

Anti-TNF therapy in ankylosing spondylitis: insights for the clinician

Laura C. Coates, Helena Marzo-Ortega, Alexander N. Bennett and Paul Emery

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Abstract: The introduction of tumour necrosis factor (TNF)-blocking therapy has revolutionized the management of ankylosing spondylitis (AS) over the last decade. This review highlights the current evidence relating to the use of TNF-blocking therapy in AS. International guidelines for the use of TNF blockers in AS are summarized. An outline of the evidence for efficacy and safety of these drugs is included, highlighting recent data from registries and real-life observational studies. Such cohort data is also reviewed highlighting the evidence for 'switching' TNF blockers in AS in the case of non-response or adverse events. The potential new application of TNF blockers in preradiographic axial spondyloarthritis (SpA) or 'early AS' is discussed with reviews of two recent studies in this area. Finally research into the possible additional impacts of TNF therapies is reviewed. The question of whether TNF blockers are truly disease modifying in AS remains unanswered with conflicting reports. The additional burden of AS in terms of cardiovascular disease is now becoming understood. Recent data from basic science studies highlights the potential impact of TNF blockers on this excess cardiovascular morbidity and mortality. Future studies and registry data will be able to assess whether TNF blockers have an additional role in controlling systemic inflammation and its associated cardiovascular risk.

Keyword: ankylosing spondylitis, TNF-blocking therapy, treatment

When is anti-TNF indicated?

The introduction of tumour necrosis factor (TNF) blocking therapy has revolutionized the management of ankylosing spondylitis (AS). Prior to the availability of these drugs, physiotherapy and non-steroidal anti-inflammatory drugs (NSAIDs) were the only treatment options available. However, anti-TNF therapy is not indicated for all patients with AS, and is only used in cases refractory to conventional therapy. The original studies recruited patients with confirmed AS (modified New York criteria with evidence of sacroiliitis on conventional radiography [Van Der Linden *et al.* 1984]) and active disease [defined using the Bath Ankylosing spondylitis disease activity index (BASDAI) [Garrett *et al.* 1994] and spinal pain visual analogue scale (VAS) of >4 cm].

Guidelines for the use of anti-TNF therapies in clinical practice in AS have been produced based on the evidence from the large randomized controlled trials. The Assessments in Ankylosing Spondylitis (ASAS) group produced guidelines

in 2003 [Braun *et al.* 2003] and these have since been revised in 2006 [Braun *et al.* 2006]. They state that the conditions for treatment with anti-TNF therapy should be diagnosis of AS (usually by the modified NY criteria), active disease (BASDAI >4 and expert opinion) for at least 4 weeks, failure of NSAIDs for a minimum 3-month trial, failure of intra-articular steroids (if indicated) and failure of sulfasalazine (if predominant peripheral arthritis).

The usual precautions and contraindications for anti-TNF therapy should also be applied. They recommend that disease activity levels should be followed using the BASDAI and the ASAS core set, and that a response is defined as a reduction in BASDAI of at least 50% or 2 units. They suggest that response should be assessed at 6–12 weeks after starting on therapy using these criteria. Most national guidelines have been based on these recommendations including the National Institute for Health and Clinical Excellence (NICE) guidelines in the UK.

Correspondence to:

Paul Emery
Section of
Musculoskeletal Disease,
University of Leeds,
2nd floor, Chapel
Allerton Hospital, Leeds,
LS7 4SA, UK
p.emery@leeds.ac.uk

Laura C. Coates
Helena Marzo-Ortega
Alexander N. Bennett
Section of
Musculoskeletal Disease,
University of Leeds, Leeds,
UK

What is the evidence base for anti-TNF in ankylosing spondylitis?

There are currently three anti-TNF blockers licenced for use in AS (infliximab, etanercept and adalimumab), and an additional drug has been tested in phase-III studies and is awaiting approval (golimumab). All of these technologies have shown clear efficacy against placebo in AS [Inman *et al.* 2008; Van Der Heijde *et al.* 2006, 2005a; Davis *et al.* 2003], with marked improvements in pain, functional ability and inflammatory markers such as C reactive protein (CRP). Open-label extensions to these randomised controlled trials (RCTs) have confirmed an ongoing anti-inflammatory effect whilst therapy is maintained, but the majority of patients have flared after treatment discontinuation [Baraliakos *et al.* 2005a; Brandt *et al.* 2005].

Observational data from cohorts treated with anti-TNF has also confirmed sustained efficacy. In the Leeds cohort of an initial 113 AS patients treated with anti-TNF, the vast majority (79%) showed a sustained response to therapy with only 13% being non-responders and 8% changing therapy due to adverse effects [Coates *et al.* 2008]. A similar sustained response and limited toxicity has been documented in the Finnish national registry [Konttinen *et al.* 2007].

Safety of anti-TNF in ankylosing spondylitis

In both short-term RCTs and long term extension studies, the side-effect profile and safety record of anti-TNF therapies has been acceptable. This has been confirmed with data from observational registries now that the drugs are available for clinical use [Konttinen *et al.* 2007]. Caution is still recommended and ASAS suggest the following contraindications to treatment to ensure safety [Braun *et al.* 2006]: pregnancy or breastfeeding; active infection; patients at high risk of infection; patients with history of lupus or multiple sclerosis; malignancy or premalignant states excluding basal cell carcinoma and malignancies diagnosed and treated more than 10 years previously (where the probability of total cure is very high).

Risk of infection is a recognized risk with anti-TNF therapy. Some early meta-analyses of RCTs showed an increased risk of serious infection [Bongartz *et al.* 2006], but later meta-analyses with larger numbers only found an increased risk if high dose (2–3 times the recommended dose) anti-TNF therapy was used

[Leombruno *et al.* 2009]. In particular, the reactivation of tuberculosis (TB) is a recognized risk of therapy with anti-TNF therapy and local/national guidelines have been developed for screening of patients prior to treatment initiation. These may involve chest radiographs, tuberculin skin test and/or blood tests for latent TB such as the Quantiferon or T-spot test [British Thoracic Society Standards of Care Committee, 2005].

Risk of malignancy is a theoretical concern if tumour necrosis factor is blocked. For that reason, meta-analyses of randomized trials have been performed to study this further and registries of anti-TNF treated patients have been established in many countries. However much of the research has investigated patients with rheumatoid arthritis (RA) treated with anti-TNF therapy and there are no large publications concerning malignancy risk in AS. It is known that patients with RA have an increased risk of lymphoma related to their disease, meaning that the risk based on data from RA patients cannot be directly transferred to patients with AS. However in the absence of large AS malignancy studies, it provides some information regarding possible risks.

The South Swedish Arthritis Treatment Group register reported a possible increased risk of lymphoma in patients with RA treated with anti-TNF, however this was based on a small number of patients (five lymphoma cases). Following on from this, a large review was published in the *Journal of the American Medical Association* in 2006. This pooled data from nine RCTs of anti-TNF ($n=3493$) and found a pooled odds ratio for malignancy of 3.3 in anti-TNF-treated patients compared to placebo patients [Bongartz *et al.* 2006].

However when similar methods were applied in 2009 to 18 RCTs ($n=8808$), there was no increased risk identified for death, serious adverse events, serious infection, lymphoma or other cancers [Leombruno *et al.* 2009]. Ongoing publications from registries has also been reassuring. Data from the American National Data Bank for Rheumatic Diseases showed no increase in lymphoma amongst patients on anti-TNF therapy [Wolfe and Michaud, 2007]. A recently published Swedish study showed no significant overall increase in the already elevated lymphoma occurrence in RA. Interestingly, RA patients starting TNF therapy in 1998–2001 accounted for the

entire increase in lymphoma risk, while duration of therapy or type of TNF agent did not affect the relative risk [Askling *et al.* 2009]. This raises the possibility that changes in the selection of patients may influence the observed risk. Patients treated with anti-TNF when it was first available are likely to have had more severe arthritis and may have had a related increased risk of lymphoma independent of their treatment.

Can anti-TNF therapy be used in preradiographic axial spondyloarthritis?

A current challenge for the management of AS is to identify these patients early before structural damage has occurred, as it is known that these changes seen on conventional radiography may take up to 10 years to develop [Mau *et al.* 1988]. This means that the use of the New York criteria as a prerequisite for treatment may exclude patients with early disease. There is therefore an increasing emphasis on the early diagnosis of AS and there is a recognized potential for the use of other imaging techniques such as magnetic resonance imaging (MRI) to diagnosis axial SpA [Marzo-Ortega *et al.* 2009; Braun *et al.* 2006]. This is more so since recent work has shown that active MRI sacroiliitis in preradiographic SpA predicts the development of AS at 8 years [Bennett *et al.* 2008].

To date, two studies have addressed the use of anti-TNF therapy in preradiographic axial SpA [Barkham *et al.* 2009; Haibel *et al.* 2008]. The first study used adalimumab or placebo in a cohort of patients with active axial SpA [Haibel *et al.* 2008]. Patients enrolled into this study had to either be HLA-B27 positive or have MRI evidence of sacroiliac joint (SIJ) osteitis. This study showed a significant benefit with adalimumab in terms of symptoms, pain and inflammatory markers, similar to the response seen in established AS. None of the patients had sufficient changes to fulfil the modified NY criteria, but many of them had relatively long symptom durations.

The second study used infliximab or placebo in a cohort of patients with active early inflammatory back pain (less than 3 years duration), HLA-B27 positivity and MRI evidence of SIJ osteitis [Barkham *et al.* 2009]. This study confirmed a significant benefit with infliximab in terms of clinical response and also showed significant improvement in MRI measurements of osteitis. Interestingly, the response rates in this study were dramatically higher than that of the previous

adalimumab study with ASAS partial remission rates of 56%. Superior responses have been shown in established AS for patients with shorter disease durations (less than 10 years) and it may be that treatment of patients with very early disease may be more effective.

What is the evidence for switching drugs in ankylosing spondylitis?

To date, there have been no randomized controlled trials to investigate the use of switching TNF-blocking therapies. It is recognized that a proportion of patients will have to stop their first TNF-blocking therapy due to inefficacy or side effects. However there have been no interventional studies to determine the optimal treatment following this first anti-TNF failure. Three reports from observational cohorts have investigated the use of second- and third-line drugs [Coates *et al.* 2008; Pradeep *et al.* 2008; Conti *et al.* 2007]. Each cohort includes only a small number of drug switches as the majority of patients continued on their first anti-TNF therapy. All three have confirmed a significant response to second or third anti-TNF therapies, although there is probably a reduced chance of response following an initial drug failure. This reduced response is seen more frequently in the cases switched because of inefficacy when compared with patients who switched due to adverse events [Pradeep *et al.* 2008].

Are TNF blockers true disease modifiers?

In addition to improving clinical and laboratory signs and symptoms of AS, treatment with anti-TNF therapy has been shown to reduce levels of inflammation within the bone (osteitis) seen on MRI. In other inflammatory arthritides such as RA, reduction of disease activity and inflammation has been shown to correlate with structural progression in studies with both standard disease modifying drugs [Grigor *et al.* 2004] and with all of the TNF therapies. However, RA is associated with bone destruction causing erosions rather than AS which is characterized by new bone formation in the form of fused SIJs and spinal syndesmophytes. The link between inflammation and bone formation is still not well understood. Studies using mouse models of spondyloarthritis and human tissue have suggested an uncoupling of inflammation and bone formation with alternative pathways such as signalling of bone morphogenetic protein [Lories and Lutyen, 2007; Lories *et al.* 2007] and the Wnt pathway [Diarra *et al.* 2007].

Clinical follow up of AS patients treated with anti-TNF therapy has shown differing results. Unlike RA, where progression in bony damage can be identified in a 6- or 21-month period, studies analysing progression in AS need to measure progression over a longer time period. No placebo-controlled trials have ever been long enough to accurately compare spinal progression for ethical and practical reasons. Experts in the field have acknowledged that a 'gold standard' RCT with structural progression as its primary endpoint is impossible in AS due the slow and variable spinal progression and the lack of an acceptable comparator drug [Van Der Heijde *et al.* 2005b]. Studies to date have used historical, cohort controls and have come to different conclusions. After 2 and 4 years of treatment with infliximab in a small cohort of AS patients, it was suggested that their rate of spinal disease progression [measured by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)] was slower than expected when compared to control populations never treated with anti-TNF therapy [Baraliakos *et al.* 2007, 2005b]. However, analysis of patients treated with etanercept and infliximab during and after the phase III RCT did not confirm a significant difference in new bone formation when compared to the same historical control group [Van Der Heijde *et al.* 2008a, 2008b]. Importantly, even when there is a failure to completely halt bony progression there is still an improvement in function/range of movement, again contrasting with the situation in RA.

What is the burden of cardiovascular disease in ankylosing spondylitis and is this affected by TNF blockade?

Like many inflammatory rheumatic diseases, an increased risk of cardiovascular morbidity and mortality has been shown in AS. The mortality rate for patients with AS is approximately twice that of the general population and the majority of this increase is related to cardiovascular disease [Peters *et al.* 2004; Lehtinen, 1993]. Valvular disease has been a well-recognized complication of AS for many years, but more recently, the increased rate of atherosclerotic disease is also being recognized [Heeneman and Daemen, 2007; Divecha *et al.* 2005].

Patients with AS have been found to have a higher rate of traditional cardiovascular risk factors such as hypertension [Alves *et al.* 1988], dyslipidaemia [Van Halm *et al.* 2006] and metabolic syndrome [Papadakis *et al.* 2009]. Also, it is well recognized

that the pathogenesis of atherosclerosis involves inflammatory mechanisms, and it may be that the inflammatory pathology of AS is an independent risk factor for atherosclerosis [Abou-Raya and Abou-Raya, 2006]. Research showing a link between disease activity and cardiovascular risk factors such as lipid changes [Van Halm *et al.* 2006] and metabolic syndrome [Papadakis *et al.* 2009] support the interaction between cardiovascular risk and systemic inflammation related to AS. Using echocardiography, an increased rate of cardiac microvascular dysfunction has been identified in AS patients compared to matched controls. This level of microvascular dysfunction was shown to correlate well with systemic markers of inflammation such as CRP and TNF levels [Caliskan *et al.* 2008].

This link between systemic inflammatory markers and microvascular dysfunction raises the possibility that effective treatment of inflammation may be useful in controlling cardiovascular risk as well as disease activity. A Dutch group analysed endothelial microvascular function in patients with AS before and after treatment with etanercept. They confirmed impaired microvascular function in AS patients compared to controls and also showed a significant improvement in some parameters following 1 month's treatment with etanercept [Van Eijk *et al.* 2009]. Further data are needed to see if this improvement in microvascular function correlates with an improvement in ongoing cardiovascular risk. Registry data of AS patients treated with anti-TNF will help us to analyse the cardiovascular morbidity and mortality in treated patients. The demonstrated link between inflammation and cardiovascular risk factors highlights the need for a control population with similar disease activity for comparison. However, this may be difficult to recruit for both ethical and practical reasons.

Conclusions

To summarize, the advent of biologic therapies which block the TNF alpha-inflammatory pathway has led to an efficacious and safe treatment strategy for the first time in AS. Longer term data from large cohorts both in the research and real life setting will address the question of whether disease modification and improvement in mortality are achievable goals in this disease (key points are given in Box 1).

Box 1. Anti-TNF therapy in ankylosing spondylitis: Key points.

Anti-TNF therapies are recommended for patients with refractory AS and have strong evidence from multiple RCTs.

The safety record for anti-TNF therapies in both short term RCTs and longer term registries is acceptable as long as appropriate screening is completed prior to starting treatment.

Two small studies have suggested a significant benefit with anti-TNF treatment in preradiographic axial SpA but further research is needed.

There is evidence to support switching patients to alternative anti-TNF therapies in the case of adverse events or non-response.

The question of whether anti-TNF therapies are truly disease-modifying is yet to be answered, but regardless of this, the therapies are beneficial to both symptoms and function even in patients with advanced disease.

Patients with AS have an increased risk of cardiovascular disease, partially related to chronic inflammation, and there is some early suggestion that anti-TNF therapy may impact on this.

Conflict of interest statement

None declared.

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