New developments in ankylosing spondylitis—status in 2021

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Abstract
Axial SpA (axSpA) is a common rheumatic disease characterized by inflammation leading to bone formation and functional impairment. TNF-\(\alpha\) and IL-17 represent established targets in axSpA. TNF-\(\alpha\) and IL-17 inhibitors have demonstrated efficacy in clinical trials and are currently approved biologic DMARDs for all subsets of the disease. Several lines of evidence implicate a role of an IL-23–IL-17 axis in the disease pathogenesis. In this light, and given the success of IL-17 blockade in axSpA, a similar good response to IL-23 was anticipated. Nevertheless, two clinical trials of anti-IL-23 monoclonal antibodies in axSpA have clearly exhibited negative results. This failure has raised theories for a degree of IL-23 independent pathway. The Janus kinase (JAK) pathway is also a potential therapeutic target, since several cytokines, including those involved in the IL-23–IL-17 axis, signal through the JAK family of tyrosine kinases. Further studies and more extended evaluation of response to cytokine inhibition across different tissues will be required to improve our understanding of SpA pathogenesis and determine its optimal management.

Key words: spondyloarthritis, ankylosing spondylitis, clinical trials, anti-TNF-\(\alpha\), IL-23–IL-17 axis

Introduction
Axial SpA (axSpA) is a disease characterized by inflammation and new bone formation in the spine [1]. According to Assessment of SpondyloArthritis International Society (ASAS) classification criteria, the disease spectrum includes two types: radiographic axial SpA, called AS, and non-radiographic axSpA (nr-axSpA) [2]. AxSpA is relatively common among inflammatory arthritides, with a prevalence of up to 1.40\% [3]. The disease typically starts in the SI joints, but can involve any part of the spine, as well as the peripheral joints and the entheses [4]. Enthesitis is a hallmark feature of axSpA, with entheses being well-characterized as a key target of musculoskeletal inflammation [5]. An understanding of the enthesitis-based model in disease pathogenesis has emerged as a matter of importance in AS-associated inflammation in the last 2 decades. Mechanical stress has been suggested to be important for initiation and potentially maintenance of inflammation, a notion explaining the disease distribution in the weight-bearing areas [6]. Nearly half of axSpA patients experience extramusculoskeletal manifestations, including anterior uveitis, psoriasis and inflammation of the terminal ileum, with all these tissues representing sites subject to biomechanical stress, sharing remarkable biomechanical properties with entheses [7].

New bone formation and structural damage in the SI joints and spine as consequences of inflammation have been well-defined in axSpA. The inflammatory lesions of the axial skeleton can be well-depicted in MRI [8]. It has been suggested that subchondral bone marrow is replaced by a granulation tissue carrying osteoblasts, which promote new bone formation, leading to intra-articular ankylosis of the facet joints [9]. Development of syndesmophytes and finally ankyloses in the spine as a result of inflammation can lead to restriction of spinal mobility and dysfunction [10]. The mechanisms of interaction between inflammation and new bone formation

\begin{itemize}
 \item The IL-23–IL-17 axis seems to play an important role in the pathogenesis of ankylosing spondylitis (AS).
 \item Anti-TNF-\(\alpha\) and anti-IL-17 agents are effective for AS, unlike IL-23 blockade.
 \item Theories of partial uncoupling of IL-17 production from IL-23 have been proposed.
\end{itemize}
have not been fully elucidated. Our understanding of this interaction is important for the prevention of long-term structural damage. Basic research has highlighted a key role for TNF-α and IL-23–IL-17 cytokine dysregulation in the aetiology of AS [11]. IL-23 acts as an upstream driver of Th17 cells, the T lymphocytes producing IL-17 [12]. Single nucleotide polymorphisms identified by genome-wide association studies (GWAS) implicate the IL-23–IL-17 axis in AS [13]. Acquiring tissue from the affected sites is difficult. Hence, in human SpA, the main evidence that the IL-23–IL-17 axis plays a pathogenic role comes from clinical studies of IL-17 and IL-23 blockers.

**TNF inhibition**

The use of TNF inhibitors (TNFis) in AS followed their success in treating other inflammatory conditions. Suggestive for introduction was the demonstration of TNF-α overexpression in the SI joints of AS patients [14]. On the basis of evidence from clinical trials, TNF-α appears to have an established role in AS pathogenesis, being effective and indicated after NSAIDs failure for both AS [15–21], with no limitation, and nr-axSpA [22–26] if there is an elevated CRP and/or inflammation on MRI [27]. Given that many studies suggest that patients with AS with elevated baseline CRP levels respond better to TNFi [28, 29], the latter limitation would rationally be applied in AS as well. However, the disease per se, with ~40% of AS patients having normal baseline CRP levels, does not allow for such a recommendation [30]. Results from clinical trials initially showed that TNFis do not retard new bone formation, at least when administered up to 2 years [31, 32]. Nevertheless, more recent data point to the direction that long-term TNFi exposure leads to a reduction of MRI inflammation and exerts beneficial effects on spinal radiographic progression in axSpA [33–35].

Studies regarding the persistence of clinical response after TNFi withdrawal are available. TNFi discontinuation has not proved successful, since almost all AS [36] and half of the nr-axSpA patients [24] have been shown to experience a clinical relapse within several weeks to months. Efficacy after re-treatment may be as good as before discontinuation in AS, but not in nr-axSpA patients, considering that ~40% of the latter did not reach their disease activity status as before withdrawal 3 months after treatment reintroduction [24]. On the contrary, TNFi dose reduction in axSpA in remission has been proven to be an approach similarly effective as continuous TNFi treatment [37]. A key question remains, how we can effectively perform dose reduction? There are aspects of evidence suggesting ‘the slower the better’. In patients with sustained remission, one could slowly increase the dosing interval and transit to the lowest effective dose [38]. TNFi dose reduction up to 50% in patients with early axSpA in sustained remission was shown to be a feasible option to avoid flares and reduce costs [39].

Meta-analyses on the safety of TNFis in AS identified a higher incidence of adverse events (AEs) compared with placebo [40–42]. AEs were similar to the ones reported in other inflammatory conditions, including injection site reactions, higher risk of haematological malignancy, worsening of heart failure, risk of tuberculosis and hepatitis reactivation. Nevertheless, no significant difference in the incidence of serious AEs (SAEs) between biologic DMARDs (bDMARDs) and placebo was identified.

**IL-17 inhibition**

IL-17A has been found to be a key mediator of inflammation in axSpA, psoriasis, and PsA. Therefore biologic agents targeting IL-17A signalling pathways have been developed for treating these entities [43]. Secukinumab, a fully human IgG1/κ monoclonal antibody (mAb) selectively binds to IL-17A, leading to inhibition of its interaction with the IL-17 receptor. Its approval for the whole spectrum of axSpA is based on results of the MEASURE clinical trial program [43–46] and the PREVENT trial [47] for AS and nr-axSpA, respectively. Its long-term efficacy and safety was confirmed in both naïve and TNFi-experienced patients [48]. In addition to improving symptoms and disease activity in AS, extension studies and an ongoing randomized controlled trial (RCT) have confirmed that, at least mid-term, secukinumab is associated with low risk of radiographic progression [49, 50].

The efficacy of IL-17A inhibition in AS was confirmed in the studies of ixekizumab, a recombinant humanized IgG4κ mAb that selectively binds and neutralizes IL-17A. All three COAST studies (COAST-V, -W and -X) in AS TNFi-naïve and TNFi-experienced patients and patients with nr-axSpA, respectively, met their primary endpoints [51–53]. Netakimab, a humanized IgG1 mAb targeting IL-17A, was found superior to placebo in TNFi-naïve axSpA patients [54]. A phase III study of brodalumab, a mAb inhibiting the IL-17 receptor A, in Asian patients with AS and nr-axSpA met its primary end point [55]. Bimekizumab, an IgG1 monoclonal antibody that binds to an epitope expressed on both IL-17A and IL-17F, selectively neutralizes both cytokines [56]. Dual inhibition of IL-17A and IL-17F in patients with AS resulted in improvements in disease activity, quality of life and function in a phase IIb study [57]. There are currently two phase 3 trials: BE MOBILE 1 (NCT03928704) in nr-axSpA and BE MOBILE 2 (NCT03928743) in AS patients. Both trials are reported as of Nov 2, 2021 in clinicaltrials.gov as active/ongoing; however, BE MOBILE 2 is active but no longer recruiting. Although two separate entities, PsA with axial involvement and axSpA have overlapping characteristics [58]. Patients with PsA with axial manifestations seem to have a good response to the same biologics as patients with axSpA, a fact recently confirmed with IL-17A inhibition in the MAXIMIZE trial [59]. IL-17 inhibition has shown an acceptable safety profile in RCTs, with nasopharyngitis and local oral fungal infections being commonly reported AEs [60]. No increase in the incidence of SAEs or in drug discontinuation due to AEs compared with placebo has been identified in these studies.
Patients' outcomes in clinical trials of both TNFi and anti-IL-17 biologics are in line with the goals defined by the ASAS and EULAR for the management of axSpA. Both classes of bDMARDs are recommended as second-line treatment in axSpA and axial involvement of PsA [27, 61].

IL-23 inhibition

Considering the good response of AS patients to IL-17 inhibition and evidence showing blockade of IL-23 as a promising therapeutic modality in AS [62], similar positive outcomes were expected in trials of IL-23 inhibitors. That was not the case, however, as the studies of anti-IL-12/23 inhibitor ustekinumab [63] and risankizumab, a selective inhibitor of the IL-23 p19 subunit [64], did not meet their primary endpoints. The initial question raised by these results was whether there were flaws in the study design. This assumption was rejected, given that the patient population was similar to that of other AS studies; the treatment agents had previously shown efficacy in psoriasis, PsA and IBD; the pharmacokinetics were analogous to those in psoriasis and, at least for risankizumab, there was no evidence of improvement in any outcome. Consequently, the next question is why IL-23 inhibition does not work in AS. A hypothesis for the difference in efficacy of IL-17 and IL-23 inhibition in AS is that IL-17 and IL-23 are at least partially uncoupled. Data from SpA animal models reported that IL-23 inhibition could affect IL-17 production only before disease induction, suggesting that IL-23 could be important for the initiation but not the persistence of SpA [65]. Moreover, IL-17 is not only produced by Th17 cells, but also by certain innate cell types such as γδ T cells, mucosal-associated invariant T cells (MAITs), invariant natural killer T cells and innate lymphoid cells 3 (ILC3) [66, 67]. Although, IL-23-dependent production of IL-17 by γδ T cells has been described in murine entheses [68], evidence suggests that in human enthesis this happens in an IL-23-independent manner [69]. IL-17A and IL-17F production by MAIT cells was also demonstrated to be IL-23-independent and was driven by other cytokines such as IL-12 and IL-18 [70].

Several studies have highlighted the role of the IL-36 family of cytokines and their antagonist IL-38 in the pathogenesis of psoriatic skin disease [71, 72] and in synovial inflammation [73] in patients with PsA. IL-36 has been shown to induce the production of T cell-derived cytokines including IL-17A. It is hypothesized that IL-36 could be involved in the pathogenesis of SpA by increasing the production of pro-inflammatory cytokines such as IL-23, IL-17, IL-22, TNF-α and IL-6. These findings point in the direction of IL-23-independent induction of inflammation by IL-17 in AS not responding to IL-23 inhibition. A further assumption is that within the SpA spectrum, cytokines exert discrete pathogenetic actions, depending on the tissue. In vitro studies have shown that the extent of IL-23’s contribution to IL-17 production depends on cell-to-cell interactions at different anatomic sites and is greater in skin than in synovium or bone marrow [74, 75]. This theory could partly explain discrepancies of treatment effects across the SpA spectrum: the efficacy of IL-23 inhibition in psoriasis [76] but not in axSpA, the efficacy of IL-12/23 inhibition in ulcerative colitis [77] and the failure of IL-17 inhibition in Crohn’s disease [78, 79].

JAK inhibition

Inhibition of the Janus kinase (JAK) pathway with targeted synthetic DMARDs (tsDMARDs) has recently been shown to be a good additional strategy to effectively manage AS. JAKs are associated with receptors of numerous cytokines, with those involved in the IL-12–IL-23 axis among them. A phase 3 study of the JAK1/3 inhibitor tofacitinib in AS patients met its primary end point [80]. Similarly, phase 2/3 and phase 2 studies of the preferential JAK1 inhibitors upadacitinib and filgotinib, respectively, were both successful across a wide range of disease parameters [81, 82]. Primary results regarding radiographic progression are promising, with AS patients experiencing clinically meaningful reductions in spinal MRI inflammation at week 12 with both tofacitinib and filgotinib [83, 84]. The incidences of AEs, SAEs and withdrawals due to AEs did not differ between JAK inhibitors and placebo in RCTs. No new safety signals were detected in AS studies [85]. To date, upadacitinib is the only JAK inhibitor approved by the European Medicines Agency for AS. JAK inhibitors have not been evaluated in nr-axSpA.

Discussion

Introduction of bDMARDs has been a major breakthrough in axSpA [86]. TNFis have proved highly effective in controlling inflammation in clinical trials, with similar efficacy across all TNF blockers [87]. Their benefits are confirmed by real-world evidence in both nr-axSpA and AS [88]. Long-term data indicate their possible protective effect on spinal radiographic progression [35]. Even so, 20–30% of patients with axSpA do not respond adequately to TNF inhibitors, leading to the need for targeting alternative pathways of the disease [89]. Preclinical and clinical data resulted in a high level of interest in IL-17 as a potential therapeutic target in SpA and gave rise to the development of anti-IL-17 antibodies. Our current armamentarium includes mAbs inhibiting IL-17A, while promising dual inhibition of IL-17A and IL-17F is being investigated. No difference was observed in the response of AS patients to either TNF-α or IL-17A in clinical trials. In contrast, fewer patients with nr-axSpA achieved a 40% improvement in ASAS criteria (ASAS40) in studies of anti-IL-17A compared with those of anti-TNF-α (Table 1). One would assume that TNF-α inhibition works better than anti-IL-17A in nr-axSpA. However, this discrepancy is a consequence of the design of anti-IL-17A studies. After a specific time point, patients were allowed to switch to open-label anti-IL-
## Table 1: ASAS40 response at different timepoints in Phase 3 clinical trials in axSpA

| Disease | Study | bDMARD/tsDMARD | Primary endpoint | ASAS40 response to bDMARD/tsDMARD at week 12, 14, 16 and 24, % | ASAS40 response to placebo at week 12, 14, 16 and 24, % | ASAS40 response difference vs placebo at week 12, 14, 16 and 24, % | ASAS40 response to bDMARD/tsDMARD at week 52, % |
|---------|-------|----------------|------------------|-------------------------------------------------------|-------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------|
| AS      | ASSERT [15] | Infliximab | ASAS20 at week 24 | 47 | 12 | 35 | NA |
|         | Etanercept [16, 17] | ASAS20 at week 12 | 39.9 | 13.1 | 26.8 | 50.7 |
|         | ATLAS [18, 19] | Adalimumab | ASAS20 at week 12 | 40 | 19.3 | 20.7 | 57.9 (NRI) |
|         | GO-RAISE [20, 90] | Golimumab | ASAS20 at week 14 | 40 | 19.3 | 20.7 | 57.9 (NRI) |
|         | RAPID-axSpA [21, 91] | Certolizumab pegol | ASAS20 at week 12 | 40 | 19.3 | 20.7 | 57.9 (NRI) |
|         | MEASURE 1 [43] | Secukinumab | ASAS20 at week 16 | 42 | 13 | 29 | 51 |
|         | MEASURE 2 [43] | Secukinumab | ASAS20 at week 16 | 36 | 11 | 25 | 49 |
|         | MEASURE 4 [45] | Secukinumab | ASAS20 at week 16 | 38.8 | 28.2 | 10.6 | 51.3 |
|         | MEASURE 5 [46] | Secukinumab | ASAS20 at week 16 | 43.9 | 17 | 26.9 | 60.6 |
|         | COAST-W [52] | Ixekizumab | ASAS40 at week 16 | 25.4 | 12.5 | 12.9 | 34.2 |
|         | COAST-V [51] | Ixekizumab | ASAS40 at week 16 | 48 | 18 | 30 | 53.1 |
|         | SELECT-AXIS [81] | Upadacitinib | ASAS40 at week 14 | 52 | 26 | 26 | NA |
|         | TORTUGA [82] | Filgotinib | Change of ASDAS from baseline to week 12 | 38 | 19 | 19 | NA |
| nr-axSpA | EMBARK [22, 92] | Etanercept | ASAS40 at week 12 | 33.3 | 14.8 | 18.5 | 53.9 (observed) |
|         | ABILITY-1 [23, 93] | Adalimumab | ASAS40 at week 12 | 36 | 15 | 21 | 61.3 (observed) |
|         | ABILITY-3 [24] | Adalimumab | Withdrawal study. The proportion of patients not experiencing a flare during the double-blind period of 28 weeks | week 12:59 | NA | NA | NA |
|         | GO-AHEAD [25, 94] | Golimumab | ASAS40 at week 16 | 56.7 | 23 | 33.7 | 76.3 |
|         | C-AXSPAND [26] | Certolizumab pegol | Major improvement in ASDAS at week 52 | 49 (observed) | 11.6 (observed) | 37.4 (observed) | 74.4 (observed) |
|         | RAPID-axSpA [21] | Certolizumab pegol | ASAS20 at week 12 | 47.8 | 16 | 31.8 | 57.7 (NRI) |
|         | PREVENT [47] | Secukinumab | ASAS40 at week 16 | 41.5 | 29.2 | 12.3 | 35.4 (64 observed) |
|         | COAST-X [53] | Ixekizumab | ASAS40 at weeks 16 and 52 | 35 | 19 | 16 | 30 |

*aIn approved dosing regimen when applicable. bBased on the primary end point. cData available at week 48. dPhase 2/3 clinical trial. ePhase 2 clinical trial. NA: not available; NRI: non-responder imputation.
17A or to the standard of care based on clinical judgement. All these patients were imputed as non-responders, although a percentage of them had actually achieved ASAS40 at the time of the switch. To date TNF-α and IL-17 blockers are the only approved bDMARDs for axSpA that have long-term efficacy and safety data available [90–95]. However, some patients may still experience inadequate response and require alternative treatments.

Success of IL-17 blockade raised the question of the therapeutic value of targeting upstream activators of Th17 cells rather than IL-17 itself. This concept, along with data supporting the existence of an anti-IL-23–IL-17 axis in axSpA and the effect of IL-23 inhibition in other diseases in the SpA spectrum, led to studies of anti-IL-23 in axSpA. Surprisingly, blockade of IL-23 did not work in the trials. Theories for uncoupling of IL-17 production from IL-23 emerged from this failure. Several observations pointed to the identification of cell types other than Th17 as a source of IL-17, findings suggesting that IL-23 can inhibit inflammation induced by IL-17 only early in the disease course and the notion that the extent to which IL-23 is necessary for IL-17 production depends on the tissue microenvironment. The failure of published IL-23 trials reminded us that preclinical data and data on animal models cannot be directly extrapolated to humans. It cannot be excluded that the various affected structures, such as enthesis and the synovium, might respond differently to treatments such as IL-23 blockade. Before making a statement for a class effect in axSpA, more data from clinical studies are required. In this sense, gusekumab, an anti-IL-23 mAb, has been shown to improve axial symptoms in the subgroups of patients with sacroiliitis through week 24 in its phase 3 studies in PsA [96].

Despite the progress, there is a lot to learn in axSpA regarding the available bDMARDs. It remains unclear whether TNF and IL-17 are equally important in all patients with axSpA, whether the two cytokines could be simultaneously safely inhibited, which component of IL-17 is optimal to inhibit and to what extent IL-17A production is dependent on IL-23. Additionally, a definite answer regarding the effect of bDMARDs in radiographic progress is still pending. Finally, long-term data of RCTs regarding the effect of tsDMARDs on axSpA are not available. Future research could help us optimize the management strategies with the available agents and improve our understanding of the mechanisms connecting inflammation to new bone formation in order to develop new treatment modalities.

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Data availability statement
Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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