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ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieid20

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To cite this article: Leticia Garcia-Montoya & Paul Emery (2021) Disease modification in ankylosing spondylitis with TNF inhibitors: spotlight on early phase clinical trials, Expert Opinion on Investigational Drugs, 30:11, 1109-1124, DOI: 10.1080/13543784.2021.2010187

To link to this article: https://doi.org/10.1080/13543784.2021.2010187

Published online: 11 Dec 2021.

EXPERT OPINION ON INVESTIGATIONAL DRUGS
2021, VOL. 30, NO. 11, 1109–1124
https://doi.org/10.1080/13543784.2021.2010187

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REVIEW

Disease modification in ankylosing spondylitis with TNF inhibitors: spotlight on early phase clinical trials

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ABSTRACT

Introduction: Ankylosing spondylitis (AS) is a chronic inflammatory disease whose main hallmark is involvement of the axial skeleton. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line treatment; however, their use is limited because of side effects. Tumor necrosis factor inhibitors (TNFi) are a safe and effective therapy, and they have been approved for the management of AS.

Areas covered: This is a review of the efficacy of TNFi in disease modification in AS. It is focused on results from early-phase clinical trials; however, it also discusses the most relevant findings in order to optimize anti-TNF treatment. A literature search was done using PubMed, Medline, Embase, Google Scholar, and Cochrane library, looking for scientific publications from inception to August 2021. Further information was retrieved from ClinicalTrial.gov and Clinicaltrialsregister.eu.

Expert opinion: TNFi have demonstrated short- and long-term improvements in all aspects of disease activity, as well as physical function in patients with AS. They have drastically revolutionized the management of the disease; and even though new drugs have become available in the market, TNFi has not been displaced for the treatment of AS, and still constitute the best alternative when NSAIDs are no-longer an option.

ARTICLE HISTORY
Received 8 June 2021
Accepted 21 November 2021

KEYWORDS
Ankylosing spondylitis; anti-TNF; axial; clinical trial; disease modification; early phase; review; spondyloarthritis; TNF inhibitors; TNFi

1. Introduction

Ankylosing spondylitis (AS) is a chronic rheumatic condition that belongs to the family of Spondyloarthritides. This group of diseases share a similar genetic and immunological background, and their most characteristic feature is involvement of the axial skeleton. AS typically affects the sacroiliac joints (SIJs) and entheses, potentially leading to spinal ankylosis; however, it can also cause peripheral arthritis, uveitis, or dactylitis. AS has a prevalence of 0.23% in Europe, being more frequent in males, and can lead to important disability through restriction of spinal mobility [1–3].

In this article, we provide a review of the efficacy of Tumor Necrosis Factor (TNF) inhibitors (TNFi) in disease modification in AS. We will focus on early phase clinical trials, but we will also discuss relevant findings and the latest highlights in order to provide a better insight of the efficacy of these drugs, with the views of optimizing anti-TNF treatment.

A literature review was done using PubMed, Medline, Embase, Google Scholar, and the Cochrane library, looking for scientific publications from inception to August 2021. Multiple searches were performed combining the theme 'ankylosing spondylitis' (searched as: AS, ankylosing spondylitis, spondyloarthritis, spondyloarthropathies, axial spondyl*) with the Boolean operator 'AND' and one of the following: infliximab, etanercept, adalimumab, certolizumab, golimumab, TNF, Tumo(u)r necrosis factor*, TNFi, anti-TNF, biologic*, early phase, clinical trial, phase I, phase 1, phase II, phase 2, phase IIa, phase 2a, phase IIb, and phase 2b. Further information was retrieved from ClinicalTrial.gov and Clinicaltrialsregister.eu. Only articles published in English were selected. The references cited were chosen based on their relevance to the contents of this review.

1.1. Management of ankylosing spondylitis

According to ASAS/EULAR recommendations [4,5], non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment for AS; however, response may not be sufficient in some patients, and others require their continuous use in order to avoid symptoms; which given the potential risks and/or side effects associated with NSAIDS, is not always possible. In these cases, treatment with TNFi is indicated. There is no evidence to support the use of conventional disease modifying anti-rheumatic drugs (DMARDs) before or combined with TNFi in patients with axial disease; however, sulfasalazine (SSZ) may be considered as an alternative, in patients with peripheral arthritis and no axial involvement.

1.2. THE role of TNF-α in ankylosing spondylitis

TNFi are called so because they bind to tumor necrosis factor-α (TNF-α), inhibiting its actions. This cytokine is mainly secreted by monocytes and macrophages; however, it can also be produced by NK cells, T-cells, neutrophils, and other

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nonimmune cells, such as fibroblasts. TNF-α is involved in the pathogenesis of several rheumatic diseases and can activate multiple signaling pathways, promoting the release of inflammatory mediators like IL-1, IL-6, and the activation of macrophages, B-cells or T-cells among other immune mechanisms [6,7].

Human leukocyte antigen (HLA)-B27 is known to play an important role in the pathogenesis of AS, with an estimated heritability of over 20% (8). Studies have shown that patients with spondyloarthritis (SpA) present high levels of NK and CD4 + T-cells, and they express the receptor KIR3DL2, which recognizes cell surface HLA-B27 homodimers. These cells are reported to produce TNF-α and IFN-gamma. Additionally, when KIR3DL2+ CD4 + T-cells are stimulated by antigen presenting cells that express HLA-B27 homodimers, they produce high levels of IL-17; which at the same time has been proved to act synergistically with TNF-α to release inflammatory mediators that influence bone metabolism [8,9].

As mentioned above, the SIJs are typically affected in AS; therefore, it makes sense that TNF-α is detected in high amounts near the sites of new bone formation in these joints [10]. Also, the fact that this is actually present in early stages of the disease suggests that TNF-α is likely to have a direct role in the pathogenesis of AS [11]. Additionally, this is supported by a study showing improvement of the histological changes in the synovial membrane of peripheral joints after treatment with TNFi, such as reduction of the vascularity and the number of macrophages [12].

There are currently five TNFi approved for AS: infliximab, etanercept, adalimumab, golimumab, and certolizumab, and even though they have a similar mechanism of action, due to their different structure, they present slightly different characteristics.

2. TNF inhibitors for the treatment of ankylosing spondylitis

2.1. *Infliximab*

Infliximab is a human/murine (75% and 24%, respectively) neutralizing, monoclonal chimeric antibody of IgG1 K isotype, with specificity and high affinity for human TNF-α [13]. It is approved for the treatment of AS at a dose of 5 mg/kg, administered as an intravenous (i/v) infusion. In treatment initiation, this dose should be repeated 2 and 6 weeks after the first infusion, and then every 6–8 weeks [14].

Infliximab was the first TNFi to be approved for the treatment of rheumatic diseases.

An open-label pilot study assessed the efficacy and safety of a loading dose regime of infliximab in patients with SpA [15]. It included 21 patients, 10 of them with AS. Infusions of 5 mg/kg of infliximab were administered at weeks 0,2 and 6, and participants were assessed at baseline, on days 3,7,14 and every 2 weeks. In patients with AS, axial assessment took place at baseline, days 14, 42, and 84. A significant decrease in the acute phase reactants, patient, and physician global assessment visual analogue scale (VAS) could be seen as early as in day 3 since treatment initiation, and was maintained up to day 84; demonstrating the efficacy of the loading dose of infliximab in axial and peripheral articular manifestations. No serious adverse events (SAEs) were reported, and no treatment was discontinued because of adverse events (AEs).

Another study also aimed to assess the safety and efficacy of infliximab versus placebo in patients with active SpA [16]. This double-blind, placebo-controlled trial included 40 patients with active disease; 21 out of which had AS. Participants were randomized to either a loading dose of infliximab 5 mg/kg (at weeks 0, 2, and 6) (n = 20) or placebo (n = 20). Nine and 12 of the AS patients were randomized to those arms respectively. Efficacy and safety were assessed at weeks 1,2,6,8 and 12. Results showed that infliximab led to a significant improvement in disease activity, evaluated using physician and patient 100-mm VAS. Acute phase reactants and early morning stiffness (EMS) of the spine decreased in the infliximab group; and the Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores also experienced a significant improvement compared with placebo. One of the patients receiving infliximab was withdrawn from the study due to tuberculosis infection; however, this was consistent with previously reported cases in post-marketing experience; and screening tests had not been performed.

A 12-week, placebo-controlled, randomized study assessed response to infliximab 5 mg/kg in active AS [17]. Seventy patients were recruited: 35 were allocated in the placebo arm and 35 in the infliximab arm. Both arms received infusions at weeks 0, 2, and 6. At week 12, 53% of patients receiving infliximab had experienced at least a 50% regression of the disease, compared with the 9% of placebo. This could be evidenced in the BASDAI, BASFI and Bath Ankylosing Spondylitis Metrology Index (BASMI); but also, in the quality of life. Furthermore, disease response with infliximab treatment was maintained at years 1, 2, and 3, as assessed in an open-label extension phase [18–20]. During this time, infliximab was well tolerated and the safety profile was comparable to be observed for the approved indications. The 4th and 5th year extensions of the trial showed no signs of loss of response [21].A 30-week open-label prospective study including 19 patients with active AS suggested that the combination of infliximab with methotrexate (MTX) could increase the therapeutic response to the drug [22]; however, a randomized, double-blind placebo-controlled trial including 38 participants with active AS failed to show evidence of a significant difference between Assessment in Ankylosing Spondylitis (ASAS)20 and other clinical assessments in patients with the additional MTX [23]. As other studies suggested, any positive effect could be related to the presence of human anti-chimeric antibodies (HACA), which are reduced in patients receiving a combination of MTX and infliximab (15%) compared with those receiving infliximab alone (53%) [24].

A study assessed 4-year radiographic progression of AS patients receiving infliximab [25]. Radiographs of the cervical and the lumbar spine had been performed at baseline, at 2 and 4 years. These were scored using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) method [26]. The infliximab arm consisted of a total of 33 patients who originally joined a randomized controlled trial (RCT) and had complete radiographic data. They received infliximab 5 mg/kg

i/v every 6 weeks for 3 years, and after that, medication was re-started in case of clinical relapse. Comparison was made with patients from the historical OASIS cohort [27], and results suggested that even though infliximab did not stop structural progression in AS, it may decelerate it.

Multiple studies have investigated the impact of infliximab in the evolution of inflammatory changes in magnetic resonance imaging (MRI) in patients with AS. Short term, this was assessed in the ASSERT study [28]; a double-blind, placebo-controlled trial including subjects with active disease. Patients were randomized at an 8:3 ratio to Infliximab 5 mg/kg (n = 194) or placebo (n = 72) i/v every 6 weeks with a loading dose at weeks 0,2 and 5. MRI of the spine was performed at BL and week 24, and were scored using a previously described method [29]. At week 24, a decrease in spinal inflammation was evident in patients receiving infliximab, whereas those in the placebo arm presented sustained inflammatory changes.

Another study evaluated the MRI images of patients included in previously mentioned RCTs [17,19]. These were performed at baseline, 3 months and 2 years, and were scored using Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity (ASspiMRI-a) method [29]. Data from 20 patients who had received infliximab for 102 weeks were available: spinal inflammation decreased significantly, as early as 12 weeks after treatment initiation, and this was sustained long term; however, minor inflammation was still present in spite of 2 years of therapy [30].

2.2. Etanercept

Etanercept is a dimeric fusion protein of the human TNF receptor, linked to the Fc portion of human IgG1 [31]. It is produced by recombinant deoxyribonucleic acid (DNA) and it is approved for the treatment of AS at a dose of 25 mg twice a week or 50 mg weekly subcutaneous (sc) [32].

The first etanercept trial in AS was a double-blind, placebo-controlled study, including 40 patients with active disease [31]. Participants were randomized to either 25 mg of etanercept twice weekly or placebo, and were followed-up for 4 months. At the end of the trial, 80% of the patients on etanercept had responded to treatment, compared to the 30% of the ones in the placebo group. Improvements were evidenced in disease activity, measured by EMS, spinal pain, quality of life and acute phase reactants among other parameters. A longitudinal analysis showed that patients responded rapidly and this was maintained over time; and safety-wise, no SAEs were reported.

An open-label 6-month extension of the previous study [33] confirmed the sustained benefit from etanercept therapy, whereas at 4 months' time, 74% of etanercept patients had achieved ASAS20 [34], this increased to the 94% at 10 months' time. Twenty-six percent of patients receiving placebo achieved this endpoint at 4 months' time, and 84% of these patients who later received etanercept reached ASAS20. Furthermore, 81% of the patients receiving etanercept achieved ASAS50 [35] at the 10-month timepoint.

A phase II trial evaluated the efficacy of etanercept in patients with active AS [36]. The study included 30 participants and had two phases; the first one was a placebo-controlled, 6-week observational period, where patients were randomized to either etanercept 25 mg twice weekly (n = 14) or placebo (n = 16). After that phase, both groups were treated with etanercept until completing a total of 12 weeks and were followed up for at least 24 weeks. Results showed the efficacy of etanercept in a short-term bases, with 57% of the patients in the etanercept group presenting ≥50% reduction of disease activity at the 6-week timepoint, compared with the 6% in the placebo group. An extension of the study confirmed the efficacy and safety of the drug over 1 year of treatment, including discontinuation and re-administration [37]; and a 2-year extension assessed MRI-imaging outcomes after 2 years of continuous treatment, showing a 75% of improvement of spinal lesions but yet, minor persistent inflammation in 64% of patients by the end of the study [38].

The long-term safety and efficacy of continuous treatment with etanercept 2 × 25 mg sc/week in AS was assessed in a 7-year extension trial [39] that included 26 patients from the previous study [36] who had discontinued etanercept, but had to re-start therapy four months later due to a relapse. Sixty-two participants completed the 7-year follow-up and results confirmed the safety and efficacy of continuous treatment with etanercept in AS: not only disease activity [measured with BASDAI, Ankylosing Spondylitis Disease Activity Score (ASDAS) and acute phase reactants] improved but also function (assessed by BASFI), and metrology (assessed by BASMI), with sustained low levels throughout the study: over half of the patients remaining on therapy and 31% in partial remission at the end of year 7.

Radiographic progression in the SIJs was evaluated in patients receiving etanercept for up to 6 years, as part of the extension of the ESTHER trial [40]. Radiographs of the SIJs were performed at baseline, years 2, 4, and 6. A reduction of radiographic progression was evidenced in patients that had received etanercept long term.

Etanercept's efficacy was also supported by a multicentre, double-blind, randomized clinical trial [41] including 84 patients with axial SpA. Etanercept 25 mg and placebo were administered twice weekly to 45 and 39 patients, respectively. ASAS20 response was achieved in a significantly higher number of patients on etanercept starting from week 2, and this was maintained until week 12. ASAS50 and ASAS70 responses were also achieved by a higher number of patients of the etanercept group at weeks 2, 4, and 8. Like in previous studies, etanercept also led to a decrease of acute phase reactants and improved BASDAI and spinal flexion.

The phase 2, randomized, open-label ESTHER trial, compared the capacity of 48 week-treatment with etanercept (n = 40) vs SSZ (n = 36), in order to reduce inflammatory lesions in early axial SpA, using whole-body magnetic resonance imaging (MRI) [42]. The number of locations with enthesitis decreased by 58%; and 80% of inflammatory lesions in the spine cleared by week 48, after treatment with etanercept; suggesting it could potentially have a preventative role in the development of early chronic changes [43]. A three-year extension of the ESTHER trial also used MRI to assess different inflammatory lesions in the spine and SIJs of 41 patients with early axial SpA receiving etanercept. Results showed that there

was a small amount of osteitis in these patients and there was a very low rate of new lesions during 3 years of continuous treatment [44]. Furthermore, there was no increase of fatty lesions in the spine and SIJs during the length of the study [45]. The maintenance of clinical response that had been evidenced in the 48-week trial was confirmed in the long-term at the 3-year and 10-year extensions of the study [46,47].

Another study [48] investigated the effect of 2 years of etanercept treatment on radiographic progression in patients with AS. Cervical and lumbar spine radiographs were performed at two timepoints (96 weeks apart) in patients enrolled in a phase III study receiving etanercept 25 mg twice weekly, and were compared with the radiographs of a TNF-naïve large prevalence cohort. Modified Stoke AS Spine Score (mSASSS) method was used to assess primary outcome, and the mean score change was similar in both groups, suggesting that TNF might be independent from structural progression.

2.3. Adalimumab

Adalimumab is a fully human recombinant IgG1 monoclonal antibody, with a high affinity for human TNF [49]. It is approved for the treatment of AS administered in a single dose of 40 mg sc, every other week [50].

The safety and efficacy of Adalimumab in AS were assessed in a randomized, double-blind, placebo-controlled study [49]. A total of 315 patients with active AS were recruited: 107 received placebo and 208 were randomized to adalimumab 40 mg sc every other week. ASAS20 response at week 12 was achieved in over 58.2% of participants receiving Adalimumab and 20.6% of subjects in the placebo arm. This response was sustained through week 24 for the adalimumab patients. Furthermore, Adalimumab treatment showed significant improvements in all ASAS20 components at both 12 and 24-week timepoints.

Even sub-analysis of small subgroups showed better outcomes for the adalimumab patients: 50% (3/6) and 66.7% (4/6) of patients with total spinal ankylosis receiving adalimumab achieved ASAS20 response at week 12 and 24, respectively, whereas none of the placebo arm did (0/5) at any of those two timepoints. Looking at HLA-B27 positive participants, 62% (101/163) of the ones receiving adalimumab achieved ASAS20 response at week 12 vs 23.5% (20/85) of the placebo ones. Among the HLA-B27 negative participants, 43.9% (18/41) who were on adalimumab vs 10% of those who were receiving placebo achieved ASAS20 at week 12.

The study also showed ASAS40 response was achieved at 12 weeks' time in around 39% of patients on the adalimumab arm and 13% on the placebo arm; and these remained stable at week 24. Additionally, 45.2% of patients on adalimumab experienced ≥50% improvement in BASDAI at week 12 vs 15.9% of patients on the placebo arm.

Looking at other parameters, adalimumab also demonstrated significant improvement in C-reactive protein (CRP) levels, BASMI, Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and physician's global assessment of disease activity at week 12, that were maintained at week 24; once again supporting the sustained efficacy of the drug. Finally, the safety profile was satisfactory and comparable to other TNFi in the market.

A randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of adalimumab in early axial SpA (without radiological sacroiliitis), refractory to conventional treatment [51]. A total of 46 patients were included in the study: 22 of them were allocated to receive adalimumab at the standard dose and 24 to receive placebo. The study consisted of an initial phase II lasting for 3 months and was completed by all patients, followed by a 9-month phase III, open-label extension; which was completed by 38 patients.

ASAS20 response at week 12 was achieved by 68.2% and 25% of adalimumab and placebo treated patients, respectively, whereas ASAS40 response at this same timepoint was achieved by 54.5% of adalimumab patients and 12.5% of placebo-treated patients.

In addition, response to adalimumab was sustained; with over 50% of adalimumab patients presenting ASAS40 response at 52 weeks' time. This trial also showed improvement of EMS, spinal assessments, back pain, and quality of life. A young age, short disease duration and a high CRP seem to be predictors of a better response. Adalimumab had an overall good safety profile, with SAEs reported in five patients; however, none of them were related to the drug.

The long-term efficacy of adalimumab in AS was assessed in the open-label extension of the phase III, double-blind, clinical trial, ATLAS [52]. Patients with active AS (n = 315) were initially randomized 2:1 to either adalimumab 40 mg (n = 208) or placebo sc (n = 107) every other week, for 24 weeks. After that, participants from both arms received adalimumab and were followed up for 4.5 further years. By the end of year 5, the benefits in physical function, disease activity and spinal mobility were sustained.

Radiographic progression in TNFi-naive AS patients receiving adalimumab was assessed combining the results of the cervical and lumbar spine X-rays of the ATLAS study with another phase III, double-blind, placebo-controlled trial. Pooled data from both studies were compared with the radiographic progression in a historical cohort of AS patients, who were also TNFi-naïve and were not receiving any biologic drug [53]. After 2 years of treatment, the mean change in mSASSS from baseline to year 2 did not seem to differ between patients receiving adalimumab and those from the historical cohort.

An open-label pilot study investigated the efficacy of adalimumab in active AS using MRI among other parameters [54]. Participants received adalimumab 40 mg sc every other week for 52 weeks; those who failed to achieve BASDAI50 between weeks 12 and 28 were given the drug on a weekly basis. MRI of the spine and SIJs (including T1, T2 and STIR sequences) were performed before treatment and at weeks 12 and 52, and they were available in 7 and 8 patients, respectively. A scoring system previously described [29] was used, but modified to only account for acute inflammation: both the spinal and SIJs mean scores had a substantial decrease at weeks 12 and 52. Even though these did not reach statistical significance (probably due to the small number of patients), data supported a remarkable and continuous reduction of acute inflammatory lesions with adalimumab treatment.

A later study was especially designed to investigate MRI changes in the SIJs in patients with SpA [55]: this was a 48-week phase IV, double-blind, placebo-controlled trial. Patients (n = 52) were randomized to either adalimumab 40 mg (n = 25) or placebo (n = 27) sc every other week for 12 weeks. At that timepoint, participants in the placebo arm were switched to the same regime of adalimumab; follow-up continued until week 48. An MRI was performed at weeks 0, 12, 24, and 48. Berlin (for inflammation and fatty lesions) and Spondyloarthritis Research Consortium of Canada (SPARCC) scores (for structural lesions: fatty lesions, bone erosions and backfill) were used: individuals on active drug experienced a significant improvement within 12 weeks of adalimumab treatment; and this was associated with resolution of erosions and backfill.

2.4. Certolizumab

Certolizumab pegol is a PEGylated antigen-binding fragment of a recombinant human monoclonal antibody that binds selectively, and neutralizes TNFα [56]. It is approved for the treatment of AS at with a loading dose of 400 mg (administered as two sc injections of 200 mg each) at weeks 0, 2, and 4; and a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks [57].

The efficacy of certolizumab in AS has been confirmed in phase III clinical trials. RAPID-axSpA [58], a double-blind, placebo-controlled study included 325 patients with active axial disease [AS and non-radiographic axial SpA (nr-axSpA)], who were randomized 1:1:1 to either placebo, certolizumab 200 mg every 2 weeks or certolizumab 400 mg every 4 weeks. The study lasted a total of 24 weeks, and of 57.7%-63.6% of patients treated with certolizumab achieved ASAS20 response at week 12, compared with 38.2% in the placebo arm. In addition, the effect of certolizumab on as ASAS and ASDAS scores was evident as early as in week 1; and improvements in BASDI, BASDAI and BASMI were persistent at week 24. The 4-year open-label extension of the study (with all arms receiving certolizumab after week 24) demonstrated that improvements in clinical and patient reported outcomes were sustained over 4 years [59]. This extension was also used to assess radiographic progression and the evolution of MRI inflammation of patients with axial spondyloarthritis [60]. MRI and radiograph of the SIJs and the spine were performed at baseline and weeks 12, 48, 96 and 204, and were scored using SPARCC and mSASSS methods respectively. Patients treated with certolizumab (both AS and nr-axSpA) presented early reduction of inflammation on MRI that were sustained until the end of the study. Radiographic spinal progression seemed to be slowed; especially in years 3 and 4; and SIJs changes were limited in the overall period.

In addition to its efficacy, one of the most important highlights of certolizumab is that it can be used safely during pregnancy, including the third trimester: the mother to infant transplacental transport of immunoglobulin G (IgG) is mediated by the Fc receptor, and it occurs in the second and third trimesters of pregnancy. The fact that certolizumab does not have an IgG Fc region means that it cannot bind FcRn and therefore will not transfer across the placenta.

The phase I CRIP study evaluated the placental transfer of certolizumab in 16 pregnant women (≥30 weeks of pregnancy) receiving certolizumab for their approved indication [AS, rheumatoid arthritis (RA), psoriatic arthritis, etc.] [61], and confirmed that the placental drug transfer to the infant was from non to minimal, supporting that there is no drug exposure to the fetus in the third trimester. This is consistent with no increased rate of major congenital malformations that was confirmed in the study. These data support the use of certolizumab throughout pregnancy, when necessary, to control disease activity.

CRADLE, another phase I study [62] evaluated certolizumab concentrations in human breast milk in 17 lactating women that received the drug for one of its approved indications, at least 6 weeks post-partum. Results showed that the relative infant dose quantified was 0.15% of maternal dose, and therefore not considered to be of clinical concern. The safety profile in infants whose mothers had been exposed to certolizumab was comparable to unexposed infants of similar age. These findings suggest that certolizumab treatment is compatible with breast feeding.

2.5. Golimumab

Golimumab is a human IgG1 TNFα antagonist monoclonal antibody [63]. It is approved for the treatment of AS at a dose of 50 mg sc monthly [64,65]. Efficacy and safety were assessed in phase III studies like the GO-RAISE. This was a randomized, double-blind, placebo-controlled trial, including 356 patients with active disease [66]. Participants were randomized to placebo (n = 78), golimumab 50 mg (n = 138) or golimumab 100 mg (n = 140) every 4 weeks with a ratio of 1:1.8:1.8 and were allowed to continue with their DMARD therapy. At week 24, ASAS40 was achieved in 15.4%, 43.5% and 54.3% of patients receiving placebo, golimumab 50 mg and 100 mg, respectively. Other relevant scores such as the BASDAI or the BASFI also showed significant improvement; but the BASMI was an exception. No new safety concerns were identified and golimumab was well tolerated.

A cross-over was performed at week 24 of the study, and patients who were receiving placebo were switched to golimumab 50 mg every 4 weeks. Improvement of physical function, signs, and symptoms in both golimumab arms were sustained at week 104; including BASMI [67]. Patients were followed-up for 5 years: therapy was blinded until week 104, and from then to week 252, the dose of golimumab could be adjusted. Data confirmed that the clinical improvements were sustained long-
term and safety concerns for golimumab did not differ from other TNFi [68].

Radiographic progression was assessed in the 4-year extension of the GO-RAISE trial [69]. Cervical and lumbar x-rays were performed at baseline and weeks 104 and 208 and were scored using the mSASSS method. Radiographic changes remained stable at 2 and 4 years for both golimumab doses; however, golimumab did not inhibit radiographic progression in the spine.

Axial inflammation was also investigated in the study [70]: a spine MRI was performed at baseline, weeks 14 and 104 and

images were scored using ASspiMRI-a method. Data from 98 patients were available, and those who received golimumab experienced a significant reduction in spinal inflammation; which was maintained until the end of year 4.

Efficacy and safety of i/v golimumab in AS was assessed in the GO-ALIVE trial; a phase III, double-blind, placebo-controlled study [71]. A total of 208 patient with active disease were included in the trial and they were randomized 1:1 to either placebo (n = 103) or golimumab 2 mg/kg i/v (n = 105) at weeks 0, 4, 12 and then every 8 weeks. At week 16, ASAS20 was achieved in 73.3% of patients receiving golimumab vs 26.2% in the placebo group. At that timepoint, the placebo group had a crossover and received golimumab 2 mg/kg at weeks 16, 20 and every 8 weeks thereafter; improvements were observed 4 weeks later. For both arms, drug efficacy was maintained at week 28. Follow-up continued for 1 year; and ASAS20, ASAS40, BASDAI, and BASFI were sustained in both groups receiving golimumab [72].

2.6. TNFi efficacy at addressing extraarticular manifestations

2.6.1. Uveitis

There is a general agreement that adalimumab, certolizumab and golimumab therapies are associated with a decrease in the number of uveitis flares [73–75]; however, there is controversial data regarding the protective role of infliximab and etanercept. In 2005, a review reported that both infliximab and etanercept were efficacious at decreasing the number of flares of anterior uveitis [76]; however, results from the Swedish biologics register suggest that the risk of uveitis flare is increased when initiating etanercept [73]. In contrast, a recent Korean study reported that the recurrence rate of uveitis was higher with infliximab than with etanercept [77].

Even though the prevalence of anterior uveitis in AS reaches 25%, the incidence of uveitis flares per year can be quite low [76]. Considering this, grouping the results of several studies seems to be a reasonable option; however, the disparity of characteristics among the studies can complicate withdrawing conclusions.

2.6.2. Psoriasis

Psoriasis is present in 9.3% of patients with AS [78]. Infliximab, etanercept, adalimumab, and certolizumab are licensed for the treatment of plaque psoriasis; however, depending on the severity of the skin disease, the dosage may need to be adjusted in treatment in etanercept and adalimumab [14,32,50,57]. Even though they all have demonstrated their efficacy at managing the disease, a meta-analysis supported that infliximab was significantly more effective [79].

It should be born in mind that TNFi can also be the trigger for paradoxical psoriasis, even in absence of a personal of family history of the disease; however, these lesions tend to subside after discontinuation of the TNFi or the use of topical treatment alone [80].

2.6.3. Inflammatory bowel disease

Inflammatory bowel disease (IBD), either in the form of Crohn's disease (CD) or ulcerative colitis (UC) is present in 6.8% of patients with AS [78]. Etanercept is the only TNFi that is not licensed for the treatment of any form of IBD; furthermore, some reports have associated it with flareups or new onset of the disease [81]. Whereas infliximab and adalimumab are approved for the treatment of both CD and UC, certolizumab is authorized for the treatment of CD and golimumab has an approved indication for UC [14,50,57,64].

A systematic review and meta-analysis showed that infliximab might be more efficacious than adalimumab and golimumab at inducing clinical response and mucosal healing in patients with UC [81,82]. Another meta-analysis assessed efficacy in CD, finding no differences between infliximab and adalimumab; however, certolizumab was not included in the search as it had not been licensed for CD in Europe at that time [83].

2.7. Biosimilars

One of the main reasons for the limited access to TNFi in some regions is their elevated cost. As a result of this, multiple TNFi biosimilars have been developed and are currently in use in Europe [approved by the European Medicines Agency (EMA)] and the United States [approved by the Food and Drug Administration (FDA)]:

CT-P13 (Remsima, Inflectra) is a biosimilar of Infliximab (Remicade®). Comparative studies have shown that there are no significant differences in pharmacokinetics, tolerance, drug retention, treatment duration, efficacy, and safety in the short- and long-term treatment of patients with AS [84,85]; and therefore biosimilars have been approved for the same indications as their originator (when a biosimilar drug is licensed for one of the indications the original drug was approved, license for other indications can be extrapolated to the biosimilar without the need to carry out head-to-head comparative studies). Other approved infliximab biosimilars are SB2 (Flixabi/Renflexis) and PF-06438179 (Zessly/Ixifi) [86].

Etanercept (Enbrel®) already has two biosimilars whose use has been approved in Europe and the United States: SB4 (Benepali), GP2015 (Erelzi). Efficacy and safety of SB4 vs originator etanercept were assessed in a 52-week phase III, randomized, double-blind trial [87]: Results showed that both drugs were similar in these two aspects, including radiographic progression and tolerance. A minor difference was the incidence of anti-drug antibodies (ADA); which was lower in SB4 than in the original etanercept by week 52 (1.0 and 13.2%, respectively). GP2015 achieved its license after demonstrated similar efficacy and safety as the originator in the EGALITY study, a double-blind, randomized, trial in patients with plaque psoriasis [88]. The third etanercept biosimilar, Nepexto has not yet been approved by the FDA [86].

Multiple adalimumab (Humira®) biosimilars have been licensed, and ABP501 (Amgevita/Solymbic/Amjevita) was the first one. This was followed by BI 695501 (Cyltezo), FKB327 (Hulio), GP2017 (Hyrimoz), MBS11022 (Idacio) (not approved in the US), PF-06410293 (Amsparity/Abrilada) and SB5 (Imraldi/Hadlima). All of them met were confirmed to share a similar structure, biological properties, efficacy, and safety as the original adalimumab [86].

3. Conclusion

TNFi are a safe and effective therapy for the treatment of patients with AS, who have failed to NSAIDs or these are contraindicated. Even though new drugs with different mechanisms are now in the market, the good short-term and long-term results of TNFi gives them a central role in the management of axial disease.

4. Expert opinion

The efficacy of TNFi's is overall similar, leading to a significant improvement of clinical, laboratory, imaging, and patient reported outcomes (Table 1).

Safety-wise, TNFi are comparable, with few SAEs, some of which can be prevented by doing the appropriate tests in advance. Furthermore, pre-biologic screening has also been implemented into clinical practice and has become a standard procedure before TNFi initiation., The fact that less than 10% of patients discontinue in long-term studies because of side-effects, reflects the safety of these drugs [47].

Considering this, in order to make an optimized treatment approach, it is important to address the whole clinical picture of the patient, and focus on the particular advantages and disadvantages of one drug over the other. The prevalence of extra-articular manifestation in AS is fairly common. They can have a significant impact on patient outcomes, and therefore, they should be a key therapeutic consideration.

Due to conflictive data regarding the effect of infliximab and etanercept in uveitis, in patients with a history of this manifestation, the use of adalimumab, certolizumab or golimumab is preferred.

Golimumab has not received approval for the treatment of psoriasis; and therefore, should be the least favored TNFi option in patients diagnosed with this skin disease. Infliximab has shown better results than the other TNFi in patients with psoriasis; and hence could be a better choice unless combined therapy with methotrexate is not possible.

In patients with IBD, etanercept should be avoided. For CD, infliximab, adalimumab and certolizumab are all similarly good choices; and in UC, infliximab may be preferable over adalimumab or golimumab.

Pregnancy is another aspect that should be taken into account when choosing a TNFi agent: in women of childbearing potential (especially if conception is wanted), or women who are breastfeeding, certolizumab would be the treatment of choice.

In spite of the outstanding results of TNFi for the management of AS, approximately 1/5 patients have either primary or secondary treatment failure; providing evidence that there is still room for improvement [47].

With the exception of etanercept, one of the reasons for TNFi secondary treatment failure is the formation of ADA. Multiple trials have demonstrated that these are associated with lower drug levels and a reduced response to treatment [89–91]; on the other hand, combined therapy of TNFi and DMARDs is associated with a smaller proportion of patients developing ADA, compared with TNFi monotherapy [92,93]. This is particularly relevant in order to increase long-term maintenance of therapy, especially in patients receiving infliximab; therefore, in case of intolerance or contraindication to methotrexate, this biologic may not be the first option.

Since they became available, one of the main questions surrounding TNFi is whether they can prevent radiographic progression; unfortunately, this has not been answered yet. Some studies suggest that TNFi might be able to decelerate bone damage [25,60,94] or at least, stabilize it perhaps by reducing disease activity [69,95]. Even though, none of these trials has been able to prove that this process can be stopped, this hypothesis has not yet been ruled out.

Structural changes in the spine tend to progress more in patients who experience symptoms for over 5 years, compared to those with shorter disease duration (≤5 years) [96], implying that there could be a 'window of opportunity' if TNFi is commenced early. This is supported by a study that reported increased radiographic progression in patients that commenced TNFi therapy >10 years after diagnosis, compared with those who had an earlier administration [97].

Additionally, studies that support reduction of structural damage report these beneficial effects of TNFi after 2 years of continuous treatment; which tends to be in years 3 and 4 [25,59]. However, many studies assessing radiographic progression are only 2 years long.

In contrast with the conflictive results regarding radiographic progression, all studies seem to agree on the efficacy of TNFi for axial disease, assessed by MRI. Data show that a significant reduction of spinal and SIJs inflammation can be achieved as early as 12 weeks after treatment initiation, and these improvements are sustained over the years [28,60,70]. Improvements of MRI scores are associated with resolution of erosions and backfill and up to a 75% of reduction of spinal lesions [55]. In spite of these remarkable results, some 2 and 3-year studies have reported minor persistence of inflammation, by the end of the trial [30,44]; however, new-onset osteitis is maintained at a very low rate.

The heterogenicity of the trials available, with different inclusion/exclusion criteria and the multiple confounding factors make it difficult to perform comparisons among studies.

Disease modification, and in particular the evolution of structural changes can be especially challenging in placebo-controlled trials, as it is not ethical to keep patients on placebo for years, knowing that new bone formation and ankylosis are not reversible.

An additional complication is the modest number of participants included in early phase clinical trials and the long follow-up required to assess radiographic progression. Considering that AS patients are a young population, it is not surprising that up to 1/6 of them discontinue long-term studies wishing to conceive; which reduces even more the final study population and the reliability of the results.

Another area for improvement relates to the safety assessment of TNFi during pregnancy. Certolizumab is the first TNFi whose use throughout pregnancy has been approved by the EMA; but besides that, all TNFi are classified as category B, which reflects that no well-control studies exist in pregnant women. At the moment, contraception is advised for several months after the last TNFi dose; however, 50% of women with

Table 1. Early phase clinical trials that contributed to the support the use of TNF inhibitors in ankylosing spondylitis

DRUG EVALUATED	TYPE OF STUDY	PATIENTS INCLUDED	TREATMENT REGIMES	STUDY DURATION	ASPECTS ASSESSED	FINDINGS	ADVERSE EVENTS	REF.
Infliximab	Open label, pilot study	Treatment resistant SpA with active disease N=21 (AS, n=10)	Loading dose of 3x5mg/kg i/v infusions of infliximab at weeks 0,2 and 6	84 days	- Efficacy (Patient VAS, BASDAI, BASFI, BASMI, psoriasis/PASI) - Safety	Decrease in acute phase reactants, patient and physician global assessment as early as in day 3, and maintained up to day 84.	Minor side effects (n=12): Nausea, dizziness, headache, fatigue, diarrhoea, palpitations, burning feeling in eyes	[15] Van den Bosch
Infliximab	Randomised, double-blind, placebo-controlled trial	Active SpA N=40 (AS, n=21)	Loading dose of infliximab 5mg/kg (n=20) or placebo (n=20) at weeks 0, 2 and 6	12 weeks	- Efficacy (BASDAI, BASFI, DFI, PASI, BASMI, spinal VAS) - Safety	Significant improvement of clinical and laboratory parameters, short-term.	SAEs in the infliximab arm (n=2): - Patient withdrawn due to tuberculosis infection. - Septic arthritis secondary to a procedure Minor AEs (n=21): minor infections, nausea, abdominal, pain, skin itching, headache, dizziness, fatigue	[16] Van den Bosch
Infliximab	Randomised, placebo-controlled trial	Severe AS N=70	Loading dose of infliximab 5mg/kg (n=34) or placebo (n=35) i/v at weeks 0, 2 and 6	12 weeks	- Efficacy (ASAS20 and 50, BASDAI, BASFI, BASMI, SF-36) - Safety	Significant improvement of clinical parameters, metrology and quality of life in patients receiving infliximab.	SAEs (n=3); in the infliximab arm which required WD from study: - Tuberculosis - Bronchiocentric allergic granulomatosis of the lung - Transient leucopenia Mild AEs: upper respiratory tract infection	[17] Braun
Infliximab	Open-label, observational 1st year extension study of a 3-month, randomised, placebo-controlled trial	Active AS N=65	Infliximab 5mg/kg i/v every 6 weeks (n=30), with a loading dose for those who had been randomised to placebo (n=35) in the anterior study phase	1 year	- Efficacy (ASAS20, BASDAI, BASFI, BASMI, BASRI-s) - Safety	Significant improvements in functioning, metrology parameters and quality of life; with rapid reduction of BASDAI scores >50%.	Safety profile similar to post-marketing experience. SAES (n=4); which required WD from study: - ANA- associated symptoms (n=3) - Hepatitis (n=1) Mild to moderate AEs: upper respiratory tract infection, headache, elevated transaminase levels, sinusitis	[18] Braun
Infliximab	Open-label, observational 2nd year extension of an original 3-month randomised, placebo-controlled trial	Active AS N=52	Infliximab 5 mg/kg i/v every 6 weeks (up to week 102).	2 years (1-year extension)	- Efficacy (BASDAI, BASFI, BASMI, ASAS40, SF-36) - Safety	Sustained improvement of symptoms seen during the 1st year. A 50% reduction of BASDAI was evidenced in 58% of patients at week 102. Persistence of low levels of acute phase reactants.	90% of patients reported ≥1 AE; most commonly mild to moderate : RTI, infection, rhinitis, herpes simplex, etc. SAEs (n=6; 2 of them related to the study drug): - Infussion related - MSK pain 3 of these patients discontinued the study	[19] Braun
Infliximab	Open-label, observational 3rd year extension of an original 3-month randomised, placebo-controlled trial	Active AS N=46	Infliximab 5 mg/kg i/v every 6 weeks (up to week 156).	3 years (1-year further extension)	- Efficacy (ASAS20 and 40, BASDAI, BASFI, BASMI, SF-36) - Safety	Sustained efficacy and maintenance of clinical response. Persistence of low acute phase reactants. Good drug tolerance.	96% of patients reported ≥1 AE; most freq. RTI, diarrhoea, rhinitis. SAEs (n=6); however none were related to infliximab	[20] Braun

(*Continued*)

Table 1. (Continued).

DRUG EVALUATED	TYPE OF STUDY	PATIENTS INCLUDED	TREATMENT REGIMES	STUDY DURATION	ASPECTS ASSESSED	FINDINGS	ADVERSE EVENTS	REF.
Infliximab	Open-label 4th and 5th year extension of an original 3-month randomised, placebo-controlled trial	Active AS at baseline N=42	Infliximab 5mg/kg i/v every 6 weeks, until the end of year 5	5 years (years 4 and 5)	- Efficacy (BASDAI, BASFI, BASMI, ASAS20 and 40, PatGA, PhysGA) - Safety	Efficacious treatment: 1/3 remained in remission; 1/3 low disease activity (BASDAI<3), 20% BASDAI>4 No indication of loss of response.	95% of patients reported ≥1 AE, Mos freq. were bronchitis, increase of liver enzymes. SAEs (n=6). Two of them related to infliximab and led to WD: - Recurrent vaginal infections - Repeated RTI	[21] Braun
Etanercept	Randomised, double-blind, placebo-controlled trial	Active AS N=40	Either 25mg of etanercept sc or placebo (n=20), twice weekly	4 months	- Efficacy (EMS, nocturnal spinal pain, BASFI, phVAS, SJC) - Safety	Rapid and sustained clinical response to treatment by patients receiving etanercept.	No SAEs or WD due to AEs. Most common AEs: injection site reaction, minor infections (RTI).	[31] Gorman
Etanercept	Open-label extension of a randomised, double-blind, placebo-controlled trial	Active AS N=38	25mg of etanercept sc twice weekly	10 months (6-month extension)	- Efficacy (ASAS20, 50 and 70; EMS, nocturnal spinal pain, BASFI, patient VAS, SJC) - Safety	Improvement of axial manifestations of AS: ASAS20 achieved by 94% of patients	No SAEs or WD due to AEs. Reported AEs were consistent with blinded phase of the study.	[33] Davis
Etanercept	Phase II double-blind trial. Two phases: 1) Randomised, placebo-controlled 2) Observational	Active AS N=30	- Phase 1: Either 25mg of etanercept sc twice weekly (n=14) or placebo (n=16) - Phase 2: etanercept 25mg sc twice weekly until completing 12 weeks of treatment	- Phase 1: 6 weeks - Phase 2: 24 weeks	- Efficacy (BASDAI, BASFI, BASMI, spinal pain, PhVAS, ASAS20, BASRI-s) - Safety	Short term efficacy of etanercept:>50% of patients achieved BASDAI50 at week 6. By week 9, 80% of patients achieved BASDAI50. Disease relapse after treatment cessation.	No SAEs or WD due to AEs. Most common AEs: injection site reaction, minor infections (RTI).	[36] Brandt
Etanercept	Open-label extension of a phase II, double-blind, randomised, placebo-controlled trial	Active AS N=26	25 mg of etanercept sc twice weekly	54 weeks (rest of year 1)	- Efficacy (BASDAI, spinal pain, BASFI, BASMI, ASAS20 and 40) - Safety (Including discontinuation and re-administration)	Etanercept is efficacious and safe after re-administration over 1 year, with 58% of patients achieving a 50% improvement of BASDAI at week 54.	SAEs (n=5): - Upper RTI - Diarrhoea - Chest discomfort - Renal colic - New onset of CD; which recovered after etanercept discontinuation (patient withdrawn as a result) Most commmon ninor AEs: RTI, bronchitis, diarrhoea, cough.	[37] Brandt
Etanercept	Open-labelxtension of a phase II, randomised, double-blind, placebo-controlled trial	Active AS N=26	25 mg of etanercept sc twice weekly	2 years	- Clinical efficacy (ASAS20 and 40, BASDAI, BASFI, BASMI, SF-36) - Imaging: MRI outcomes (ASspiMRI-a) - Safety	BASDAI50 achieved by 54% of patients at week 102 and efficacy sustained over 2 years. Improvement of active spinal lesions by 75%; however, minor persistent inflammation in 64% of patients after 2 years.	SAEs (n=5): - New onset of CD; which recovered after etanercept discontinuation (patient withdrawn as a result) - Late state lung carcinoma (patient withdrawn) - Other SAEs not treatment related Most common minor AEs: RTI, fever of unclear origin, diarrhoea.	[38] Baraliakos

(*Continued*)

Table 1. (Continued).

DRUG EVALUATED	TYPE OF STUDY	PATIENTS INCLUDED	TREATMENT REGIMES	STUDY DURATION	ASPECTS ASSESSED	FINDINGS	ADVERSE EVENTS	REF.
Etanercept	Open-label extension of a phase II, randomised, double-blind, placebo-controlled trial	Active AS N=26	2x25mg of etanercept sc weekly	7 years	- Efficacy (BASDAI, ASAS20 and 40, ASDAS, spinal pain, BASMI, BASFI, PhysGA) - Safety	Sustained long-term efficacy and safety of etanercept. More than 50% of patients remain on treatment after 7 years of continuous administration.	AEs: recurrencce of uveitis (the majority after treatment initiation) in 44% of patients. SAEs that lead to WD: - Development of CD - Reactivation of CD - Lung carcinoma - Death (likely due to heart attack)	[39] Baraliakos
Etanercept	Randomised, double-blind, placebo-controlled trial	Active AS N=84	Either 25 mg of etanercept sc (n=45) or placebo (n=39), twice weekly	12 weeks	- Efficacy (ASAS20, 50 and 70, BASDAI, BASFI, spinal pain) - Safety	Good tolerance and efficacy of etanercept, showing a reduction of clinical symptoms and signs as soon as from week 2.	AEs mostly mild to moderate. No WD due to safety issues. SAEs (n=1): acute myocardial infarction	[41] Calin
Etanercept	Phase II, randomised, open-label trial (ESTHER)	Early axial SpA with inflammatory lesions on MRI N=76	A) 25 mg of etanercept sc twice weekly (n=40) B) SSZ 2-3g daily, given orally (n=36)	48 weeks	Comparison of potential to reduce active inflammatory lesions on whole-body MRI	MRI lesions had a more significant improvement for patients receiving etanercept vs SSZ. This improvement was correlated with good clinical response	Similar number of AEs in both treatment arms. RTI was the most common. SAEs (etanercept=3; SSZ=7); only 3 treatment related (etanercept=1; SSZ=2)	[42] Song
Etanercept	Extension of a phase II, randomised, open-label trial (ESTHER)	Early axial SpA with inflammatory lesions on MRI N=41	25 mg of etanercept sc twice weekly	3 years	- Clinical efficacy (BASDAI, BASFI, ASDAS, BASMI, ASAS partial remission) - Imaging: fluctuation of osteitis on MRI - Safety	There was sustained clinical response in patients receiving etanercept throughout 3 years. A small amount of osteitis was present after 3 years, but the rate of new lesions was very slow.	SAEs (n=3): - Sarcoidosis (patient withdrawn) - Other 2 not drug related Most common AEs: RTI (42%),	[44] Song [46] Song
Etanercept	Extension of a phase II, randomised, open-label trial (ESTHER)	Early axial SpA with inflammatory lesions on MRI N=19	25 mg of etanercept sc twice weekly	10 years	- Efficacy (ASDAS, ASQoL, BASDAI, BASFI, BASMI, MASES, EQ-5D, ASAS20 and 40) - Safety	Good tolerance, safety profile and sustained clinical response over 10 years of etanercept treatment.	SAEs (n=39); only 7 possibly related to treatment; out of whicn 3 resulted in study WD: Most relevant reasons for discontinuation: sarcoidosis, demyelinating neurological disease, lymphoma, uveitis	[47] Proft
Adalimumab	Randomised, double-blind, placebo-controlled trial	Active AS N=315	Either adalimumab 40mg sc (n=208) or placebo (n=107), every other week	24 weeks	- Efficacy (ASAS20, BASDAI, spine pain, EMS, BASFI, BASMI) - Safety	Good tolerance. Sustained and significant reduction of signs and symptoms in patients receiving adalimumab, appearing as early as by the end of week 2	A higher percentage of patients in the adalimumab arm reported AEs; however; most of them were minor-moderate. Similar incidence of infections in adalimumab and placebo patients.	[49] Van der Heijde

(*Continued*)

Table 1. (Continued).

DRUG EVALUATED	TYPE OF STUDY	PATIENTS INCLUDED	TREATMENT REGIMES	STUDY DURATION	ASPECTS ASSESSED	FINDINGS	ADVERSE EVENTS	REF.
Adalimumab	Randomised, double-blind, placebo-controlled trial	Active SpA without radiographic sacroiliitis N=46	Phase 1: either placebo (n=24) or adalimumab 40mg sc (n=22), every other week for 12 weeks. Phase 2: open-label extension up to week 52.	52 weeks	- Efficacy (BASDAI, BASFI, BASMI, EQ-5D, ASQoL, MASES, ASAS20 and 40) - Safety	Good clinical efficacy and safety profile in patients without radiographic sacroiliitis, refractory to conventional treatment.	SAEs (n=5); however, none were drug related. Similar numbers of AEs in adalimumab and placebo arm; most common RTI.	[51] Haibel
Certolizumab	Phase I, prospective study (CRIB)	Women ≥30 weeks pregnant receiving certolizumab for locally approved indication (RA, SpA/AS, PsA and CD) N=16	Certolizumab sc: either 200mg every 2 weeks (n=15) or 400 mg every 4 weeks (n=1).	8 weeks of follow-up from delivery	Evaluation of placental transfer of certolizumab	From no to minimal placental transfer of certolizumab to infants. Treatment is safe during pregnancy.	Most AEs were mild-moderate. SAEs: - Mothers (n=2): Arressted labour, prolonged labour - Infants (n=1): unspecified infection	[61] Mariette
Certolizumab	Phase I, prospective study (CRADLE)	Lactating women ≥6 weeks postpartum, receiving certolizumab for an approved indication (RA, SpA/AS, PsA and CD) N=17	Certolizumab sc: either 200mg every 2 weeks (n=16) or 400 mg every 4 weeks (n=1)	9 weeks	- Pharmacokinetics - Evaluation of the transfer and concentration of certolizumab in breast milk	From no to minimal certolizumab transfer from plasma to breast milk. Treatment is safe during breast feeding.	AEs in mothers and infants were mostly mild to moderate SAEs (n=1): mother developed a breast abscess	[62] Clowse

AEs= adverse events; ANA=anti-nuclear antibodies; AS= ankylosing spondylitis; ASAS= Assessment in Ankylosing Spondylitis; ASDAS= Ankylosing Spondylitis Disease Activity Score; ASQoL=Ankylosing Spondylitis Quality of Life questionnaire; ASspiMRI-a= Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity; BASDAI= Bath Ankylosing Spondylitis Disease Activity Index; BASFI= Bath Ankylosing Spondylitis Functional Index; BASMI= Bath Ankylosing Spondylitis Metrology Index; BASRI-s=Bath Ankylosing Spondylitis Radiology Index for the spine; CD=Crohn's disease; DFO= Dougados Functional Index; EMS=early morning stiffness; EQ-5D= European Quality of Life Five Dimension; i/v=intravenous; MASES=Maastricht Ankylosing Spondylitis Enthesitis Score; MRI=Magnetic resonance imaging; MSK=musculoskeletal; MTX= methotrexate; PASI= Psoriasis Area Severity Index; PatGA=patient's global assessment; PhysGA=physician's global assessment; PhVAS=physician's VAS; RA=rheumatoid arthritis; RTI=respiratory tract infection; sc= subcutaneous; SJC=swollen joint count; SpA= spondyloarthritis; SSZ= sulfasalazine; VAS= visual analogue scale; WD= withdrawal

rheumatic diseases experience flares requiring drug intervention [98]; which means that in real life medical practice, TNFi treatment may be maintained throughout pregnancy if clinically needed. A comprehensive investigation on the safety of TNFi in pregnancy is required; however, there are ethical reasons that withhold this research due to potential side effects of the drugs [99].

There are several aspects that also need further research to be carried out: for i.e. preliminary data suggests that patients with total spinal ankylosis could benefit from TNFi therapy [49]; however, most trials exclude these patients from participation. Another example is entheseal inflammation; which is not thoroughly investigated in early phase clinical trials: uveitis has a low prevalence in AS, and assessment is difficult given the low number of patients in these studies.

Looking forward in AS, most of the efforts seem to be focused on finding new molecules that can interfere with other inflammatory pathways: from the family of the Janus Kinases (JAK) inhibitors, tofacitinib has successfully gone through phase II trials [100] and is currently being assessed in phase III studies [101]. Upadacitinib, a selective JAK1 inhibitor demonstrated its efficacy in a phase II/III RCT (the SELECT-AXIS 1 study), and has recently received approval for the treatment of AS by the EMA [102].

Regarding the IL-17 pathway, secukinumab is probably the most relevant therapeutic agent. The short-term and long-term efficacy of this anti-IL-17A in AS was assessed in the phase III, double-blind, randomized, placebo-controlled MEASURE studies and their extensions. Trials MEASURE 1 and 2 showed significantly better outcomes (ASAS20 and 40, BASDAI, SF-36, BASFI and EQ-5D) for patients receiving either regime of secukinumab (75 mg or 150 mg sc every 4 weeks; with either a sc or i/v loading dose) compared with placebo; and these improvements were sustained until year 5. The studies also found less changes in spinal scores (mSASSS) compared with previous TNFi studies [103,104].

MEASURE 3 compared the efficacy, safety and tolerability of two secukinumab regimes vs placebo: 150 mg and 300 mg sc every 4 weeks both preceded by an i/v loading dose of 10 mg/kg. As expected, both regimes provided a significant improvement in AS outcomes that was maintained until week 52 [105].

Additionally, a phase II pilot study suggested that 2-year treatment with secukinumab provided regression of spinal inflammation on MRI; however, only a small the number of patients were included [106].

Like secukinumab, ixekizumab (an IL-17 antagonist) is also approved for the treatment of AS [107,108]; brodalumab recently demonstrated significant improvement for the treatment of axial SpA [109], and the efficacy of bimekizumab is currently being investigated in phase II trials [110]. IL-23 inhibition seemed to be a promising therapeutic target; however, the results of a phase II trial assessing risankizumab in AS did not meet the primary endpoint and failed show evidence of better clinical improvements than placebo [111].

There is a high socio-economic burden associated to AS [112], and due to their outstanding clinical results and their good safety profile, TNFi represent a major therapeutic advance in the short and long-term management of the disease. Rather than searching for new molecules to add to the TNFi family, perhaps the future lies with the development of biosimilars, and the optimization of TNFi administration.

Funding

This paper was not funded.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Declaration of interest

P. Emery has provided expert advice to Pfizer, Abbvie, Amgen, MSD, Roche, Sanofi, BMS, Novartis, Lilly, Gilead, Samsung, Celltrion; and has received grants from Abbvie, BMS, and Samsung. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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