Review

Efficacy and safety of biologics in treating ankylosing spondylitis and their impact on quality of life and comorbidities: a narrative review

Abdulrahman Bandar Alotaibi , Danah Abdullah Albarrak * , Yousef Alammari

Posted Date: 13 October 2023

doi: 10.20944/preprints202310.0721.v1

Keywords: efficacy and safety, ankylosing spondylitis; biologics; quality of life.

Efficacy and Safety of Biologics in Treating Ankylosing Spondylitis and Their Impact on Quality of Life and Comorbidities: A Narrative Review

Abdulrahman Bandar Alotaibi [1], Danah Abdullah Albarrak [2,*] and Yousef Mohammed Alammari [1]

[1] College of Medicine, Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia.
[2] College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.
* Correspondence: dana.albarrak0@gmail.com Contact no. +966 594373374 .

Abstract: Ankylosing spondylitis (AS) is a chronic inflammatory arthritis that affects the axial skeleton, causing intense pain, progressive joint destruction, and a gradual reduction in physical function. It has been recognized not only as affecting the axial skeleton but as a systemic disease. Since it also causes an increase in the rates of inflammatory bowel disease, psoriasis, acute anterior uveitis, and mental disorders affecting the quality of life. Furthermore, an association with neurological and cardiovascular events is documented. With the advent of biologics, treating AS dramatically changed due to its high efficacy and tolerable safety. AS can be treated with various biological treatments. Nevertheless, there are differences in traits, including rapidity of onset, long-term efficacy, safety profile, and influence on comorbidities. A better understanding of such traits enables clinicians to make the best decision for each patient, increasing persistence, extending medication survival, enhancing patient satisfaction, and reducing the disease effect of ankylosing spondylitis. In this article, we emphasize biologics' efficacy and safety profile in patients with ankylosing spondylitis. In addition, we discuss the impact of biologics on comorbidities and health-related quality of life.

Keywords: efficacy and safety; ankylosing spondylitis; biologics; quality of life

Ankylosing spondylitis (AS) background, pathogenesis, and therapeutic targets

AS is a classic inflammatory arthritis that affects the axial skeleton. It is characterized by acute and chronic inflammation causing intense pain, progressive joint destruction, and a gradual reduction in physical function [1–3].AS is a multifactorial condition with a known hereditary cause HLA-B27 genotype (human leukocyte antigen) [2], and it is also known to be a prototype disease for a class of conditions known as spondyloarthritis

(SpA). These illnesses share clinical, radiological, and genetic characteristics, including an increase in the rates of inflammatory bowel disease (IBD), psoriasis, and acute anterior uveitis (AAU), ultimately known as extra-articular manifestations (EAM) [3]. AS affects males more commonly and typically manifests in the second and third decade of life, and rarely occurs after the age of 45 [4]. It is difficult to precisely state the prevalence due to the lack of literature compared to other rheumatic diseases, however, the prevalence of AS has been estimated to range between 0.1% and 1.4% globally [5]. Moreover, a systematic review by Dean le et al. attempted to illustrate the global prevalence of AS in Europe, Asia, North America, Latin America, and Africa. The reported frequency of AS varies significantly between continents, but there is some consistency within these regions. Compared to Latin America (10.2, weighted mean 12.2 per 10 000), AS is more prevalent in Europe (mean 23.8 and weighted mean 18.6 per 10,000) and Asia (mean 16.7, weighted mean 18.0 per 10 000). A systematic review that aimed to estimate the global prevalence of AS in North America and Africa reported 31.9 and 7.4 AS cases per 10,000 people, respectively. Additionally, the anticipated number of AS cases in Europe and Asia ranges from 1.30 to 1.56 million and 4.63 to 4.98 million, respectively. In all investigations, the average gender ratio is 3.4:1. (males: females) [6]. Chronic inflammation progressively causes the vertebral column to ossify, which results in substantial impairments in physical function and spinal movement, and ultimately impacts the quality of life [7]. The main focus

 doi:10.20944/preprints202310.0721.v1

of this literature review is to discuss the efficacy and safety of biologics in treating AS and their impact on quality of life and comorbidities.

AS develops as a result of complex interplay that remains partially understood. However, certain factors have been identified to play an essential part in the process, including genetics, certain infections, environmental exposure, and sex hormones appear to play a role in the pathogenesis. Based on emerging evidence, the pathophysiological response in AS has been identified as a combination of auto-inflammatory and autoimmune processes [8]. AS has a vital genetic component with high monozygotic twin concordance and a high heritability rate of 63% and 90%, respectively [9,10]. The presence of major histocompatibility complex (MHC) class I allele HLA-B27 accounts for significant genetic risk, which is found in more than 90 % of patients with AS [11]. Multiple theories on the role of HLA-B27 have been hypothesized, including the presentation of arthritogenic peptides, NK receptors recognition of HLA-B27 cell surface dimer, and HLA-B27 is unique propensity to misfold during its biosynthesis triggering a proinflammatory endoplasmic reticulum (ER) stress [12,13]. However, a study conducted in 2014 compared AS and non-AS-associated HLA-B27 subtypes and suggests that disease-associated alleles have increased intracellular aggregates of MHC misfolded protein, the functional impact of which is still unclear, with lack of an explicit ER stress [14]. Undisputedly, HLA-B27 plays a critical role in AS pathogenesis. However, recent estimates propose that it only accounts for 20– 25 % and 40 % of the total heritability and genetic risk, respectively [10,15]. In non-HLA-B27, Genome-wide association studies (GWASs) have identified common single nucleotide polymorphisms (SNPs) to have a highly significant association with AS [16–18]. Interestingly, many of these genes are found along distinct immunomodulatory pathways [15,19]. In particular, multiple genes affect the development and activity of Th17, a recently identified population of T helper cells named so for their production of interleukin (IL)-17 [20]. Th17 cells develop from naive T cells under conditions where the expression of IL-23 receptor (IL-23R) is induced by TGF-β and proinflammatory cytokines such as IL-6 and IL-1β However, for Th17 cells to become pathogenic, they require IL-23, which may be produced by innate immune cells including macrophages and dendritic cells [21]. GWAS has identified genes that influence the IL-17/IL-23 pathway, including cytokines and cytokine receptors (IL23R, IL12B, IL6R, IL1R1, IL1R2, IL27), signaling molecules downstream of the IL-23R (JAK2, STAT3, TYK2), and gene products transducing signals from infectious stimuli [18].

The IL-17/IL-23 pathway remains the major pathway in AS. Consequently, the interleukin-17 (IL-17) axis is the established target of AS therapy, although the IL-23/Th 17 axis has lately received interest as a potential inflammatory mechanism. Innate immune cells that generate IL-17 are more prevalent during inflammation. IL-17A and IL-17F, two members of the IL-17 cytokine family, show 50% structural similarity, comparable proinflammatory properties, and communicate via the same receptor complex. IL-17A and IL-17F can be specifically neutralized by the monoclonal antibody known as bimekizumab [22,23]. In order to induce and maintain Th17 cells, IL-23 is a crucial factor [24,25]. Studies have demonstrated a link between AS risk and IL-23 receptor (IL-23R) polymorphism. Additionally, studies have indicated that IL-23 contributes to disease pathophysiology [26,27]. The clinical hypothesis that direct and specific suppression of IL-23 will have therapeutic effects in patients with AS is supported by using IL-17A inhibitors (such as secukinumab) in treating AS.

Efficacy and safety of biologics in treating AS

The International Association of AS and the European Union Against Rheumatism (EULAR) recommend nonsteroidal anti-inflammatory drugs (NSAIDs), biologics, disease-modifying antirheumatic drugs (DMARDs), analgesics, steroids, non-drug treatments (such as education, exercise, and physical therapy), and surgical intervention to treat AS symptoms. However, there is no proof that traditional disease-modifying antirheumatic medications (DMARDs) are effective in axial illness [28].

Biologics agents are becoming increasingly popular globally due to their clear benefits in working rapidly and efficiently compared to conventional pharmacies in treating AS. Compared to rheumatoid arthritis (RA), the selection of biologics for AS is more limited [28]. For the treatment of

 doi:10.20944/preprints202310.0721.v1

AS, only IL-17 and tumor necrosis factor (TNF)-inhibitors have successfully met primary objectives in clinical trials [28,29], making them the current standard of care in biological therapy. Adalimumab (ADA), certolizumab (CZP), etanercept (ETN), golimumab (GOL), and infliximab (INF) are the five TNF-α that have been authorized for use in patients with active AS [28]. A recent study demonstrated that TNF inhibits disease activity and shields the spine's structural integrity [30]. In addition, various evidence illustrates that the IL-17 pathway has been identified as an effective therapeutic target in treating ankylosing spondylitis [31–34]. Indeed, people with ankylosing spondylitis have higher levels of IL-17 and 23-producing cells in their circulation and target organs, making IL-17 inhibitors a primary therapeutic target [33–37].

Seven biologic medications have been extensively compared regarding efficacy, tolerability, and safety in treating AS using network meta-analyses based on high-quality RCTs. Those biologics are:

1. IL-6 inhibitor (i.e., tocilizumab),
2. IL-17A inhibitor (i.e., secukinumab, ixekizumab, and netakimab),
3. IL-17A/F inhibitor (i.e., bimekizumab),
4. IL-23 inhibitor (i.e., risankizumab and ustekinumab),
5. JAK inhibitor (i.e., filgotinib, upadacitinib, and tofacitinib),
6. TNF-α inhibitor FC fusion protein (i.e., etanercept), and
7. TNF-α fully human monoclonal antibody (i.e., infliximab, adalimumab, certolizumab pegol, and golimumab).

Their principal findings could be summarized in three points: First, the IL-17 A/F dual variable domain inhibitor, which has the best effectiveness and safety, has the best chance of being the best therapeutic option. Second, TNFi had the most significant impact on reducing disease activity and enhancing functional capacity. Third, it was discovered that JAK inhibitors considerably outperformed a placebo in the primary network. According to the cluster-rank analysis, INF is the safest and most effective biologic medication for treating AS, while IL17(bimekizumab) inhibitor is the most potent and well-tolerated biologic medication [38].

Another meta-analysis conducted by Deodhar A et al. [39] to examine the relative efficacy of eleven kinds of IL17Ai, JAK inhibitor, and TNFi medications (i.e., adalimumab, certolizumab pegol, etanercept, filgotinib, golimumab, infliximab, ixekizumab, risankizumab, secukinumab, tofacitinib, and ustekinumab). The Outcomes assessed were ≥ 20% improvement in the Assessment of Spondyloarthritis International Society Criteria (ASAS20), Bath Ankylosing Spondylitis Functional Index (BASFI), and CRP at weeks 12–16. They found that tofacitinib 5 mg was the top-ranked treatment for ASAS20 response, followed by intravenous (IV) golimumab 2 mg/kg. Golimumab IV 2 mg/kg and infliximab 5 mg/kg were the top two ranked treatments for change from baseline in BASFI and changed from baseline in CRP.

Baeten D et al. conducted a trial to assess the efficacy of secukinumab (anti–IL-17A monoclonal antibody) in treating patients with active AS. A total of 371 were randomly assigned to receive secukinumab or a placebo. They concluded that at week 16, ankylosing spondylitis signs and symptoms were significantly reduced by Secukinumab at a subcutaneous dose of 150 mg, with either subcutaneous or intravenous loading dose (10 mg per kilogram of body weight). A 75 mg subcutaneous dose of secukinumab significantly improved the patient's condition only when a more significant intravenous loading dose was used. Additionally, 30 to 40 percent of the trial participants have had anti-TNF failed trials in treating AS. As a result, secukinumab might be helpful to individuals whose prior anti-TNF therapy was unsuccessful and in patients who have never received TNF medications [40]. Similar outcomes were shown for the secondary endpoints, which included a decrease in the score of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Ankylosing Spondylitis Quality of Life (ASQoL), the Short Form (SF)-36 health survey, and the levels of C reactive protein (CRP) [40].

Many complications have been documented in the Baeten D et al. study and are relevant to previous studies regarding safety concerns about using secukinumab [38,39]. The incidence of infections or infestations was higher with secukinumab than with placebo. For the duration of treatment, patients receiving secukinumab experienced 0.7, 0.9, and 0.7 occurrences per 100 patient-

 doi:10.20944/preprints202310.0721.v1

years, respectively, of grade 3 or 4 neutropenia, candida infections, and Crohn's disease [40]. The significant role that IL-17 plays in host defense against fungal infections, particularly in mucosal areas, is likely the cause of the increased occurrence of Candida infection.

In addition, compared to individuals using secukinumab to treat psoriasis or psoriatic arthritis, people with AS in secukinumab therapy exhibit a higher propensity to develop inflammatory bowel disease. However, this could be explained by the fact that a sizable proportion of AS patients have histological results that resemble those of inflammatory bowel disease [39,40]. Moreover, compared to patients with psoriasis or psoriatic arthritis, people treated with secukinumab for AS tend to get uveitis more frequently, which is most likely because anterior uveitis is the extra-articular symptom of AS that occurs most frequently [41].

Chao Chen et al. performed a network meta-analysis including 14 trials (2672 patients) to compare the effectiveness of all biologics in treating active AS. Except for secukinumab and tocilizumab, most biological treatment regimens were more successful than placebo in all outcomes evaluated. There were no significant differences between biological treatments for AS, except that infliximab 5 mg was preferable to tocilizumab. Given the probability that infliximab 5 mg/kg would be considered the best biological treatment for AS. At the same time, secukinumab had the highest probability of being ranked the second best[42]. Those findings were consistent with Migliore A et al. comparison between subcutaneous biologic agents in treating AS [43].

A retrospective study on Italian AS patients was done with 283 individuals. As the first anti-TNF medications, patients had received treatment with ADA (18.7%), ETN (26.8%), and INF (54.4%). This group had a very high partial remission rate (57.6%), and there were no discernible differences in the likelihood of achieving partial remission among TNF blockers [44]. TNF-inhibitor usage was linked to a greater risk of herpes zoster than those who did not use disease-modifying antirheumatic medications in a population-based research conducted in South Korea on AS patients [45]. Regarding the development of neoplasms, most studies did not reveal evidence of a higher risk of malignancies among AS patients who used TNF inhibitors [46].

Another possible therapeutic target for AS is the JAK pathway, a new therapeutic class for immune-mediated inflammatory diseases. A selective JAK1 inhibitor called upadacitinib is being investigated for additional immune-mediated inflammatory conditions, including psoriatic arthritis, ulcerative colitis, Crohn's disease, and atopic dermatitis [47–49]. Axial spondyloarthritis may be treated by targeting JAK pathways, and two phases 2 studies have demonstrated the efficacy of JAK inhibitors (tofacitinib and filgotinib) in treating AS [50,51]. In a study done by van der Heijde D et al. to assess the efficacy of upadacitinib after 14 weeks of therapy, individuals with active AS experienced a marked improvement in the disease activity, function, and axial inflammation on MRI when given oral upadacitinib 15 mg once daily [51]. Moreover, no fatalities, serious infections, herpes zoster, cancer, venous thromboembolic events, or malignancies were observed [52].

A study by van der heijde et al. investigated the efficacy of Ixekizumab (a high-affinity monoclonal antibody that selectively targets IL-17A) and ADA. Subcutaneous (SC) 80mg Ixekizumab was given every 2 weeks for 83 patients and the same dose over 4 weeks for 81 patients, and the ADA group was given 40 mg SC over 2 weeks. The main goal was to compare the percentage of patients who achieved an ASAS40 response, a composite indicator of clinical improvement in axial spondyloarthritis. The result showed that more than half of the patients who received 80 mg SC for two weeks achieved ASAS40 compared to 48% of those who took the exact dosage for four weeks, while 36% on ADA achieved ASAS40[53]. Similar to secukinumab, Ixekizumab is an IL-17A antagonist. Ixekizumab and secukinumab, however, vary in several molecular and pharmacokinetic properties. For instance, ixekizumab's in vitro binding affinity to IL-17A is 18 pmol/L instead of secukinumab's 100-200 pmol/L.m, which can lead to extra safety or effectiveness profiles [54].

Impact of biologics on health-related quality of life and comorbidities

Health-related quality of life (HRQoL) in AS patients has been reported to be decreased, especially in those with higher disease activity, functional disability, and peripheral involvement [55–

 doi:10.20944/preprints202310.0721.v1

57]. Consequently, with the introduction of biologics in treating AS, multiple studies aimed to assess their impact on patients and HRQoL.

TNF-α blockers were found to have a possible antidepressant effect [58]. A 6 weak longitudinal study conducted back in 2010 investigated the impact of TNF-alpha antagonist therapy on depression, anxiety, and quality of life (QOL) In AS patients. They concluded that mental health scores improved after the beginning of the treatment. In particular, a significant reduction in depression and anxiety scores was observed after the second and third infusions of infliximab, an anti-TNF treatment. Additionally, QOL scores reflected similar improvement as well [59]. Another study investigated the impact of TNF inhibitors on the risk of development of dementia in AS patients. Even though AS patients had a higher prevalence of Alzheimer's disease compared to the general population, among the patients with AS, those treated with TNF inhibitors had lower rates of Alzheimer's disease [60].

Multiple studies revealed the positive impact of biologics on HRQoL in AS patients. A recent study revealed that biological agents are superior in improving QoL in AS patients compared to those receiving only a placebo or standard therapy [61]. A 24-week randomized controlled study evaluated the impact of adalimumab on HRQoL in patients with active AS. Adalimumab significantly improved HRQoL and physical health in active AS patients throughout the 24 weeks of the study [62]. Furthermore, a 3-year outcome-based randomized controlled trial concluded that adalimumab significantly improved physical function, disease activity, and HRQoL in AS patients [63]. Another study aimed to evaluate the effect of TNF inhibitors (namely infliximab and etanercept) in AS patients over 65 years, which revealed significant improvement in HRQoL and functional disability [64].

Additionally, TNF inhibitors have been shown to reduce pain and fatigue in patients with AS, improving QOL [65]. Furthermore, another randomized controlled trial assessing the impact of certolizumab pegol on AS patients revealed improvements in pain level, fatigue, sleep, and HRQoL in both AS and non-radiographic axial SpA patients [66]. Moreover, a randomized, double-blind placebo control multicenter study conducted in 2020 aimed to investigate the effect of golimumab on HRQoL in AS through 28 weeks. The patients were randomized to receive golimumab or placebo at weeks 0, 4, and 12 and every 8 weeks, with placebo crossover to golimumab at weeks 16, 20, and every 8 weeks. The results revealed that more remarkable improvement in HRQoL was observed early in the golimumab group at week 8 and throughout week 16 compared to the placebo group. After the placebo group crossover to golimumab at week 16, both groups reported similar HRQoL improvement at week 28 [67].

Furthermore, a more recent systematic review and meta-analysis aimed to investigate the impact of biological therapy, namely tumor necrosis factor (TNF) inhibitors or Interleukin-17A (IL-17A) antibody agents, on HRQoL in AS patients, specifically those with radiographic axial spondyloarthritis (r-axSpA). The analysis included 16 randomized clinical trials; the results revealed an association between using biological agents and significant improvement in HRQoL among patients with r-axSpA [68]. A 12-week double-blind, multicenter study conducted in 2007 assessed the effect of etanercept 50 mg once weekly vs. 25 mg twice weekly on the QOL in AS patients. Both dosing regimens significantly improved patient function and QOL [69] in a randomized open-label study aimed to assess HRQoL and the impact of etanercept therapy among AS patients. It was noted that patients with active AS reported a significant reduction in AS, especially across the physical domains. After the initiation of etanercept therapy, significant improvement in HRQoL was observed among AS patients, with tremendous improvements reported in the physical domains [70].

Moreover, a 12-week double-blind, randomized control trial observed improvement in QoL of patients with active AS who received bimekizumab, an IL-17A/F inhibitor [71]. Additionally, compared to placebo AS, patients who received ixekizumab (IL-17A inhibitor) reported improvement in QoL, including pain level, fatigue, and sleep [72]. Furthermore, multiple studies investigated the impact of JAK inhibitors, namely Upadacitinib, and tofacitinib, on QoL in AS patients. All concluded that treatment with JAK inhibitors significantly improved disease activity, QoL, and work productivity [73–75].

Conclusion

Our study offers a thorough narrative evaluation of the use of biological medicines in treating individuals with AS who may currently be treated with a wide range of biological medications. However, there are differences in traits, including rapidity of onset, long-term efficacy, safety profile, and implications on comorbidities. A better knowledge of such traits enables clinicians to make the best decision for each patient, increasing persistence, extending medication survival, enhancing patient satisfaction, and reducing the impact of AS on the quality of life.

Author Contributions: conceptualization: Abdulrahman B Alotaibi; writing, reviewing and editing: all authors. All authors made significant intellectual contributions to the manuscript.

Funding: The authors did not receive support from any organization for the submitted work

Informed Consent Statement: This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflicts of Interest: The authors have no competing interests to declare that are relevant to the content of this article.

References

1. Dougados M, Baeten D. Spondyloarthritis. Lancet. 2011, 377:2127-37. 10.1016/S0140-6736(11)60071-8
2. Bhoi P, Bessette L, Bell MJ, Tkaczyk C, Nantel F, Maslova K. Adherence and dosing interval of subcutaneous antitumor necrosis factor biologics among patients with inflammatory arthritis: analysis from a Canadian administrative database. BMJ open. 2017, 7. 10.1136/bmjopen-2017-015872
3. Stolwijk C, Tubergen AV, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. Ann Rheum Dis. 2015, 74:65-73. 10.1136/annrheumdis-2013-203582
4. Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007, 369:1379-90. 10.1016/S0140-6736(07)60635-7
5. Akkoc N. Are spondyloarthropathies as common as rheumatoid arthritis worldwide? A review. Curr Rheumatol Rep. 2008,10:371-8. 10.1007/s11926-008-0060-3
6. Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. Rheumatology (Oxford). 2014, 53:650-7. 10.1093/rheumatology/ket387
7. Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A. Ankylosing spondylitis: an overview. Ann Rheum Dis 2002, ;61. 10.1136/ard.61.suppl_3.iii8
8. Alexander M: Ankylosing Spondylitis Pathogenesis and Pathophysiology. Ankylosing Spondylitis [Working Title]. Alexander M (ed): IntechOpen, London, United Kingdom; 2023. 1-33. 10.5772/intechopen.109164
9. Boonen A, Severens JL. Ankylosing spondylitis: what is the cost to society, and can it be reduced? Best Pract Res Clin Rheumatol. 2002, 16:691-705. 10.1053/berh.2002.0244
10. Brown MA, Kennedy LG, MacGregor AJ, et al. Susceptibility to ankylosing spondylitis in twins: the role of genes, HLA, and the environment. Arthritis Rheum. 1997, 40:1823-28. 10.1002/art.1780401015
11. Reveille JD. An update on the contribution of the MHC to susceptibility. Clin Rheumatol. 2014, 33:749–57. 10.1007/s10067-014-2662-7
12. Colbert RA, Tran TM, Layh-Schmitt G. HLA-B27 misfolding and ankylosing spondylitis. Mol Immunol. 2014, 57:44-51. 10.1016/j.molimm.2013.07.013
13. Taurog JD. The role of HLA-B27 in spondyloarthritis. J Rheumatol. 2010, 37:2606-16. 10.3899/jrheum.100889
14. Jeanty C, Sourisce A, Noteuil A, et al. HLA-B27 subtype oligomerization and intracellular accumulation patterns correlate with a predisposition to spondyloarthritis. Arthritis Rheumatol. 2014, 66: 2113-23. 10.1002/art.38644
15. International Genetics of Ankylosing Spondylitis Consortium (IGAS), Cortes A, Hadler J, et al. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. Nat Genet. 2013, 45:730-38. 10.1038/ng.2667
16. Ko CL, Lin WZ, Lee MT, et al. Genome-wide association study reveals ethnicity-specific SNPs associated with ankylosing spondylitis in the Taiwanese population. J Transl Med. 2022, 20. 10.1186/s12967-022-03701-3
17. Sarin R, Wu X, Abraham C. Inflammatory disease protective R381Q IL23 receptor polymorphism decreases primary CD4+ and CD8+ human T-cell functional responses. Proc Natl Acad Sci U S A. 2011, 108:9560-5. 10.1073/pnas.1017854108

18. The Australo-Anglo-American Spondyloarthritis Consortium (TASC), the Wellcome Trust Case Control Consortium 2 (WTCCC2), Evans D, et al. Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility. Nat Genet. 2011, 43:761-7. 10.1038/ng.873
19. Davidson SI, Liu Y, Danoy PA, et al. Association of STAT3 and TNFRSF1A with ankylosing spondylitis in Han Chinese. Ann Rheum Dis. 2011, 70:289-92. 10.1136/ard.2010.133322
20. Diveu C, McGeachy MJ, Cua DJ. Cytokines that regulate autoimmunity. Curr Opin Immunol. 2008, 20:663-8. 10.1016/j.coi.2008.09.003
21. Langrish CL, McKenzie BS, Wilson NJ, de Waal MR, Kastelein RA, Cua DJ. IL-12 and IL-23: master regulators of innate and adaptive immunity. Immunol Rev. 2004, 202:96-105 10.1111/j.0105-2896.2004.00214.x
22. Rezaiemanesh A, Abdolmaleki M, Abdolmohammadi K, et al. Immune cells are involved in the pathogenesis of ankylosing spondylitis. Biomed Pharmacother. 2018, 100:198-204. 10.1016/j.biopha.2018.01.108
23. Hymowitz SG, Filvaroff EH, Yin J, et al. IL-17s adopt a cystine knot fold: structure and activity of a novel cytokine, IL-17F, and implications for receptor binding. EMBO J. 2001, 20:5332-41. 10.1093/emboj/20.19.5332
24. Zeng L, Lindstrom MJ, Smith JA. Ankylosing spondylitis macrophage production of higher levels of interleukin-23 in response to lipopolysaccharide without induction of a significant unfolded protein response. Arthritis Rheum. 2011, 63:3807-17. 10.1002/art.30593
25. Gaffen SL, Jain R, Garg AV, Cua DJ. The IL-23–IL-17 immune axis: from mechanisms to therapeutic testing. Nat Rev Immunol. 2014, 14:585-600. 10.1038/nri3707
26. Australo-Anglo-American Spondyloarthritis Consortium (TASC). Genome-wide association study of ankylosing spondylitis identifies non-MHC susceptibility loci. Nat Genet. 2010, 42:123-7. 10.1038/ng.513
27. Benham H, Rehaume LM, Hasnain SZ, et al. Interleukin-23 mediates the intestinal response to microbial β-1, 3-glucan, and the development of spondyloarthritis pathology in SKG mice. Arthritis Rheum. 2014, 66:1755-67. 10.1002/art.38638
28. Min HK, Kim HR, Lee SH, Hong YS, Kim MY, Park SH, Kang KY. Clinical efficacy of alternative TNF inhibitor and secukinumab between primary non-responder and secondary non-responder of prior TNF inhibitor in ankylosing spondylitis. Mod Rheumatol. 2023, 3:194-201. 10.1093/mr/roac005
29. Zhu W, He X, Cheng K, et al. Ankylosing spondylitis: etiology, pathogenesis, and treatments. Bone Res. 2019, 7:22. 10.1038/s41413-019-0057-8
30. Koo BS, Oh JS, Park SY, et al. Tumour necrosis factor inhibitors slow radiographic progression in patients with ankylosing spondylitis: 18-year real-world evidence. Ann Rheum Dis. 2020, 79:1327-32. 10.1136/annrheumdis-2019-216741
31. Glatigny S, Fert I, Blaton MA, Lories RJ, Araujo LM, Chiocchia G, Breban M. Proinflammatory Th17 cells are expanded and induced by dendritic cells in spondylarthritis-prone HLA–B27–transgenic rats. Arthritis Rheum. 2012, 64:110-20. 10.1002/art.33321
32. Sherlock JP, Joyce-Shaikh B, Turner SP, et al. IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+ CD4− CD8− entheseal resident T cells. Nat Med. 2012, 18:1069-76. 10.1038/nm.2817
33. 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(6):1647-56. 10.1002/art.24568
34. Bowness P, Ridley A, Shaw J, et al Th17 cells expressing KIR3DL2+ and responsive to HLA-B27 homodimers are increased in ankylosing spondylitis. J Immunol. 2011, 186:2672-80. 10.4049/jimmunol.1002653
35. Kenna TJ, Davidson SI, Duan R, et al. Enrichment of circulating interleukin-17–secreting interleukin-23 receptor–positive γ/δ T cells in patients with active ankylosing spondylitis. Arthritis Rheum. 2012, 64:1420-9. 10.1002/art.33507
36. Appel H, Maier R, Wu P, et al. Analysis of IL-17+ cells in facet joints of patients with spondyloarthritis suggests that the innate immune pathway might be of greater relevance than the Th17-mediated adaptive immune response. Arthritis Res Ther. 2011, 13. 10.1186/ar3370
37. Noordenbos T, Yeremenko N, Gofita I, van de Sande M, Tak PP, Caňete JD, Baeten D. Interleukin-17–positive mast cells contribute to synovial inflammation in spondylarthritis. Arthritis Rheum. 2012, 64:99-109. 10.1002/art.33396
38. Cao Z, Guo J, Li Q, Li Y, Wu J. Optimal Biologic Drugs for the Treatment of Ankylosing Spondylitis: Results from a Network Meta-Analysis and Network Metaregression. Biomed Res Int. 2022, 2022. 10.1155/2022/8316106
39. Deodhar A, Chakravarty SD, Cameron C, et al. A systematic review and network meta-analysis of current and investigational treatments for active ankylosing spondylitis. Clin Rheumatol. 2020, 39:2307–15. 10.1007/s10067-020-04970-3
40. Baeten D, Sieper J, Braun J, et al. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med. 2015; 373:2534-48. 10.1056/NEJMoa1505066

41. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis—results of two phases 3 trials. N Engl J Med. 2014; 371:326-38. 10.1056/NEJMoa1314258
42. Chen C, Zhang X, Xiao L, Zhang X, Ma X. Comparative effectiveness of biologic therapy regimens for ankylosing spondylitis: a systematic review and a network meta-analysis. Medicine (Baltimore). 2016, 95. 10.1097/MD.0000000000003060
43. Migliore A, Bizzi E, Bernardi M, Diamanti AP, Laganà B, Petrella L. Indirect comparison between subcutaneous biologic agents in ankylosing spondylitis. Clin Drug Investig. 2015, 35:23-9. 10.1007/s40261-014-0246-6
44. Spadaro A, Lubrano E, Marchesoni A, et al. Remission in ankylosing spondylitis treated with anti-TNF-α drugs: a national multicentre study. Rheumatology (Oxford). 2013, 52: 1914-9. 10.1093/rheumatology/ket249
45. Lim DH, Kim YJ, Kim SO, Hong S, Lee CK, Yoo B, Kim YG. The risk of herpes zoster in patients with ankylosing spondylitis: analysis of the Korean National Health Insurance Service–sample cohort database. Mod Rheumatol. 2018, 28:168-73. 10.1080/14397595.2017.1325034
46. Wroński J, Fiedor P. The safety profile of tumor necrosis factor inhibitors in ankylosing spondylitis: are TNF inhibitors safer than we thought? J Clin Pharmacol. 2019, 59:445-62. 10.1002/jcph.1348
47. Beck L, Hong C, Hu X, Chen S, Calimlim B, Teixeira H, Guttman-Yassky E. Upadacitinib effect on pruritus in moderate-to-severe atopic dermatitis; from a phase 2b randomized, placebo-controlled trial. Ann Allergy Asthma Immunol. 2018, 121:21. 10.1016/j.anai.2018.09.063
48. Sandborn WJ, Feagan BG, Panes J, et al. Safety and efficacy of ABT-494 (upadacitinib), an oral JAK1 inhibitor, as induction therapy in patients with Crohn's disease: results from CELEST. United European Gastroenterol J. 2017, 52:1308-9 10.1016/S0016-5085(17)34357-3
49. Yassky EG, Thaçi D, Pangan AL, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2020, 145:877-84. 10.1016/j.jaci.2019.11.025
50. Heijde DV, Deodhar A, Wei JC, et al. Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomized, placebo-controlled, dose-ranging study. Ann Rheum Dis. 2017, 76:1340-7. 10.1136/annrheumdis-2016-210322
51. Heijde DV, 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 randomized, placebo-controlled, phase 2 trial. Lancet. 2018, 392:2378-87. 10.1016/S0140-6736(18)32463-2
52. Heijde DV, Song IH, 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. 10.1016/S0140-6736(19)32534-6
53. Heijde DV, Wei JC, 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 antirheumatic drugs (COAST-V): 16-week results of phase 3 randomized, double-blind, active-controlled and placebo-controlled trial. Lancet. 2018, 392:2441-51. 10.1016/S0140-6736(18)31946-9
54. Paul C. Ixekizumab or secukinumab in psoriasis: what difference does it make? Br J Dermatol. 2018, 178:1003-5. 10.1111/bjd.16497
55. Yılmaz O, Tutoğlu A, Garip Y, Ozcan E, Bodur H. Health-related quality of life in Turkish patients with ankylosing spondylitis: impact of peripheral involvement on quality of life in terms of disease activity, functional status, the severity of pain, and social and emotional functioning. Rheumatol Int. 2013, 33:1159-63. 10.1007/s00296-012-2510-5
56. Sallam RA, Elbahnasawy AS. Health-related quality of life (HRQoL) in ankylosing spondylitis patients: Relation to clinical features, disease activity, and radiographic damage. Egypt. Rheumatol. 2020, 42:287-90. 10.1016/j.ejr.2020.02.006
57. Yacoub Y, Amine B, Laatiris A, Abouqal R, Hassouni NH. Health-related quality of life in Moroccan patients with ankylosing spondylitis. Clin Rheumatol. 2011, 30:673-7. 10.1007/s10067-010-1613-1
58. Arısoy O, Bes C, Cifci C, Sercan M, Soy M. The effect of TNF-alpha blockers on psychometric measures in ankylosing spondylitis patients: a preliminary observation. Rheumatol Int. 2013, 33:1855-64. 10.1007/s00296-013-2671-x
59. Ertenli, I., Ozer, S., Kiraz, S. et al. Infliximab, a TNF-alpha antagonist treatment in patients with ankylosing spondylitis: the impact on depression, anxiety and quality of life level. Rheumatol Int. 2012, 32:323-30. 10.1007/s00296-010-1616-x
60. Watad A, McGonagle D, Anis S, et al. TNF inhibitors have a protective role in the risk of dementia in patients with ankylosing spondylitis: Results from a nationwide study. Pharmacol Res. 2022, 182. 10.1016/j.phrs.2022.106325

61. Tański W, Świątoniowska-Lonc N, Dudek K, Jankowska-Polańska B. Benefit of biological drugs for quality of life in patients with ankylosing spondylitis: A systematic review and meta-analysis of clinical trials. Adv Exp Med Biol. 2021, 1335:63-78. 10.1007/5584_2020_611
62. Davis JC Jr, Revicki D Heijde DM, Rentz AM, Wong RL, Kupper H, Luo MP. Health-related quality of life outcomes in patients with active ankylosing spondylitis treated with adalimumab: results from a randomized controlled study. Arthritis Rheum. 2007, 57:1050-7. 10.1002/art.22887
63. Heijde DM, Revicki DA, Gooch KL, et al. Physical function, disease activity, and health-related quality-of-life outcomes after 3 years of adalimumab treatment in patients with ankylosing spondylitis. Arthritis Res Ther. 2009, 11. 10.1186/ar2790
64. Abalos-Medina GM, Ruiz-Villaverde G, Sánchez-Cano D, Ruiz-Villaverde R, Ocaña-Peinado F, Villaverde-Gutiérrez C. Nivel funcional y calidad de vida en espondilitis anquilosante. Estudio piloto tras 16 semanas de tratamiento anti-TNF [Functional level and quality of life in ankylosing spondylitis, pilot study after 16 weeks TNF blocker treatment]. Rev Esp Geriatr Gerontol. 2010, 45:331-4. 10.1016/j.regg.2010.04.010
65. Wu Q, Inman RD, Davis KD. Tumor necrosis factor inhibitor therapy in ankylosing spondylitis: differential effects on pain and fatigue and brain correlates. Pain. 2015,156:297-304. 10.1097/01.j.pain.0000460310.71572.16
66. Sieper J, Kivitz A, Tubergen AV, Deodhar A, Coteur G, Woltering F, Landewé R. Impact of Certolizumab Pegol on Patient-Reported Outcomes in Patients With Axial Spondyloarthritis. Arthritis Care Res. 2015, 67:1475-80. 10.1002/acr.22594
67. Reveille JD, Deodhar A, Ince A, at al. Effects of Intravenous Golimumab on Health-Related Quality of Life in Patients with Ankylosing Spondylitis: 28-Week Results of the GO-ALIVE Trial. Value Health. 2021, 23:1281-5. 10.1016/j.jval.2020.04.1837
68. Ho A, Younis I, Le QA. Impact of biologics on health-related quality of life in patients with Ankylosing spondylitis: A systematic review and meta-analysis of randomized controlled trials. Semin Arthritis Rheum. 2022, 54. 10.1016/j.semarthrit.2022.151996
69. Braun J, McHugh N, Singh A, Wajdula JS, Sato R. Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. Rheumatology (Oxford). 2007, 46:999-1004. 10.1093/rheumatology/kem069
70. Davis JC, van der Heijde D, Dougados M, Woolley JM. Reductions in health-related quality of life in patients with ankylosing spondylitis and improvements with etanercept therapy. Arthritis Rheum. 2005, 53:494-501. 10.1002/art.21330
71. Heijde DV, Gensler LS, Deodhar A, Baraliakos X, Poddubnyy D, Farmer MK, et al. LB0001 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. Ann Rheum Dis. 2018,77. 10.1136/annrheumdis-2018-eular.7889
72. Mease P, Walsh JA, Baraliakos X, et al. Translating improvements with ixekizumab in clinical trial outcomes into clinical practice: ASAS40, pain, fatigue, and sleep in ankylosing spondylitis. Rheumatol Ther. 2019, 6:435-50. 10.1007/s40744-019-0165-3
73. Navarro-Compán V, Baraliakos X, Magrey M, et al. Effect of upadacitinib on disease activity, pain, fatigue, function, health-related quality of life and Work Productivity for biologic refractory ankylosing spondylitis. Rheumatol Ther. 2023, 10:679-91. 10.1007/s40744-023-00536-2
74. McInnes IB, Ostor AJK, Mease PJ, et al. Effect of upadacitinib on reducing pain in patients with active psoriatic arthritis or ankylosing spondylitis: post hoc analysis of three randomised clinical trials. RMD Open. 2022, 8. 10.1136/rmdopen-2021-002049
75. Navarro-Compán V, Wei JC-C, Van den Bosch F, et al. Effect of tofacitinib on pain, fatigue, health-related quality of life and work productivity in patients with active ankylosing spondylitis: results from a phase III, randomised, double-blind, placebo-controlled trial. RMD Open. 2022, 8. 10.1136/rmdopen-2022-002253