropathy that affects the small-fibre nerves, both myelinated and unmyelinated, involved with the sensation of skin and other organs.

SLE but is an exciting area of future investigation. The demonstration of antibody-mediated pain has important implications for treatment of fibromyalgia and disease-related nociplasticity (in many clinical settings, including SLE), especially in light of new approaches such as chimeric antigen receptor T cells that might more effectively eliminate antibody-producing cells than current agents[7,122]. In this regard, it will be important to determine if the autoantibodies that mediate pain can also mediate other aspects of nociplasticity (such as fatigue and cognitive impairment) in SLE and in other autoimmune and inflammatory diseases in which nociplasticity can occur.

Emerging evidence suggests that autoantibodies in SLE can affect neural function. Antibodies that target the *N*-methyl-D-aspartate (NMDA) receptor can elicit major neuropsychological effects in mice, especially when administered intracerebrally. These antibodies bind to the GluN2A and GluN2B subunits of the NMDA receptor to potentiate signalling by glutamate and induce excitotoxic cell death. Following cell death, microglia activation can lead to synaptic changes in the surviving neurons in the brain. As entry of the antibodies into the brain requires disruption of the blood–brain barrier, the clinical manifestations depend on the manner in which the barrier is disrupted, leading to behavioural or cognitive changes[123,124]. Interestingly, these antibodies can cross-react with DNA, linking neuropsychological findings in SLE with ANA expression[125,126].

Imaging

An important limitation in studying nociplasticity in humans is the paucity of validated biomarkers, whether for research or clinical purposes. To help identify and validate biomarkers, the analysis of central nervous system pathways and regions (including the brain, the brainstem and the spinal cord) by using functional MRI can help to identify mechanistic changes that correlate with symptomatology, pointing to aberrant 'rewiring' of brain circuitry[127–129].

Current data on brain imaging of patients with SLE indicate a variety of functional changes[130]. Given the range of neuropsychiatric

findings in patients with SLE, linking the observed changes in neural circuitry with specific symptoms is currently challenging. Functional MRI findings have been associated with fatigue in multiple sclerosis and RA[131,132], which supports the use of this approach in creating a dataset across autoimmune and inflammatory diseases that identifies common pathways for type 2 SLE symptoms as different reflections of nociplasticity.

Genetics, epigenetics and genomics

Many studies have investigated the association between genetic risk factors and pain, with examples of single-gene systems in humans that can alter pain intensity[133,134]; for example, mutations in the gene for the voltage-gated sodium channel Nav 1.7 are associated with painful neuropathy[135]. In addition, patterns of gene expression and epigenetic modification that are associated with different pain types in humans and animals have been identified[136,137]. Although the heterogeneity of pain patterns in SLE complicates biomarker identification, a preliminary 'bookend' study on patients with type 1 and type 2 SLE did find genomic signatures that were associated with each symptom category[100]. The ability to subset patients with SLE on the basis of genetic or genomic markers is quickly advancing, but, to be insightful, biomarker analysis must be combined with detailed clinical phenotyping to determine patterns associated with pain; however, genomic subsetting might also provide mechanistic understanding of clinical features that vary from patient to patient[138]. In this regard, increasingly powerful and sophisticated informatics methods can enable the analysis of large data sets from different diseases that are characterized by pain to determine common mechanisms[139].

Box 3 | Biopsychosocial influences on pain

Pain is a complex symptom that, by definition, involves a sensory and emotional experience that is perceived as unpleasant; other descriptors (such as aversive and distressing) might also be informative because, for many patients, pain is much more serious than implied by the word unpleasant[168]. By nature, pain is subjective and personal and differs from nociception, as pain can occur without direct stimulation of nociceptive pathways. Furthermore, for a given stimulus, the level of reported pain by individuals can be highly variable[22]. Together, these considerations suggest that pain as a symptom can be better understood in the context of the individual patient (such as someone with SLE) by incorporating the influence of other factors (including an emotional component) that can influence the experience of pain[169,170]. This approach forms the basis of the biopsychosocial model[24,171]. This model encompasses three factor types: biological, psychological and social. Biological factors include genetics, disease severity, inflammation and neural function. Psychological factors include mood (such as depression and anxiety), stress, catastrophic thinking and coping. Social factors are many and inter-related and include socio-economic status, social support and social learning. The different factors can interact with each other and bidirectionality is possible, as chronic pain can lead to mood changes whereas socio-environmental factors can lead to psychological stress[24,172]. In the context of SLE, these factors can also alter the course of disease because fragmented care and insurance status, for example, are associated with worse clinical outcomes in lupus nephritis[173]. In assessing pain in SLE, the biopsychosocial model focuses on the value of exploring more fully the various factors that can influence the pain experience and, to the greatest extent possible, develop targeted interventions; these interventions can address mood, sleep, interpersonal stress and social support, among other factors[174].

Sex and gender

The role of sex and gender in pain is a very complicated subject because of the many factors (genetic, hormonal and psychosocial) that influence biological responses[22,140]. Although studies in rheumatology have focused on sex as a risk factor for autoimmune and inflammatory disease, studies of host defence have highlighted that women have a more robust immune response to infection and vaccination[141]. In this scenario, autoimmunity is a complication of an immune system poised to respond to infection. Given the interplay between the nervous and immune systems, however, an increase in pain responsiveness could be a further manifestation of the heightened immune system activity observed in women.

As SLE overwhelmingly affects women, few studies have had adequate numbers of men to determine differences between men and women in pain and pain-related symptoms. Available data nevertheless suggest that, overall, men and women with SLE have a similar disease course, although men might accrue damage more quickly than women[142,143]. Furthermore, in some studies, men have a lower frequency of musculoskeletal disease than women, whereas women report higher levels of pain than men; men and women with SLE might differ in the number of regions identified as painful as well as the regions affected[142–144]. These studies also indicate that women experience greater cognitive impairment than men. Thus, sex might influence the development of pain and other manifestations of nociplasticity, but larger studies are needed to better understand the role of sex and gender in SLE.

Treatment

Owing to the heterogeneity and variability of SLE and the interplay of type 1 and type 2 manifestations, a personalized and multimodal treatment approach will probably improve outcomes. In implementing such an approach, assessment of the extent of both type 1 and type 2 disease activity is essential to avoid treating type 2 disease activity as type 1 disease activity and inadequately treating those patients with type 2 manifestations. At present, there are many clinical measures that can be used for assessment of type 2 manifestations that can be readily incorporated into routine clinical care (Box 2).

As in the case of fibromyalgia and other nociplastic pain conditions, treatment involves a variety of non-pharmacological and pharmacological interventions[145–147]. Non-pharmacological approaches include exercise, cognitive behavioural therapy and stress reduction. Depending on the patient, psychosocial interventions might also be important (Box 3). Pharmacological approaches for nociplastic pain conditions typically include anti-depressants, serotonin reuptake inhibitors and anticonvulsants. Some immunosuppressive medications might also have analgesic effects because of their actions on signalling pathways in neural tissues (such as baricitinib)[49]. As antibodies might have a role in promoting pain in SLE, strategies to reduce B cells or decrease antibody levels might also reduce pain (such as rituximab, belimumab or mycophenolate mofetil)[148]. Expanding the assessment of both type 1 and type 2 SLE manifestations will therefore be of value in understanding the impact of current as well as future therapies. Such an effort would involve using outcome measures that enable the

assessment of the activity both type 1 and type 2 SLE. These measures include those used for fibromyalgia and a global assessment tool that has been developed for type 2 SLE[149].

Conclusion

Pain is one of the most prominent and debilitating symptoms of SLE and reflects the complex interplay of the nervous system and immune system, a process known as neuroinflammation or neuroimmune dysfunction. Many patients with SLE have fibromyalgia, which is characterized as nociplastic pain and is associated with fatigue, cognitive impairment and mood change resulting from central and peripheral sensitization; the term nociplasticity has previously been proposed to encompass these symptoms because of their frequent coexistence. The division of symptoms into two categories (type 1 and type 2) provides a framework to promote holistic and personalized care, as well as scientific investigation. In this framework, type 1 symptoms are classic manifestations of autoimmunity, whereas type 2 symptoms include pain and pain-related symptoms that derive from nociplasticity. In view of the powerful tools of immunology, neurobiology and pain medicine, we believe that the use of these constructs can improve patient care and lead to new therapies that provide more comprehensive and effective management of the symptoms of SLE.

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