Review Article

Biologics and biosimilars in axial spondyloarthritis: Lots of kids on the block!

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Abstract

The management of axial spondyloarthritis (axSpA) has been completely transformed since the introduction of biologic therapies. Tumor necrosis factor inhibitors (TNFis) were the first effective drug therapies in people affected with axSpA who had previously failed to respond to nonsteroidal anti-inflammatory drugs. Currently, there are five TNFis licensed for the treatment of established axSpA, traditionally known as ankylosing spondylitis or radiographic axSpA, with four of them also available for use in the nonradiographic axSpA disease group. More recent developments comprise new drugs designed to block the interleukin-17 or JAK inflammatory pathways. The high cost associated to these drugs has been the main limiting factor for their use and availability at global level, a problem that will, in part, be addressed with the recent introduction of biosimilars, with comparable efficacy and safety profile at lower cost. The fast arrival of so many "kids on the block" poses many challenges for the clinician in order to choose the right drug for each patient and brings the need for feasible, well-validated biomarkers of treatment response to the forefront of research in axSpA.

Key Words: *Axial spondyloarthritis, biologics, biosimilars, management*

Introduction

The advent of biologic therapies for the treatment of axial spondyloarthritis (axSpA) two decades ago completely changed the outlook of this disease which for the first time benefited from specifically developed targeted therapies. Until then, nonsteroidal anti-inflammatory drugs (NSAIDs) were the only treatment available for axSpA, since conventional synthetic disease-modifying antirheumatic drugs (sDMARDs) are not effective in this condition. Several treatment trials of TNF inhibitors (TNFis) in patients with AS were published after 2000, showing significant improvements in clinical symptoms, C-reactive protein (CRP) levels, and magnetic resonance imaging (MRI)-detectable inflammation in the sacroiliac joints (SIJs) or spine. The level of efficacy of TNFi in patients with AS in whom conventional therapies had failed was seen as a breakthrough in the treatment of this disease.

Biosimilar medicines are developed in order to provide alternative products, usually at a lower cost than the original biological agents. Biosimilars are recognized to be a highly similar version of a biological drug and should have comparable quality, safety, and effectiveness.

Newer therapies for axSpA developed in recent years include interleukin-17 (IL-17) inhibitors and JAK inhibitors (JAKis), contributing to enhance the already richly populated treatment armamentarium available in axSpA.

Tumor Necrosis Factor-Alpha Inhibitor Therapies

Tumor necrosis factor (TNF)-alpha is a bioactive cytokine that plays a crucial role in the inflammatory and pain pathways. Inhibition of TNF can decrease the inflammatory response, and this approach has been used in the treatment of autoimmune and autoinflammatory conditions including rheumatoid arthritis (RA), psoriasis, and psoriatic arthritis. Over the last two decades, five TNFi agents have been successfully introduced in the treatment of axSpA: a mouse–human chimeric monoclonal antibody (mAb) to TNF (infliximab), two human monoclonal

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antibodies to TNF (adalimumab [ADA] and golimumab), a humanized Fab fragment of anti-TNF linked to polyethylene glycol (certolizumab), and a soluble recombinant form of the TNF cellular receptor (etanercept) which, on binding, blocks the activity of TNF. All of them are currently approved for the treatment of radiographic axSpA (r-axSpA), traditionally known as ankylosing spondylitis (AS), while four of them (ADA, certolizumab, etanercept, and golimumab) are also licensed for use in the nonradiographic disease group (nonradiographic axSpA [nr-axSpA]) in many countries around the world. Infliximab has also been evaluated in patients with early axSpA[1] and nr-axSpA.[2]

According to the ASAS/EULAR recommendations, TNFis are considered in patients with axSpA who have active disease despite having received conventional treatment.[3] These conventional therapies are limited to NSAIDs, as sDMARDs such as methotrexate or sulfasalazine commonly used in other inflammatory arthritis, are of no proven efficacy. On average, a therapeutic trial of NSAIDs is expected to encompass at least two different NSAIDs, given for a minimum of 4 weeks.

The clinical efficacy of TNFi was initially demonstrated in r-axSpA (AS).[4-8] Overall, TNFi showed a significant improvement in clinical, laboratory, and imaging parameters of disease activity evaluated on randomized, placebo-controlled Phase III and IV trials.[4-8] The rates of response of clinical parameters such as the ASAS20 and ASAS40 criteria in AS (r-axSpA) ranged between 57%–64% and 40%–50%, respectively, as compared to 19%–37% and 15%–19%, respectively, in the placebo groups.[4-8] A Cochrane analysis published in 2015 including 18 randomized, controlled trials in AS (r-axSpA) concluded that patients treated by TNFi were three to four times more likely to achieve an ASAS40 response at 6 months.[9] This analysis also showed improvements in physical function and spinal inflammation as evaluated by the MRI Spondyloarthritis Research Consortium of Canada (SPARCC) score.[10]

Following the publication of the ASAS classification criteria in 2009, clinical trials were specifically designed for the nr-axSpA group[5,11-13] confirming results seen in the earlier trials in AS, demonstrating the clinical efficacy of the different TNFi agents when compared to placebo.[5,11-13] However, entry criteria differed between studies, and it was soon observed that for ADA, etanercept, and golimumab, results were only significant for patients with objective signs of inflammation, that is, patients with elevated serum CRP levels or evidence of inflammation on SIJ MRI.[11-13] Indeed, no difference in the primary outcome was observed between the TNFi arm (ADA, etanercept, or golimumab) and placebo for the patients who were CRP negative and did not have objective MRI inflammation at inclusion. Other studies, such as the RAPID axSpA study, consequently included only subjects with objective evidence of inflammation which included either an elevated CRP or the presence of bone edema at the SIJ on MRI.[5,14]

One area of interest has been to explore whether the r-axSpA and nr-axSpA disease groups differ in their response to TNFi. Indeed, a recent systematic literature review analyzed the results of clinical trials for the full spectrum of the disease, including studies performed in nr-axSpA[15] confirming the treatment effect for both the radiographic and nonradiographic forms of axSpA, with ASAS40 response rates between 44.5% and 47.7% for radiographic, and between 33.3% and 61% for nr-axSpA, respectively. The number needed to treat (NNT) was similar between the two groups (r-axSpA: 2.6–5.2 and nr-axSpA: 2.3–5.4). While specific trials were conducted for ADA, etanercept, and golimumab in nr-axSpA, only one clinical trial, the RAPID-axSpA study,[5] included patients with both AS and nr-axSpA, showing a similar response rate to certolizumab in both the groups.

Long-Term Efficacy of Tumor Necrosis Factor Inhibitor in Axial Spondyloarthritis

Long-term response to TNFi was maintained in AS with a rate of ASAS20 responders of 82% at 5 years.[16] Similarly, response was also maintained in nr-axSpA: in the long-term extension analysis of the RAPID axSpA trial, where ASAS40 response at week 96 was equivalent between patients with AS and nr-axSpA.[17]

Predictors of Response to Tumor Necrosis Factor Inhibitor Therapy in Axial Spondyloarthritis

Post hoc analysis of earlier studies in r-axSpA/AS identified young age, short disease duration, male sex, elevated CRP, low Bath AS Functional Index, active inflammation on SIJ MRI, and also the absence of smoking[18-20] as the best predictors for a significant treatment response. Added to that, no previous exposure to biologics was also shown to be a predictor of response in the RHAPSODY study.[21] As mentioned, subsequent studies in the nr-axSpA disease group confirmed CRP and active MRI inflammation as the best predictors of a good response[13] and their presence is now mandatory for the use of TNFi in this patient category as reflected in the different treatment indication. Radiographic sacroiliitis (at least Grade 2 bilaterally or Grade 3 unilaterally according to the modified New York criteria) in r-axSpA/AS is sufficient to initiate a TNFi, hence the EULAR recommendation outline taking into account the CRP and MRI (if available) to aid the decision-making process in order to start a TNFi.[3]

Effect of Treatment with Tumor Necrosis Factor Inhibitors in Radiographic Progression

TNFis are effective in controlling symptoms of active axSpA in several RCTs, as described above. In the context

of axSpA, the "perfect" therapy would ideally lead to full remission of symptoms and signs of disease, hence avoiding any spinal deformity by halting disease progression as shown by radiographic damage, i.e. development of spinal syndesmophytes or sclerosis, erosions, or ankylosis at the SIJ level. Current data obtained from MRI studies show that most of the available TNFi drugs have a significant effect on reducing inflammation in the spine and SIJs in axSpA.[22] This reported effect becomes evident from week 12 and is maintained on long-term use.[22]

The link between spinal inflammatory lesions and future development of syndesmophytes has been investigated in several randomized controlled trials (RCTs). Overall, and regardless of the TNFi agent studied, a relationship has been shown between inflammation in the vertebral bodies and the subsequent development of new formation or syndesmophytes at the same level in the spine. A syndesmophyte is more likely to develop from a prior inflammatory lesion, supporting a relationship between inflammation and ankylosis.[23] A higher risk for future development of new bone formation was also suggested with the simultaneous presence of inflammation and fat deposition,[24,25] with some studies reporting a paradoxical increase in new bone formation after the improvement of vertebral corner inflammation.[26] However, data also suggest that nearly 60% of newly developed syndesmophytes had neither inflammatory nor fatty lesions on baseline assessment[24] which is likely the result of the cross-sectional nature of these reports. Further, incomplete suppression of inflammation (elevated CRP or positive SIJ MRI) in patients with AS appears to be a relevant factor for new bone formation.[14]

Interestingly, there appears to be a higher progression rate in patients who delayed starting TNFi for more than 10 years than those who started earlier,[27] suggesting that treatment response appears enhanced with shorter disease duration. Although taken together, the available data, including real-life cohorts, suggest an effect of TNFi in slowing down disease progression as shown by radiographic outcomes,[28] it remains to be shown whether complete ablation of disease progression can be achieved. Recent studies performed in the nr-axSpA disease group suggest that radiographic progression of spinal lesions is, overall, low in nr-axSpA,[29] and new data coming from studies performed in nr-axSpA with shorter disease duration are expected to confirm these results.

Interleukin-17 Inhibitor Therapies

Circulating IL-17A secreted by specialized lymphocytes (T helper-17 cells, IL-17-producing CD8(+) T-cells, gamma delta T-cells, and type 3 innate lymphoid cells)[30] has been found to be elevated in AS compared to healthy controls, which added to the rationale for the development of treatments targeting IL-17A in SpA.[31] There are currently two IL-17A inhibitors: secukinumab and ixekizumab (IXE), being specifically studied in r-axSpA/AS.

The first results of a proof-of-concept trial of secukinumab in r-axSpA/AS were confirmed by two large, placebo-controlled trials: the MEASURE1 and MEASURE2 studies.[32] These trials included patients who were TNFi naïve or who had previously failed to respond to a TNFi. Secukinumab 150 mg administered subcutaneously proved to be effective in both studies, showing ASAS40 response rates of 42% and 32% (NNT: 3.4 and 4) in MEASURE1 and MEASURE2, respectively. The effective dose was 150 mg, while a lower dose (75 mg) gave positive results only after an IV loading dose in MEASURE1. Secukinumab demonstrated better results in TNFi-naïve patients when compared to TNFi-experienced patients, but positive effects were also seen for these latter patients: ASAS40 43.2% versus 25%, respectively.[33] Finally, secukinumab yielded a sustained response in the long-term follow-up of MEASURE2, with 70.1% and 60.9% of patients maintaining an ASAS20 and ASAS40 response at 3 years with the 150 mg dose.[34] Secukinumab has also been shown to reduce MRI spinal inflammation early after its first administration in patients with AS, with a sustained resolution of inflammation during continuous administration every 4 weeks up to week 94.[35]

IXE is another anti-IL-17A agent and its efficacy in r-axSpA/AS was demonstrated in two large, placebo-controlled trials. In the COAST-V trial, patients with r-axSpA/AS and inadequate response or intolerance to NSAIDs were randomized to receive either IXE 80 mg subcutaneously every 2 weeks (Q2W) or every 4 weeks (Q4W) or placebo.[36] This trial had an active reference arm with ADA at the usual dose of 40 mg SC Q2W. All patients were TNFi naïve. At weeks 16 and 52, the rate of ASAS40 responders was 52% and 51% (IXE QW2), 48% and 53% (IXE Q4W), 36% and 51% (ADA/IXE), and 19% and 47% (PBO/IXE). The second study, COAST-W, included patients with active AS and prior inadequate response to at least one TNFi. The study had a similar design to the COAST-V trial, except that there was no active TNFi arm. Again, at weeks 16 and 52, there was a significantly higher proportion of ASAS40 responders (primary criterion) in both IXE arms (80 mg Q2W and Q4W) compared to placebo (31% and 31% IXE Q2W, 25% and 34% IXE Q4W, and 14% and 39% PBO/IXE, respectively).[37] As reported for secukinumab, the response rate was lower in patients previously exposed to TNFi than in TNFi-naïve patients.

Both agents have recently been trialed in the nr-axSpA disease groups with preliminary data at 16 weeks showing benefit of secukinumab in the PREVENT study, data presented in the 2019 ACR annual meeting in Atlanta, and IXE in the COAST-X study, with ASAS40 at week 16 of 35% for IXE Q4W, 40% for IXE Q2W, and 19% for placebo and ASAS40 at week 52 of 30% for IXE Q4W, 31% for IXE Q2W, and 13% for placebo.[38]

Considering the significant role of Th17 cells in driving entheseal inflammation, the expectations that IL-17 inhibition can decrease radiographic progression are high. Preliminary results from MEASURE1 show a positive effect from secukinumab in reducing radiographic progression in AS.[39] More data are expected from long-term follow-up of clinical trials and real-life use of IL-17A inhibitors in axSpA.

Bimekizumab, a humanized monoclonal IgG1 antibody that selectively inhibits both IL17-A and IL17-F, has shown promising results in a Phase IIb trial in AS. At week 12 (primary endpoint), up to 47% of patients on bimekizumab achieved ASAS40 response, compared to 13% in the placebo arm.[40] Phase III trials in r-axSpA and nr-axSpA are currently recruiting.

JAK Inhibitors

Activation of JAK pathways stimulates the expression of survival factors, cytokines, chemokines, and other molecules that facilitate leukocyte cellular trafficking and cell proliferation, contributing to inflammatory and autoimmune disorders. Hence, the JAK family has evoked considerable interest for the potential treatment of inflammatory diseases, leading to the development of various JAKis with different selectivity profiles against JAK1, JAK2, JAK3, and nonreceptor tyrosine-protein kinase TYK2.[41]

Tofacitinib is a first-in-class pan-JAKi with potent inhibition of JAK3 and JAK1 and minor inhibition of JAK2. It interrupts the signal transduction of cytokines that contribute to the aberrant immune response in AS/r-axSpA. In a 16-week Phase II study, 200 patients with active AS/r-axSpA were randomized to receive one of the three doses of tofacitinib (2, 5, or 10 mg), or placebo, twice daily for 12 weeks, with 4 weeks of follow-up.[42] Patients were assessed by MRI at baseline and after 12 weeks of treatment. A higher proportion of patients receiving tofacitinib 10 mg twice daily experienced an ASAS20 response than those taking tofacitinib 5 or 2 mg or placebo. Improvements in other clinical measures, including ASAS40, AS Disease Activity Score with CRP, and Bath AS Disease Activity Index-50, were comparable for placebo and all tofacitinib doses. The 5- and 10-mg regimens resulted in significantly improved SPARCC SIJ and spine scores from baseline to week 12, compared with placebo. The 12-week safety profile was similar to that reported for tofacitinib studies in other indications, and no new safety signals or concerns were identified. Dose-dependent laboratory measures also appeared normal, resolving back to baseline values by week 16 of treatment. Tofacitinib 5 and 10 mg twice daily demonstrated greater clinical and imaging efficacy than placebo in reducing the signs and symptoms of disease in adults with active AS/r-axSpA.[42] These results suggest that JAK inhibition may present a new mode of action for managing AS and could add to the currently limited treatment options; however, more trials are needed to adequately evaluate the treatment effect of JAKis in AS (r-axSpA).

Biosimilars

Biosimilars are biologic medicinal products that contain a version of the active substance of an already authorized original biologic drug. For biosimilar drug approval, data must be generated to establish whether a biosimilar can safely and effectively be used instead of the originator product.[43] Similarity to the reference product in terms of quality characteristics, biologic activity, efficacy, and safety must be established before biosimilar products can be marketed in the USA, Europe, or other regulated countries. Numerous batches of the innovator reference product are routinely tested to establish the characteristic range. Manufacturers must provide high-quality evidence of similar efficacy and safety outcomes, including a comprehensive immunogenicity assessment to satisfy the stringent requirements for the European Medicines Agency (EMA) and Food and Drug Administration (FDA) approval.[43]

Several biosimilars to TNFi are now available for the treatment of AS/r-axSpA. Infliximab biosimilar was the first EU-approved mAb biosimilar, obtaining market authorization in September 2013 for all approved indications of the innovator drug. In November 2015, the EMA recommended marketing approval for an etanercept biosimilar for the treatment of AS/r-axSpA, and in July 2016, the FDA approved biosimilar of ADA to treat AS/r-axSpA.

Although highly efficacious, biologic therapy for chronic inflammatory disease is expensive. The expectation among patients, treating physicians, and health-care providers is that biosimilars should be equal or highly similar in efficacy, comparable in safety, including immunogenicity, but lower in price than their reference products. The introduction of biosimilars can help expand access to safe and effective treatment options for clinicians and patients.

Drug Tapering

A highly relevant clinical question for patients and clinicians alike is whether long-term biologic therapy can be tapered, discontinued, or even stopped. To date, there are a limited number of studies that have addressed this. Long-term extensions of existing cohorts treated with TNFi have shown that although achieving a state of remission is possible,[5,11,44,45] symptom relapse can occur after TNFi treatment discontinuation.[46] For instance, 97% of patients in one study relapsed when infliximab was discontinued after 3 years of continuous treatment although retreatment with infliximab was safe and resulted in clinical improvement in all patients to a state similar to that before the treatment was stopped.[46] However, a

recent study, ABILITY-3,[47] showed that in patients with nr-axSpA who achieved sustained remission with ADA, a substantial number (43%) who flared after treatment withdrawal did not regain a state of inactive disease after retreatment with ADA. Regarding tapering, successful results with TNFi have been published without substantial relapse.[48,49] Therefore, identifying predictors for the axSpA patient population in whom these treatment strategies can be safely applied is an important research goal.

Scenario in Asian Countries

Biologics and biosimilar drugs have been used increasingly in the Asian countries such as India, China, and Japan, with much cheaper cost and better outcome. Long-term data have not been published yet, and observational studies suggest that the most common biologic prescribed was etanercept. The most common indication for biologics was for the spondyloarthropathy group of disorders. However, other biosimilar drugs are being increasingly used as their availability has become better.[50,51] In a study on Chinese patients with RA, etanercept was used by 66.6% (including Yi Sai Pu® 58.1%, Enbrel® 6.1%, and Qiangke® 2.4%) patients. Tocilizumab, ADA, and infliximab were used by 17.0%, 7.5%, and 6.6% of patients, respectively.[52] Japanese insurance database suggests a wide variance in using biologics for RA.[53]

Conclusions

The last 20 years has seen outstanding progress in the therapeutics of axSpA alongside growing knowledge in the diagnosis and characterization of this disease. The new biologic drugs have proven efficacious and safe therapies that can contribute significant long-term benefits in disease activity control, reduced rate of disease progression, and enhanced quality of life in a substantial proportion of affected individuals. The advent of newer agents, with different mechanisms of action and alternative routes of administration, has contributed to expand the current drug armamentarium. Yet, the challenge remains to allow for "the right treatment to be given to the right patient at the right time." A deeper understanding of pathogenesis and natural history of the disease, together with biomarkers for disease response and progression, remain key research challenges in axSpA for the next decade and beyond.

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Conflicts of interest

There are no conflicts of interest.

References

1. Sieper J, Lenaerts J, Wollenhaupt J, Rudwaleit M, Mazurov VI, Myasoutova L, *et al*. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: Results from the double-blind, placebo-controlled INFAST study, Part 1. Ann Rheum Dis 2014;73:101-7.
2. Barkham N, Keen HI, Coates LC, O'Connor P, Hensor E, Fraser AD, *et al*. Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. Arthritis Rheum 2009;60:946-54.
3. van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, *et al*. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017;76:978-91.
4. van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J, *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.
5. Landewé R, Braun J, Deodhar A, Dougados M, Maksymowych WP, Mease PJ, *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.
6. Davis JC Jr., Van Der Heijde D, Braun J, Dougados M, Cush J, Clegg DO, *et al*. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum 2003;48:3230-6.
7. Inman RD, Davis JC Jr., Heijde DV, Diekman L, Sieper J, Kim SI, *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.
8. van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson 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.
9. Maxwell LJ, Zochling J, Boonen A, Singh JA, Veras MM, Tanjong Ghogomu E, *et al*. TNF-alpha inhibitors for ankylosing spondylitis. Cochrane Database Syst Rev 2015;4:CD005468.
10. Toussirot E. Pharmacological management of axial spondyloarthritis in adults. Expert Opin Pharmacother 2019;20:1483-91.
11. Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA, *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.
12. Dougados M, van der Heijde D, Sieper J, Braun J, Maksymowych WP, Citera G, *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.
13. Sieper J, van der Heijde D, Dougados M, Maksymowych WP,

Scott BB, Boice JA, *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.

14. Braun J, Baraliakos X, Hermann KG, Xu S, Hsu B. Serum C-reactive Protein Levels Demonstrate Predictive Value for Radiographic and Magnetic Resonance Imaging Outcomes in Patients with Active Ankylosing Spondylitis Treated with Golimumab. J Rheumatol 2016;43:1704-12.
15. Sepriano A, Regel A, van der Heijde D, Braun J, Baraliakos X, Landewé R, *et al*. Efficacy and safety of biological and targeted-synthetic DMARDs: A systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. RMD Open 2017;3:e000396.
16. Braun J, Baraliakos X, Listing J, Fritz C, Alten R, Burmester G, *et al*. Persistent clinical efficacy and safety of anti-tumour necrosis factor alpha therapy with infliximab in patients with ankylosing spondylitis over 5 years: Evidence for different types of response. Ann Rheum Dis 2008;67:340-5.
17. Sieper J, Landewé R, Rudwaleit M, van der Heijde D, Dougados M, Mease PJ, *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.
18. Rudwaleit M, Listing J, Brandt J, Braun J, Sieper J. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. Ann Rheum Dis 2004;63:665-70.
19. Rudwaleit M, Schwarzlose S, Hilgert ES, Listing J, Braun J, Sieper J. MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. Ann Rheum Dis 2008;67:1276-81.
20. Chung HY, Machado P, van der Heijde D, D'Agostino MA, Dougados M. Smokers in early axial spondyloarthritis have earlier disease onset, more disease activity, inflammation and damage, and poorer function and health-related quality of life: Results from the DESIR cohort. Ann Rheum Dis 2012;71:809-16.
21. Rudwaleit M, Claudepierre P, Wordsworth P, Cortina EL, Sieper J, Kron M, *et al*. Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. J Rheumatol 2009;36:801-8.
22. Sari I, Haroon N. Disease modification in axial spondyloarthritis. Best Pract Res Clin Rheumatol 2018;32:427-39.
23. Maksymowych WP, Chiowchanwisawakit P, Clare T, Pedersen SJ, Østergaard M, Lambert RG. Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: Evidence of a relationship between inflammation and new bone formation. Arthritis Rheum 2009;60:93-102.
24. Baraliakos X, Heldmann F, Callhoff J, Listing J, Appelboom T, Brandt J, *et al*. Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. Ann Rheum Dis 2014;73:1819-25.
25. Machado PM, Baraliakos X, van der Heijde D, Braun J, Landewé R. MRI vertebral corner inflammation followed by fat deposition is the strongest contributor to the development of new bone at the same vertebral corner: A multilevel longitudinal analysis in patients with ankylosing spondylitis. Ann Rheum Dis 2016;75:1486-93.
26. Pedersen SJ, Chiowchanwisawakit P, Lambert RG, Østergaard M, Maksymowych WP. Resolution of inflammation following treatment of ankylosing spondylitis is associated with new bone formation. J Rheumatol 2011;38:1349-54.
27. Haroon N, Inman RD, Learch TJ, Weisman MH, Lee M, Rahbar MH, *et al*. The impact of tumor necrosis factor α inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum 2013;65:2645-54.
28. Maas F, Arends S, Wink FR, Bos R, Bootsma H, Brouwer E, *et al*. Ankylosing spondylitis patients at risk of poor radiographic outcome show diminishing spinal radiographic progression during long-term treatment with TNF-α inhibitors. PLoS One 2017;12:e0177231.
29. Protopopov M, Poddubnyy D. Radiographic progression in non-radiographic axial spondyloarthritis. Expert Rev Clin Immunol 2018;14:525-33.
30. Bridgewood C, Watad A, Cuthbert RJ, McGonagle D. Spondyloarthritis: New insights into clinical aspects, translational immunology and therapeutics. Curr Opin Rheumatol 2018;30:526-32.
31. Shen H, Goodall JC, Hill Gaston JS. Frequency and phenotype of peripheral blood Th17 cells in ankylosing spondylitis and rheumatoid arthritis. Arthritis Rheum 2009;60:1647-56.
32. Baeten D, Sieper J, Braun J, Baraliakos X, Dougados M, Emery P, *et al*. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med 2015;373:2534-48.
33. Sieper J, Deodhar A, Marzo-Ortega H, Aelion JA, Blanco R, Jui-Cheng T, *et al*. Secukinumab efficacy in anti-TNF-naive and anti-TNF-experienced subjects with active ankylosing spondylitis: Results from the MEASURE 2 Study. Ann Rheum Dis 2017;76:571-92.
34. Marzo-Ortega H, Sieper J, Kivitz A, Blanco R, Cohen M, Delicha EM, *et al*. Secukinumab provides sustained improvements in the signs and symptoms of active ankylosing spondylitis with high retention rate: 3-year results from the phase III trial, MEASURE 2. RMD Open 2017;3:e000592.
35. Baraliakos X, Borah B, Braun J, Baeten D, Laurent D, Sieper J, *et al*. Long-term effects of secukinumab on MRI findings in relation to clinical efficacy in subjects with active ankylosing spondylitis: an observational study. Ann Rheum Dis 2016;75:408-12.
36. van der Heijde D, Cheng-Chung Wei J, Dougados M, Mease P, Deodhar A, Maksymowych WP, *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.
37. Dougados M, Wei JC, Landewe R, Sieper J, Baraliakos X, Van den Bosch F, *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). Annals of the Rheumatic Diseases 2020;79:176-85.
38. Deodhar A, van der Heijde D, Gensler LS, Kim TH, Maksymowych WP, Østergaard M, *et al*. Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): A randomised, placebo-controlled trial. Lancet 2020;395:53-64.
39. Braun J, Baraliakos X, Deodhar A, Baeten D, Sieper J, Emery P, *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.
40. van der Heijde D, Gensler LS, Deodhar A, Baraliakos X, Poddubnyy D, Farmer MK, *et al*. Dual neutralisation of IL-17A and IL-17F with bimekizumab in patients with active ankylosing spondylitis (AS): 12-week results from a phase 2b, randomised,

double-blind, placebo-controlled, dose-ranging study (abstract no. LB0001). Ann Rheum Dis 2018;77 Suppl: A70.

41. Tahir H. Therapies in ankylosing spondylitis-from clinical trials to clinical practice. Rheumatology (Oxford) 2018;57:vi23-8.
42. van der Heijde D, Deodhar A, Wei JC, Drescher E, Fleishaker D, Hendrikx T, *et al*. Tofacitinib in patients with ankylosing spondylitis: A phase II, 16-week, randomised, placebo-controlled, dose-ranging study. Ann Rheum Dis 2017;76:1340-7.
43. Jacobs I, Petersel D, Isakov L, Lula S, Lea Sewell K. Biosimilars for the Treatment of Chronic Inflammatory Diseases: A Systematic Review of Published Evidence. BioDrugs 2016;30:525-70.
44. Spadaro A, Lubrano E, Marchesoni A, D'Angelo S, Ramonda R, Addimanda O, *et al*. Remission in ankylosing spondylitis treated with anti-TNF-α drugs: a national multicentre study. Rheumatology (Oxford) 2013;52:1914-9.
45. Lubrano E, Perrotta FM, Marchesoni A, D'Angelo S, Ramonda R, Addimanda O, *et al*. Remission in nonradiographic axial spondyloarthritis treated with anti-tumor necrosis factor-α drugs: An Italian multicenter study. J Rheumatol 2015;42:258-63.
46. Baraliakos X, Listing J, Brandt J, Zink A, Alten R, Burmester G, *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.
47. Landewé R, Sieper J, Mease P, Inman RD, Lambert RG, Deodhar A, *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.
48. Gratacos J, Pontes C, Juanola X, Sanz J, Torres F, Avendano C, *et al*. Non-inferiority of dose reduction versus standard dosing of TNF-inhibitors in axial spondyloarthritis. Arthritis Res Ther 2019;21:11.
49. Park JW, Kim HA, Shin K, Park YB, Kim TH, Song YW, *et al*. Effects of tapering tumor necrosis factor inhibitor on the achievement of inactive disease in patients with axial spondyloarthritis: A nationwide cohort study. Arthritis Res Ther 2019;21:163.
50. Shobha V, Rao V, Desai AM, Jois R, Srikantiah C, Dharmanand BG, *et al*. Prescribing patterns and safety of biologics in immune-mediated rheumatic diseases: Karnataka biologics cohort study group experience. Indian J Rheumatol 2019;14:17-20.
51. Kumar A, Goel A, Lapsiwala M, Goyal M, Dembla G. Clinical experience with two etanercept biosimilars in Indian patients with spondyloarthritis. Indian J Rheumatol 2017;12:139-45.
52. An Y, Liu T, He D, Wu L, Li J, Liu Y, *et al*. The usage of biological DMARDs and clinical remission of rheumatoid arthritis in China: A real-world large scale study. Clin Rheumatol 2017;36:35-43.
53. Kamata Y, Minota S. Wide difference in biologics usage and expenditure for the treatment of patients with rheumatoid arthritis in each prefecture in Japan analyzed using "National Database of Health Insurance Claims and Specific Health Checkups of Japan". Rheumatol Int 2018;38:663-8.