The introduction of etanercept (ETN; Enbrel®), and other TNF-blockers, has revolutionized the treatment of patients with ankylosing spondylitis. ETN, as with other approved TNF-blockers, shows good efficacy in treating spinal disease, especially if patients are treated early. Furthermore, studies involving ETN demonstrate good long-term efficacy. This review summarizes the data on ETN in the treatment of ankylosing spondylitis and non-radiographic axial spondyloarthritis, and discusses topics such as its efficacy in treating extra-articular manifestations, dose modifications and immunogenicity of ETN, and switching between ETN and other TNF-blockers, as well as radiographic progression and safety.

**Keywords:** ankylosing spondylitis • axial spondyloarthritis • biosimilars • etanercept • extra-articular manifestations • immunogenicity • MRI • radiographic progression • TNFα-inhibitor • uveitis

Ankylosing spondylitis (AS) is a chronic inflammatory disease that is characterized by chronic inflammatory back pain, enthesitis, inflammation in the sacroiliac joints (SI-joints) and peripheral arthritis, but also extra-articular symptoms, such as acute anterior uveitis (AAU), inflammatory bowel disease and psoriasis [1].

In 2009, 25 years after introduction of the modified New York criteria [2], the Assessment of SpondyloArthritis international Society (ASAS) axial spondyloarthritis (SpA) classification criteria were published [3]. According to these criteria, patients can be classified as having axial SpA already in the non-radiographic stage (non-radiographic axial SpA), for example, if the radiographs of the SI-joints do not show chronic inflammatory changes. Active inflammation (bone marrow edema) of the SI-joints, as shown by MRI, is an important part of these new criteria [4].

During the last few years, effective referral strategies have been proposed when a patient with chronic low back pain should be referred to a rheumatologist [5]. According to the recommendations from the ASAS and the European League Against Rheumatism, in active disease, nonsteroidal anti-inflammatory drugs (NSAIDs) should be administered to patients first [6]. After failure of at least two NSAIDs for a total of 4 weeks in patients with predominant axial disease, TNF-blockers are recommended according to ASAS [7]. Among the TNF-blockers that are currently labelled for treatment of active AS, four agents including infliximab (IFX), etanercept (ETN; Enbrel®), adalimumab (ADA) and golimumab are available; for the treatment of axial disease all these TNF-blockers show a very similar response rate with approximately 40–45% of patients reaching a so-called ASAS40 response or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 response [8–11].

This review summarizes the data regarding ETN in the treatment of AS and non-radiographic axial SpA and discusses topics such as its efficacy in treating extra-articular manifestations including uveitis, dose modifications of ETN, immunogenicity, switching between ETN and other TNF-blockers, as well as radiographic progression and safety.
ETN is a fully humanized dimeric fusion protein consisting of the extracellular ligand-binding domain of the humanized 75 kDa TNF-α receptor linked to the Fc portion of human IgG1 [201]. ETN is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kDa [202]. ETN, which has a half-life of 4.3 days [201], neutralizes the proinflammatory cytokine TNF-α and is an effective and approved treatment option for several immune-mediated inflammatory diseases including psoriatic arthritis (PsA), plaque psoriasis (PsO; including PsO in children aged 6 years or older), rheumatoid arthritis (RA), AS and polyarticular juvenile idiopathic arthritis in patients aged 2 years or older [10,12,13].

Treatment of established AS with ETN
The first clinical trials with ETN in AS with MRI have already demonstrated a beneficial effect in terms of both clinical and MRI findings [14,15]. In the following randomized placebo-controlled trials of ETN, which included a higher number of patients, improvement of disease parameters and other parameters was reported [10,12,16]. Subsequently ETN was approved for the treatment of active AS and has since shown stable response rates in long-term treatment over several years [17].

In another randomized controlled trial (ASCEND) the efficacy of ETN (n = 379; 50 mg subcutaneous [sc.] once weekly) was evaluated versus sulfasalazine (SSZ; n = 187; up to 3 g daily per os) in patients with established AS with a disease duration of 7.6 years [18]. In this trial, the primary end point, which was an ASAS20 response at week 16, was reached significantly more often in ETN-treated patients compared with SSZ-treated patients (75.9 vs 52.9%; p = 0.0001) [18]. A subgroup analysis of the ASCEND population also demonstrated that, in terms of efficacy on peripheral symptoms, ETN was superior to SSZ [19].

The question was whether treatment with TNF-blockers also works in AS patients with advanced disease. In this context an interesting study (SPINE trial) was performed with ETN [20]. In this 12-week randomized placebo-controlled trial 39 AS patients were treated with ETN 50 mg sc. once weekly versus 43 patients who received placebo. All patients had advanced disease with a mean disease duration of 21 years and a mean modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) of 37 out of 72. Improvement in BASDAI (normalized net incremental area under the curve between baseline and week 12), which was the primary outcome, was significantly greater in the ETN group compared with the placebo group (-19.8 ± 16.5 vs -11.0 ± 16.4; p = 0.019) [20]. A good clinical response in the ETN-group was also illustrated by BASDAI50 or ASAS40-response rates of 46 and 44% versus 23 and 23% in the placebo group, respectively.

In summary, ETN shows a good and stable efficacy in patients with established and also advanced disease. The next question was whether early treatment would improve the efficacy rates.

Treatment of early axial SpA with ETN
During the last years many efforts have been made to improve an early diagnosis [21]. In addition, predictors for a major clinical response have been identified, which included – amongst others – shorter disease duration [22–24]. To date, a total of four clinical studies with TNF-blockers (including one trial with ETN [25]) have been performed in patients with SpA, demonstrating a very good response in a high percentage of patients, especially in those with a disease duration of less than 3–5 years (Table 1 [24–27]). All four clinical trials have in common that an elevated disease activity (BASDAI ≥ 4) despite intake of NSAIDs had to be present, that MRIs were performed and that the ASAS classification criteria were fulfilled (Table 1) [3].

In a trial in which ETN was used in early axial SpA, disease duration was less than 5 years [25]. Patients were treated for 48 weeks prospectively with ETN (25 mg biweekly [BIW] sc.; n = 40) versus SSZ (SSZ; n = 36; ESTHER trial: “Effects of Etanercept versus Sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole body MRI”) [25]. All patients underwent whole-body MRIs, which allowed the assessment of active inflammatory lesions of the spine, the SI-joints and enthesitic sites. MRI reading was performed by two blinded readers for treatment and time point of examination. The mean disease duration was short with a mean of 2.9 years. The primary end point (reduction of active inflammation on whole-body MRI) was reached significantly more often by ETN- compared with SSZ-treated patients in terms of reduction of active inflammatory lesions of the SI-joints (69 vs 35%; p = 0.02), of the spine (57 vs 7%; p = 0.01) and also for the number of MRI-proven enthesitic sites (58 vs 0%; p = 0.04). There was also a significantly better clinical response in the ETN- versus SSZ-group (ASAS partial remission reached in 50 vs 19%; p = 0.006). MRI examples for the reduction of active inflammatory lesions in the sacroiliac joints, the spine and entheses are shown in Figure 1 [25].

Another interesting aspect in this context is the role of SSZ in axial SpA. Here, the ASAS/European League Against Rheumatism-recommendations stay unchanged [6]; although patients who were treated with SSZ reached ASAS remission in 19% after 1 year of treatment, this rate – although inclusion criteria were not directly comparable – corresponds with the remission rate of 13% in the placebo group (in a placebo-controlled trial)
Table 1. Comparison of clinical trials with TNF-blockers in early axial spondyloarthritis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study design</th>
<th>Number of patients included</th>
<th>Mean disease duration (years)</th>
<th>Male/HLA-B27 positive (%)</th>
<th>Non-radiographic SpA/AS (%)</th>
<th>Active inflammatory lesions at baseline (%)</th>
<th>Primary outcome parameter of trial</th>
<th>Clinical response: ASAS partial remission</th>
<th>MRI response: reduction of active inflammation on MRI</th>
<th>Notable features</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETN</td>
<td>48-week open-label clinical trial comparing ETN vs SSZ</td>
<td>76 (40 ETN vs 36 SSZ)</td>
<td>2.9</td>
<td>58/82</td>
<td>48.7/51.3</td>
<td>MRI SIJ and/or spine: 100</td>
<td>Reduction of active inflammation on MRI of the SIJ and spine at week 48</td>
<td>Week 48: 50 (ETN) vs 19% (SSZ)</td>
<td>Week 48: reduction in ETN vs SSZ group in SIJ (69.2 vs 35.2%; p = 0.02); in spine (57 vs 7%; p = 0.01); enthesitis (58 vs 0%; p = 0.04)</td>
<td>First trial using ETN in early axial SpA; long treatment (1 year), systematic analysis of MRI</td>
</tr>
<tr>
<td>IFX</td>
<td>16-week placebo-controlled trial</td>
<td>40 (20 IFX vs 20 placebo)</td>
<td>1.25</td>
<td>75/100</td>
<td>88/12¹</td>
<td>MRI-SIJ and/or spine: 100</td>
<td>Change of MRI SIJ score at week 16</td>
<td>Week 16: 55.6 (IFX) vs 12.5% (placebo)</td>
<td>Week 16: median MRI score (baseline = 3.5) reduced significantly in IFX vs placebo (-2.0 vs 0; p = 0.033)</td>
<td>Very short disease duration; all patients HLA-B27 positive and with 'positive' MRI</td>
</tr>
<tr>
<td>ADA</td>
<td>12-week placebo-controlled trial with open extension until week 52</td>
<td>46 (22 ADA vs 24 placebo)</td>
<td>7–8</td>
<td>54/67</td>
<td>100/0</td>
<td>MRI-SIJ: 65</td>
<td>ASAS40 at week 12</td>
<td>Week 12: 22.7 (ADA) vs 0% (placebo)¹</td>
<td>Week 12: active inflammation on MRI was no predictor for good clinical response</td>
<td>First trial in axial SpA; good clinical response in subgroup of patients with short disease duration</td>
</tr>
<tr>
<td>ADA</td>
<td>12-week placebo-controlled trial with extension up to week 144</td>
<td>185 (94 ADA vs 91 placebo)</td>
<td>10.1</td>
<td>45/78</td>
<td>100/0</td>
<td>MRI-SIJ: 48.1</td>
<td>ASAS40 at week 12</td>
<td>Week 12: reduction of MRI SIJ score -3.2 (ADA) vs -0.6 (placebo); p = 0.003; reduction MRI spinal score -1.8 (ADA) vs -0.2 (placebo); p = 0.001</td>
<td>Study resulted in approval for the first TNF-blocker for non-radiographic axial SpA</td>
<td></td>
</tr>
</tbody>
</table>

¹X-ray of SIJ was performed in 34 of 40 patients. In four of 34 patients (12%) modified New York criteria were fulfilled [2].

²In the subgroup of patients with a disease duration of <3 years ASAS remission was 53%.

ADA: Adalimumab; AS: Ankylosing spondylitis; ASAS: Assessment of SpondyloArthritis international Society; ASAS40: Response according to ASAS criteria for 40% improvement; ETN: Etanercept; IFX: Infliximab; SIJ: Sacroiliac joints; SpA: Spondyloarthritis; SSZ: Sulfasalazine.
with IFX in early axial SpA [26]. So far, traditional disease-modifying anti-rheumatic drugs including SSZ play a minor role the treatment of axial SpA, and it is still recommended to intensify treatment in primary axial disease with TNF-blockers in case of NSAID failure.

The results of the most recent and largest clinical trial in non-radiographic axial SpA have recently been published [27]. This international randomized placebo-controlled trial in which patients with non-radiographic axial SpA were treated with ADA versus placebo finally led to the approval of ADA for the treatment of active axial SpA patients.

In the studies mentioned in Figure 2, all AS patients had to have elevated disease activity measured by a BASDAI of >4 despite intake of NSAIDs. Although study populations are not directly comparable, the available data suggest that the earlier treatment with ETN was initiated, the higher the response rates (Figure 2). Thus, early treatment of patients with axial SpA offer the opportunity of inducing remission in up to 50% of patients.

Treatment of extra-articular manifestations with ETN

As described above, TNF-blockers in AS have proven similar efficacy for treating axial disease [8–11]. However, AS patients also suffer from peripheral arthritis [28] and from extra-articular manifestations such as PsO, enthesitis, inflammatory bowel disease or AAU [29–31].

In contrast to the monoclonal antibodies IFX and ADA that have shown good efficacy in treating gastrointestinal symptoms of Crohn’s disease (CD), ulcerative colitis, as well as associated articular inflammation [32,33,203], ETN was not able to improve signs and symptoms of inflammatory bowel disease although articular symptoms had improved [34]. Accordingly ETN is not indicated for the treatment of CD [35,202]. Some case reports even suggested that CD persists or even flares during ETN therapy [34,36]. IFX and ADA are therefore preferred anti-TNF agents compared with ETN in the setting of inflammatory bowel disease.

According to the available evidence, none of these TNF-blockers (ETN, IFX, ADA and golimumab) can be preferred for the treatment of PsO [37,202–204].

AAU, which is one of the most frequent extra-articular manifestations [30], can be treated with topical glucocorticosteroids. If this is not successful TNF-blockers can be an effective treatment option. However, the question is what the role of ETN is, especially as some earlier case series and studies described new onset or flares of AAU, or even a total lack of efficacy of ETN in AS patients [38–45]. In these studies the incidence of AAU decreased during treatment with monoclonal antibodies (IFX: 47.4 vs 9.0 per 100 patient years [44] and 61.7 vs 2.6 per 100 patient years [44]; or ADA: 60.5 vs 0 per 100 patient years [45]) while it even increased during ETN treatment (54.6 vs 58.5 per 100 patient years [43]; or 34.3 vs 60 per 100 patient years [44]). The good efficacy of the monoclonal antibody ADA (significant reduction in AAU rates from 15 to 7.4 per 100 patient years) was confirmed in a recent 12-week open-label clinical trial called the RHAPSODY study, which included a high number of AS patients (n = 1250) but lacked a control group [46].

The role of ETN in terms of treating AAU was further elaborated by Braun et al. who compared pooled AAU rates from different AS clinical trials [47]. In this study, a significantly lower AAU flare rate of only 6.8 per 100 patient years was found in patients who were treated with TNF-blockers (IFX or ETN), compared with a rate of 15.6 per 100 patient years in patients who received placebo. Although statistical significance was not reached, the incidence of anterior uveitis flares among patients treated with IFX were lower (3.4 per 100 patient years [95% CI: 1.1–8.0]) compared with patients treated with ETN (7.9 per 100 patient years [95% CI: 5.5–11.1]).

The most recent systematic analysis published by Sieper et al. assessed the pooled frequency of AAU in different clinical trials of ETN in AS patients (three open label, one active controlled [SSZ as comparator] and four placebo controlled [48]). A significant difference

---

**Figure 1. Examples for MRI before and after 48 weeks of treatment with etanercept.** Sacroiliac joints: (A) Baseline MRI sacroiliac joint score 15.5 and (B) week 48 MRI sacroiliac joint score 0. Spine: (C) baseline MRI spine score 11.5 and (D) week 48 MRI spine score 1. Enthesitis of lateral condyle of femur of right knee (dorsal view): (E) MRI baseline with enthesitis and (F) week 48 without enthesitis. Reproduced with permission from the *Annals of Rheumatic Diseases* [25].
was detected in AAU event rates per 100 patient years in favor of ETN versus placebo: 8.6 versus 19.3, respectively. Compared with SSZ similar AAU event rates were found for ETN: 10.7 for ETN versus 14.7 for SSZ. A limitation of this analysis might be that the pooled placebo data are only derived from rather short placebo phases in the analyzed trials. On the other hand, these are the most valid controlled data available. In conclusion, it seems to be clear that ETN does not lead to an increase of the AAU event rate in AS patients. Furthermore, the available data and clinical experience suggest that the monoclonal antibodies such as IFX or ADA would be a more effective choice in the minority of AS patients with frequent severe attacks of AAU, even though no head-to-head trials are available.

Enthesitis is a characteristic and frequent finding affecting up to 50% of SpA patients [31,49–52]. Most placebo-controlled trials of TNF-blockers have not demonstrated a consistent impact of treatment on enthesitis scores [9,11,16]. However, one has to be aware that enthesitis assessment is very heterogeneous and not well standardized; for example there are various enthesitis assessment tools [15,16,53–56]. Regarding the efficacy of ETN on enthesitis, there are two interesting imaging studies demonstrating that enthesitis shown on MRI improves in the Heel study (SpA and MRI-proven enthesitis) [57] or in the ESTHER trial (early axial SpA patients; various MRI-proven enthesitis sites) [25]. The reason for the poor correlation between clinical and MRI-proven enthesitis remains unclear [58]. In summary, according to the available data no TNF-blocker can be preferred for the treatment of AS patients with enthesitis [59].

Dose modification of ETN in AS/axial SpA

According to the label, ETN should be administered sc. in a dose of 2 × 25 mg weekly or 50 mg once weekly. The question arose whether efficacy could be increased with increased dose of ETN.

A recent randomized placebo-controlled trial in patients with active AS evaluated whether 50 mg sc. twice weekly has a higher efficacy compared with 50 mg sc. administered once weekly [60]. However, after 12 weeks of treatment response rates such as ASAS20 and ASAS40 were not statistically different between the two groups (37 vs 34% and 25 vs 25%, respectively) suggesting that the approved dose seems to be sufficient at least on the group level.

Some studies also evaluated the possibility of a dose reduction of ETN [61–63]. In a Spanish study, the dose of ETN was successfully reduced with different dose-reduction schemes in 16 out of 51 (32%) patients, according to the treating rheumatologist and patient’s preference, in AS patients with low disease activity – defined as a BASDAI <4 and normal CRP values [61].

After a mean follow up of 26 months, none of the 16 AS patients required any dose re-increase [61].

A South Korean study in which 109 AS patients in an observational setting were investigated found that ETN intervals could successfully be increased from 4.7 days at 3 months to 12.1 days at 21 months. At the same time BASDAI values declined from 8.5 to 0.6 after 21 months, which was also accompanied by a decrease in CRP [62]. In another retrospective South Korean study; (n = 27), low clinical disease activity was induced with 50 mg ETN once weekly and maintained with ETN 25 mg once weekly [63].

In a recently published Chinese 12-month open-label clinical trial 97 AS patients were treated with ETN 25 mg sc. twice weekly for 6 months (with concomitant methotrexate treatment) followed by 25 mg once weekly in patients with good symptom control [64]. In total, 78 patients (80%) were regarded as responders and at the end of the first 6 months [64], and during the last 6 months these 78 patients, with good control of both symptoms and radiological progression, reduced the ETN...
dose as planned to 25 mg sc. once weekly; in the end only four out of 78 patients (5%) showed a relapse of the disease, while all other patients remained stable or even continuously improved [64].

A recent retrospective study assessed dose changes of different TNF-blockers including ETN in clinical practice in France in 189 AS patients with a mean follow up of 43.5 months [65]. In these patients a state of low disease activity or remission (defined as a BASDAI <1, absence of peripheral arthritis and/or enthesitis and normal CRP) was achieved in 65 patients (35%). Several dose reductions of the TNF-blocker dose were performed. In case of ETN, the most frequently performed dose modification was the use of 25 mg once weekly or 50 mg every 10–14 days (mean intervals for ETN 25/50 mg application were 6.6/12.3 days at 6 months and 8.0/10.0 days at 36 months) [65].

Besides dose reduction some studies evaluated the question whether it would be possible to entirely discontinue TNF-blocker therapy once a state of low disease activity or remission was reached (drug-free remission) [24,66–68]. In these studies treatment with TNF-blockers was stopped in AS patients who reached a state of remission or inactive disease. These trials demonstrated flare rates of nearly 100% after treatment with IFX [66] or ETN [67], 83% in patients with non-radiographic axial SpA after 1 year of ADA [24] and in 60% of patients with axial SpA with a symptom duration of <3 year after 16 weeks of IFX [68].

The latest evidence providing data on drug-free remission come from the ESTHER trial, which assessed ETN versus SSZ in early axial SpA [69]. As described above, all patients demonstrated active inflammation on the baseline MRI in the SI-joints and/or the spine. After 48 weeks of treatment only those patients who were in ASAS remission and MRI remission (defined as being free of active inflammation on MRI) were observed without active treatment for 1 year more. Although 33% of ETN-treated patients reached this strict remission criterion (clinical and MRI remission) at year 1, only 8% of ETN-treated patients stayed in drug-free remission at year 2.

When comparing the flare rates in the different studies, one has to bear in mind the different definitions for ‘remission’ and ‘flare’. To summarize, data suggest that dose reduction of TNF-blockers including ETN may be possible in some AS patients [70]. Treatment discontinuation may be possible in approximately 10% of patients with early axial SpA.

**Immunogenicity**

In RA it has been clearly demonstrated that antibodies against TNF-blockers may develop which is associated with reduced efficacy of TNF-blockers [71]. Also in the field of AS a few studies have investigated the development of antibodies to ETN and other TNF-blockers. These studies indeed found a significant difference between ETN and monoclonal antibodies (IFX, ADA). Table 2 summarizes the frequency of antibody formation for the different TNF-blockers.

The data presented below reflect the percentage of patients whose test results were considered positive for antibodies to ETN or other TNF-blockers in an ELISA assay. The results depend on the diagnostic properties of the assay and might be influenced by sensitivity and specificity of the assay, handling of samples, intake of drugs and patients’ disease. Due to these limitations of direct comparison of the incidence of antibody formation against ETN with the incidence of antibody formation against other TNF-blockers might be difficult. On the other hand, when the same working groups investigated immunogenicity in different TNF-blockers, clear differences were found (Table 2).

Two studies have evaluated the frequency of antibody formation against ETN, and in both studies no antibodies have been detected at all [72,73]. In one of these studies a group of 53 AS patients was investigated and the serum drug levels increased from 2.7 mg/l after

<table>
<thead>
<tr>
<th>Type of TNF-blocker</th>
<th>Patients (n)</th>
<th>Antibody formation against TNF-blocker (%)</th>
<th>Duration of follow up</th>
<th>Antibody formation associated with lack of efficacy and/or increase in side effects</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETN 53</td>
<td>0</td>
<td>6 months</td>
<td>Not applicable</td>
<td>[72]</td>
<td></td>
</tr>
<tr>
<td>ETN 20</td>
<td>0</td>
<td>12 months</td>
<td>Not applicable</td>
<td>[73]</td>
<td></td>
</tr>
<tr>
<td>IFX 8</td>
<td>25</td>
<td>24 weeks</td>
<td>Yes</td>
<td>[74]</td>
<td></td>
</tr>
<tr>
<td>IFX 20</td>
<td>20</td>
<td>12 months</td>
<td>Yes</td>
<td>[73]</td>
<td></td>
</tr>
<tr>
<td>IFX 94</td>
<td>25</td>
<td>~7 years</td>
<td>Yes</td>
<td>[77]</td>
<td></td>
</tr>
<tr>
<td>IFX 91</td>
<td>15</td>
<td>Up to 39 months</td>
<td>Yes</td>
<td>[78]</td>
<td></td>
</tr>
<tr>
<td>ADA 35</td>
<td>31</td>
<td>6 months</td>
<td>Yes</td>
<td>[76]</td>
<td></td>
</tr>
<tr>
<td>ADA 20</td>
<td>30</td>
<td>12 months</td>
<td>Yes</td>
<td>[73]</td>
<td></td>
</tr>
</tbody>
</table>

ADA: Adalimumab; ETN: Etanercept; IFX: Infliximab.
3 months to 3.0 mg/l after 6 months with no difference between responders and nonresponders [72]. This has also been noted in other rheumatic diseases [74] and so failure of clinical response in AS patients cannot be due to anti-ETN antibodies.

Pooled data from studies with different rheumatic diseases demonstrated that antibodies to the TNF-receptor portion or other protein components of ETN developed in approximately 6% of adult patients with RA, AS, PsA or PsO [202]. These antibodies were all nonneutralizing [202]. In the PsO studies the exposure of ETN was up to 120 weeks, and the percentage of patients testing positive at the assessed time points of 24, 48, 72 and 96 weeks ranged from 3.6 to 8.7%. The proportion of patients tested positive for anti-ETN antibodies increased with the duration of the trials. However, the clinical significance of this finding is unknown because no clear correlation of antibody development to clinical response or adverse events could be observed [202].

In contrast to the quite low frequency of antibody formation against ETN, few studies show that antibody formation against IFX and ADA occurs in approximately 20–30% of AS patients within up to 7 years. This is partly associated with a lack of clinical efficacy and increase of side effects, such as infusion reactions in case of IFX (Table 2) [73–76].

In a very recent study from a Spanish group, Plasencia et al. described the development of antibodies to IFX in approximately 25% of SpA patients (out of 94 initially evaluated patients, among them 50 AS patients). Antibodies mostly occurred after the six infusions, and patients with antibody formation presented a higher disease activity, shorter drug survival (4.3 vs 8.2 years) and a higher rate of adverse events [77]. Similarly to another study from France [78], in the study by Plasencia it was also reported that methotrexate (MTX) might have a beneficial influence on preventing antibody formation [77]. Limitations of this study include the retrospective study design, that data were not stratified according to diagnosis and that it is unclear to what degree the development of anti-IFX antibodies was an independent factor contributing to lack of treatment response, since no regression analysis was performed. In RA [79,80] and CD (81) adding an immunosuppressant drug (such as MTX or azathioprine) is associated with a lower development of anti-TNF-blocker antibody expression; however, two studies with IFX in AS suggest that there is no difference whether or not IFX is combined with MTX [82,83]. In addition, data from the Norwegian registry showed that drug survival in AS after 1 year is not different between patients who receive a combination of a TNF-blocker plus MTX or a TNF-blocker alone [84], which again is different from PsA or RA registries [84]. Moreover, a recent extensive pharmacokinetic analysis has shown that combining of MTX and IFX does not increase the exposure to IFX over IFX alone in patients with AS, and the two groups did not differ in disease activity or biomarkers of inflammation [85].

To summarize, there is not enough evidence to justify combination of MTX with a TNF-blocker therapy in SpA because there is no controlled data proving an improved efficacy or tolerability [59]. It also remains unclear whether it is useful to measure anti-TNF-blocker antibodies in clinical practice.

**Switching between TNF-blockers**

Despite the good efficacy of TNF-blockers, the treating rheumatologists have to take care after AS patients who failed treatment to TNF-blockers (primary and secondary nonresponders). On the background of missing alternatives in clinical practice after failure of a first TNF-blocker, a second or even third TNF-blocker is often prescribed [86]. However, the question is what the evidence is for switching between TNF-blockers, including switching to ETN or from ETN to another TNF-blocker.

The first studies describing successful switching between TNF-blockers included rather small numbers of patients and mostly reported switching from IFX to ETN [87–90]. Data from other studies from France (222 SpA patients, ~50% on ETN therapy, 50% switchers) [91], Norway (514 TNF-naive AS patients, 15% switchers) [92], and Denmark (1436 AS patients, ~16% ETN, ~30% switchers) [93], showed retention rates for the second TNF-blocker after 1–2 years of 60–65% [91,92]; the studies also showed that the response rate to the second or third TNF-blocker might be lower compared with the first TNF-blocker, but that this response rate is still clinically significant (increase of the number needed to treat to achieve a good response at 6 months: number needed to treat 1.9, 2.7 and 3.4 for first, second and third TNF-blocker, respectively) [93]. Predictors that were identified for longer adherence to the second TNF-blocker included male gender and a low baseline functional index. However, no information was available on an ideal switching combination, so there was also no separate information on ETN.

Interestingly, separate information about switching options comes from an open-label Phase III clinical trial of ADA in AS (RHAPSODY) [94]. In this trial the response to ADA was compared in TNF-blocker naive (n = 924) versus TNF-blocker exposed (ETN or IFX) AS patients (n = 326; pretreatment with IFX in n = 162 patients, with ETN in n = 85 or with both IFX and ETN in n = 79) [94]. Furthermore, in this study the response was better in the TNF-naive group but still there was a significant response in the TNF-blocker exposed group (BASDAI50: 63 vs 41%; ASAS40: 59 vs 38%). Interestingly, the probability of reaching a BASDAI50
response was significantly higher for patients who had received only IFX compared with only ETN before the study (BASDAI50: 48 vs 33%). However, the number of patients who only received ETN as a first TNF-blocker were small. Response rates in this study at 12 weeks were lower in patients who had discontinued the prior TNF-blocker (IFX or ETN) because of primary failure compared with secondary failure/intolerance (BASDAI50: 26 vs 42/46%; ASAS40: 26 vs 43/39%). So, in this study patients who initially did not show a response to a first TNF-blocker were less likely to show a response to a second TNF-blocker [94].

In summary, observational data support the current practice of switching between TNF-blockers, including ETN. However, because treatment options for TNF-blocker failures are limited in AS [86], this data may be biased and controlled studies are necessary. Among the switch options there is only evidence from the RHAPSODY trial that switching between the monoclonal antibodies (IFX to ADA) might work better than switching from ETN to ADA. However, these data are limited and more data are definitively needed from controlled studies.

Radiographic progression
As described previously, treatment of active AS/axial SpA patients with TNF-blockers has shown high efficacy for treating signs and symptoms [8–10,24–26] and also for the suppression of active inflammation of SI-joints and/or spine on MRI [24,25,95,96]. Given this good clinical efficacy the question was whether TNF-blockers such as ETN, were able to retard radiographic progression in AS. One study investigated the effect of ETN on radiographic progression in AS [97]. In that study, radiographs of the cervical and lumbar spine from 257 AS patients who received ETN (25 mg twice weekly) for up to 96 weeks were compared with radiographs from 175 patients from a large observational cohort (OASIS) who had not been treated with TNF-blockers before [98]. Radiographs performed at two time points up to 96 weeks apart from patients in both study populations were read by two blinded independent readers. The primary end point was the 96-week change in the mSASSS (0–72). There was no significant difference in the change in the mSASSS from baseline among patients who received ETN (mean ± SD: 0.91 ± 2.45) versus those from the OASIS group (0.95 ± 3.18). The failure to retard the growth of syndesmophytes as shown on X-rays over a treatment period of 2 years was also observed in three other trials with other TNF-blockers [97,99,100]. This is in contrast to RA or PsA where TNF-blockers successfully proved to retard radiographic progression. These findings led to an intense discussion about whether or not there is a link between active inflammation and new bone formation in AS [101–104]. Finally, several studies have now shown that vertebral inflammation as detected on the short tau inversion recovery sequence MRI predicts the development of new syndesmophytes [103–108]. In fact, the majority of new syndesmophytes develop from vertebral corners with either inflammation on short tau inversion recovery images or fat metaplasia on T1-weighted sequence. Two reports have shown that inflammatory lesions undergo fat metaplasia [109]. The data supports a window of opportunity for disease modification whereby early and effective intervention with anti-inflammatory therapy may be able to prevent structural progression [108,110].

To summarize, so far, TNF-blockers were not able to show that they are able to retard radiographic progression in the spine of AS patients. However, in the above mentioned studies in which radiographic progression was assessed after 2 years of follow up comparing data from randomized controlled trials with patients from the OASIS cohort [97,99,100] follow up might have been too short; after a longer follow up there might be a protective effect. Furthermore, interesting recent data suggest a role of NSAIDs in slowing down radiographic progression in AS patients with pre-existing syndesmophytes and elevated CRP levels [91,111,112]. It remains unclear whether early treatment with a TNF-blocker might be able to retard radiographic progression or whether combining a TNF-blocker with an NSAID might be superior to TNF-blocker monotherapy.

Etanercept biosimilars in AS
TNF-blockers are not only very potent anti-inflammatory drugs, but they are also quite expensive drugs. The introduction of biosimilars could change the biological market [90,113].

There are at least two ETN biosimilars [114,115]. The first one is AVG01 (AVENTTM®), which is developed by Avesthagen Limited in India [114], and is a fusion protein that combines the extracellular domain portion of the human TNF receptor (p75) with a Fc region of human IgG1. AVG01 and Enbrel show differences in the glycosylation profile, and it is not possible to determine the clinical consequences of such changes other than by conducting clinical trials, as even small differences in glycosylation may have a theoretical impact upon protein structure, function and immunogenicity [116]. Immunogenicity may take time to develop and may occur as a rare event, so it is important that the clinical trials have a long enough duration to be able to detect these events [117].

The second ETN biosimilar was launched in China in 2005 by Shanghai CP Goujian Pharmaceutical Company as a biosimilar version of ETN under the name Yisaipu® [115]. At the 2009 AAPS National Biotechnology Conference, So and colleagues released preliminary data comparing ETN with the Chinese biosimilar Yisaipu [115].
The authors concluded that Yisaipu has 4.5-fold more aggregates compared with ETN; they demonstrated additional protein fragments with cSDS-PAGE with a higher concentration of low molecular protein fragments. The clinical relevance of these differences is unknown.

Regarding safety, one of the most prominent examples for safety issues caused by the manufacturing process is the development of cases of pure red cell aplasia (PRCA) in renal dialysis patients receiving erythropoietin-blocking antibodies to the biologic also neutralizes native erythropoietin, resulting in PRCA, which induces a low reticulocyte count and a decrease or even absence of erythroblasts in the bone marrow [120]. While between 1988 and 1998 only three cases of this syndrome were reported in epoetin-treated patients [120], there was a rise in PRCA between 1998 and 2002 in patients with chronic renal failure increasing to approximately 250 documented cases. In total, 92% of the cases were associated with the use of Eprex® (sc.), an erythropoietin product marketed outside the USA [120]. In 2002, the application route of Eprex was changed so that the product should be administered parenterally rather than via sc. [120]. After these changes were implemented, the exposure-adjusted incidence of Eprex-associated PRCA was reduced by 83% worldwide, dropping almost to pre-1998 levels [120].

Safety (malignancy) in AS during TNF-blocker treatment

Regarding the new development of malignant tumors an earlier meta-analysis demonstrated a significantly increased risk during TNF-blocker treatment in RA patients [122]; however, subsequent meta-analyses and observational study data did not confirm these findings [123–127]. However, it has to be noted that an increased risk for basal cell cancer (odds ratio [OR]: 1.5; 95% CI: 1.2–1.8) and possibly melanoma (OR: 2.3; 95% CI: 0.9–5.4) in TNF-blocker users as compared with TNF-blocker nonusers was found [123]. In another meta-analysis that analyzed data from more than 20,000 patients (RA, psoriasis, PsA, AS and CD) from 74 randomized controlled trials [124], there was also no increased risk for cancer (0.84% of TNF-blocker users vs 0.64% of TNF-blocker nonusers) except an elevated risk of 2.02 (95% CI: 1.11–3.95) for non-melanoma skin cancers.

In contrast to earlier data from the Swedish Biologics Register [129], subsequent studies could not confirm an increased lymphoma risk over the elevated lymphoma risk in RA patients in general [130]. Furthermore, no increase over time or with TNF-blocker treatment was found [131]. Unlike RA, data suggest that there is no increased lymphoma risk in AS [132].

Data from a French RATIO registry provide different data regarding lymphoma risk with different TNF-blockers [133]. Among 38 patients with a new diagnosis of lymphoma (31 of whom had non-Hodgkin’s lymphoma and five of whom had Hodgkin’s lymphoma), there were 27 patients with RA and seven with SpA (three PsA and four AS). The authors found that patients receiving ETN had a lower risk compared with those treated with ADA or IFX with respective standardized incidence ratios of 0.9 (0.4–1.8) versus 4.1 (2.3–7.1) and 3.6 (2.3–5.6), respectively. In addition, the exposure to ADA or IFX versus ETN was found to be an independent risk factor for lymphoma in this case–control study with an OR of 4.7 (1.3–17.7) and 4.1 (1.4–12.5), respectively. For RA and SpA, the standardized incidence ratios was 2.3 (1.6–3.3; p < 0.0001) and 1.9 (0.9–4.0; p = 0.09), respectively. Due to the small number of patients however, no clear conclusion can be drawn from this data in SpA patients.

To summarize, TNF-blockers seem to have an acceptable safety profile. The treating doctors should be aware of an increased risk for non-melanoma skin cancer. As far as lymphoproliferative diseases – including lymphoma – are concerned, no definitive conclusions can be drawn and larger data sets need to be analyzed [59].

Future perspective

Axial SpA, as it is currently understood, is a disease continuum that consists of an earlier non-radiographic axial SpA stage (often characterized by bone marrow edema on MRI of sacroiliac joints) and the classical radiographic stage (when the modified New York criteria are fulfilled on conventional X-ray). Recent data help us to understand predictors of disease progression. Parameters, which are associated with spinal disease progression, include pre-existing syndesmosphytes [134,135], elevated CRP [134], cigarette smoking [134] and male gender [136]. For progression in the SI-joints an elevated CRP [137], bone marrow edema in the SI-joints on MRI and HLA-B27 positivity [138] have been identified.

With the introduction of the ASAS classification criteria for axial SpA [49], more and more clinical trials apply these criteria, such as the randomized, placebo-controlled trials with different TNF-blockers [27,139]. It can be expected that next to ADA, which has recently been approved in Europe for the treatment of active non-radiographic axial
SpA, certolizumab could also get an approval based on the results of a recently presented study [139].

Future challenges also include the question on whether TNF-blockers – perhaps if used earlier – will prove that radiographic progression can be slowed down. Furthermore, in terms of treatment alternatives to TNF-blockers there is an intensive search for other non-TNF-blocker biologicals; however, no other drug has so far reached the same clinical efficacy [140–144]. The results of future clinical trials using other biologicals (e.g., ustekinumab, an antibody against IL-12/IL-23 [205], or drugs targeting small molecules such as tofacitinib) are awaited with great interest.

Financial & competing interests disclosure
IH Song has received consulting fees or other remuneration from Pfizer Pharmaceuticals, Merck Sharp Dohme/Schering Plough, Abbott Immunology Pharmaceuticals. J Sieper has received consultant and/or speaker fees and/or grants from Pfizer Pharmaceuticals, Merck Sharp Dohme/Schering Plough, Abbott Immunology Pharmaceuticals, UCB. 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 apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- The Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial spondyloarthritis (SpA) cover both patients with ankylosing spondylitis (AS; fulfilling the modified New York criteria) and patients with non-radiographic axial SpA (who often have bone marrow edema on MRI of the sacroiliac joints).
- Furthermore, in the update of the ASAS recommendations after failure of nonsteroidal anti-inflammatory drugs (at least two nonsteroidal anti-inflammatory drugs for a total of 4 weeks), TNF-blockers are recommended in predominantly axial disease. Disease-modifying antirheumatic drugs are not recommended in axial disease.
- So far, four TNF-blockers are approved for the treatment of AS, and one TNF-blocker (adalimumab) is also approved for the treatment of active non-radiographic axial SpA.
- Etanercept (ETN) has proven good efficacy for treatment of axial disease in patients with axial SpA. The efficacy seems to be better with short disease duration with ASAS partial remission rates up to 50%. ETN cannot be recommended for treatment of inflammatory bowel disease in AS patients. For treatment of uveitis in AS patients the monoclonal antibodies seem to be superior compared with ETN.
- Dose reduction of ETN in clinical practice is being performed successfully.
- Different immunogenicity studies in AS and SpA patients have shown no antibody formation against ETN, but against infliximab or adalimumab in up to 25–30%. The clinical relevance of this finding is not clear. So far, it is not recommended to use disease-modifying antirheumatic drugs such as methotrexate with TNF-blockers.
- On the background of missing treatment alternatives to TNF-blockers, it is good that there are encouraging observational data suggesting that switching from one TNF-blocker to another TNF-blocker is effective, although the probability of a satisfactory response seems to decrease with the number of TNF-blockers used. There are not enough data to recommend a specific sequence of TNF-blockers.
- More studies are needed to evaluate the potential of TNF-blockers including ETN to retard radiographic progression in the spine.
- The role of biosimilars in the treatment of axial SpA needs further evaluation, especially in terms of safety.

References

Papers of special note have been highlighted as:
- of interest
- of considerable interest


First multicenter, randomized, placebo-controlled trial using the TNF-blocker adalimumab for patients with non-radio graphic axial SpA. This trial lead to approval of the first TNF-blocker in Europe for active non-radiographic axial SpA.


Review: Clinical Trial Outcomes

Song & Sieper


One of two prospective placebo-controlled randomized trials evaluating whether a combination therapy of methotrexate with the TNF-blocker infliximab is superior to infliximab monotherapy. According to the data of this trial, the combination therapy was not superior. Thus, the data of this trial are in line with the Assessment of SpondyloArthritis international Society recommendations, which do not recommend the use of disease-modifying antirheumatic drugs in axial SpA.


Data from the huge Danish registry on switching of TNF-blockers in ankylosing spondylitis patients showing that even after switching to the second or third TNF-blocker a clinically relevant response can still be expected, although the number needed to treat increases with every new TNF-blocker (number needed to treat up to 3.4 for the third TNF-blocker).

A nice study and discussion of the literature about the relationship between suppression of active inflammation and the influence on new bone formation.

The first trial that demonstrated a beneficial effect of nonsteroidal anti-inflammatory drugs on retardation of syndesmophyte growth in the spine of ankylosing spondylitis patients who took nonsteroidal anti-inflammatory drugs on a regular basis versus on demand.


The first trial that demonstrated a beneficial effect of nonsteroidal anti-inflammatory drugs on retardation of syndesmophyte growth in the spine of ankylosing spondylitis patients who took nonsteroidal anti-inflammatory drugs on a regular basis versus on demand.


127 Strangfeld A, Hierte F, Rau R et al. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. Arthritis Res. Ther. 12(1), R5 (2010).


■ Websites

201 SmPC. Enbrel® 25 mg powder and solvent for solution for injection. www.medicines.org.uk/emc/medicine/3343/spc#PHARMACEUTICAL PhầnSốtiʌnUspublication


204 Remicade® (Infliximab) summary of product characteristics. www.accessdata.fda.gov/drugsatfda_docs/label/2011/103772s5295lbl.pdf

205 ClinicalTrials Database: NCT01330901, www.clinicaltrials.gov/show/NCT01330901