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New developments in ankylosing spondylitis—status in 2021

Kalliopi Klavdianou[1,2], Styliani Tsiami [1] and Xenofon Baraliakos [1]

Abstract

Axial SpA (axSpA) is a common rheumatic disease characterized by inflammation leading to bone formation and functional impairment. TNF-α and IL-17 represent established targets in axSpA. TNF-α 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-α, IL-23–IL-17 axis

Rheumatology key messages

- The IL-23–IL-17 axis seems to play an important role in the pathogenesis of ankylosing spondylitis (AS).
- Anti-TNF-α and anti-IL-17 agents are effective for AS, unlike IL-23 blockade.
- Theories of partial uncoupling of IL-17 production from IL-23 have been proposed.

SUPPLEMENT

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

[1]Rheumazentrum Ruhrgebiet Herne, Ruhr-University Bochum, Herne, Germany and [2]Department of Rheumatology, 'Asklepieion' General Hospital, Athens, Greece

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Correspondence to: Xenofon Baraliakos, Rheumazentrum Ruhrgebiet Herne, Ruhr-University Bochum, Claudiusstr. 45, Herne 44649, Germany. E-mail: xenofon.baraliakos@elisabethgruppe.de

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 pathogenetic 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 reachieve 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 midterm, 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 clincialtrials.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 MAXIMISE 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[a] at week 12, 14, 16 and 24[b], %	ASAS40 response to placebo at week 12, 14, 16 and 24[b], %	ASAS 40 response difference *vs* placebo at week 12, 14, 16 and 24[b], %	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 and 24	week 12: 45 week 24: 45	week 12: 16 week 24: 14	week 12: 29 week 24: 31	61[c]
	ATLAS [18, 19]	Adalimumab	ASAS20 at week 12	39.9	13.1	26.8	50.7
	GO-RAISE [20, 90]	Golimumab	ASAS20 at week 14	week 24: 43.5	week 24: 15.4	28.1	74.5 (observed)
	RAPID-axSpA [21, 91] (AS patients)	Certolizumab pegol	ASAS20 at week 12	40	19.3	20.7	57.9 (NRI)[c]
	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
		Brodalumab [55]	ASAS40 at week 16	48.3 (NRI 46.0)	29.1 (NRI 25.8)	16.2 (NRI 20.2)	NA
		Tofacitinib [80]	ASAS20 at week 16	40.6	12.5	28.1	NA
	SELECT-AXIS [81][d]	Upadacitinib	ASAS40 at week 14	52	26	26	NA
	TORTUGA [82][e]	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) 46.2 (NRI)[c]
	ABILITY-1 [23, 93]	Adalimumab	ASAS40 at week 12	36	15	21	61.3 (observed) 49.7 (NRI)
	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	ASAS20 at week 16	56.7	23	33.7	76.3
	C-AXSPAND [26]	Certolizumab pegol	Major improvement in ASDAS at week 52	49 (observed) 47.8 (imputed)	11.6 (observed) 11.4 (imputed)	37.4 (observed) 36.4 (imputed)	74.4 (observed) 56.6 (imputed)
	RAPID-axSpA [21] (nr-axSpA patients)	Certolizumab pegol	ASAS20 at week 12	47.8	16	31.8	57.7(NRI)[c]
	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
		Brodalumab [55]	ASAS40 at week 16	35.3 (NRI 35.3)	21.4 (NRI 18.8)	13.9	NA

[a]In approved dosing regimen when applicable. [b]Based on the primary end point. [c]Data available at week 48. [d]Phase 2/3 clinical trial. [e]Phase 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 entheses 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, guselkumab, 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.

References

1 Dougados M, Baeten D. Spondyloarthritis. Lancet 2011; 377:2127–37.

2 Rudwaleit M, van der Heijde D, Landewé 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;68:777–83.

3 Reveille JD, Witter JP, Weisman MH. Prevalence of axial spondylarthritis in the United States: estimates from a cross-sectional survey. Arthritis Care Res (Hoboken) 2012;64:905–10.

4 Baraliakos X, Sewerin P, de Miguel E *et al.* Achilles tendon enthesitis evaluated by MRI assessments in patients with axial spondyloarthritis and psoriatic arthritis: a report of the methodology of the ACHILLES trial. BMC Musculoskelet Disord 2020;21:767.

5 Schett G, Lories RJ, D'Agostino M-A *et al.* Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol 2017;13:731–41.

6 Jacques P, Lambrecht S, Verheugen E *et al.* Proof of concept: enthesitis and new bone formation in spondyloarthritis are driven by mechanical strain and stromal cells. Ann Rheum Dis 2014;73:437–45.

7 McGonagle D, Stockwin L, Isaacs J, Emery P. An enthesitis based model for the pathogenesis of spondyloarthropathy. Additive effects of microbial adjuvant and biomechanical factors at disease sites. J Rheumatol 2001;28:2155–9.

8 Braun J, Baraliakos X. Imaging of axial spondyloarthritis including ankylosing spondylitis. Ann Rheum Dis 2011; 70(Suppl 1):i97–103.

9 Bleil J, Maier R, Hempfing A *et al.* Granulation tissue eroding the subchondral bone also promotes new bone formation in ankylosing spondylitis. Arthritis Rheumatol 2016;68:2456–65.

10 Poddubnyy D, Protopopov M, Haibel H *et al.* High disease activity according to the Ankylosing Spondylitis Disease Activity Score is associated with accelerated radiographic spinal progression in patients with early axial spondyloarthritis: results from the GErman SPondyloarthritis Inception Cohort. Ann Rheum Dis 2016;75:2114–8.

11 Lories RJ, Haroon N. Evolving concepts of new bone formation in axial spondyloarthritis: insights from animal models and human studies. Best Pract Res Clin Rheumatol 2017;31:877–86.

12 Langrish CL, Chen Y, Blumenschein WM *et al.* IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. J Exp Med 2005;201: 233–40.

13 Brown MA, Wordsworth BP. Genetics in ankylosing spondylitis – current state of the art and translation into

clinical outcomes. Best Pract Res Clin Rheumatol 2017; 31:763–76.

14 Braun J, Bollow M, Neure L *et al.* Use of immunohistologic and in situ hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. Arthritis Rheum 1995;38:499–505.

15 van der Heijde D, Dijkmans B, Geusens P *et al.* Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582–91.

16 Davis JCJ, van der Heijde D, Braun J *et al.* Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum 2003;48:3230–6.

17 Davis JC, van der Heijde DM, Braun J *et al.* Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. Ann Rheum Dis 2005;64: 1557–62.

18 van der Heijde D, Kivitz A, Schiff MH *et al.* Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2006;54: 2136–46.

19 Sieper J, van der Heijde D, Dougados M *et al.* Early response to adalimumab predicts long-term remission through 5 years of treatment in patients with ankylosing spondylitis. Ann Rheum Dis 2012;71:700–6.

20 Inman RD, Davis JCJ, van der Heijde D *et al.* Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum 2008;58: 3402–12.

21 Landewé 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.

22 Dougados M, 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; 66:2091–102.

23 Sieper J, van der Heijde D, Dougados M *et al.* Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis 2013;72:815–22.

24 Landewé R, Sieper J, Mease P *et al.* Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. Lancet 2018;392:134–44.

25 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;67:2702–12.

26 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;71:1101–11.

27 van der Heijde D, Ramiro S, Landewé R *et al.* 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76: 978–91.

28 Glintborg B, Østergaard M, Krogh NS *et al.* Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. Ann Rheum Dis 2010;69:2002–8.

29 Arends S, Brouwer E, van der Veer E *et al.* Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. Arthritis Res Ther 2011;13:R94.

30 Baraliakos X, Szumski A, Koenig AS, Jones H. The role of C-reactive protein as a predictor of treatment response in patients with ankylosing spondylitis. Semin Arthritis Rheum 2019;48:997–1004.

31 van der Heijde D, Landewé R, Baraliakos X *et al.* Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. Arthritis Rheum 2008;58:3063–70.

32 van der Heijde D, Landewé R, Einstein S *et al.* Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. Arthritis Rheum 2008;58:1324–31.

33 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.

34 Sepriano A, Ramiro S, Wichuk S *et al.* Tumor necrosis factor inhibitors reduce spinal radiographic progression in patients with radiographic axial spondyloarthritis: a longitudinal analysis from the Alberta prospective cohort. Arthritis Rheumatol 2021;73:1211–19.

35 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;72:733–49.

36 Baraliakos X, Listing J, Brandt J *et al.* Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. Arthritis Res Ther 2005;7:R439–44.

37 Závada J, Uher M, Sisol K *et al.* A tailored approach to reduce dose of anti-TNF drugs may be equally effective, but substantially less costly than standard dosing in patients with ankylosing spondylitis over 1 year: a propensity score-matched cohort study. Ann Rheum Dis 2016;75:96–102.

38 Lian F, Zhou J, Wang Y *et al.* Efficiency of dose reduction strategy of etanercept in patients with axial spondyloarthritis. Clin Exp Rheumatol 2018;36:884–90.

39 Landewé 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;79:920–8.

40 Ma Z, Liu X, Xu X *et al.* Safety of tumor necrosis factor-alpha inhibitors for treatment of ankylosing spondylitis: a meta-analysis. Medicine (Baltimore) 2017;96:e7145.

41 Liu W, Wu Y-H, Zhang L *et al.* Efficacy and safety of TNF-α inhibitors for active ankylosing spondylitis patients: multiple treatment comparisons in a network meta-analysis. Sci Rep 2016;6:32768.

42 Maxwell LJ, Zochling J, Boonen A *et al.* TNF-alpha inhibitors for ankylosing spondylitis. Cochrane Database Syst Rev 2015;4:CD005468.

43 Baeten D, Sieper J, Braun J *et al.* Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med 2015;373:2534–48.

44 Pavelka K, Kivitz A, Dokoupilova E *et al.* Efficacy, safety, and tolerability of secukinumab in patients with active ankylosing spondylitis: a randomized, double-blind phase 3 study, MEASURE 3. Arthritis Res Ther 2017;19:285.

45 Kivitz AJ, Wagner U, Dokoupilova E *et al.* Efficacy and safety of secukinumab 150 mg with and without loading regimen in ankylosing spondylitis: 104-week results from MEASURE 4 study. Rheumatol Ther 2018;5:447–62.

46 Huang F, Sun F, Wan W-G *et al.* Secukinumab provided significant and sustained improvement in the signs and symptoms of ankylosing spondylitis: results from the 52-week, phase III China-centric study, MEASURE 5. Chin Med J (Engl) 2020;133:2521–31.

47 Deodhar A, Blanco R, Dokoupilová 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 2021;73:110–20.

48 Baraliakos X, Braun J, Deodhar A *et al.* Long-term efficacy and safety of secukinumab 150 mg in ankylosing spondylitis: 5-year results from the phase III MEASURE 1 extension study. RMD Open 2019;5:e001005.

49 Braun J, Baraliakos X, Deodhar A *et al.* Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study. Ann Rheum Dis 2017;76:1070–7.

50 Baraliakos X, Østergaard M, Gensler LS *et al.* Comparison of the effects of secukinumab and adalimumab biosimilar on radiographic progression in patients with ankylosing spondylitis: design of a randomized, phase IIIb study (SURPASS). Clin Drug Investig 2020;40:269–78.

51 van der Heijde D, Wei JC-C, 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 anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. Lancet 2018;392:2441–51.

52 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 inhibitors. Arthritis Rheumatol 2019;71:599–611.

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

54 Erdes S, Nasonov E, Kunder E *et al.* Primary efficacy of netakimab, a novel interleukin-17 inhibitor, in the treatment of active ankylosing spondylitis in adults. Clin Exp Rheumatol 2020;38:27–34.

55 Wei JC-C, Kim T-H, Kishimoto M *et al.* Efficacy and safety of brodalumab, an anti-IL17RA monoclonal antibody, in patients with axial spondyloarthritis: 16-week results from a randomised, placebo-controlled, phase 3 trial. Ann Rheum Dis 2021;doi:10.1136/annrheumdis-2020-219406.

56 Glatt S, Helmer E, Haier B *et al.* First-in-human randomized study of bimekizumab, a humanized monoclonal antibody and selective dual inhibitor of IL-17A and IL-17F, in mild psoriasis. Br J Clin Pharmacol 2017;83:991–1001.

57 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.

58 Baraliakos X, Coates LC, Braun J. The involvement of the spine in psoriatic arthritis. Clin Exp Rheumatol 2015;33(5 Suppl 93):S31–5.

59 Baraliakos X, Gossec L, Pournara E *et al.* Secukinumab in patients with psoriatic arthritis and axial manifestations: results from the double-blind, randomised, phase 3 MAXIMISE trial. Ann Rheum Dis 2020;80:582–90.

60 Wang P, Zhang S, Hu B *et al.* Efficacy and safety of interleukin-17A inhibitors in patients with ankylosing spondylitis: a systematic review and meta-analysis of randomized controlled trials. Clin Rheumatol 2021;doi:10.1007/s10067-020-05545-y.

61 Gossec L, Baraliakos X, Kerschbaumer A *et al.* EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis 2020;79:700–12.

62 Paine A, Ritchlin CT. Targeting the interleukin-23/17 axis in axial spondyloarthritis. Curr Opin Rheumatol 2016;28:359–67.

63 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;71:258–70.

64 Baeten D, Østergaard M, Wei JC-C *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;77:1295–302.

65 van Tok MN, Na S, Lao CR *et al.* The initiation, but not the persistence, of experimental spondyloarthritis is dependent on interleukin-23 signaling. Front Immunol 2018;9:1550.

66 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;75:2124–32.

67 Venken K, Jacques P, Mortier C *et al.* RORγt inhibition selectively targets IL-17 producing iNKT and γδ-T cells enriched in spondyloarthritis patients. Nat Commun 2019;10:9.

68 Reinhardt A, Yevsa T, Worbs T *et al.* Interleukin-23-dependent γ/δ T cells produce interleukin-17 and accumulate in the enthesis, aortic valve, and ciliary body in mice. Arthritis Rheumatol 2016;68:2476–86.

69 Cuthbert RJ, Watad A, Fragkakis EM *et al.* Evidence that tissue resident human enthesis γδT-cells can produce IL-17A independently of IL-23R transcript expression. Ann Rheum Dis 2019;78:1559–65.

70 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.

71 Walsh PT, Fallon PG. The emergence of the IL-36 cytokine family as novel targets for inflammatory diseases. Ann N Y Acad Sci 2018;1417:23–34.

72 Yuan X, Peng X, Li Y, Li M. Role of IL-38 and its related cytokines in inflammation. Mediators Inflamm 2015;2015:807976.

73 Boutet M-A, Nerviani A, Lliso-Ribera G *et al.* Interleukin-36 family dysregulation drives joint inflammation and therapy response in psoriatic arthritis. Rheumatology (Oxford) 2020;59:828–38.

74 Noack M, Ndongo-Thiam N, Miossec P. Interaction among activated lymphocytes and mesenchymal cells through podoplanin is critical for a high IL-17 secretion. Arthritis Res Ther 2016;18:148.

75 Noack M, Ndongo-Thiam N, Miossec P. Role of podoplanin in the high interleukin-17A secretion resulting from interactions between activated lymphocytes and psoriatic skin-derived mesenchymal cells. Clin Exp Immunol 2016;186:64–74.

76 Reich K, Armstrong AW, Langley RG *et al.* Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. Lancet 2019;394:831–9.

77 Sands BE, Sandborn WJ, Panaccione R *et al.* Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2019;381:1201–14.

78 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;61:1693–700.

79 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;111:1599–607.

80 Deodhar A, Sliwinska-Stanczyk P, Xu H *et al.* Tofacitinib for the treatment of ankylosing spondylitis: a phase III, randomised, double-blind, placebo-controlled study. Ann Rheum Dis 2021;doi:10.1136/annrheumdis-2020-219601.

81 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;394:2108–17.

82 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;392:2378–87.

83 Maksymowych WP, van der Heijde D, Baraliakos X *et al.* Tofacitinib is associated with attainment of the minimally important reduction in axial magnetic resonance imaging inflammation in ankylosing spondylitis patients. Rheumatology (Oxford) 2018;57:1390–9.

84 Baraliakos X, Østergaard M, Landewé RBM *et al.* Effects of filgotinib on spinal lesions in ankylosing spondylitis: magnetic resonance imaging data from the TORTUGA trial. 2021;80:83–4.

85 Lee YH, Song GG. Janus kinase inhibitors for treating active ankylosing spondylitis: a meta-analysis of randomized controlled trials. Z Rheumatol 2020;doi:10.1007/s00393-020-00948-3.

86 So A, Inman RD. An overview of biologic disease-modifying antirheumatic drugs in axial spondyloarthritis and psoriatic arthritis. Best Pract Res Clin Rheumatol 2018;32:453–71.

87 Callhoff J, Sieper J, Weiß A, Zink A, Listing J. Efficacy of TNFα blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. Ann Rheum Dis 2015;74:1241–8.

88 Michelena X, Zhao SS, Dubash S *et al.* Similar biologic drug response regardless of radiographic status in axial spondyloarthritis: data from the BSRBR-AS registry. Rheumatology (Oxford) 2021;doi:10.1093/rheumatology/keab070.

89 Furst DE, Louie JS. Targeting inflammatory pathways in axial spondyloarthritis. Arthritis Res Ther 2019;21:135.

90 Braun J, Deodhar A, Inman RD *et al.* Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 104-week results of the GO-RAISE study. Ann Rheum Dis 2012;71:661–7.

91 Sieper J, Landewé R, Rudwaleit M *et al.* Effect of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis: results from a phase III randomized trial. Arthritis Rheumatol 2015;67:668–77.

92 Dougados M, van der Heijde D, Sieper J *et al.* Effects of long-term etanercept treatment on clinical outcomes and objective signs of inflammation in early nonradiographic axial spondyloarthritis: 104-week results from a randomized, placebo-controlled study. Arthritis Care Res (Hoboken) 2017;69:1590–8.

93 van der Heijde D, Sieper J, Maksymowych WP *et al.* Clinical and MRI remission in patients with

nonradiographic axial spondyloarthritis who received long-term open-label adalimumab treatment: 3-year results of the ABILITY-1 trial. Arthritis Res Ther 2018;20: 61.

94 van der Heijde D, Dougados M, Maksymowych WP *et al.* Long-term tolerability and efficacy of golimumab in active non-radiographic axial spondyloarthritis: results from open-label extension. Rheumatology (Oxford) 2021;20:keab346.

95 Dougados M, Wei JC-C, Landewé 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;79:176–85.

96 Mease P, Helliwell P, Gladman D *et al.* Efficacy of guselkumab, a monoclonal antibody that specifically binds to the p19 subunit of IL-23, on axial-related endpoints in patients with active PsA with imaging-confirmed sacroiliitis: week-52 results from two phase 3, randomized, double-blind, placebo-controlled studies. Arthritis Rheumatol 2020;72(Suppl10):abstract 2025.