

# Adalimumab: effective TNF-blockade therapy for ankylosing spondylitis

Pascale Schwab &  
Atul Deodhar<sup>†</sup>

<sup>†</sup>Author for correspondence  
Oregon Health & Science  
University, Division of  
Arthritis and Rheumatic  
Diseases, Oregon Health &  
Science University,  
3181 S.W. Sam Jackson Park  
Road, Portland OR, USA  
Tel.: +1 503 494 8963;  
Fax: +1 503 494 1022;  
deodhara@ohsu.edu

The armamentarium available for the treatment of ankylosing spondylitis (AS) has for decades been inadequate. The recent introduction of tumor necrosis factor (TNF) antagonists for the treatment of AS has proven pivotal and provided patients with AS an effective treatment option. Indeed both infliximab, a human-mouse chimeric monoclonal antibody directed against TNF, and etanercept, a construct of the Fc portion of the human IgG with soluble receptor of TNF, have demonstrated in clinical trials to improve symptoms of pain and stiffness, physical function, quality of life, as well as MRI inflammation. In 2006, another anti-TNF agent, adalimumab, which is a fully human monoclonal antibody, was approved for the treatment of AS. This report reviews the pharmacologic characteristics of adalimumab as well as its efficacy and safety in AS.

## Need for new treatments for ankylosing spondylitis

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease characterized by axial (spinal and sacroiliac) joint inflammation and, at times, peripheral arthritis (predominantly involving large joints). The incidence of AS is estimated at 0.5–8.2/100,000 individuals and prevalence rates in the range of 0.2–1.2% have been reported [1]. AS usually begins in adolescence and early adulthood, rarely after the age of 45 years, and is about two- to three-times more frequent in men than women. The etiology of AS is unknown, but genetic association with the *HLA-B27* allele has clearly been demonstrated [2]. Primary pathology in AS begins at the entheses or sites of ligamentous and tendinous insertions to bone [3]. Persistent inflammation results in bony erosions, cartilage destruction, new bone formation and bony ankylosis. Patients experience back pain and tenderness, stiffness on inactivity, rare peripheral joint swelling, and eventually persistent loss of spinal and joint mobility. Diagnosis of AS is based on the modified New York classification criteria, which require the presence of inflammatory low back pain, limitation in spinal mobility or limitation in chest expansion in addition to radiographic evidence of sacroiliitis [4].

Traditionally, treatment for AS has focused on relieving symptoms of pain and stiffness and relied on physical therapy and NSAIDs [5]. When taken continuously, celecoxib has been shown in one study to reduce spinal radiographic progression [6], although this observation has not been reproduced. NSAIDs are used long term by approximately 80% of patients

with AS, however, they are associated with unacceptable adverse effects in 20–25% of users [7]. Corticosteroid injections directed at sites of musculoskeletal inflammation may be considered. Surgical interventions such as hip replacement or spinal surgery in selected patients may be of value [8]. Attempts at using DMARDs that have traditionally been effective for rheumatoid arthritis (RA; e.g., sulfasalazine or methotrexate) have been disappointing in AS. A recent Cochrane analysis concluded that there is not enough evidence to support any benefit of methotrexate in the treatment of AS [9]. Likewise, although sulfasalazine may benefit patients with peripheral arthritis and spinal pain in early AS [10], it has not been shown to improve physical function, spinal mobility and enthesitis [11]. AS patients need agents that not only improve the signs and symptoms of the disease and improve physical function, but also arrest radiographic progression.

## Anti-TNF therapy for AS

Prior to the advent of anti-TNF therapy, a community-based population survey reported substantial disease activity and functional impairment in 75% of AS patients despite conventional therapy [12]. The identification of TNF mRNA and protein in inflamed sacroiliac joints [13] provided the initial rationale for testing anti-TNF agents in AS. During the last 5 years, the use of these agents has had a profound impact on the treatment of AS. The Assessment in AS (ASAS) international working group, together with the European League Against Rheumatism (EULAR), currently recommend treatment with a TNF inhibitor for patients with persistent disease activity as measured by a Bath Ankylosing Spondylitis Disease

**Keywords:** adalimumab,  
ankylosing spondylitis,  
biologic therapy, enthesitis,  
sacroiliitis, TNF antagonists

future medicine part of fsg

Activity Index (BASDAI) of four or more, and failure to improve despite 3 months of therapy with at least two NSAIDs [8].

The first two anti-TNF drugs to be available on the market were infliximab, a chimeric anti-TNF monoclonal antibody, and etanercept, an IgG Fc/p75 TNF receptor fusion molecule. The efficacy and short-term safety of infliximab infusion at 5 mg/kg every 6 weeks in the treatment of AS were demonstrated in a 24-week, placebo-controlled randomized trial (the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy [ASSERT] trial) [14]. Improvements in disease activity, physical function, metrology and quality of life were observed in 61% of patients receiving active drug versus 19% receiving placebo, and these improvements were sustained through the end of the trial. Spinal MRI conducted in the majority of these patients at baseline and at 24 weeks revealed almost complete resolution of spinal inflammation in patients receiving infliximab, regardless of baseline disease activity [15]. However, these striking improvements in MRI images did not lead to prevention of radiographic progression for patients receiving infliximab in ASSERT who were compared with a historical control group of patients with AS who had never used biologics [16]. Open-label trials have shown continued efficacy and safety of infliximab after 3–4 years [17,18].

The efficacy of etanercept has likewise been established in several double-blind, randomized placebo-controlled trials. One trial randomized 40 patients with AS to either etanercept 25 mg twice weekly or placebo. Significant improvements in morning stiffness, spinal pain, function, quality of life, enthesitis, chest expansion and inflammatory markers were observed for patients who received etanercept [19]. A larger, 24-week, multicenter, randomized placebo-controlled, Phase III trial further confirmed these results. ASAS20 was achieved by 59% of patients in the etanercept group and by 28% of patients in the placebo group at week 12 [20]. An open-label extension of this trial demonstrated sustained efficacy and safety for up to 2 years, with 74% of patients achieving an ASAS20 [21]. Patients who had participated in a 6-month German study of etanercept and had experienced recrudescence of symptoms after the end of the trial were enrolled in an open-label extension and have been followed for up to 2 years. These patients have responded to the re-introduction of etanercept, indicating that efficacy does not persist after its discontinuation, but does indeed

return with its re-institution [22]. MRI studies in patients treated with etanercept have shown a substantial decrease in spinal inflammation, with no progression at 2 years [23]. However, as is the case with infliximab, the comparison of spinal radiographs of patients who received 2 years of etanercept therapy with radiographs from a historical control group of AS patients never treated with a biologic drug indicated that etanercept did not prevent radiographic progression [24].

#### **Adalimumab: a subcutaneously administered, fully human anti-TNF monoclonal antibody**

Adalimumab, originally approved for the treatment of RA, has now been approved to treat psoriatic arthritis, AS and Crohn's disease.

#### **Adalimumab chemistry & pharmacodynamics**

Adalimumab is a recombinant human IgG1 monoclonal antibody specific for human TNF. It is produced by recombinant DNA technology in a mammalian expression system. Supplied as a sterile, preservative-free solution for subcutaneous administration, adalimumab binds to soluble as well as receptor-bound TNF and blocks its interaction with the p55 and p75 TNF receptors. *In vitro*, it also lyses surface TNF-expressing cells in the presence of complements. Unlike etanercept, it does not block lymphotoxin. Adalimumab may also modulate expression of adhesion molecules involved in leukocyte migration and decreases acute-phase reactants [25].

#### **Adalimumab pharmacokinetics**

The pharmacokinetics of adalimumab in AS patients are similar to those in patients with RA. Following a single subcutaneous injection of adalimumab 40 mg to a healthy human volunteer, the maximum peak concentration and the time to reach maximum concentration were 4.7 +/- 1.6 mg/l and 131 +/- 56 h, respectively. The absolute bioavailability of adalimumab was 64%. The mean terminal half-life was approximately 10–20 days across studies. Greater clearance occurs in the presence of anti-adalimumab antibodies, and decreased clearance has been noted with increasing age. No pharmacokinetics data are available for patients with hepatic or renal impairment [25]. Pharmacokinetics of adalimumab in patients with active AS showed that mean trough concentrations of adalimumab were 6–7 mg/ml for monotherapy versus 7–9 mg/ml with concomitant methotrexate

administration, which is similar to trough concentrations for patients with RA. Anti-adalimumab antibodies were detected in 8.3% of patients but did not appear to be associated with increased number of adverse events [26].

### *Clinical efficacy*

In an open-label trial of 15 NSAID-refractory patients with moderate to severely active AS who were treated with adalimumab 40 mg every other week, all patients who completed the study (87%) experienced a substantial improvement during the 52-week treatment period [27]. Response to treatment was noted as early as 2 weeks after start of therapy and continued to increase. After 52 weeks, a BASDAI response of greater than 50% was observed in 60% of patients, and an ASAS40 response in 67% of patients. After switching to weekly dosing, three of seven patients who did not reach a BASDAI50 improvement between 12 and 24 weeks then became responders. The median C-reactive protein (CRP) concentration decreased to a normal

range within 2 weeks of therapy. Although not statistically significant, likely because of the small number of patients, sacroiliac and spinal inflammation MRI scores decreased compared with pretreatment baselines [27].

The Adalimumab Trial Evaluating Long-Term Efficacy and Safety for Ankylosing Spondylitis (ATLAS) [28] was the pivotal double-blind, randomized, placebo-controlled trial that demonstrated the safety and efficacy of adalimumab in patients with active AS and helped lead to its AS indication. A total of 347 patients were screened, 315 of which were randomized (2:1) to receive adalimumab 40 mg every other week or placebo for a 24-week period. Of note, six patients in the active treatment group and five in the placebo group had total spinal ankylosis. The primary efficacy end point was the percentage of patients achieving an ASAS20 at 12 weeks. Secondary outcomes included the ASAS20 at week 24 and multiple measures of disease activity, spinal mobility and function (Box 1). As early as week 12, patients who were

#### **Box 1. Measured secondary end points in the ATLAS trial.**

##### ***Secondary measures that improved at 12 and 24 weeks ( $p < 0.001$ vs placebo)***

- Patients global assessment of disease activity
- Total back pain
- BASFI
- BASDAI
- C-reactive protein
- BASMI
- Lumbar side flexion
- Intermalleolar distance
- Cervical rotation
- MASES
- BAS-G
- Nocturnal pain
- Physicians global assessment of disease activity
- ASAS40
- ASAS 5/6
- Partial remission

##### ***Secondary measures that did not improve at 12 and 24 weeks ( $p > 0.05$ vs. placebo)***

- Tragus to wall
- Anterior lumbar flexion
- Chest expansion
- Swollen joint count
- Tender joint count

*BASFI: Bath ankylosing spondylitis functional index; BASDAI: Bath ankylosing spondylitis disease activity index; BASMI: Bath ankylosing spondylitis metrology index; MASES: Maastricht ankylosing spondylitis enthesitis score; BAS-G: Bath ankylosing spondylitis patient global score; ASAS40 40% improvement in three out of four ASAS measures; ASAS 5/6 20% improvement in five out of six domains, consisting of the four ASAS20 criteria plus spinal mobility and acute-phase reactants.*

*p-values were calculated by analysis of covariance, comparing adalimumab to placebo; if a patient received early-escape open-label adalimumab prior to the end of the 24 weeks, the last observation prior to escape to open-label adalimumab therapy was carried forward.*

*Data taken from [28].*

nonresponders were allowed to move to the open-label portion of the study. By week 24, 74 of the 107 (69.2%) patients initially assigned to placebo had taken advantage of the early-escape protocol and were receiving open-label adalimumab. By contrast, 81 of the 208 (38.9%) patients originally assigned to adalimumab had entered the early escape protocol. Of the patients receiving adalimumab, 58.2% achieved ASAS20 at 12 weeks versus 20.6% of placebo-treated patients, a difference that was statistically significant ( $p < 0.001$ ). Likewise, at week 24, 50.5% of adalimumab-treated patients versus 18.7% of placebo-treated patients experienced an ASAS20 ( $p < 0.001$ ). Most notably, of the six patients with complete ankylosis who were receiving adalimumab, three experienced an ASAS20 by week 12, and 4 had achieved it by week 24. By contrast, none of the placebo-treated patients who had complete ankylosis had an ASAS20 response. In addition, a statistically significant improvement (vs placebo) in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), which assesses tenderness at 13 entheses [29], was demonstrated by patients in the adalimumab group. This is a unique finding given that patients treated with infliximab in the infliximab Phase III trial (ASSERT), which employed the Mander Enthesitis Index, a more complex measurement of enthesal tenderness at 66 entheses, did not demonstrate improvement in enthesitis. However, there was a statistically significant improvement in the self-reported enthesitis component of the BASDAI questionnaire in ASSERT [14]. In the comparable Phase III etanercept trial, a clinical enthesitis index was not measured [20,21]. Treatment with adalimumab was also associated with a statistically significant improvement in all four individual components of the ASAS20, including the patient's global assessment of disease activity, the patient's assessment of pain, the patient's assessment of function measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) score, and the degree of inflammation represented by the severity and duration of morning stiffness (last two questions on the BASDAI). Furthermore, statistically significant improvements in total BASDAI, CRP, Bath Ankylosing Spondylitis Metrology Index (BASMI), the Bath Ankylosing Spondylitis Patient Global Score (BAS-G), nocturnal pain and physician's global assessment of disease activity were noted at 12 and 24 weeks for adalimumab- versus placebo-treated patients [28].

### **Safety of adalimumab in AS**

In the ATLAS trial, the overall incidence of adverse events at 24 weeks was greater for the adalimumab- versus placebo-treated patients (75 vs 59.8%;  $p < 0.05$ ). Similarly, the overall incidences of any infection (31.7 vs 21.5%, not statistically significant) and injection-site reactions (10.1 vs 2.8%,  $p < 0.05$ ) were greater for adalimumab-treated patients. There was no difference in the occurrence of serious adverse events, and no serious infections were reported for the adalimumab-treated group. Nasopharyngitis and headache occurred in more than or equal to 5% of study patients. Only nasopharyngitis was reported at a notably greater rate for patients receiving adalimumab. No cases of tuberculosis, granulomatous infections, demyelination, drug-induced lupus, congestive heart failure, malignancy, or death were observed [28].

### **Safety of adalimumab**

Most long-term safety data for adalimumab, as well as the other TNF inhibitors, are available from RA trials and postmarketing surveillance from the use of these agents in the treatment of RA. The use of TNF antagonists in RA has been associated with some adverse events, including serious infections, demyelinating syndromes, congestive heart failure, lupus-like syndromes and lymphoproliferative disorders. It has been difficult to determine whether treatment with TNF antagonists or the underlying disease necessitating the use of these agents is responsible for some of these adverse events. In a report by Schiff *et al.*, the safety of adalimumab in patients enrolled in RA clinical trials was reviewed, and rates of selected adverse events of interest reported in the clinical trial safety database were reported [30]. A total of 10,050 patients had been treated with adalimumab, and more than 300 had experienced up to 5 years of exposure, representing 12,506 patient-years (PYs; Table 1). Rate of serious infections was 5.1/100 PYs, which is comparable to published rates for the RA population not treated with anti-TNF therapy. Four cases of histoplasmosis were reported, all in patients residing in endemic areas. Cases of tuberculosis (TB) were reported more frequently in Europe, where the prevalence of TB is greater than in North America. The rate for TB was also greater prior to initiation of appropriate TB screening measures (Figure 1). Standardized incidence ratio (SIR) for lymphoma in patients exposed to adalimumab was 3.19 (95% confidence interval [CI]: 1.78–5.26),

**Table 1. Rates of selected adverse events in rheumatoid arthritis trials of adalimumab.**

	All RA trials as of 8/31/02* E/100-PYs (number of patients)	All RA trials as of 4/15/05† E/100-PYs (number of patients)
Serious infections	4.9	5.1
Tuberculosis	0.27	0.27
Histoplasmosis	0.06 (4)	0.03 (4)
Demyelinating diseases	0.08 (4)	0.08 (10)
Lymphoma	0.21 (10)	0.12 (15)
Lupus-like syndromes	0.08 (4)	0.10 (13)
Congestive heart failure	0.29	0.28

\*n = 2468; 4870 PYs; †n = 10,050, 12,506 PYs.

E/100-PYs, events per 100-PYs.

PYs: Patient years; RA: Rheumatoid arthritis.

Adapted from [30].

which is comparable to SIRs for RA patients naive to anti-TNF therapy [31–34]. Cases of demyelinating disorders were reported, including six cases of multiple sclerosis. Lupus-like syndromes, mostly characterized by cutaneous lesions, photosensitivity and serositis without internal organ involvement, were described in 13 patients [30].

Likewise, postmarketing safety data are mainly derived from spontaneous reports of adverse events in patients receiving adalimumab for the treatment of RA. From the date of its first US FDA approval (December 31, 2002) through June 30, 2005, the estimated adalimumab patient exposure was 78,522 PYs. Rates of selected adverse events are listed in Table 2 [30].

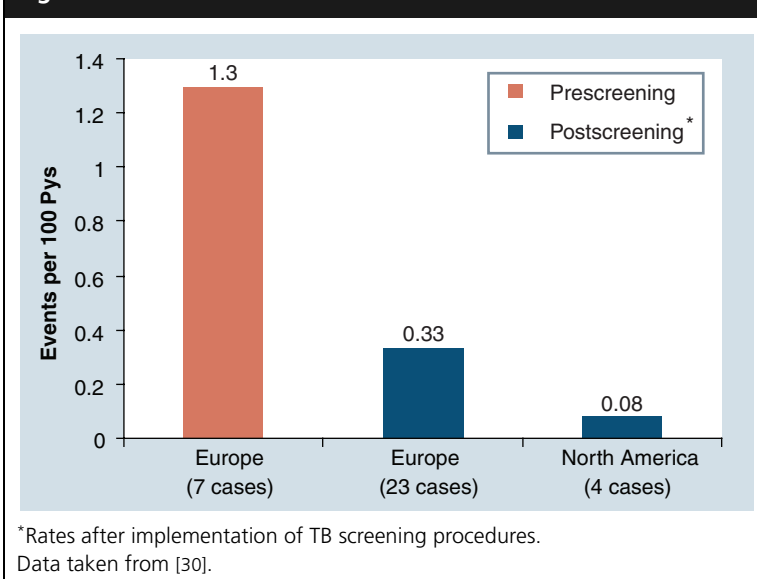
A recent study that reported on rates of serious infection in the British Society for Rheumatology Registry found that, after adjustment for baseline risk, anti-TNF therapy in patients with active RA was not associated with an increased risk of overall serious infections versus traditional DMARD treatment. By contrast, an increased risk of serious skin and soft tissue infections was detected. No differential in infection risk was seen between the three available anti-TNF drugs [35].

### Regulatory affairs

Adalimumab is commercially available in the US and more than 65 other countries. It has been approved by the FDA for the treatment of RA, psoriatic arthritis, AS and Crohn's disease. The European Medicines Agency has likewise approved the use of adalimumab in Europe for the same indications.

### Conclusion

Adalimumab is an effective therapy for patients with NSAID-refractory or intolerant AS. It has been demonstrated to alleviate symptoms of stiffness, spinal and enthesal pain, and to improve physical function and quality of life. In longitudinal studies, adalimumab reduced MRI changes associated with active disease, although its ability to inhibit radiographic progression is not yet known and is currently being evaluated. The ATLAS trial is the only trial of a TNF antagonist in AS to have demonstrated symptom improvement in several patients with seemingly total spinal ankylosis. Adalimumab is administered subcutaneously every other week for the treatment of AS in the same dosage as is used to treat RA. Increasing the dosing frequency to

**Figure 1. TB Rates in adalimumab RA clinical trials.**

**Table 2. Selected events in the US post-marketing period 31/12/02–30/6/05.**

Adverse events	Reported rates* (E/100-PYs)
Tuberculosis	0.02
Lymphoma	0.04
Congestive heart failure	0.06
Demyelinating disease	0.01
Systemic lupus erythematosus	0.03
Opportunistic infections	0.06
Blood dyscrasias	0.08

\*78,522 PYs.

PYs: Patient years.

Data taken from [30].

every week has been shown to help some patients who have not responded to standard dosing schedule [27]. TB screening and treatment of latent disease are essential, as is heightened awareness for the development of demyelinating syndromes, lupus-like reactions, CHF and lymphoma. Long-term efficacy data from the ATLAS trial are currently being collected and evaluated.

Where should adalimumab fit in the treatment algorithm for AS when two other anti-TNF drugs are already available? Although greatly efficacious, treatment with infliximab and etanercept may encounter certain limitations. Infliximab is an intravenous compound requiring administration in an infusion center. As a human-mouse chimeric antibody, it has been associated with infusion reactions and may lose efficacy in the face of neutralizing human antichimeric antibodies as in the treatment of RA. Etanercept on the other hand, unlike infliximab and adalimumab, is ineffective in the treatment of inflammatory bowel disease [36]. While true Crohn’s disease is observed in approximately 7% of AS patients, endoscopic lesions similar to Crohn’s disease have been

documented in 40% of patients with AS [37]. Furthermore, although a recent meta-analysis demonstrated that both etanercept and infliximab equally decreased the number of uveitis flares in AS patients, the trend favored infliximab [38]. Uveitis occurs in approximately 40% of AS patients throughout their lifetime and is generally easily treated. Refractory uveitis, though rare in AS [39], may not respond as effectively to treatment with etanercept as it does to treatment with the monoclonal antibodies directed against TNF [40].

The need for another TNF antagonist for patients with AS is acute, especially for patients who have experienced adverse reactions to either infliximab or etanercept, those who would prefer to inject a drug subcutaneously rather than come in for an infusion, and those who require treatment of concurrent Crohn’s disease or refractory uveitis and who may benefit more from treatment with an anti-TNF monoclonal antibody than from a receptor blocker [36–40]. Whether adalimumab will work in AS patients who have failed one or the other anti-TNF drugs, as it has in RA, remains to be demonstrated.

**Box 2. Disease activity measures in AS.**

- Bath ankylosing spondylitis disease activity index (BASDAI): a validated instrument for measuring disease activity on a visual analog scale of 0–10, which includes 6 measures: fatigue; AS neck, back, and hip pain; pain and swelling in joints other than neck, back or hip; level of discomfort from tender areas to touch or pressure; overall level of morning stiffness; duration of morning stiffness.
- Bath ankylosing spondylitis functional index (BASFI): a validated instrument for measuring the ability to perform specific tasks on a visual analog scale of 0–10.
- Bath ankylosing spondylitis metrology index (BASMI): semiquantitative assessments of anterior lumbar flexion, lateral lumbar flexion, cervical rotation, occiput to wall distance and intermalleolar distance.
- Assessment in ankylosing spondylitis 20 and 40 (ASAS20 and ASAS40): respectively, 20% and 40% improvement in three of four of the following: patient global assessment (PGA), pain, physical function (BASFI) and morning stiffness.
- Assessment in ankylosing spondylitis 5/6 (ASAS5/6): 20% improvement in five out of six domains: the four components of the ASAS20; spinal mobility (BASMI); C-reactive protein .

### Future perspective

Many questions regarding the use of TNF antagonists' inhibitors in AS remain unanswered and will require future research. Timing and duration of treatment as well as cost will need to take into consideration identification of individuals at risk for poor outcome, effect of treatment on disease progression and potential toxicity [41]. TNF antagonists represent an expensive therapy, and their long-term economic impact on productivity and disability in the treatment of AS remains to be evaluated [42].

Novel therapies for patients with AS who are either unresponsive to or intolerant of TNF-inhibitors need to be pursued. A large body of scientific evidence has implicated T cells in the pathogenesis of the spondyloarthropathies [43]. Abatacept, a CTLA-4-Ig fusion receptor antagonist that interferes with T-cell co-stimulation and antigen-dependent T-cell activation, could therefore conceivably have therapeutic benefits in ankylosing spondylitis. Autoantibody formation

does not characterize ankylosing spondylitis. Although plasma cells and B cells are present in inflamed tissues of patients with spondyloarthropathies [43], their presence is likely non-specific. Rituximab, a CD20 monoclonal antibody that results in B-cell depletion and is approved for the treatment of RA, will be studied in an investigator initiated study in AS [Pers. Comm.].

### Financial & competing interests disclosure

*Dr Deodhar has received payments for educational lectures, teleconferences and serving on advisory boards for Centocor and Genentech, companies that may have a commercial interest in the results of this research. This potential conflict of interest has been reviewed and managed by OHSU. Dr Deodhar has 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

### Mechanism of action

- Adalimumab is a fully human monoclonal antibody directed against circulating and membrane-bound TNF.

### Dosage & administration

- Adalimumab is self-administered subcutaneously at a dosage of 40 mg every other week. Decreasing the dosing interval to every week may be beneficial in some patients.

### Clinical efficacy

- The efficacy of adalimumab in ankylosing spondylitis (AS) has been demonstrated in the Adalimumab Trial Evaluating Long-Term Efficacy and Safety for Ankylosing Spondylitis (ATLAS) trial, a pivotal randomized placebo-controlled trial.
- Of the patients receiving adalimumab, 58.2% achieved assesment in AS (ASAS)20 at 12 weeks versus 20.6% of placebo-treated patients, a difference that was statistically significant.
- Statistically significant improvements in secondary outcome measures such as ASAS20 at 24 weeks, ASAS40, ASAS 5/6, as well as measures of function, quality of life, metrology and inflammatory markers were also demonstrated.
- Adalimumab effectively treats enthesitis, as demonstrated by a statistically significant improvement in the 13-point enthesitis score (MASES) versus placebo.
- A handful of patients with total spinal ankylosis, for the first time included in a clinical trial of a TNF antagonist in AS, achieved an ASAS20 following treatment with adalimumab.
- Whether adalimumab inhibits radiographic progression is not known.

### Safety

- In clinical trials, adalimumab appears to be well-tolerated in the treatment of AS. Injection-site reactions and overall increased risk of infection were greater for adalimumab versus placebo-treated AS patients, but only the difference in injection-site reactions was statistically significant. Post-marketing surveillance data will need to be monitored as adalimumab is used more widely in AS.
- As in the case with infliximab and etanercept, reactivation of latent tuberculosis in patients with rheumatoid arthritis treated with adalimumab has been reported. Patients starting adalimumab for AS likewise need to be screened for latent tuberculosis and treated appropriately prior to beginning adalimumab.

**Bibliography**

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Sieper J, Rudwaleit M, Khan MA, Braun J: Concepts and epidemiology of spondyloarthritis. *Best Pract. Res. Clin. Rheumatol.* 20(3), 401–417 (2006).
2. D’Agostino MA, Olivieri I: Enthesitis: *Best Pract. Res. Clin. Rheumatol.* 20(3), 473–86 (2006).
3. Smith JA, Marker-Hermann E, Colbert RA: Pathogenesis of ankylosing spondylitis: current concepts. *Best Pract. Res. Clin. Rheumatol.* 20(3), 571–591 (2006).
4. Van der Linden S, Valkenburg HA, Cats A: Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum.* 27(4), 361–368 (1984).
5. Elyan M, Khan MA: The role of non-steroidal anti-inflammatory medications and exercise in the treatment of ankylosing spondylitis. *Curr. Rheumatol. Rep.* 8(4), 255–259 (2006).
6. Wanders, van der Heijde D, Landewe R *et al.*: Non-steroidal anti-inflammatory drugs reduce radiographic progression in ankylosing spondylitis. *Arthritis Rheum.* 52(6), 1634–1636 (2005).
7. Zochling J, Bohl-Buehler MHJ, Baraliakos X *et al.*: Non-steroidal anti-inflammatory drug use in ankylosing spondylitis- a population-based survey. *Clin. Rheumatol.* 25, 794–800 (2006).
8. Zochling J, van der Heijde D, Burgos-Vargas R *et al.*: ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann. Rheum. Dis.* 65, 442–452 (2006).
- **Evidence-based recommendations for the treatment of ankylosing spondylitis (AS) by the Assessment in AS international working group and the European League Against Rheumatism.**
9. Chen J, Liu C, Lin J: Methotrexate in ankylosing spondylitis (Review). *Cochrane Database of Systematic Reviews.* Issue 4 (2006). Art. No: CD004524. doi: 10.1002/14651858.CD004524.pub3.
10. Braun J, Zochling J, Baraliakos X *et al.*: Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicenter randomised controlled trial. *Ann. Rheum. Dis.* 65(9), 1147–1153 (2006).
11. Chen J, Liu C: Sulfasalazine for ankylosing spondylitis (Review). *Cochrane Database of Systematic Reviews.* 2, Art No. CD004800. DOI: 10.1002/14651858.CD004800.pub2 (2005).
12. Herman J, Mueller T, Yazdani-Biuki B *et al.*: High disease activity of ankylosing spondylitis in the community before the introduction of tumor necrosis factor blockers. *Ann. Rheum. Dis.* 66, 561–562 (2007).
13. Braun J, Bollow M, Neure L *et al.*: Use of immunohistologic and in situ hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. *Arthritis and Rheum.* 38(4), 499–505 (1995).
14. Van der Heijde D, Dijkmans B, Geusens P *et al.*: Efficacy and safety of infliximab in patients with ankylosing spondylitis: Results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum.* 52, 582–591 (2005).
- **Randomized, placebo controlled trial demonstrating efficacy of infliximab in AS.**
15. Braun J, Landewe R, Kay-Geert A *et al.*: Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab. *Arthritis Rheum.* 54(5): 1646–1652 (2006).
16. Van der Heijde D, Landewe R, Deodhar A *et al.*: Radiographic progression in patients with ankylosing spondylitis after 2 years of treatment not inhibited with. *EULAR Abstract OP0111* (2007).
17. Van den Bosch F, Devinc M, Kruihof E *et al.*: A prospective long-term study of the efficacy and safety of infliximab in 107 patients with spondyloarthropathy. *Arthritis Rheum.* 50(Suppl.), S611 (2004).
18. Braun J, Baraliakos X, Brandt J *et al.*: Persistent clinical response to the anti-TNF alpha antibody infliximab in patients with ankylosing spondylitis over 3 years. *Rheumatol.* 44, 670–676 (2005).
19. Gorman JD, Sack KE, Davis JC Jr: Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. *N. Engl. J. Med.* 346(18), 1349–1356 (2002).
20. Davis JC Jr, van der Heijde D, Braun J *et al.*: Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum.* 48(11), 3230–3236 (2003).
- **Randomized controlled trial demonstrating the efficacy of etanercept in AS.**
21. Davis JC Jr, van der Heijde D, Braun J *et al.*: Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. *Ann. Rheum. Dis.* 64(11), 1557–1562 (2005).
22. Brandt J, Listing J, Haibel H *et al.*: Long-term efficacy and safety of etanercept after re-administration in patients with active ankylosing spondylitis. *Rheumatol.* 44, 342–348 (2005).
23. Baraliakos X, Brandt J, Listing J *et al.*: Outcome of patients with active ankylosing spondylitis after two years of therapy with etanercept: clinical and magnetic resonance imaging data. *Arthritis Rheum.* 53, 856–863 (2005).
24. Van der Heijde D: Two-year etanercept therapy does not inhibit radiographic progression in patients with AS. *EULAR (Abstract OP0090)* (2006).
25. HUMIRA (adalimumab) package insert. Abbott, revised 2/2007.
26. Peng J, Noertersheuser P, Paulson S *et al.*: Pharmacokinetics of adalimumab in patients with active ankylosing spondylitis – the ATLAS trial. Presented at: *European League Against Rheumatism (EULAR)*. Amsterdam, The Netherlands (Abstract SA T0285) (2006).
27. Haibel H, Rudwaleit M, Brandt HC *et al.*: Adalimumab reduces spinal symptoms in active ankylosing spondylitis: clinical and magnetic resonance imaging results of a fifty-two-week open-label trial. *Arthritis Rheum.* 54(2), 678–681 (2006).
28. Van der Heijde D, Kivitz, Schiff MH *et al.*: Efficacy and safety of adalimumab in patients with ankylosing spondylitis (ATLAS). *Arthritis Rheum.* 54(7), 2136–2146 (2006).
- **Randomized, placebo controlled trial demonstrating efficacy of adalimumab in AS.**
29. Heuft-Dorenbosch L, Spooenberg A, van Tubergen A *et al.*: Assessment of enthesitis in ankylosing spondylitis. *Ann. Rheum. Dis.* 62, 127–132 (2003).
30. Schiff MH, Burmester GR, Kent JD *et al.*: Safety analyses of adalimumab (HUMIRA) in global clinical trials and US post-marketing surveillance of patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 65, 889–894 (2006).
- **Safety data available from clinical trials and US post-marketing surveillance on adalimumab in the treatment of rheumatoid arthritis.**
31. Gridley G, McLaughlin JK, Ekblom A *et al.*: Incidence of cancer among patients with rheumatoid arthritis. *J. Natl. Cancer Inst.* 85, 307–311 (1993).
32. Mellemkjaer L, Linet MS, Gridley G *et al.*: Rheumatoid arthritis and cancer risk. *Eur. J. Cancer.* 32, 1753–1757 (1996).
33. Isomaki HA, Hakulinen T, Joutsenlathi U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. *J. Chronic Dis.* 31, 691–696 (1978).



34. Baeclumnd E, Ekblom A, Sparen P *et al.*: Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case control study. *BMJ* 317, 180–181 (1998).
35. Dixon WG, Watson K, Lunt M *et al.*: Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy. *Arthritis Rheum.* 54(8), 2368–2376 (2006).
36. Sandborn WJ, Hanauer SB, Katz S *et al.*: Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. 121(5), 1088–1094 (2001).
37. Leirisalo-Repo M, Turunen U, Stenman S *et al.*: High frequency of silent inflammatory bowel disease in spondyloarthritis. *Arthritis Rheum.* 37(1), 23–31 (1994).
38. Braun J, Baraliakos X, Listing J *et al.*: Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. *Arthritis Rheum.* 52(8), 2447–2451 (2005).
39. Rosenbaum JT: Acute anterior uveitis and spondyloarthropathies. *Rheum. Dis. Clin. North Am.* 18(1), 143–151 (1992).
40. Galor A, Perez VL, Hamel JP *et al.*: Differential effectiveness of etanercept and infliximab in the treatment of ocular inflammation. *Ophthalmology* 113(12), 2317–2323 (2006).
41. Jois RN, Gaffney K, Keat A: Anti-tumor necrosis factor therapy for ankylosing spondylitis- unresolved issues. *Rheumatology* 46(6), 899–901 (2007).
42. McLeod C, Bagust A, Boland A *et al.*: Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. *Health Technol. Assess* 11(28), 158–158 (2007).
43. Fitzgerald O, McInnes I: Spondyloarthritis: disease at the crossroads of immunity. *Best Pract. Res. Clin. Rheumatol.* 20(5), 949–967 (2006).
44. Appel H, Khune M, Spiekermann S *et al.*: Immunohistologic analysis of zygapophysal joints in patients with ankylosing spondylitis. *Arthritis Rheum.* 54(9), 2845–2851 (2006).

#### Affiliations

- *Pascale Schwab, MD*  
Oregon Health & Science University, Division of Arthritis and Rheumatic Diseases, Oregon Health & Science University,  
3181 S.W. Sam Jackson Park Road, Portland OR, USA  
Tel.: +1 503 494 8963;  
Fax: +1 503 494 1022;  
schwabp@ohsu.edu
- *Atul Deodhar, MD, MRCP*  
Oregon Health & Science University, Division of Arthritis and Rheumatic Diseases, Oregon Health & Science University,  
3181 S.W. Sam Jackson Park Road, Portland OR, USA  
Tel.: +1 503 494 8963;  
Fax: +1 503 494 1022;  
deodhara@ohsu.edu