Clinical efficacy of TNF-α inhibitors: an update

Over the last decade, TNF-α antagonists became the most powerful tools for controlling patient suffering from a number of rheumatic diseases. Infliximab, etanercept and adalimumab can induce remission and prevent both clinical and radiological disease progression in rheumatoid arthritis with significant improvement in patients' symptoms, function and quality of life. They improve joint symptoms and significantly retard radiographic progression in psoriatic arthritis. TNF-α antagonists have been demonstrated to reduce disease activity, retard radiologic progression and increase quality of life in ankylosing spondylitis patients. Long-term follow-up studies demonstrated sustained efficacy and acceptable safety profiles that were comparable in rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. Etanercept is the only US FDA-approved TNF antagonist for juvenile rheumatoid arthritis. TNF-α antagonists may improve some clinical manifastations of Behçet's disases, including uveitis. Tuberculosis and some other granulomatous infections are likely to occur more frequently among patients treated with monoclonal antibodies than among those treated with soluble TNF receptors. During the first 6 years of therapy, no overall elevation of cancer risk was observed with any of the three TNF antagonists. TNF antagonists were not associated with any major further increase in the already increased lymphoma risk in rheumatoid arthritis. Frequent monitoring of serum transaminase levels and viral load was suggested for TNF antagonist use in hepatitis B and C infection. They might reduce some important costs to the patients; however, studies with additional detailed cost calculations are required.

KEYWORDS: adalimumab ▪ ankylosing spondylitis ▪ anti-TNF-α ▪ arthritis ▪ etanercept ▪ infliximab ▪ inhibitors ▪ juvenile rheumatoid arthritis ▪ psoriatic ▪ rheumatoid arthritis

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Rheumatoid arthritis (RA) is a progressive, destructive, inflammatory disease resulting in disability and death. It is one of the most frequent chronic inflammatory joint disease as it affects approximately 0.5–1% of the world's population. It has a significant negative impact on quality of life, with job functioning as well as resultant healthcare costs to the community. Treatment concepts of the disease have undergone major changes over the last 100 years. Various agents known as disease-modifying antirheumatic drugs (DMARDs), of which methotrexate (MTX) is currently widely used alone or in combination with other DMARDs, are used as treatment. Other DMARDs include sulfasalazine, hydroxychlorokin and leflunomide. Induction of remission state can be achieved by combining with the available potent biological agents as early as possible. RA etiology remains unknown, but a 20-year study on its pathogenesis has led to identification of new therapeutic targets. Many of the new medications modify the immune response by blocking the effects of proinflammatory cytokines, or by affecting immune cells, such as B lymphocytes, or on interaction with T cells and antigen-presenting cells. It has been found that TNF-α plays a pivotal role in the pathogenesis of inflammed synovium in RA [1–3]. However, TNF is not the only cytokine involved in the pathogenesis of RA. IL-1 and IL-6 receptor antagonists also play an important role by inhibiting disease activity. Depleting circulating $CD20^+$ B lymphocytes using monoclonal anti-CD20 antibodies or by blocking the costimulatory signal (CD28-CD80/86) for T-cell/antigen-presenting cell interactions are other therapeutic options in patients resistant to TNF-α inhibitors.

The TNF inhibitors that have been approved for clinical use to treat RA are infliximab, adalimumab and etanercept. Infliximab is a chimeric mouse–human monoclonal antibody, whereas adalumimab is a fully humanized monoclonal antibody; both agents are specific for TNF. Etanercept is a fusion protein comprising the ligand-binding portion of the human p75 TNF receptor (TNFRIII) and the Fc fragment of human IgG1. The TNF inhibitors cause their primary effect by blocking the interaction of TNF with cell surface receptors. Biologic

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anti-TNF, often used in combination with MTX, is now the first choice of treatment when other DMARDs fail in clinical practice [4–8].

TNF inhibitors can induce remission and prevent both clinical and radiological disease progression in RA with significant improvement in patients' symptoms, function and quality of life [9,10]. Treatment with anti-TNF blockers can only be initiated and continued by an appropriate specialist. Despite the significant efficacy of TNF blockers, their use is recommended to patients with severe and progressive disease who are poorly responsive to conventional therapies, mainly due to the high cost associated with these biological agents. The main traditional concept regarding the start of anti-TNF therapies is failure to respond to an adequate trial of at least three DMARDs, including MTX for a minimum 3 months; the patient must show clinical evidence of active disease, multiple, actively inflamed joints and persistently elevated inflammatory markers (erythrocyte sedimentation rate and C-reactive protein). However, disease remission is the goal for RA; that is why the question remains as to whether they are better used if given early. Since untreated inflammation leads to damage, early effective treatment has suggested that there is a therapeutic window opportunity in which the modification of underlying disease process and prevention of the damage of inflammation is allowed [1,11–14].

Studies on rapid disease control, such as the Active-Controlled Study of Patients Receiving Infliximab for the Treatment of RA of Early Onset (ASPIRE) trial, evaluated the efficacy of infliximab (3 or 6 mg/kg) in combination with MTX versus MTX alone in MTX-naive patients with early RA [1]. Superior clinical and functional outcomes were observed at 1 year in the combination groups. No significant difference in clinical efficacy was observed between the low- and high-dose infliximab groups. More patients receiving infliximab had clinically meaningful improvement in Health Assessment Questionnaire scores, and clinical remission rates at 1 year were higher than the MTX alone group. The rapid response was also observed in the Early RA (ERA) trial, which compares two monotherapies; etanercept (10 or 25 mg twice a week) and MTX, in patients with early erosive disease [15]. Although patients receiving etanercept as monotherapy had a more rapid clinical response, there were no differences in the American College of Rheumatology (ACR)20/50/70 response rates between 6 and 12 months in the MTX group and in patients receiving the higher dose of etanercept. However, the overall response was better in the etanercept group than in the patients receiving MTX alone. Adalumimab in the early RA, PREMIER study [16] included 799 patients disease with a duration of less than 3 years (mean: 0.7 years). A coprimary end point of ACR50 response was achieved in 61% of patients undergoing combination treatment, in comparison with 46 and 42% in those patients receiving monotherapy with MTX and adalumimab, respectively. The ACR20/50/70 responses were significantly higher at week 2 in the combination group, and this result was sustained over the 2-year trial period. Disease Activity Score 28 (DAS28) remission (a score of less than 2.6) was achieved by 50% of patients in combination group, but only by 25% in monotherapy groups. These were the findings in the PREMIER, ASPIRE and ERA studies that support early aggressive intervention in RA, and it is hoped that Anti-Tumor Necrosis Factor Trial in RA with Concomitant Therapy (ATTRACT) will show similar results [17,18]. Importantly, the results demonstrated that a combination of MTX and anti-TNF is superior to MTX alone in preventing progressive joint destruction, improving clinical responses and reducing disability in early disease. The additional benefit of anti-TNF therapies is retarding radiological progression; this could be explained by a direct effect of the anti-TNF therapies on osteoclasts (Table 1).

Table 1. Efficacy of the three TNF antagonists in combination with methotrexate in rheumatoid arthritis.

Drug	n	Duration	ACR50 (%)	ACR70 (%)	SDAI ≤ 3 (%)	DAS28 < 2.4 (%)	DAS28 < 1.6 (%)	Ref.
Adalimumab + MTX (PREMIER)	799	2 years	62	49	–	–	–	[16]
Infliximab + MTX (ASPIRE)	1049	54 weeks	–	–	21.3	–	–	[132]
Etanercept + MTX (TEMPO)	686	100 weeks	–	–	–	75.3	51.2	[133]

ACR: American College of Rheumatology improvement criteria; ASPIRE: Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset; DAS28: Disease Activity Score 28; MTX: Methotrexate; SDAI: Simplified Disease Activity Index; TEMPO: Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes.

Infliximab and adalimumab are monoclonal antibodies to TNF, whereas etanercept is a dimeric, soluble recombinant protein of the extracellular domain of human p75 TNF receptor fused to the Fc fragment of human IgG1. All three agents bind to TNF, but important differences exist between them in terms of their modulation to TNF: infliximab binds TNF with a greater avidity and binds it for longer. The half-life is approximately 10.5 days and its biologic effect can persist for up to 2 months. Etanercept has a half-life of 3 days and its effect on TNF is consequently short-lived. Etanercept can bind strongly to soluble TNF only; it binds reversibly, with dissociation of nearly 50% of etanercept in only 10 min. By contrast, infliximab binds TNF irreversibly and has high avidity for both soluble and transmembrane TNF. As a result, infliximab therapy results in a more complete and prolonged effect [19].

Quinn and *et al.* conducted a double-blind, randomized, placebo-controlled trial of infliximab in addition to MTX, with the aim of inducing remission in patients with RA exhibiting MRI-proven synovitis but little defect [20]. Patients with disease duration of less than 6 months received infliximab/placebo and MTX every 8 weeks for 46 weeks. After 1 year, the MRI scores were significantly better in the infliximab group, with no new erosions, and a greater percentage of the patients achieved ACR50 and ACR70 improvement criteria. Response was sustained in 70% of the patients 1 year after the cessation of the infliximab therapy. The BeST trial further supported the notion that the combination of an anti-TNF blocking drug and MTX was optimal in the treatment of early RA [21]. There are accumulations of data to suggest that treating undifferentiated arthritis with corticosteroids or MTX could delay or prevent the progression to fully developed RA. Green and colleagues demonstrated the possible reversibility of early arthritis by treatment with corticosteroid injections before diagnosis of RA [22].

Disease duration, disease-specific autoantibodies (rheumatoid factor and anticyclic citrullinated peptide antibodies) and erosions on radiograph can predict the persistent disease [23]. MRI and ultrasound have been demonstrated to be more sensitive than physical examination to show the synovitis, and they can help to increase the accuracy of predicting poor outcome [24,25]. HLA-DRB1, shared epitope and their relationship with anticyclic citrullinated peptide antibodies, *PTPN22* polymorphisms (a navigator of T-cell activation) can help to establish a predicting model and to identify the high-risk patients who are suitable for the anti-TNF therapy and can catch the 'window of opportunity'.

Side effects & contraindications

Although TNF blockers are generally well tolerated, the existence of any drawbacks to the use of these agents needs to be considered before the commencement of therapy [26–28]. TNF-antagonist therapy is commonly associated with induction of autoantibodies, including anti-dsDNA antibodies; however, anti-TNF-induced lupus is not very common. Renal, cerebral and cutaneous involvement may occur more frequently than the classical drug-induced lupus [29].

TNF is released by activated macrophages, T lymphocytes and other immune cells in response to a variety of infectious stimuli. The biologic effects of TNF are numerous and include antitumor and antiviral activity, the mediation of systemic inflammatory responses to infection and sepsis, as well as a crucial role in the host response to a variety of infections, particularly those involving *Mycobacterium tuberculosis* and other intracellular pathogens. TNF is essential in the control and containment of intracellular pathogens; it stimulates recruitment of inflammatory cells to the area of infection and stimulates the formation and maintenance of granulomas that physically contain infection. TNF also directly activates macrophages, which then phagocytose and destroy mycobacteria and other pathogens. TNF-activated macrophages engulf and kill mycobacteria and other pathogens (e.g., *Trypanosoma cruzi, Leishmania, Listeria, Klebsiella pneumoniae* and *Streptococcus pneumonia*) [30–36]. Reactivation of the latent tuberculosis (TB) infection has been reported with the initiation of anti-TNF treatment, appropriate screening of patients using the Mantoux test, a careful medical history of TB risk factors (including birth or residence in a region of high TB prevalence, previous TB or TB treatment) or other risk factors, and chest x-ray should be performed before starting the therapy [10]. Skin indurations of 5 mm or greater should be interpreted as a positive result for latent TB infection, but, owing to anergy in immunosuppressive patients, the Mantoux test can give false-negative results. QuantiFERON®-TB Gold assay is available as an alternative or adjunct for the diagnosis of latent TB [37]. This assay depends on the detection of IFN-α after whole blood is incubated

with mycobacterium TB-specific antigen. It also has the advantage of having a positive control. TB infection associated with TNF blockade frequently present with extrapulmonary manifestations. TB and some other granulomatous infections probably occur more frequently among patients treated with monoclonal antibodies than among those treated with soluble TNF receptors. The results from the British Society for Rheumatology Biologics Register indicate that the rate of TB was higher for adalimumab (144 events/100,000 person years [pyrs]) and infliximab (136/100,000 pyrs) compared with etanercept (39/100,000 pyrs) [38]. The French Research Axed on Tolerance of Biotherapies (RATIO) registry reported that the TNF antagonist use for any indication had standardized incidence ratio (SIR) of 12.2 (95% CI: 9.7–15.5) for TB development and SIR was found to be higher for therapy with infliximab and adalimumab than for therapy with etanercept (SIR 18.6 [95% CI: 13.4–25.8] and SIR 29.3 [95% CI: 20.3–42.4] vs SIR 1.8 [95% CI: 0.7–4.3], respectively) [39]. The biologic and pharmacokinetic differences between monoclonal antibodies and soluble TNF receptors have been invoked as a possible explanation for this observation [40,41]. Patients who are diagnosed with latent TB infection during screening should begin treatment for TB before TNF blockade is undertaken with 9 months of isoniazide (300 mg daily for adults). A recommended alternative is 4 months of rifampicin (600 mg daily for adults), either alone or in combination with isoniazide. Patients should be monitored for side effects, such as hepatotoxicity, on a monthly basis. After the screening, before initiation of TNF therapy, no cases of TB have been reported. Furthermore, with the highest doses of adalumimab, TB risk is highest. Therefore, after screenings for TB and dose restriction of adalumimab, no TB cases were reported.

Unlike screening for TB, there are no guidelines on screening for fungal infections, such as *Histoplasma capsulatum* and *Coccidioides immitis*, which both have latent infections similar to TB, and so in endemic areas, serological screening should be performed before initiating the TNF blockade. Furthermore, *Listeria monocytogenes* is an intracellular pathogen acquired via the ingestion of contaminated meats and diary products. Newly acquired (and fatal) cases of listeriosis have occurred in patients who were taking anti-TNF agents. Patients should be advised not to use unpasteurized dairy products while taking anti-TNF agents.

Special precautions to minimize the risk of infection should be taken in the pre- and postoperative periods in patients undergoing routine elective or emergency surgery, particularly where prosthetic implants are involved. These guidelines are empirical, but as a general guide, if surgery involves possible sepsis, such as abdominal surgery, it would be best to omit the anti-TNF therapy until the patient shows postoperative healing. In the case of elective surgery, omitting a dose of treatment preoperatively may lessen the risk of infection. By contrast, reducing the circulating TNF-α and overwhelming inflammatory responses in sepsis has led to successful outcomes using the anti-TNF antibody and the TNF receptor protein in animal models. A review of the role of anti-TNF antibody in sepsis has concluded that anti-TNF treatment is partially effective and may confer a small survival benefit [10,42,43].

The analysis of a Swedish national cohort of 67743 RA patients demonstrated that TNF antagonists were not associated with any major further increase in the already increased lymphoma risk in RA [44]. In the analysis of the National Data Bank for Rheumatic Diseases data for 19,591 participants, RA patients receiving anti-TNF plus MTX did not show an increased incidence of lymphoma when compared with patients receiving MTX treatment alone [45]. Meta-analytic and exposure pooled analyses of more than 8800 RA patients in randomized, controlled trials did not show an increased risk for lymphoma (odds ratio [OR]: 1.26; 95% CI: 0.52–3.06) or composite end point of noncutaneous cancers plus melanomas (OR: 1.31; 95% CI: 0.69–2.48) [46]. Etanercept was reported to lower the cancer risk during the first years of follow-up, whereas adalimumab increased the risk in the first year of therapy. During the first 6 years of therapy, no overall elevation of cancer risk was observed with any of the three TNF antagonists [47]. In a nationwide survey carried out in Turkey, 15 malignancies were found among 2199 TNF-α antagonist users. Overall data did not show an increased risk of cancer associated with TNF-α antagonist use. However, ten patients were etanercept users and when analyzed separately, etanercept appeared to have an increased risk (SIR: 2.3). The study had some limitations, such as data were not available for background risk factors [48]. Although cancer constitutes one of the concerns for commencing TNF blocker, one study remarked the safety and good tolerability of infliximab treatment in patients with advanced cancer [49].

Despite animal and human studies highlighting the importance of TNF-α in the pathogenesis of heart failure, randomized, controlled trials have shown a lack of efficacy of anti-TNF-α agents in patients with advance heart failure. RA patients have a higher risk of heart failure than the general population. There are recommendations to avoid the use of anti-TNF-α agents in patients with heart failure, especially in those with worse functional classes [50].

Anti-TNF-α agents are classified as category B (no documented human toxicity) by the US FDA. Animal studies with a soluble TNF receptor /IgG heavy chain chimeric protein and monoclonal antibody report no maternal toxicity, embryotoxicity or teratogenicity. However, anti-TNF antibodies are species specific and only a few human studies are available. The molecular structure of adalumimab, infliximab and etanercept, composed of dimers with a ligand binding portion of the p75 receptor linked to the Fc portion of human IgG1, permit little placental transfer during the first trimester, but placental transfer cannot be excluded during the second and third trimesters [51,52]. Contraindications for the use of anti-TNF-α blockers are shown in **Box 1**.

The most common side effects of these therapies are injection site reactions to subcutaneously administered drugs (local erythema and swelling usually subside within 24 h, and can be lessened by antihistaminics), or infusion reactions with infliximab; it is not necessary to stop the treatment and these side effects do not interfere with the efficacy of the drugs [40].

Development of antibodies against the drug – human antichimaeric antibodies (HACA; infliximab) or human antihuman antibodies (HAHA; etanercept/adalumimab) – is a problem for TNF therapies. The incidence of HACA production to infliximab is reported to be approximately 10% and appears to be associated with lower serum infliximab concentrations and a slightly higher incidence of infusion reactions [53]. Concomitant therapy with low-dose MTX greatly diminished the appearance of this antibody [1,54]. The least HAHA antibody development has been observed in response to etanercept with an incidence of approximately 5% [55].

Retrospective series of eight patients suggests that treatment with anti-TNF-α therapy can be used in HIV patients without advanced disease with associated rheumatic diseases [56]. In a study involving 31 patients with RA with concomitant hepatitis C virus (HCV) infection, TNF-α blockers seemed to be safe, provided there is close monitoring of clinical and virological data (mainly alanine aminotransferase and HCV viremia) [57]. In a paper reviewing the records of four patients with spondyloarthropathy and HBV infection, routine HBV testing before treatment initiation of TNF antagonists was suggested. Use of antiviral therapy proflacticly in case of viral load increase was recommended under TNF antagonist therapy. Considering the risk of escape phenomenon after several years, continuous viral-load monitoring was also emphasized for patients undergoing antiviral therapy [58]. In a retrospective review of 11 patients, use of TNF-α blockers in patients with HBV or HCV was associated with a transient transaminitis, but appeared to be safe overall. Frequent monitoring of serum transaminase levels and viral load was suggested for both groups [59]. For HBV, viral load monitoring 3 months after therapy has terminated was also recommended [60].

Cost–effectiveness

The anti-TNF drugs are substantially more expensive than traditional DMARDs. There are several arguments concerning cost–effectiveness. In a subanalysis of the BeST study, depending on the way in which productivity is valued, the cost of infliximab could be compensated for by savings in productivity [61]. A recent study has demonstrated that the combination of adalimumab and MTX has the ability to reduce RA-related job loss and loss of work time in patients with early RA in comparison with the use of MTX alone [62].

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by sacroiliitis, spondylitis and periferal arthritis of mainly large joints. The disease has a great impact on a patient's quality of life and employement. Exercise and NSAIDs are the main first-line treatment options. NSAIDs may retard disease

Box 1. Contraindications for the use of TNF-α.

Absolute

- Active infections (including infected prosthesis and severe sepsis)
- History of recurrent or chronic infections (e.g., bronchiectasis)
- After previous, untreated tuberculosis
- Moderate-to-severe congestive heart failure
- Multiple sclerosis or optic neuritis
- Combination treatment with anakinra (IL-1 receptor antagonist)
- Reactive or recent history (past 10 years) of malignancies except for skin cancer

Relative

- Pregnancy
- Lactation
- HIV, hepatitis B and C infection

progression when regularly used [63], but may have some cardiovascular implications and certainly not all patients respond to NSAIDs alone. Sulfasalazine has been shown to have an effect on periferal arthritis, but not axial disease. MTX may also have a modest periferal effect [64].

Anti-TNF-α treatment becomes a salvage treatment of AS after failure of MTX and partial effect of sulfasalazine and limited effect of NSAIDs. In a randomized, controlled study, infliximab was shown to be effective in disease regression and improvement in function and quality of life in AS after 12 weeks [65]. This effect was sustained after 2 years of maintenance therapy (58%) [66]. Sustained efficacy and safety has also been shown in a larger cohort [67]. Follow-up studies up to 3 years showed a durable clinical response without loss of efficacy, and treatment was well tolerated by the patients [68]. After 5 years of follow-up, 55% of 69 patients were eligible for evaluation and partial clinical remission was observed in 34% [69]. In the same cohort, some radiographic progression was observed after 4 years of therapy [70], and infliximab appeared to have more effect on disease activity and function than on structural damage. Discontinuation of long-term therapy with infliximab had eventually led to relapse of disease activity with a mean time of 17.5 weeks [71].

A small 52-week, open-label pilot study of adalimumab-treated AS patients showed a substantial improvement of clinical and MRI outcome measures, comparable to other TNF blocking agents with Assessment in AS (ASAS) 40 rate of 67%, remarking the group effect of TNF blocker in the treatment for active AS [72]. In a multicenter, double-blind, randomized, controlled trial, 58% of adalimumab-treated patients (121 of 208) achieved an ASAS20 response, 45% of the patients in the adalimumab had at least a 50% improvement in the Bath AS Disease Activity Index (BASDAI) at week 12. Adalimumab was well tolerated during the 24-week study period [73]. More adalimumab-treated than placebo-treated active AS patients achieved patient acceptable symptom state (PAS) at week 12 (42.3 vs 22.4%) in active AS [74]. Adalimumab had significantly improved symptoms of pain, fatigue and stiffness in patients with AS. Improved symptoms were associated with improved physical function and health-related quality of life at week 12. Treatment effects occurred rapidly (within 2 weeks) and were maintained through 24 weeks of treatment [75]. At 2 years, 255 (82%) of the original 311 Adalimumab Trial Evaluating Long-Term Safety and Efficacy for AS (ATLAS) patients continued receiving adalimumab treatment. Improvements in ASAS responses observed in ATLAS were sustained during long-term treatment; 64.5% (200/310) were ASAS20 responders, 50.6% (157/310) were ASAS40 responders [76]. The BASDAI and ASAS responses that were achieved during the 24-week, double-blind study period were sustained for up to 2 years. Long-term improvements in physical function and mobility were achieved.

In a multicenter, randomized, placebo-controlled, double-blind trial of adults with moderate-to-severe active AS, the ASAS20 was achieved by 57% of patients in the etanercept group at week 24. All individual ASAS components, acute phase reactant levels and spinal mobility measures were also significantly improved [77]. After the completion of the randomized, controlled trial of etanercept of the 277 AS patients, the study was carried over as an open-label extension for 168 weeks.

Table 2. Short- and long-term efficacy of the TNF-antagonist treatment in ankylosing spondylitis.

Drug	n	Duration	ASAS20 (%)	ASAS40 (%)	ASAS50 (%)	ASAS5/6 (%)	BASDAI50 (%)	Ref.
Adalimumab	15	52 weeks	73	67	–	–	60	[72]
	208	12 weeks	58	–	–	–	45	[73]
	311	2 years	64.5	50.6	–	–	–	[76]
Etanercept	277	24 weeks	57	–	–	–	–	[77]
	257	96 weeks	71	–	–	61	–	[78]
	–	192 weeks	81	–	–	–	–	–
Infliximab	35	12 weeks	65	–	50	–	53	[65]
	201	24 weeks	61.2	–	–	–	–	[67]
	–	102 weeks	73.9	59.4	–	–	–	–
	54	54 weeks	–	–	–	–	63	[66]
	–	102 weeks	–	–	–	–	58	–
	38	5 years	84	–	63	–	–	[69]

ASAS: Assessment in Ankylosing Spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

ASAS20 response rate at week 96 was 71% and at week 192 was 81%. ASAS 5/6 response rates were 61% at week 96 and 60% at 144 weeks. Etanercept had been well tolerated and no unexpected adverse effect was observed [78]. Short- and long-term results of etanercept and persistent anti-inflammatory effect with no loss of efficacy were confirmed by these studies (TABLE 2).

In a 6-month observational, multinational study, patients with AS had experienced improvement in health-related quality of life by TNF-α antagonist use (infliximab and etanercept) that was comparable to, and sometimes greater than, that observed in RA patients [79].

Switching from one TNF inhibitor to another appeared to have a similar efficacy profile to the initial treatment. Authors conclude that switching is a worthwhile strategy in some AS patients [80].

Who should be treated with TNF antagonist? ASAS consensus for the treatment of AS includes fulfilling the 1984 modified New York criteria for definitive AS, having active disease with a BASDAI score of more than 4 and expert opinion and adequate trial of at least two NSAIDs. Patients with periferal arthritis should also have at least one corticosteroid injection and therapeutic trial of sulfasalazine [81].

The rate of development of functional impairment, physician's global assessment of current disease activity, physician's global assessment of cumulative disease activity, presence of hip arthritis and physician's global assessment of disease severity were the most important variables in judging whether a patient should be treated with TNF-blocking therapy among Dutch physicians. Multivariate analysis of Outcome in AS International Study (OASIS) data (79 patients) demonstrated that male sex, function and radiographic damage were the only independent determinants of a decision to start TNF-blocking drugs [82].

The French Society for Rheumatology recommended TNF-α antagonist therapy in patients with AS if: the patient had a definitive diagnosis of AS; the patient is active for more than 1 month, with a BASDAI score of 4 in patients with predominantly axial disease or a tender/swollen joint count of three and with a physician assessment of disease activity of 4/10; there is failure of at least three NSAIDs in patients with axial disease or of DMARD therapy in patients with peripheral disease; and the patient has no contraindications to TNF-α antagonist therapy. The treatment objective was at least a two-point improvement in the BASDAI score in axial disease or a 30% improvement in joint count in patients with periferal disease. In nonresponders, higher doses of infliximab or more closely spaced injections, or switching to another TNF blocker, were recommended [83].

In daily rheumatology practice, anti-TNF treatment was iniatiated in 44% of definite AS patients at a median of 2 months after the clinical evaluation. More than 85% of patients had increased BASDAI despite previous NSAID use [84].

Data for 1200 patients show that approximately half of the patients with AS were commenced on TNF-blocking drugs, although prescription rates have been shown to vary across physicians and countries. The most important determinant for beginning TNF-blocker therapy was considered to be disease activity and severity; however, this did not always meet the ASAS recommendations. Of the patients considered to be candidates for TNF blockers, 40% had not fulfilled ASAS recommendations with respect to previous use of NSAIDs or BASDAI (>4) [85].

Are TNF inhibitors cost effective in treatment of AS? In a 6-month, randomized, placebo-controlled trial, functional impairment and disease activity were significantly associated with active AS, and infliximab treatment significantly improved productivity and reduced workday loss in AS patients [86]. Infliximab use had been associated with a reduction in mean inpatient days from 11.1 days to 0.6 or 2.9 days after 1 or 2 years of treatment, and the authors concluded that the use of infliximab in patients with active AS might reduce some important costs of AS; however, they emphasize the requirement of studies with additional detailed cost calculations [87].

Evidence indicated that over short timeframes anti-TNF-α therapies are unlikely to be considered cost effective [88]. All the three TNF inhibitors have been demonstrated to be effective in the treatment of AS. Adalimumab was used as a dose of 40 mg every other week, etanercept 25 mg twice weekly or 50 mg weekly, and infliximab 5mg/kg for three loading dose, and there after at every 6–8 weeks. Economic costs were substantial with the three drugs, while infliximab might be somewhat higher in respect to a patient's weight or due to loading doses at the commencement of the therapy [88]. Adalimumab, when used according to UK treatment guidelines, is cost effective compared with conventional therapy for treating AS patients over long periods of time [89].

Is low-dose infliximab treatment effective for AS? Direct drug costs were significantly lower when a low-dose infliximab regimen was used. However, there is debate on the efficacy of a low-dose infliximab regime in AS. In a small-scale study of 22 patients, low-dose infliximab (3 mg/kg at 8 weekly infusions) was effective in the treatment of AS. A total of 50% of the patients achieved 50% BASDAI response at 3 months, and benefit was sustained until 12 months. Higher doses were required in a small proportion of patients when treatment was partially effective. Authors conclude that titrating the dose and frequency of infusions might be required in individual patients in order to achieve optimal response [90]. One study demonstrated that for some patients the disease might be controlled with long intervals between infusions [91]; while another study indicated that continuous treatment of AS with infliximab is more efficacious than on-demand treatment [92]. In some patients, low-dose (3 mg/kg) infliximab therapy is associated with sustained effectiveness in patients with AS in the real-world setting. This effectiveness has been maintained over a period of 4 years [93]. A total of 16 psoriatic arthritis, 12 AS and two undifferentiated spondyloarthropathy patients with substantial active axial disease received six infliximab infusions. The mean infliximab dose was increased from 3.5 mg/kg at the first infusion to 4.3 mg/kg at the seventh infusion. In the majority of the patients, low starting doses of infliximab required subsequent adjustment [94].

Is combination therapy more effective than TNF antagonists? As opposed to that observed for RA, there was no additional clinical or MRI improvement with the addition of MTX to infliximab in AS [92,95].

Are TNF antagonists effective for advanced disease? After 12 weeks of adalimumab therapy, patients with advanced but active AS, including those with structural damage of more than 80% of the vertebrae, had achieved improvements in signs and symptoms similar to those attained by patients whose AS was not advanced [96]. In the subgroup analysis of the ATLAS study, in AS patients with total spinal ankylosis, adalimumab treatment resulted in rapid and clinically significant improvement in the signs and symptoms of active disease; effectiveness and safety of the drug were sustained for at least 2 years (total ankylosis) [97]. In severe active AS with spinal ankylosis, infliximab also resulted in significant improvements in health-related quality of life, and the majority of the patients returned to full-time employment [98].

Do TNF-α inhibitors reduce spinal inflammation, do they have effect on radiographic progression?

A randomized, multicenter, double-blind, placebo-controlled study demonstrated that adalimumab significantly reduced both spinal and sacroiliac joint inflammation in patients with active AS after 12 weeks of treatment, and the reduction in inflammation was maintained for at least 52 weeks. Patients who received adalimumab, even those who were ASAS non-responders, showed MRI evidence of significant reduction in spinal inflammation [99].

After 3 months of infliximab therapy of 20 AS patients, in correlation with clinical improvement, significant regression of spinal inflammation was observed using MRI activity scores [100]. When compared with the placebo group, improvement in MRI activity score after 6 months was significantly greater in AS patients who received infliximab. Almost complete resolution of spinal inflammation was seen in most patients [101]. Long-term clinical and MRI examinations demonstrated that the patients treated during the first 3 months showed additional improvement of active spinal lesions after 2 years. Minor spinal inflammation was still detected after 2 years of infliximab treatment [102]. After 2 years of etanercept therapy of the 26 patients with AS, MRI evaluations demonstrated a 75% improvement of active spinal lesions; however, minor spinal inflammation was still detected in 64% of patients [103].

Ankylosing spondylitis patients who had received infliximab from baseline through week 96 had not shown a statistically significant difference in inhibition of structural damage progression at year 2, as assessed using the Modified Stokes AS Spinal Score (mSASSS) scoring system employing plain radiographs of the spine, when compared with radiographic data from the historical control OASIS cohort, which comprised AS patients having treatments other than TNF blockers [104]. Similar results were obtained with etanercept [105]. Syndesmophytes are the best predictors of radiographic progression [106]. Radiographic damage at baseline was a predictor for more radiographic progression. A small-scale study suggests that patients with baseline damage who were treated with infliximab had a trend for less radiographic progression after 2 years when compared with the the early German AS Cohort (GESPIC). Scoring was made by the mSASSS [107]. A total of 33 AS patients were evaluated at baseline, 2 and 4 years, and radiologic progression was

compared with OASIS cohort. Radiographic examination revealed that infliximab did not completely inhibit, but decelerated, radiographic progression in patients with AS [108]. This was explained by the different nature of AS as compared with RA where osteodestruction is prevalent rather than new bone formation. The need of larger studies were emphasized [108].

Data from four placebo-controlled studies of infliximab and etanercept showed that both drugs decreased the frequency of anterior uveitis flares; although the difference was not significant, anterior uveitis occurred less frequently with infliximab [109]. Etanercept therapy was associated with a significantly greater number of reported uveitis cases when compared with infliximab and adalimumab in two medication side effect registries, authors recommended to change to infliximab if a patient develops uveitis during etanercept therapy [110].

Psoriatic arthritis is a chronic arthritis of periferal joints and axial skelton, associated by psorasis. It runs a chronic course and leads to significant debility and morbidity in some patients. In patients who are resistant to DMARDs, anti-TNF therapies became the next armotorium.

In a 24-week, randomized, controlled trial of adalimumab, patients treated with adalimumab showed a 58% ACR20 response, 59% achieved 75% Psoriasis Area and Severity Index (PASI) improvement response, and had a -0.2 decrease in modified total sharp score (mTSS). Adalimumab also improved disability and quality-of-life scores [111]. In the open-label extention study, at week 48, ACR20, ACR50 and ACR70 response rates were 56, 44 and 30%, respectively. The PASI75 rate was 58%. Mean change from baseline in the mTSS was 0.1 [112]. ACR response rates and improvement in skin disease were maintained over 2 years. Mean change in mTSS was -0.2 compared with 1 in the placebo group [113]. Adalimumab significantly reduced all aspect of psoriatic disease, including joint and skin manifestations, disability due to joint disease and decreased quality of life. Favorable risk–benefit profile was also maintained over 2 years. Inhibition of structural damage was also apparent over 2 years.

Relatively low-dose infliximab (3 mg/kg) infusion significantly decreases T-cell and macrophage infiltration in synovial tissue of patients with psoriatic arthritis 48 h after treatment [114].

Infliximab at 5mg/kg dose had a ACR20 response rate of 58%. It also improved associated psoriasis, dactilytis and enthesopathy [115]. It significantly retarded radiographic progression starting from 6 months continuing over 1 year of treatment [116]. At week 94, improvement in joint and skin symptoms were sustained and estimated annual rate of radiographic progression was smaller than estimated baseline rate of progression [117].

In a randomized, controlled study, etanercept at week 24 had a ACR20 response rate of 59% and PASI75 rate of 23%. At 1 year, radiographic progression was also inhibited [118]. A 2-year open-label extention study showed sustained efficacy and maintenance of radiographic inhibition (Table 3) [119].

Golimumab, a new human anti-TNF monoclonal antibody, at 50 and 100 mg doses, also inhibited psoriatic artritic and skin lesion and improved psoriatic nail lesions [120].

Approximately a third of patients do not respond to MTX adequately in juvenile RA (JRA) [121]. A multicenter, open-label, extended-treatment trial demonstrated that children with severe, longstanding, MTX-resistant polyarticular JRA had sustained clinical improvement with more than 2 years of continuous etanercept treatment. Of the 43 patients, 81% met the JRA 30%, 79% met the JRA 50%, and 67% met the JRA 70% definitions of improvement. Etanercept was generally well tolerated and no increase in the rates of adverse events were seen over time [122]. In the 4-year analysis of 32 patients, etanercept demonstrated an acceptable safety profile in children with polyarticular-course JRA and provides significant

Table 3. Short- and long-term efficacy of the TNF-antagonist treatment in psoriatic arthritis.

Drug	n	Duration	ACR20 (%)	PsARC (%)	PASI75 (%)	Ref.
Adalimumab	151	24 weeks	58	60	59	[111]
	144	104 weeks	58	63.5	62	[113]
Infliximab	100	14 weeks	58	77	64	[115]
	87	98 weeks	62	–	64	[117]
Etanersept	101	24 weeks	59	70	23	[118]
	141	2 years	64	84	(PASI50) 62	[119]

ACR20: American College of Rheumatology Criteria of 20% improvement; PsARC: Psoriatic Arthritis Response Criteria; PASI: Psoriasis Area and Severity Index.

improvement in disease activity [123]. An acceptable safety profile of etanercept therapy was maintained for up to 8 years in the study population of JRA patients along with improvements in the signs and symptoms of JRA [124].

In a small-scale study in patients switching from twice- to once-weekly administration, there was no loss of efficacy and no increase in toxicity [125]. Retrospective chart review of eight children showed that in children with unsatisfactory response to standard-dose etanercept, an increased dose or treatment prolongation might not offer any additional benefit [126].

Owing to the concerns of the anti-TNF-induced lupus syndrome [29], there are not many studies of TNF antagonists in systemic lupus erythematozus (SLE). In one pilot study, four of the nine patients in the treatment arm could not be evaluated owing to infusion reactions to infliximab; the remaining patients had improvements in SLE Disease Activity Index (SLEDAI) scores at the end of a 24-week period [127]. In another study series, three doses of infliximab were given to nine patients with intractable lupus nephritis. A total of six patients had improvements in urinary findings and/or SLE activity and urinary protein excretion after 6 months [128]. In one patient, infliximab was terminated due to pyelonephritis. Of the remaining eight patients, urinary protein decreased after anti-TNF-α therapy in six patients, and the SLEDAI improved in five patients. Urinary findings and/or SLE activity improved in six patients. Of the patients whose urinary protein levels decreased after anti-TNF-α therapy, proteinuria recurred 6 months after anti-TNF-α therapy in one patient [128].

Behçet disease is a multisystem disease of veins and arteries of all sizes, characterized by mucocutaneous, arthicular, ocular, gastrointestinal and neurologic involvement. In cases refractory to standard therapy, TNF-α antagonists are becoming an alternative option.

In patients with Behçet uveitis, therapy with infliximab considerably reduced the required daily dose of both corticosteroids and immunosuppressive drugs [129]. In a 4-week, double-blind, placebo-controlled study, etanercept decreased the mean number of oral ulcers, nodular lesions and papulopustular lesions in Behçet patients. It did not affect the pathergy reaction [130]. In patients with resistant entero-Behçet disease, infliximab treatment resulted in a rapid and dramatic improvement in clinical and intestinal manifestations. Oral and genital ulceration, uveitis, skin manifestation and arthritis improved within 4 weeks, while ileocecal ulceration improved in all patients and disappeared completely by 6–12 months [131].

Conclusion

TNF-α inhibitors can induce remission and prevent both clinical and radiological disease progression in RA with significant improvement in patients' symptoms, function and quality of life. They are effective in disease regression and improvement in function and quality of life in AS, and long-term follow-up studies showed durable clinical efficacy and safety. The most important determinant for beginning TNF-blocker therpy was considered to be disease activity and severity. They may reduce some important costs of AS; however, studies with additional detailed cost calculations are required. TNF-α inhibitor treatment also resulted in a

Executive summary

- TNF inhibitors can induce remission and prevent both clinical and radiological disease progression in rheumatoid arthritis with significant improvement in patients' symptoms, function and quality of life.
- Reactivation of the latent tuberculosis (TB) infection has been reported with the initiation of anti-TNF treatment. Appropriate TB screening should be performed before starting the therapy. The rate of TB was higher for adalimumab and infliximab than etanercept.
- During the first 6 years of therapy, no overall elevation of cancer risk was seen with any of the three TNF-antagonists.
- Use of TNF antagonists is not recommended in advanced heart failure.
- Frequent monitoring of transamine levels and viral load are recommended in patients with hepatitis C and B infection.
- They may reduce some important costs to the patients, but studies with detailed cost calculations are required.
- TNF-antagonist treatment is effective in the short term and long term in ankylosing spondylitis (AS).
- The most important determinant for beginning TNF-blocker therapy was considered to be disease activity and severity.
- There is debate on the efficacy of low-dose infliximab regime in AS.
- TNF-α inhibitor treatment also resulted in rapid and clinically significant improvement in the signs and symptoms of active disease in patients with total spinal ankylosis.
- They decelerate but did not completely inhibit radiographic progression in patients with AS.
- In psoriatic arthritis, they improve joint and skin symptoms and retard radiographic progression.
- Etanercept is the only US FDA-approved TNF-α blocker for juvenile rheumatoid arthritis.
- TNF-α antagonists may improve some clinical manifastations of Behçet's disases, including uveitis.

rapid and clinically significant improvement in the signs and symptoms of active disease in patients with total spinal ankylosis. They reduced both spinal and sacroiliac joint inflammation, they decelerate, but do not completely inhibit, radiographic progression in patients with AS. In psoriatic arthritis they improve joint and skin symptoms and retard radiographic progression. Etanercept is the only US FDA-approved TNF-α blocker for JRA. TNF-α antagonists may improve some clinical manifastations of Behçet's disases, including uveitis.

Future perspective

TNF antagonists retard but do not completely inhibit radiological progression in AS; there is need for new therapeutic modalities to inhibit other pathways of inflammation – that is, IL-17 and IL-23. Drugs targeting new bone formation may become a new avenue for therapeutic strategies in AS. More controlled studies are needed for the use of TNF antagonists in Behçet disease. Future studies will delineate the use of TNF antagonists in familial Mediterranean fever, SLE and Takayasu arteritis.

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