

# Axial spondyloarthritis: new advances in diagnosis and management

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## ABSTRACT

Axial spondyloarthritis (axSpA) is an inflammatory disease of the axial skeleton associated with significant pain and disability. Previously, the diagnosis of ankylosing spondylitis required advanced changes on plain radiographs of the sacroiliac joints. Classification criteria released in 2009, however, identified a subset of patients, under the age of 45, with back pain for more than three months in the absence of radiographic sacroiliitis who were classified as axSpA based on a positive magnetic resonance imaging or HLAB27 positivity and specific clinical features. This subgroup was labeled non-radiographic (nr)-axSpA. These patients, compared with those identified by the older New York criteria, contained a larger percentage of women and demonstrated less structural damage. However, their clinical manifestations and response to biologics were similar to radiographic axSpA. The discovery of the interleukin (IL) IL-23/IL-17 pathway revealed key molecules involved in the pathophysiology of axSpA. This discovery propelled the generation of antibodies directed toward IL-17A, which are highly effective and demonstrate treatment responses in axSpA that are similar to those observed with anti-TNF agents. The finding that agents that block IL-23 were not effective in axSpA came as a surprise and the potential underlying mechanisms underlying this lack of response are discussed. New agents with dual inhibition of the IL-17A and F isoforms and some oral small molecule agents that target the Jak-STAT pathway, have also shown efficacy in axSpA.

## Introduction

Low back pain, the fifth most common symptom leading to physician visits in the United States, affects approximately 80% of individuals over their lifespan.<sup>1</sup> Fortunately, most of these episodes are short lived, due to mechanical causes and respond to medications, physiotherapy, and time. However, chronic back pain (duration lasting >three months) occurs in approximately 20% of the US population based on the National Health and Nutrition Examination (NHANES) survey conducted in 2009-10: applying additional criteria such as individuals under the age of 40, back pain characterized by insidious onset, morning stiffness, and improvement with exercise but not rest and pain that is worse at night is present in 5% to 6% of normal subjects.<sup>2</sup> Some of these patients will have spondyloarthritis, a condition for which an array of therapies is now available. Regrettably, delay in the diagnosis of spondyloarthritis remains a major barrier that varies widely in different countries but overall time to referral has decreased. Previous studies reported the delay from symptom onset to the diagnosis of

ankylosing spondylitis was 11 years in Europe<sup>3</sup> and 13.5 years in the US.<sup>4</sup> Other estimates, however, report earlier referral following initial symptoms but delay intervals vary from country to country. Analysis of a large US commercial administrative database showed a delay of 11 months from the development of back pain to rheumatology referral<sup>5</sup> and a study based on questionnaires to rheumatologists from 56 countries found that a referral delay of >three years was more common in Western Europe and other countries of the world when compared with Canada and the US.<sup>6</sup>

While the challenges of timely diagnosis and treatment remain formidable obstacles, it became apparent that the diagnosis of ankylosing spondylitis, which required advanced changes on radiographs of the sacroiliac joints (SIJ), was not capturing a population of patients with inflammatory back pain and clinical features of spondyloarthritis. This realization catalyzed a revision of the classification criteria under the heading axial spondyloarthritis (axSpA), to be discussed in detail below, and unveiled an expanded subgroup of patients

### Sources and selection criteria

We searched PubMed English language manuscripts from January 1 2000 to December 2019. We searched on key words or combinations of key words, including “axial spondyloarthritis”, “spondyloarthropathy”, “ankylosing spondylitis”, “IL-17”, “IL-23”, “monoclonal antibodies”, “inhibitors”, “non-radiographic”, “radiographic”, “treatment recommendations and pathway”. We also reviewed references within the retrieved manuscripts to identify additional relevant literature, some of which was published before 2000. We prioritized phase II and phase III trials but we also included well designed studies derived from observational cohorts. We also focused on quality basic science manuscripts that contributed to the understanding of key mechanisms underlying cytokine interactions in the IL-23/IL-17 pathway.

without radiographic findings who have chronic back pain and improve with treatment. Moreover, the increased number of patients at risk under the diagnostic heading of axSpA was accompanied by an expansion of effective treatment options for these patients. Genome-wide pooling studies have shown a significant association of the rare allele of the IL-23 receptor R381Q single nucleotide polymorphism, which conferred protection against psoriatic arthritis, ankylosing spondylitis, and Crohn’s disease, emphasizing the importance of IL-23 in many autoimmune diseases.<sup>7-10</sup> This review will discuss key elements of axSpA related to diagnosis, the unveiling of a pivotal pathogenetic pathway centered on the cytokines IL-23 and IL-17, and current and future treatment options.

### Epidemiology

Incidence estimates per 100 000 patient years derived from a systematic review of population studies in ankylosing spondylitis varied from 0.4 (Iceland) to 15.0 (Canada).<sup>11</sup> Non-radiographic axSpA incidence rates are not published. The global prevalence of ankylosing spondylitis ranges from 9 to 30 per 10 000 in the general population but again wide variance is observed in studies from different countries.<sup>12</sup> In the only US population based study, based on NHANES data, the overall age adjusted prevalence of definite and probable SpA was 0.9% to 1.4% (95% confidence interval 0.7 to 1.1) depending on the criteria used.<sup>13</sup> Ankylosing spondylitis prevalence rates per 100 000 persons also showed considerable variation (16 studies: 6.5 in Japan to 540.0 in Turkey).<sup>11</sup> Estimates for the prevalence of axSpA, which encompasses radiographic and non-radiographic subsets, ranged from 20 per 10 000 in South East Asia to 161 per 10 000 in northern Arctic communities.<sup>14</sup> The variance in these estimates is attributed to study population, geographic location, ascertainment methods, data sources, and case definition.

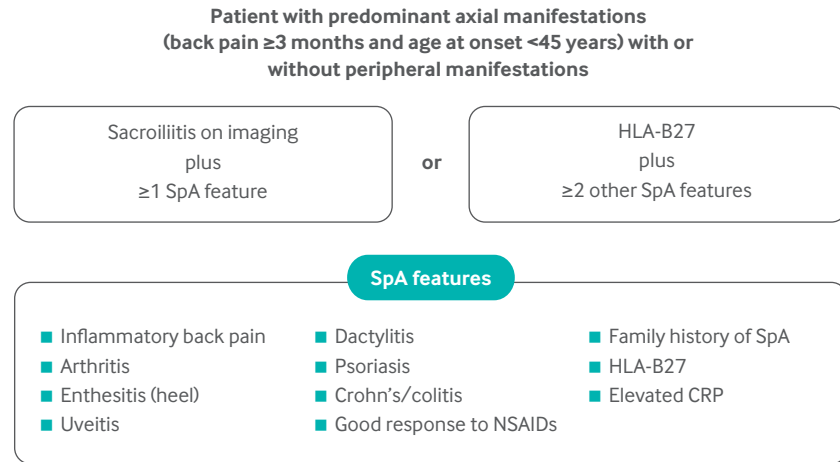
### New perspectives on spondyloarthritis based on revised definitions of disease

The symptom complex of inflammatory back pain, based on the features outlined above, would appear to be an important trigger for referral to rheumatology. Based on the high specificity (72-91.7%) of three different sets of inflammatory back

pain criteria for the diagnosis of SpA, many clinicians assume that most patients who meet these criteria will have features of SpA at some time point, if not evident on initial presentation.<sup>2 15 16</sup> This assumption is not supported by the evidence. The low prevalence of SpA in a population based back pain cohort was documented in a retrospective longitudinal study of patients with new onset inflammatory back pain followed over a 12 year period and only 30% of these patients were ultimately diagnosed with axSpA.<sup>17</sup> This study, however, had some limitations that included a small sample size and the concern that many primary care doctors did not inquire about inflammatory back pain over time, and, ultimately, only a fraction of these patients were evaluated by a rheumatologist.<sup>18</sup> Nevertheless, characteristic features of inflammatory back pain or chronic low back pain in an individual  $\leq 45$  years is an important clue that should raise suspicion and generate the retrieval of additional information regarding other SpA features with subsequent testing for HLAB27 and C reactive protein, coupled in the appropriate setting with imaging (particularly magnetic resonance imaging (MRI) of the SIJ).

Classification criteria for ankylosing spondylitis published in 1984 were based on the presence of radiographic changes in the SIJ consistent with the prevailing opinion that the disease originated in this location.<sup>19</sup> It became apparent over time, however, that most younger patients with chronic back pain and inflammatory features did not meet these radiographic criteria and they were labeled “undifferentiated SpA.”<sup>20</sup> This diagnosis lacked clarity and generated confusion among clinicians regarding the relevance, natural history, and therapeutic approach for this relatively large patient subgroup. In recognition of this problem and to address other deficiencies regarding the diagnosis and classification of ankylosing spondylitis, and based on clinical observations that the disease is present for years before the observation of radiographic damage to skeletal structures, the Assessment of SpondyloArthritis International Society (ASAS) published a set of new classification criteria that included both a genetic and an imaging arm (fig 1).<sup>21</sup> In addition to radiographic findings, MRI features were inserted in the imaging arm.

Many patients without radiographic findings manifest MRI findings of bone marrow edema (BME) adjacent to the SIJ, suggestive of osteitis.<sup>22</sup> Some patients have structural changes, including erosions, ankylosis, and fat deposition.<sup>23</sup> Consensus criteria were developed by ASAS to define active sacroiliitis in SpA by the presence of either one BME lesion on two consecutive MRI slices or  $\geq 2$  lesions on a single slice.<sup>24 25</sup> These new classification criteria generated enthusiasm regarding the possibility of early diagnosis and intervention in patients who would not meet the 1984 Ankylosing Spondylitis Criteria but demonstrated MRI abnormalities in the setting of inflammatory back pain, a long sought-after goal by clinicians.



**Fig 1 | Assessment of SpondyloArthritis International Society (ASAS) revised axSpA classification criteria.** Classification criteria for axSpA from the ASAS.<sup>21</sup> Patients with and without definite radiographic sacroiliitis are included in the criteria. A patient with chronic back pain ( $> 3$  months) and age at onset less than 45 years can be classified in the presence of sacroiliitis (either definite radiographic sacroiliitis or active inflammation of sacroiliac joints on MRI, suggestive of sacroiliitis associated with SpA) plus at least one typical SpA feature, or in the presence of HLA-B27 plus at least two other SpA features. Sensitivity 82.9%, specificity 84.4%; n=649 patients with chronic back pain and age at onset less than 45 years. The imaging arm (sacroiliitis) alone has a sensitivity of 66.2% and a specificity of 97.3%. Elevated C reactive protein is considered a feature of SpA in the presence of chronic back pain

We have a better understanding of the patient characteristics of those who fall under the classification criteria in the imaging arm with a positive MRI and negative radiograph, termed nr axSpA, versus those patients who have radiographic findings consistent with ankylosing spondylitis. Imaging findings observed in axSpA are depicted in fig 2. The level of disease activity, pain measures, and functional impairment are similar, whereas patients with nr axSpA are more likely to be female (2:1 male: female r axSpA vs 1:1 ratio in nr axSpA), demonstrate lower C reactive protein levels, and, by definition, show less structural damage. Both groups respond equally to biologic agents. The progression from non-radiographic to radiographic SpA is 10-20% over the first year, depending on baseline features such as elevated C reactive protein or positive MRI and 20.3% over two to six years.<sup>26</sup> The new classification has facilitated earlier diagnosis, generated clinical trials that target a wider group of patients, particularly women, and provided new impetus to better understand the natural history of axSpA. However, classification criteria are not designed for diagnosis. Certainly, some features in classification criteria can be helpful in the clinic and define patients for further study, but they do not capture the full context of the individual patient, including differential diagnostic elements in a particular setting and clinical judgment.

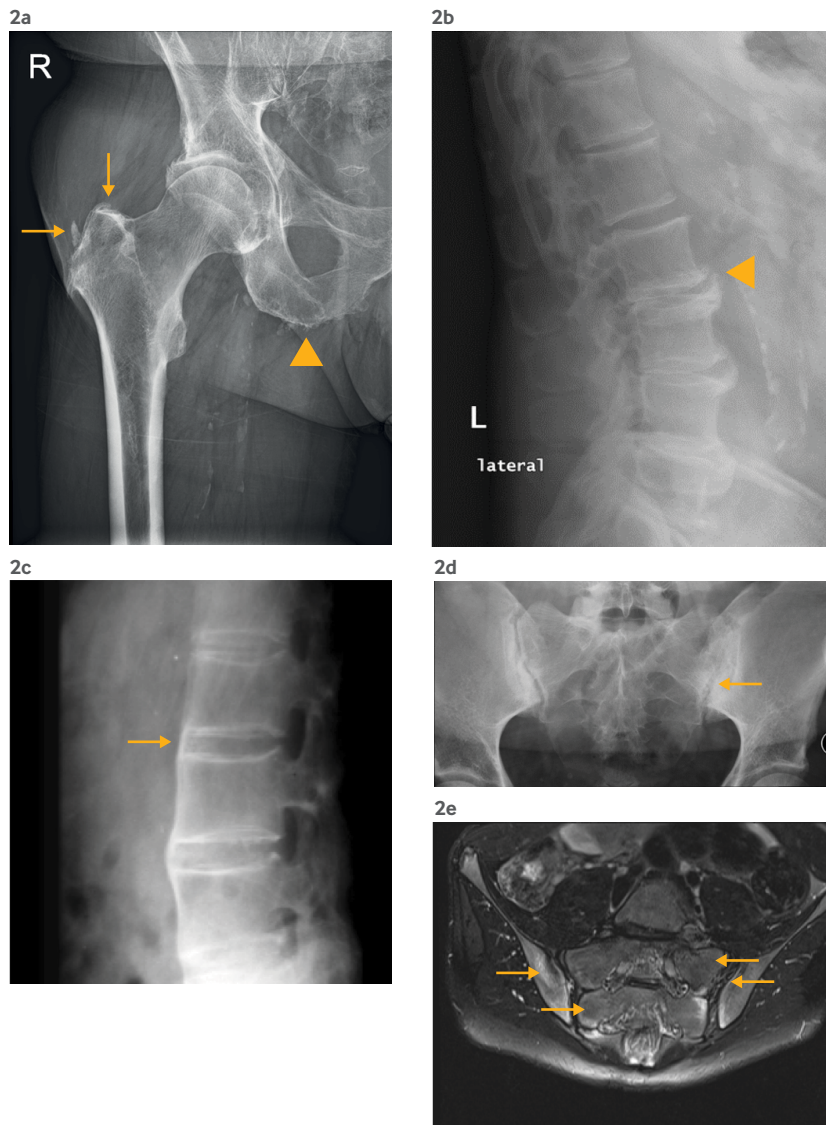
The inclusion of MRI into the diagnostic classification and treatment algorithm illuminated a population of patients who are candidates for early intervention and, in some cases, biologic agents. However, some studies indicate that many patients with chronic persistent low back pain have low level back muscle endurance not correlated with other

SpA clinical features, raising concerns about the sensitivity and specificity of clinical MRI testing. Postpartum females, increasing age, and obesity were variables associated with low level back muscle endurance that was not indicative of SpA.<sup>27</sup> Moreover, athletes engaged in active sports such as hockey or running demonstrated signals of back muscle endurance on MRI that, in a quarter of cases, would meet imaging criteria for axSpA, and these athletes did not have low back pain symptoms and were all HLAB27 negative.<sup>28</sup> Thus, caution must be applied when interpreting these MRI findings and clinical judgment is vital. Moreover, substantial variation in the interpretation of back muscle endurance in the SIJ by radiologists remains a challenge.<sup>29</sup> Findings more likely to be supportive of axSpA on MRI, in addition to back muscle endurance, are erosions, fatty change, and ankylosis.<sup>30</sup> One study found that including structural findings (fatty lesions and erosions) in the ASAS axSpA imaging criteria can reliably classify patients in the presence or absence of conventional radiographs.<sup>31</sup>

### Therapeutics in axSpA

#### Physical therapy, exercise, and inhibition of the TNF pathway

Revised treatment recommendations for axSpA have been published.<sup>32</sup> The treatment algorithm is centered on early treatment with non-steroidal anti-inflammatory drugs (NSAIDs) combined with physical therapy and exercise. Evidence to support the efficacy of physical therapy was examined in a systemic review in which regular exercise improved disease activity, pain, function, and spinal mobility, but the effect size was small.<sup>33</sup> Another systematic review found moderate to low quality evidence



**Fig 2 |** Imaging findings in axSpA. (2a) Enthesophytes present on the hip (arrows) and the pelvic rim (arrowheads) represent ossification of entheses. (2b) Large paramarginal bulky syndesmophytes characteristic of spinal involvement in psoriatic arthritis. (2c) Syndesmophytes are marginal vertical shafts of bone that begin at the sites of enthesial attachment (arrow). (2d) Radiographic axSpA. The sclerotic changes are bilateral and at the tip of the arrow are more advanced changes of erosion, sclerosis, and pseudo widening of the SI joint. (2e) MRI changes of bone marrow edema (arrows) in a patient with inflammatory back pain and HLAB27+ but a normal plain radiograph of the SIJ (nr axSpA)

that exercise programs probably slightly improve function, may reduce pain, and probably slightly reduce global patient assessment of disease activity, when compared with no intervention in axSpA.<sup>34</sup> In a randomized, assessor blinded, controlled trial of 100 patients, high intensity exercise for three months significantly reduced pain, stiffness, fatigue, and inflammation in axSpA patients.<sup>35</sup> Despite the impressive results reported in this trial, aggressive exercise programs in patients with axSpA may be counterproductive based on the evidence of MRI imaging findings of osteitis in healthy athletes mentioned above,<sup>28</sup> reports that patients with

ankylosing spondylitis engaged in jobs requiring dynamic flexibility (repeated bending, stretching, twisting, and reaching) and whole body vibration demonstrated more functional limitation and radiographic damage,<sup>36 37</sup> and the finding of enthesophytes (abnormal bony projections at the attachment of a tendon or ligament at sites) at focal sites of high biomechanical stress in the feet of animal models, mimicking the mechanical stress in the lower extremities of axSpA patients.<sup>38</sup> Studies utilizing computed tomography scanning with computer modeling in patients with longstanding ankylosing spondylitis have shown a pattern of syndesmophyte formation in the spine that corresponds to previously demonstrated and known areas of heightened mechanical stress in the human spinal column.<sup>39</sup> To date, however, no definitive link has been established between exercise and the development of syndesmophytes in the spine.

NSAIDs are recommended for early treatment of axSpA.<sup>40-42</sup> High to moderate quality evidence indicates that NSAIDs are efficacious in the treatment of axSpA, and moderate to low quality evidence indicates harms may not differ from placebo in the short term. Continuous use of NSAIDs may reduce radiographic spinal progression shown in some but not all studies, but this requires confirmation.<sup>43</sup> NSAIDs are more effective if prescribed early in disease course and, in one trial, 35% of patients exhibited a significant response within four weeks.<sup>44</sup> The preference of one agent over another has not been demonstrated in clinical trials but low level evidence indicates that NSAIDs can augment clinical treatment response when added to biologic agents.<sup>40</sup> Chronic use of glucocorticoids is best avoided because the high doses required for response are associated with significant long term morbidity.<sup>45</sup> Disease modifying anti-rheumatic drugs (DMARDs) (sulfasalazine, hydroxychloroquine) are not effective for the treatment of axial disease (very low to moderate quality evidence).<sup>46</sup> Methotrexate combination with anti-TNF agents did not improve therapeutic response although it may be considered in patients on infliximab to lessen the development of anti-drug antibodies.<sup>40</sup>

Anti-TNF agents (adalimumab, certolizumab etanercept, golimumab, infliximab) are approved for treatment of radiographic axSpA in Europe and the US. Moderate to high level quality evidence supports a clinically important benefit of these agents compared with placebo for improvement in disease activity and function, and achieving partial remission in ankylosing spondylitis in the short term.<sup>47</sup> The primary outcome measure in many axSpA trials is the ASAS40, a composite measure defined as a 40% improvement in three of four domains that include global and pain assessments, and function and stiffness evaluations.<sup>48</sup> Randomized controlled trials (RCTs) in patients with nr axSpA reported significant improvement in the ASAS 40 (in weeks) recorded as patients (% ASAS40: % active drug, % placebo, P-value). The trials demonstrated the

superiority of adalimumab % ASAS40, W12 (185, 36, 15,  $P < 0.001$ ), etanercept % ASAS40, W12 (225, 33.3, 14.7,  $P < 0.001$ ), and certolizumab % ASAS40 major improvement, W52 (317, 47.2, 7.0,  $P < 0.0001$ ).<sup>49-51</sup> The suppression of abnormal MRI signals was also observed following treatment with these agents in some patients. Elevated C reactive protein, short symptom duration (or young age), and active MRI inflammation are the best predictors for a good response to TNF blockers in patients with nr axSpA.<sup>52</sup> Caveats regarding the use of biologics in patients with nr axSpA have been raised based on possible overdiagnosis, incomplete pain assessment, and favorable long term outcomes. MRI assessments in this population have low sensitivity and specificity, structural progression is rare, and centralized pain is more prevalent in this group of patients than in those with radiographic axSpA.<sup>53 54</sup>

The ability of NSAIDs or anti-TNF agents to inhibit radiographic progression in axSpA is not established. Radiographic progression is monitored with the modified Stoke AS Spine Score (mSASSS) that was designed to track syndesmophyte growth and radiographic progression.<sup>55</sup> The reliability, sensitivity to change, and high inter-reader variability of this outcome measure have raised concerns regarding its clinical validity coupled with a poor correlation between decline in function and progressive elevation of the mSASSS score.<sup>56</sup> Clinical trials focused on the ability of NSAIDs to limit structural progression in axSpA yield conflicting data and, at this time, additional trials to address this question are in progress.<sup>57</sup> Initial studies comparing radiographic progression in patients on anti-TNF agents with historic cohorts not exposed to biologics did not show significant differences in mSASSS scores at two years.<sup>58 59</sup> Two observational cohorts, however, did find that anti-TNF agents can block progression, particularly if these drugs were taken for more than two years. In the first observational study that applied propensity scoring, a 50% reduction in the mSASSS score was observed in patients on anti-TNF agents, particularly patients who received early and continuous therapy.<sup>32</sup> In the second study, decreased progression was observed in those patients who received anti-TNF agents before the monitored radiographic interval: duration of time on an anti-TNF agent was also noted to be a variable associated with less progression on radiography.<sup>60</sup> A systematic review and meta-analysis found that anti-TNF agents may exert a protective effective on spinal progression if employed for  $\geq$ four years of treatment, but these authors strongly urged the need for additional studies to formally address this important question.<sup>61</sup>

The treatment landscape of axSpA was dominated by anti-TNF agents from 2003 to 2016. The discovery of the IL-23/IL-17 pathway in 2005, however, revealed new treatment targets along with molecules and signaling pathways that proved pivotal in the pathophysiology of not only axSpA,

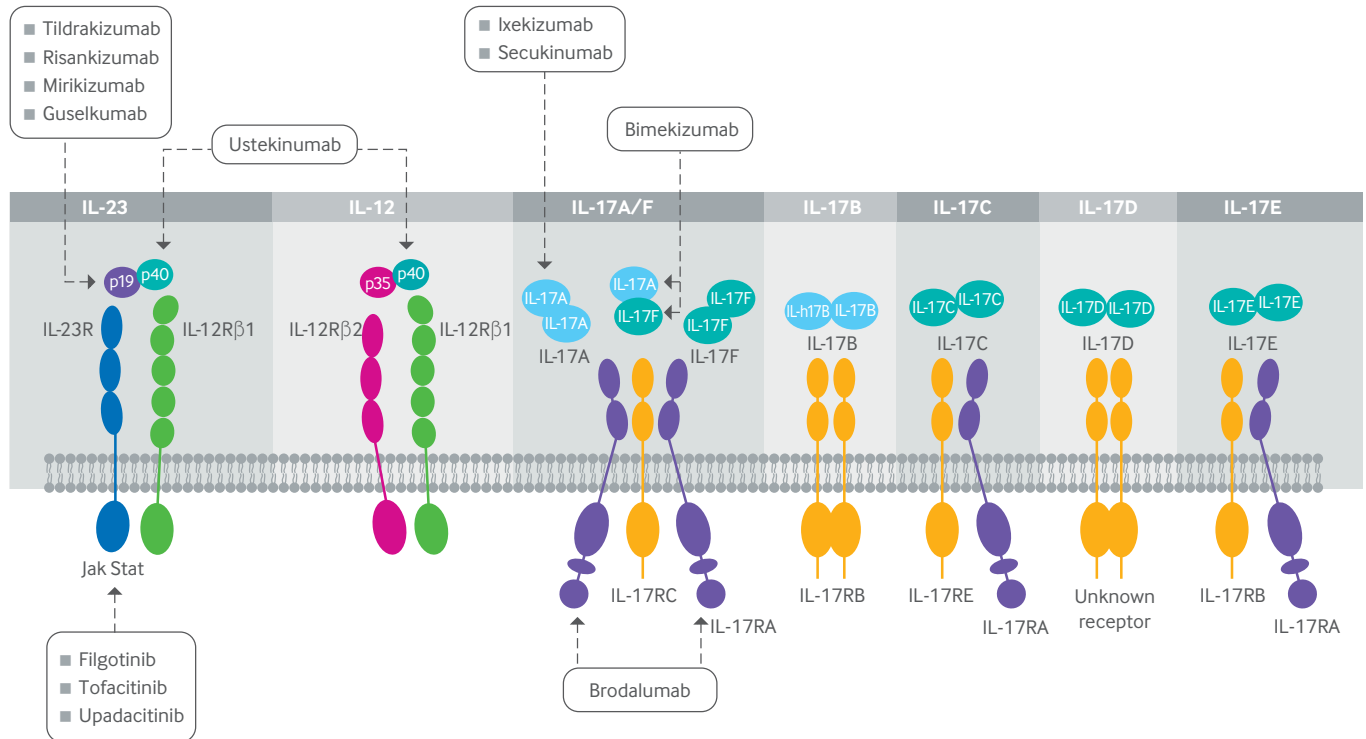
but psoriasis and psoriatic arthritis as well.<sup>62</sup> Over a relatively short period of time, new agents that target molecules in this pathway were developed and have proven effective for a range of immune mediated inflammatory disorders.

### Targeting the IL23/IL-17 pathway in axSpA

Interleukin 23 is a pleiotropic cytokine critical for the differentiation, survival, and expansion of conventional ( $\alpha\beta$ ) T cells and unconventional ( $\gamma\delta$ ) T cells, which regulate a plethora of immune responses.<sup>63 64</sup> The modulation of IL-17 producing cells by IL-23 is commonly known as the IL-23/IL-17 axis in inflammation. However, despite this close relationship and interdependence of expression between these two cytokines, some research revealed that IL-17 can be produced by many cell types independently of IL-23. Similarly, IL-23 has important immune functions independent of T cells and/or IL-17 producing cells. Hence our understanding of the IL-23/IL-17 axis in inflammation is evolving.

IL-23 is a heterodimeric cytokine, composed of a p19 and a p40 subunit. It binds IL-23R and IL-12R $\beta$ 1 (referred to as IL-23R complex), the latter being shared with IL-12,<sup>65</sup> and IL-12 is also a heterodimeric cytokine, which consists of a p35 and p40 subunit. Ustekinumab is a fully human IgGk1 monoclonal antibody designed to inhibit the p40 subunit which is shared among IL-23 and IL-12 cytokines. Therefore, this antibody does not exert selective inhibition of the IL-12 or IL-23 pathways. Thus, new molecules were developed to directly inhibit the IL-23p19 subunit and these agents include tildrakizumab, risankizumab, mirikizumab, and guselkumab. Several of these inhibitors are in clinical trials and results in SpA patients are discussed below. IL-23 engagement of the human IL-23R complex<sup>66</sup> recruits Janus kinases, Jak2, and Tyk2, directly to IL-23R and IL-12R $\beta$ 1, respectively, and induces T helper 17 (Th17) specific cell differentiation, as evidenced by increased gene expression of IL-17A.<sup>66-68</sup> Jak1 and Jak3 are the remaining two family members of the Jak family and can be activated by other pathways including IL-15, IL-21, IL-2,4, and gp130 receptor family (IL-6) and IL-22. The benefits of the Jak-STAT signaling pathway inhibition by filgotinib, upadacitinib, tofacitinib, and BMS 986-165 are currently being investigated in SpA.

IL-17A is a member of the IL-17 family of cytokines (IL-17, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F<sup>69</sup>) (fig 3). IL-17A is produced as a 35-kDa homodimer or heterodimer with IL-17F by  $\alpha\beta$  T cells, innate lymphoid cells including  $\gamma\delta$  T cells, innate-like lymphoid cells, mast cells, and neutrophils.<sup>70 71</sup> Direct inhibition of IL-17 is a major undertaking with multiple targets to consider including IL-17A (secukinumab, ixekizumab), and dual inhibitors of IL-17A and IL-17F such as bimekizumab. IL-17 binds IL-17R (IL-17RA/IL-17RC), which is expressed by various cells such as monocytes, lymphocytes, lymphoid tissue inducer cells, epithelial cells, synoviocytes, fibroblasts, and keratinocytes.<sup>72 73</sup>



**Fig 3 | Schematic presentation of the structure of the IL-23, IL-12, and IL-17 family of cytokines, their receptors, and the mechanism of their inhibition. The IL-17/STAT pathways are not illustrated for simplicity**

Brodalumab binds to the IL-17 receptor and is approved for the treatment of psoriasis.<sup>74</sup> A phase III trial in psoriatic arthritis was suspended because of concerns about major side effects including depression and suicidal behavior.<sup>75</sup>

Despite the critical importance of this pathway, the structure of IL-23 in complex with its IL-23 receptor was only recently determined.<sup>76</sup> Surprisingly, this study showed that upon binding to IL-23R this interaction partially restructures the IL-23p19 subunit of IL-23. This observation may account for the diversified and unpredictable signaling properties of this cytokine.<sup>77</sup> The presence of multi-protein assemblies and/or co-receptors at the cell surface remains to be investigated.<sup>78-79</sup> Some evidence also highlighted interactions of IL-23 with immunoreceptors in human peripheral blood mononuclear cells, suggesting the multiple binding possibilities of IL-23:IL-23R signaling via protein assemblies.<sup>80</sup> These novel interactions suggest that IL-23 signaling is more diversified than previously appreciated and thus can involve multiple transducers and effectors to activate multiple signaling pathways, as reviewed.<sup>81</sup>

Additionally, careful consideration should be given to the role of IL-23 in Th17 cell modulation, because Th17 cells can also secrete other factors besides IL-17A such as TNF, IFN- $\gamma$ , RANKL, and IL-22, which further diversify the molecular landscape of IL-23/IL-17 signaling. Thus, the different “varieties” of Th17 cells described in the literature may account

for the propagation of pathology observed in axSpA patients.<sup>82</sup>

Finally, despite many attempts to elucidate the molecular mechanisms that govern pathogenicity in axSpA as well as psoriatic arthritis, a host of critical questions remain unanswered. Despite the inherent limitations in recapitulating the human disease, experimental animal models provide unique insights regarding IL-23 pathobiology. For example, IL-23 overexpression induces immediate activation of myeloid cells within the bone marrow, resulting in synovitis and erosive polyarthritis.<sup>83</sup> It was subsequently reported that at later time points, IL-23 induces enthesitis (inflammation at the sites of attachments of tendons, ligaments, and joint capsules to bone), reported to arise by the IL-23 activation of enthesial CD4-CD8-T resident cells.<sup>84</sup> However, other studies showed that enthesitis can occur in the absence of T and B cells via the activation of stromal cells.<sup>85</sup> These studies were aligned with previous observations that T lymphocytes are not required for the spontaneous development of enthesial ossification, leading to marginal ankylosis in experimental mice.<sup>70-73</sup> Collectively, these data suggest that multiple pathways may contribute to murine experimental axSpA pathology including CD4<sup>+</sup>, CD4<sup>+</sup> T cells, and myeloid and stromal cells.

Some evidence that osteoclasts regulate the egress of neutrophils by excavating transcortical vessels (through the process of bone resorption) in both mouse and human bone transiting from the inner to

the outer bone<sup>72</sup> deepens our understanding of how IL-23 induced myeloid activation promotes systemic and local musculoskeletal inflammation. These vessels provide a direct conduit for neutrophils and monocytes to move from the bone marrow to adjacent joints or to the peripheral circulation. This concept is relevant because neutrophil accumulation is involved not only in enthesitis<sup>86</sup> but also in new bone formation<sup>87</sup> and skin inflammation<sup>88</sup> associated with the IL-23/IL-17 axis. Taken together, animal models have been extremely informative in providing insights into the effects of the IL-23-IL-17 pathway on synovitis, enthesitis, and bone remodeling observed in axSpA.

#### The discovery of the IL-23/17 pathway and new targets for therapy

The efficacy of the IL-17 blockade in radiographic axSpA was demonstrated in two phase III RCT clinical trials. Both secukimumab, % ASAS40, W16 (371, 42, 13,  $P < 0.001$ )<sup>89</sup> and ixekizumab, % ASAS40, W16 (341, 48, 18,  $P < 0.0001$ )<sup>90</sup> showed efficacy for treatment of ankylosing spondylitis with a similar response magnitude observed with anti-TNF agents. The effect of secukinumab on radiographic progression (syndesmophyte formation) was examined in a phase III RCT:  $\Delta$ mSASSS, W104 (253,  $0.31 \pm 1.94$ ,  $0.54 \pm 2.45$ ,  $P = \text{NS}$ ). The time point of two years is quite early to assess structural outcomes and further longitudinal analyses are planned.<sup>91</sup> Data on the ability of ixekizumab to inhibit structural progression is not available. Patients who had previous exposure to anti-TNF agents also demonstrated a higher response than patients on placebo.<sup>92,93</sup> Some studies in patients with nr axSpA showed that the agents ixekizumab, % ASAS40, W52 (303, 30, 13,  $P = 0.009$ ),<sup>94</sup> and secukinumab, % ASAS40, W16 (555, 41.5, 29.2,  $P < 0.05$ ),<sup>95</sup> show similar levels of efficacy to patients with radiographic axSpA. The most recent treatment recommendations suggest a switch to an anti-IL-17 agent only after a primary anti-TNF inhibitor non-response.<sup>40</sup>

It was expected, based on the mechanism of action and the central contribution of IL-23 to axial disease in animal models of spondylitis discussed above, that inhibition of this cytokine would also be an effective strategy. In support of this view was the finding that patients with ankylosing spondylitis responded to ustekinumab in a small open label study<sup>96</sup> but a phase III RCT trial failed to show a

significant effect on relief of inflammation or pain in radiographic axSpA and was terminated.<sup>97</sup> Moreover, a dose ranging (18 mg, 90 mg, 180 mg) phase III RCT trial targeting IL-23 in axSpA with risankizumab also proved to be ineffective % ASAS40, W12 (159, 20.5, 20.5, 15, 17.5,  $P = \text{NS}$ ).<sup>98</sup> The marked lack of response in both of these trials was unexpected and directly challenged the IL-23/17 paradigm of SpA pathogenesis.

#### Mechanistic insights into the lack of efficacy of IL-23 blockade in axSpA

The unresponsiveness of axSpA patients to IL-23 antibody therapy was unexpected and triggered a reappraisal of the postulated mechanisms of action that were based on in vitro data and preclinical models outlined above. A key point to emphasize is that Th17 cells may arise by IL-23 dependent and independent pathways, and they demonstrate a great deal of functional plasticity (maintenance of homeostasis, pathologic, and regulatory functions) which is highly dependent on local environmental cues. Moreover, many types of different cells ( $\gamma\delta$  T cells, innate lymphocyte type 3 cells, and mucosal associated invariant T cells) produce IL-17.<sup>82</sup> With these points in mind, several explanations for the inefficacy of IL-23 blockade in axSpA can be envisioned (box 1).

Key effector cells in the SIJ or spine may release IL-17 independent of IL-23. Human soft tissues and perienthesial bone harvested at the time of spine surgery from non-axSpA patients showed that  $\gamma\delta$  T cells from these tissues released IL-17 in the absence of IL-23R expression.<sup>99</sup> However, these observations contradict data that claim the initiator mechanism to be dependent on IL-23R<sup>+</sup> enthesial T cells.<sup>84</sup> Whether studies in non-axSpA tissues are informative regarding mechanisms in diseased tissues remains to be determined.

Interactions of mesenchymal and immune cells promote synovial inflammation in axSpA.<sup>100</sup> Uncoupling of IL-23 and IL-17 may be tissue specific. Indeed, in vitro studies show that mesenchymal cells from skin triggered IL-17 release via an IL-23 dependent pathway, while mesenchymal cells from synovial tissues triggered IL-17 release by T activated cells independent of IL-23.<sup>101,102</sup> A similar IL-17 response independent of IL-23R<sup>+</sup> T cells was reported for adipose tissue derived mesenchymal stromal cells.<sup>103</sup> These findings do not explain why IL-23 inhibition is effective in peripheral joints and not in the spine. Whether divergent pathways of IL-17 production differentiate mesenchymal cells from peripheral joints and the spine awaits further study.

In classic histopathologic studies of inflamed tissues in the SIJ, François and colleagues demonstrated mild synovitis in early disease with limited synovial hyperplasia and infiltrates containing a low to moderate number of monocytes, and lymphocytes followed in the later stages by chondroid metaplasia and joint destruction.<sup>104</sup> Monocytes and dendritic cells are the primary cells releasing IL-23 and, in the

#### Box 1: Potential explanations for the non-responsiveness of axSpA patients to IL-23 inhibition

- Enthesial cells, which promote inflammation in the axial skeleton, lack the IL-23R
- Crosstalk between immune cells and mesenchymal or stromal cells does not require IL-23
- Monocytes and dendritic cells, which release IL-23, are in low abundance in axial skeletal tissues
- IL-23 is pivotal for the initiation of disease but not involved in ongoing inflammation
- IL-23 and IL-23R complex diversify the signal to multiple effectors and transducers that are not inhibited by IL-23 and/or IL-23R blockade

synovium of rheumatoid joints and in psoriatic skin, abundant monocyte, dendritic cells are likely a rich source of IL-23.<sup>105 106</sup> A low number of dendritic cells in axSpA tissues may provide an explanation for the lack of an IL-23 driven process, but a careful enumeration of these cells has not been performed.

Another viable explanation is that IL-17 producing cells arrive in the SIJ from other sites, having already been activated by IL-23. A gut joint axis has been proposed to link dysbiosis and gut infections with inflammatory spine disease, and supportive evidence for this can be found in animal models and magnetic resonance imaging.<sup>107 108</sup> In this model, Th17 cells arise in the gut driven by either IL-23 dependent or independent mechanisms, circulate to the joint, and release IL-17. Activation of key effector cells in the gut, however, does not explain why IL-23 inhibition is ineffective in axSpA, given that such therapy should affect cells in both the intestine and the spine.

Interleukin-23 may be a pivotal cytokine in the initiation of the disease during the preclinical or early phase of axSpA but may not be required to maintain ongoing inflammation. Indeed, just this type of role was shown to be present for IL-23 in rheumatoid arthritis.<sup>109</sup> The IL-23 axis and Th17 cells altered the glycosylation pattern of autoreactive IgG antibodies, rendering them pathogenic. It is unlikely that IL-23 is fostering the early stages of axSpA via this same mechanism but it is conceivable that alternative pathways are triggered by this cytokine as an early or initiating event. Another potential explanation supporting early involvement of IL-23 in disease pathogenesis is that the IL-23 and the IL-23R complex can diversify the signal to multiple effectors and transducers that are not inhibited by IL-23 and/or IL-23R blockade, as discussed previously. This signal diversification may activate inflammatory cells in the axial skeleton that lack IL-23R. It is also important to mention that trials of radiographic axSpA include patients with more advanced disease and not patients with new onset or early stage axial inflammation.

#### The therapeutic pipeline in axSpA

Despite the greater treatment options for patients with axSpA, several challenges remain. First, the efficacy observed with the IL-17 blockade is of similar magnitude to that observed with anti-TNF agents. Second, in spite of this degree of comparable efficacy among the therapeutic agents, about half the patients in clinical trials do not see a significant difference in primary outcomes. Third, oral options are not available, and lastly, high cost and difficulty with access to modern treatment regimens remain a challenging barrier for many patients.

Currently only biologics that inhibit IL-17 or TNF are approved, but several agents with novel modes of action are under investigation. Bimekizumab (a dual inhibitor of both IL-17A and IL-17F) was shown to be effective in ankylosing spondylitis in a phase II trial and a phase III study is in progress.<sup>110</sup> Inhibitors of the Jak-STAT pathways have also been investigated

in phase II axSpA trials. Several agents inhibit specific Jak-STAT pathways (fig 4). Inhibition of Jak 1 may interfere with interferon  $\alpha$ ,  $\beta$ , and  $\gamma$  signaling and decreased IL-6 and IL-22 with potential to alter Th1 and Th17 differentiation and bone remodeling in axSpA.<sup>112 113</sup> Furthermore, diminished IL-7 signaling in response to Jak 3 inhibition may block differentiation and function of innate lymphoid cells, important effectors in this disorder.<sup>114</sup> Tofacitinib blocks Jak 1, 2, 3 and demonstrated efficacy in a phase II study.<sup>115</sup> Upadacitinib and filgotinib inhibit Jak 1 and they also demonstrated efficacy for ankylosing spondylitis in phase II studies, and phase III trials are anticipated or under way for all three of these agents.<sup>116 117</sup> Agents that target Tyk 2, which is involved in IL-23/IL-17 signaling, may be effective for this disease although, as previously discussed, the validity of IL-23 as a target in axial disease has been challenged.<sup>118-120</sup> Since pain is a significant component of ankylosing spondylitis, agents that target associated comorbidities such as depression, centralized pain, and sleep disorders may prove to be effective for overall disease activity and for improving function, particularly when administered with an agent that targets the inflammatory components of this disorder.<sup>120 121</sup>

#### Emerging treatments

Several placebo controlled RCTs are under way to investigate the efficacy and safety of novel agents in radiographic and non-radiographic axSpA (table 1). Phase III RCT trials are under way to examine the efficacy and safety of bimekizumab, an antibody that blocks IL-17A and F isoforms in axSpA. Subcutaneous secukinumab is approved for the treatment of ankylosing spondylitis, but an RCT is recruiting patients to examine if intravenously administered secukinumab is an effective and well tolerated treatment in axSpA. The efficacy and safety of namilumab, an agent that blocks GM-CSF, was examined in a phase 2b proof of concept study. Five separate RCTs are under way or about to begin to determine the efficacy and safety of tofacitinib, upadacitinib, and filgotinib in axSpA.

#### Guidelines

Three separate international guidelines for the management of axSpA were published between 2016 and 2020. The 2016 update of the ASAS-EULAR Management Recommendations for Axial SpA was developed with AGREE II<sup>122 123</sup> methodology to formulate consensus around five overarching principles and 13 treatment recommendations.<sup>41</sup> The 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 Non-radiographic Axial Spondyloarthritis Update Recommendations from 2015 used GRADE methodology<sup>124 125</sup> to obtain consensus on five groups of recommendations pertaining to four different axSpA patient subgroups



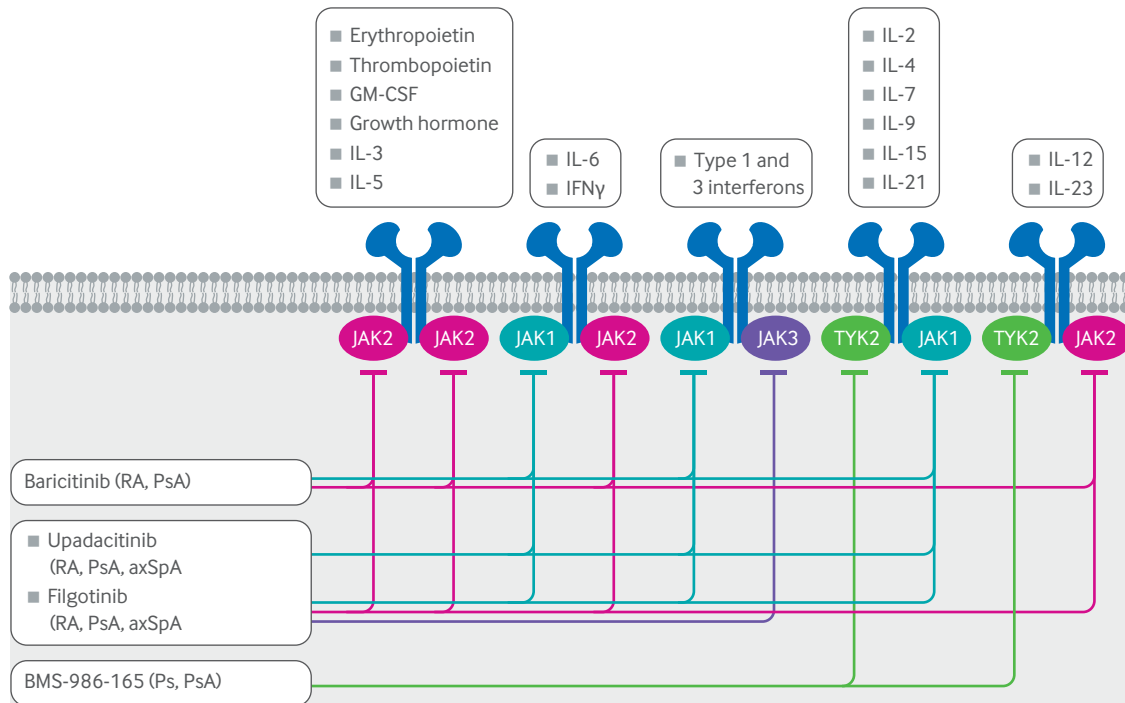


Fig 4 | Selectivity of Jak inhibitors. Specific cytokines signal through different Jak kinases. Ps-psoriasis, PsA-psoriatic arthritis, RA-rheumatoid arthritis (Revised from O'Shea J et al *Nat Rev Rheum* 2019; 15:75)<sup>111</sup>

and the fifth on disease activity assessment and imaging.<sup>40</sup> The 2018 APLAR Axial Spondyloarthritis Treatment Recommendations were also developed with GRADE methodology to produce 14 recommendations based on evidence summaries and consensus.<sup>42</sup> High level evidence was available for the use of NSAIDs and exercise, starting a biologic DMARD in patients with active disease despite conventional therapy, and avoidance of conventional synthetic DMARDs for the treatment of axial disease in all three documents.

### Conclusions

Advances in the diagnosis and treatment of axSpA have unfolded at a rapid pace over the past 20 years. This period was punctuated with a new classification of disease, which expanded the patient population at risk and provided new insights regarding disease course and new opportunities for earlier intervention. The revision in the classification criteria was accompanied by the discovery of the IL-

23/IL-17 pathway which is located at the epicenter of inflammation in axSpA. This pathway yielded a number of potential targets (IL-17, IL-23) expanding the treatment options for patients with this group of disorders. Agents that block IL-17A are highly effective for axSpA, with treatment responses that are of similar magnitude to those observed with anti-TNF agents. The inability of the IL-23 blockade to block axial inflammation was unexpected and generated a range of possibilities to explain the divergence of response in the axial skeleton in contrast to the peripheral joints. Several new therapeutic options are currently under investigation, including agents that block both IL17A and F isoforms, and oral medications that target the Jak-STAT pathways. Despite the progress, significant challenges remain. Treatment response is still far from ideal for many patients and we lack the biomarkers to identify patients with chronic back pain who are at increased risk to progress to axial spondyloarthritis and to predict which medication is most appropriate for

Table 1 | Emerging agents for the treatment of axSpA

Agent	Target	Indication	Enrollment	Status	Trial ID
Bimekizumab	IL17, A, F	nr axSpA/AS	240/300	R/R	NCT03928704/NCT03928743
Secukinumab (IV)	IL-17A	axSpA	500	R	NCT04156620
Namilumab	GM-CSF	axSpA	42	C	NCT03622658
Tofacitinib	Jak1, 2, 3	Ankylosing spondylitis	270	A	NCT03502616
Upadacitinib	Jak 1	axSpA	690	R	NCT04169373
Filgotinib	Jak 1	Ankylosing spondylitis naïve/exposed	408/576	New/new	NCT0448370/NCT0443687

R=recruiting; C=completed; A=active; New=not recruiting yet; GM-CSF=granulocyte macrophage colony stimulating factor; naïve/exposed refers to prior treatment with a biologic disease modifying agent

## RESEARCH QUESTIONS

- Why is inhibition of IL-23 effective for peripheral joint and cutaneous inflammation but not for axial disease?
- How can we effectively identify and treat comorbidities (centralized pain, anxiety and depression, obesity) that amplify pain pathways in axSpA?
- What are the biomechanical factors and signaling pathways that promote pathologic new bone formation?
- Will therapies that combine different biologic DMARDs or a biologic DMARD with a Jak inhibitor evolve as effective and safe treatment options in patients with persistent disease activity despite aggressive treatment?

## HOW PATIENTS AND MEMBERS OF THE PUBLIC WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Patients and members of the public were not directly involved in the drafting or writing of this manuscript.

an individual patient. Another persistent barrier is the marked delay in diagnosis that typifies the experience for many of our patients. Certainly, education targeted at practitioners in primary care, physiotherapists, physiatrists, and spine specialists may help in decreasing the lag between disease onset and diagnosis, but the interventions that will meet with success for this vexing problem are likely to vary from region to region. Finally, the advance in technologies that reveal cell subsets and pathways in tissues at the single cell level will no doubt uncover novel targets and enable the development of a new generation of targeted biologics and oral small molecules to improve response to therapy in patients with axSpA.

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