Efficacy of anti–tumor necrosis factor therapy for extra-articular manifestations in patients with ankylosing spondylitis: a meta–analysis

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Abstract

Background: We performed a meta-analysis to evaluate the effect of anti–tumor necrosis factor (TNF) therapy on the frequency of extra–articular manifestations (EAMs) in patients with ankylosing spondylitis (AS).

Methods: We searched with the terms ‘ankylosing spondylitis’, ‘infliximab’, ‘etanercept’, ‘adalimumab’, ‘golimumab’, ‘certolizumab’, ‘TNF inhibitor/blocker/antagonists’ or ‘anti-TNF’ on MEDLINE, EMBASE and Cochrane Library for randomized controlled trials (RCTs) of ≥12 weeks with parallel or crossover design of TNF inhibitor versus placebo to treat uveitis, inflammatory bowel disease (IBD) and/or psoriasis of AS, published before February 2014.

Results: We found 8 RCTs that fit our criteria. Anti–TNF therapy was associated with less uveitis than placebo in patients with AS (OR: 0.35, 95% CI: 0.15–0.81, P = 0.01). Subgroup analysis showed receptor fusion proteins were more efficacious for uveitis than placebo (OR: 0.30, 95% CI: 0.09–0.94, P = 0.04), but monoclonal antibodies were not (OR: 0.43, 95% CI: 0.12–1.49, P = 0.18). Anti–TNF therapy and placebo group did not significantly differ in treating IBD in AS patients (OR: 0.75, 95% CI: 0.25–2.29, P = 0.61). In subgroup analysis, neither monoclonal antibodies (OR: 0.45, 95% CI: 0.10–1.92, P = 0.28) nor receptor fusion proteins (OR: 1.52, 95% CI: 0.25–9.25, P = 0.65) significantly differed from placebo in treating IBD. We found no suitable reports on psoriasis.

Conclusions: Anti–TNF therapy was preventive for flares or new onset of uveitis in AS patients, and might be an alternative for these patients. However, monoclonal anti–TNF antibodies and TNF receptor fusion proteins were not efficacious for IBD in AS patients.

Keywords: Ankylosing spondylitis, Anti-TNF therapy, Extra–articular manifestations, Uveitis, Inflammatory bowel disease, Meta–analysis

**Background**

Ankylosing spondylitis (AS) is a chronic, progressive, inflammatory rheumatic disease that primarily affects the sacroiliac joints [1]. AS is primarily a disease of the axial skeleton, but some patients have peripheral joint involvement [2]. AS also has some extra–articular manifestations (EAMs). An epidemiological study in Belgium found that 42% of patients with definite AS had one or more EAMs [3]. EAMs mostly occurred in the eye (uveitis), gastrointestinal tract (inflammatory bowel disease, IBD) and skin (psoriasis) [4].

Uveitis, which is characterized by pain with red eye and photophobia, increased tear production and blurring of vision [5], occurs in approximately 20–30% of AS patients during the course of their disease, and is considered the most common EAM [6,7]. Non–steroidal anti–inflammatory drugs (NSAIDs) can only relieve uveitis symptoms for a short period in AS patients, but cannot change the course of their disease or prevent structural damage. NSAIDs treatment can also increase the tendency towards osteoporosis if used for a longer period of time. Some evidence indicates that disease–modifying anti–rheumatic drugs (DMARDs) can reduce uveitis recurrence [8,9], TNF is present at high concentrations in both aqueous humor and serum of patients with uveitis [10], and may participate actively in the...
pathogenesis of uveitis. In recent years, several trials have demonstrated the efficacy of anti–TNF therapy in reducing acute uveitis [11,12].

IBD is characterized by a chronic inflammation of the gut mucosa and includes Crohn’s disease (CD) and ulcerative colitis (UC). A recent systematic review and meta-analysis showed the pooled prevalence of IBD in patients with AS to be 6.8% [7]. Traditionally, treatment of IBD has relied on corticosteroids to reduce flares and on immunomodulators to maintain remission [13]. Aminosalicylic acid is widely used to treat UC, but its use in CD is controversial [14]. Several recent trials have demonstrated the efficacy of anti–TNF therapy in reducing IBD [15].

Psoriasis is a systemic inflammatory cutaneous disease with plaque lesions and nail deformities. The pooled prevalence of psoriasis, a secondary disorder in AS, was 9.3% in patients with AS [7].

In a 2010 update by the Assessments in Ankylosing Spondylitis International Society and the European League against Rheumatism (ASAS/EULAR) of recommendations for the management of AS [16], NSAIDs are considered the first-line drug treatment for AS patients with pain and stiffness; DMARDs and intra-articular injections of glucocorticoids in patients with peripheral arthritis may also be considered, although there is no evidence to support the use of these medications for axial diseases; anti–TNF therapy is another option for patients with persistently high disease activity despite conventional treatments.

Infliximab (INF) is a chimeric mouse–human monoclonal immunoglobulin G (IgG) 1 antibody [17]. Adalimumab (ADA) [18], golimumab (GOL) [18] and certolizumab (CZP) [19] are humanized monoclonal anti–TNF-α antibodies. Etanercept (ETA) [20] is a dimeric fusion protein of the TNF receptor linked to the Fc portion of human IgG1.

Additionally, trials of anti–TNF therapy in AS have yielded impressive results [21-25] and a recent systematic review and meta–analysis [26] described the benefits of anti–TNF therapy in patients with AS. However, only a small trial has reported on the efficacy of anti–TNF therapy for EAMS of AS [11], and further meta–analysis could strengthen this evidence. Therefore, we performed a meta–analysis of randomized clinical trials (RCTs) to provide an up–to–date and comprehensive picture of the clinical efficacy of anti–TNF therapy for the most common EAMS in patients with AS—uveitis, IBD and psoriasis.

**Methods**

We captured all relevant studies published before February 2014 on MEDLINE, EMBASE and the Cochrane Library using following search terms: ‘ankylosing spondylitis’, ‘infliximab’, ‘etanercept’, ‘adalimumab’, ‘golimumab’, ‘certolizumab’, ‘TNF inhibitor/blocker/antagonists’ or ‘anti–TNF’.

**Results**

A total of 1,395 relevant articles were retrieved from various databases of which 801 were excluded after scanning.
After carefully reading the abstracts and an additional 65 articles for various reasons, including duplicates, not RCT or no required data (Figure 1), 8 RCTs were retained for meta-analysis [31-38]. Overall, included studies were of adequate methodological quality (mean modified Jadad score 6.875 for included studies, and all 8 studies had a score ≥6). Included studies, basic characteristics of enrolled patients and details about drug therapy are presented in Table 1.

The pooled analysis included 1,770 patients (1,223 randomized to anti-TNF therapy and 547 to placebo). Six trials [32-36,38] reported on uveitis that occurred in 7 patients in the anti-TNF therapy group and 16 in the placebo group; 5 trials [31,33,34,37,38] reported on IBD that occurred in 5 patients in the anti-TNF therapy group and 4 in the placebo group. No included trial reported on psoriasis.

Anti-TNF therapy was associated with less uveitis than placebo in patients with AS (OR: 0.35, 95% CI: 0.15–0.81, P = 0.01, Figure 2). Subgroup analysis for uveitis in patients with AS showed TNF receptor fusion proteins to be more efficacious than placebo (OR: 0.30, 95% CI: 0.09–0.94, P = 0.04); whereas monoclonal anti-TNF antibodies did not significantly differ from placebo (OR: 0.43, 95% CI: 0.12–1.49, P = 0.18). Analysis for IBD in these patients found that the anti-TNF therapy and placebo did not significantly differ (OR: 0.75, 95% CI: 0.25–2.9, P = 0.61, Figure 3); and neither monoclonal anti-TNF antibodies (OR: 0.45, 95% CI: 0.10–1.92, P = 0.28 versus placebo) or receptor fusion proteins (OR: 1.52, 95% CI: 0.25–9.25, P = 0.65 versus placebo) significantly differed from placebo. Funnel plot analysis showed symmetry, which indicates that publication bias was not a significant factor in these studies (Figures 4 and 5).

Analysis of risk of bias showed that only 3 trials reported their methods of sequence generation and allocation concealment in detail [32,35,36]. Blinding was performed properly in all included trials. All trials were free from incomplete outcome data and free from selective outcome reporting as well as other sources of bias. All 8 included trials had low or moderate risk of bias (Table 1).

Discussion
This meta-analysis compared anti-TNF therapy with placebo in patients with AS. The results indicate significant positive benefits of anti-TNF agents to treat uveitis in these patients. For IBD treatment outcomes, the anti-TNF therapy group and the placebo group did not significantly differ. However, Subgroup analysis showed the receptor fusion protein ETA was more efficacious than placebo for uveitis in this patient population, whereas...
| Study                  | No. of patients | Age (years) | Male patients N (%) | Duration of AS (years) | Study Duration (weeks) | Medications allowed during the study | Modified Jadad Score | Risk of bias | Sequence generation | Allocation concealment | Blinding | Incomplete outcome data | Selective outcome reporting | other sources of bias |
|-----------------------|-----------------|-------------|---------------------|------------------------|------------------------|-------------------------------------|---------------------|--------------|---------------------|------------------------|----------|----------------------|--------------------------|------------------------|
| ADA                   | 315             | 315         | 24                  | 6                      | ?                      | DMARDs, NSAIDs and glucocorticoids  | 6                   | ?            | ?                   | √                      | √        | √                    | √                        | √                      |
| van der Heijde D. 2006 | 208             | 41.7 ± 11.69| 157 (75.5)          | 11.3 ± 9.99            | 24                     | DMARDs, NSAIDs and glucocorticoids | 6                   | ?            | ?                   | √                      | √        | √                    | √                        | √                      |
| Placebo               | 107             | 43.4 ± 11.32| 79 (73.8)           | 10.0 ± 8.34            | 24                     | DMARDs, NSAIDs and glucocorticoids | 6                   | ?            | ?                   | √                      | √        | √                    | √                        | √                      |
| ETA                   | 30              | 38.9 ± 9.1  | 10 (71.4)           | 14.9 ± 8.3             | 24                     | NSAIDs                             | 8                   | √            | √                   | √                      | √        | √                    | √                        | √                      |
| ETA 25 mg twice weekly | 14              | 32.0 ± 7.5  | 12 (75)             | 11.4 ± 8.8             | 24                     | DMARDs, NSAIDs and glucocorticoids | 6                   | ?            | ?                   | √                      | √        | √                    | √                        | √                      |
| Placebo               | 16              | 38.9 ± 9.1  | 10 (71.4)           | 14.9 ± 8.3             | 24                     | DMARDs, NSAIDs and glucocorticoids | 6                   | ?            | ?                   | √                      | √        | √                    | √                        | √                      |
| Davis JC Jr. 2003     | 277             | 42.1 (24–70)| 105 (76)           | 10.1 (0–30.7)          | 24                     | DMARDs, NSAIDs and glucocorticoids | 6                   | ?            | ?                   | √                      | √        | √                    | √                        | √                      |
| ETA 25 mg twice weekly | 138             | 41.9 (18–65)| 105 (76)           | 10.5 (0–35.3)          | 24                     | DMARDs, NSAIDs and glucocorticoids | 6                   | ?            | ?                   | √                      | √        | √                    | √                        | √                      |
| Placebo               | 139             | 41.9 (18–65)| 105 (76)           | 10.5 (0–35.3)          | 24                     | DMARDs, NSAIDs and glucocorticoids | 6                   | ?            | ?                   | √                      | √        | √                    | √                        | √                      |
| van der Heijde D. 2006 | 356             | 39.8 ± 10.7 | 114 (76)           | 10.0 ± 9.1             | 12                     | DMARDs, NSAIDs and glucocorticoids | 6                   | ?            | ?                   | √                      | √        | √                    | √                        | √                      |
| ETA 25 mg twice weekly | 150             | 41.5 ± 11.0 | 109 (70)           | 9.0 ± 8.7              | 12                     | DMARDs, NSAIDs and glucocorticoids | 6                   | ?            | ?                   | √                      | √        | √                    | √                        | √                      |
| ETA 50 mg weekly      | 155             | 40.1 ± 10.9 | 40 (78)            | 8.5 ± 6.8              | 12                     | DMARDs, NSAIDs and glucocorticoids | 6                   | ?            | ?                   | √                      | √        | √                    | √                        | √                      |
| Placebo               | 51              | 40.1 ± 10.9 | 40 (78)            | 8.5 ± 6.8              | 12                     | DMARDs, NSAIDs and glucocorticoids | 6                   | ?            | ?                   | √                      | √        | √                    | √                        | √                      |
| IFX                   | 69              | 40.6 ± 8.0  | 23 (68)            | 16.4 ± 8.3             | 12                     | NSAIDs                             | 8                   | √            | √                   | √                      | √        | √                    | √                        | √                      |
| IFX 5 mg/Kg           | 34              | 39.0 ± 9.1  | 22 (63)            | 14.9 ± 9.3             | 12                     | NSAIDs                             | 8                   | √            | √                   | √                      | √        | √                    | √                        | √                      |
| Placebo               | 35              | 40.6 ± 8.0  | 23 (68)            | 16.4 ± 8.3             | 12                     | NSAIDs                             | 8                   | √            | √                   | √                      | √        | √                    | √                        | √                      |
| Marzo-Ortega H. 2005  | 42              | 39.0 ± 9.1  | 22 (63)            | 14.9 ± 9.3             | 12                     | NSAIDs, oral corticosteroids       | 8                   | √            | √                   | √                      | √        | √                    | √                        | √                      |
| IFX 5 mg/Kg + MTX     | 28              | 41 (28–74)  | 23 (82.14)         | 8 (0–41)               | 12                     | NSAIDs                             | 8                   | √            | √                   | √                      | √        | √                    | √                        | √                      |
| Placebo + MTX         | 14              | 39 (30–56)  | 11 (78.57)         | 10 (0–35)              | 12                     | NSAIDs                             | 8                   | √            | √                   | √                      | √        | √                    | √                        | √                      |
Table 1 Basic characteristics of included studies (Continued)

| Study          | Drug Formulation | Total Participants | Mean Age (SD) | Mean DAS28 | Mean ESR/CRP |
|----------------|------------------|--------------------|---------------|------------|--------------|
| Inman RD. 2008 | GOL 50 mg        | 138                | 38 (29–46)    | 102 (73.8) | 5.15 (1.60–11.60) |
|                | GOL 100 mg       | 140                | 38 (30–47)    | 98 (70.0)  | 5.20 (1.50–13.25) |
|                | Placebo          | 78                 | 41 (31–50)    | 55 (70.5)  | 7.25 (2.80–18.60) |
| Landewé R. 2014| CZP 200 mg every 2 weeks | 111              | 39.1 ± 11.9   | 67 (60.4)  | 6.9 (0.3–34.2) |
|                | CZP 400 mg every 4 weeks | 107              | 39.8 ± 11.3   | 68 (63.6)  | 7.9 (0.3–44.8) |
|                | Placebo          | 107                | 39.9 ± 12.4   | 65 (60.7)  | 7.7 (0.3–50.9) |

ADA = adalimumab; ETA = etanercept; IFX = infliximab; GOL = golimumab; CZP: certolizumab; MTX = methotrexate; DMARDs = disease-modifying antirheumatic drugs; NSAIDs = non-steroidal anti-inflammatory drugs; SSA = sulfasalazine; HCQ = hydroxychloroquine; √, low risk of bias; ?, unclear risk of bias.
monoclonal anti-TNF antibodies were not. Neither monoclonal antibodies nor receptor fusion proteins significantly differed from placebo in treating IBD.

Anti-TNF therapy has been shown to be beneficial for the treatment of uveitis in patients with AS. A retrospective study [39] of patients with spondyloarthropathy further confirms the efficacy of anti-TNF therapy in reducing acute uveitis flares. Therefore, all available data imply that ETA would not be as effective as monoclonal anti-TNF antibodies [40-42]. However, our results differed. This discrepancy may reflect the biggest difference between our study and previous ones; we included trials

Figure 2 Meta-analysis of uveitis between anti-TNF therapy and placebo for ankylosing spondylitis.

Figure 3 Meta-analysis of inflammatory bowel disease between anti-TNF therapy and placebo for ankylosing spondylitis.
that were all prospective RCTs whereas previous studies were almost all retrospective which tend to show larger risk values. Moreover, the mechanisms of anti-TNF antibodies and receptor fusion proteins are different; besides TNF-α, ETA also inhibits TNF-β. In an animal model of uveitis, higher TNF-β levels were found; ETA would therefore be expected to be even more effective [43]. More RCTs are required to further define the effect of ETA in AS patients with uveitis.

Braun et al. [44] investigated flare-ups or new-onset IBD in patients with AS who were treated with INF, ETA and ADA. New-onset and flares of IBD are infrequent in

![Funnel plot of included trials that reported uveitis.](image1)

![Funnel plot of included trials that reported inflammatory bowel diseases.](image2)
AS patients who receive anti-TNF therapy. The results showed that only INF and ADA might prevent IBD activity, both of which were associated with significant IBD rate reductions compared with ETA. The incidence of new-onset IBD in patients treated with placebo was not statistically different from that for any anti-TNF agent. ETA is not effective in controlling active CD [45]; in fact, cases have been reported of possible associated CD flare-ups [46] or new-onset CD [47] in AS patients undergoing ETA therapy. In our meta-analysis, we found that neither monoclonal anti-TNF antibodies nor TNF receptor fusion proteins were efficacious for IBD, but monoclonal anti-TNF antibodies had lower OR (implying greater efficacy) than TNF receptor fusion proteins. Only 5 small RCTs in our analysis had AS patients with IBD who were treated with anti-TNF agents. More RCT data is needed to establish the efficacy of anti-TNF antibodies for IBD in these patients.

Although anti-TNF agents are effective in treating skin and nail lesions of psoriasis [48,49], treatment with anti-TNF agents also can result in new manifestations of psoriasis for some patients [50]. We were unable to assess this in our meta-analysis because the included trials had no reported data of psoriasis.

The present study evaluated the efficacy of anti-TNF therapy on the frequency of EAMs in patients with AS. Anti-TNF therapy including ETA could be a credible alternative for AS patients who have uveitis. However, no anti-TNF therapy was efficacious for treating IBD in patients with AS. The 8 included studies that met the inclusion criteria had high-moderate Jadad scores; therefore the conclusions of this systematic analysis are reliable. More high-quality, large prospective RCTs with long-term follow-up are needed to confirm the efficacy and outcomes of anti-TNF therapy for EAMs of AS.

Conclusions
Compared with placebo, anti-TNF therapy including ETA was associated with significantly fewer flares and new onset of uveitis, but were not significant efficacious for treating IBD in AS patients. This meta-analysis of patient-level data from 8 RCTs significantly advances the notion that anti-TNF therapy may be a credible alternative for AS patients with uveitis. Future studies involving anti-TNF therapy for EAMs of AS are needed.

Abbreviations
TNF: Anti-tumor necrosis factor; AS: Ankylosing spondylitis; EAM: Extra-articular manifestation; RCT: Randomized controlled trial; IBD: Inflammatory bowel disease; CD: Crohn’s disease; UC: Ulcerative colitis; ASAS: Assessments in Ankylosing Spondylitis International Society; EULAR: European League Against Rheumatism; NSAIDs: Non-steroidal anti-inflammatory drugs; DMARDs: Disease-modifying antirheumatic drugs; INF: Infliximab; IgG: Immunoglobulin G; ADA: Adalimumab; GOL: Golimumab; CZP: Certolizumab; ETA: Etanercept; OR: Odds ratio; CI: Confidence interval; HLA: Human leukocyte antigen.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
DW and NZ conceived and designed the study. DW, LHX and TJ analyzed and interpreted the data. YYG, NNX and SZ contributed to acquisition of data. All authors helped draft the manuscript and its revisions for critically important intellectual content, and gave final approval of the version to be published.

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