Editorial introduction

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

SECTION EDITOR

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Diagnostic delay in axial spondyloarthritis – a past or current problem?

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Purpose of review
To evaluate recent data on diagnostic delay in axial spondyloarthritis (axSpA), factors affecting the delay, potential ways of early diagnosis improvement, and risks associated with early diagnostic approaches.

Recent findings
Although axSpA can be diagnosed nowadays within the first months after symptom onset, the diagnostic delay remains with several years still remarkably high in many parts of the world. Female gender, human leukocyte antigen-B27 negativity, and younger age at disease onset are among factors associated with a delayed referral to a rheumatologist and consequently with a larger diagnostic delay. Early referral algorithms are helpful in the identification of patients with a high probability of axSpA among patients with chronic back pain. A careful diagnostic evaluation with correct imaging interpretation is required to avoid misdiagnosis of axSpA in patients with unspecific back pain.

Summary
The diagnostic delay is still considerable in axSpA. The ways to early diagnosis in axSpA are well defined. Imaging findings should always be considered in the clinical context to avoid axSpA misdiagnosis.

Keywords
ankylosing spondylitis, axial spondyloarthritis, diagnosis, diagnostic delay

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease from the group of spondyloarthritides affecting primarily the axial skeleton – sacroiliac joints and spine [1]. Depending on the presence or absence of the definite radiographic sacroiliitis (>=grade 2 bilaterally or >=grade 3 unilaterally according to the grading system of the modified New York criteria [2]) axSpA is classified as radiographic (also termed ankylosing spondylitis – AS) or nonradiographic, respectively [3]. AxSpA is associated with the presence of the human leukocyte antigen (HLA)-B27 (in approx. 80–95% in the Caucasian population) and can manifest with peripheral musculoskeletal (arthritis, enthesitis, or dactylitis) or extra-musculoskeletal (acute anterior uveitis, psoriasis, inflammatory bowel disease) features [1]. The disease usually starts in the third or fourth life decade; onset after 50 years of age is very rare [1].

The hallmark of axSpA is back pain caused by inflammation in the sacroiliac joints and/or spine. Back pain is typically localized in the lower back and/or in the buttocks and is long-lasting. Back pain that is present for 3 months and longer is called chronic back pain. Back pain associated with axSpA typically has characteristics of so-called inflammatory back pain: slow onset, improvement with exercises, no improvement with rest, night pain, morning stiffness for >30 min, alternating buttock pain. Importantly, the presence of inflammatory back pain does not automatically mean the presence of an inflammatory origin, i.e., of axSpA; inflammatory back pain can be found in patients with mechanical, degenerative diseases of the spine and sacroiliac joints [4].

Imaging for the detection of inflammatory/post-inflammatory changes in the axial skeleton has been a cornerstone of the diagnosis of axSpA already for many years. Radiographic evidence of sacroiliac

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KEY POINTS

- We still face the problem of a large diagnostic delay (several years) in axial spondyloarthritis, although there is a substantial geographic variability.
- Early referral of patients with suspicion of axial spondyloarthritis to a rheumatologist and an appropriate diagnostic workup are the keys to a timely diagnosis.
- The increased risk of overdiagnosis is a potential downside of the early recognition programs that can be overcome by the application of an appropriate diagnostic approach.

joints involvement (definite radiographic sacroiliitis) is not only a part of the classification criteria for AS and axSpA but still an important part of the diagnostic approach [5]. Structural damage development in sacroiliac joints and spine takes months to years to develop – this was a natural reason for the diagnostic delay in the 1980s and early 1990s. With the introduction of magnetic resonance imaging (MRI) in the diagnostic and classification approaches in axSpA, early detection of inflammatory changes in the axial skeleton became possible bringing the opportunity of shortening the diagnostic delay in axSpA.

Why is a timely diagnosis of axSpA important? Short symptom duration has been consistently shown as a predictor of good response to anti-inflammatory treatment (most of the data is available for tumor necrosis factor – blockers) [6–8]. Furthermore, early initiation of effective anti-inflammatory treatment is likely to be able to prevent or retard development of the structural damage in the spine – one of the main factors determining the long-term outcome of axSpA [9].

In this review, we discuss the current diagnostic delay in axSpA, reasons for a late diagnosis, ways to improve the early diagnosis, and potential downsides of early recognition programs in axSpA.

How long is the diagnostic delay in axial spondyloarthritis today?

The diagnostic delay is usually defined as the time between the onset of first symptoms (back pain in axSpA) and the time-point of the diagnosis. In the vast majority of cases, the date of the back pain onset cannot be verified and researchers rely on the patient-reported date of onset that is associated with the risk of a recall bias. In any case, it should be attempted to differentiate between nonspecific back pain that is very common in the population and back pain caused by axSpA that is typically chronic and has inflammatory characteristics.

Two decades ago, Feldtkeller *et al.* reported a diagnostic delay of about 9 years in patients with AS that was calculated from a survey completed by 1080 members of the German and Austrian patient organizations [10]. A recent analysis based on a patient survey linked to insurance claims data in 1677 patients with a confirmed diagnosis on axSpA/AS showed a mean diagnostic delay of 5.7 years (median of 2.3 years), however, without a clear declining trend in the last two decades [11] that could have been expected after introduction of the axSpA concept, axSpA classification criteria [3] and conduction of trails focussing on the nonradiographic axSpA population. A similar conclusion came out from a study conducted in the UK, which included 1193 patients with physician-verified diagnosis axSpA. Sykes *et al*. identified a mean diagnostic delay of 8.5 years (median of 5.0 years) without a trend for reduction in the last years [12]. In the PROSpA study conducted in the USA, the diagnostic delay was with approximately 14 years even longer [13]. A recent analysis from the European Map of Ankylosing Spondylitis project [14] that included 2652 patients from 13 European countries with a self-reported diagnosis of axSpA/AS showed a mean diagnostic delay of 7.4 years with substantial variation across countries – Fig. 1 [15]. A recent meta-analysis of the diagnostic delay included a total of 64 studies from different countries around the world (most of them – from Europe). The mean diagnostic delay was 6.7 in this analysis with a high level of heterogeneity – Fig. 1 [16▪▪]. Again, no improvement over time was observed. Remarkably, high-income countries exhibited a longer diagnostic delay than middle-income countries [16▪▪] that might be related, however, to the fact that severe cases are recognized relatively quickly, whereas less severe cases might require longer until diagnosis in the high-income countries but could remain undiagnosed at all in lower-income countries.

What are the reasons for a long diagnostic delay in axial spondyloarthritis?

Three decades ago the definite diagnosis of axSpA/AS could only be established based on the detection of structural damage in the sacroiliac joints and/or in the spine on the plain radiographs. With modern imaging techniques (especially MRI) allowing for the detection of active inflammation, the diagnosis of axSpA can be potentially established immediately after disease onset. Despite that, establishing the diagnosis still might take years as discussed above. Many factors affect the diagnostic delay. In some

FIGURE 1. Mean diagnostic delay in axial spondyloarthritis/ankylosing spondylitis in years reported between 2010 and 2020 in different countries around the world [15,16▪▪].

cases, nonpersisting mild symptoms at the beginning of the diseases might be considered as not sufficient enough to consult a doctor, but in many cases, the delay is related to the healthcare system. It should be stressed, however, that the timely diagnosis within the first months after disease onset is desirable but not critical in all patients with axSpA. In cases with persistent high inflammatory activity (as reflected by elevated C-reactive protein and by active inflammation on MRI of the sacroiliac joints and spine – risk factors for structural damage development [9]), the early diagnosis is required to start effective anti-inflammatory treatment. At the same time, in patients with the low level of inflammation, low level of symptoms, and nonprogressive disease course, the role of early diagnosis in the improvement of the long-term disease outcome is less clear and requires further investigations.

Back pain is very common in the general population; according to the recent data from the German national cohort study, 23% of the general population (aged 20–75) suffers or suffered in the past from chronic back pain (duration >=3 months) [17]. With the anticipated prevalence of axSpA of about 1% in the general population, axSpA would be responsible for only 4–5% of the cases of chronic back pain in the general population. Thus, the vast majority of chronic back pain cases are related to other, non-inflammatory (degenerative, mechanic) causes. This represents one of the major challenges – how to identify patients with a high probability of axSpA among patients with back pain?

Back pain patients are normally evaluated first by general practitioners but also by other healthcare professionals dealing with back pain: orthopaedists, neurologists, and nonphysician specialists such as physiotherapists and chiropractors. Thus, lack of awareness of axSpA as a potential reason for back pain on this level would be one of the first hurdles on the way to the early diagnosis bringing patients from one specialist to another one. The number of healthcare professionals visited was independently associated with a longer diagnostic delay in a recent pan-European study [15].

Several studies showed consistently that HLA-B27-negativity and female gender are associated with a longer diagnostic delay [11,15,16▪▪]. The absence of other SpA-features such as peripheral and extra-musculoskeletal manifestations was also found to be associated with a longer diagnostic delay in a few studies [15], although the presence of psoriasis was associated with a longer diagnostic delay in a recent work [11] that might be related to the impact of psoriasis has on the disease phenotype. In addition, young age at back pain onset [11,16▪▪] was associated with a longer diagnostic

delay in some studies that might be related to not taking seriously back pain in young persons by both patients and physicians. Further studies addressing patients' journey before axSpA diagnosis are needed to determine the exact role of the factors described above.

How can the early recognition of axial spondyloarthritis be improved?

Overall, it seems that an increase of the awareness among healthcare professionals about the possibility of inflammatory disease as a reason for chronic back pain is the leading way to bring patients with axSpA to appropriate specialists (in most cases – to a rheumatologist) promptly. How can this be achieved? We have to offer to nonrheumatology specialists a simple tool based on 'red flags' indicating a high probability of axSpA in a patient with chronic back pain. Limiting the age of back pain onset to 45 years or less seems to be important here given the epidemiological data on the axSpA onset (typically between 20 and 40 as discussed above). However, this combination (chronic back pain + onset before 45 years of age) would be still too frequent in the general population [17] to be used as a referral strategy. Most likely, a combination of these entry criteria with at least one additional parameter typical for SpA should be requested. This is also reflected in the Assessment of Spondyloarthritis International Society (ASAS) recommendations on the identification and referral of patients with a high probability of axSpA by nonrheumatology specialists [18] that demand the presence of chronic back pain + onset before 45 years of age + at least one additional feature suggestive of SpA (e.g., inflammatory back pain, HLA-B27, peripheral or extra-musculoskeletal manifestation). Several strategies more or less compatible with this recommendation have been proposed and evaluated in the last years [18–23]. Remarkably, all these strategies perform similarly well increasing the probability of axSpA from 5% (expected prevalence of axSpA among unselected patients with back pain) to 30–40% [18] meaning that the rheumatologist would need to see 2–3 patients to identify one with axSpA. In any case, a good referral strategy should be easy to apply and should take into account the local situation including both referral practices and particular SpA characteristics in the region. For instance, the strategy that is being applied already for more than 15 years in Berlin demanding the presence of chronic back pain that started before 45 years of age plus inflammatory back pain or HLA-B27 positivity or sacroiliitis on imaging [24] might not be applicable in areas where the association with HLA-B27 is known to be low (e.g., Arab countries) or where imaging is normally not performed or not available at the primary care level. A universal strategy that could be applicable everywhere in the world could be chronic back pain + age at the onset before 45 + inflammatory characteristics of back pain.

Importantly, although the ASAS recommendation for early referral addresses nonrheumatology specialists, it should be actively offered by rheumatologists with the intention of the improvement or shaping the referral pathway. We do hope that the application of early referral strategies is able to shorten the diagnostic delay in axSpA, the formal proof of such an effect is still to be demonstrated. Furthermore, despite the fact that early treatment is associated with a better treatment response as outlined above and is likely to prevent/retard structural damage progression, the association between earlier diagnosis and better long-term outcome has not been shown so far.

Recently, we investigated the possibility of self-screening and self-referral of patients with chronic back pain to a rheumatologist using an online screening tool (https://www.bechterew-check.de/). Patients who reported chronic back pain with onset before before 45 years of age plus at least one additional SpA feature (inflammatory back pain features, good response to nonsteroidal anti-inflammatory drugs, enthisitic or articular pain with swelling, HLA-B27 positivity, elevated acute phase reactants, history of psoriasis, inflammatory bowel disease or uveitis, family history of SpA and related disorders) were evaluated in a specialized SpA center. Those results were compared to the performance of the physician-based referral using the above-described Berlin referral rule. In the end, about 20% of the patients in the online screening group received the diagnosis of SpA (as compared to 40% in the physician-referred group) [25▪] that is certainly better than 5% in unselected chronic back patients but substantially worse than the physician-based pathway. We concluded, therefore, that the online-based screening algorithms can be used in specialized centers and for the general awareness increase but the focus of early referral activities should be certainly on physicians primarily seeing patients with back pain.

What are the potential downsides of early recognition programs in axial spondyloarthritis?

Early diagnosis of any diseases always implies a careful exclusion of other potential reasons for patient complaints. This is especially true for axSpA – the probability of non-inflammatory

reasons is always higher than the probability of axSpA in patients with back pain. Rheumatologists seeing patients with chronic back pain and short symptom duration (a few months) cannot rely on the presence of structural damage in the sacroiliac joints on X-rays that is usually absent at the early disease stage and often needs MRI to confirm or to exclude the presence of inflammatory affection of the axial skeleton [26▪]. The presence or absence of MRI changes often drives the diagnostic decision in one or another direction. Especially important in this context the potential for overdiagnosis of axSpA (potentially resulting in overtreatment) because of the presence of unspecific, mechanically induced bone marrow edema in the sacroiliac joints and/or spine. In the last years, there have been several works showing that bone marrow edema in the sacroiliac joints resembling bone marrow edema in axSpA can be observed in joggers, hockey players [27], postpartum women [28], patients with osteitis condensans ilii [29] and other mechanical/degenerative conditions and even in healthy subjects [30]. Most recently, a population-based study reported the prevalence of MRI changes suggestive of axSpA in apparently healthy subjects aged <45. Bone marrow edema in sacroiliac joints and spine was detected in 17.2% and in 27.5% of the cases [31▪] suggesting that MRI changes in the sacroiliac joints have overall higher specificity (about 83%) as compared to the spine (about 72%) for the diagnosis of axSpA. It is important to stress that the MRI – being one of the most powerful diagnostic tools for axSpA in the hand of the rheumatologists – should not play the all-decisive role and imaging findings should always be considered in the context of other findings including other reasons for back pain and changes seeing in the image.

CONCLUSION

The diagnostic delay in axSpA is still considerable in many parts of the world. Late referral to a rheumatologist is one of the leading factors resulting in a late diagnosis. Early identification of patients with a high probability of axSpA among patients with chronic back pain and appropriate diagnostic workup including imaging are keys to the timely diagnosis of axSpA.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

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

1. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet 2017; 390:73–84.
2. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984; 27:361–368.
3. Rudwaleit M, van der Heijde D, Landewe R, *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009; 68:777–783.
4. Poddubnyy D, Callhoff J, Spiller I, *et al.* Diagnostic accuracy of inflammatory back pain for axial spondyloarthritis in rheumatological care. RMD Open 2018; 4:e000825.
5. Mandl P, Navarro-Compan V, Terslev L, *et al.* EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. Ann Rheum Dis 2015; 74:1327–1339.
6. Rudwaleit M, Listing J, Brandt J, *et al.* Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. Ann Rheum Dis 2004; 63:665–670.
7. Sieper J, Lenaerts J, Wollenhaupt J, *et al.* Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1. Ann Rheum Dis 2014; 73:101–107.
8. Sieper J, van der Heijde D, Dougados M, *et al.* Efficacy and safety of adalimumab in patients with nonradiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis 2013; 72:815–822.
9. Poddubnyy D, Sieper J. Mechanism of new bone formation in axial spondyloarthritis. Curr Rheumatol Rep 2017; 19:55.
10. Feldtkeller E, Bruckel J, Khan MA. Scientific contributions of ankylosing spondylitis patient advocacy groups. Curr Opin Rheumatol 2000; 12:239–247.
11. Redeker I, Callhoff J, Hoffmann F, *et al.* Determinants of diagnostic delay in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data. Rheumatology 2019; 58:1634–1638.
12. Sykes MP, Doll H, Sengupta R, Gaffney K. Delay to diagnosis in axial spondyloarthritis: are we improving in the UK? Rheumatology 2015; 54:2283–2284.
13. Deodhar A, Mease PJ, Reveille JD, *et al.* Frequency of axial spondyloarthritis diagnosis among patients seen by US rheumatologists for evaluation of chronic back pain. Arthritis Rheumatol 2016; 68:1669–1676.
14. Garrido-Cumbrera M, Poddubnyy D, Gossec L, *et al.* The European map of axial spondyloarthritis: capturing the patient perspective-an analysis of 2846 patients across 13 countries. Curr Rheumatol Rep 2019; 21:19.
15. Garrido-Cumbrera M, Navarro-Compán V, Bundy C, *et al.* Identification of Parameters Associated with a Diagnostic Delay in Axial Spondyloarthritis: Results from the European Map of Axial Spondyloarthritis (EMAS). Arthritis Rheumatol 2020; 72(suppl 10)Abstract 1865.
16. ▪▪ Zhao SS, Pittam B, Harrison NL, *et al.* Diagnostic delay in axial spondyloarthritis: a systematic review and meta-analysis. Rheumatology 2021; 60:1620–1628.
A recent meta-analysis of the diagnostic delay in axSpA
17. Schmidt CO, Gunther KP, Goronzy J, *et al.* [Frequencies of musculoskeletal symptoms and disorders in the population-based German National Cohort (GNC)]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2020; 63:415–425.
18. Poddubnyy D, van Tubergen A, Landewe R, *et al.* Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis. Ann Rheum Dis 2015; 74:1483–1487.
19. Baraliakos X, Tsiami S, Redeker I, *et al.* Early recognition of patients with axial spondyloarthritis-evaluation of referral strategies in primary care. Rheumatology 2020; 59:3845–3852.
20. Brandt HC, Spiller I, Song IH, *et al.* Performance of referral recommendations in patients with chronic back pain and suspected axial spondyloarthritis. Ann Rheum Dis 2007; 66:1479–1484.
21. Braun A, Gnann H, Saracbasi E, *et al.* Optimizing the identification of patients with axial spondyloarthritis in primary care–the case for a two-step strategy combining the most relevant clinical items with HLA B27. Rheumatology 2013; 52:1418–1424.

22. Poddubnyy D, Vahldiek J, Spiller I, *et al.* Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care. J Rheumatol 2011; 38:2452–2460.
23. van Hoeven L, Vergouwe Y, de Buck PD, *et al.* External validation of a referral rule for axial spondyloarthritis in primary care patients with chronic low back Pain. PloS One 2015; 10:e0131963.
24. Sieper J, Rudwaleit M. Early referral recommendations for ankylosing spondylitis (including preradiographic and radiographic forms) in primary care. Ann Rheum Dis 2005; 64:659–663.
25. Proft F, Spiller L, Redeker I, *et al.* Comparison of an online self-referral tool
■ with a physician-based referral strategy for early recognition of patients with a high probability of axial spa. Semin Arthritis Rheum 2020; 50:1015–1021.

Comparison of online screening and physician-based referral tools for early identification of patients with high probability axSpA

26. Poddubnyy D. Classification vs diagnostic criteria: the challenge of diagnos-
■ ing axial spondyloarthritis. Rheumatology 2020; 59:iv6–iv17.

A critical appraisal of the diagnostic approach in axSpA and differences to a classification approach

27. Weber U, Jurik AG, Zejden A, *et al.* Frequency and anatomic distribution of magnetic resonance imaging features in the sacroiliac joints of young athletes: exploring 'Background Noise' toward a data-driven definition of sacroiliitis in early spondyloarthritis. Arthritis Rheumatol 2018; 70:736–745.
28. Hoballah A, Lukas C, Leplat C, *et al.* MRI of sacroiliac joints for the diagnosis of axial SpA: prevalence of inflammatory and structural lesions in nulliparous, early postpartum and late postpartum women. Ann Rheum Dis 2020; 79:1063–1069.
29. Poddubnyy D, Weineck H, Diekhoff T, *et al.* Clinical and imaging characteristics of osteitis condensans ilii as compared with axial spondyloarthritis. Rheumatology 2020; 59:3798–3806.
30. de Winter J, de Hooge M, van de Sande M, *et al.* Magnetic Resonance Imaging of the Sacroiliac Joints Indicating Sacroiliitis According to the Assessment of SpondyloArthritis international Society Definition in Healthy Individuals, Runners, and Women With Postpartum Back Pain. Arthritis Rheumatol 2018; 70:1042–1048.
31. Baraliakos X, Richter A, Feldmann D, *et al.* Frequency of MRI changes suggestive of axial spondyloarthritis in the axial skeleton in a large population-based
■ cohort of individuals aged <45 years. Ann Rheum Dis 2020; 79:186–192.

Important data on the prevalence of MRI changes suggestive of SpA in the general populations

Educational needs and challenges in axial spondyloarthritis

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Purpose of review
Axial spondyloarthritis (axSpA) affects 0.5–1% of the population in many regions of the world. This review summarizes the challenges in medical education around axSpA with attention to evidence around delayed diagnosis, clinician familiarity with typical axSpA features, such as inflammatory back pain and adherence to accepted management principles.

Recent findings
Clinicians who commonly manage patients with chronic back pain or other typical axSpA features are not consistently aware of the concept of inflammatory back pain and common extra-spinal manifestations. Further, clinicians may not be familiar with the nonradiographic spectrum of axSpA. Management of patients with possible axSpA does not consistently follow principles that would establish an axSpA diagnosis, and diagnosis of axSpA remains delayed by 6–7 years on average, with evidence suggesting management disparities on the basis of sex and race in some cases. Referral recommendations have increased the probability of axSpA diagnosis up to about 40% and, may complement educational efforts in axSpA.

Summary
Educational efforts in axSpA should focus on providing front-line clinicians with a better understanding of inflammatory back pain, the nonradiographic form of axSpA, and accepted principles in axSpA management.

Keywords
axial spondyloarthritis, diagnostic delay, education, referral strategies

INTRODUCTION

Recent developments in axial spondyloarthritis (axSpA) have advanced our understanding of this complex disease. AxSpA is a spectrum of clinically related conditions that encompasses radiographic axSpA (r-axSpA; formerly called ankylosing spondylitis) and the more recently defined nonradiographic axial spondyloarthritis (nr-axSpA). Although an ankylosing spondylitis is established through clinical findings and sacroiliac joint X-ray, nr-axSpA is diagnosed based on clinical grounds and a normal X-ray with or without evidence of sacroiliitis on MRI [1].

The prevalence of axSpA differs geographically depending on multiple factors (e.g. HLA-B27 risk allele prevalence and race). The 2010 National Health and Nutrition Examination Survey (NHANES) estimated that, in the United States, axSpA prevalence is 1.4%, and r-axSpA specifically has a prevalence of 0.55% [2]. Without effective treatment, up to 40% of those with nr-axSpA progress to the radiographic form over 10 years [3]. Those with r-axSpA are at risk for syndesmophyte formation elsewhere in the spine, which results in reduced mobility and function.

Over the past two decades, major discoveries in SpA pathogenic mechanisms have led to the introduction of new treatment modalities, specifically those that target the TNF, IL-17/IL-23, and Janus Kinase pathways [4,5]. In addition to the benefits of medications in controlling pain and disease activity, both observational and trial data suggests that

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KEY POINTS

- Diagnostic delay in axial spondyloarthritis remains 6–7 years, and likely reflects under-recognition by clinicians.
- Many front-line nonrheumatologist clinicians who commonly manage patients with chronic back pain or other typical axial spondyloarthritis features lack familiarity with the concepts of inflammatory back pain and the nonradiographic spectrum of spondyloarthritis.
- Medical education should be enhanced around axial spondyloarthritis, and healthcare systems should implement referral rules as a complement to education.

tumor necrosis factor (TNF) inhibitors, especially with early and prolonged use, may halt or at least slow radiographic progression [6–8]. Limited data suggests that radiographic progression is also diminished with secukinumab [9].

Given advances in identifying axSpA, and the effects of therapies in both controlling symptoms and preventing radiographic progression, it is imperative that those with axSpA are identified and treated early. However, some aspects of axSpA management remain suboptimal, and therefore, form the basis for an educational agenda, which we will outline here.

THE ICEBERG PHENOMENON: THE GAP BETWEEN THE EXPECTED AND REPORTED PREVALENCE OF AXIAL SPONDYLOARTHRITIS

Low back pain is extremely common among adults [10,11]. Inflammatory back pain (IBP), the cardinal feature of axSpA is characterized by morning stiffness, improvement with NSAIDs and exercise, and worsening with rest. Although IBP is classically associated with axSpA, the presence of IBP alone is insufficient to establish an axSpA diagnosis. According to the NHANES survey, IBP was present in 5–6% of United States adults, whereas spondyloarthritis prevalence was estimated at 0.4–1.4% [12–14]. However, observational data have shown a much lower prevalence of diagnosed axSpA; data from the Northern California Kaiser Permanente group reported the prevalence axSpA was only 0.2%, with an ankylosing spondylitis prevalence of 0.1% [15]. Although the discrepancy between the estimated and observed prevalence of axSpA may be partly explained by study methods and/or geographical differences, this gap also raises concern for under-recognition of axSpA by clinicians. As with any disease state, some affected people will remain undiagnosed as they do not seek medical care, either as they perceive pain/stiffness as 'normal', or because symptoms remit spontaneously or with over-the-counter NSAIDs and or exercise [16]. However, as management of axSpA also targets radiographic progression and comorbidities, it is critical that people with axSpA are identified and diagnosed early in order to optimize disease outcomes.

CLINICIAN AWARENESS OF INFLAMMATORY BACK PAIN AND THE AXIAL SPONDYLOARTHRITIS SPECTRUM IS LIMITED OUTSIDE OF RHEUMATOLOGY

Patients with chronic back pain often seek care from primary care physicians or general practitioners, osteopathic physicians, pain specialists, chiropractors or physical therapists. However, patients with axSpA may also present with extra-articular features, such as psoriasis, inflammatory bowel disease, or uveitis, prompting evaluation by a dermatologist, gastroenterologist or ophthalmologist. Therefore, it is prudent for clinicians within each of these specialties to be familiar with axSpA.

Unfortunately, data suggests that among general practitioners and clinicians who commonly manage back pain, knowledge of the axSpA spectrum and IBP features is poor. A study of general practitioners found that only 60% were aware that there was a difference between a mechanical and inflammatory back pain pattern [17]. Another study reported that only 5% of the primary care physicians were able to identify all features of IBP or the four key symptoms suggestive of IBP [20]. Familiarity with IBP was better among chiropractors and osteopaths, but still imperfect with 23% reporting lack of confidence with the concept of IBP [18].

Studies of nonrheumatologist clinicians who commonly evaluate back pain patients showed that although ankylosing spondylitis is well recognized and understood, the terms 'axial spondyloarthritis' and 'nonradiographic' were less well known [18–20]. For example, 75% of chiropractors and osteopaths were not familiar with nonradiographic axSpA in a 2019 study [20]. Further, accuracy in axSpA diagnosis and adherence to management guidelines is variable [21,22]. A retrospective study showed that the majority of patients diagnosed with ankylosing spondylitis (63%) were diagnosed by a nonrheumatologist clinician rather than a rheumatologist. Of such patients, only 42% were found to have ankylosing spondylitis on a subsequent rheumatology evaluation [23]. Further, a survey of primary care physician (PCP) and specialists identified inconsistencies in the perceptions and approach to the

diagnosis and management of axSpA, including infrequently checking HLA-B27 among patients with IBP and lack of awareness about axSpA treatments [19,20]. More than 20% thought that diagnosis of ankylosing spondylitis was a challenge and unmet need amongst PCPs [19].

Poor awareness of axSpA and its key features is highlighted by the prolonged average time to axSpA diagnosis, which is a problem globally. As one example, a United States-based study reported an average of 14 years delay between the onset of symptoms and axSpA diagnosis [24]. Other studies suggested an average of 10 years delay, with axSpA tending to have longer diagnostic delay than psoriatic arthritis or rheumatoid arthritis [25–27]. Recently, Redeker *et al.* [28▪] examined health insurance data from Germany, and reported a mean diagnostic delay of 6–7 years, from 1996 to 2015. Unfortunately, diagnostic delay was not reduced over time.

Taken together, the continued long diagnostic delay and gaps in axSpA knowledge among clinicians who are likely to encounter axSpA patients highlights need for improved education in axSpA among clinicians from multiple disciplines, and likely throughout their careers as scientific advances in pathophysiology and axSpA management continue to evolve.

DISPARITIES IN BACK PAIN AND AXIAL SPONDYLOARTHRITIS MANAGEMENT

Beyond the diagnostic delay that exists generally for axSpA diagnosis, there is concern that further disparities may exist based on patient demographic factors (e.g. sex, educational level, race/ethnicity) or based on other factors influencing access to healthcare (e.g. health insurance, location of residence).

AxSpA has historically been thought to be more common in male individuals compared with female individuals by a ratio of 2–3 : 1; however, this ratio is now known to be approximately 1 : 1. Although recognition of axSpA has increased in female patients, women are still under recognized and have higher average disease activity and reduced quality of life relative to men [29]. Female patients have a significant longer delay in diagnosis (8.8 versus 6.5 years), and persistent clinician bias about axSpA being predominantly a male disease is a contributing factor [30]. Additionally, differing disease presentations, slower radiographic progression and lower response rates to established therapies should serve as a focus of educational strategies to improve management of axSpA in female patients [31].

Data also suggests disparities in management based on patient race/ethnicity. Literature on back pain more generally, has shown that despite back pain severity and interference being greater among black and Hispanic Americans, members of these groups are less likely to be evaluated with advanced imaging, less likely to be referred for physical therapy and less likely to be prescribed opioid analgesics than whites [32–37]. Although the association of race and disease outcomes may be partly related to socioeconomic factors, a statistical analysis adjusting for each of these factors found that race was independently associated with back pain severity and interference [38]. This raises concern that clinicians may underrecognize or under-appreciate the significance and burden of back pain in nonwhite patients.

A recent study by Singh and Magrey demonstrates that disparities in back pain management may also hold true in management of axSpA. This study, using data from a large United States-based informatics platform, found that black Americans with axSpA had greater disease activity and comorbidity burden than whites with axSpA [39▪]. Although there may be true race-based differences in axSpA manifestations, another explanation is that clinicians missed axSpA diagnoses more commonly among blacks with mild symptoms than among whites with mild symptoms. One reason for these findings may be the central role of HLA-B27 in classification criteria and its relatively lower prevalence of HLA-B27 among black and Hispanic Americans [40]. However, given racial disparities in back pain management more generally, Singh and Magrey's finding demonstrate a need to ensure that educational efforts in axSpA apply diagnostic and management principles equitably across racial and ethnic groups.

STRATEGIES TO IMPROVE RECOGNITION OF AXIAL SPONDYLOARTHRITIS

As the diagnostic delay in axSpA remains a major challenge, several studies have examined strategies to prompt appropriate referral of patients with an increased probability of axSpA to rheumatologists.

The evidence for formal educational in axSpA is limited. Standardized patient cases simulating axSpA improved referral rates among general practice residents (+71% education group versus +15% control group). Authors of this study recommended such education in combination with a clinician referral tool targeted at SpA [41].

The majority of data around clinician education on axSpA has assessed the effects of various referral strategies in clinical practice. Referral strategies in axSpA have generally focused on patients with chronic back pain (Table 1). It is necessary for referral strategies to have both high sensitivity and

Table 1. Studies examining referral strategies for axial spondyloarthritis

Study: First author, publication year	IBP as a referral criterion	HLA-B27 positivity	Sacroiliitis on imaging	Axial SpA diagnosis	Number of participants	Location(s)	Ref.
Brandt, 2007	52.9%	51.7%	35.1%	45.4%	350	Germany	[42]
Hermann, 2009	90%	80%	–	33%	92	Austria	[43]
Braun, 2011	100%	30%	–	35.1%	322	Germany	[44]
Poddubnyy, 2011 (strategy 1)	78%	44.7%	55.7%	41.8%	318	Germany	[45]
Sieper, 2013 (strategy 1)	93.2%	27.8%	52.3%	35.6%	504	Multinational	[46]
Juanola, 2013 (strategy 1)	100%	11.7%	8.3%	25.4%	60	Spain	[47]
Haroon, 2015 (AAU patients)	62%	54%	–	40%	72	Ireland	[48]
van Hoeven, 2015	100% LBP 33.3% IBP	6.2%	–	16.4%	579	Netherlands	[49]
Deodhar, 2016	94%	49%	100%	46.8%	751	USA	[24]
Proft, 2020	56.1% 56.9%	21.6% 59.8%	–	19.4% 39.2%	180 OSR 181 BRT	Germany	[50▪]

AAU, acute anterior uveitis; BRT, Berlin physician-based referral tool; IBP, inflammatory back pain; LBP, low back pain; OSR, online self-referral tool; strategy 1: patients have to meet the criteria of chronic back pain (>3 months in duration) with an early age of onset (<45 years), in addition to at least one of the following: inflammatory back pain, HLA B27 positivity and sacroiliitis on imaging, in order to be referred to a rheumatologist.

specificity, such that axSpA cases are not missed, and that rheumatology practices are not overburdened with evaluation of back pain patients. Although, strictly speaking, referral strategies are not education, incorporating a referral tool into a clinical practice workflow or electronic health record, serves as a reminder to busy clinicians to consider axSpA among patients who meet referral criteria.

The majority of studies on referral strategies have been done in Europe using varying definitions of IBP or components of IBP. Studies by Poddubnyy and Sieper (MASTER and RADAR) both included referral arms based on IBP, HLA-B27, NSAID response and family history of SpA; finding that the referral strategies resulted in axSpA diagnoses among about 40% of referred patients, a marked increase beyond the 5% expected probability of axSpA among those with chronic back pain [2,45,46]. Although it was expected that these simple referral strategies would be applicable across geographic locales, similar rules resulted in axSpA diagnoses among 33% of those referred in Hong Kong, and 16% of those referred from primary care providers in the Netherlands [49,51].

In 2015, the Assessment of SpondyloArthritis international Society (ASAS) published recommendations for referral of patients with a suspicion of axSpA, including those with chronic back pain with a young age of onset, and at least one additional axSpA feature or parameter [52]. Whenever referral strategies were tested in observational axSpA cohorts, there was no strategy that combined high sensitivity and specificity, and it was recommended that the ideal strategy may vary by geographic region, depending on prevalence of each referral parameter [53].

More recently, a study by Proft and colleagues in Germany evaluated a self-referral tool and found that 19% of patients who were self-referred using the online tool were subsequently diagnosed with axSpA. This proportion was lower than the 39% diagnosed with axSpA in the physician-based referral program, but still above the expected 5% prevalence of axSpA [50▪].

There is limited data on the performance of referral strategies in the Americas. Deodhar *et al.'* study in the United States suggested that it is effective for front-line clinicians to refer patients with chronic back pain for at least 3 months beginning at age less than 45 years, and the presence of at least one of three SpA features, as this strategy resulted in axSpA diagnosis among 47% of those referred (specificity of 79% and sensitivity of 81%) [24].

Beyond chronic back pain populations, Dublin Uveitis Evaluation Too (DUET) is an Irish cohort that aimed to select patients with acute anterior uveitis (AAU) that might benefit from an evaluation by a rheumatologist [48]. Approximately 40% of the AAU patients referred were subsequently diagnosed with axSpA [48].

Despite the fact that most of the tested referral strategies have increased the probability of early detection of axSpA, none of them have resulted in axSpA diagnosis in more than 50% of those referred. Given limitations in the Rheumatology workforce, it is necessary to continue to refine referral recommendations as a complement to broader medical education initiatives in axSpA. However, there are several key gaps in our understanding of the effects

of educational interventions in axSpA beyond the context of referrals, and whether educational interventions benefit patient outcomes. It is not known if different intervention strategies are more effective than others in improving clinician knowledge. Finally, it remains unknown if a specific group of healthcare providers should be the focus of educational efforts in terms of efficiency, and optimizing axSpA patient outcomes.

CONCLUSION

Education on axSpA should be enhanced among healthcare providers globally. The evidence for this need lies in the continued years-long diagnostic delay for axSpA, which causes many patients to miss the 'window of opportunity' to treat axSpA early and prevent radiographic progression, functional limitations, and disability that comes with advanced disease. Clinicians across many disciplines are unfamiliar with the concepts of IBP and nonradiographic disease and there is variable application of accepted management principles.

Education in axSpA should be improved, given that axSpA prevalence is estimated at 0.5–1% in many locales, and that back pain is highly prevalent across the world. Outreach needs to target clinicians who care for patients with chronic back pain or other typical axSpA features. Education needs to highlight equitable implementation of management principles and referral recommendations, including application within groups in which axSpA may have been historically underrecognized. Clinicians need to have periodic educational updates as the scientific knowledge in axSpA continues to advance.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

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

- ■ of special interest
- ■■ of outstanding interest

1. Rudwaleit M, Landewe R, van der Heijde D, *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis 2009; 68:770–776.
2. Reveille JD, Weisman MH. The epidemiology of back pain, axial spondyloarthritis and HLA-B27 in the United States. Am J Med Sci 2013; 345:431–436.
3. Protopopov M, Poddubnyy D. Radiographic progression in nonradiographic axial spondyloarthritis. Expert Rev Clin Immunol 2018; 14:525–533.
4. Ward MM, Deodhar A, Gensler LS, *et al.* 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Rheumatol 2019; 71:1599–1613.
5. van der Heijde D, Song IH, Pangan AL, *et al.* Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. Lancet 2019; 394:2108–2117.
6. Haroon N, Inman RD, Learch TJ, *et al.* The impact of tumor necrosis factor α inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum 2013; 65:2645–2654.
7. van der Heijde D, Baraliakos X, Hermann K-GA, *et al.* Limited radiographic progression and sustained reductions in MRI inflammation in patients with axial spondyloarthritis: 4-year imaging outcomes from the RAPID-axSpA phase III randomised trial. Ann Rheum Dis 2018; 77:699–705.
8. Karmacharya P, Duarte-Garcia A, Dubreuil M, *et al.* Effect of therapy on radiographic progression in axial spondyloarthritis: a systematic review and meta-analysis. Arthritis Rheumatol 2020; 72:733–749.
9. Braun J, Baraliakos X, Deodhar A, *et al.* Secukinumab shows sustained efficacy and low structural progression in ankylosing spondylitis: 4-year results from the MEASURE 1 study. Rheumatology (Oxford) 2019; 58:859–868.
10. Deyo RA, Mirza SK, Martin BI. Back pain prevalence and visit rates: estimates from US national surveys. Spine 2006; 31:2724–2727.
11. Hoy D, Bain C, Williams G, *et al.* A systematic review of the global prevalence of low back pain. Arthritis Rheum 2012; 64:2028–2037.
12. Weisman MH, Witter JP, Reveille JD. The prevalence of inflammatory back pain: population-based estimates from the US National Health and Nutrition Examination Survey, 2009-10. Ann Rheum Dis 2013; 72:369–373.
13. Lawrence RC, Felson DT, Helmick CG, *et al.* Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. Arthritis Rheum 2008; 58:26–35.
14. Reveille JD. Epidemiology of spondyloarthritis in North America. Am J Med Sci 2011; 341:284–286.
15. Curtis JR, Harrold LR, Asgari MM, *et al.* Diagnostic prevalence of ankylosing spondylitis using computerized healthcare data, 1996 to 2009: underrecognition in a US healthcare setting. Permanent J 2016; 20:15–151.
16. Garg N, van den Bosch F, Deodhar A. The concept of spondyloarthritis: where are we now? Best Pract Res Clin Rheumatol 2014; 28:663–672.
17. van Onna M, Gorter S, van Meerendonk A, van Tubergen A. General practitioners' perceptions of their ability to identify and refer patients with suspected axial spondyloarthritis: a qualitative study. J Rheumatol 2014; 41:897–901.
18. Yong CY, Hamilton J, Benepal J, *et al.* Awareness of axial spondyloarthritis among chiropractors and osteopaths: findings from a UK Web-based survey. Rheumatol Adv Pract 2019; 3:rkz034.
19. Jois RN, Macgregor AJ, Gaffney K. Recognition of inflammatory back pain and ankylosing spondylitis in primary care. Rheumatology 2008; 47:1364–1366.
20. Mathieson HR, Merashli M, Gaffney K, Marzo-Ortega H; BRITSpA (British Society for Spondyloarthritis). Poor awareness of inflammatory back pain and axial spondyloarthritis among secondary care specialists. Clin Rheumatol 2016; 35:2627–2628.
21. Hurwitz EL, Li D, Guillen J, *et al.* Variations in patterns of utilization and charges for the care of low back pain in North Carolina, 2000 to 2009: a statewide claims' data analysis. J Manipulative Physiol Ther 2016; 39:252–262.
22. Shmagel A, Foley R, Ibrahim H. Epidemiology of chronic low back pain in US adults: data from the 2009–2010 National Health and Nutrition Examination Survey. Arthritis Care Res (Hoboken) 2016; 68:1688–1694.
23. Deodhar A, Mittal M, Reilly P, *et al.* Ankylosing spondylitis diagnosis in US patients with back pain: identifying providers involved and factors associated with rheumatology referral delay. Clin Rheumatol 2016; 35:1769–1776.
24. Deodhar A, Mease PJ, Reveille JD, *et al.* Frequency of axial spondyloarthritis diagnosis among patients seen by us rheumatologists for evaluation of chronic back pain. Arthritis Rheumatol 2016; 68:1669–1676.
25. Sieper J, van der Heijde D, Dougados M, *et al.* Efficacy and safety of adalimumab in patients with nonradiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis 2013; 72:815–822.
26. Kiltz U, Baraliakos X, Karakostas P, *et al.* The degree of spinal inflammation is similar in patients with axial spondyloarthritis who report high or low levels of disease activity: a cohort study. Ann Rheum Dis 2012; 71:1207–1211.
27. Sørensen J, Hetland ML. Diagnostic delay in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: results from the Danish Nationwide DANBIO Registry. Ann Rheum Dis 2015; 74:e12–e112.
28. ■ Redeker I, Callhoff J, Hoffmann F, *et al.* Determinants of diagnostic delay in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data. Rheumatology (Oxford) 2019; 58:1634–1638.

Diagnostic delay in axSpA remains 6–7 years and did not improve in the latter time period

29. Baumberger H, Khan MA. SAT0417 Gradual progressive change to equal prevalence of ankylosing spondylitis among males and females in Switzerland: data from the Swiss ankylosing spondylitis society (SVMB). Ann Rheum Dis 2017; 76:929.
30. Slobodin G, Reyhan I, Avshovich N, *et al.* Recently diagnosed axial spondyloarthritis: gender differences and factors related to delay in diagnosis. Clin Rheumatol 2011; 30:1075–1080.
31. Rusman T, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender differences in axial spondyloarthritis: women are not so lucky. Curr Rheumatol Rep 2018; 20:1–12.
32. Kohns DJ, Haig AJ, Uren B, *et al.* Clinical predictors of the medical interventions provided to patients with low back pain in the emergency department. J Back Musculoskelet Rehabil 2018; 31:197–204.
33. Milani CJ, Rundell S, Jarvik JG, *et al.* Associations of race and ethnicity with patient-reported outcomes and healthcare utilization among older adults initiating a new episode of care for back pain. Spine 2018; 43:1007.
34. Ly DP. Racial and ethnic disparities in the evaluation and management of pain in the outpatient setting. Pain Med 2019; 20:223–232.
35. Stokes A, Berry KM, Hempstead K, *et al.* Trends in prescription analgesic use among adults with musculoskeletal conditions in the United States. JAMA network open 2019; 2:e1917228–e11917228.
36. Karran EL, Grant AR, Moseley GL. Low back pain and the social determinants of health: a systematic review and narrative synthesis. Pain 2020; 161:2476–2493.
37. King C, Liu X. Racial and ethnic disparities in opioid use among US adults with back pain. Spine 2020; 45:1062–1066.
38. Aroke EN, Jackson P, Overstreet DS, *et al.* Race, social status, and depressive symptoms: a moderated mediation analysis of chronic low back pain interference and severity. Clin J Pain 2020; 36:658–666.
39. Singh DK, Magrey MN. Racial differences in clinical features and comorbidities in ankylosing spondylitis in the United States. J Rheumatol 2020; 47:835–838.

■ This study used data from a large United States-based informatics platform and found that black Americans with axSpA had greater disease activity and comorbidity burden than whites with axSpA.

40. Karmacharya P, Balls-Berry JE, Davis JM. True difference or detection bias: racial differences in clinical features and comorbidities in ankylosing spondylitis in the United States. J Rheumatol 2020; 47:1150–11150.
41. van Onna M, Gorter S, Maiburg B, Waagenaar G. A. vT. Education improves referral of patients suspected of having spondyloarthritis by general practitioners: a study with unannounced standardised patients in daily practice. RMD Open 2015; 1:e000152.
42. Brandt HC, Spiller I, Song IH, *et al.* Performance of referral recommendations in patients with chronic back pain and suspected axial spondyloarthritis. Ann Rheum Dis 2007; 66:1479–1484.
43. Hermann J, Giessauf H, Schaffler G, *et al.* Early spondyloarthritis: usefulness of clinical screening. Rheumatology (Oxford) 2009; 48:812–816.
44. Braun A, Saracbasi E, Grifka J, *et al.* Identifying patients with axial spondyloarthritis in primary care: how useful are items indicative of inflammatory back pain? Ann Rheum Dis 2011; 70:1782–1787.
45. Poddubnyy D, Vahldiek J, Spiller I, *et al.* Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care. J Rheumatol 2011; 38:2452–2460.
46. Sieper J, Srinivasan S, Zamani O, *et al.* Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study. Ann Rheum Dis 2013; 72:1621–1627.
47. Juanola X, Fernandez-Sueiro JL, Torre-Alonso JC, *et al.* Comparison of 2 referral strategies for the diagnosis of axial spondyloarthritis in Spain. The RADAR study. Reumatol Clin 2013; 9:348–352.
48. Haroon M, O'Rourke M, Ramasamy P, *et al.* A novel evidence-based detection of undiagnosed spondyloarthritis in patients presenting with acute anterior uveitis: the DUET (Dublin Uveitis Evaluation Tool). Ann Rheum Dis 2015; 74:1990–1995.
49. van Hoeven L, Vergouwe Y, de Buck PD, *et al.* External validation of a referral rule for axial spondyloarthritis in primary care patients with chronic low back pain. PLoS One 2015; 10:e0131963.
50. Proft F, Spiller L, Redeker I, *et al.* Comparison of an online self-referral tool with a physician-based referral strategy for early recognition of patients with a high probability of axial SpA. Semin Arthritis Rheum 2020; 50:1015–1021.

■ An online self-referral tool for patients resulted in axSpA diagnosis among 19% of patients. Clinician referral and patient self-referral strategies had different performances.

51. Mok CC, Tam LS, Leung MH, *et al.,* Hong Kong Society of Rheumatology. Referral strategy for early recognition of axial spondyloarthritis: consensus recommendations from the Hong Kong Society of Rheumatology. Int J Rheum Dis 2013; 16:500–508.
52. Poddubnyy D, van Tubergen A, Landewe R, *et al.,* Assessment of SpondyloArthritis international Society. Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis. Ann Rheum Dis 2015; 74:1483–1487.
53. Abawi O, van den Berg R, van der Heijde D, van Gaalen FA. Evaluation of multiple referral strategies for axial spondyloarthritis in the SPondyloArthritis Caught Early (SPACE) cohort. RMD Open 2017; 3:e000389.

Inflammatory back pain: a concept, not a diagnosis

Fiona Louise Coath and Karl Gaffney

Purpose of review
The concept of inflammatory back pain (IBP) describes a cohort of patients with chronic back pain (CBP) who have distinct clinical characteristics, rather than being a diagnosis in and of itself. IBP is a common and important feature of axial spondyloarthritis (axSpA) but this is not the only differential. This review examines the utility of IBP in both primary and secondary care settings.

Recent findings
There are a number of suggested referral strategies for patients with suspected axSpA that include IBP. These strategies attempt to strike a balance between ensuring potential axSpA patients are not overlooked, whilst simultaneously not overwhelming secondary care services. Their success relies on the clinicians who first encounter these patients being familiar with IBP as a concept; however, it is still poorly recognized by many healthcare professionals. IBP may be helpful as part of a referral strategy; however, other clinical features, laboratory investigations and radiology must be incorporated for the final diagnostic outcome in axSpA.

Summary
Delayed diagnosis is a major clinical problem in axSpA and is associated with worse clinical outcomes. When recognized and utilized correctly, IBP can be a useful tool to promote prompt referral to rheumatology services.

Keywords
axial spondyloarthritis, inflammatory back pain, nonradiographic axial spondyloarthritis

INTRODUCTION

Inflammatory back pain (IBP) is an important presenting feature of axial spondyloarthritis (axSpA), estimated to be present in 75% at initial presentation and 88% during the course of the disease [1,2▪▪]. However, axSpA is by no means the only differential diagnosis in patients presenting with IBP. In a cross-sectional study of primary care patients with IBP, the prevalence of axSpA was low, ranging from 0.66 to 5.3% depending on the classification criteria used [3]. The prevalence of axSpA among IBP patients referred to secondary care is higher given this is an enriched cohort with an element of selection bias. In this review, we examine the utility of IBP in the primary and secondary care setting.

INFLAMMATORY BACK PAIN: A CONCEPT

IBP is a term encompassing a range of clinical features in patients with chronic back pain (CBP). These include age of onset less than 40 years, insidious onset, pain persisting for more than 3 months, prolonged morning stiffness lasting more than 30 min, improving with exercise, not relieved by rest, nocturnal pain, alternating buttock pain and good response to NSAIDs [4]. This concept was first proposed by Calin *et al.* [5] in 1977 as a simple, cheap and readily reproducible screening technique to detect axSpA. Since then, other IBP classification criteria have been proposed, which employ various combinations of these features – Berlin and Assessment of SpondyloArthritis international Society (ASAS) (Table 1) [5–7].

These three IBP criteria attempt to standardize groups of patients for epidemiology purposes, but have also been used to evaluate the utility of IBP in the referral and diagnosis of axSpA. Using these criteria, the minimum estimated prevalence of IBP among people with CBP in the UK population is 7.7% (95% confidence interval (CI) 6.2–9.5) by ASAS, 13.5% (95% CI 11.5–15.8) by Calin and 15.4% (95% CI 13.3–17.8) by Berlin [8]. In this study, the prevalence of IBP was not significantly

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KEY POINTS

- IBP refers to a set of characteristic symptoms among patients with CBP.
- IBP can be an important presenting feature of axial spondyloarthritis but it is not the only differential diagnosis, which needs to be considered.
- IBP should not be assessed in isolation but in the context of the wider clinical picture.
- IBP is a useful concept to promote referral to rheumatology services but its utility is limited beyond this with regards diagnosis.

different across age groups, despite the cohort having an age range of 20–80 years [8]. In a Danish secondary care cohort of patients aged 18–40 years with low CBP, 67% met at least one of the criteria and 16% all three [9]. However, only 11% of the cohort received an axSpA diagnosis. In DIVERS (Diagnostic accuracy of inflammatory back pain study), the physician impression on the presence or absence of IBP varied depending on whether they were blinded to the wider clinical history, with only moderate agreement (kappa = 0.45) [1]. Although the authors term this 'diagnostic bias', it is probably more reflective of real-life practice. In DIVERS, the three IBP criteria had similar sensitivities to both each other and the original data; ASAS (74.4%, 95% CI 68.1–80.8), Calin (79.4%, 95% CI 73.5–85.4) Berlin (81.1%, 95% CI 75.4–86.8). However, all had lower specificity than observed in the original criteria development studies; Calin (52.1%, 95% CI 19.6–31.3), Berlin (32.3%, 95% CI 26.2–38.6) ASAS (39.5%, 95% CI 33.0–46.1). Both the blinded and nonblinded rheumatologist evaluation performed better, highlighting the importance of wider clinical correlation. Whether the same would have been seen for non-rheumatologists was not examined. Analysis of individual features that make up IBP shows variation and inconsistency in their predictive performance. This may, therefore, explain improved performance of global assessment versus IBP classification criteria in some studies, something the experienced rheumatologist will do intuitively [1]. The Berlin criteria is the only one to include buttock pain. A recent study by Baraliakos *et al.* [10▪▪] found this was the only anatomical location that helped differentiate axSpA from other noninflammatory lower back pain. Similar trends with regards lower specificity of IBP criteria have been observed in other cohorts [11▪]. A possible reason for the unexpectedly low specificity may be because of testing these criteria on unselected primary care referrals, rather than the enriched axSpA cohorts, which were used to originally develop them; the latter introduces a level of circularity bias [11▪].

Although IBP is an important feature of axSpA, it is not always present and is not mandatory for diagnosis [12▪]. The ASAS classification criteria for axSpA include it as a feature, not an entry criterion (Fig. 1) [13]. There is a general consensus that IBP may be helpful in selection of patients for referral [12▪,14▪]. Although the IBP criteria have low specificity, they may be helpful as an aide-mémoire for clinicians less practiced at pattern recognition of IBP. As diagnostic delay a particular concern in axSpA, the criteria need not be applied too rigidly, excluding patients from referral if they just miss the 'cut off'. It should be remembered the criteria are for classification, intended to standardize patients for research purposes. This should not replace clinical acumen or overrule any ongoing concerns to continue investigation. However, beyond referral, IBP appears of less value to the rheumatologist, who will typically incorporate other clinical features, laboratory tests and imaging findings before reaching the final diagnostic outcome.

A word of caution is required regarding the use of classification criteria inappropriately. The ASAS classification criteria have been influential in promoting the concept of early disease before damage is

Table 1. Summary of inflammatory back pain criteria

Calin (1977)	Berlin (2006)	ASAS (2009)
Age <40 at onset	Waking in the second half of the night with back pain	Age <40 years at onset
Duration >3 months	Alternating buttock pain	Insidious onset
Insidious onset	Morning stiffness >30 min	Improves with exercise
Associated with morning stiffness	Improvement with exercise, not with rest	No improvement with rest
Improves with exercise	–	Night back pain that improves on activity (getting up)
Criteria fulfilled if at least four parameters met	Criteria fulfilled if at least two parameters met	Criteria fulfilled if at least four parameters met

Data from [5–7]. Summary of IBP Criteria. ASAS, Assessment of SpondyloArthritis International Society classification.

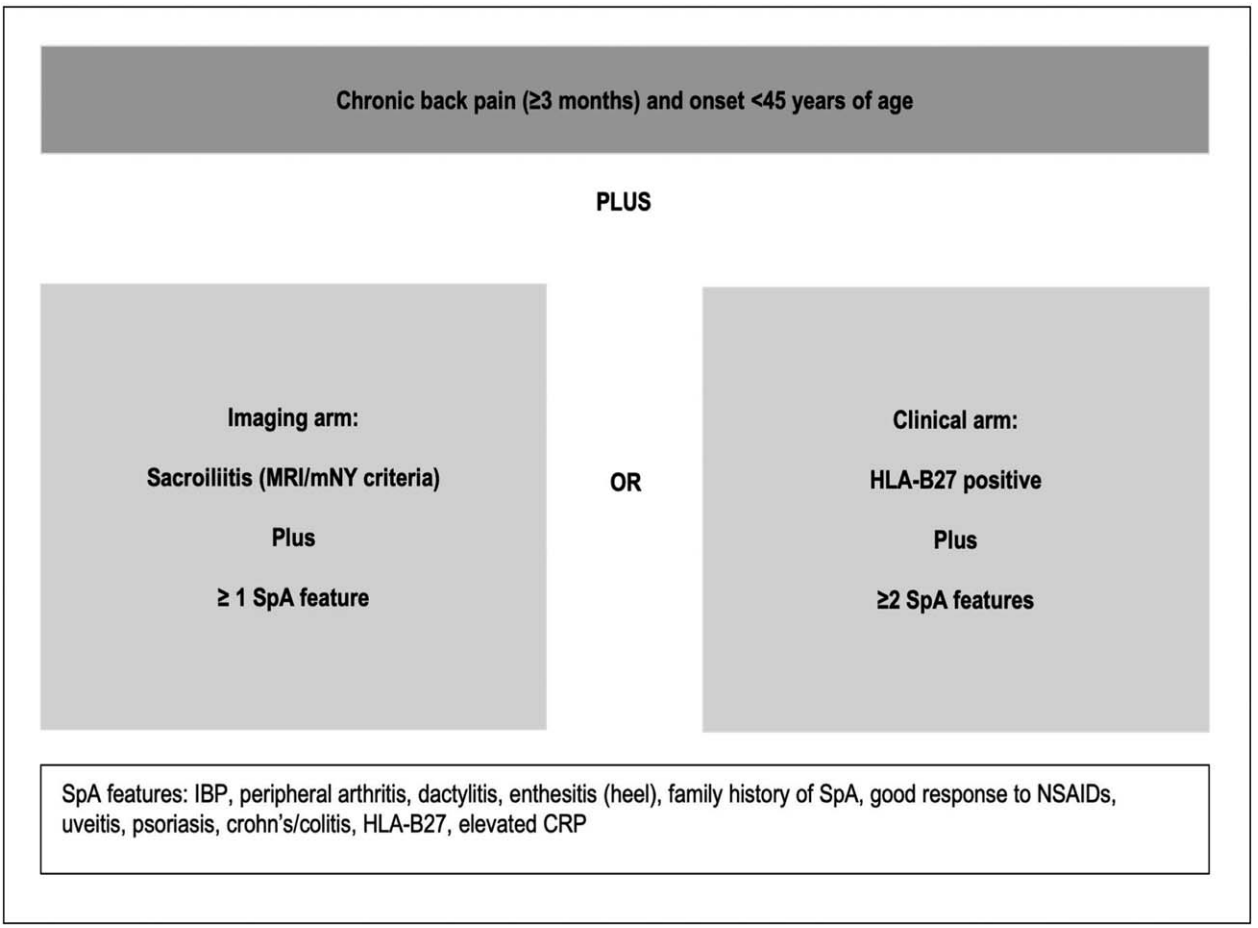

FIGURE 1. Data from [13]. Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis.

evident on X-ray, termed non-radiographic axSpA (nr-axSpA). A 51% increase in new axSpA diagnoses in the 5 years following publication of these criteria has been reported [15]. It is of concern that there has been a tendency for rheumatologists to use these criteria to establish a diagnosis, rather than their intended purpose of identifying a homogenous set of patients for research post-diagnosis, a necessity in what can be a phenotypically heterogenous condition. As Poddubnyy *et al.* [14▪] highlights, classification criteria do not, therefore, consider other important differentials for back pain including fractures, infection and malignancy. A multinational study of 478 rheumatologists from the USA, Canada, Brazil, India and Turkey, found 66% of respondents commonly used the ASAS classification criteria in their clinical practice for diagnosis [16▪]. Interestingly rheumatologists who were early on in their career ($\leq$5 years from completion of training) were more likely to 'always' use the criteria compared with those with more than 30 years' experience ($P = 0.046$). The imaging arm of the ASAS criteria has also led to the hasty adoption of MRI for diagnosis without full critical analysis. Although promising, lack of standardized imaging and reporting protocols limit the sensitivity and specificity of MRI [17]. Recent studies have advised caution, noting a high frequency of inflammatory and degenerative change in both axSpA and non-axSpA patients [18▪▪,19,20], emphasizing the importance of clinical correlation when interpreting these images and declaring a scan 'positive'.

INFLAMMATORY BACK PAIN IN REFERRAL STRATEGIES

There have been a number of proposed referral strategies for patients with suspected axSpA, most of which incorporate IBP. Abawi *et al.* [21] evaluated 13 strategies in the SPACE (Leiden SPondyloArthritis Caught Early) cohort. Although all included IBP, the definitions differed slightly and not all required this domain to be met to qualify for referral. From patients who met the ASAS axSpA classification criteria, 77% would not have been referred by one or more of the strategies assessed. Of patients without axSpA, 96% would have been referred using at least one of the strategies. The ASAS and Brandt I

were the most sensitive strategies, both achieving 98%. Brandt I triggers referral if a patient is HLA-B27 positive and they have at least one of three specified IBP features [22]. The ASAS strategy recommends referral if a patient less than 45 years of age has CBP for more than 3 months and at least one spondyloarthritis feature (IBP, peripheral and extra-articular manifestations or raised acute phase reactants) [23]. However, both of these demonstrated low specificity, 11% and 18%, respectively. The MASTER strategy was found to have an acceptable balanced sensitivity and specificity, of 64% and 76%, respectively, and gave the highest liklihood ratio (LR)+2.68 [21]. MASTER is, however, a little more involved, requiring assessment for IBP, HLA-B27, family history of axSpA and response to NSAIDs, and then referring if two of these are present [24].

It is apparent that choosing a referral strategy is a balance between ensuring axSpA patients are not overlooked, whilst simultaneously not overwhelming secondary care services with inappropriate referrals. It must also be remembered that those using these strategies will be primary care physicians, who often have limited appointment times [25▪]. The RADAR (Recognising and Diagnosing Ankylosing Spondylitis Reliably) study compared a simpler and more complex strategy yielding similar results [26]. In these circumstances, the pragmatic approach would be to adopt the simpler strategy, which is likely to have a better uptake. A number of referral strategies require knowledge of HLA-B27 status. A recent study by Baraliakos *et al.* [10▪▪] recognizes that this may not always be feasible in primary care, as well as being a potential unnecessary use of resources. They recommend a two-step strategy, whereby HLA-B27 is only required if a patient does not qualify by clinical features alone. Some would advocate an even simpler strategy of referring any patient with IBP who is younger than 45 to avoid both delayed and erroneous diagnosis [27▪].

UNDERSTANDING OF INFLAMMATORY BACK PAIN WITHIN PRIMARY CARE

Reliable use of IBP in referral strategies depends on physicians having a sufficient understanding of the concept. This has been identified as a significant knowledge gap, with only 5% of general practitioners being able to identify all recognized IBP features [4]. Delay to diagnosis in axSpA is multifactorial but general practitioners themselves identify poor awareness of axSpA and attributing back pain to other causes as part of the problem [25▪]. Low agreement between referring clinicians and rheumatologists on the presence of IBP has been repeatedly observed (kappa = 0.16) [28]. A survey of chiropractors and osteopaths reported good recognition of IBP as a concept but only 63% were familiar with the term axSpA [29▪]. A UK survey of 132 musculoskeletal physiotherapists found poor differentiation between IBP and axSpA presentations, from other nonspecific causes of back pain, and poor recognition of national referral guidelines [30▪]. Reassuringly this is seen to improve with education programs [12▪]. A recent study comparing the clinical impression of allied healthcare professionals with axSpA training (including physiotherapists, occupational therapists and advanced care practitioners), to that of rheumatologists, found there was a moderate agreement on the likelihood of an axSpA diagnosis in newly referred patients with CBP (kappa = 0.52) [31▪]. A significant contributor to diagnostic delay in axSpA has been inappropriate referral to other musculoskeletal services before reaching a rheumatologist. Therefore, extending education to the clinicians running these services may help promote timely referral. There are expanding and easily accessible resources and initiatives for primary care practitioners, including programmes developed through the National Axial Spondyloarthritis Society (NASS) and British Society for Spondyloarthritis (BRITSpA) [32]. Supporting primary care is still an unmet need, with only 21% of clinical commissioning groups having a specific IBP referral pathway, which typically incorporates a certain level of education on initiation [33▪]. In the review of their 'Early Inflammatory Back Pain Service', Adshead *et al.* [33▪] describe the positive impact that an integrated education and referral pathway had on both their diagnostic yield and delay, the latter of which has been reduced to a median of 3 years. This is an improvement on the median 5-year delay reported within the UK over a similar time period [15].

UNDERSTANDING OF INFLAMMATORY BACK PAIN WITHIN SECONDARY CARE

Poor recognition of IBP is not confined to primary care. From a survey of secondary care professionals likely to encounter extra-articular manifestations of axSpA (including gastroenterology, ophthalmology, dermatology, genito-urinary medicine, spinal surgery and orthopaedics), only 28% could identify all recognized IBP features, and 81% were not aware of nr-axSpA as a diagnostic term [34]. This is of particular concern as several studies have identified a significant burden of undiagnosed axSpA in patients with extra-articular manifestations. This again has been a target for NASS educational activities, including the 'Back Pain Plus' campaign [35]. The ASPAU study estimated a minimum axSpA prevalence of 20.2% from an acute anterior uveitis cohort, of which one quarter were undiagnosed [36]. In a retrospective longitudinal study of 124 patients with new-onset

IBP, uveitis was identified as one of the most important predictors for developing spondyloarthritis, including axSpA, conferring a five-fold increased risk over the median 13.2 year follow-up period [37]. In response, several screening tools have been proposed. The Dublin Uveitis Evaluation Tool (DUET) recommends rheumatology referral if a patient presenting with uveitis is under the age of 45 years, with a history of back or peripheral joints pain, and is either HLA-B27 positive or has a history of psoriasis [38]. The SENTINEL working group incorporate aspects of IBP in their recommendations, suggesting referral in patients under 45 years of age with a history of CBP, regardless of HLA-B27 status [39].

Spondyloarthritis is the commonest extra-intestinal manifestation of inflammatory bowel disease (IBD). Peripheral spondyloarthritis is more prevalent but sacroiliitis is still estimated to occur in approximately 10% of patients [40]. Features of IBP are incorporated into several screening tools. Queiro *et al.* [41] proposed a three-question strategy, from which a patient was considered positive if they met two or more of the following criteria – CBP, morning stiffness more than 30 min and night back pain, which interrupts sleep. When tested on a cohort of 112 patients, this gave a sensitivity of 87.5%, specificity of 89.8% and LR+ of 8.6 (4.5–16.2). There is a concern that using CBP as a criteria is not descriptive enough and does not distinguish from non-inflammatory causes. This is seen in the DETAIL (DETection of Arthritis in Inflammatory boweL diseases) questionnaire, whereby 'duration of back pain more than 3 months' had the lowest LR out of the six included questions [42]. DETAIL is a self-administered questionnaire. The study suggested answering affirmatively to three or more questions gives a post-test probability for spondyloarthritis of more than 75%. Being self-administered, the questions are open to patient interpretation. Patients answering affirmatively to four or more questions but without evidence of spondyloarthritis were all diagnosed with fibromyalgia. The IBIS-Q (IBd Identification of Spondyloarthritis Questionnaire) is also self-administered but has tried to overcome the effect of concomitant conditions, such as fibromyalgia, by using psychometric analysis to remove questions, which may pertain to non-inflammatory pain [43▪]. This questionnaire achieved a sensitivity of 93%, specificity of 77% and positive-predictive value of 77% for spondyloarthritis in IBD.

DIFFERENTIAL DIAGNOSIS

The presence of IBP is not tantamount to a diagnosis of axSpA. In the retrospective longitudinal study of IBP by Wang *et al.* [37], there was a 30% probability of developing spondyloarthritis but a higher 43% probability of symptom resolution. Fifteen patients from the 124-patient cohort were actively identified to have other conditions including degenerative disc disease, fibromyalgia and systemic lupus erythematosus [37]. It is important not to attribute symptoms to expected age-related disease. For example, there is a high prevalence of facet joint osteoarthritis in individuals over 40 years of age but this correlates poorly with symptoms [44]. Of course, a primary concern is not to miss important differentials with high morbidity and mortality, including vertebral fracture, discitis, malignancy or cauda equina. Systematic reviews have shown varying performance of so-called 'red flag' features [45]. Certain features were more significant, for example, a prior history of malignancy increased the risk of metastatic spinal disease. On a pragmatic level, clinicians must remember that although these other differentials are rare, so is axSpA. Clinical correlation is key.

CONCLUSION

IBP is an important presenting feature of axSpA that can persist throughout the disease course. When understood and utilized correctly, it can be a useful tool to promote prompt referral to rheumatology services. This is of vital importance, as despite updated referral guidelines and recently published quality standards [46,47▪▪], diagnostic delay remains a significant ongoing challenge. Current evidence shows that delayed diagnosis in axSpA is associated with worse clinical, humanistic and economic outcomes [48▪▪]. Recognition of IBP by healthcare professionals, with prompt and appropriate onward referral to rheumatology may help shorten this unacceptable diagnostic delay and improve long-term outcomes.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

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

- ▪ of special interest
- ▪▪ of outstanding interest

1. Poddubnyy D, Callhoff J, Spiller I, *et al.* Diagnostic accuracy of inflammatory back pain for axial spondyloarthritis in rheumatological care. RMD Open 2018; 4:e000825.

2. López-Medina C, Ramiro S, van der Heijde, *et al.* Characteristics and burden
■■ of disease in patients with radiographic and nonradiographic axial Spondyloarthritis: a comparison by systematic literature review and meta-analysis. RMD Open 2019; 5:e001108.

This systematic review with pooled analysis of 60 studies published between 2009 and 2018 compared the clinical characteristics of radiographic and nonradiographic axial spondyloarthritis. Similar phenotypes were seen between the two, including a high prevalence of inflammatory back pain. Even though increased structural damage is by definition observed in the radiographic group, there was no statistically significant difference in disease activity and patient-reported outcomes.

3. Hamilton L, Macgregor A, Toms A, *et al.* The prevalence of axial spondyloarthritis in the UK: a cross-section cohort study. BMC Musculoskelet Disord 2015; 16:392.
4. Jois RN, Macgregor AJ, Gaffney JK. Recognition of inflammatory back pain and ankylosing spondylitis in primary care. Rheumatology (Oxford) 2008; 47:1364–1366.
5. Calin A, Porta J, Fries JF, Schurman DJ. Clinical history as a screening test for ankylosing spondylitis. JAMA 1977; 237:2613–2614.
6. Rudwaleit M, Metter A, Listing J, *et al.* Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. Arthritis Rheum 2006; 54:569–578.
7. Sieper J, van der Heijde D, Landewe R, *et al.* New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). Ann Rheum Dis 2009; 68:784–788.
8. Hamilton L, Macgregor A, Warmington V, *et al.* The prevalence of inflammatory back pain in a UK primary care population. Rheumatology (Oxford) 2014; 53:161–164.
9. Arnbak B, Hendricks O, Hørslev-Petersen K, *et al.* The discriminative value of inflammatory back pain in patients with persistent low back pain. Scand J Rheumatol 2016; 45:321–328.
10. Baraliakos X, Styliani T, Redeker I, *et al.* Early recognition of patients with axial
■■ spondyloarthritis – evaluation of referral strategies in primary care. Rheumatology (Oxford) 2020; 59:3845.

This large prospective multicentre study evaluated the utility of a two-step referral strategy for patients with chronic back pain. Patients who were under 45 years of age with chronic back pain were questioned as to whether they had features of IBP, with the addition of HLA-B27 testing if not enough features are present. Only using HLA-B27 whenever insufficient clinical features were present would save on testing and the associated costs of this. It showed good sensitivity and specificity of several combinations of IBP features.

11. de Hooge M, van Gaalen FA, Renson T, *et al.* Low specificity but high
■ sensitivity of inflammatory back pain criteria in rheumatology settings in Europe: confirmation of findings from a German cohort study. Ann Rheum Dis 2019; 78:1605–1606.

This study looks at the diagnostic utility of IBP parameters and the ASAS criteria using multicentre observational data from the Be-Giant and SPACE cohorts. IBP parameters showed high sensitivity with low specificity for the diagnosis of axSpA. Therefore, IBP is useful in referral strategies, but of less use to the rheumatologist in making a final diagnosis.

12. Barnett R, Ingram T, Sengupta R. Axial spondyloarthritis 10 years on: still
■ looking for the lost tribe. Rheumatology (Oxford) 2020; 59:iv25–iv37.

This review identifies several issues of concern in axial spondyloarthritis that are contributing to continued diagnostic delay, as well as recommendations for referral strategies and education.

13. Rudwealeit M, van der Heijde D, Landwew R, *et al.* The development of Assessment of Spondyloarthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009; 68:777–783.
14. Poddubnyy D. Classification vs diagnostic criteria: the challenge of diagnos-
■ ing axial spondyloarthritis. Rheumatology (Oxford) 2020; 59:iv6–iv17.

This review eloquently highlights the important issue of inappropriate use classification criteria for diagnostic purposes in axial spondyloarthritis.

15. Sykes MP, Doll H, Sengupta R, Gaffney K. Delay to diagnosis in axial spondyloarthritis: are we improving in the UK? Rheumatology (Oxford) 2015; 54:2283–2284.
16. Rich-Garg N, Danve A, Choi D, *et al.* Assessing rheumatologists' attitudes and
■ utilization of classification criteria for ankylosing spondylitis and axial spondyloarthritis: a global effort. Clin Rheumatol 2020; 40:949–954.

This multinational survey of 478 rheumatologists highlights the inappropriate use of classification criteria for diagnostic purposes. This was also seen to be done more frequently by rheumatologists who were relatively early in their careers.

17. Lukas C, Cyteval C, Dougados M, Weber U. MRI for diagnosis of axial spondyloarthritis: major advance with critical limitations 'Not everything that glisters is gold (standard)'. RMD Open 2018; 4:e000586.
18. Baraliakos X, Richter A, Feldmann D, *et al.* Frequency of MRI changes
■■ suggestive of axial spondyloarthritis in the axial skeleton in a large population-based cohort of individuals aged <45 years. Ann Rheum Dis 2020; 79:186–192.

This large population-based cohort study showed a high frequency of sacroiliac and spinal MRI changes suggestive of axial spondyloarthritis according to ASAS definitions. Lesions of smaller size and number were inconclusive for diagnosis, and increasing lesions were seen with advancing age, suggesting these are secondary to degenerative change.

19. de Bruin F, ter Horst S, Bloem HL, *et al.* Prevalence of degenerative changes of the spine on magnetic resonance images and radiographs in patients aged 16-45 years with chronic back pain of short duration in the spondyloarthritis caught early (space) cohort. Rheumatology 2016; 55:56–65.
20. de Bruin F, Treyvaud MO, Feydy A, *et al.* Prevalence of degenerative changes and overlap with spondyloarthritis-associated lesios in the spine of patients from the DESIR cohort. RMD Open 2018; 4:e000657.
21. Abawi O, van den Berg R, van der Heijde D, van Gaalen FA. Evaluation of multiple referral strategies for axial spondyloarthritis in the SPACE cohort. RMD Open 2017; 3:e000389.
22. Brandt HC, Spiller I, Song IH, *et al.* Performance of referral recommendations in patients with chronic back pain and suspected axial spondyloarthritis. Ann Rheum Dis 2007; 66:1479–1484.
23. Poddubnyy D, van Tubergen A, van Landewé R, *et al.* Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis. Ann Rheum Dis 2015; 74:1483–1487.
24. Poddubnyy D, Vahldiek J, Spiller I, *et al.* Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care. J Rheumatol 2011; 38:2425–2460.
25. Lapane KL, Khan S, Shridharmurthy D, *et al.* Primary care physician perspec-
■ tives on barriers to diagnosing axial spondyloarthritis: a qualitative study. BMC Fam Pract 2020; 21:204.

An interesting survey of primary care physicians identifying important barriers to diagnosis of axial spondyloarthritis, including lack of awareness of the condition among nonrheumatologists and constraints of primary care time and facilities.

26. Sieper J, Srinivasan S, Zamani O, *et al.* Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study. Ann rheum Dis 2013; 72:1621–1627.
27. Ritchlin C, Adamopoulos IE. Axial spondyloarthritis: new advances in diag-
■ nosis and management. BMJ 2021; 372:m4447.

This interesting review highlighting continued issues in the delayed diagnosis of axial spondyloarthritis, including the need for improved targeted education in primary care and for those who would routinely encounter these patients at their first presentation.

28. Ruth López-González R, Hernández-Sanz A, Almodóvar-González R, *et al.* Are spondyloarthropathies adequately referred from primary care to specialized care? Reumatol Clin 2013; 9:90–93.
29. Yong CY, Hamilton J, Benepal J, *et al.* Awareness of axial spondyloarthritis
■ among chiropractors and osteopaths: findings from a UK Web-based survey. Rheumatol Adv Pract 2019; 3:rkz034.

This large survey of 382 chiropractors and osteopaths identifies poor recognition of the terms radiographic and nonradiographic axSpA in comparison to the term ankylosing spondyloarthritis. This is a potential barrier to earlier referral and diagnosis before structural damage is seen, and is therefore, a target for education activities.

30. Steen E, McCrum C, Cairns M. Physiotherapists' awareness, knowledge and
■ confidence in screening and referral of suspected axial spondyloarthritis: a survey of UK clinical practice. Musculoskeletal Care 2021; Feb 5. doi: 10.1002/msc.1537. [Epub ahead of print]

This UK-based survey of 132 physiotherapists found lower than expected awareness of axSpA and national referral guidelines, with only 67% of respondents identifying potential inflammatory cause for back pain appropriately.

31. Passalent L, Hawke C, Lawson DO, *et al.* Advancing early identification of
■ axial spondyloarthritis: an interobserver comparison of extended role practitioners and rheumatologists. J Rheumatol 2020; 47:524–530.

This single-centre study evaluated the inter-observer agreement of extended role practitioners with specialist training and rheumatologists as to the presence of inflammatory or mechanical back pain in 57 patients. A moderate agreement on the likelihood of an axSpA diagnosis was seen (kappa = 0.52), indicating the importance of education for clinicians who are likely to first encounter potential axSpA patients in primary care.

32. National Axial Spondyloarthritis Society (NASS). Resources for health professionals. Available at: https://nass.co.uk/homepage/health-professionals/resources-for-health-professionals/. [Accessed 13 April 2021]
33. Adshead R, Donnelly S, Knight P, Tahir H. Axial spondyloarthritis: overcoming
■ the barriers to early diagnosis – an early inflammatory back pain service. Curr Rheumatol Rep 2020; 22:59.

This review highlights barriers to early diagnosis of axSpA by evaluating the service outcomes from a single centre experience in the UK. They describe the positive impact an integrated education and referral pathway on diagnostic yield and delay, which was reduced to a median of 3 years over 8 years of data collection, better than the median 5-year delay reported within the over a similar time period.

34. Mathieson H, Merashil M, Gaffney K, Marzo-Ortega. Poor awareness of inflammatory pack pain and axial spondyloarthritits among secondary care specialists. Clin Rheumatol 2016; 35:2627–2628.
35. National Axial Spondyloarthritis Society (NASS). Back Pain Plus. Available at: https://nass.co.uk/homepage/health-professionals/back-pain-plus/. [Accessed 13 April 2021]
36. Sykes MP, Hamilton L, Jones C, Gaffney K. Prevalence of axial spondyloarthritis in patients with acute anterior uveitis: a cross-sectional study utilising MRI. RMD Open 2018; 4:e000553.
37. Wang R, Crowson CS, Wright K, Ward MM. Clinical evolution in patients with new-onset inflammatory back pain: a population-based cohort study. Arthritis Rheumatol 2018; 70:1049–1055.

38. Haroon M, O'Rourke M, Ramasamy P, *et al.* A novel evidence-based detection of undiagnosed spondyloarthritis in patients presenting with acute anterior uveitis: the DUET (Dublin Uveitis Evaluation Tool). Ann Rheum Dis 2015; 74:1990–1995.
39. Juanola X, Santamaría EL, Cordero-Coma M; SENTINEL Working Group. Description and prevalence of spondyloarthritis in patients with anterior uveitis: the SENTINEL Interdisciplinary Collaborative Project. Ophthalmology 2016; 123:1632–1636.
40. Karrenman MC, Lumie JJ, Hazes JMW, Weel AEAM. The prevalence and incidence of axial and peripheral spondyloarthritis in inflammatory bowel disease: a systematic review and meta-analysis. J Crohns Colitis 2017; 11:631–642.
41. Queiro R, Rodríguez-Caminero S, Riestra S, *et al.* Performance of two screening questionnaires for inflammatory arthritis in patients with inflammatory bowel disease. Biomed Res Int 2018; 2018:8618703.
42. Di Carlo M, Luchetti MM, Benfaremo D, *et al.* The DETection of Arthritis in Inflammatory boweL diseases (DETAIL) questionnaire: development and preliminary testing of a new tool to screen patients with inflammatory bowel disease for the presence of spondyloarthritis. Clin Rheumatol 2018; 37:1037–1044.
43. ▪ Variola A, Zanolin ME, Cipriano G, *et al.* The IBIS-Q [IBd Identification of Spondyloarthritis Questionnaire]: a novel tool to detect both axial and peripheral arthritis in inflammatory bowel disease patients. J Crohn Colitis 2020; 14:1680–1686.
The IBIS-Q (IBd Identification of Spondyloarthritis Questionnaire) is a self-administered 42-item questionnaire, achieving a sensitivity of 93%, specificity of 77% and positive-predictive value of 77% for spondyloarthritis in inflammatory bowel disease.
44. Kalichman L, Li L, Kim DH, *et al.* Facet joint osteoarthritis and low back pain in the community-based population. Spine (Phila Pa 1976) 2008; 33:2560–2565.
45. Downie A, Williams CM, Henschke N, *et al.* Red flags to screen for malignancy and fracture in patients with low back pain: systematic review. BMJ 2013; 347:f7095.
46. NICE. Spondyloarthritis in over 16 s: diagnosis and management 2017. Available at: https://www.nice.org.uk/guidance/ng65. [Accessed 15 February 2021]
47. ▪▪ Kiltz U, Landewé RBM, van der Heijde D, *et al.* Development of ASAS quality standards to improve the quality of health and care service for patients with axial spondyloarthritis. Ann Rheum Dis 2020; 79:193–201.
The ASAS taskforce have identified and agreed nine quality standards for improving care for axSpA patients. These cover key areas of presentation, diagnosis and differential diagnosis, treatment and management. They recommend patients with suspicious symptoms are referred within 3 working days and assessed by a specialist within 3 weeks of referral.
48. ▪▪ Yi E, Ahuja A, Rajput T, *et al.* Clinical, economic, and humanistic burden associated with delayed diagnosis of axial spondyloarthritis: a systematic review. Rheumatol Ther 2020; 7:65–87.
This systematic review of 21 studies showed a general trend towards worse clinical, economic and humanistic outcomes in axSpA patients with a delayed diagnosis. These patients had a greater likelihood of work disability.

Low-dose computed tomography for axial spondyloarthritis: update on use and limitations

Robert G.W. Lambert[a], *Kay Geert A. Hermann*[b], *and Torsten Diekhoff*[b]

Purpose of review
Recent developments in low-dose computed tomography (ldCT) have greatly reduced radiation exposure levels. This article reviews what a ldCT is and its use and limitations for imaging axial spondyloarthritis.

Recent findings
Detection of structural damage in bone with CT is far superior to radiography and ldCT of the sacroiliac joints (SIJ) can now be done at radiation exposure levels equivalent to, or even less than, conventional radiography. ldCT should be considered a 'first-choice' test for arthritis imaging, and wherever available, SIJ ldCT may completely replace conventional radiography. Radiation exposure in the spine with ldCT is lower than conventional CT. However, it is unclear whether the additional information regarding structural damage changes in the spine provided by ldCT will alter patient management sufficiently often to merit switching from spinal radiography to ldCT in routine clinical practice. In addition, ldCT cannot assess osteitis disease activity for which MRI remains the best test.

Summary
ldCT of the sacroiliac joints (SIJ) can be done at radiation exposure levels equivalent to, or less than, radiography and ldCT may completely replace SIJ radiography. However, the role of spinal ldCT for spondyloarthritis is not clear and MRI is far superior for detecting disease activity.

Keywords
computed tomography, low-dose computed tomography, sacroiliac joint, sacroiliitis, spondyloarthritis

INTRODUCTION

For over 100 years, the conventional radiograph (X-ray) has been the mainstay of radiology for arthritis. It offers superb overall assessment on a single image, high spatial resolution and excellent contrast between bone and soft-tissues but has limited contrast between different soft-tissues. Computed tomography (CT) is fundamentally based on the same interactions between X-rays and human tissues with many similar properties to radiography with the advantage that CT images are projected as multiplanar, cross-sectional datasets free of superimposition of overlapping structures. Radiation exposures with CT are often much higher than radiography and this has been a limiting factor in the universal application of CT. In recent years, low-dose CT (ldCT) has become widely available and technical advances have broadened the scope of its ability to investigate arthropathy.

WHAT IS LOW-DOSE COMPUTED TOMOGRAPHY OF THE AXIAL SKELETON?

Unfortunately, there is no international agreement as to what constitutes a ldCT scan with no simple answer to this question. Ideally, there would be a single radiation exposure limit below which the scan would be considered 'Low Dose'. However, many factors influence exposure dose, especially patient size and the body part being scanned. Applying a single limit is not practical and reported radiation exposures vary widely. For example, reported mean exposure dose for pelvis ldCT [1] was three times another recent report [2] and 47 times the dose of a dedicated SIJ protocol [3▪▪]. This latter study confirmed that by using tin filtration, SIJ ldCT radiation dose can be reduced even further to 0.11 mSv, which is the same dose as PA and lateral chest

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KEY POINTS

- ldCT of the sacroiliac joints (SIJ) can be done with radiation exposure levels equivalent to, or even less than, conventional radiography of the SIJ.
- ldCT of the SIJ is quick to perform and interpret and should completely replace SIJ radiography in daily clinical practice, wherever access is available.
- ldCT of the entire spine is 'very low radiation risk' and its superiority over radiography for detecting structural damage is convincing.
- It is time consuming to review all the joints in the entire spine on ldCT, and this may hinder the application of spinal ldCT in routine clinical practice.

radiography, while maintaining diagnostic quality. There is also no agreement on whether any chosen limit would apply to each location separately or to the entire body. For example, if the ldCT exposure limit for any part of the spine or pelvis was 1 mSv, what would be the exposure limit for scanning the cervical, thoracic and lumbar spine and sacroiliac joints? Would it be 1 or 4 mSv? There is no agreement on this issue.

A variety of processes may be used to reduce CT dose (filtered back projection, iterative reconstruction, tin filtration); however, these technical details are beyond the scope of this article. What can be clearly stated is that: advanced CT technologies have been able to substantially reduce radiation exposure (85–95% reduction) [3▪▪,4]; ldCT of the sacroiliac joints (SIJ) can be consistently done with less than 1 mSv radiation dose, at exposure levels equivalent to, or even less than, conventional radiography [3▪▪,5▪,6] and an effective radiation dose of less than 1 mSv is considered to be 'minimal risk' [7]. The 'minimal risk' of 0.5 mSv with SIJ ldCT is equivalent to 1/4 of the annual additional risk because of cosmic radiation exposure for airline crew or about 100 h of high-altitude flight in jet aircraft, and is 1/6 of the annual exposure to natural background radiation in the USA.

LOW-DOSE COMPUTED TOMOGRAPHY OF THE AXIAL SKELETON: GENERAL ADVANTAGES

The output of a CT scan is a high resolution multiplanar set of images. CT is widely available with no absolute contraindications. Image acquisition and reconstruction are much less subject to operator variation than ultrasound or MRI and the acquisition is so fast that motion artifact related to patient discomfort or claustrophobia is almost never a problem. Consequently, CT is fast, easily tolerated, high resolution and generally consistent.

LOW-DOSE COMPUTED TOMOGRAPHY OF THE SACROILIAC JOINTS

The diagnosis of axial spondyloarthritis is most often confirmed by identifying the presence of inflammatory arthropathy involving the SIJ – sacroiliitis. The structural damage changes that occur in sacroiliitis may be seen on radiographs. However, at earlier stages of disease when erosion is mild, radiographs are notoriously difficult to interpret with poor intrareader and interreader reliability, even with expert training [8–10]. The problem is threefold: the convoluted anatomy of the SIJ means that it is never possible to get all of the articular surface in profile, and sometimes none of it is in profile (Fig. 1); the most critical early-stage finding is erosion, which is difficult to identify in any joint when the articular surface is not in profile; and complex bony anatomy and pelvic structures result in overlap, including bowel gas and stool, that may look like erosion superimposed on bone of variable contour and density. ldCT resolves all of these problems. The bony anatomy is beautifully demonstrated, free from all overlap. Erosion, and all the other radiographic features of arthropathy, such as sclerosis, joint space narrowing, joint space widening, intraarticular bone formation, ankylosis, intraarticular gas, osteophytes and pseudarthrosis, are all clearly and consistently visualized (Fig. 2).

Diagnostic application

ldCT has been shown to be highly specific (93–100%) for axial spondyloarthritis (axSpA) in two studies [6,11▪]. It has moderate sensitivity (44%) for nonradiographic axial spondyloarthritis (nr-axSpA) [11▪] and is, of course, highly sensitive for modified New York criteria X-ray positive ankylosing spondyloarthritis with overall sensitivity for axSpA (ankylosing spondyloarthritis and nr-axSpA) of 77–86% [6,11▪]. The reliability of interpretation of ldCT is far superior to radiography. For global positivity for axSpA, ldCT reliability is very good with substantial agreement ($k = 0.62$) compared with radiography, which has only fair agreement ($k = 0.33$) [6]. As it is fast, reliable and specific for the diagnosis of axSpA with no additional radiation exposure, it has been recommended that ldCT should completely replace radiography of the SIJ in adults [3▪▪,5▪]. At the very least, ldCT is an excellent method for resolving cases where the radiographic result is indeterminate.

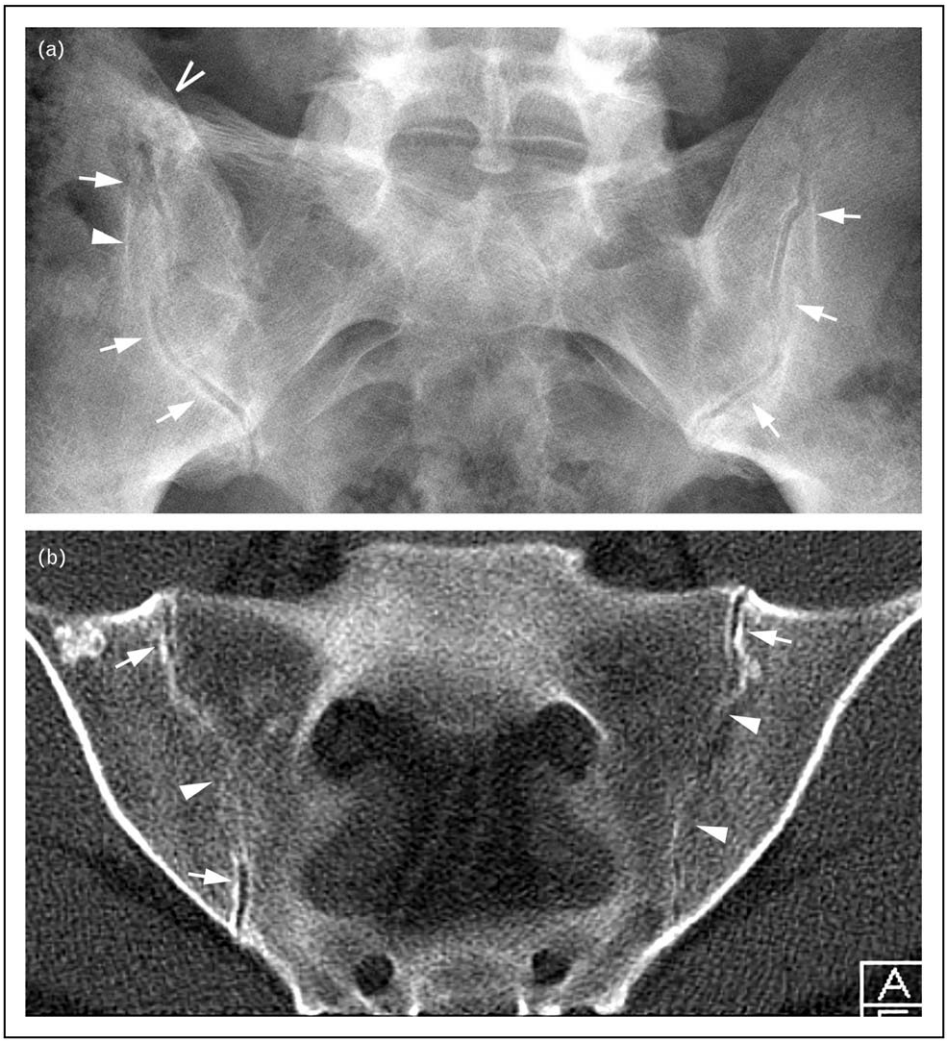

FIGURE 1. Radiographically occult findings may be revealed on low-dose computed tomography. SIJ images in a patient with known axial spondyloarthritis. Radiography (a) shows clearly defined joint spaces with smooth margins at many locations (arrows) but with subtle blurring in the midpart (arrowhead). Capsular ossification is noted on the right (open arrowhead) but there are no definite findings of axial spondyloarthritis. ldCT (b) also shows preserved joint space (arrows) in the anterosuperior and posteroinferior parts of the SIJ. However, the ldCT scan reveals extensive ankylosis in the midpart of the SIJ (arrowheads) that is invisible on radiography. The ankylosis is not well depicted in the radiograph as it is present only in parts of the joint that are not parallel to the X-ray beam. The joint space that is in profile is relatively unremarkable.

Disadvantages

The critical disadvantage of ldCT is its insensitivity for the detection of inflammation in soft tissues and both inflammation and fatty change in bone marrow. The presence of bone marrow edema (BME) is a crucial observation in the detection of the earliest phase of inflammatory sacroiliitis. BME is the MRI feature that is most sensitive for the detection of sacroiliitis and is an essential component of the classification of nr-axSpA [12]. Consequently, if a ldCT is negative for axSpA, that does not rule it out and an MRI may still be necessary. Further, the limited ability to detect BME prevents the use of ldCT for the assessment of disease activity or response to therapy for which MRI is clearly the superior test.

Dual-energy computed tomography

Dual-energy CT (DECT) can be used to create a 'virtual noncalcium CT' image capable of detecting BME in the SIJ. The technique appears to be about 90% sensitive and specific compared with MRI detection of BME and is reliable ($k = 0.8$) when sclerotic areas are excluded [13]. It also allows the detection of crystal deposition in soft tissues, especially sodium urate crystal deposits in gout. Unfortunately, DECT of the axial skeleton cannot be done at low dose as

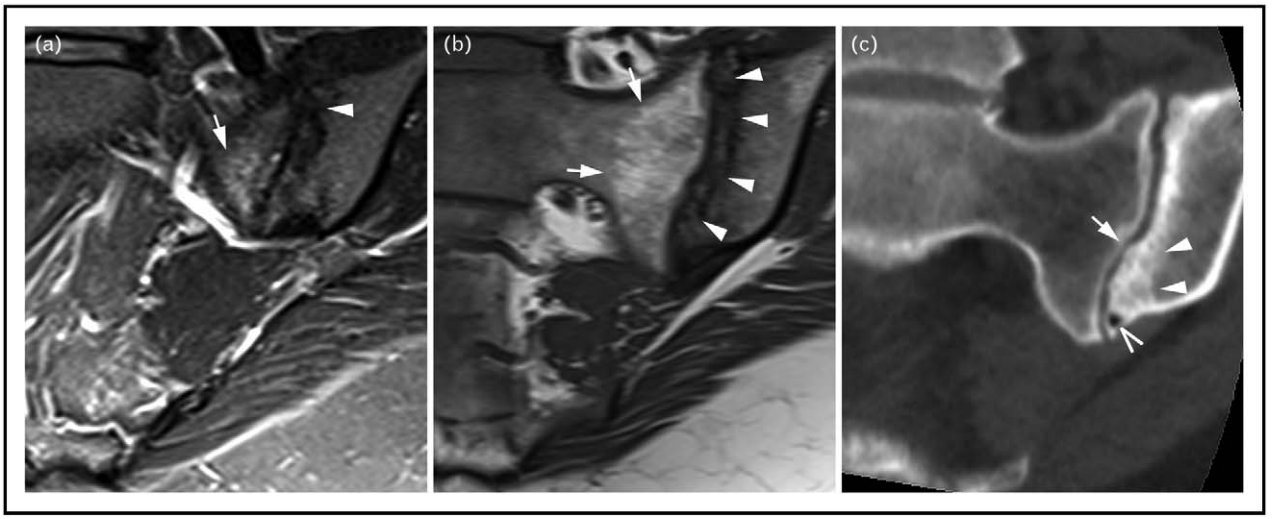

FIGURE 2. Low-dose computed tomography may be easier to interpret than MRI. This 45-year-old, HLA-B27 negative female patient presented with low back pain for 6 years, including similar pain during pregnancy 4 years previously. C-reactive protein was normal, there was no evidence of psoriasis, uveitis, dactylitis, or any other clinical feature of SpA. The short-tau inversion recovery (STIR) MRI sequence (a) shows mild bone marrow edema (BME) of the sacrum (arrow). Heterogeneous signal in the lower ilium is of uncertain significance but definite sclerosis (arrowhead) is present superiorly, confirmed on T1 MRI (b). Irregularity of the joint space on T1 (arrowheads in b), with possible joint space widening, is concerning for possible subtle iliac erosion. Fat metaplasia in sacral bone marrow (arrows) is easily seen. The MRI diagnosis was considered uncertain and ldCT was ordered (c). It shows subchondral sclerosis (arrowheads), joint space narrowing (arrow) and a pneumatocyst (open arrowhead) in the lower third of the SIJ, with no evidence of erosion. Although all the MRI and CT findings are consistent with biomechanical changes caused by osteoarthritis and possible mild osteitis condensans ilii (OCI), the degenerative findings on ldCT scan are much easier to interpret. ldCT, low-dose computed tomography.

low-energy X-rays are disproportionately absorbed in larger scan volumes, and the resulting loss of image quality must be compensated with correspondingly higher radiation exposure. For example, Wu *et al.* reported mean radiation dose of 7.4 mGy for the SIJ, which is 15 times the mean dose for ldCT [13].

When to perform low-dose computed tomography?

Which test should be done first will depend on local factors. ldCT may be the first choice if access to MRI is restricted. If MRI is readily available, then SIJ MRI would definitely be recommended. Even then, there is still an important role for ldCT for cases that are indeterminate on MRI as ldCT may be an excellent complementary test for further evaluation of difficult MRI cases (Fig. 2). However, newer MRI sequences offer equivalent bone information to CT and MRI may supplant the role of SIJ ldCT, if cost and availability are similar [6,14].

LOW-DOSE COMPUTED TOMOGRAPHY OF THE SPINE

Diagnostic ascertainment of axial spondyloarthritis is much less frequently an issue for spine imaging as most axSpA patients have SIJ disease prior to spine involvement. In contrast, detection of the presence or progression of structural damage in the spine has major prognostic significance in SpA and is a focus of intense research into the disease-modifying properties of biologic therapies.

The structural damage changes of greatest concern are significantly different in the spine and SIJ. In the SIJ, the most important structural damage is erosion. However, erosion is less frequent in the spine and the primary focus of spinal radiography or CT for SpA is detection of syndesmophytes and ankylosis (Fig. 3). The typical syndesmophyte is a small vertically orientated spur of bone arising from the edge of the vertebral endplate, at the perimeter of the intervertebral disc. Radiographs can show syndesmophytes well where they are seen in profile and free of superimposed structures, such as at the anterior aspects of the cervical and lumbar vertebral bodies. However, it is not always possible to get the vertebral endplates in profile and detection of fine detail in the thoracic spine is almost impossible with radiography because of overlapping ribs and lungs. So for axSpA, it is standard practice to perform only lateral views of the cervical and lumbar spine. With CT scanning, all the vertebral bodies, discs and facet joints are seen in high contrast and free of superimposition.

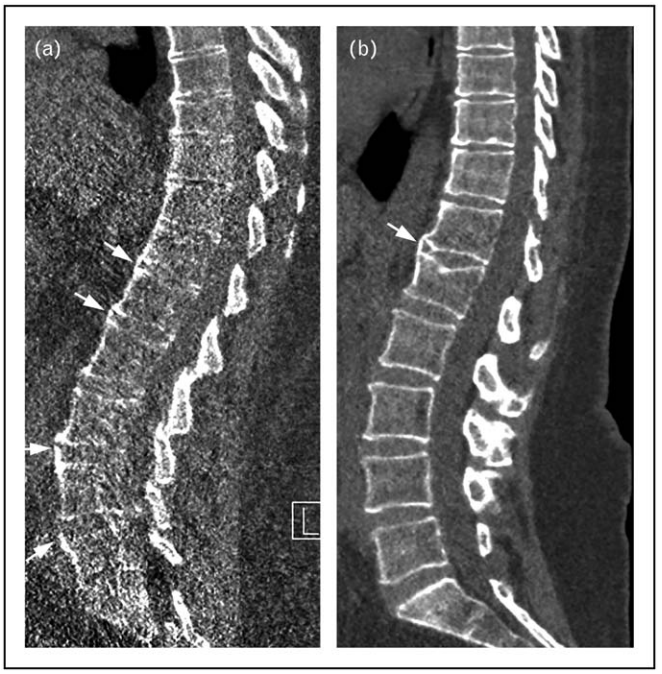

FIGURE 3. Radiation dose and image quality depend on patient size. Two patients with known ankylosing spondylitis (AS) were referred for ldCT assessment of syndesmophytosis and ankylosis. A large 50 year-old man (201 cm height, 136 kg weight) had 'low-dose CT' with exposure dose of 6.47 mGy (a). This is substantially less than would have been required for a full-dose CT in this patient. Signal strength is suboptimal and the resultant images are nondiagnostic quality at the posterior aspects of many vertebral bodies. However, the ldCT clearly shows multiple anterior syndesmophytes in the lumbar spine (arrows). A smaller 56-year-old woman (160 cm weight, 73 kg weight) had ldCT with exposure dose of 2.83 mGy (b). Image quality is very good and anterior ankylosis is clearly seen at T12/L1, although it is not known whether this was related to AS or an old L1 vertebral body compression injury. Both CT scans were performed with the same acquisition and reconstruction algorithms, and are displayed at the identical window setting. ldCT, low-dose computed tomography.

Radiation exposure

ldCT of the entire spine has been successfully performed in 59 out of 60 subjects with effective radiation dose of 4 mSv, including all 23 discovertebral units (DVU) from C2 to S1 [15]. This compares with radiation doses in the range of 2.7 mSv for multiple radiographic views of the cervical, thoracic and lumbar spine, and 0.36 mSv for lateral-only views at each spine level [16,17]. One can argue that comparison with the multiple-view series is more appropriate as clinicians would not hesitate to do all radiographic views if they were of clinical value and showed the target lesions. Thoracic spine radiographs are not performed in this setting as the images are useless even though the thoracic spine is involved. Standard dose CT of the entire spine is seldom performed because of its higher dose, for example, scanning the thoracolumbar spine from T5-L4 covering (11 DVU) involves a mean radiation dose of 8 mSv [18]. So it can be reasonably stated that ldCT of the entire spine with 4 mSv of radiation dose is: 'Very Low Risk' [7], significantly lower dose than full-dose CT of the entire spine (15 mSv [16]), and in the same risk category as, and only slightly more radiation than, multiple radiographic views of the entire spine (2.7 mSv [7,16]). It should be noted that large patients will be subject to greater radiation dose for both radiography and CT than the average numbers quoted (Fig. 3). However, for very large patients, increasing the radiation dose with CT almost always improves image quality but for radiography, the images may be of nondiagnostic quality no matter how large the radiation dose.

Diagnostic application

The incentive to do ldCT of the spine is the ability to see all levels projected free from overlapping structures. The most commonly used radiographic scoring system, mSASSS, only evaluates 12 DVU in the cervical and lumbar spine, and only the anterior corners of the vertebral bodies [19]. Whereas, ldCT will visualize all 23 DVU levels and with much greater consistency. With mSASSS, change in score can only be reliably detected with intervals of two or more years and new syndesmophytes are typically observed only in ~30% of patients [20,21]. de Bruin *et al.* [15] have shown that the thoracic spine contributes about 60% of total CT Syndesmophyte Score (CTSS) and 65% of the change score in their cohort. The highest percentage of patients (63%) and the highest percentage of vertebrae showing new syndesmophytes (63–68%) were in the thoracic spine, which is completely omitted with mSASSS. The same investigators compared CTSS using ldCT to mSASSS using radiography and showed that three to five times the number patients had three or more new or growing syndesmophytes with CTSS versus mSASSS, with most progression occurring in the thoracic spine [22]. These findings are in agreement with research done with standard-dose CT, which showed that structural damage changes of axSpA predominantly occur in the thoracic spine, and in this cohort, thoracic syndesmophytes were universally present in patients without visible lumbar syndesmophytes on either radiographs or CT [18].

ldCT of the entire spine is relatively new, and multiple aspects of this tool are currently unknown.

Can ldCT detect significant change over shorter intervals, such as 1 year? If this were to be the case, it could be a game changer for structural damage research in axSpA. Reader reliability was very good with CTSS; however, only two readers were used for this project and many logistical issues were not revealed, such as the duration and form of reader training, and the number of exercises required to reach proficiency. So it is unknown whether this reliability can be repeated in other settings. Interpretation of spine radiographs usually focusses on the structural damage changes related to the intervertebral discs even though facet joints and costovertebral joints (CVJ) are commonly involved. However, it is unknown whether the superior detection of change in structural damage in these small joints by ldCT would alter clinical or research outcomes.

Disadvantages

The major clinical disadvantage of ldCT is its inability to detect active disease in the form of bone marrow edema in the vertebrae and inflammation in facet joints and at entheses (Fig. 4). As with the SIJ, MRI is far better at detecting activity and this may be the more important question in day-to-day practice.

Radiography is cheaper, and usually more accessible than CT. In addition, radiographic images are generally very accessible to the rheumatologist. Two lateral radiographs of the cervical and lumbar spine may provide limited information but physicians can review them in a few seconds. The ldCT datasets are enormous with thousands of images. Although they can be reviewed quite quickly by scrolling through them with high-quality computers, the time needed to download the data and review each level,

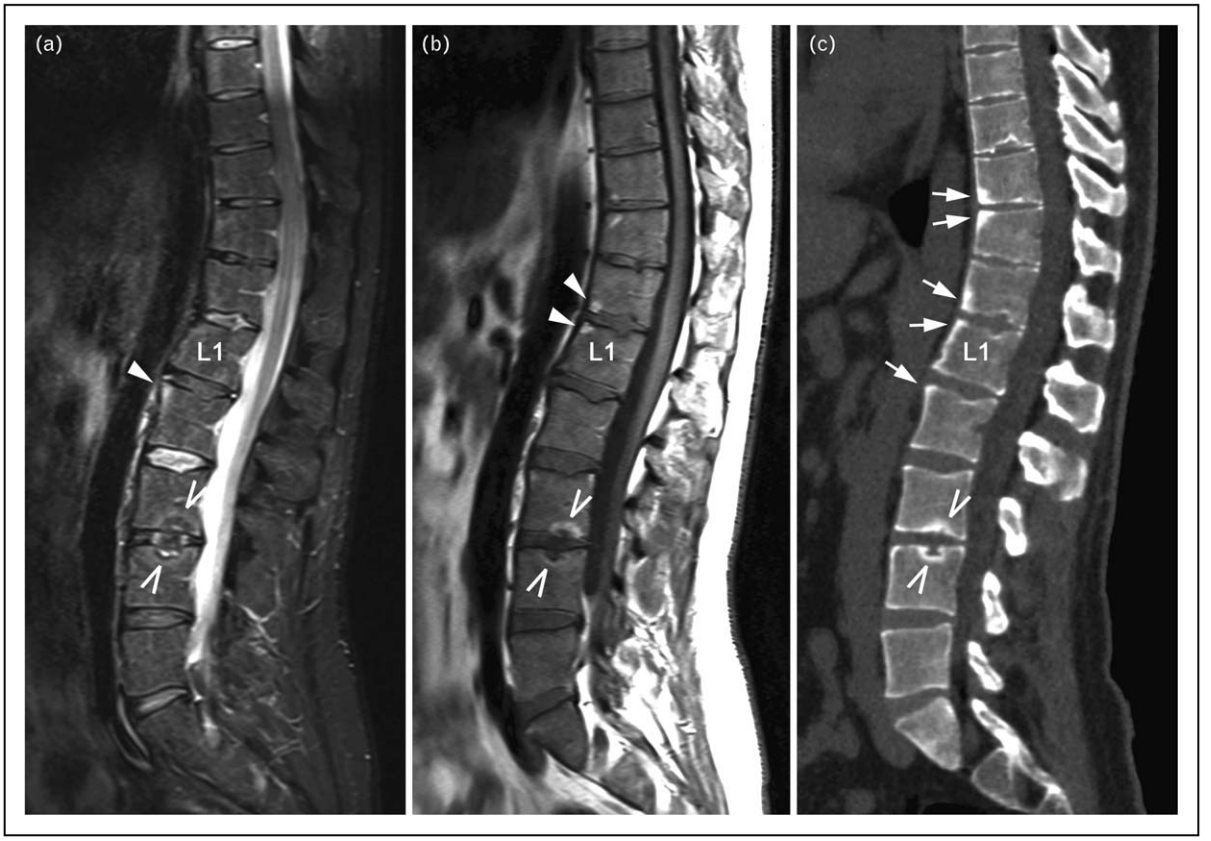

FIGURE 4. MRI and low-dose computed tomography provide complimentary information in the spine. A 38-year-old male patient with known axial spondyloarthritis and new low back pain underwent MRI with STIR (a) and T1 (b) sequences and ldCT of the spine (c). An inflammatory lesion is present at the anterosuperior corner of L2 with bone marrow edema (BME) on STIR [arrowhead in (a)]. Multiple small corner fat lesions are seen on T1, best appreciated anteriorly at T12/L1 [arrowheads in (b)]. The BME and fat lesions are not visible on ldCT. Foci of sclerosis at the anterior corners of multiple vertebral bodies are clearly seen on ldCT (arrows) but are either not visible at all or are much harder to discern on MRI. Vertebral endplate erosion is visible at L3/4 on STIR, T1 and ldCT (open arrowheads), more obvious at L4 and more subtle at L3. The information on each image is additive and the nature of the erosion, sclerosis, BME, fat metaplasia and inflammation in the erosion cavities cannot be fully appreciated without simultaneous interpretation of all three images. ldCT, low-dose computed tomography.

comparing them to previous time points, is a daunting task and not practical for a busy rheumatologist. The CTSS score is a research tool that is not intended for clinical practice; however, the output of an ldCT is fundamentally identical to a standard dose CT in terms of both spatial resolution and bone/soft-tissue contrast and so it may be suitable for an automated quantitative analysis of syndesmophyte volume and height, such as described by Tan *et al.* [18]. Although this will be hampered by increased noise in low-dose images, automated techniques are often suitable for further development with artificial intelligence, which could resolve many of the logistical obstacles to its widespread application.

ldCT could be used to assess the spine looking for complications of disease, such as spinal stenosis, fractures through areas of ankylosis and fragility fractures in osteoporosis although standard CT, scintigraphy and/or MRI are more likely to be used in these circumstances. Currently, there is no role for spinal ldCT in children with axSpA because of radiation exposure.

CONCLUSION

ldCT of the SIJ can be done at exposure levels equivalent to, or less than, conventional radiography and should be considered 'minimal risk' for radiation exposure. SIJ ldCT is fast and reliable with excellent diagnostic performance, and wherever available, it should completely replace radiography of the SIJ in daily clinical practice.

With respect to the spine, the superiority of ldCT over radiography for detecting structural damage is convincing and ldCT of the entire spine is 'very low radiation risk'. However, MRI is superior for detecting disease activity and the critical question remains as to whether the additional information regarding structural damage in the spine provided by ldCT is important enough to justify the slight increase in radiation dose and whether rheumatologists need this information for the betterment of the care of their patients or only for research purposes.

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None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

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

1. Zabak E, Omar H, Boothe E, *et al.* Radiation dose reduction for musculoskeletal computed tomography of the pelvis with preserved image quality. Skeletal Radiol 2019; 48:375–385.
2. Kim JN, Park HJ, Kim MS, *et al.* Radiation dose reduction in extremity multidetector CT: a comparison of image quality with a standard dose protocol. Eur J Radiol 2021; 135:109405.
3. ■■ Korcakova E, Stepankova J, Suchy D, *et al.* Is ultra low-dose CT with tin filtration useful for examination of SI joints? Can it replace X-ray in diagnostics of sacroiliitis? Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2021; doi: 10.5507/bp.2021.008. [Epub ahead of print]

This study shows that radiation exposure from low-dose CT of the SIJ (0.11mSv) can be reduced to the same level as a chest x-ray (two views) while maintaining diagnostic quality.

4. Hackenbroch C, Feilhuber M, Halt D, *et al.* Low-dose CT in pelvic imaging: comparing dose and image quality in relation to clinical value in a phantom study. AJR Am J Roentgenol 2021; 216:453–463.
5. ■ Chahal BS, Kwan ALC, Dhillon SS, *et al.* Radiation exposure to the sacroiliac joint from low-dose CT compared with radiography. AJR Am J Roentgenol 2018; 211:1058–1062.

This study confirmed that ldCT of the SIJ can be consistently done at exposure levels equal to or less than radiography and recommended that ldCT should completely replace radiography of the SIJ.

6. Diekhoff T, Hermann KG, Greese J, *et al.* Comparison of MRI with radiography for detecting structural lesions of the sacroiliac joint using CT as a standard of reference: results from the SIMACT study. Ann Rheum Dis 2017; 76:1502–1508.
7. Martin CJ. Effective dose: how should it be applied to medical exposures? Br J Radiol 2007; 80:639–647.
8. Braun J, Sieper J, Bollow M. Imaging of sacroiliitis. Clin Rheumatol 2000; 19:51–57.
9. Puhakka KB, Jurik AG, Egund N, *et al.* Imaging of sacroiliitis in early seronegative spondylarthropathy: assessment of abnormalities by MR in comparison with radiography and CT. Acta Radiol 2003; 44:218–229.
10. van Tubergen A, Heuft-Dorenbosch L, Schulpen G, *et al.* Radiographic assessment of sacroiliitis by radiologists and rheumatologists: does training improve quality? Ann Rheum Dis 2003; 62:519–525.
11. ■ Ye L, Liu Y, Xiao Q, *et al.* MRI compared with low-dose CT scanning in the diagnosis of axial spondyloarthritis. Clin Rheumatol 2020; 39:1295–1303.

This study confirms that ldCT identifies evidence of SpA changes in a significant proportion of nr-axSpA cases and is highly specific for axSpA.

12. Lambert RG, Bakker PA, van der Heijde D, *et al.* Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. Ann Rheum Dis 2016; 75:1958–1963.
13. Wu H, Zhang G, Shi L, *et al.* Axial spondyloarthritis: dual-energy virtual noncalcium CT in the detection of bone marrow edema in the sacroiliac joints. Radiology 2019; 290:157–164.
14. Jans LBO, Chen M, Elewaut D, *et al.* MRI-based synthetic CT in the detection of structural lesions in patients with suspected sacroiliitis: comparison with MRI. Radiology 2021; 298:343–349.
15. de Bruin F, de Koning A, van den Berg R, *et al.* Development of the CT Syndesmophyte Score (CTSS) in patients with ankylosing spondylitis: data from the SIAS cohort. Ann Rheum Dis 2018; 77:371–377.
16. Mettler FA, Huda W, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology 2008; 248:254–263.
17. Teeuwisse W, Geleijns J, Veldkamp W. An inter-hospital comparison of patient dose based on clinical indications. Eur Radiol 2007; 17:1795–1805.
18. Tan S, Yao L, Ward MM. Thoracic syndesmophytes commonly occur in the absence of lumbar syndesmophytes in ankylosing spondylitis: a computed tomography study. J Rheumatol 2017; 44:1828–1832.
19. Creemers MC, Franssen MJ, van't Hof MA, *et al.* Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis 2005; 64:127–129.
20. Spoorenberg A, de Vlam K, van der Linden S, *et al.* Radiological scoring methods in ankylosing spondylitis. Reliability and change over 1 and 2 years. J Rheumatol 2004; 31:125–132.
21. Baraliakos X, Listing J, Rudwaleit M, *et al.* Progression of radiographic damage in patients with ankylosing spondylitis: defining the central role of syndesmophytes. Ann Rheum Dis 2007; 66:910–915.
22. de Koning A, de Bruin F, van den Berg R, *et al.* Low-dose CT detects more progression of bone formation in comparison to conventional radiography in patients with ankylosing spondylitis: results from the SIAS cohort. Ann Rheum Dis 2018; 77:293–299.

REVIEW

OPEN

Out of the shadow of interleukin-17A: the role of interleukin-17F and other interleukin-17 family cytokines in spondyloarthritis

Nataliya Yeremenko[a,b]

Purpose of review
The last decade has witnessed tremendous advances in revealing an important role for the interleukin (IL)-17 cytokine family in the pathogenesis of spondyloarthritis (SpA). Although most attention has been focused on IL-17A, a potential role of other IL-17 family members in inflammation and tissue remodelling is emerging. Herein, I review recent studies covering the role of IL-17B-F cytokines in the pathogenesis of SpA.

Recent findings
Several recent studies provided new insights into the cellular source, regulation and function of IL-17F. IL-17F/IL-17A expression ratio is higher in psoriatic skin compared to SpA synovitis. IL-17F-expressing T cells produce different proinflammatory mediators than IL-17A-expressing cells, and IL-17F and IL-17A signal through different receptor complex. Dual IL-17A and IL-17F neutralization resulted in greater suppression of downstream inflammatory and tissue remodelling responses. Furthermore, there is additional evidence of IL-23-independent IL-17 production. In contrast to IL-17A, IL-17F and IL-17C, which play proinflammatory roles in skin and joint inflammation, an anti-inflammatory function is proposed for IL-17D. An increase in IL-17E is associated with subclinical gut microbiome alterations after anti-IL-17A therapy in SpA patients.

Summary
IL-17 family cytokines may act as agonists or antagonists to IL-17A contributing in concert to local inflammatory responses. Understanding their function and identifying their cellular sources, and molecular mechanisms driving their expression will be the key to designing rational therapies in SpA.

Keywords
interleukin-17C, interleukin-17D, interleukin-17E, interleukin-17F, interleukin-17 family cytokines, spondyloarthritis

INTRODUCTION

Strong evidence from clinical trials firmly placed interleukin 17A (IL-17A) in the centre of the pathogenesis of the spondyloarthritides (SpA), the group of related but phenotypically heterogeneous conditions that share common genetic and pathogenetic features [1–6]. Responders to anti-IL-17A therapy included naïve patients and those who did not respond to previous treatments [7–10]. Importantly, emerging evidence indicates that targeting IL-17A slows down structural damage (including bone erosions and pathological new bone formation) as IL-17A blockade inhibits radiographic disease progression in both, psoriatic arthritis (PsA) [6,11] and ankylosing spondylitis (AS) [12]. In addition, recent data suggest that IL-17A inhibition improves enthesitis in patients with PsA [13] and AS [14].

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KEY POINTS

- Innate cells, including MAIT, γδ T cells and ILC3s do not require IL-23 for IL-17F and IL-17A production.
- IL-17F-expressing and IL-17A-expressing T cells are differentially regulated and produce different pro-inflammatory mediators.
- A dominant IL-17F signature has been observed in PsO skin compared with a stronger IL-17A signature in SpA synovium.
- Preclinical data support the concept that dual blockade of IL-17A and IL-17F is required for optimal inhibition of downstream inflammatory and tissue remodelling responses.
- Clinical trials of dual IL-17A and IL-17F inhibition indicate high efficacy in PsO, PsA and AS.
- Head-to-head studies of bimekizumab and anti-IL-17A treatment are required to further evaluate whether targeting of both, IL-17A and IL-17F cytokines is superior to inhibition of IL-17A alone.
- The IL-17 family cytokines may act complementary or antagonistic to IL-17A contributing to the local inflammatory responses in SpA.

As to the related extra-articular manifestations, anti-IL-17A therapy demonstrated impressive clinical efficacy in treating skin psoriasis (PsO) [3,15,16], but was not effective in treating colitis [17] or uveitis [18]. In contrast, unexpectedly, blocking IL-23, the cytokine upstream of IL-17A was not effective in AS [19,20] though anti-IL-23 therapy did improve colitis [21,22]. Overall, the IL-17 axis holds great promise for the development of further disease-modifying therapeutic opportunities in SpA. However, the inability of IL-17A blockers to cover the entire disease spectrum and to achieve a major clinical response and sustained remission underscores the importance of the identification of additional drivers of the pathologic immune responses, tissue-specific pathways, and hierarchies. The list of attractive candidates comprises other IL-17 family members: IL-17B, IL-17C, IL-17D, IL-17E and IL-17F [23–25]. These structurally related to IL-17A yet less well-characterized cytokines could play complementary or antagonistic roles, hence may affect IL-17A-driven tissue inflammation and/or remodelling, contributing to the pathology of SpA. This review highlights the most recent studies featuring the role of IL-17B-F cytokines in SpA.

INTERLEUKIN-17F

Among the IL-17 family members, IL-17F shares the highest homology (55%) with IL-17A. Both cytokines can exist as disulphide-linked homodimers or as IL-17A/IL-17F heterodimers [26]. It was postulated that IL-17F is co-produced with IL-17A by Th17 cells under the control of STAT3 and RORgt transcription factors [27] and signals via the same heterodimeric receptor consisting of IL-17RC and IL-17RA. Similar to IL-17A, although to a lesser extent, IL-17F can synergize with other pro-inflammatory molecules, particularly with tumor necrosis factor alpha, but also with IL-1β, interferon (IFN)-γ and lipopolysaccharide, amplifying its inflammatory potential [28]. Therefore, a similar, albeit less potent pro-inflammatory function has been proposed for IL-17F in driving pathogenic responses. Recent studies have provided new insights into the cellular source, regulation and function of IL-17F.

Interleukin-23-independent production of interleukin-17A and interleukin-17F

Cole and colleagues [29▪▪] present important novel insight into the biology of IL-17A-producing and IL-17F-producing innate cells. They demonstrated that IL-17F is the dominant isoform produced by *in vitro*-stimulated mucosal-associated invariant T (MAIT) cells, a unique population of innate-like T cells with restricted T cell receptor (TCR) diversity that can function through both TCR-dependent and -independent pathways [30,31]. IL-17A-producing MAIT cells were identified in PsO skin [32] and PsA and AS joint [33–35], and their potential role in SpA pathogenesis is emerging [36,37]. Importantly, Cole *et al.* showed that MAIT cells can produce IL-17F (and IL-17A) in an IL-23-independent fashion, in response to TCR triggering combined with IL-12 and IL-18 cytokines stimulation *in vitro* [29▪▪]. In addition, ILC3s and γδ T cells were also capable of an IL-23-independent IL-17A and IL-17F production [29▪▪], supporting recent evidence that human entheseal γδ T cells can produce IL-17A without IL-23 receptor expression [38]. These data prompt the notion that IL-23-independent IL-17A and IL-17F production is a feature shared among innate lymphocyte family members [29▪▪]. Remarkably, the cytokine milieu that tunes the IL-17A and IL-17F production seems to be cell-type dependent. In contrast to MAIT and γδ T cells, which were dependent on IL-12 for IL-23-independent IL-17A and IL-17F production, ILC3s did not require IL-12 or IL-23 and produced IL-17A and IL-17F upon stimulation with IL-1β, IL-2 and IL-7 [29▪▪]. The ability of T cells and innate(-like) lymphocytes to produce IL-17A in response to cytokines other than canonical IL-23, in particular to IL-7 and IL-9 [34,39,40], has been demonstrated before [41–43]. Such IL-12-IL-23-independent IL-17A and IL-17F production by these, presumably (but not yet

proven) pathogenic cellular subsets could explain why targeting p19 subunit that is unique to IL-23, or p40 subunit common to both, IL-12 and IL-23, were not efficacious in AS [19,20]. As to the peripheral disease, our recent study investigating cellular and molecular changes in the PsA joint in response to IL-12/IL-23 blockade with ustekinumab revealed that although ustekinumab suppressed synovial inflammation through modulation of key pathogenic pathways, expression of IL-17A and IL-17F remained unaffected [44], supporting IL-23-independent IL-17A and IL-17F production in PsA joint. Whether it has a pathogenetic significance has to be assessed in head-to-head clinical trials of IL-17A or IL-17A-IL-17F versus IL-23 antagonists. Yet, a recent retrospective study in PsA demonstrated that treatment with secukinumab has a greater persistence rate than the treatment with ustekinumab [45]. Taken together, the emergence of distinct pathways culminating in the secretion of IL-17A and IL-17F cytokines, in addition to the canonical IL-23/IL-17A pathway, underscores the importance of the IL-17A/IL-17F axis in the pathogenesis of SpA, provides insights into understanding results of clinical trials and urges to identify pathogenic cell populations in target tissues.

Distinct regulation and function of interleukin-17F

Recent findings challenged the notion that IL-17F has a redundant role in SpA pathogenesis. In the study of Cole *et al.*, only a minor population of MAIT cells produced IL-17A upon *in vitro* stimulation despite uniform expression of RORgt. Instead, MAIT cells as well as ILC3s and γδ T cells produced predominantly IL-17F [29▪▪], supporting the concept that IL-17A and IL-17F are differentially regulated [46,47]. High expression of IL-17F can be also induced in canonical CD4+ T cells [48▪▪], but in contrast to innate lymphocytes, this process is dependent on IL-23. In this study, Burns *et al.* identified and characterized three CD4+ T cell subsets: IL-17A+IL-17F-, IL-17A+IL-17F+, and IL-17A-IL-17F+. Interestingly, these populations displayed different cytokine profiles: while all subsets contained similarly high frequencies of cells expressing TNF, IL-17A-IL-17F+ cells expressed less IL-10 and GM-CSF and more IFN-γ compared to IL-17A+IL-17F- CD4+ T cells [48▪▪]. Based on previous molecular characterization of IL-10-expressing Th17 subsets [49], the authors proposed that IL-17F-expressing CD4+ T cells might represent the 'pathogenic' subtype, although in-depth molecular and functional characterization of these cells is required to conclude about their pathogenicity. Notably, IL-17F and IL-17A-expressing T cells differ not only in their molecular profiles but also are differentially regulated. Comparing the induction of CD4+ T cells by LPS-activated monocytes versus soluble anti-CD28 mAb and L-1β and IL-23 stimulation, Burns and colleagues observed that while both stimuli induced IL-17A+IL-17F+ CD4+ T cells, only the latter resulted in IL-17F+IL-17A- CD4+ T cells [48▪▪]. Further analysis revealed that IL-17F expression in CD4+ T cells is driven by high-strength TCR stimulation in the presence of IL-23 and IL-1β. IL-17F induction is partially mediated via IL-2-dependent mechanism, as IL-2 blockade significantly reduced the CD28-mediated increase in frequencies of IL-17F+ CD4+ T cells [48▪▪], in line with previous findings showing that high levels of IL-2 shift the balance between IL-17A and IL-17F towards IL-17F production by murine T cells *in vitro* [50]. Interestingly, another study in mice demonstrated that the activation of transmembrane TNF (tmTNF)-TNF Receptor 2 signalling stimulates IL-2 expression and regulates IL-2 mRNA stability [51]. Given a marked increase of tmTNF in SpA synovitis and its impact on key pathological features of SpA [52] along with the observation that IL-17F levels are strikingly higher than IL-17A in the blood of patients with SpA [53] it might be revealing to examine tmTNF-IL-17F axis in SpA. Importantly, reports by Cole *et al.* and Burns *et al.* demonstrate that IL-17F is not only differentially regulated but also significantly contributes to inflammation, as dual IL-17A and IL-17F blockade were more effective at reducing IL-17-driven pro-inflammatory responses by human dermal fibroblasts [29▪▪] and synovial fibroblasts [48▪▪] compared to blockade of IL-17A alone, according to previous findings [54] (Fig. 1). Attempting to detect IL-17F-expressing cells *ex vivo*, Cole *et al.* confirmed the presence of single-positive for IL-17A or IL-17F, as well as double-positive MAIT cells in psoriatic lesional skin [29▪▪] (Fig. 1). In contrast, Burns *et al.* failed to detect the presence of IL-17F-expressing cells in PsA synovial fluid directly *ex vivo*, although confirmed the potential of synovial fluid mononuclear cells to produce IL-17F upon *in vitro* stimulation [48▪▪]. Could be these discrepancies explained by tissue-specific expression of IL-17F? Previous findings demonstrated that IL-17F levels are approximately 30-fold higher than IL-17A levels in PsO skin [53]. Our recent study using paired biopsies of skin and synovium collected from PsA patients with active PsO confirmed a higher IL-17F to IL-17A ratio in the inflamed skin and revealed that the relative expression of IL-17A versus IL-17F is inversed in inflamed joint and skin compartments with IL-17A being more than 30-fold higher than IL-17F in the joint [55▪] (Fig. 1). Taken together these *in vitro* and *ex vivo*

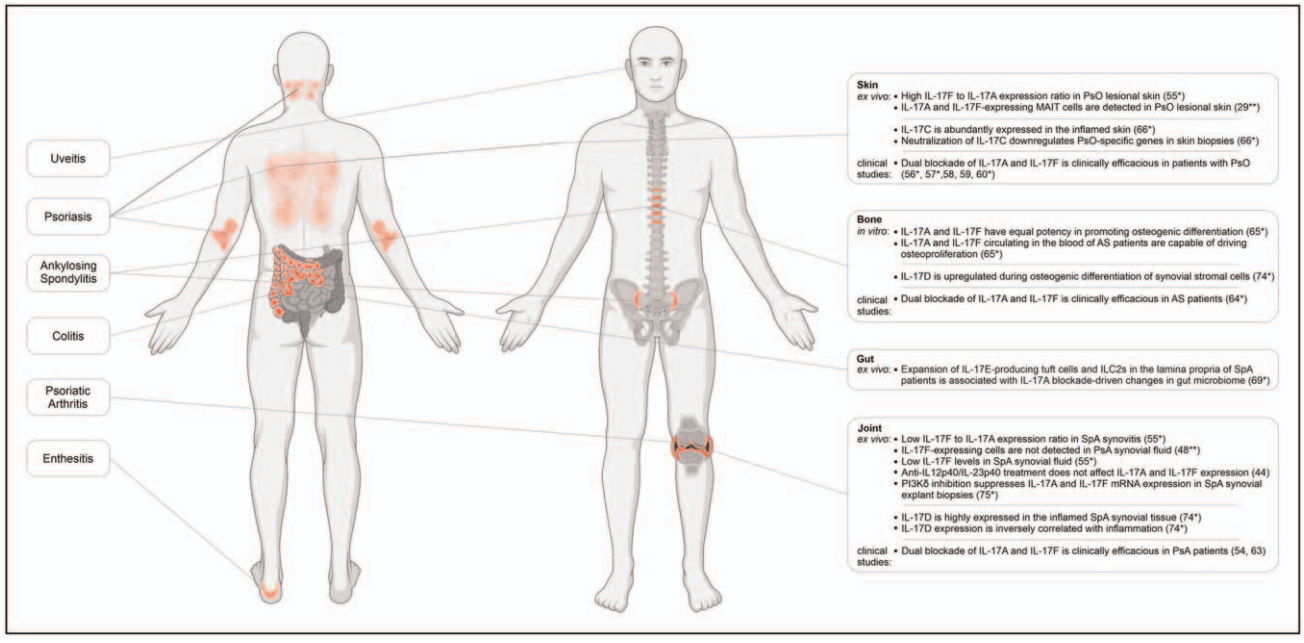

FIGURE 1. Recent *ex vivo, in vitro and in vivo* evidence supporting the role of IL-17 family cytokines in the pathogenesis of SpA. Created with BioRender.com. SpA, spondyloarthritis.

data point towards a nonredundant role for IL-17F and provide new pathobiological insights in joint versus skin inflammation, suggesting that (1) the contribution of IL-17F to chronic tissue inflammation may be more prominent in the skin than in joint; (2) IL-17F has the potential to contribute to pathology, therefore dual blockade of IL-17A and IL-17F can further reduce inflammation.

The preclinical data supporting the efficacy of the dual IL-17A and IL-17F blockade is further underpinned by recent clinical-trials evidence for bimekizumab, a humanized monoclonal IgG1 antagonist neutralizing both cytokines [54]. Two recent Phase 3 studies reported the safety and efficacy of bimekizumab for the treatment of moderate to severe plaque PsO [56▪,57▪] confirming phase 2 findings [58,59] and revealing the superiority of dual IL-17A and IL-17F targeting to the targeting of IL-12/IL-23 in achieving complete skin clearance. Similarly, simultaneous inhibition of IL-17A and IL-17F in patients with PsO was more effective than inhibition of TNF in terms of the speed, depth and durability of skin clearance [60▪]. Superior efficacy of IL-17A blockade relative to inhibition of IL-12/IL-23[61] and TNF [62] in clearing skin PsO has been demonstrated previously. Ongoing head-to-head comparator study of bimekizumab and anti-IL-17A treatment (BE RADIANT, http://clinicaltrials.gov/ct/show/NCT03536884) will provide important knowledge on whether targeting of both cytokines is clinically more beneficial than inhibition of IL-17A alone. Bimekizumab is also effective in treating peripheral and axial SpA. It has been first assessed in the proof-of-concept study [54] and strengthened in followed up phase 2b study that patients with PsA, who were administered bimekizumab, showed marked and sustained improvements in their condition compared with placebo [63]. Also, for an axial disease, a phase 2b study revealed a rapid onset and greater ASAS40 response rates as well as sustained improvements across secondary outcomes of disease activity for bimekizumab versus placebo [64▪].

Role in bone pathology

Another recent study employing an *in vitro* model of osteogenic differentiation of human periosteal cells puts forward the argument that IL-17F does not only contribute to IL-17A but has equal potency in promoting osteogenic differentiation, in contrast to its less potent role in driving inflammatory responses [65▪] (Fig. 1). IL-17A and IL-17F cytokines, circulating in the blood of AS patients, are also functionally active as they were capable of driving osteoproliferation *in vitro* [65▪] (Fig. 1). Accordingly, neutralization of both cytokines by bimekizumab resulted in greater suppression of γδ or Th17 T-cell supernatants-mediated, or AS patient's serum-mediated *in vitro* bone formation than the blockade of IL-17A or IL-17F individually [65▪]. These results provide further scientific evidence to validate the clinical relevance of the dual IL-17A and IL-17F blockade in patients with AS for preventing or suppressing pathological periosteal bone formation.

OTHER MEMBERS OF THE INTERLEUKIN-17 FAMILY

A very limited number of recent studies address the role of other IL-17 family members in SpA. Lauffer *et al.* demonstrated that IL-17C, a member of the IL-17 family that, in contrast to IL-17A and IL-17F, is mainly produced by epithelial cells and keratinocytes, is broadly expressed in the inflamed skin of patients with various inflammatory skin diseases including but not limited to PsO [66▪]. The study revealed that IL-17C establishes a self-amplifying circuit in synergy with TNF, leading to the secretion of pro-inflammatory cytokines by keratinocytes and the recruitment of immune cells to the site of inflammation (Fig. 1). Using human disease models, Lauffer *et al.* demonstrated significant downregulation of PsO-specific genes after neutralization of IL-17C, considering IL-17C as a promising drug target for the treatment of inflammatory skin diseases [66▪]. However, since IL-17C is regulated by IL-17A and TNF, as both therapies rapidly reduce IL-17C expression in PsO skin [67,68], the added-value of the developing of IL-17C-specific therapy in SpA needs to be further established.

Another recent study suggests an association between IL-17A blockade-driven changes in the gut microbiome of SpA patients and the expansion of IL-17E-producing tuft cells and ILC2s in the lamina propria [69▪]. Whether IL-17E drives gut inflammation after IL-17A inhibition remains to be assessed. IL-17E has been shown to promote PsO [70], however, its role in gut inflammation is confusing as it has been demonstrated to induce colitis [71,72] or to protect against colitis [73].

IL-17D is the least investigated member of the IL-17 family. Our recent data on the cellular source and function of IL-17D suggest its unique position among other IL-17 family cytokines [74▪]. First, IL-17D is abundantly expressed in inflamed SpA joint, higher than other IL-17 cytokines. Second, IL-17D is expressed by stromal cells, in particular, by cells similar to multipotent mesenchymal stromal cells. Third, IL-17D expression inversely correlates with inflammation (Fig. 1). Furthermore, IL-17D is upregulated during osteogenic differentiation of synovial stromal cells *in vitro*. However, *in vitro* functional assays in bone precursor cells and *in vivo* experiments in *IL-17d–/–* mice failed to demonstrate a critical role for IL-17D in bone homeostasis. Instead, *IL-17d–/–* mice were more prone to arthritis development than littermate controls and presented with enhanced systemic inflammation at the peak of serum-transfer arthritis [74▪]. Based on these data it is tempting to propose that IL-17D exerts an anti-inflammatory effect on synovial cells, yet further research is required to address its role in the pathogenesis of SpA.

DIRECTIONS FOR FUTURE RESEARCH

Further investigations of the exact mechanisms of production and function of IL-17 family members will provide novel insights into their roles in SpA pathogenesis and may have direct relevance for the targeted therapy. Could we imagine other ways to target IL-17A and IL-17F production? Recently we demonstrated that PI3Kδ inhibition dampens both IL-17A and IL-17F expression in innate-like lymphocytes and Th17 cells in IL-23-independent and the dependent manner *in vitro* as well as in primary cells derived from blood and synovial fluid of SpA patients [75▪]. This inhibition has functional anti-inflammatory and anti-remodelling effects on target cells, such as synovial fibroblasts. Furthermore, we demonstrated that the PI3K-Akt-mTOR pathway is active in the SpA joint and PI3Kδ inhibition suppresses IL-17A and IL-17F expression in SpA synovial explant biopsies *ex vivo* [75▪]. In light of the results from in vitro models, simultaneous suppression of IL-17A and IL-17F is a promising direction in IL-17-mediated diseases, however, more data is needed to conclude about its added value on clinical response over IL-17A inhibition. Moreover, accumulating evidence suggests that IL-17A and IL-17F may exert distinct, even opposite downstream activities, which may impact the clinical outcome. For instance, IL-17A-blockade is ineffective for Crohn's disease [17]. It was concluded, that IL-17A is important for maintaining barrier integrity and has a protective role in colitis [76]. However recent data may suggest an alternative explanation. First, the IL-17F pathway has been demonstrated to promote inflammation in the intestines through its effect on the intestinal microbiome. Consequently, IL-17F neutralization suppressed the development of colitis whereas blocking of IL-17A did not [77]. Second, a recent mechanistic study revealed that IL-17A inhibits the expression of IL17-lineage cytokines through a negative feedback loop. Accordingly, the loss of IL-17A in Th17 cells did not reduce their pathogenicity, resulting in the elevated expression of GM-CSF and IL-17F cytokines [78]. Third, recent findings demonstrated that in contrast to IL-17A homodimers or IL-17A/IL-17F heterodimers that signal via heterodimeric IL-17RA/IL-17RC receptor, IL-17F preferentially associates with IL-17RC homodimers, leading to IL-17RA-independent signalling [79▪]. Given that it is plausible to propose that aggravation of Crohn's pathology by IL-17A neutralization could be not due to a decrease

in IL-17A but rather due to upregulation of IL-17F and increased signalling via IL-17RC/IL-17F axis. In this context, it is perhaps not surprising that anti-IL-17RA treatment with brodalumab resulted in worsening Crohn's disease [80].

CONCLUSION

Accumulating evidence suggests that IL-17 family members have tissue-specific functions in inflammation. Their differential cellular sources, expression levels and function in different target tissues could contribute to tissue-discrete results for IL-17 axis inhibition across the SpA spectrum. Additionally, there is evidence for interaction between IL-17 cytokines, including self-reinforcing, feed-forward as well as negative feedback mechanisms leading to agonistic or antagonistic effects on tissue inflammation and/or remodelling. Therefore understanding the function of IL-17 family cytokines, as well as detailed characterization of cellular subsets and molecular mechanisms culminating in their expression, will be the key to designing rational therapies in SpA.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

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

- ■ of special interest
- ■■ of outstanding interest

1. Baeten D, Sieper J, Braun J, *et al.* Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med 2015; 373:2534–2548.
2. McInnes IB, Mease PJ, Kirkham B, *et al.* Secukinumab, a human antiinterleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015; 386:1137–1146.
3. Mease PJ, van der Heijde D, Ritchlin CT, *et al.* Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis 2017; 76:79–87.
4. Mease PJ, Genovese MC, Greenwald MW, *et al.* Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. N Engl J Med 2014; 370:2295–2306.
5. Mease PJ, McInnes IB, Kirkham B, *et al.* Secukinumab inhibition of interleukin-17A in Patients with psoriatic arthritis. N Engl J Med 2015; 373:1329–1339.
6. Mease P, van der Heijde D, Landewe R, *et al.* Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. Ann Rheum Dis 2018; 77:890–897.
7. Sieper J, Deodhar A, Marzo-Ortega H, *et al.* Secukinumab efficacy in anti-TNF-naive and anti-TNF-experienced subjects with active ankylosing spondylitis: results from the MEASURE 2 Study. Ann Rheum Dis 2017; 76:571–592.
8. Deodhar A, Poddubnyy D, Pacheco-Tena C, *et al.* Efficacy and safety of ixekizumab in the treatment of radiographic axial spondyloarthritis: sixteen-week results from a Phase III randomized, double-blind, placebo-controlled trial in patients with prior inadequate response to or intolerance of tumor necrosis factor inhibitors. Arthritis Rheumatol 2019; 71:599–611.
9. Deodhar A, van der Heijde D, Gensler LS, *et al.* Ixekizumab for patients with nonradiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial. Lancet 2020; 395:53–64.
10. Dougados M, Wei JC, Landewe R, *et al.* Efficacy and safety of ixekizumab through 52 weeks in two phase 3, randomised, controlled clinical trials in patients with active radiographic axial spondyloarthritis (COAST-V and COAST-W). Ann Rheum Dis 2020; 79:176–185.
11. van der Heijde D, Mease PJ, Landewe RBM, *et al.* Secukinumab provides sustained low rates of radiographic progression in psoriatic arthritis: 52-week results from a phase 3 study, FUTURE 5. Rheumatology 2020; 59:1325–1334.
12. Braun J, Baraliakos X, Deodhar A, *et al.* Secukinumab shows sustained efficacy and low structural progression in ankylosing spondylitis: 4-year results from the MEASURE 1 study. Rheumatology 2019; 58:859–868.
13. Gladman DD, Orbai AM, Klitz U, *et al.* Ixekizumab and complete resolution of enthesitis and dactylitis: integrated analysis of two phase 3 randomized trials in psoriatic arthritis. Arthritis Res Ther 2019; 21:38.
14. Schett G, Baraliakos X, Van den Bosch F, *et al.* Secukinumab efficacy on enthesitis in patients with ankylosing spondylitis: pooled analysis of four pivotal Phase 3 studies. J Rheumatol 2021; Mar 15:jrheum.201111. doi: 10.3899/jrheum.201111. [Epub ahead of print]
15. Thaci D, Blauvelt A, Reich K, *et al.* Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol 2015; 73:400–409.
16. Gordon KB, Colombel JF, Hardin DS. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med 2016; 375.
17. Hueber W, Sands BE, Lewitzky S, *et al.* Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut 2012; 61:1693–1700.
18. Dick AD, Tugal-Tutkun I, Foster S, *et al.* Secukinumab in the treatment of noninfectious uveitis: results of three randomized, controlled clinical trials. Ophthalmology 2013; 120:777–787.
19. Baeten D, Ostergaard M, Wei JC, *et al.* Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: results of a randomised, double-blind, placebo-controlled, proof-of-concept, dose-finding phase 2 study. Ann Rheum Dis 2018; 77:1295–1302.
20. Deodhar A, Gensler LS, Sieper J, *et al.* Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. Arthritis Rheumatol 2019; 71:258–270.
21. Sands BE, Sandborn WJ, Panaccione R, *et al.* Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2019; 381:1201–1214.
22. Hanzel J, D'Haens GR. Antiinterleukin-23 agents for the treatment of ulcerative colitis. Expert Opin Biol Ther 2020; 20:399–406.
23. Li H, Chen J, Huang A, *et al.* Cloning and characterization of IL-17B and IL-17C, two new members of the IL-17 cytokine family. Proc Natl Acad Sci USA 2000; 97:773–778.
24. Lee J, Ho WH, Maruoka M, *et al.* IL-17E, a novel proinflammatory ligand for the IL-17 receptor homolog IL-17Rh1. J Biol Chem 2001; 276:1660–1664.
25. Starnes T, Robertson MJ, Sledge G, *et al.* Cutting edge: IL-17F, a novel cytokine selectively expressed in activated T cells and monocytes, regulates angiogenesis and endothelial cell cytokine production. J Immunol 2001; 167:4137–4140.
26. Dubin PJ, Kolls JK. Interleukin-17A and interleukin-17F: a tale of two cytokines. Immunity 2009; 30:9–11.
27. Zhou L, Littman DR. Transcriptional regulatory networks in Th17 cell differentiation. Curr Opin Immunol 2009; 21:146–152.
28. Onishi RM, Gaffen SL. Interleukin-17 and its target genes: mechanisms of interleukin-17 function in disease. Immunology 2010; 129:311–321.
29. ■■ Cole S, Murray J, Simpson C, *et al.* Interleukin (IL)-12 and IL-18 synergize to promote MAIT cell IL-17A and IL-17F production independently of IL-23 signaling. Front Immunol 2020; 11:585134.

This work demonstrated that innate lymphocytes, including MAIT cells, gd T cells and ILC3s produce predominantly IL-17F cytokine and identified IL-17F-producing cells in psoriatic lesional skin. The authors extended a previous finding that dual blockade of IL-17A and IL-17F is required for optimal inhibition of downstream inflammatory responses. Furthermore, this study provides further evidence towards the contribution of IL-17A and IL-17F to tissue inflammation independently of IL-23, advancing our understanding of divergent results of therapeutic targeting IL-17A and IL-23 in AS.

30. Kjer-Nielsen L, Patel O, Corbett AJ, *et al.* MR1 presents microbial vitamin B metabolites to MAIT cells. Nature 2012; 491:717–723.
31. Treiner E, Duban L, Bahram S, *et al.* Selection of evolutionarily conserved mucosal-associated invariant T cells by MR1. Nature 2003; 422:164–169.
32. Teunissen MBM, Yeremenko NG, Baeten DLP, *et al.* The IL-17A-producing CD8+ T-cell population in psoriatic lesional skin comprises mucosa-associated invariant T cells and conventional T cells. J Investig Dermatol 2014; 134:2898–2907.
33. Menon B, Gullick NJ, Walter GJ, *et al.* Interleukin-17+CD8+ T cells are enriched in the joints of patients with psoriatic arthritis and correlate with disease activity and joint damage progression. Arthritis Rheumatol 2014; 66:1272–1281.
34. Gracey E, Qaiyum Z, Almaghlouth I, *et al.* IL-7 primes IL-17 in mucosal-associated invariant T (MAIT) cells, which contribute to the Th17-axis in ankylosing spondylitis. Ann Rheum Dis 2016; 75:2124–2132.
35. Raychaudhuri SK, Abria C, Mitra A, Raychaudhuri SP. Functional significance of MAIT cells in psoriatic arthritis. Cytokine 2020; 125:154855.
36. Hayashi E, Chiba A, Tada K, *et al.* Involvement of mucosal-associated invariant T cells in ankylosing spondylitis. J Rheumatol 2016; 43:1695–1703.
37. Toussirot E, Saas P. MAIT cells: potent major cellular players in the IL-17 pathway of spondyloarthritis? RMD Open 2018; 4:e000821.
38. Cuthbert RJ, Watad A, Fragkakis EM, *et al.* Evidence that tissue resident human enthesis gammadeltaT-cells can produce IL-17A independently of IL-23R transcript expression. Ann Rheum Dis 2019; 78:1559–1565.
39. Webster KE, Kim HO, Kyparissoudis K, *et al.* IL-17-producing NKT cells depend exclusively on IL-7 for homeostasis and survival. Mucosal Immunol 2014; 7:1058–1067.
40. Hassane M, Jouan Y, Creusat F, *et al.* Interleukin-7 protects against bacterial respiratory infection by promoting IL-17A-producing innate T-cell response. Mucosal Immunol 2020; 13:128–139.
41. Yoshiga Y, Goto D, Segawa S, *et al.* Invariant NKT cells produce IL-17 through IL-23-dependent and -independent pathways with potential modulation of Th17 response in collagen-induced arthritis. Int J Mol Med 2008; 22:369–374.
42. Hasegawa E, Sonoda KH, Shichita T, *et al.* IL-23-independent induction of IL-17 from gammadeltaT cells and innate lymphoid cells promotes experimental intraocular neovascularization. J Immunol 2013; 190:1778–1787.
43. Lee JS, Tato CM, Joyce-Shaikh B, *et al.* Interleukin-23-independent IL-17 production regulates intestinal epithelial permeability. Immunity 2015; 43:727–738.
44. Fiechter RH, de Jong HM, van Mens LJJ, *et al.* IL-12p40/IL-23p40 blockade with ustekinumab decreases the synovial inflammatory infiltrate through modulation of multiple signaling pathways including MAPK-ERK and Wnt. Front Immunol 2021; 12:611656.
45. Letarouilly JG, Flachaire B, Labadie C, *et al.* Secukinumab and ustekinumab treatment in psoriatic arthritis: results of a direct comparison. Rheumatology (Oxford) 2020; Nov 24:keaa710. doi: 10.1093/rheumatology/keaa710. [Epub ahead of print]
46. Melton AC, Melrose J, Alajoki L, *et al.* Regulation of IL-17A production is distinct from IL-17F in a primary human cell co-culture model of T cell-mediated B cell activation. PLoS One 2013; 8:e58966.
47. Gomez-Rodriguez J, Sahu N, Handon R, *et al.* Differential expression of interleukin-17A and -17F is coupled to T cell receptor signaling via inducible T cell kinase. Immunity 2009; 31:587–597.
48. ■■ Burns LA, Maroof A, Marshall D, *et al.* Presence, function, and regulation of IL-17F-expressing human CD4(+) T cells. Eur J Immunol 2020; 50:568–580.
This study provides evidence that IL-17A and IL-17F are differentially regulated upon T cell stimulation and that IL-17F-producing and IL-17A-producing CD4+ T cells display different cytokine profiles. Findings demonstrate that IL-17F contributes to inflammation since dual IL-17A and IL-17F blockade is more effective at reducing inflammatory cytokine production than blockade of IL-17A alone.
49. Aschenbrenner D, Foglierini M, Jarrossay D, *et al.* An immunoregulatory and tissue-residency program modulated by c-MAF in human TH17 cells. Nat Immunol 2018; 19:1126–1136.
50. Yang XP, Ghoreschi K, Steward-Tharp SM, *et al.* Opposing regulation of the locus encoding IL-17 through direct, reciprocal actions of STAT3 and STAT5. Nat Immunol 2011; 12:247–254.
51. Miller PG, Bonn MB, McKarns SC. Transmembrane TNF-TNFR2 impairs Th17 differentiation by promoting Il2 expression. J Immunol 2015; 195:2633–2647.
52. Kaaij MH, van Tok MN, Blijdorp IC, *et al.* Transmembrane TNF drives osteoproliferative joint inflammation reminiscent of human spondyloarthritis. J Exp Med 2020; 217:e20200288.
53. Kolbinger F, Loesche C, Valentin MA, *et al.* beta-Defensin 2 is a responsive biomarker of IL-17A-driven skin pathology in patients with psoriasis. J Allergy Clin Immunol 2017; 139:923–932e8.
54. Glatt S, Baeten D, Baker T, *et al.* Dual IL-17A and IL-17F neutralisation by bimekizumab in psoriatic arthritis: evidence from preclinical experiments and a randomised placebo-controlled clinical trial that IL-17F contributes to human chronic tissue inflammation. Ann Rheum Dis 2018; 77:523–532.
55. ■ Chen S, Blijdorp IC, van Mens LJJ, *et al.* Interleukin 17A and IL-17F expression and functional responses in rheumatoid arthritis and peripheral spondyloarthritis. J Rheumatol 2020; 47:1606–1613.
This study demonstrates that IL-17A and IL-17F expression are higher in psoriatic skin compared to the inflamed SpA joint, with a striking inverse IL-17A/IL-17F expression ratio in the joint compared to the skin compartment in SpA. These data suggest that the relative contribution of IL-17F in chronic tissue inflammation may be more prominent in the skin than in joints.
56. ■ Gordon KB, Foley P, Krueger JG, *et al.* Bimekizumab efficacy and safety in moderate to severe plaque psoriasis (BE READY): a multicentre, double-blind, placebo-controlled, randomised withdrawal phase 3 trial. Lancet 2021; 397:475–486.
This phase 3 randomised controlled trial study showed a rapid and substantial response in patients with moderate to severe plaque psoriasis, which was durable over 56 weeks. These data further support the therapeutic value of dual inhibition of IL-17A and IL-17F in PsO.
57. ■ Reich K, Papp KA, Blauvelt A, *et al.* Bimekizumab versus ustekinumab for the treatment of moderate to severe plaque psoriasis (BE VIVID): efficacy and safety from a 52-week, multicentre, double-blind, active comparator and placebo controlled phase 3 trial. Lancet 2021; 397:487–498.
The head-to-head trial evaluated dual IL-17A and IL-17F versus IL-12/IL-23 inhibition in psoriasis over 52 weeks, with results suggesting that bimekizumab is superior to ustekinumab and placebo as shown by significantly higher response rates for all primary and secondary endpoints.
58. Blauvelt A, Papp KA, Merola JF, *et al.* Bimekizumab for patients with moderate to severe plaque psoriasis: 60-week results from BE ABLE 2, a randomized, double-blinded, placebo-controlled, phase 2b extension study. J Am Acad Dermatol 2020; 83:1367–1374.
59. Papp KA, Merola JF, Gottlieb AB, *et al.* Dual neutralization of both interleukin 17A and interleukin 17F with bimekizumab in patients with psoriasis: Results from BE ABLE 1, a 12-week randomized, double-blinded, placebo-controlled phase 2b trial. J Am Acad Dermatol 2018; 79:277–286e10.
60. ■ Warren RBA, Bagel J, Papp KA, *et al.* Bimekizumab efficacy and safety versus adalimumab in patients with moderate to severe plaque psoriasis: results from a multicenter, randomized, double-blinded active comparator-controlled phase 3 trial (Be Sure). SKIN J Cutan Med 2021; 5:s15.
The head-to-head trial in patients with moderate to severe plaque psoriasis that demonstrated uperiority of bimekizumab to adalimumab over 16 weeks of treatment in terms of the speed, depth and durability of skin clearance.
61. Blauvelt A, Reich K, Tsai TF, *et al.* Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study. J Am Acad Dermatol 2017; 76:60–69e9.
62. Griffiths CE, Reich K, Lebwohl M, *et al.* Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet 2015; 386:541–551.
63. Ritchlin CT, Kavanaugh A, Merola JF, *et al.* Bimekizumab in patients with active psoriatic arthritis: results from a 48-week, randomised, double-blind, placebo-controlled, dose-ranging phase 2b trial. Lancet 2020; 395:427–440.
64. ■ van der Heijde D, Gensler LS, Deodhar A, *et al.* Dual neutralisation of interleukin-17A and interleukin-17F with bimekizumab in patients with active ankylosing spondylitis: results from a 48-week phase IIb, randomised, double-blind, placebo-controlled, dose-ranging study. Ann Rheum Dis 2020; 79:595–604.
This is the first study of bimekizumab in patients with active AS, demonstrating that bimekizumab-treated patients had rapid and significant ASAS40 responses versus placebo at week 12, supported by all secondary efficacy endpoints. These results validate a dual neutralisation of IL-17A and IL-17F with bimekizumab as a novel therapeutic option for the treatment of AS.
65. ■ Shah M, Maroof A, Gikas P, *et al.* Dual neutralisation of IL-17F and IL-17A with bimekizumab blocks inflammation-driven osteogenic differentiation of human periosteal cells. RMD Open 2020; 6:e001306.
This study shows a direct equal effect of IL-17A and IL-17F on progenitor cells from the periosteum. T helper 17 or γδ-T cell supernatants or serum obtained from patients with AS potently stimulated in vitro bone formation, which was blocked deeper by dual inhibition of IL-17A and IL-17F than by neutralisation of IL-17A or IL-17F alone.
66. ■ Lauffer F, Jargosch M, Baghin V, *et al.* IL-17C amplifies epithelial inflammation in human psoriasis and atopic eczema. J Eur Acad Dermatol Venereol 2020; 34:800–809.
This study reported elevated IL-17C in various inflammatory skin diseases and demonstrated that IL-17C amplifies epithelial inflammation and immune cell influx to the skin. IL-17C depletion significantly reduced inflammatory mediators in human skin biopsies of psoriasis ex vivo.
67. Chiricozzi A, Guttman-Yassky E, Suarez-Farinas M, *et al.* Integrative responses to IL-17 and TNF-alpha in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. J Investig Dermatol 2011; 131:677–687.
68. Krueger JG, Wharton KA Jr, Schlitt T, *et al.* IL-17A inhibition by secukinumab induces early clinical, histopathologic, and molecular resolution of psoriasis. J Allergy Clin Immunol 2019; 144:750–763.
69. ■ Manasson J, Wallach DS, Guggino G, *et al.* Interleukin-17 inhibition in spondyloarthritis is associated with subclinical gut microbiome perturbations and a distinctive interleukin-25-driven intestinal inflammation. Arthritis Rheumatol 2020; 72:645–657.
This study reported that IL-17 inhibition-induced subclinical gut inflammation and intestinal dysbiosis in SpA patients is associated with overexpression of IL-25/IL-17E–producing cells, suggesting that IL-17i-induced Crohn's disease might be driven by a specific IL-17 pathway.
70. Senra L, Stalder R, Alvarez Martinez D, *et al.* Keratinocyte-derived IL-17E contributes to inflammation in psoriasis. J Investig Dermatol 2016; 136:1970–1980.
71. Reynolds JM, Lee YH, Shi Y, *et al.* Interleukin-17B antagonizes interleukin-25-mediated mucosal inflammation. Immunity 2015; 42:692–703.

72. Camelo A, Barlow JL, Drynan LF, *et al.* Blocking IL-25 signalling protects against gut inflammation in a type-2 model of colitis by suppressing nuocyte and NKT derived IL-13. J Gastroenterol 2012; 47:1198–1211.

73. McHenga SS, Wang D, Janneh FM, *et al.* Differential dose effects of recombinant IL-25 on the development of dextran sulfate sodium-induced colitis. Inflamm Res 2010; 59:879–887.

74. Chen SMC, van Tok. Melissa, *et al.* Interleukin-17D, a cytokine derived from
■ stromal cells, attenuates joint inflammation. Arthritis Rheumatol 2020; 72(suppl 10); https://acrabstracts.org/abstract/interleukin-17d-a-cytokine-derived-from-stromal-cells-attenuates-joint-inflammation/. [Accessed 26 April 2021]

This study demonstrates that expression of IL-17D is localized to synovial stromal cells and inversely correlates with synovial inflammation in SpA. Mice lacking IL-17D. This suggests that IL-17D may exert an anti-inflammatory effect on joint inflammation in SpA and requires further investigation.

75. Chen S, Paveley R, Kraal L, *et al.* Selective targeting of PI3Kdelta suppresses
■ human IL-17-producing T cells and innate-like lymphocytes and may be therapeutic for IL-17-mediated diseases. J Autoimmun 2020; 111:102435.

This publication reports that selective inhibition of PI3Kδ suppresses IL-23-dependent and IL-23-independent production IL-17A and IL-17F by Th17-like cells and innate T cells from a healthy donor and SpA primary cells. This inhibition has a functional impact on the inflammatory and tissue remodelling responses in target cells in psoriasis and SpA. This supports a rationale to target PI3Kδ in IL-17-driven diseases.

76. O'Connor W Jr, Kamanaka M, Booth CJ, *et al.* A protective function for interleukin 17A in T cell-mediated intestinal inflammation. Nat Immunol 2009; 10:603–609.

77. Tang C, Kakuta S, Shimizu K, *et al.* Suppression of IL-17F, but not of IL-17A, provides protection against colitis by inducing Treg cells through modification of the intestinal microbiota. Nat Immunol 2018; 19:755–765.

78. Chong WP, Mattapallil MJ, Raychaudhuri K, *et al.* The cytokine IL-17A limits Th17 pathogenicity via a negative feedback loop driven by autocrine induction of IL-24. Immunity 2020; 53:384–397e5.

79. Goepfert A, Lehmann S, Blank J, *et al.* Structural analysis reveals that
■ the cytokine IL-17F forms a homodimeric complex with receptor IL-17RC to drive IL-17RA-independent signaling. Immunity 2020; 52:499–512e5.

This publication reports the crystal structure of the extracellular domain of human IL-17RC in complex with IL-17F, providing a structural basis for IL-17F signalling through IL-17RC and suggesting the possibility of IL-17RA-independent IL-17 signalling pathways.

80. Targan SR, Feagan B, Vermeire S, *et al.* A randomized, double-blind, placebo-controlled phase 2 study of brodalumab in patients with moderate-to-severe Crohn's disease. Am J Gastroenterol 2016; 111:1599–1607.

Intestinal dysbiosis in spondyloarthritis – chicken or egg?

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Purpose of review
The well-established link between intestinal inflammation and spondyloarthritis (SpA) remains largely unexplained. Recent sequencing technologies have given access to a thorough characterization of the gut microbiota in healthy and disease conditions. This showed that inflammatory bowel disease (IBD) is associated with dysbiosis – i.e., disturbed gut microbiota composition – which may contribute to disease pathogenesis. Whether gut dysbiosis exists in SpA and could contribute to disease development or be a bystander consequence of chronic inflammation is a question of major interest.

Recent findings
Several metagenomic studies have been performed in SpA. Most of them concerned faecal samples and showed dysbiosis consisting in a reduction of microbial biodiversity in a way similar to what has been described in IBD. They also highlighted changes in microbial taxa composition that could contribute to the inflammatory process. Likewise, healthy carriers of human leukocyte antigen (HLA)-B27 exhibited gut dysbiosis, indicating that this predisposing allele could exert its pathogenic effect by influencing microbiota composition, and possibly by driving antigen-specific cross-reactive immune response. On the other hand, SpA treatments were associated with a reduction of dysbiosis, showing that it is at least in part a consequence of inflammation.

Summary
Recent insights from metagenomic studies warrant further investigations to identify the mechanisms by which microbial dysbiosis could contribute to SpA development. This would bring novel therapeutic opportunities aiming at correcting detrimental changes.

Keywords
ankylosing spondylitis, HLA-B27, inflammatory bowel disease, microbiota, spondyloarthritis

INTRODUCTION

Spondyloarthritis (SpA) refers to a group of inflammatory disorders affecting predominantly the axial skeleton joints and to a lesser extent the peripheral joints and entheses. These rheumatic disorders are also characterized by their frequent combination with several extra-articular inflammatory manifestations, including uveitis, psoriasis and, most interestingly with regard to the present topic, inflammatory bowel disease (IBD), i.e., Crohn's disease (CD) or ulcerative colitis. Hence, the risk of developing overt IBD is 20-fold higher in SpA than in the general population [1▪▪]. Furthermore, systematic ileocolonoscopic examination with intestinal biopsies has shown histological inflammation in an even larger proportion of patients [1▪▪]. Although firmly established, the link between gut inflammation and SpA remains to be fully understood. It may, at least in part, involve disturbances of gut microbiota composition and function, a situation referred to as dysbiosis. Of note, both inflammation and dysbiosis may contribute to an increased frequency of irritable bowel syndrome symptoms in SpA patients [2▪]. An association between IBD and dysbiosis is now well established, both contributing reciprocally to each other [3▪▪]. Whether similar

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KEY POINTS

- Gut dysbiosis in SpA is characterized by a reduction of microbial diversity as in other inflammatory disorders, including IBD.
- Both the genetic background (HLA-B27) and the inflammatory state appear to contribute to gut dysbiosis in SpA.
- Increased content of *R. gnavus*, a proinflammatory bacteria, and reduced content of strict anaerobic bacteria having antiinflammatory properties could contribute to SpA development.
- Gut microbiota in SpA is enriched in antigenic peptides suitable for HLA-B27 binding and reactive with CD8+ T cells from SpA patients.

phenomena apply to SpA is an unresolved question of major interest.

DYSBIOSIS IN SPONDYLOARTHRITIS: WHAT IS THE EVIDENCE?

Gut microbiota refers to the wealth of microbes, including bacteria, fungi, archæ and viruses, that populate the digestive tract. The most abundant, residing in the colon are dominated by strictly anaerobic bacteria that are largely uncultivable in routine. It has remained a black box, until the soaring during the last decade of high throughput sequencing technologies, including bacterial 16S rDNA and full genome sequencing. This has opened the door to decipher the intestinal microbial content at unprecedented scale in healthy and also in pathologic conditions [4▪▪].

In SpA patients, those metagenomic studies have mostly been applied to stool samples, because of their accessibility. Only two studies have concerned intestinal biopsies, aiming at investigating the mucosal-associated bacterial community, which is also the most likely to be directly involved in disease pathogenesis, owing to its close proximity with the intestinal epithelium and the underlying immune system [5▪]. Most of the reported studies have shown that gut microbiota composition differed between SpA and healthy controls. One of the most consistent variations in stool samples appeared to be a reduction of microbiota diversity in SpA, a finding similar to what has been described in several other chronic disorders, notably IBD [6–8,9▪,10▪▪] (Table 1) In contrast, the mucosal-associated community appeared enriched in intestinal biopsies, especially in inflamed areas, an observation which could potentially be explained by an alteration of the mucosal barrier integrity with increased porosity towards luminal microbiota [17,18].

Table 1. Significance of some of the microbiota changes reported in SpA with regard to disease pathogenesis

Observation	Consequence of inflammation Possible mechanism	Effect on inflammation Possible mechanism	Reference
Faecal samples			
Reduction of microbial diversity	Loss of strict anaerobes due to oxidative milieu	Indirect (imbalance between pro and anti-inflammatory species)	[6–8,9▪,10▪▪,11]
Decrease of *Lachnospiraceae* and *Ruminococceae* Clostridiales • *Coprococcus catus* • *Eubacterium rectale* • *Faecalibacterium prausnitzii* • *Roseburia unilinivorans*	Loss of species extremely sensitive to oxygen	Loss of main producers of anti-inflammatory short chain fatty acids (butyrate, propionate)	[8,9▪,12▪]
Depletion of *Bacteroides fragilis*	Unknown	Loss of anti-inflammatory species	[8]
Enrichment of *Ruminococcus gnavus*	Survival advantage of aerotolerant taxa	Increased mucus degradation Production of pro-inflammatory polysaccharide	[7,13,14▪▪]
Enrichment of adherent-invasive *Escherichia coli* [a]	Survival advantage of facultative anaerobes	Increased bacterial invasiveness and induction of Th17 immunity	[15,16]
Enrichment of bacterial species displaying HLA-B27-binding peptides	Unknown	Stimulation of HLA-B27-restricted antigen-specific cross-reactive CD8+ T cell response	[9▪,12▪]
Mucosal biopsy samples			
Increased microbial richness	Loss of mucosal barrier integrity	Microbial invasion of intestinal mucosa	[17–19]

SpA, spondyloarthritis.
[a]Shown in SpA patients with concomitant Crohn's disease.

Regarding microbial taxonomic differences between SpA and controls, one of the puzzling issues with interpreting results of metagenomic studies is their lack of consistency, even between those performed by the same investigators, as comprehensively reviewed recently [5▪]. This can be explained by several limitations due to technical approach and/or study design. For instance, sequencing of 16S rDNA bacterial genomic region has been the most frequently used technic, due to its relative cheapness. However, it does not allow to accurately identify bacteria at the species level in most cases but rather gives access to family or gender identification, which is quite imprecise. Even the more expensive and thorough shotgun sequencing is a continuously evolving field, resulting in the recognition of an increasing variety of bacterial species that may uncover novel findings as recently shown in the case of SpA [20▪▪]. Another issue relates to statistical power limitations, considering the large variability of gut microbiota composition between individuals – each harbouring hundreds of species – and the relatively few numbers of samples analyzed together in one single study. Moreover, many parameters related or not to the disease of interest, including age, gender, body mass index, diet, disease duration and activity, treatments, comorbidities, are likely to influence microbiota composition and need to be taken into consideration, reducing further statistical power [3▪▪].

Keeping such limitations in mind, only four of the published studies used a replication design to reduce the risk of false-positive discovery. In our French study, we applied 16S rDNA sequencing to stool samples collected in two consecutive cohorts [7]. In both cohorts, we identified *Rumincoccus gnavus*, a Gram-positive member of the Clostridiales order, *Lachnospiraceae* family and *Blautia* genus as increased in SpA, as compared to several control groups, i.e. unrelated healthy controls, healthy siblings of SpA and rheumatoid arthritis patients. Interestingly, the greatest abundance of *R. gnavus* was observed in the subgroup of SpA patients having an history of IBD and correlated positively with disease activity, even if IBD was in remission in most of the cases. The three other studies were performed in the Chinese population using shogun sequencing. Each of them compared from 85 to 127 SpA with similar numbers of healthy control samples, that were split into discovery and validation cohorts for statistical analyses [8,9▪,12▪]. Only a few of the species identified as differently abundant between SpA and controls overlapped between those studies. This is the case of *Coprococcus comes* and *Eubacterium rectale*, two Clostridiales bacteria, that were decreased, whereas *Bifidobacterium adolescentis* was conversely increased in SpA, each finding being reported in two studies. Several other species were shared between studies but with variations in the opposite direction. For instance, an increase in *Prevotella copri*, a Bacteroidales bacterium positively associated with early rheumatoid arthritis, was reported in SpA patients untreated with disease-modifying drug in two studies [8,9▪], but was conversely decreased in untreated patients in the 3rd one [12▪]. Similarly, *Faecalibacterium prausnitzii*, a Clostridiales bacterium of the *Ruminococcaceae* family, negatively associated with IBD was found decreased in SpA in two studies [9▪,12▪] but increased in the 3rd one [8].

Shotgun sequencing gives also access to microbiota function prediction, based on genes identification. Analysis of such information might be considered as more relevant than taxonomic differences, given the redundancy of genes function between distinct taxa. Several differences were reported between SpA and controls in the three foregoing shotgun sequencing studies, but once again without clear consistency. Among the most interesting findings, a study showed decreased abundance in SpA of microbial genes responsible for the synthesis of several essential amino acids in human and of vitamin B6, an essential cofactor for such synthesis [12▪]. Another showed that SpA microbiota harboured increased abundance of genes involved in oxidative phosphorylation, lipopolysaccharide (LPS) synthesis and glycosaminoglycan degradation, whereas in contrast, genes involved in butanoate metabolism, glycolysis and neoglucogenesis were decreased [9▪]. Some of those variations - increased LPS, decreased butyrate synthesis- could bear pro-inflammatory consequences, as discussed below.

WHAT FACTORS CONTRIBUTE TO DYSBIOSIS IN SPONDYLOARTHRITIS?

Identifying the cause of dysbiosis would be important to interpret its significance. Dysbiosis may be driven by factors responsible for the development of the disease process (e.g. genetic background and environmental triggers), by the disease process itself or by some of its consequences, including therapeutic interventions (Table 2).

Common genetic polymorphisms appear to be weakly associated with microbiome composition in healthy individual [26,27▪]. However, this could be different for genetic variants exerting strong impact on disease predisposition. Indeed, HLA-B27, the main factor of susceptibility to SpA, was shown as associated with specific microbiota composition in healthy siblings of SpA patients and in unrelated carriers [7,21▪]. Those observations indicate that

Table 2. Arguments for 'chicken' and 'egg' hypotheses regarding gut dysbiosis in SpA

List of arguments	References
''Chicken'' hypothesis: gut dysbiosis as a possible cause of SpA	
• Evidence that gut dysbiosis may precede SpA development	
HLA-B27, the major genetic factor predisposing to SpA, is associated with dysbiosis in healthy carriers, which could initiate the disease process	[7,21▪]
Breastfeeding in the early infancy is associated with lower risk of developing SpA than bottle-feeding, suggesting that factors influencing microbiota composition could favor the development of SpA	[22]
Tonsilitis and tonsillectomy in infancy are associated with increased risk of SpA, whereas appendicitis and appendicectomy are protective, suggesting that modification of gut microbiota could influence SpA development	[23]
• Gut dysbiosis could contribute to SpA development	
Decreased *Lachnospiraceae* and *Ruminococceae* family species results in reduced synthesis of short chain fatty acids with anti-inflammatory properties (butyrate, propionate)	[8,9▪,12▪]
Increased *Ruminococcus gnavus* could be responsible for inflammation by producing pro-inflammatory polysaccharide and initiating the degradation of mucus	[7,13,14▪▪]
Bacteroides vulgatus, a mucus-degrading bacterial species is pathogenic in the HLA-B27 transgenic rat model of SpA	[5▪]
Impairment of the gut mucosal barrier would allow microbes to attach to the mucosa and/or invade it, thereby triggering inflammation	[19]
Increased LPS synthesis may provide pro-inflammatory constituents	[9▪,19]
IgA^+-coated *E. coli* from CD-SpA contained significantly more adherent-invasive *Escherichia coli* strains that induced Th17 immunity and more severe colitis and inflammatory arthritis in genetically predisposed mice	[15]
Gut microbiota from SpA patients is enriched in antigenic peptide motifs that could bind to HLA-B27 and trigger an IFN-γ response in CD8+ T cells from those patients	[9▪,12▪]
• Correcting microbial dysbiosis could ameliorate SpA	
Antibiotic treatment improves experimental SpA	[19,24▪]
''Egg'' hypothesis:gut dysbiosis as a consequence of SpA	
Oxidative stress resulting from inflammation could be responsible for a reduction of microbial diversity by inducing the loss of species extremely sensitive to oxygen (strict anaerobes)	[11]
SpA treatment attenuates the intensity of dysbiosis, indicating that the importance of inflammation likely dictates the intensity of dysbiosis	[9▪,12▪,25▪]

SpA, spondyloarthritis.

HLA-B27 may predispose to SpA at least in part by influencing microbiota composition.

Environment

Environmental cues exert greater influence than genetic make-up on gut microbiota composition [26,27▪]. However, until now, only few retrospective studies have concerned their potential association with SpA. Regarding factors known to affect gut microbiota establishment in the early infancy, an history of breastfeeding was associated with a lower risk of developing SpA than bottle-feeding, whereas there was no significant influence of the mode of birth delivery, i.e. vaginal *vs.* caesarean [22,28,29]. Regarding infectious events in childhood, tonsilitis and tonsillectomy were associated with increased risk of developing SpA in adulthood, whereas it was the contrary for appendicitis and appendicectomy [23]. Those associations could hypothetically unveil a role of microbiota in determining the risk of SpA, considering that those conditions may influence the control of microbiota colonization directly or indirectly, as a consequence of antibiotic treatments [27▪,29].

Inflammation

Dysbiosis could be a direct consequence of inflammation, as shown in IBD. For instance, increased blood flow and production of reactive species of oxygen by neutrophils concur to create an oxidative stress in the gut mucosa, diffusing to the lumen. This could influence the gut microbiota composition by inhibiting the growth of strict anaerobes - particularly, members of the *Lachnospiraceae* and *Ruminococcaceae* families of Clostridiales, including *F. prausnitzi*i- and favouring an expansion of facultative anaerobes and aerotolerant species, including *Enterobacteriaceae*, *Streptococcus*, lactobacilli and particular strains of *R. gnavus* [11,30]. There is however no direct evidence for such mechanism in SpA, in

the absence of overt IBD, except in animal models. For instance, mice immunized with proteoglycan (PG) from cartilage or intervertebral disk, develop a disease very similar to ankylosing spondylitis (AS) including inter-vertebral disk inflammation and ossification and peripheral joint arthritis. Dysbiosis was evidenced in faeces from the PG-immunized mouse as compared to healthy control group, consisting in a reduced microbial diversity on one hand and in a relative increase of Firmicutes and Proteobacteria phyla and a decrease of Bacteroidetes, in the other [24▪,25▪].

Treatments

Albeit of interest, the role of SpA treatment in dysbiosis has only been marginally studied until now. Dysbiosis is generally most important in untreated patients with active disease and the effect of treatments appears secondary to a reduction of inflammation, rather than their direct consequence [9▪,12▪,25▪]. This indicates that at least some of the dysbiosis features are consecutive to the inflammatory process.

DOES DYSBIOSIS CONTRIBUTE TO DISEASE PATHOGENESIS?

This is the million-dollar question, since positive answer may open the track for specific therapeutic intervention. Such possibility has been well documented in the case of IBD and several arguments support it as well in the case of SpA.

Alteration of anti-inflammatory functions

A number of strict anaerobes bacteria from the resident gut microbiota contribute to mucosal tolerance by producing butyrate and propionate short-chain fatty acids, that promote regulatory T cell development and enhance mucus production from goblet cells, strengthening the mucosal barrier [10▪▪]. Several of them were shown as depleted in SpA in one or more metagenomic studies. This is the case of Clostridiales from the *Ruminococcaceae* and *Lachnospiraceae* families, that are extremely sensitive to oxygen, including *F. praunitizii*, *Coprococcus catus* and *Roseburia inulinivorans* [9▪,12▪]. *Bacteroides fragilis* is another anaerobes involved in mucosal immune tolerance maintenance by producing a surface polysaccharide A, which was also depleted in SpA [8].

Pro-inflammatory properties of taxa increased in spondyloarthritis

In contrast to strict anaerobes, several strains of *R. gnavus* are aerotolerant, a characteristic which may confer them a survival advantage in oxidative milieu [30]. This could explain an increased abundance of this species, proportional to disease activity, in SpA [7]. Interestingly, this bacterium exhibits several properties that may contribute to direct pathogenicity. Hence, *R. gnavus* strains were shown to produce a glucorhamman polysaccharide that delivers a pro-inflammatory signal through Toll like receptor 4, leading to the production of tumor necrosis factorα by dendritic cells [14▪▪]. Moreover, it has the capacity to initiate the degradation of the PG mucin-2, which is the principal constituent of intestinal mucus by removing its terminal sialic acid [13]. This renders the mucin core glycans accessible to enzymatic degradation by other bacteria, thus potentially favouring degradation of the mucus and weakening the mucus barrier.

Alteration of the mucus barrier could contribute to abnormal presence of adherent and invasive bacteria within the gut mucosa, increased intestinal permeability and increased serum levels of bacterial products such as LPS that were reported in SpA patients [19]. Interestingly, *Bacteroides vulgatus* another mucin-degrading bacterium, was shown as pathogenic in the HLA-B27 transgenic rat model of SpA and bacteria adherent to intestinal epithelium as well as alterations of epithelial tight junctions were also reported in those rats, but restored after antibiotic treatments [5▪,19].

Dysbiosis, a putative link between spondyloarthritis and inflammatory bowel disease

A causal relationship between dysbiosis and SpA could be easier to demonstrate in the context of IBD, where dysbiosis appears more intense than in isolated SpA. For instance, a correlation between *R. gnavus* abundance and SpA activity was most obvious in patients having a history of IBD. Another candidate bacterium that takes advantage of oxidative milieu is adherent-invasive *Escherichia coli* (AIEC) that was found expanded in IBD and shown to provoke mucosal inflammation [16]. It was implicated as a possible driver of joint inflammation in a study performed in HLA-B27-negative patients with active CD, associated or not with peripheral SpA [15]. In this study, patients having peripheral SpA differed from those with isolated CD by an enrichment in the *Enterobacteriaceae* family of Proteobacteria, the abundance of which correlated positively with SpA activity index. Immunoreactivity to microbiota was further assessed by separately sequencing IgA-coated (IgA^+) and noncoated bacteria from faecal samples. As previously shown, CD patients had greater richness in IgA^+ coated bacteria than healthy

controls [3▪▪]. Moreover, significant enrichment of *Escherichia/Shigella* was observed in the IgA^+ fraction of CD-SpA patients, as compared to those with isolated CD, that correlated positively with SpA activity index. IgA^+-coated *E. coli* from CD-SpA contained significantly more AIEC strains that induced Th17 immunity and more severe colitis and inflammatory arthritis in genetically predisposed mice [15].

Dysbiosis could drive antigen-specific immune response responsible for spondyloarthritis

Antigen-specific theories suppose that SpA could be driven by a HLA-B27-restricted pathogenic CD8+ T cell, directed against microbial antigen and cross-reactive with self-antigen, by virtue of molecular mimicry [31]. In that case, the triggering microbe could originate from the gut. In favor of such 'arthritogenic peptide', recurrent CD8+ T cell clonotypes specific for SpA patients were repeatedly detected in the blood and enriched in the inflamed synovium from AS patients and bacterial-induced reactive arthritis, consistent with a common trigger [32,33,34▪▪]. Two of the metagenomic studies performed in SpA yielded some evidence in support of those theories [9▪,12▪]. The firs one identified an enrichment among the metagenome sequences of SpA patients of bacterial peptides homologous to known HLA-B27 epitopes and several of those peptides were further shown to trigger a CD8+ T cell-mediated interferon (IFN)-γ response in peripheral blood mononuclear cells (PBMC) from SpA patient but not from healthy control [12▪]. The second study analyzed the proteome from bacteria species significantly increased in SpA and identified three peptides with significant homology (> 80%) with self-antigens known to be presented by HLA-B27 to CD8+ T cells from SpA patients [9▪]. Those peptides were tested for their capacity to trigger an INF-γ response in PBMC, as an indicator of CD8+ T cell activation. Interestingly, one of them, derived from *B. fragilis* and homologous to a type II collagen (a cartilage-specific antigen) peptide was recognized by SpA but not control PBMC [9▪].

CONCLUSION

Several metagenomic studies have shown gut microbiota dysbiosis in SpA, generally associated with a reduction of microbial diversity. Dysbiosis appeared most pronounced in SpA with active disease and reduced in treated patients, indicating that it is at least in part consecutive to inflammation. However, some of the reported microbial changes could directly contribute to SpA pathogenesis, either by favoring an inflammatory response or by eliciting antigen-specific immunity. Elucidating those questions could lead to therapeutic intervention.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

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

1. Gracey E, Vereecke L, McGovern D, *et al.* Revisiting the gut–joint axis: links ▪▪ between gut inflammation and spondyloarthritis. Nat Rev Rheumatol 2020; 16:415–433.
This is a comprehensive review of current knowledge and mechanistic hypotheses concerning the relationship between gut inflammation and spondylarthritis.
2. Wallman JK, Mogard E, Marsal J, *et al.* Irritable bowel syndrome symptoms in ▪ axial spondyloarthritis more common than among healthy controls: is it an overlooked comorbidity? Ann Rheum Dis 2020; 79:159–161.
This cohort study shows that irritable bowel syndrome symptoms are twice more frequent in axial SpA patients without overt IBD than in healthy controls.
3. Schirmer M, Garner A, Vlamakis H, Xavier RJ. Microbial genes and pathways ▪▪ in inflammatory bowel disease. Nat Rev Microbiol 2019; 17:497–511.
This review highlights current knowledge of gut microbial factors linked to IBD pathogenesis.
4. Gotschlich EC, Colbert RA, Gill T. Methods in microbiome research: past, ▪▪ present, and future. Best Pract Res Clin Rheumatol 2019; 33:101498.
A thorough review of the current technical approaches used to study the microbiome.
5. Breban M, Beaufrère M, Glatigny S. The microbiome in spondyloarthritis. Best ▪ Pract Res Clin Rheumatol 2020; 33:101495.
A comprehensive review of the relationship between microbiome and SpA.
6. Scher JU, Ubeda C, Artacho A, *et al.* Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease: gut microbiota in PsA. Arthritis Rheumatol 2015; 67:128–139.
7. Breban M, Tap J, Leboime A, *et al.* Faecal microbiota study reveals specific dysbiosis in spondyloarthritis. Ann Rheum Dis 2017; 76:1614–1622.
8. Wen C, Zheng Z, Shao T, *et al.* Quantitative metagenomics reveals unique gut microbiome biomarkers in ankylosing spondylitis. Genome Biol 2017; 18:142.
9. Zhou C, Zhao H, Xiao X, *et al.* Metagenomic profiling of the pro-inflammatory ▪ gut microbiota in ankylosing spondylitis. J Autoimmun 2020; 107:102360.
This is one of two recently published metagenomic study of gut microbiota in Chinese AS patients, using shotgun sequencing technic.
10. Durack J, Lynch SV. The gut microbiome: relationships with disease and ▪▪ opportunities for therapy. J Exp Med 2019; 216:20–40.
This review details the role of the gut microbiome in modulating host health with a focus on immunomodulation and discusses strategies for manipulating the gut microbiome for the management or prevention of chronic inflammatory conditions.
11. Henson MA, Phalak P. Microbiota dysbiosis in inflammatory bowel diseases: in silico investigation of the oxygen hypothesis. BMC Syst Biol 2017; 11:145.
12. Yin J, Sternes PR, Wang M, *et al.* Shotgun metagenomics reveals an ▪ enrichment of potentially cross-reactive bacterial epitopes in ankylosing spondylitis patients, as well as the effects of TNFi therapy upon microbiome composition. Ann Rheum Dis 2020; 79:132–140.
This is one of two recently published metagenomic study of gut microbiota in Chinese AS patients, using shotgun sequencing technic.

13. Crost EH, Tailford LE, Monestier M, *et al.* The mucin-degradation strategy of *Ruminococcus gnavus*: the importance of intramolecular trans-sialidases. Gut Microbes 2016; 7:302–312.

14. ■■ Henke MT, Kenny DJ, Cassilly CD, *et al. Ruminococcus gnavus*, a member of the human gut microbiome associated with Crohn's disease, produces an inflammatory polysaccharide. Proc Natl Acad Sci USA 2019; 116: 12672–12677.

This mechanistic study shows that *R. gnavus* produces a glucorhamnan polysaccharide that induces inflammatory cytokine secretion by dendritic cells, dependent on TLR4.

15. Viladomiu M, Kivolowitz C, Abdulhamid A, *et al.* IgA-coated *E. coli* enriched in Crohn's disease spondyloarthritis promote TH17-dependent inflammation. Sci Transl Med 2017; 9:eaaf9655.

16. Atarashi K, Tanoue T, Ando M, *et al.* Th17 cell induction by adhesion of microbes to intestinal epithelial cells. Cell 2015; 163:367–380.

17. Tito RY, Cypers H, Joossens M, *et al.* Brief Report: dialister as a microbial marker of disease activity in spondyloarthritis. Arthritis Rheumatol 2017; 69:114–121.

18. Costello M-E, Ciccia F, Willner D, *et al.* Brief report: intestinal dysbiosis in ankylosing spondylitis: gut microbiome and AS-related genes. Arthritis Rheumatol 2015; 67:686–691.

19. Ciccia F, Guggino G, Rizzo A, *et al.* Dysbiosis and zonulin upregulation alter gut epithelial and vascular barriers in patients with ankylosing spondylitis. Ann Rheum Dis 2017; 76:1123–1132.

20. ■■ Nayfach S, Shi ZJ, Seshadri R, *et al.* New insights from uncultivated genomes of the global human gut microbiome. Nature 2019; 568:505–510.

This large-scale study implemented novel computational approach to analyze thousands of already published gut metagenomes, resulting in the identification of over 2,000 new gut metagenome species, and bringing the number of known species to 4,558. Applying this methodology to the data published by Wen C. *et al.* (Ref #8) allowed the description of novel metagenome species associations with AS.

21. ■ Asquith M, Sternes PR, Costello M, *et al.* HLA alleles associated with risk of ankylosing spondylitis and rheumatoid arthritis influence the gut microbiome. Arthritis Rheumatol 2019; 71:1642–1650.

This metagenomic study performed in two cohorts of healthy individuals shows that the gut microbiota is significantly different between HLA-B27 carriers and other individuals.

22. Montoya J, Matta NB, Suchon P, *et al.* Patients with ankylosing spondylitis have been breast fed less often than healthy controls: a case-control retrospective study. Ann Rheum Dis 2016; 75:879–882.

23. Lindström U, Exarchou S, Lie E, *et al.* Childhood hospitalisation with infections and later development of ankylosing spondylitis: a national case-control study. Arthritis Res Ther 2016; 18:240.

24. ■ Yang L, Liu B, Zheng J, *et al.* Rifaximin alters intestinal microbiota and prevents progression of ankylosing spondylitis in mice. Front Cell Infect Microbiol 2019; 9:44.

This study shows that rifaximin treatment reduces the severity of PG-induced model of AS in mice, while restoring altered intestinal barrier function.

25. ■ Liu B, Yang L, Cui Z, *et al.* Anti-TNF-therapy alters the gut microbiota in proteoglycan-induced ankylosing spondylitis in mice. MicrobiologyOpen 2019; 8:e97.

This study shows that anti-TNF treatment reduces the severity of PG-induced model of AS in mice, while restoring altered microbiota composition and intestinal barrier function.

26. Rothschild D, Weissbrod O, Barkan E, *et al.* Environment dominates over host genetics in shaping human gut microbiota. Nature 2018; 555:210–215.

27. ■ The Milieu Intérieur Consortium. Scepanovic P, Hodel F, Mondot S, *et al.* A comprehensive assessment of demographic, environmental, and host genetic associations with gut microbiome diversity in healthy individuals. Microbiome 2019; 7:130.

This metagenomic study of healthy individuals highlights the predominant influence of environmental factors over common genetic polymorphisms on gut microbiota composition.

28. Lindström U, Forsblad-d'Elia H, Askling J, *et al.* Perinatal characteristics, older siblings, and risk of ankylosing spondylitis: a case-control study based on national registers. Arthritis Res Ther 2016; 18:16.

29. Bokulich NA, Chung J, Battaglia T, *et al.* Antibiotics, birth mode, and diet shape microbiome maturation during early life. Sci Transl Med 2016; 8:343ra82.

30. Hall AB, Yassour M, Sauk J, *et al.* A novel *Ruminococcus gnavus* clade enriched in inflammatory bowel disease patients. Genome Med 2017; 9:103.

31. Breban M, Costantino F, André C, *et al.* Revisiting MHC genes in spondyloarthritis. Curr Rheumatol Rep 2015; 17:516.

32. May E, Dulphy N, Frauendorf E, *et al.* Conserved TCR β chain usage in reactive arthritis; evidence for selection by a putative HLA-B27-associated autoantigen: May *et al.* TCR in HLA-B27-restricted CTL and reactive arthritis. Tissue Antigens 2002; 60:299–308.

33. Komech EA, Pogorelyy MV, Egorov ES, *et al.* CD8+ T cells with characteristic T cell receptor beta motif are detected in blood and expanded in synovial fluid of ankylosing spondylitis patients. Rheumatology 2018; 57:1097–1104.

34. ■■ Hanson AL, Nel HJ, Bradbury L, *et al.* T-cell receptor immunosequencing reveals altered repertoire diversity and disease-associated clonal expansions in ankylosing spondylitis patients. Arthritis Rheumatol 2020; 72:1289–1302.

This extensive profiling of the T-cell receptor repertoire in HLA-B27-positive AS patients and healthy controls, evidenced an increased incidence of homologous CD8+ T cell clonotypes in AS patients, matching those previously isolated from AS or reactive arthritis patients.

Janus kinase–signal transducers and activators of transcription cell signaling in Spondyloarthritis: rationale and evidence for JAK inhibition

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Purpose of review
The Janus kinase–signal transducers and activators of transcription (JAK–STAT) signaling proteins represent a group of intracellular kinase molecules that play a central role in the signaling pathways induced by cytokines, chemokines, and certain growth factors associated with systemic and local inflammation of autoimmune diseases including in Spondyloarthritis (SpA). Here, we will discuss (i) the functional significance of the JAK–STAT kinase cascades in the inflammatory-proliferative processes of SpA and its cellular/molecular mechanisms (ii) progress in the development of oral synthetic JAK inhibitors (JAKi) and their therapeutic efficacies in SpA.

Recent findings
Development JAKi is a fast-moving field in the medical science. Several new-generation JAKi are being identified for psoriatic arthritis and ankylosing spondylitis. It is expected these JAKi likely to have higher potency and less adverse effects.

Summary
Here, we are providing an updated review on the significance of JAK–STAT signaling proteins in SpA with an emphasis on new-generation of JAK–STAT inhibitors for the treatment of SpA.

Keywords
Janus kinase–signal transducers and activators of transcription, signaling molecules, Spondyloarthritis, therapy

INTRODUCTION

Spondyloarthritis (SpA) is a class of heterogeneous group of immune-mediated inflammatory diseases. These autoimmune diseases represent overlapping of genetic predisposition, various similarities in the inflammatory cascades, clinical features, spinal inflammation, radiological features and associated comorbidities. Recent evidences support that cytokine-induced Janus kinases (JAK) signaling system are important in the pathogenesis of SpA and here we will discuss the evidence for JAK cell signaling in SpA and its therapeutic evidence [1,2▪▪].

Enthesitis is considered to be the key pathologic event for spondyloarthropathy. Inflammation at the sites where ligaments/tendons get inserted on the surface of the bone is termed enthesitis. However advanced imaging more so the molecular imaging, suggests that enthesitis is a broader process that affects the insertion tendons along with the bone, and the adjacent soft tissue [3]. Continued biomechanical stress and chronic micro-injuries at the enthesis trigger a friction-induced local inflammatory response and angiogenesis. This may help homing of critical pathologic inflammatory cells and induce enthesitis and also could be a contributing factor for inflammation of the adjacent bone and synovium [1,3]. However, the process likely to be more complex. How a localized inflammation from a mechanical stress would interact to induce a systemic immune response dysregulation remains unclear.

Integrated interactions of antigen-presenting cells with T-cell phenotypes along with adhesion molecules, and lesional cytokines develop inflammatory

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KEY POINTS

- JAK-STAT signaling proteins regulate proliferation and its associated cytokine network of various T-cell subpopulations including the Th17 cells which play a critical role in the pathogenesis of spondyloarthritis (SpA).
- This is an updated review on the significance of JAK-STAT signaling proteins in SpA and its clinical use.
- Currently available first generation JAK inhibitors (JAKi) have shown efficacy with acceptable safety in a number of SpA conditions.
- Next generation JAKi are currently in trials for treatment of AS and PsA with the expectations to have a higher efficacy and less adverse events.

proliferative cascades which lead to diverse clinical phenotypes for SpA [1,4,5]. The activated T cells regulate the local tissue response and damage through their cytokines and an integrated interaction with multiple inflammatory cells with innate functions such as macrophages and neutrophils [1,6▪▪,7,8]. It is also well-demonstrated that cytokines have crucial functions in the development, differentiation, and regulation of the immune cells.

Cytokines act on its cell surface receptors to induce intracellular signaling system. Following interactions with a cytokine the receptor's extracellular domain produce conformational changes in the intracellular domain, this leads to phosphorylation of the cytoplasmic kinase proteins, activation of the transcription factors and thus induction of the signal transduction events (Fig. 1). A family of intracellular tyrosine kinases (TYK2) known as JAKs are involved with the signaling process of multiple cytokines associated for induction of inflammation (Fig. 2) [9,10▪]. Because of these functions of JAKs a new field has emerged to understand the regulatory role of JAKs in the pathogenesis of SpA and its therapeutic evidence [1,2▪▪,10▪,11,12]. In this chapter, we will discuss the functional significance of the JAK–STAT (signal transducers and activators of transcription) kinase cascades in the inflammatory-proliferative process of autoimmune diseases with a focus on its role in the pathogenesis of SpA and possible use of the oral synthetic JAK–STAT kinase inhibitors in different diseases associated with SpA.

JANUS KINASE–SIGNAL TRANSDUCERS AND ACTIVATORS OF TRANSCRIPTION KINASE PATHWAY

The family of JAK constitutes of four JAKs- JAK1, JAK2, JAK3, and TYK2 and the STAT family has seven members (STAT 1, 2, 3, 4, 5, 5a, and 6) [1,9,10▪]. The JAKs are associated with the intracellular domain of cytokine receptor subunits of the class I and class II receptor superfamily. Various cytokines with array of functions bind to type I and II receptors such as interferon (IFN)-like cytokines, IFNs, various growth factors/hormones, and colony-stimulating factors (Fig. 2) [13].

REGULATORY ROLE OF THE JANUS KINASE–SIGNAL TRANSDUCERS AND ACTIVATORS OF TRANSCRIPTION SIGNALING SYSTEM IN THE PATHOGENESIS OF SPONDYLOARTHRITIS

The JAK–STAT pathway is one of the major cellular signaling system and its association with multiple cytokines which impact growth, apoptosis, and activation of T and B lymphocytes indicates its regulatory role in the pathogenesis of autoimmune diseases (Fig. 2) [1,9,13–15]. Tyk2 and JAKs are recruited by multiple cytokines (Fig. 2) which influences several following possible functions of T cells which are required for immune-mediated inflammation in autoimmune disease [4,5,6▪▪,7–9,10▪, 14,15]:

(1) IL-2: A growth factor for T cells
(2) IL9: A growth factor for T cells and also induce pannus formation
(3) IL-12: An inducing factor for Th1 differentiation
(4) IL-22: An inflammatory cytokine for psoriasis, psoriatic arthritis (PsA) and ankylosing spondylitis (AS)
(5) IL-23: An inducing factor for Th17 differentiation
(6) IFN-γ: Proinflammatory cytokine for psoriatic disease

Thus, these functions of all the above cytokines substantiate that JAK–STAT kinase cascades are expected to have a role in the pathogenesis of psoriasis, PsA, and AS.

Various studies in animal models substantiate a regulatory role of JAK–STAT system in SpA. In an IL-23 dependent SKG mouse model of SpA arthritis was induced with curdlan. Inhibition of the JAK/STAT pathway was evaluated by experimental by a JAK inhibitor (JAKi); which was given by oral gavage twice daily for 30 days. Treatment with this JAKi suppressed both inflammation and periosteal/entheseal bone formation. Clinical and histologic inflammation scores were significantly decreased by JAKi in SKG mice ($P < 0.05$) [16]. JAKi of different selectivity have shown to reduce Th17 type responses in CD4+ T cells from patients with AS

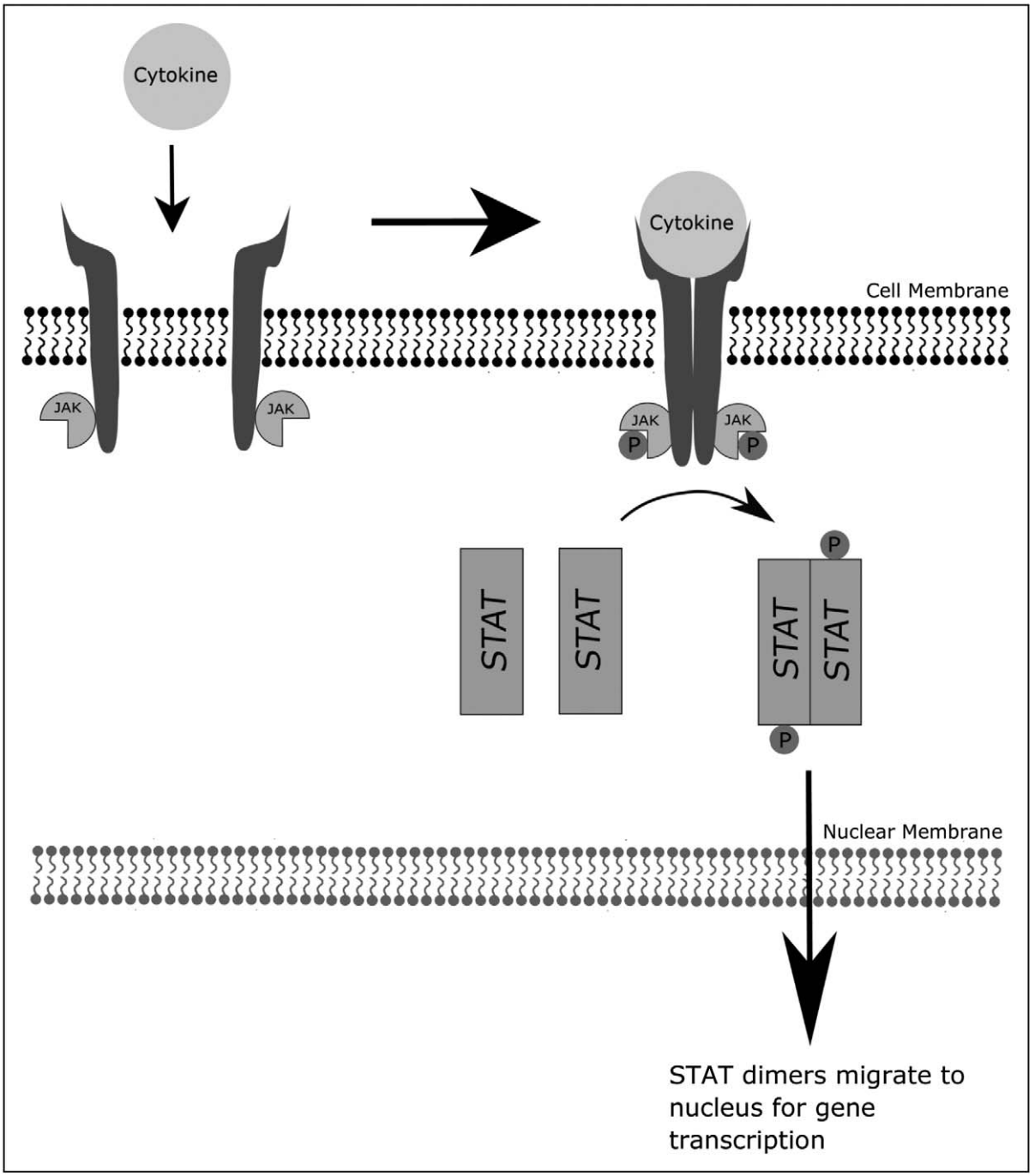

FIGURE 1. Cytokine-induced JAK/STAT signaling transduction. Binding of a cytokine on the cell surface receptor induces conformational changes to its intracellular domain and leads to phosphorylation of the JAK proteins. Phosphorylation of the intracellular domain recruits the STATs via their SH2 domains and leads to activation/phosphorylation and dimerization of the STAT protein. The activated STAT homo/hetero dimmers migrate to the nucleus and binds to specific DNA-binding sites and participates in gene transcriptions. As mentioned in the Figure 2 JAK/STAT induced signal transduction regulates multiple biological/cellular functions for immune response, cell trafficking and induction of inflammation. JAK/STAT, Janus kinase/signal transducers and activators of transcription.

[17]. Further, with siRNA JAK1, JAK2, JAK3 and TYK2 were silenced in CD4+ T cells and production of multiple Th17 cytokines (IL-17A, IL-17F, and IL-22) in these CD4+ T cell could be inhibited [17]. A number of SNPs associated with the TYK2 locus can influence autoimmune diseases including AS. Some of these exonic SNPs are known to reduce the function of TYK2 and thereby inhibits inflammatory

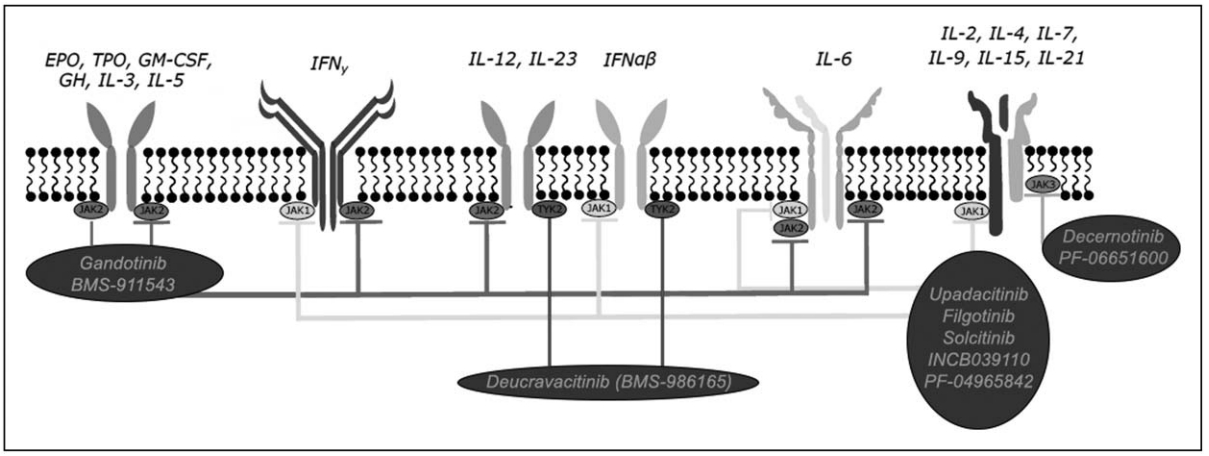

FIGURE 2. JAK–STAT signaling in spondyloarthritis and its therapeutic importance. This figure describes some of the cytokines that bind to type I and type II receptors such as interferons, interleukins, interferon-like cytokines, hormones, growth factors, and colony-stimulating factors. It is important to notice that IL-2, IL-6, IL-9, IL-12 and IL-23 participate in JAK–STAT activation. All these cytokines have a potential to play a critical role in the immune response which includes T cell proliferation, differentiation and cell trafficking. IL-23 induced upregulation of IL-17 and IL-22 are known to play critical roles in inducing synovitis, pannus formation, bone erosion and bone proliferation; the hallmark pathological events in spondyloarthritis. Next generation JAKi blocks a specific JAK molecule; here several next generation JAKi are mentioned along with their JAK targets. JAKi, Janus kinase inhibitors; JAK/STAT, Janus kinase/signal transducers and activators of transcription.

cytokine cell signaling. It has been reported that one of such SNP is associated with several autoimmune diseases and thus has a potential to confer protection, however, this polymorphism does not impact on nonautoimmune domains and does not make susceptible to infections [18]. In the SKG mouse model for SpA NDI-031407A a specific TYK2 inhibitor has been reported to block disease progression [19▪]. MRI imaging showed prevention of joint space narrowing and bone marrow edema. Further, in the IL-23 mini-circle model NDI-031407 also protected mice from enthesis-related synovitis and bone marrow edema [19▪]. It also has been noticed that the frequency of loss of-function of a TYK2 SNP (rs12720356) was higher in AS patients whose disease was less progressive evidenced by lower rates of spinal fusion. This provides further evidence that targeting TYK2 could be an effective treatment for AS [19▪].

Thus, polymorphisms of JAK–STAT kinases may be another plausible mode of mechanism in the etiology of spondyloarthritic diseases. In addition to TYK2; JAK2 polymorphisms have been reported to be associated with AS [20], nucleotide polymorphisms in the JAK–STAT signaling system have also been noticed in Crohn's disease (CD) [21] and STAT 3 polymorphism has been linked to psoriasis [22].

JAK1, JAK2, and TYK2 are expressed ubiquitously in mammals, whereas JAK3 is primarily expressed by hematopoietic/immune cells and associates with only the common γ-chain. Cytokines that signal through the common γ-chain include IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, which are integral to lymphocyte activation, proliferation, and differentiation. Because of these tofacitinib ($C_{16}H_{20}N_6O$, MW 312.370 Da), a small organic molecule, has been primarily prepared to target JAK3 with the aim to develop the treatment for autoimmune arthritis [23]. However, there are also reports suggesting that tofacitinib targets JAK1 and JAK2 with half-maximal inhibitory concentration (IC50) values similar to those of JAK3 [24].

JAK1 and JAK2 are expressed in nonimmune cells, including the joint synovial cells. These findings have opened opportunities to investigate other possible cellular targets for JAKi, such as their regulating role in keratinocyte biology in psoriasis and synovial cells (fibroblast-like synoviocyte [FLS]), in PsA, and in rheumatoid arthritis (RA) [25,26].

In vivo studies in PsA suggests that pannus formation and activation of the Th17 cells in the synoviym is regulated by the JAK/STAT kinase system. In a coculture study of synovial fibroblasts derived from PsA patients or PsA synovial explants with tofacitinib reduced expression of JAK phosphoproteins. This study observed that in PsA explants, tofacitinib can inhibit JAK1/JAK2, which in turn inhibits FLS migration and secretion of certain FLS chemokines [27]. Also, recently we reported that in PsA the generation of the pathologic IL-17$^+$ TEM cells and their proliferation are regulated by IL23 induced JAK2/STAT3 signaling proteins, and

Table 1. List of JAK–STAT inhibitors: The First Generation and the Next Generation JAK inhibitors (JAKi)

JAK inhibitors	Target
First Generation	
Tofacitinib	JAK1/JAK3
Ruxolitinib	JAK1/JAK2
Baricitinib	JAK1/JAK2
Next-Generation	
Decernotinib (VX-509)	JAK3
Upadacitinib (ABT494)	JAK1> JAK2,JAK3
Filgotinib GLPG0634	JAK1>JAK2
Peficitinib (ASP015K)	Pan-JAK
Solcitinib (GSK2586184)	JAK1
Deucravacitinib (BMS-986165)	TYK2
INCB039110	JAK1>JAK2
STA-21	STAT3
PF-06700841	TYK2/JAK1
PF-06651600	JAK3
PF-04965842	JAK1
PF-06263276	Pan-JAK

JAK/STAT, Janus kinase/signal transducers and activators of transcription; TYK2, intracellular tyrosine kinases.

tofacitinib inhibited IL-23-induced proliferation of these IL-17$^+$ TEM cells [28].

Janus kinase inhibitors and its clinical use

Many JAKi have been developed over recent years (Table 1). The first-generation JAKi do not display high specificity, demonstrating activity against three or even all four of the JAK family members (also termed as pan- JAKi). Selectivity against specific JAKs is a desirable feature of the newer JAKi, primarily in terms of mitigating side effects.

First-generation Janus kinase inhibitors

First-Generation JAKi are those JAKi that target multiple JAKs; includes ruxolitinib, tofacitinib, and baricitinib.

Ruxolitinib

Ruxolitinib is a JAK1 and JAK2 inhibitor [29]; FDA-approved for polycythemia vera and so far not much studies have been done in SpA.

Tofacitinib

Tofacitinib is the first JAKi approved for use in autoimmune diseases. It inhibits JAK1/JAK3 with some activity against JAK2 and negligible activity toward TYK2 [30,31]. Therapeutic role of tofacitinib in SpA is described in the next section.

Baricitinib

Baricitinib is a selective JAK1/JAK2 inhibitor and so far not much work is done on SpA [32].

Next-generation Janus kinase inhibitors

Next-generation JAKi have selective inhibitory activity for a specific JAK. Whereas the first-generation JAKi such as tofacitinib has shown clinical efficacy in the treatment of multiple autoimmune conditions like RA, PsA and inflammatory bowel disease it is expected that the first-generation non-selective pan-JAKi likely to be associated with adverse effects such as leukopenia, neutropenia and anemia. This raised the potential use and development of JAKi with selective activity for a specific JAK (Fig. 2 and Table 1). In principle these next-generation JAKi might be used to treat selected inflammatory disorders with lower dose and less adverse effects. Array of biotechnology companies have been successful in developing JAKi with this goal of making a molecule with a high efficacy but minimal off target effects (Table 1). These newer JAKi are isoform specific to JAK1, JAK2, JAK3 and TYK2. It is postulated that next-generation JAKi may have a higher efficacy and less adverse events.

A list for these Next Generation JAKi are provided in the Table 1. Among these upadasitinib is only FDA approved for RA.

JANUS KINASE INHIBITORS: NOVEL THERAPIES FOR SPONDYLOARTHRITIS

The possible mechanisms of action of JAKi in SpA are described in the earlier section. Here we will discuss the current status of clinical use of JAKi in SpA and about the JAKi currently going through clinical trials in SpA.

Psoriatic arthritis

As mentioned above the JAK/STAT pathway mediates cytokine signaling in PsA likely through the IL-23 and IL-17 cytokine axis [1,28].

A phase III trial demonstrated that tofacitinib at doses of 5 mg or 10 mg twice daily in patients with PsA with possible prior DMARD use can improve clinical burden of disease, in several clinical domains such as reduction of arthritis, enthesitis, and dactylitis [33]. This phase III trial was a double-blind, placebo-controlled and also had an active-control arm with adalimumab. Compared to 33% response in the placebo group, it was reported that ACR20 response rates at month 3 were 50% in the 5 mg tofacitinib group and 61% in the 10-mg tofacitinib group ($P < 0.001$ between 10-mg dose with placebo; $P = 0.01$ between 5-mg dose with placebo);

whereas the ACR20 response rate was 52% in the adalimumab group. However at 12 month, both the 5 mg and the 10 mg arms of this tofacitinib trial had ACR20 responses around 60%.

Upadacitinib preferentially inhibits JAK-1. It is already approved by FDA for RA. Upadacitinib is currently in phase III trial for PsA. Data from this phase III trial (RINVOQ) suggest significant efficacy of updacitinib in PsA. The primary endpoint was ACR20 response at week 12 compared to the placebo arm. ACR20 response with daily dose of 15 mg of upadacitinib was around 60% whereas the placebo group had only 36% response [34].

Filgotinib, a selective JAK1 inhibitor has also demonstrated a promise in PsA. A phase II clinical trial (EQUATOR) has reported that at 16th week 52 among 65 patients (80%) achieved a ACR20 response in the filgotinib group compared to 22 (33%) among 66 subjects in the placebo group [35].

Ankylosing spondylitis

Tofacitinib

In a Phase 2 trial with tofacitinib favorable results have been reported in placebo-controlled, dose-ranging study. In this 12 weeks study AS patients were randomized to one of three doses of tofacitinib (2 mg, 5 mg, 10 mg; all twice daily). Patients on 5 mg twice daily dose achieved the primary end point ASAS20 response (Assessment in AS 20% improvement)] at week 12, at significantly higher rates compared with placebo [36]. Further the follow-up Phase 3 study has also demonstrated a very promising outcomes. In this 16 weeks double-blind placebo-controlled study patients on tofacitinib (5 mg twice daily) showed ASAS20 response of 56.4% compared to 29.4% in placebo; and ASAS 40% responders were 40.6% compared to 12.5% in the placebo group [37].

Filgotinib

In a Phase II placebo-controlled study filgotinib has demonstrated improved disease activity significantly more than the placebo group; separation of various outcome measures from the placebo group was observed at 4–8 weeks [38]. Filgotinib at 200 mg once daily was assessed in patients with active AS. In this 12 week phase 2 study activity was assessed by the AS Disease Activity Score (ASDAS). ASDAS was noted to improve with filgotinib in 33% compared 2% in the pacebo group.

Upadacitinib

Similarly in a placebo-controlled Phase 2/3 trial upadasitinib at 15 mg daily was assessed in active AS patients refractory to NSAIDs. Significantly more patients on upadacitinib had an ASAS 40 response at week 14 compared to the placebo group (52% versus 26%) [39]. Other outcomes like sacroiliac joint inflammation by MRI spine, were found to be superior for upadacitinib,

Inflammatory bowel disease

Tofacitinib

Tofacitinib is FDA approved indication for the treatment of adult patients with ulcerative colitis (UC) who have had an inadequate therapeutic response with either conventional therapies or with a biologic agent [40]. In UC compared to PsA and RA higher doses of tofacitinib such as 10 mg twice daily may be required for treatment [40].

Upadacitinib and peficitinib have also shown efficacy in UC in early phases of clinical trials and currently going through further evaluations [41,42].

In CD, tofacitinib failed to show any clinical efficacy [43]. However current studied with upadacitinib and filgocitinib are promising [44,45].

Psoriasis

Several JAKi and TYK2 inhibitors have been evaluated in psoriasis. Both tofacitinib and baricitinib have shown superior clinical efficacy in respect to PASI 75 response compared to the placebo. However, PASI 75 response was found to be much lower than bDMARDS currently in use [46,47]. Whereas, TYK2 inhibitor BMS-986165 seems to be very promising for psoriasis with PASI 75 response around 75% [48]. Trials with other JAK/STAT inhibitors are ongoing and it is expected JAK/STAT inhibitors to be a new option for treatment of psoriasis.

Safety of Janus kinase inhibitors

In this article discussion of safety and adverse effect of JAKi in details is out of scope. Overall, the safety profile of JAKi is reasonably good and does not vary among the different inhibitors. Cytopenias, especially low neutrophils and lymphocytes may occur but this was not observed to be more frequent compared to the placebo arm [49]. Also, incidence rates for serious infections overall were similar to the subjects treated with biological disease-modifying antirheumatic drugs (bDMARDs) and which was about 2.5–3.8 per 100 patient-years [50▪▪,51–53]. It appears that tofacitinib is likely to have a higher risk for herpes zoster infection compared with

bDMARDs; which is generally mild and limited to a single dermatotome [54,55].

Overall with tofacitinib the frequency of malignancies (other than nonmelanoma skin cancer) remained stable over time, and was found to be of same range compared to biologics among RA patients [56].

Numerically higher rates of deep vein thrombosis and pulmonary embolism (DVT/PE) were seen in some studies in JAKi-treated patients compared to the placebo; which suggests possibility of increased risk for venous thromboembolism (VTE) [50▪▪,57▪▪]. For brief information on this issue: (i) we are referring this FDA report about more VTE/PE for baricitinib at 4 mg [58▪▪] and (ii) to the EMA report on a still ongoing trial with tofacitinib versus anti-TNFs among patients with RA with cardiovascular risk factors; here also more VTE/PE and deaths were noticed with significantly higher dose of tofacitinib that is 10 mg twice daily but numerically more events of thromboembolism were also noticed for tofacitinib 5 mg BID dose [59▪▪,60▪▪]. These important information are now in the package inserts of all available JAKi (black box warnings); more long-term data and further studies are needed to address this issue [61,62].

SUMMARY

The novel oral JAKi have brought a paradigm shift in the treatment of autoimmune rheumatologic diseases.

(1) The JAK–STAT kinase system plays a pivotal role in the development and surveillance of the immune system. The JAK–STAT signaling proteins modulate proliferation/activation of the effector memory T cells and is associated with the cytokine network of various T-cell subpopulations including its regulatory role on the Th7 cells which play a pivotal role in the pathogenesis of SpA.
(2) Owing to their ability to simultaneously block multiple signaling pathways it is expected that that new generations of JAKi likely to deliver higher potency and less adverse effects.
(3) Already several JAKi have shown efficacy with acceptable safety in a number of SpA conditions. Encouraging findings of the undergoing clinical trials with JAKi in SpA are promising and suggest that JAK based more therapeutic options for SpA are on the way.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

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

1. Raychaudhuri SK, Raychaudhuri SP. Janus kinase/signal transducer and activator of transcription pathways in spondyloarthritis. Curr Opin Rheumatol 2017; 29:311–316.
2. ▪▪ Nash P, Kerschbaumer A, Dörner T, *et al.* Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. Ann Rheum Dis 2021; 80:71–87.
An evidence based article on therapeutic relevance of JAK inhibitors in autoimmune diseases including spondyloarthritis.
3. Kehl AS, Corr M, Weisman MH. Enthesitis: New Insights into pathogenesis, diagnostic modalities, and treatment. Arthritis Rheumatol 2016; 68: 312–322.
4. Raychaudhuri SP, Raychaudhuri SK. IL-23/IL-17 axis in spondyloarthritis-bench to bedside. Clin Rheumatol 2016; 35:1437–1441.
5. Chudnovskiy A, Pasqual G, Victora GD. Studying interactions between dendritic cells and T cells in vivo. Curr Opin Immunol 2019; 58:24–30.
6. ▪▪ Raychaudhuri SK, Abria C, Raychaudhuri SP. Polyfunctional TEM cells in psoriatic arthritis synovium skewed towards Th17 cells. Ann Rheum Dis 2019; pii: annrheumdis-2019-216658. PMID: 31862702.
This article reports that effector memory T cells in psoriatic arthritis are polyfunctional in respect to their cytokine profile. Thus, provides evidence that JAK inhibitors likely to be highly effective in spondyloarthrtis because JAK kinase proteins regulate multiple critical cytokines associated with diseases processes of SpA.
7. Raychaudhuri SP, Raychaudhuri SK. Mechanistic rationales for targeting interleukin-17A in spondyloarthritis. Arthritis Res Ther 2017; 19:51.
8. Raychaudhuri SK, Abria C, Maverakis EM, Raychaudhuri SP. IL-9 receptor: Regulatory role on FLS and pannus formation. Cytokine 2018; 111:58–62.
9. Villarino AV, Gadina M, O'Shea JJ, Kanno Y. SnapShot: JAK-STAT signaling II. Cell 2020; 181:1696–1696.e1.
10. ▪ Gadina M, Le MT, Schwartz DM, ET L. Janus kinases to jakinibs: from basic insights to clinical practice. Rheumatology 2019; 58(Suppl 1):i4–i16.
This is an excellent review on JAK-STAT signaling pathway, its relevance to autoimmune diseases, and principles for JAK-STAT-targeted therapy in autoimmune diseases.
11. Kerschbaumer A, Smolen JS, Nash P, *et al.* Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a systematic literature research. RMD Open 2020; 6:e001374.
12. Gerstenberger BS, Ambler C, Arnold EP, *et al.* Discovery of Tyrosine Kinase 2 (TYK2) Inhibitor (PF-06826647) for the treatment of autoimmune diseases. J Med Chem 2020; 63:13561–13577.
13. Clark JD, Flanagan ME, Telliez JB. Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. J Med Chem 2014; 57:5023–5038.
14. Kundu-Raychaudhuri S, Abria C, Raychaudhuri SP. IL-9, a local growth factor for synovial T cells in inflammatory arthritis. Cytokine 2016; 79:45–51.
15. Banerjee S, Biehl A, Gadina M, *et al.* Drugs JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects 2017; 77:521–546.
16. Maeda Y, Huang T, Manning C, *et al.* Blockade of the JAK/STAT pathway inhibits inflammation and bone formation in two murine models of spondyloarthritis. Arthritis Rheumatol 2018; 70(Suppl. 10).
17. Hammitzsch A, Chen L, de Wit J, *et al.* Inhibiting ex-vivo Th17 responses in Ankylosing Spondylitis by targeting Janus kinases. Sci Rep 2018; 8:15645.
18. Dendrou CA, Cortes A, Shipman L, *et al.* Resolving TYK2 locus genotype-to-phenotype differences in autoimmunity. Sci Transl Med 2016; 8:363ra149.
19. ▪ Gracey E, Hromadova D, Lim M, *et al.* TYK2 inhibition reduces type 3 immunity and modifies disease progression in murine spondyloarthritis. J Clin Investig 2020; 130:1863–1878.
This article provide evidence for regulatory role of TYK2 in the pathogenesis of spondyloarthritis, its cellular and molecular mechanisms and its potential as a therapeutic target in SpA
20. Chen C, Zhang X, Wang Y. Analysis of JAK2 and STAT3 polymorphisms in patients with ankylosing spondylitis in Chinese Han population. Clin Immunol 2010; 136:442–446.

21. Ferguson LR, Han DY, Fraser AG, *et al.* Genetic factors in chronic inflammation: Single nucleotide polymorphisms in the STAT-JAK pathway, susceptibility to DNA damage and Crohn's disease in a New Zealand population. Mutat Res 2010; 690:108–115.

22. Ellinghaus D, Ellinghaus E, Nair RP, *et al.* Combined analysis of genome-wide association studies for Crohn disease and psoriasis identifies seven shared susceptibility loci. Am J Hum Gen 2012; 90:636–647.

23. Pesu M, Candotti F, Husa M, *et al.* JAK3, severe combined immunodeficiency, and a new class of immunosuppressive drugs. Immunol Rev 2005; 203:127–142.

24. Meyer DM, Jesson MI, Li X, *et al.* Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. J Inflamm 2010; 7:41.

25. Honma M, MinamiHori M, Takahashi H, *et al.* Podoplanin expression in wound and hyperproliferative psoriatic epidermis: Regulation by TGFβ and STAT3 activating cytokines, IFNγ, IL6, and IL22. J Dermatol Sci 2012; 65:134–140.

26. Boyle DL, Soma K, Hodge J, *et al.* The JAK inhibitor tofacitinib suppresses synovial JAK1STAT signalling in rheumatoid arthritis. Ann Rheum Dis 2015; 71:440–447.

27. Gao W, McGarry T, Orr C, *et al.* Tofacitinib regulates synovial inflammation in psoriatic arthritis, inhibiting STAT activation and induction of negative feedback inhibitors. Ann Rheum Dis 2016; 75:311–315.

28. Raychaudhuri SK, Abria C, Raychaudhuri SP. Regulatory role of the JAK STAT kinase signaling system on the IL-23/IL-17 cytokine axis in psoriatic arthritis. Ann Rheum Dis 2017; 76:e36.

29. Deisseroth AB, Kaminskas E, Grillo J, *et al.* US Food and Drug Administration approval: ruxolitinib for the treatment of patients with intermediate and high risk myelofibrosis. Clin Cancer Res 2012; 18:3212–3217.

30. Clark JD, Flanagan ME, Telliez J-B. Discovery and development of Janus Kinase (JAK) inhibitors for inflammatory diseases. J Med Chem 2014; 57:5023–5038.

31. T Virtanen A, Haikarainen T, Raivola J, Silvennoinen O. Selective JAKinibs: prospects in inflammatory and autoimmune diseases. BioDrugs 2019; 33:15–32Choy EH.

32. Choy EHS, Miceli-Richard C, González-Gay MA, *et al.* The effect of JAK1/JAK2 inhibition in rheumatoid arthritis: efficacy and safety of baricitinib. Clin Exp Rheumatol 2019; 37:694–704.

33. Mease P, Hall S, FitzGerald O, *et al.* Tofacitinib or adalimumab versus placebo for psoriatic arthritis. N Engl J Med 2017; 377:1537–1550.

34. Mease PJ, Lertratanakul A, Anderson JK, *et al.* Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. Rheum Dis 2020; annrheumdis-2020-218870. doi: 10.1136/annrheumdis-2020-218870. Online ahead of print.

35. Mease P, Coates LC, Helliwell PS, *et al.* Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. Lancet 2018; 392:2367–2377.

36. van der Heijde D, Deodhar A, Wei JC, *et al.* Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study. Ann Rheum Dis 2017; 76:1340–1347.

37. Deodhar A, Sliwinska-Stanczyk P, Xu H, *et al.* Tofacitinib for the treatment of adult patients with ankylosing spondylitis: primary analysis of a phase 3, randomized, double-blind, placebo-controlled study [abstract]. Arthritis Rheumatol 2020; 72(suppl 10).

38. van der Heijde D, Baraliakos X, Gensler LS, *et al.* Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial. Lancet 2018; 392:2378–2387.

39. van der Heijde D, Song I-H, Pangan AL, *et al.* Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. Lancet 2019; 394:2108–2117.

40. Sandborn WJ, Ghosh S, Panes J, *et al.* Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med 2012; 367: 616–624.

41. Sands BE, Sandborn WJ, Feagan BG, *et al.* Peficitinib, an oral Janus kinase inhibitor, in moderate-to- severe ulcerative colitis: results from a randomized, phase 2 study. J Crohns Colitis 2018; 12:1158–1169.

42. Sandborn WJ, Ghosh S, Panes J, *et al.* Efficacy and safety of upadacitinib as an induction therapy for patients with moderately-to-severely active ulcerative colitis: data from the phase 2B study U-ACHIEVE. United Europ Gastroenterol J 2018; 6:A74.

43. Panes J, Sandborn WJ, Schreiber S, *et al.* Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. Gut 2017; 66:1049–1059.

44. Vermeire S, Schreiber S, Petryka R, *et al.* Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the Fitzroy study): results from a phase 2, double-blind, randomised, placebo-controlled trial. Lancet 2017; 389:266–275.

45. Ma C, Jairath V, Vande Casteele N. Pharmacology, efficacy and safety of JAK inhibitors in Crohn's disease. Best Pract Res Clin Gastroenterol 2019; 38-39:101606.

46. Strober BE, Gottlieb AB, van de Kerkhof PCM, *et al.* Benefit–risk profile of tofacitinib in patients with moderate-to-severe chronic plaque psoriasis: pooled analysis across six clinical trials. Br J Dermatol 2019; 180:67–75.

47. Papp KA, Menter MA, Raman M, *et al.* A randomized phase 2B trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis. Br J Dermatol 2016; 174:1266–1276.

48. Papp K, Gordon K, Thaci D, *et al.* Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. N Engl J Med Overseas Ed 2018; 379:1313–1321.

49. Smolen JS, Genovese MC, Takeuchi T, *et al.* Safety profile of Baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. J Rheumatol 2019; 46:7–18.

50. ■■ Sepriano A, Kerschbaumer A, Smolen JS, *et al.* Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2020; 79:760–770.

This article provides a systematic literature review (SLR) about the safety of synthetic (s) including JAKi and biological (b) disease-modifying anti rheumatic dugs (DMARDs)

51. Cohen SB, Tanaka Y, Mariette X, *et al.* Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. Ann Rheum Dis 2017; 76:1253–1262.

52. Genovese MC, Smolen J, Takeuchi T, *et al.* FRI0123: safety profile of Baricitinib for the treatment of Rheumatoid Arthritis up to 8.4 years: an updated integrated safety analysis. Ann Rheum Dis 2020; 79(Suppl. 1):638.

53. Cohen SB, van Vollenhoven R, Curtis JR, *et al.* THU0187: Safety profile of Upadacitinib up to 3 years of exposure in patients with Rheumatoid Arthritis. Ann Rheum Dis 2020; 79(Suppl. 1):315.

54. Curtis JR, Xie F, Yun H, *et al.* Real world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis 2016; 75:1843–1847.

55. Curtis JR, Xie F, Yang S, *et al.* Risk for herpes zoster in Tofacitinib-treated glucocorticoids. Arthritis Care Res 2019; 71:1249–1254.

56. Curtis JR, Lee EB, Kaplan IV, *et al.* Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical development programme. Ann Rheum Dis 2016; 75:831–841.

57. ■■ Desai RJ, Pawar A, Weinblatt ME, *et al.* Comparative risk of venous thromboembolism in rheumatoid arthritis patients receiving tofacitinib versus those receiving tumor necrosis factor inhibitors: an observational cohort study. Arthritis Rheumatol 2019; 71:892–900.

See Ref [60■■].

58. ■■ FDA briefing. document arthritis advisory committee meeting April 23, [2018] 2019. Available https://www.fda.gov/media/112372/download (accessed February 1, 2021).

See Ref [60■■].

59. ■■ EMA confirms. Xeljanz to be used with caution in patients at high risk of blood clots. 2019. Available https://www.ema.europa.eu/en/news/ema-confirms-xeljanz-be-used-caution-patients-high-riskblood-clots (accessed February 1, 2021).

See Ref [60■■].

60. ■■ Safety study of tofacitinib versus tumor necrosis factor (TNF) inhibitorin subjects with rheumatoid arthritis. 2020. Available https://clinicaltrials.gov/ct2/show/NCT02092467 (accessed Feb 1, 2021).

Overall, the safety profile of JAKi is reasonably good. There are some concerns about increased risk for venous thromboembolism (VTE) following treatment with JAKi. Long-term data and further studies are needed to identify the risks for VTE; reference numbers 54-59 provides relevant information on this issue.

61. Mease P, Charles-Schoeman C, Cohen S, *et al.* Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data. Ann Rheum Dis 2020; 79:1400–1413.

62. Nash P, Coates LC, Kivitz AJ, *et al.* Safety and efficacy of tofacitinib in patients with active psoriatic arthritis: interim analysis of OPAL Balance, an Open-Label, Long-Term Extension Study. Rheumatol Ther 2020; 7:553–580.

Patient educational needs and challenges in psoriatic arthritis

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Purpose of review
To provide an overview of the recent research publications on educational needs of patients with psoriatic arthritis (PsA) and the associated challenges.

Recent findings
The rate of good treatment adherence in PsA can be as low as 57.7% and successful patient education can help improve treatment adherence. Also, 78.7% of patients who stopped their disease modifying anti-rheumatic drugs during the first wave of the COVID-19 pandemic did so without the advice of their clinician. In delivering educational needs, the aspects of disease process, treatment, self-help measures, managing pain, movement, psychological and social needs should all be addressed, whilst at the same time, recognising that PsA patients with multidomain disease, are likely to be dealing with more than just pain. Arthritis self-care management education is potentially beneficial, but up to 11% of educational YouTube videos may contain misleading patient opinion and many existing apps do not meet the needs of the patients with PsA.

Summary
Significant room for improvement exists in treatment adherence in PsA and patient education addressing the relevant educational needs could assist with this issue. However, patients should be advised to be wary of internet videos and other educational aids that were not created by health professionals.

Keywords
health literacy, patient education, psoriatic arthritis

INTRODUCTION

Psoriatic arthritis (PsA) is a complex chronic immune-mediated disease of the joints and extra-articular organs which is characterised by flare-ups and diverse domains of manifestations. As a part of pursuing patient-centred holistic care, requisite patient education is vital for empowering the patient as a partner in their care [1]. With clinical domains of PsA including peripheral arthritis and tenosynovitis, enthesitis, dactylitis, and skin and nail disease; it is unsurprising that a newly diagnosed patient is faced with a learning curve that could be steep and challenging, depending on the individual PsA patient characteristics and their access to appropriate education about their condition. In addition, comorbidities have the tendency to complicate the course, management and quality of life in PsA. Patients with PsA often develop not only uveitis and inflammatory bowel disease, but also excess cardiovascular disease, pulmonary and psychiatric morbidities [2]. In this review, we discuss the evolution and benefit of patient education, as well as the needs and challenges as applicable to patients with PsA.

The changing landscape of patient education

Patient education has undergone immense evolution over the last few decades. It used to be delivered by the healthcare provider from an authoritarian and paternalistic standpoint in which the patient is a passive recipient and told what is best for them [3]. However, this approach has now shifted into a more effective patient-centred one, which actively embraces patient engagement and shared decision making, whilst recognising that patient education is a fundamental and crucial step to successful patient management [3]. The concept of Health Literacy Universal Precautions as recommended by experts proposes that the delivery of patient education be done from an approach that presumes that all of the

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KEY POINTS

- Treatment adherence in PsA can be as low as 57.7% but therapeutic patient education can improve treatment adherence.
- Patient education should address the educational needs of the patients while covering aspects of disease process, treatment, self-help measures, pain management, movement, psychological and social needs.
- Patients may be exposed to conflicting information from different sources and online videos on PsA may contain misleading information particularly if they were not made by healthcare professionals.

targeted individuals have literacy challenges. The Agency for Healthcare Research and Quality Health Literacy Universal Precautions Toolkit is an excellent resource for advancing organisational priorities to promote a more effective health literacy environment [3,4]. Patients and patient relatives and carers-targeted health education on PsA and its management has to rely on methods that are mindful of the complexities of the content and the potential challenges to its delivery and reception. To foster inclusiveness and patient-centred health education programmes, it is essential for organizations to create an environment that equips the workforce with a heightened sensitivity for health literacy [4]. This is the ability of an individual to access, interpret and apply health information in a process that includes the vital role of the society in making the comprehensible information available [5].

Therapeutic patient education: an enabler towards treatment adherence

Effective therapeutic patient education as part of PsA management, can promote treatment adherence, an issue that currently requires further improvement among patients with PsA. In a retrospective real-world study of 10-year treatment of PsA with Adalimumab and Etanercept among Italian patients, an adherence level of 0.83 was found for Adalimumab and 0.84 for Etanercept [6▪]. The amount of these PsA medications the patients actually used, may in reality have been significantly less, since the definition of adherence used was based on the ratio of the daily dose received from the pharmacy to the prescribed daily dose. Using the Morisky Medication Adherence Scale (MMAS-4^{TM}), the percentage of PsA patients with good adherence to subcutaneous anti-tumour necrosis factor agents after being subjected to some form of therapeutic patient education mode was 75.7% [7▪]. Depending on the treatment, the proportions of patients with good adherence in the multinational study from the ALIGN cohort of patients was found to be between 57.7% and 70.4% [8▪]. Similarly, the ADhER-1 study of adherence to biological therapies, also using the MMAS-4^{TM}, found a value of 62.5% of good adherence among patients with PsA [9▪]. This was higher than the adherence among rheumatoid arthritis patients, but lower than the level of adherence among the ankylosing spondylitis patients.

Educational needs: the conceptional structure that should be adopted and delivered

Effective needs-based patient education is the springboard for patient empowerment to enable successful management of the multidimensional impacts of PsA. Delivering either generic or personalised patient education as a part of ongoing care is best built around a framework of needs, that if met, could yield the result of best treatment outcomes and high quality of life. The Educational Needs Assessment Tool (ENAT) that was developed in the UK and has now seen several cross-cultural adaptations, is a clinically practical instrument for determining needs-based patient education [10,11▪,12]. Without the proper determination of educational needs and targeting of the relevant aspects with educational interventions, valuable amounts of educational time and activities could end up being deployed to low-impact educational interventions, with crucial aspects of patient education being overlooked. Afterall, more than 10% of patients with PsA in a Portuguese study were not interested in being given any form of education regarding their disease [11▪]. The ENAT is a self-administered questionnaire that can also be used by researchers to determine the educational needs of the patient at the time of administration. In an online survey of educational needs of patients with various rheumatic and musculoskeletal diseases (RMDs), Hirsch *et al.* identified that the educational needs of patients vary by disease groups and that healthcare professionals need to assess disease-specific needs for education in order to achieve high quality of care [13].

Disease process education

Receiving the diagnosis of a chronic disease such as PsA, for the first time, can be a lot to take in and can be quite a shock for a patient. In a recent systematic review of nonadherent behaviour among patients with RMDs, the provision of education to patients

on disease process was identified as one of the ways to reduce nonadherence [14▪]. However, it can also be overwhelming to be faced with a seemingly endless amount of information about the disease at the point of diagnosis. Patients with PsA and other rheumatic diseases often find themselves in a position of significant lack of knowledge about their disease and this can add to patient anxiety and distress. The layering of information can greatly assist with this. Layering requires the provision of graded amounts of education using practical methods. The minimum amount of required information should form the base layer on which practical interests and theoretical interests may be layered in turn [15]. In general, clinicians should resist the urge to subject the patient to cognitive overload even when the patient appears to be welcoming more in a single session, since the processing and practical utilization of the information will become challenging soon after the patient leaves the consultation [16].

Treatment decision making

With an ever-expanding therapeutic armamentarium and the complexities of therapeutic decision making, there has never been a time when patients needed to be more informed about their treatment than now. In addition, the therapeutic goal in PsA of 'treat to target' which aims to move patient's disease activity into remission or low disease activity state, will benefit from adequate patient education, either in terms of achieving the intended therapeutic goal or with the patient coming to terms with the difficulty in achieving this goal [2]. Since the outbreak of the COVID-19 pandemic, various aspects of healthcare have relied more heavily on virtual interactions than ever before and educational programmes and consultations are now frequently adapted for telehealth. In an analysis of the survey conducted through the Arthritis Power Patient-Powered Research Network and the CreakyJoints patient community conducted by George *et al.* 14.9% stopped their disease modifying anti-rheumatic drugs (DMARDs), of which 78.7% of these were not recommended by a clinician [17▪]. The lack of access to telehealth was identified to confer an odds ratio of 2.26 for discontinuing DMARDs [17▪]. In a published guideline based on literature review and expert consensus, a French group recommended that 'knowledge both of the disease and of the treatment and patients' perceptions of the benefit/risk of the treatment are key elements in drug adherence' and 'In the context of shared decision-making/therapeutic alliance, caregiver-patient communication about treatment is a key factor in drug adherence' ([18] page 8).

Self-help measures and self-efficacy

Most patients tend to prefer to have an active role in their own care. These self-help efforts may instil more confidence in the patient if their overall condition improves and may promote a positive attitude towards long-term care. Self-efficacy is being increasingly recognised as an important aspect of chronic disease management. A recent randomised controlled trial assessing the efficacy of a self-management program for joint protection and physical activity among Taiwanese patients determined that the self-management program based on self-efficacy theory led to statistically significant improvement in physical functioning and self-management behaviours 6 months after initiation of the intervention [19]. In a quasi-experimental study, Oroh *et al.* assessed the effect of Arthritis Self-Care Management Education and Home-Based Exercise on self-efficacy and Activities of Daily Living (ADL) of patients [20▪]. Their study found that both interventions improved self-efficacy and ADL, leading to the recommendation that nurses incorporate these methods into independent nursing management of patients with arthritis [20▪]. Li *et al.* conducted a prospective study of the efficacy of a multifaceted counselling intervention to improve physical activities and patient-reported outcomes (PROs) [21]. They recruited patients with RMDs and provided education and counselling as the interventions. Outcomes were measured using a Fitbit and web application to obtain physical activity-related feedback and four follow-up calls were undertaken to collect PROs. Their results revealed a significant impact of the intervention on pain and perceived walking habit, whereas time spent on moderate-to-vigorous physical activities increased but did not reach statistical significance. If unsupported by appropriate education, self-help attempts may be counterproductive to the primary goal of treatment, as seen in many patients who discontinued their DMARDs in the midst of the COVID-19 pandemic for fear that this treatment might predispose them to catch the SARS-CoV-2 virus [17▪].

Mobile health applications have gained more popularity in the last 5 years. Barring the limitation of technological illiteracy among mostly the elderly patients, mobile apps designed for the purpose of self-help tend to be useful among patients with inflammatory arthropathies. In a study that involved patients in Europe, the United States, Canada and Australia; half of the patients had used a self-help mobile app before [22▪]. Various existing apps were described by these patients as time-wasting and they generally felt that they failed to meet the patients' needs. All participants agreed to the need for bespoke apps. Patients were particularly interested in apps that could help them achieve self-monitoring of

relevant parameters (74.9%), monitoring of disease activity (63.9%), and facilitate communication directly with their clinicians (57.8%) [22▪].

Pain management education

The sources of pain in PsA are quite diverse. In addition to musculoskeletal pain, pain could also arise from the skin as part of the manifestations of psoriasis. In a recently published protocol for a systematic scoping review, researchers from Croatia have set out to review the body of evidence regarding pain in psoriasis while excluding papers referring to pruritus or other nonnociceptive aspects of the disease [23]. Typically, rheumatologists are less likely to pay attention to the skin as part of the sources of the patient's pain. Consequently, the outcome of this project may shed some light on the weight of evidence and the possible need to pay more attention to skincare advice provision as part of PsA education. A study based on the analysis of data from the Corrona PsA/Spondyloarthritis Registry, which compared disease attributes, quality of life and work productivity between PsA patients with single domain disease, against those with multidomain disease, concluded that the multidomain presenters are more likely to have pain and fibromyalgia among other problems [24▪]. Multidomain presentation may thus be a surrogate for early recognition of the likelihood of greater pain. For these patients, self-help measures for coping with fibromyalgia may be beneficial.

Mobility management education

The educational needs of Portuguese patients with ankylosing spondylitis and PsA were assessed in a recently published cross sectional analytical study [11▪]. Using the Portuguese version of the ENAT to assess educational needs, a negative correlation was found between the duration of disease and an interest in educational need in the movement domain. At first sight, this finding is unexpected, but may reflect the possibility that those patients with longstanding disease, some of whom have developed irreversible limitation of range of motion in one or more joints, may have come to terms with their disability and do not wish to be bothered with mobility-related information, which they consider unlikely to change their situation.

Psychological needs-related education

The skin component of PsA is a major cause of psychological disturbance in PsA patients. In a comparative study of patients with severe skin disease and articular disease on one arm, against those PsA patients with only mild skin disease on the other arm, Brihan *et al.* used the Rosenberg Self-Esteem Scale and found that patients with severe skin disease had lower self-esteem [25▪]. Among the male patients with both severe cutaneous disease and PsA, those with higher education (college or tertiary) also had lower self-esteem than those with only secondary education.

In a study involving patients with PsA in Australia and New Zealand, focus groups of patients were interviewed along three themes [26]. One of these themes was the 'impact on daily life leading to social withdrawal and reduced work productivity'. The study concluded that foot problems led to functional disability and altered self-concept leading to a cascade of socio-economic and psychological consequences. A recent cross-sectional study of patients attending outpatient clinics for PsA showed that anxiety and depression as well as being unemployed, having high fatigue scores, sleep disturbances, disability measured by the Modified Health Assessment Questionnaire and the presence of comorbidities, all predicted a low quality of life [27].

Social needs-related education

The social support requirements of patients with PsA are diverse. Often, social support may help patients cope with the nonmodifiable aspects of their disease and can also provide them with the knowledge to improve their coping strategies. Hammer *et al.* in a Danish nationwide cross-sectional study of 664 patients, found that younger patients were interested in one-to-one sessions with psychologists, or another patient [28▪]. In general, they were also interested in educational sessions, events and online support services. Older patients were more interested in listening to researchers. Women were more likely to be interested in having one-to-one sessions with healthcare workers, question-and-answer sessions with occupational therapists, physical activity and online resources. Patients with spondyloarthritis were significantly more interested than patients with rheumatoid arthritis in attending discussion groups, seeing psychologists, discussing with other patients, attending stress and anger management sessions and online communications. Also, patients with shorter duration of disease were found to be more likely to be interested in one-to-one sessions with rheumatology professionals, listening to talks of experienced patients and online support services. Other studies have shown that there is value in promoting more educational sessions on sexual health [29], and the supportive role that spouses and other relatives can play [30,31].

As part of ongoing PsA holistic management, health education around lifestyle adjustments such as smoking cessation and weight loss, offer vital adjuncts to therapy as cardiovascular risk is reduced and dermatological and articular symptoms may be drastically alleviated [32]. Education around pregnancy and the extent of available evidence on the safety of specific DMARDs for pregnant and lactating women may provide the clinician with insights into the thought process of the patient around reproductive health and help to address concerns and forestall surprising patient decisions, based on the patient being ill-informed.

Overview of challenges of patient education

As highlighted already, on the road to effective patient education with regards to PsA and its management, stand a long list of challenges to the tradition and practice of teaching, counselling and informing patients, thereby making a one-size-fits-all model impractical. As a result, there is now an increasing recognition of the need to undertake personalised patient education alongside personalised medicine for these patients.

Organisational factors

Organisational priorities and pressures may push the necessity for structured patient educational programmes down the list of importance. If, as a result, there is no allocated time for rheumatologists, nurse practitioners or other relevant healthcare professionals to deliver education to patients with PsA, this reduces the options of sources from which, these patients can derive accurate and reliable information about their disease. The structure, resource and processes committed to patient education are strongly linked to the organisational culture [3]. Where organisational will is lacking, this can be a major impediment to meeting the educational aspect of the care needs of these patients. Clinicians may struggle to rush through the educational contents of the consultation within the limit of time available and this will potentially set the stage for information overload and for ineffective educational delivery [16,33].

Educational materials

The traditional methods of delivering patient education such as group teaching and handing out educational manuals are increasingly being supplemented with a range of tools which include online resources, multimedia, mobile apps, Virtual Reality devices and other new technologies. The quality of the information from these various sources and teaching aids can vary greatly. To complicate matters, patients can sometimes come across conflicting information from online support groups, friends, relatives, media and their healthcare worker [16]. Elangovan *et al.* studied the content, reliability and quality of the top 200 English-language YouTube videos on spondyloarthritis [34▪]. Viewer interactions with the videos in the form of number of views, likes, dislikes, comments and subscribers were documented. Using a modified five-point DISCERN tool and a five-point Global Quality Scale to assess reliability and quality respectively, the researchers determined that 11% and 3% had misleading patient opinion and misleading information, respectively. The main areas of misinformation were with regards to clinical features and treatment. Another study on the quality of Secukinumab information videos on YouTube showed that there was no difference between the rate of viewer interactions with the videos between the high, intermediate and low-quality categories [35]. Since online educational materials developed by healthcare professionals are more likely to contain high-quality information, it may be a worthwhile idea for healthcare organisations to consider injecting more relevant educational materials into their online presence. Conversely, online patient organisations and support groups may consider the use of healthcare professional moderators on their forums, where appropriate, to steer the sharing of educational materials among patients away from misinformation.

Educator factors

A lot depends on the communication skills, extent of knowledge and the style of delivery of information by the person giving the disease-related patient education. Barriers to effective communication may include the use of medical jargon without providing adequate explanation [36]. Communication can even be more difficult, irrespective of the robustness of the communication skill of the educator, if the depth of knowledge on the topic is shallow [37]. For example, this factor played a major role in the chaos of health education regarding the COVID-19 infection that took place in the early stage of the pandemic, when there were too many unknowns [38]. If the educator fails to adopt a patient-centred approach that pays attention to the patient's literacy level and does not refrain from delivering information overload, the success of the effort may be significantly limited. Using the patient-centred education model in the training of patient educators could increase the confidence

of the educators and promote better shared decision-making practices [39].

Patient factors

Individual patient characteristics may offer a long list of obstacles to successful patient education. This is one of the reasons why a generic approach to delivering patient education Is often unlikely to work. The health literacy level of the target person is often the first barrier and for this reason, it is best to approach each patient initially with a simple and clear message, with the intention of providing as basic a level of knowledge as their likelihood of comprehension demands and to present written educational materials at a primary school reading level [3]. In addition, problems such as dementia, anxiety, social phobias, visual and hearing impairment, depression, fibromyalgia and fatigue may also present a major challenge. These complexities have to be put into context, whilst pursuing effective learning.

Additionally, the cultural background and beliefs of the patient may present further difficulties. In this age of 'fake news', a concept of mistrust of information which has even been promoted by politicians [40–42]; conspiracy theories and strong negative beliefs not backed by evidence, can make the patient impervious to useful information [43]. This is often encountered, for example, among antivaxxers thereby creating impediments for the recommended standard vaccinations for patients treated with DMARDs for their PsA and as part of the campaign against COVID-19 [44].

CONCLUSION

PsA is a complex disease that is best managed through a holistic approach that empowers the patient and their relatives with the knowledge that enables them to be active partners in their own care. Adopting a patient-centred model of patient education that recognises the impact of the various clinical domains of the disease as well as the co-morbidities, provides a robust process for achieving good care and outcomes as long as Health Literacy Universal Precautions are observed.

Needs-based patient education should capture the evidence-based aspects of educational requirements of PsA and PsA management for each patient with this condition. This could give the patient increased confidence in living with their disease, as well as providing a better chance of preventing nonadherence or treatment discontinuation against medical advice. To ensure effectiveness, these interventions should include education on the disease process, treatment, self-help measures, managing pain, mobility, psychological and social needs. However, standing in the way of delivering high-quality patient education are a range of obstacles that can be divided into challenges related to organisational factors, educational materials, educator factors and patient factors. As more of these obstacles are overcome, there is likely to be an accompanying increase in the effectiveness and the recognition of the importance of educational interventions in the management of PsA.

Best practices for educating patients with PsA in the rheumatology clinic

- Recognise the level of health literacy of patient and present information as simple as possible.
- Assess and address the educational needs of patients.
- Recognise the manifest PsA domains in the patient as well as co-morbidities and provide relevant educational needs.
- Address the risk of misinformation from nonprofessional online sources.
- Provide access for urgent advice.
- Adopt a partnership approach and avoid taking an authoritarian stance.
- Consider layering of information and avoid information overload.
- Assign reasonable self-help roles to the patient and provide them with the needed knowledge.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

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

1. Marques CJ, Bohlen K, Lampe F. Participation in a preoperative patient education session is a significant predictor of better WOMAC total index score and higher EQ-5D-5L health status index one year after TKA or THA: A retrospective observational study. Am J Phys Med Rehabil 2021; doi: 10.1097/PHM.0000000000001689. [Epub ahead of print]

2. Calabresi E, Monti S, Terenzi R, *et al.* One year in review 2019: psoriatic arthritis. Clin Exp Rheumatol 2020; 38:1046–1055.
3. Karl JI, Mion LC. Nurse-delivered patient education in the acute care setting: challenges and opportunities. Geriatr Nurs 2020; 41:187–190.
4. Isibel D. Improving Health Literacy at the Organizational Level. J Dr Nurs Pract 2020; 13:79–83.
5. Ancker JS, Grossman LV, Benda NC. Health literacy 2030: is it time to redefine the term? J Gen Intern Med 2020; 35:2427–2430.
6. ■ Santoleri F, Romagnoli A, Costantini A. Adalimumab and etanercept adherence, persistence and switch in the treatment of psoriatic arthritis: 10-year real-life analysis. Expert Opin Drug Saf 2020; 19:93–97.

This study analysed 10-year real-world data on adherence with Adalimumab and Etanercept

7. ■ Fayet F, Fan A, Rodere M, *et al.* Adherence to subcutaneous anti-TNF treatment in chronic inflammatory rheumatism and therapeutic patient education. Patient Prefer Adherence 2020; 14:363–369.

This study assessed the impact of therapeutic patient education on treatment adherence among patients with rheumatoid arthritis, ankylosing spondylosis and psoriatic arthritis receiving anti-tumour necrosis factor biologics.

8. ■ Smolen JS, Gladman D, McNeil HP, *et al.* Predicting adherence to therapy in rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis: a large cross-sectional study. RMD Open 2019; 5:e000585.

This multinational study explored the link between treatment adherence and patient believe, patient demographic, disease characteristics and medication types in rheumatoid arthritis, psoriatic arthritis and ankylosin spondylitis.

9. ■ Núñez-Rodríguez J, González-Pérez Y, Nebot-Villacampa MJ, *et al.* Adherence to biological therapies in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. (Study ADhER-1). Semergen 2021; 47:81–90.

This study assessed the predictors of treatment adherence among patients with inflammatory arthritis and also determined the impact of subcutaneous biologic being administered by a family member on adherence.

10. Favero M, Ometto F, Salaffi F, *et al.* Validation of the Italian version of the educational needs assessment tool in rheumatoid arthritis patients and factors associated with educational needs. J Pers Med 2020; 10:150.
11. ■ Marques ML, Ferreira RJO, Machado PM, *et al.* Educational needs in people with ankylosing spondylitis and psoriatic arthritis: a cross-sectional study. Clin Exp Rheumatol 2020; 38:282–288.

This study specifically examined the educational needs among patients with psoriatic arthritis and ankylosing spondylitis and assessed the determinants of the patients' educational needs.

12. Sung YK, Kim H, Cha SJ, *et al.* Developing the Korean Educational Needs Assessment Tool (Korean ENAT) in rheumatoid arthritis: cross-cultural validation using Rasch analysis. Korean J Intern Med 2020; doi: 10.3904/kjim.2019.422. [Epub ahead of print]
13. Hirsch JK, Toussaint L, Offenbacher M, *et al.* Educational needs of patients with rheumatic and musculoskeletal diseases attending a large health facility in Austria. Musculoskeletal Care 2020; 18:391–396.
14. ■ Ritschl V, Stamm TA, Aletaha D, *et al.* Prevention, screening, assessing and managing of nonadherent behaviour in people with rheumatic and musculoskeletal diseases: systematic reviews informing the 2020 EULAR points to consider. RMD Open 2020; 6:e001432.

In this review of systematic reviews, a wide scope of topics around the subject of nonadherence to prescribed treatments for rheumatic and musculoskeletal diseases covering prevention, screening, assessment and management was done and it revealed the complexity of nonadherence.

15. Walker D, Adebajo A, Bukhari M. The benefits and challenges of providing patient education digitally. Rheumatology 2020; 59:3591–3592.
16. Zirwas MJ, Holder JL. Patient education strategies in dermatology: part 1: benefits and challenges. J Clin Aesthet Dermatol 2009; 2:24–27.
17. ■ George MD, Venkatachalam S, Banerjee S, *et al.* Concerns, healthcare use, and treatment interruptions in patients with common autoimmune rheumatic diseases during the COVID-19 pandemic. J Rheumatol 2020; jrheum.201017. doi: 10.3899/jrheum.201017. [Epub ahead of print]

This paper studied the changing pattern of healthcare behaviour among patients with rheumatic diseasesduring the COVID-19 pandemic through two large communities of patients and researchers.

18. Gossec L, Molto A, Romand X, *et al.* Recommendations for the assessment and optimization of adherence to disease-modifying drugs in chronic inflammatory rheumatic diseases: a process based on literature reviews and expert consensus. Joint Bone Spine 2019; 86:13–19.
19. Shao JH, Yu KH, Chen SH. Effectiveness of a self-management program for joint protection and physical activity in patients with rheumatoid arthritis: a randomized controlled trial. Int J Nurs Stud 2020; 103752; doi: 10.1016/j.ijnurstu.2020.103752. [Epub ahead of print]
20. ■ Oroh CTM, Suprapti F, Susilo WH. Improving self-efficacy and life activities of arthritis patients: a quasy-experiment study. Enferm Clin 2020; 30 Suppl 7:30–33.

This study examined the effect of Arthritis Self-Care Management Education and Home-Based Exercise on self-efficacy and Activities of Daily Living using a nonrandomised control group.

21. Li LC, Feehan LM, Xie H, *et al.* Efficacy of a physical activity counseling program with use of a wearable tracker in people with inflammatory arthritis: a randomized controlled trial. Arthritis Care Res 2020; 72:1755–1765.
22. ■ Najm A, Lempp H, Gossec L, *et al.* Needs, experiences, and views of people with rheumatic and musculoskeletal diseases on self-management mobile health apps: mixed methods study. JMIR Mhealth Uhealth 2020; 8:e14351.

This mixed-method study examined the perspectives of patients on various mobile health apps to see if creators' goals are meeting patient need.

23. Sanader Vucemilovic A, Nujic D, Puljak L. Pain associated with psoriasis: systematic scoping review protocol. BMJ Open 2020; 10:e031461.
24. ■ Ogdie A, Hur P, Liu M, *et al.* Impact of multidomain disease presentations on patients with psoriatic arthritis in the corrona psoriatic arthritis/spondyloarthritis registry. J Rheumatol 2020; jrheum.200371. doi: 10.3899/jrheum.200371. [Epub ahead of print]

Using 5-year data from a US registry of psoriatic arthritis and spondyloarthritis, comparison was made between patients with multidomain and single-domain psoriatic arthritis in the aspects of disease characteristics, quality of life and work productivity.

25. ■ Brihan I, Ianosi SL, Boda D, *et al.* Implications of self-esteem in the quality of life in patients with psoriasis. Exp Ther Med 2020; 20:202.

This study examined the impact of psoriasis severity on the self-esteem of patients using the Rosenberg Self-Esteem Scale.

26. Carter K, Walmsley S, Chessman D, *et al.* Perspectives of patients and health professionals on the experience of living with psoriatic arthritis-related foot problems: a qualitative investigation. Clin Rheumatol 2019; 38:1605–1613.
27. Haugeberg G, Michelsen B, Kavanaugh A. Impact of skin, musculoskeletal and psychosocial aspects on quality of life in psoriatic arthritis patients: a cross-sectional study of outpatient clinic patients in the biologic treatment era. RMD Open 2020; 6:e001223.
28. ■ Hammer NM, Flurey CA, Jensen KV, *et al.* Preferences for self-management and support services in patients with inflammatory joint disease – A Danish Nationwide Cross-Sectional Study. Arthritis Care Res (Hoboken) 2020; doi: 10.1002/acr.24344. [Epub ahead of print]

This nationwide survey of patients with inflammatory arthritis examined the preferences of patients for self-management and support services reporting the differences according to patient characteristics.

29. Savel C, Cherillat MS, Berland P, *et al.* French survey on the crossed needs on sexual health for chronic inflammatory rheumatism patients and healthcare professionals. Rheumatol Int 2020; 40:1481–1491.
30. Rat AC, Brignon M, Beauvais C, *et al.* Patients and spouses coping with inflammatory arthritis: impact of communication and spousal perceived social support and burden. Joint Bone Spine 2020; 88:105125.
31. Untas A, Vioulac C, Boujut E, *et al.* What is relatives' role in arthritis management? A qualitative study of the perceptions of patient-relative dyads. Patient Prefer Adherence 2020; 14:45–53.
32. Ferraz-Amaro I, Prieto-Peña D, Palmou-Fontana N, *et al.* The Number of traditional cardiovascular risk factors is independently correlated with disease activity in patients with psoriatic arthritis. Medicina (Kaunas) 2020; 56:415.
33. Conti A, Dimonte V, Rizzi A, *et al.* Barriers and facilitators of education provided during rehabilitation of people with spinal cord injuries: a qualitative description. PLoS One 2020; 15:e0240600.
34. ■ Elangovan S, Kwan YH, Fong W. The usefulness and validity of English-language videos on YouTube as an educational resource for spondyloarthritis. Clin Rheumatol 2020; 40:1567–1573.

Using standard validated tools, this study examined the validity of content of YouTube videos on the topic of spondyloarthritis identifying the proportions of useful information, useful patient opinion, misleading patient opinion and misleading information.

35. Kocyigit BF, Akaltun MS. Does YouTube provide high quality information? Assessment of secukinumab videos. Rheumatol Int 2019; 39:1263–1268.
36. Ivynian SE, Newton PJ, DiGiacomo M. Patient preferences for heart failure education and perceptions of patient-provider communication. Scand J Caring Sci 2020; 34:1094–1101.
37. Jung MJ, Roh YS. Factors influencing the patient education performance of hemodialysis unit nurses. Patient Educ Couns 2020; S0738-3991(20)30328-1. doi: 10.1016/j.pec.2020.06.010. [Epub ahead of print]
38. Finset A, Bosworth H, Butow P, *et al.* Effective health communication – a key factor in fighting the COVID-19 pandemic. Patient Educ Couns 2020; 103:873–876.
39. Mitchell TO, Goldenberg MN. When doctor means teacher: an interactive workshop on patient-centered education. MedEdPORTAL 2020; 16:11053.
40. Naeem SB, Bhatti R, Khan A. An exploration of how fake news is taking over social media and putting public health at risk. Health Info Libr J 2020; doi: 10.1111/hir.12320. [Epub ahead of print]
41. Orso D, Federici N, Copetti R, *et al.* Infodemic and the spread of fake news in the COVID-19-era. Eur J Emerg Med 2020; 27:327–328.
42. Sample C, Jensen MJ, Scott K, *et al.* Interdisciplinary lessons learned while researching fake news. Front Psychol 2020; 11:537612.
43. O'Connor C, Murphy M. Going viral: doctors must tackle fake news in the covid-19 pandemic. BMJ 2020; 369:m1587.
44. Boodoosingh R, Olayemi LO, Sam FA. COVID-19 vaccines: getting anti-vaxxers involved in the discussion. World Dev 2020; 136:105177.

Twenty years of clinical trials in axial spondyloarthritis: what can we learn for the future?

Joachim Sieper and Denis Poddubnyy

Purpose of review
We have now about 20 years of experience with the treatment of axial spondyloarthritis with biologics, which raises the question what we can learn from past experience, and which open questions should be addressed in future investigations.

Recent findings
Many studies have shown that axSpA patients – both patients in their nonradiological and radiological stage – respond similarly well to biologic treatment and these patients should be seen as having the same disease at different stages. AxSpA respond best to TNF-blocker – and probably also to other biologics – if the disease duration is short and if objective parameters of inflammation, such as C-reactive protein or MRI are positive. Primary aim of treatment is to reach and maintain clinical remission. Once remission is achieved, it can be maintained by continuing treatment, and in a proportion of yet not well defined patients the drug dose can be reduced without inducing a flare. The recent demonstration of a good efficacy, in addition to TNF blockers, also of IL-17 inhibitors and JAK-inhibitors in axSpA patients raises the question how to select the best patients for the best treatment. Radiographic progression can best be stopped by effectively suppressing inflammation, whether different drugs have here a different effect has still to be defined. More sensitive measurements of radiographic progression are urgently needed.

Summary
Reaching and maintaining clinical remission and preventing structural bony damage is the primary treatment target in patients with axSpA. How to reach this aim best has to be further explored in the future.

Keywords
axial spondyloarthritis, prediction and maintenance of treatment response, strategy trials for defining best treatment

INTRODUCTION

When we conducted the first clinical trials in axial spondyloarthritis (axSpA) about 20 years ago only patients who had already reached the stage of ankylosing spondylitis could be included and the only effective treatment available were NSAIDs [1]. However, it soon became clear that tumour necrosis factor (TNF) blockers were very effective in active ankylosing spondylitis patients who had failed previous NSAID treatment and that the anti-TNF-effect was a class effect. This situation raised a few important questions, which had to be answered, which are still valid today also with respect to other biological and targeted synthetic disease modifying anti-rheumatic drugs (bsDMARDs and tsDMARDs) and which will be discussed in Table 1.

ARE TUMOUR NECROSIS FACTOR BLOCKERS ALSO EFFECTIVE IN PATIENTS IN THE NONRADIOGRAPHIC STAGE OF AXIAL SPONDYLOARTHRITIS?

With the emergence of MRI investigations of the sacroiliac joints and the spine since the mid-90s of the last century, it became increasingly clear that before the occurrence of structural damage in the

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KEY POINTS

- Axial spondyloarthritis patients should be seen as one group for treatment and treatment trials; the subgroups of nonradiographic and radiographic axSpA can be analysed separately in addition.
- Axial spondyloarthritis patients in the early phase of their disease and with objective signs of inflammation respond best to effective anti-inflammatory treatments.
- It has still to be determined with which biologic or targeted synthetic DMARD treatment of axSpA should be started and whether a combination therapy of these drugs is an option.

sacroiliac joints and the spine, there is bony inflammation, starting in the subchondral bone marrow [2]. Following from this, it was an important step forward to develop classification criteria for axSpA covering all axSpA patients, both in the nonradiographic and radiographic (the latter also termed ankylosing spondylitis) stage [3]. Subsequently, it was shown that nonradiographic-axSpA (nr-axSpA) patients also respond well to TNF-blocker treatment, and currently there is approval for the treatment of the whole group of axSpA with the TNF blockers etanercept, adalimumab, golimumab and certolizumab pegol (infliximab was not yet formally tested in nr-axSpA patients) in the European Union and many other parts of the world [4].

The 'Food and Drug Administration' (FDA) in the United States had been reluctant to accept nr-axSpA as part of axSpA and was afraid that there is a high spontaneous remission rate in these patients. For this reason, they asked the TNF-blocker companies to conduct placebo-controlled clinical trials over 1 year; a study design with such a long placebo-controlled phase was regarded to be ethically not possible in the EU and other countries. Until now such a trial –as asked for by the FDA – had been successfully conducted for the TNF-blocker certolizumab pegol by UCB, which resulted in approval for this drug for nr-axSpA also in the United States [5▪▪]. In this study, the percentage of patients still being on drug after 52 weeks was 79% in the certolizumab arm versus 34% in the placebo-arm and the primary outcome parameter of Assessment of SpondyloArthritis international Society (ASAS) major improvement (MI) was reached in 47.2% (75 out of 159 included patients) for certolizumab pegol treated patients versus 7% (11 our 158) in the placebo group, with similar results for the outcome parameter ASAS 40 response: 56.6 versus 15.8%, respectively. A similar 52-week placebo-controlled study – with comparable results – was performed with the IL-17A inhibitor ixekizumab in nr-axSpA (see also below). After 52 weeks, 34 (32%) of 105 patients in the placebo group had completed the full 52-week period on their originally assigned study medication versus 52 (54%) of 96 in the ixekizumab 80 mg every 4 weeks group; ASAS 40 response at week 52 was 13% out of 105 patients and 30% out of 96 patients, respectively [6▪▪] (Ixekizumab is currently the only IL-17 inhibitor approved for the indication of nr-axSpA by the US FDA). Thus, taken together, these results showed that TNF blockers and IL-17 inhibitors (see also below) are effective for the treatment of nr-axSpA and that the spontaneous remission rate (response in the placebo group) is not higher than expected. So far, there is no data available for tsDMARDs in nr-axSpA but we would expect very similar results as compared with bDMARDs.

The next question was whether the response to TNF blockers is similar in r-axSpA and nr-axSpA or not. The ASAS/EULAR recommendations for the management of axSpA demand – in addition to a correct diagnosis, evidence of disease activity and failure of conventional treatment – that patients treated with a biologic should have either radiographic evidence of sacroiliitis or typical subchondral bone marrow edema on MRI in the sacroiliac joints or a positive C-reactive protein (CRP) [7]. Thus, for nr-axSpA objective signs of inflammation – bone marrow oedema on MRI or elevated CRP – is mandatory while this is not the case for r-axSpA (=ankylosing spondylitis). This aspect of the recommendations is further supported by the fact that in the nr-axSpA trials, patients did not respond better or only slightly to TNF blockers as compared with

Table 1. Questions to be addressed in this article

(1) Patients with ankylosing spondylitis have already reached the stage of structural damage of the bone after a previous purely inflammatory stage. Are the bDMARDs and tsDMARDs also effective – and similarly effective – in patients in this early (nonradiographic) phase?
2. How can we predict good clinical response to TNF blockers and other biological (b)DMARDs and targeted synthetic (ts)DMARDs?
3. Can we (and how do we do this) taper the dose of a TNF-blocker (and other bDMARDs and tsDMARDs) in good responder patients?
4. How does the effect of TNF blockers compare with the effect of other bDMARDs and tsDMARDs? Which DMARD to use first?
5. Can any of these treatments also stop structural bony damage (radiographic progression)?

DMARDs, disease modifying anti-rheumatic drugs; TNF, tumour necrosis factor.

placebo if they were negative for both CRP and MRI inflammation at baseline [8,9]. The presence of radiographic sacroiliitis can be seen as an (indirect) objective sign of previous or ongoing inflammation having resulted in structural damage (radiographic sacroiliitis). When clinical trials in r-axSpA and nr-axSpA are compared indirectly the response rates are very similar if patients were included according to the ASAS/EULAR criteria [10]. Interestingly, such a difference between nr-axSpA and r-axSpA has not been made in a recent update of American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of axSpA [11▪].

But there are also a few studies in which the effect of TNF-blocker treatment in r-SpA and nr-axSpA could be compared directly:

(1) In the ESTHER trial, active axSpA patients with a disease duration less than 5 years and subchondral bone marrow oedema on sacroiliac joints or spine MRI at baseline were treated with etanercept or sulfasalazine for 1 year. In the etanercept group, 20 patients had a diagnosis of nr-axSpA and 20 patients of r-axSpA. The response rate was the same in both groups if they had a similar level of activity at baseline [12].
(2) In a phase 3 trial, about 300 axSpA patients with both nr-axSpA and r-axSpA – about half each – were treated in three arms with two different dosages of certolizumab pegol or with placebo [13]. All patients had a disease duration of less than 5 years and had to be CRP or MRI-inflammation positive. After 12 and 24 weeks of treatment, the response rates in the nr-axSpA and r-axSpA subgroups were the same: for example, ASAS 40 response 47.8 versus 56.5%, respectively, in the 200 mg certolizmab pegol every 2 weeks group at week 24.
(3) In another trial, 736 active axSpA patients according to the ASAS/EULAR recommendation with a disease duration of less than 5 years were treated in the first phase of this open-labelled trial for 48 weeks with certolizumab. Those patients reaching sustained remission [defined as an ankylosing spondylitis disease activity score (ASDAS) <1.3] continued then in the dose-reduction part of this trial (see below for further details). The remission rate was similar in the r-axSpA (42.%; 174/407) und the nr-axSpA (45.3%; 149/329) subgroups [14▪▪].

Thus, taken together, the treatment responses to TNF-blocking agents is similar in axSpA patients fulfilling the ASAS/EULAR requirements for initiation of bDMARDs. It is of great importance that the diagnosis is correct and that patients' symptoms are caused by inflammation and not by other reasons. Failing here is a likely explanation for the increase in higher placebo responses and relatively high-screening failures for inclusion in clinical trials seen over the recent years. On the basis of this reasoning, future trials should be conducted for the whole group of axSpA patients, subgroup analyses of nr-axSpA and r-axSpA can be performed dependent on the question addressed in the study. It should be kept in mind that the shorter the disease duration in axSpA trials will be in the future the higher the proportion of nr-xSpA patients will be in such an axSpA study.

HOW CAN WE PREDICT GOOD RESPONSE TO TUMOUR NECROSIS FACTOR BLOCKERS AND OTHER bDMARDS AND tsDMARDS?

In analysing the early ankylosing spondylosis treatment trials with TNF blockers it could be shown that patients with shorter disease duration (in this analysis: <10 years), patients with an elevated CRP and a higher score of MRI inflammation responded better [15]. This could be confirmed subsequently in a series of additional investigation:

(1) AxSpA patients with a disease duration less than 3 years, MRI inflammation in the sarcoiliac joints and HLA-B27 positivity reached an ASAS partial remission rate of 56% (versus 12% in the placebo group) after 16 weeks of treatment with infliximab [16].
(2) In the INFAST trial, axSpA patients also with a disease duration less than 3 years with MRI inflammation in the sarcoiliac joints and not yet refractory to NSAID treatment were included and were treated either with a combination of infliximab with naproxen or with naproxen alone. The ASAS partial remission rate was 62% in the infliximab and 35% in the naproxen-alone group [17]. For indirect comparison, in the older ankylosing spondylitis trials with a mean disease duration clearly above 10 years and without selection for objective signs of inflammation, the remission rate was not much better than about 20% [18].
(3) In two phase 3 trials in nr-axSpA patients treated either with adalimumab [9] or with golimumab [8], the response rates in the TNF-blocker-treated groups was not better or not much better than placebo if patients were negative for both CRP and MRI inflammation at baseline. Interestingly, CRP was an even better predictor of good response than MRI inflammation.

(4) In the phase 3 trial for the treatment of nr-axSpA patients with etanercept, the response rate was higher the higher the CRP level or the higher the MRI-inflammation score was; again CRP was a better predictor than MRI [19].
(5) In an analysis of pooled data of two axSpA trials with adalimumab and etanercept CRP positivity was especially a better predictor of a good response in patients with longer disease duration (in this analysis >4 years), while the difference between CRP-positive and CRP-negative patients was smaller in the subgroup of patients with a disease duration less than 4 years [20].
(6) In the Ability 3 trial, 673 active nr-axSpA patients were treated for 28 weeks open-label with adalimumab (for more details and for the second phase of this study, see below) [21]. Strong baseline predictors of reaching remission (ASDAS <1.3) included younger age, male sex, HLA-B27 positivity and higher MRI-inflammation score of the sarcoiliac joints [22▪].
(7) The relevance of an objective sign of inflammation as a predictor for a good TNF-blocker treatment response could also be seen in an observational cohort (the French DESIR cohort) in which patients with a diagnosis of axSpA and a disease duration of 3 years or less were included. Patients with an inflammatory MRI sacroiliitis showed clearly a better response to TNF blockers than patient without such an MRI sacroiliitis: ASAS 40 response 46 versus 21%, respectively [23].

Thus, the most consistent findings for predicting a good response to TNF-blocker therapy are short disease duration (or young age) with objective signs of inflammation, such as subchondral bone marrow inflammation on MRI or CRP. Correlations with other parameters, such as HLA-B27-positivtiy, have been reported but are less strong.

CAN WE (AND HOW DO WE DO THIS) TAPER THE DOSE OF A TUMOUR NECROSIS FACTOR BLOCKER AND OTHER bDMARDS AND tsDMARDS IN GOOD RESPONDER PATIENTS?

It is common rheumatological practise to taper down treatment of axSpA with TNF blockers if patients respond well. However, there has been until recently only limited data how to do this. Some earlier studies investigated whether treatment can be stopped at all:

(1) In the ESTHER trial (for more detail see above), axSpA patients treated with etanercept for 1 year stopped treatment if they were in clinical remission (ASAS partial remission) and if there was no longer MRI inflammation on whole-body MRI. Only 3 out of 13 (32%) remained in drug-free remission after 1 year, the majority of relapses occurred in the second half of the follow-up year [24].
(2) In the INFAST trial (for more details see above), all patients who reached remission after 6 months of treatment with a combination of infliximab and naproxen were taken off infliximab and followed up for another 6 months. Half of these patients were randomized to be treated with naproxen, the other half without any drug at all. Relapse rate (defined as failing remission) was 52% in patients treated with naproxen and 60% in patients without any treatment; however – a limitation of this study – the follow-up in this study ended already after 6 months [25]. Interestingly, 93.8 and 87.1%, respectively, remained in a status of low disease activity, defined as a BASDAI less than 3.
(3) In a larger trial, active nr-axSpA patients were treated for 28 weeks open-label with adalimumab (ability 3). Out of 673 enrolled patients, 305 (45%) achieved sustained remission and were randomized to be treated for another 48 weeks with adalimumab or placebo. Seventy percent of patients continuing adalimumab did not experience a flare versus 47% in the placebo group [21]. In this study, flare was defined as ASDAS of at least 2.1. Whenever analysed how many patients remained in remission (ASDAS <1.3) 57 versus 33%, respectively, kept the status of ASDAS inactive disease.

However, none of these studies compared continuous versus tapering versus stopping treatment in good responders. This was done recently in another study with certolizumab pegol (already mentioned briefly above). AxSpA patients who achieved sustained remission, defined by ASDAS less than 1.3, were randomized to be treated with certolizumab pegol 200 mg every 2 weeks, certolizumab 200 mg every 4 weeks or placebo. During weeks 48–96, 83.7% (87/104), 79% (83/105) and 20.2% (21/104) of patients receiving the full maintenance dose, reduced maintenance dose or placebo, respectively, were flare-free, which was defined as an ASDAS less than 2.1 [14▪▪]. Thus, certolizumab full dose and certolizimab half dose were similarly effective in avoiding a flare and clearly superior to the placebo group. However, the results look a bit different whenever analysed whether patients remained in remission (ASDAS <1.3) or not: this was achieved by 84% (87/104) in the full dose in certolizumab group,

by 55% (58/105) in the reduced certolizumab group and by 13% (14/104) in the placebo group. Predictive parameters for relapse or for keeping remission could not be identified but would be needed urgently.

Thus, the results across the different studies are relatively consistent: when stopping or reducing a TNF blocker (no comparable data yet available for the other biologics/tsDMARDs) a 1-year follow-up is necessary, stopping the drug results in a great majority of patients in a flare, and reducing the dose in good responders is acceptable if a status of low disease activity is acceptable; however, a substantial proportion of patients will lose the status of remission if the dose is reduced and it will be an important question for the future to identify markers predicting in which patients such a reduction is possible

HOW DOES THE EFFECT OF TUMOUR NECROSIS FACTOR BLOCKERS COMPARE TO THE EFFECT OF OTHER bDMARDS AND tsDMARDS? WHICH DMARD TO USE FIRST?

For a long time, TNF blockers had been the only disease modifying anti-rheumatic drugs (DMARDs) being effective in axSpA. Even conventional synthetic DMARDs do not play a role for the treatment of axSpA [10]. Targeted therapies, such as interleukin (IL)-6-inhibitors [26] or IL-23-inhibitors [27▪] failed, although some kind of efficacy was expected, indicating that we do not yet understand the pathogenesis well enough and that we still depend heavily on the conduction of clinical trials to identify new effective drugs. More recently, it was shown that IL-17A inhibitors (shown for nr-axSpA and r-axSpA) [6▪▪,28,29▪,30] and tsDMARDs [31] [currently shown only for Janus kinase (JAK) inhibitors in r-axSpA/AS – but no JAK inhibitor is yet approved for this indication by the FDA; and upadacitinib only by the European Medicines Agency (EMA) for the European Union] reach a similar efficacy in axSpA trials, which is – by indirect comparison – comparable with TNF-blocking agents. These two types of drugs are discussed in more detail elsewhere in this issue. However, it is not possible to judge on inferiority or superiority or equality of one drug compared with another one by this kind of indirect comparison. For such a comparison, head-to-head trials are essential. The only one ongoing at the moment is the one by Novartis comparing secukinumab with adalimumab in ankylosing spondylitis patients treated over 2 years with radiographic progression as the primary outcome parameter (see also below), but efficacy regarding parameters of disease activity will also be compared as secondary outcome parameters (clinicaltrials.gov; NCT03259074).

But such head-to head trials allow only comparisons on the group level and do not answer the following important – especially for daily clinical practice – questions [32]:

(1) which patient to select for which drug;
(2) do the same or different patients respond to the two types of drugs in question;
(3) when and how to switch from one drug class to the other;
(4) finally, is a combination of drugs possible (safety) and under certain circumstances more effective than a single drug.

On the basis of the fact that we have now different types of (effective) DMARDs available and that we reach still at the best a remission rate of about 40–50% of axSpA patients with our current treatment strategies carefully conducted strategy trials with a cross-over design are urgently needed and an unmet need in axSpA for the future [32].

CAN ANY OF THESE TREATMENTS ALSO STOP STRUCTURAL BONY DAMAGE (RADIOGRAPHIC PROGRESSION)?

Syndesmophyte formation in the spine is responsible on the long-term for restriction of spinal mobility and restriction of function in axSpA patients. New bone formation is normally preceded by bony inflammation, which induces subchondral granulation tissue with subsequent (and delayed) stimuli for new bone formation [2]. It has become clearer over the last years that long-term suppression of inflammation by TNF-blocking agents (longer than 2–4 years) is necessary to show also an effect of such treatment on new bone formation (syndesmophytes) [2]. It is currently not clear whether any of the available treatments for axSpA – NSAIDs, TNF blockers, IL-17-inhibitors, or JAK-inhibitors) – have an additional retarding effect on new bone formation in axSpA beyond through suppression of inflammation.

Structural damage of the spine is most frequently assessed in clinical studies by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), which captures mostly new syndesmophyte formation and growth of syndesmophyte seen on conventional X-rays. Structural damage progression in axSpA is slow, and therefore, follow-up periods of at least 2 years are necessary to see any changes/any effects of treatment. Furthermore, to see a treatment effect, investigated patients should be enriched by patients who are positive for known predictors of

progression: male sex, CRP-positivity, presence of syndesmophytes at baseline. For the mSASSS, only the cervical spine and the lumbar spine are scored and not the thoracic spine (because of overlying lung and ribs), although it has been shown that more changes and more progression is found in the thoracic spine compared with the rest of the spine [33]. As mentioned above, there is an ongoing head-to-head trial comparing treatment with adalimumab versus secukinumab over 2 years in ankylosing spondylitis, enriched for patients positive for predictors of radiographic progression, but still using normal X-rays and the mSASSS as outcome parameter (clinicaltrials.gov; NCT03259074). We are eagerly waiting for the results of this first head-to head trial in axSpA with radiographic progression as the primary outcome parameter.

However, in the future, other imaging methods should be considered for the measurement of progression of structural damage in the spine. Until now low-dose computer tomography had been investigated and compared with conventional X-rays [33] (for more details see elsewhere in this issue), which has the advantage to score also the thoracic spine and bony changes can be seen and scored clearer. Using such a method (or other newer imaging methods), it can be expected that the currently necessary observational period of at least 2 years can be shortened and that the treatment groups can be kept smaller. However, it has also to be kept in mind that a potential effect of any treatment on retarding bone formation and on long-term worsening of function is small compared with an effective therapy's immediate (and normally long-lasting) effect on disease activity, function, spinal mobility and well being through direct suppression of inflammation [34].

CONCLUSION

AxSpA should be regarded as one disease at different stages, a similar treatment response can be expected if nr-axSpA and r-axSpA show a similar level of disease activity. Short disease duration (and in this context: early and reliable diagnosis) and the presence of objective parameters of inflammation are currently the best predictors of a good treatment response. However, a rather small subgroup of CRP-negative and MRI-negative patients can also show a treatment response, probably because CRP and MRI inflammation do not cover all aspects of inflammation. In patients having achieved remission, the majority will relapse if treatment is stopped, in a proportion of patients the dose can be reduced. It has still to be better defined in which patients this is possible. The availability of several different bDMARDs and tsDMARDs opens the possibility to find the best drug for a specific patient, which is yet not clearly defined. For this, more strategy trials should be conducted in the future.

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REFERENCES AND RECOMMENDED READING

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

- ■ of special interest
- ■■ of outstanding interest

1. Braun J, Brandt J, Listing J, *et al.* Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 2002; 359:1187–1193.
2. Poddubnyy D, Sieper J. Mechanism of new bone formation in axial spondyloarthritis. Curr Rheumatol Rep 2017; 19:55.
3. Rudwaleit M, van der Heijde D, Landewe R, *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009; 68:777–783.
4. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet 2017; 390:73–84.
5. ■■ Deodhar A, Gensler LS, Kay J, *et al.* A fifty-two-week, randomized, placebo-controlled trial of certolizumab pegol in nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2019; 71:1101–1111.

Trial showing that certolizumab pegol is effective in nr-axSpA and that the spontaneous remission rate (placebo response) is low over 52 weeks in nr-axSpA patients.

6. ■■ Deodhar A, van der Heijde D, Gensler LS, *et al.* Ixekizumab for patients with nonradiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial. Lancet 2020; 395:53–64.

Placebo-controlled study over 52 weeks of patients with nr-axSpA showing that drop-out rate was clearly higher and the response clearly and significantly lower in the placebo-group compared with ixekizumab.

7. van der Heijde D, Ramiro S, Landewe R, *et al.* 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017; 76:978–991.
8. Sieper J, van der Heijde D, Dougados M, *et al.* A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2015; 67:2702–2712.
9. Sieper J, van der Heijde D, Dougados M, *et al.* Efficacy and safety of adalimumab in patients with nonradiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis 2013; 72:815–822.
10. Sieper J, Poddubnyy D. New evidence on the management of spondyloarthritis. Nat Rev Rheumatol 2016; 12:282–295.
11. ■ Ward MM, Deodhar A, Gensler LS, *et al.* 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Rheumatol 2019; 71:1599–1613.

A treatment update including also IL-17 inhibitor and JAK-inhibitors. Recommendations for nr-axSpA are extrapolated from r-aSpA/AS.

12. Song IH, Weiss A, Hermann KG, *et al.* Similar response rates in patients with ankylosing spondylitis and nonradiographic axial spondyloarthritis after 1 year of treatment with etanercept: results from the ESTHER trial. Ann Rheum Dis 2013; 72:823–825.

13. Landewe R, Braun J, Deodhar A, *et al.* Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis 2014; 73:39–47.

14. ■■ Landewe RB, van der Heijde D, Dougados M, *et al.* Maintenance of clinical remission in early axial spondyloarthritis following certolizumab pegol dose reduction. Ann Rheum Dis 2020; 79:920–928.

Important study showing that the remission rate is very similar in nr-axSpA and r-axSpA treated with the TNF-blocker certolizumab that the level of low disease activity can be kept over time if patients are treated continuously with a full dose or half a dose of certolizumab pegel but not if treated with placebo.

15. Rudwaleit M, Schwarzlose S, Hilgert ES, *et al.* MRI in predicting a major clinical response to antitumour necrosis factor treatment in ankylosing spondylitis. Ann Rheum Dis 2008; 67:1276–1281.

16. Barkham N, Keen HI, Coates LC, *et al.* Clinical and imaging efficacy of infliximab in HLA-B27-positive patients with magnetic resonance imaging-determined early sacroiliitis. Arthritis Rheum 2009; 60:946–954.

17. Sieper J, Lenaerts J, Wollenhaupt J, *et al.,* All INFAST Investigators. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, part 1. Ann Rheum Dis 2014; 73:101–107.

18. van der Heijde D, Dijkmans B, Geusens P, *et al.,* Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005; 52:582–591.

19. Dougados M, van der Heijde D, Sieper J, *et al.* Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol 2014; 66:2091–2102.

20. Weiss A, Song IH, Haibel H, *et al.* Good correlation between changes in objective and subjective signs of inflammation in short- but not long-diseased patients with axial spondyloarthritis treated with tumor necrosis factor-blockers. Arthritis Res Ther 2014; 16:R35.

21. Landewe R, Sieper J, Mease P, *et al.* Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with nonradiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. Lancet 2018; 392:134–144.

22. ■ Sieper J, Landewe R, Magrey M, *et al.* Predictors of remission in patients with nonradiographic axial spondyloarthritis receiving open-label adalimumab in the ABILITY-3 study. RMD Open 2019; 5:e000917.

In nr-axSpA patients treated with adalimumab over 48 weeks young age and MRI-inflammation score of the sacroiliac joints were important predictors for reaching clinical remission.

23. Molto A, Paternotte S, Claudepierre P, *et al.* Effectiveness of tumor necrosis factor alpha blockers in early axial spondyloarthritis: data from the DESIR cohort. Arthritis Rheumatol 2014; 66:1734–1744.

24. Song IH, Althoff CE, Haibel H, *et al.* Frequency and duration of drug-free remission after 1 year of treatment with etanercept versus sulfasalazine in early axial spondyloarthritis: 2 year data of the ESTHER trial. Ann Rheum Dis 2012; 71:1212–1215.

25. Sieper J, Lenaerts J, Wollenhaupt J, *et al.,* All INFAST Investigators. Maintenance of biologic-free remission with naproxen or no treatment in patients with early, active axial spondyloarthritis: results from a 6-month, randomised, open-label follow-up study, INFAST Part 2. Ann Rheum Dis 2014; 73:108–113.

26. Sieper J, Porter-Brown B, Thompson L, *et al.* Assessment of short-term symptomatic efficacy of tocilizumab in ankylosing spondylitis: results of randomised, placebo-controlled trials. Ann Rheum Dis 2014; 73:95–100.

27. ■ Deodhar A, Gensler LS, Sieper J, *et al.* Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. Arthritis Rheumatol 2019; 71:258–270.

Study showing that ustekinumab is not effective for the treatment of patients with active r-axSpA patients and probably also not in nr-axSpA (only interim analysis available; study was stopped).

28. Baeten D, Sieper J, Braun J, *et al.,* MEASURE 1 Study Group, MEASURE 2 Study Group. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med 2015; 373:2534–2548.

29. ■ Deodhar A, Blanco R, Dokoupilova E, *et al.* Improvement of signs and symptoms of nonradiographic axial spondyloarthritis in patients treated with secukinumab: primary results of a randomized, placebo-controlled phase III study. Arthritis Rheumatol 2020; 73:110–120.

Secukinumab was effective for the treatment of nr-axSpA compared with placebo at week 16.

30. van der Heijde D, Cheng-Chung Wei J, Dougados M, *et al.* Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying antirheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. Lancet 2018; 392:2441–2451.

31. van der Heijde D, Song IH, Pangan AL, *et al.* Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. Lancet 2019; 394:2108–2117.

32. Poddubnyy D, Sieper J. What is the best treatment target in axial spondyloarthritis: tumour necrosis factor alpha, interleukin 17, or both? Rheumatology (Oxford) 2018; 57:1145–1150.

33. de Koning A, de Bruin F, van den Berg R, *et al.* Low-dose CT detects more progression of bone formation in comparison to conventional radiography in patients with ankylosing spondylitis: results from the SIAS cohort. Ann Rheum Dis 2018; 77:293–299.

34. Poddubnyy D, Fedorova A, Listing J, *et al.* Physical function and spinal mobility remain stable despite radiographic spinal progression in patients with ankylosing spondylitis treated with TNF-alpha inhibitors for up to 10 years. J Rheumatol 2016; 43:2142–2148.