The Future of Axial Spondyloathritis Treatment

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KEYWORDS

• Spondyloarthritis • Axial spondyloarthritis • Therapy • Ankylosing spondylitis

KEY POINTS

- Secukinumab, an IL-17 inhibitor, is an effective therapy option for patients with axSpA and has been shown to be associated with decreased radiographic progression of disease.
- Ixekizumab and tofacitinib are approved for treating other forms of inflammatory arthritis and show promise in the treatment of axSpA
- New agents in trials inhibiting IL-17, IL-23, and JAK have shown improved outcomes in axSpA—further trials are needed.

INTRODUCTION

There have been significant developments in the availability of new therapeutic options in axial spondyloarthritis (axSpA) over the last number of years. Different recommendations have been published to reflect this changing landscape. In 2016, the Assessment of SpondyloArthritis International Society/European League Against Rheumatism (ASAS/EULAR) updated their management recommendations for patients with axSpA.[1] More recently, the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (ACR/SPARTAN) have updated their recommendations for the treatment of ankylosing spondylitis (AS) and nonradiographic axSpA.[2]

Recommendation 9 of the ASAS/EULAR recommendations confirms the use of an anti-tumor necrosis factor (TNF) agent for patients with persistent high disease activity despite conventional therapy. A similar recommendation is present in the ACR/SPARTAN guidelines.

The biggest change in the treatment landscape in the last few years has been the development of medications that work on an alternative pathway to the anti-TNF agents. Evidence now suggests that interleukin-17 (IL-17) plays a role as an

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inflammatory mediator in AS. Since 2016, anti-IL-17 medications have also been included in the ASAS/EULAR recommendations for initial biologic therapy in the management of axSpA. Secukinumab is a recombinant, fully human monoclonal anti-human IL-17A antibody of the IgG1/kappa isotype. Secukinumab has been available for the treatment of axSpA patients for the last 3 years. A significant body of evidence exists for the benefit of secukinumab in axSpA across a series of trials—MEASURE 1 to 5 study program[3–6] (**Table 1**).

This series of studies now has 5-year data demonstrating efficacy of secukinumab in axSpA.[7] In addition, the MEASURE 1 study has shown a low rate of radiographic progression in this cohort. In fact, no radiographic progression (modified Stoke Ankylosing Spondylitis Spine Score change from baseline of <2 units) was seen in 79% of patients receiving secukinumab over 4 years.[8]

Recommendation 10 from the ASAS/EULAR Management guidelines suggest that if an anti-TNF therapy fails, switching to another anti-TNF or an anti-IL-17 agent should be considered. The authors go on to say that in patients with a primary nonresponse to the first anti-TNF agent it may be a more rational approach to switch to another class (specifically an anti-IL-17 agent).

NEW TO MARKET TREATMENTS

TNF blockers have been the cornerstone of treatment of axSpA over the last 2 decades. Aside from biological disease-modifying antirheumatic drugs (bDMARDs), new treatments in the form of small-molecule treatments (targeted synthetic DMARDs) are showing promise in this disease area. One of the first targeted synthetic DMARDs being assessed in axSpA is a Janus kinase (JAK) inhibitor—tofacitinib—which preferentially inhibits signaling via JAK 1 and 3. A preliminary phase II study showed 63% of patients receiving 5 mg bd of tofacitinib achieved an ASAS20 response compared with 40% of patients receiving placebo at 12 weeks[9] (**Table 2**). One hundred and sixty-four patients who had baseline MRI and week 12 follow-up MRI scans during this phase II study showed that 18% patients treated with tofacitinib 5 mg bd achieved MIC (minimal important change) for the Spondyloarthritis Research Consortium of Canada (SPARCC) sacroiliac joint and spine scores compared with 0% of patients receiving placebo. There was a trend for greater clinical improvements in the tofacitinib patients who achieved MIC SPARCC scores.[10] Although no treatment-related serious adverse events were identified in the phase II study, the Food and Drug Administration have recently issued a safety alert regarding an increased risk of pulmonary embolism with tofacitinib 10 mg bd in patients with rheumatoid arthritis.

Table 1
MEASURE 4 study outcomes

	Week	Placebo (%)	Secukinumab 150 mg (%)	*P* Value	Secukinumab 150 mg + Loading (%)	*P* Value
ASAS 20	4	39	53.8	*.36*	49.1	*.36*
	16	47	61.5	*.05*	59.5	*.06*
	52	—	72	—	71.7	—
	104	—	77.5	—	74	—
ASAS40	4	17.9	26.5	*.36*	29.3	*.36*
	16	28.2	35.9	*.36*	38.8	*.19*
	52	—	54.1	—	51.3	—
	104	—	58.9	—	51.9	—

Table 2
Comparative Assessment of SpondyloArthritis International Society outcomes in trials for tofacitinib and ixekizumab

	Treatment	Placebo ASAS20 (%)	Tx Group ASAS20 (%)	Tx ASAS40 (%)	Placebo ASAS40 (%)	*P* Value
Tofacitinib						
van der Heijde et al,[9] 2017	2 mg bd	41–	52–	42.30–	20–	<.05
	5 mg bd	—	81–	46.20–	—	<.01
	10 mg bd	—	56–	38.50–	—	<.05
Ixekizumab						
COAST-V trial	q2 weeks	40–	69–	52–	18–	<.0001
	q4 weeks	—	64–	48–	—	<.001
COAST-W trial	q2 weeks	30–	50–	31–	13–	.003
	q4 weeks	—	48–	25	—	.017

Note these are not head to head trials. Tx, Treatment

There is a growing body of evidence suggesting that IL-17 is one of the key cytokines in the pathogenesis of axSpA.[11] As previously stated, secukinumab, a monoclonal antibody against IL-17A, has had market authorization for AS treatment since 2016. Phase III studies have shown good efficacy and are described elsewhere in this review. Ixekizumab, another monoclonal antibody against IL-17A, has approval for the treatment of psoriatic arthritis (PsA). Three phase III studies have assessed the efficacy of ixekizumab in axSpA. The COAST-V study assessed the efficacy of ixekizumab 80 mg every 2 or 4 weeks in patients with AS who were DMARD and TNF naive compared with adalimumab or placebo (see **Table 2**).[12] Fifty two percent of patients receiving 80 mg ixekizumab achieved an ASAS40 response compared with placebo. The COAST-W study specifically assessed the efficacy of ixekizumab 80 mg in patients who either failed or were intolerant to TNF blockers as first-line therapy. Thirty one percent of patients treated with ixekizumab 80 mg every 2 weeks exhibited an ASAS40 response at 16 weeks (**Fig. 1**). The COAST-X study is an ongoing phase III study assessing the efficacy of ixekizumab in bDMARD naive nr-axSpA.[13] Preliminary top line data have shown significant improvements in ASAS40 response in patients treated with ixekizumab at weeks 16 and 52 compared with placebo.

TREATMENTS IN TRIALS

Anti-Interleukin-17

Brodalumab

Brodalumab is a human monoclonal antibody against the IL-17 receptor A. It has previously been shown to be effective in the treatment of psoriasis leading to research in psoriatic arthritis. A phase II, randomized, double-blinded, placebo-controlled study was published in 2014 examined the efficacy and safety profile of brodalumab in psoriatic arthritis.[14] One hundred and sixty eight patients were randomized into 2 treatments arms (brodalumab 140 or 280 mg) and 1 placebo group. Patients were followed to week 12, with an open-label extension up to 5 years. Primary outcome was an ACR20 response at week 12 which was seen in 37% of patients in the 140 mg dose group and 39% ($P = .03$) in the 280 mg dose group ($P = .02$). Secondary outcomes were assessed in the extension period of the trial at week 24, showing ACR20 responses continued to increase and were highest in the 280 mg group than the 140 mg group (64% vs 51%). ACR50 and ACR70 response rates continued to improve through to week 52 in the 140 mg group.

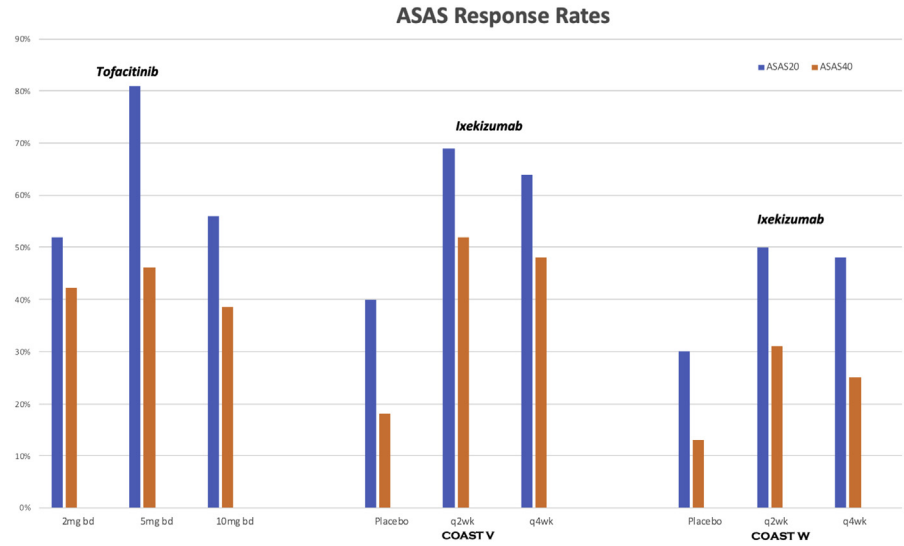

Fig. 1. Comparative ASAS outcomes in trials for tofacitinib and ixekizumab. Note these are not head-to-head trials.

Following this phase III trial, a multicenter, randomized, double-blinded, placebo-controlled study was commenced in axSpA.[15] A total of 159 patients was randomized into a placebo group or a group receiving brodalumab 210 mg and treated at weeks 1, 2, and then every 2 weeks up to week 16. Primary outcome was ASAS40 at week 16, which was found to be higher in the brodalumab group than the placebo group (43.8% vs 24.1%, $P = .018$). Change in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores were also noted in the treatment group, it is unknown if this was statistically significant. Adverse events rate was comparable between the 2 groups, and no suicidal attempts or ideation was noted during the trial period, which had previously been a concern during the drug's development for psoriasis.

Netakimab

Netakimab is a humanized monoclonal antibody targeting IL-17A. Results of a phase II, randomized, placebo-controlled trial was published out of Russia focusing on safety and pharmacokinetics in patients with active AS. Eighty-nine patients were randomized to receive 40, 80, or 120 mg of subcutaneous netakimab or placebo up to week 12. Rates of ASAS20 response in treatment groups (40/80/120 mg) were 73%, 82%, and 91% versus 43% in placebo group. No dose-dependent toxicity or serious adverse events were recorded.[16]

These results led to the development of the phase III, double-blinded, placebo-controlled, randomized ASTERA trial. This 16-week observational study evaluated the effect of netakimab on patient-reported outcomes in patients with radiographic axSpA up to 16 weeks. ASAS40 response rates at week 16 were superior in the netakimab group compared with the placebo group (40% vs 2.6%; $P<.0001$).[17] Results also demonstrated significant improvement in BASDAI, BASFI, Work Productivity and Activity Impairment response compared with placebo at week 16 ($P<.0001$).[18] Further analysis of the ASTERA patients focused on spinal and sacroiliac inflammation as seen on MRI at baseline and at week 16. Significant improvements with treatment in the Berlin spine score ($P<.0001$) and

SPARCC score ($P<.01$) were found in the netakimab group compared with the placebo group.[19] Plans for an extension trial to collect data up to 52 weeks are ongoing.

Bimekizumab

Bimekizumab is a monoclonal antibody targeting both IL-17A and IL-17F. Initially trialled in psoriasis, recent trials have been focusing on axSpA. A phase IIb, randomized, double-blind, placebo-controlled, dose-ranging study was done on 303 patients with active AS to assess efficacy and safety.[20] Primary outcome was an ASAS40 dose-response relationship at week 12, which was achieved ($P<.01$) in this study. Significantly more bimekizumab patients achieved ASAS40 at week 12 than placebo across all doses ($P<.05$). Patients in the treatment arm also had greater reductions in their BASDAI and AS Disease Activity Score (ASDAS) based on C-reactive protein than those in the placebo arm ($P<.001$). Similar rates of adverse events were noted in both groups.

Following on from this, a phase IIb, randomized, double-blind, placebo-controlled, dose-ranging study was carried out to assess the impact of bimekizumab on quality of life and patient-reported outcomes[21] in patients with active AS. This 48-week study included 303 patients with active AS randomized into treatment and placebo groups. BASDAI 50 at week 12 was achieved by 23.7% to 47.5% of patients in the treatment group versus 11.9% in the placebo group. All treatment dose groups also reported greater reductions in BASDAI, BASFI, Ankylosing Spondylitis Quality of Life Scale (ASQoL), and Patient's Global Assessment of Disease Activity compared with the placebo group at week 12. Rates of adverse events were similar in both groups.

Anti-Interleukin-23

Guselkumab

Guselkumab is an IgG1 monoclonal antibody that selectively binds to the p19 subunit of IL-23, resulting in inhibition of IL-23 signaling. Several phase III trials have demonstrated guselkumab's efficacy in psoriasis, leading to the development of trials in PsA of which there are currently results available for 2 phase II trials. The randomized phase II trial with guselkumab in PsA patients showed significant improvement in composite indices of disease activity at week 24 compared with placebo.[22] The other trial was a randomized, phase II, placebo-controlled trial, which showed a significant decrease of Routine Assessment of Patient Index Data 3 scores in the guselkumab group at week 24 compared with placebo.[23] Further pharmacodynamic studies have also demonstrated that treatment with guselkumab resulted in rapid reduction in IL-17A and IL-17F. IL-17F changes at weeks 4 and 16 were significantly associated with ACR20 responses at week 24, and IL-17A changes at week 4 and 16 were associated with PASI75 response at week 24 in the guselkumab group.

Tildrakizumab

Tildrakizumab is an IL-23 inhibitor with an anti-p19mAb blocking mechanism. This has been shown to be of therapeutic benefit in psoriasis, which has led to trials in both PsA and axSpA. Both studies are randomized, double-blinded, placebo-controlled phase IIa studies evaluating both efficacy and safety of tildrakizumab. The axSpA trial's primary outcome is to achieve a 40% improvement in a visual analogue scale score from baseline to 24 weeks with a secondary endpoint at 52 weeks.[24] Although the study is now completed, no results are currently available.

Janus Kinase Inhibitors

Filgotinib

Filgotinib is an oral selective JAK 1 inhibitor that has been theorized to have potential therapeutic benefits in many autoimmune conditions. TORTUGA was the first

randomized, placebo-controlled, phase II study to examine the efficacy of filgotinib in patients with active radiographic AS.[25] This study recruited 116 adult patients with AS with an inadequate response or intolerance to nonsteroidal anti-inflammatory drugs. Patients were required to have active AS at the time of study commencement for inclusion. The treatment arm received filgotinib 200 mg once daily for a total of 12 weeks. The primary endpoint of change in ASDAS from baseline to week 12 was higher in the filgotinib group (−1.47) than in the placebo arm (−0.57) with a mean difference between groups of −0.87 (P<.001). In the filgotinib group (n = 58) versus placebo the following outcomes were achieved at week 12: ASAS20 = 76% versus 40%; ASAS40 = 38% versus 19%; ASAS partial remission 12% versus 3%. Significant improvements in ASQoL, BASDAI, BASFI, Bath Ankylosing Spondylitis Metrology Index (BASMI), SPARCC spine and sacroiliac joint scores were noted in the treatment group compared with the placebo group.

The EQUATOR trial was a randomized, double-blinded, placebo-controlled, phase II trial investigating the efficacy and safety profile of filgotinib in patients with active psoriatic arthritis.[26] Those recruited had previously failed or shown intolerance of at least 1 conventional DMARD before study commencement. The primary endpoint was ACR20 at week 16, which was reached by 80% of the treatment group and 33% of placebo group (P<.001). The filgotinib group also demonstrated significantly higher rates of achieving secondary outcomes compared with the placebo group: ACR50 = 48% versus 15%; ACR70 23% versus 6%. No significant difference was detected in rates of adverse events.

Upadacitinib

Upadacitinib is another selective JAK1 inhibitor that has shown efficacy in rheumatoid arthritis. At present there is a phase IIb/III randomized, double-blind, placebo-controlled trial ongoing.[27] This trial is evaluating both efficacy and safety profile in active radiographic axSpA with a primary endpoint of ASAS40 response at week 14. This trial is due to be completed in November 2020.

Unsuccessful Treatments in Axial Spondyloarthritis

Abatacept

Abatacept is a cytotoxic T-lymphocyte–associated antigen 4 immunoglobulin that has been shown to selectively modulate CD80 costimulatory signaling needed for full T-cell activation. A phase II, prospective, open-label study was carried out in patients with active AS.[28] The primary outcome of ASAS40 at week 24 was seen in 13% of anti-TNF-naive patients and no patients in the anti-TNF failure group, with ASAS20 achieved by only 27% and 20% in the respective groups. At week 24 no significant change was detected in BASDAI or ASDAS in either group.

Tocilizumab

Tocilizumab is a humanized monoclonal antibody that binds to IL-6 receptors. BUILDER-1 was a 2-part, phase II/III trial assessing tocilizumab in patients with AS naive to anti-TNF therapy.[29] Patients were randomized into tocilizumab 8 mg/kg or placebo for 12 weeks. ASAS20 response rates at week 12 were similar between treatment and placebo groups (P = .28), as was ASAS40 response rates (P = .27). The BUILDER-2 trial was planned to be a phase III study on patients with inadequate response to anti-TNF treatment, however this was terminated due to failure of BUILDER-1 to achieve its primary endpoint.

Apremilast

A phase II, double-blind, placebo-controlled, single-center study was carried out in patients with active radiographic axSpA treated with an oral phosphodiesterase

4 inhibitor, apremilast.[30] Patients in the treatment arm achieved higher improvements in BASDAI, BASFI, and BASMI scores at week 12; however, results were not statistically significant. The POSTURE trial was then commenced, which was a phase III, multicenter, randomized, double-blind, placebo-controlled, parallel group study evaluating apremilast in the treatment of active radiographic axSpA.[31] The treatment group failed to achieve a superior ASAS20 response rate at week 16 over placebo and the study was terminated.

Ustekinemab

This humanized monoclonal antibody against the p40 subunit of IL-12 and IL-23 was used in a proof-of-concept study in patients with active AS.[32] Sixty-five percent of patients treated achieved ASAS40 response at week 24, with 75% achieving ASAS20. Three trials of ustekinemab were developed to evaluate efficacy in axSpA.[33] Because of the failure of the first study to achieve its primary endpoint of ASAS40 response at week 24 in the treatment group, studies 2 and 3 were discontinued.

Risankizumab

Risankizumab is a humanized monoclonal antibody against the p19 subunit of IL-23. A phase II, randomized, double-blind, placebo-controlled study was commenced in active patients with AS.[34] Treatment groups did not demonstrate significantly higher proportions of ASAS40 response over placebo leading to trial discontinuation.

SUMMARY

Significant advances have been made in the treatment of axSpA. Improved understanding of the IL-17 pathway has led to the development many medications, including secukinumab, which has been shown to improve patient outcomes in addition to decreasing radiographic progression. Ongoing drug development is focused on the IL-17/IL-23 pathway and JAK inhibitors at present. As the evidence for these medications grow, treatment guidelines will eventually be adjusted to reflect the changing treatment options. This increased range of therapies provides clinicians with greater opportunity to treat axSpA as effectively as possible.

DISCLOSURE

The authors have nothing to disclose.

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