Treatment of ankylosing spondylitis: focus on etanercept

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Abstract: Ankylosing spondylitis is a chronic inflammatory condition which preferentially affects the axial skeleton, often beginning in the sacroiliac joints. The etiology of the pathologic lesions of this condition including enthesitis, erosive articular changes, osteitis, and fibrous ankylosis, as well as changes which occur in the eye, gastrointestinal tract, cardiovascular system, and lungs is unknown; however, there is a strong association with HLA-B27, which indicates altered immunity. One of the major mediators of the immune response is TNF-α, which functions as a pleiotrophic soluble messenger primarily from macrophages. TNF-α is principally involved with activation of both normal and transformed cells, including endothelium, synoviocytes, osteoclasts, chondrocytes, and fibroblasts. The cornerstone of medical management of ankylosing spondylitis includes intensive physical therapy and nonsteroidal anti-inflammatories for symptomatic relief. However, it is becoming increasingly recognized that TNF-α blockade has an important role in the reduction of spine and joint inflammation. This review discusses the data that supports use of etanercept in the treatment of ankylosing spondylitis.

Keywords: ankylosing spondylitis, TNF-α, etanercept

Introduction

Ankylosing spondylitis is a disease included within the entity of spondyloarthopathies. This group also includes reactive arthritis, inflammatory-bowel-disease-associated arthropathy, psoriatic arthritis, and undifferentiated spondyloarthopathy. Ankylosing spondylitis is regarded as the most common subtype. Incidence rates of 0.5–8.2/100,000 population and prevalence rates of 0.2%–1.2% have been described for ankylosing spondylitis, compared with approximately double these figures for the entire group of spondyloarthopathy (Sieper et al 2006). The salient similar features within this group include: inflammatory spinal pain; radiological sacroilitis with or without clinical spondylitis; peripheral inflammatory arthritis, usually of the large joints of the lower extremities in an asymmetric, pauci-articular fashion; familial tendency; and negative tests for rheumatoid factor as well as the absence of subcutaneous rheumatoid nodules.

The European Spondyloarthropathy Study Group (ESSG) criteria (Table 1) proposed in 1991 has been used to identify patients with spondyloarthopathy; however, in clinical practice these criteria are believed to be inadequate (Amor et al 1994). There are no uniformly accepted classification criteria for distinguishing ankylosing spondylitis from the other spondyloarthopathies. The most widely accepted diagnostic criteria for ankylosing spondylitis are the Modified New York Criteria developed in 1984. These require a patient to have low back pain of at least 3 months' duration improved by exercise and not relieved by rest, limitation of lumbar spine motion in sagittal and frontal planes, and/or chest expansion decreased relative to normal values for age and sex in addition to unilateral sacroiliitis grade 3–4 or bilateral sacroiliitis grade 2–4 in order to be diagnosed with ankylosing spondylitis (Table 2) (Van der Lin et al 1984). These criteria are often used to identify patients to enroll in investigational

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Table 1 The European Spondyloarthropathy Study Group (ESSG) criteria

Inflammatory or synovitis spinal pain and one or more of the following:
- Asymmetric
- Predominantly
   lower limb
- Alternate buttock pain
- Sacroiliitis
- Enthesopathy
- Positive family history
- Psoriasis
- Inflammatory bowel disease
- Urethritis or
   cervicitis or acute diarrhea
   occurring within 1 month
   before arthritis

trials in ankylosing spondylitis. In clinical practice, ESSG criteria are inadequate for the diagnosis in individual patients as they were designed as classification criteria, with consequent high specificity and lower sensitivity.

The modified New York Criteria reflect that radiologically, ankylosing spondylitis manifests earliest in the sacroiliac joint. Initially, this may appear as pseudowidening of the joint with sclerosis in the lower third joint margins. With more advanced disease, erosions occur, followed by bony fusion. Although magnetic resonance imaging (MRI) and computed tomography are more sensitive to changes occurring within the sacroiliac joints than conventional radiography, the modified New York criteria do not currently encompass this principle (Braun et al 1994). Thus, intervention outcomes do not address the earliest stages of diseases in most clinical studies, since study participants are generally included based on conventional radiographic data.

Recent attention has focused on earlier diagnosis of ankylosing spondylitis among patients with chronic

Table 2 Diagnostic criteria for ankylosing spondylitis

Stage I	Grade II or higher bilateral radiographic sacroiliitis
Stage II	Minor radiographic evidence of spinal involvement in ≤1 spinal segment (≤3 vertebrae which equals <15% of the spine)
Stage III	Moderate radiographic evidence of spinal involvement in ≤2 spinal segments (4–12 vertebrae which equals 15–<50% of the spine)
Stage IV	Radiographic evidence of spinal involvement in >2 spinal segments (13–19 vertebrae which equals 50%–<80% of the spine)
Stage V	Widespread (≥80%) fusion of the spine (≥20 vertebrae)

Adapted from Braun et al (2002).

low back pain. This is important as effective biological therapies for early treatment have become available. Rudwaleit and colleagues have recently shown that it is possible to make a diagnosis of inflammatory back pain associated with ankylosing spondylitis when at least two of the following features are present: 1) morning stiffness >30 minutes, 2) improvement with exercise, but not with rest, 3) awakening during the second half of the night because of back pain and alternating buttocks pain (Rudwaleit et al 2006). If three of the four parameters are seen, then a disease probability of more than 90% can be achieved. The addition of unilateral or bilateral Grade 3 sacroiliitis is diagnostic for ankylosing spondylitis.

Both the modified New York Criteria and Rudwaleit's criteria highlight the typical clinical presentation of ankylosing spondylitis. The insidious alternating buttocks pain and stiffness of the spine can lead to deformity and restriction of motion secondary to syndesmophytes and alterations at the zygo-apophysial joints. The involvement of the thoracic spine commonly causes chest expansion restriction due to costovertebral joint fusion. The onset of these symptoms typically occurs between ages 15–35 years, and severe deformity and disability can result within the first 10 years (Gran and Skomsvoll 1997). It tends to affect more men than women. In most clinical studies, the activity of disease is generally defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and functional status by the Bath Ankylosing Spondylitis Disease Functional Index (BASFI), with increased levels indicating more severe disease.

The goal of treatment in ankylosing spondylitis is to ameliorate this pain and stiffness and preserve function. Nonselective nonsteroidal anti-inflammatories (NSAIDs), cyclooxygenase-2 (COX2) selective inhibitors, and nonpharmalogic interventions, such as physiotherapy and exercise, education, and lifestyle modification are well recognized as the most important initial step in management. Second-line therapies, such as sulfasalazine for peripheral arthritis, anti-TNF therapy for axial disease, and extra-articular disease are additional management considerations.

Pathogenesis of ankylosing spondylitis

The exact pathogenesis of ankylosing spondylitis is unknown; however, both genetics and environment are thought to play a role. A genetic predisposition associated with the human leukocyte antigen HLA-B27 class molecule is characteristic in ankylosing spondylitis, with 90%–95% of patients

of European descent carrying this marker (Reveille 2001). Multiple different theories have been proposed in attempt to explain the association of the HLA-B27 with ankylosing spondylitis.

The T-cell receptor theory is based on knowledge that this receptor recognizes only peptides that are in association with class I or class II MHC (Major Histocompatibility Complex) molecules. The T-cell response is thus restricted by HLA molecules. Despite an extensive search there is a lack of evidence for a special pathogenic peptide that binds HLA-B27, and most HLA-B27 carriers are free from disease; thus the receptor theory has a serious weakness (Ebringer and Wilson 2000).

The molecular mimicry theory suggests that disease results from antigenic components of micro-organisms which partially cross-react with or resemble HLA molecules (Ebringer and Wilson 2000). Not only has amino-acid sequence homology between Kleibsiella pneumoniae and HLA-B27 been demonstrated, but mean IgA antibody levels against this organism is higher in active ankylosing spondylitis patients (Ebringer and Wilson 2000). Similarly, it has been demonstrated that anti-Sacchromyces cerevisiae IgA antibodies are elevated in ankylosing spondylitis (Hoffman et al 2003).

It is possible HLA-B27 could result in impaired bacterial elimination. It has been suggested that misfolding during intracellular assembly process induces the activation of the inflammatory response following induction of endoplasmic reticulum stress, thus independently of antigen presentation (Colbert 2000). The misfolded HLA-B27 has the capacity to form covalent heavy-chain homodimers amenable to recognition by leukocyte receptors, thus immunomodulating both innate and adaptive responses to arthritogenic pathogens (Lopez de Castro 2007).

One of the key inflammatory mediators of the immune response is TNF-α. This cytokine plays a critical role in the regulation of inflammation and clearly has a role in the pathogenesis of ankylosing spondylitis. TNF-α serum levels are significantly higher in ankylosing spondylitis patients than in patients with noninflammatory back pain (Gratacos et al 1994). Elevated levels of TNF-α messenger RNA and protein were found in ankylosing spondylitis sacroiliac joint biopsy specimens (Braun et al 1995).

TNF-α is a cytokine synthesized and secreted primarily by macrophages in response to proinflammatory stimuli, such as bacterial lipopolysacchride (Ellerin et al 2003). It functions to increase inflammation, cell infiltration by upregulation of adhesion molecules, angiogenesis, upregulation of acute phase response, and articular cartilage degradation, and, in

a paracrine manner stimulates other cytokines, such as IL-1, which results in bone resorption. This inflammatory pathway is initiated when TNF is cleaved from the cell surface by a specific metalloproteinase and binds to its two receptors, TNFR-55 and TNFR-75, found in both soluble forms and on somatic cell surfaces. Studies have shown that neutralization of TNF by the chimeric monoclonal IgG1 antibody infliximab, the recombinant 75 kDa TNF receptor IgG1 fusion protein etanercept, and the fully humanized monoclonal antibody adalimumab can decrease this cascade of events.

Several associated extra-articular manifestations are not included in the definition of ankylosing spondylitis, but are well recognized and have additional management considerations. Eye inflammation, especially acute anterior uveitis, has a likelihood of 1:4 in ankylosing spondylitis (Feltkamp and Ringros 1998). The prognosis of uveitis is usually good with topical treatment, but might benefit from additional immunosuppressive therapy if chronicity develops (De Keyser et al 2004). A meta-analysis of four placebo-controlled and three open-label studies showed that anterior uveitis occurs less frequently in patients treated with TNF-α blocking agents (Braun et al 2005). There is some evidence that infliximab is more effective than etanercept in the treatment of recalcitrant uveitis (Galor et al 2006). Subclinical gut inflammation is also described as having a higher incidence in ankylosing spondylitis patients with peripheral arthritis (De Keyser et al 1998). Of interest, remission of joint inflammation is associated with a disappearance of the gut inflammation (Mielants et al 1995). Furthermore, the prevalence of ischemic heart disease, atherosclerosis, peripheral vascular disease, congestive heart failure, cerebrovascular disease, type II diabetes, hyperlipidemia, and hypertension are also higher in patients with ankylosing spondylitis than age-controls (Han et al 2006). In addition to traditional management of these problems, there is some evidence that TNF-α blockade in ankylosing spondylitis patients may modulate the inflammatory process of athersclerosis and induce a modest, but sustained, increase in serum HDL-C levels, which may have a favorable effect in reducing the cardiovascular risk in these patients (Spanakis et al 2006). The effect of TNF-α on aortitis as well as pulmonary disease, such as apical fibrosis, interstitial lung disease, emphysema, bronchietasis and pleural thickening, in ankylosing spondylitis patients remains to be seen. In one study, no correlation was observed between high-resolution computed tomography of the chest abnormalities, pulmonary function test variables, and indices of ankylosing spondylitis symptoms

and disease structural severity, possibly suggesting a different pathogenesis (Quismorio 2006). Complications such as IgA nephropathy and amyloidosis have additional management considerations.

Evidence-based treatment guidelines

New guidelines for the treatment of ankylosing spondylitis have been recently published by the ASsessment in Ankylosing Spondylitis (ASAS) working group, in collaboration with EULAR, based on a systemic review of the literature and expert opinion (Zochling et al 2006a, b). It was determined that nonpharmalogic interventions, such as physiotherapy and exercise, education, and lifestyle modification should be offered to all ankylosing spondylitis patients early and throughout the illness course (Dagfinrud et al 2005).

Meta-analyses of randomized, controlled trials suggest that nonselective nonsteroidal anti-inflammatories (NSAIDs) and cyclooxygenase-2 (COX2) selective inhibitors are first-line therapy for all ankylosing spondylitis patients with pain and stiffness. Continuous treatment with NSAIDs is capable of slowing down the progression the disease (De Keyser et al 2004). Safety concerns, such as gastrointestinal erosion, must be considered when prescribing NSAIDs.

For those refractory or intolerant to NSAIDs, the disease-modifying antirheumatic drugs (DMARDs) have been used as a second-line approach. Sulfasalazine has demonstrated some benefit in relieving peripheral joint manifestations, reducing erythrocyte sedimentation rate (ESR) and easing morning stiffness, but has no evidence of benefit in physical function, spinal mobility, pain, enthesitis, and patient-rated and physician-rated global assessment (Dougados et al 1995; Clegg et al 1999; Chen and Liu 2005). High-quality randomized, controlled trials of long duration and with large sample size are needed to clarify the effects of methotrexate (Chen et al 2006). Currently there is not enough evidence to support any benefit of methotrexate, cyclosporine, or azathioprine in the treatment of ankylosing spondylitis.

The ASAS working group, in collaboration with European League Against Rheumatism (EULAR), also determined that robust evidence is available for the cost-effectiveness of TNF-α inhibitors. The consensus of the expert panel was that anti-TNF-α treatment should be offered to all patients with high disease activity. Three anti-TNF-α agents (etanercept, infliximab, and adalimumab) have been studied for treatment of ankylosing spondylitis and are FDA approved.

Although there is some evidence to support the use of anakinra, thalidomide, and pamidronate in the treatment of ankylosing spondylitis, use of these agents was not endorsed by the expert panel (Maksymowych et al 1998; Huang et al 2002; Tan et al 2004). Of interest, thalidomide inhibits TNF-α by amplifying the degradation of messenger RNA and decreases the expression of certain cytokines.

Although there is no single accepted clinical parameter available for assessing spinal deformity and facilitating decision-making about surgical treatment of spinal deformity, spinal stenosis, and hip disease, surgery may become necessary for ankylosing spondylitis patients with refractory pain and disability. Surgical intervention is indicated when fracture and dislocation result in neurological involvement (Fox et al 1993). Even in the absence of neurological signs, if atlanto-axial and atlanto-occipital subluxation progresses substantially and the patient has severe pain and instability, surgical fusion may be necessary (Ramos-Remus et al 1997). Total hip arthroplasty is likely beneficial in patients with refractory pain or disability.

Etanercept

Etanercept is a fusion protein consisting of the extracellular portion of a human TNFR-75 fused to the Fc region of human IgG subclass I molecule. It is administered by subcutaneous self-injection, usually in a 50 mg once-a-week, or 25 mg twice-a-week dosing regimen. It binds to TNF-α preventing it from associating with the cell surface TNF-α receptor, and mimics the normal physiologic pathway of down-regulating TNF-α.

Clinical trial data show that TNF-α inhibitors are well tolerated by ankylosing spondylitis patients in the short-term. Injection site reactions of mild to moderate severity occur, and are managed with antihistamines, injection of hydrocortisone or, less commonly, cessation of therapy (Nash and Florin 2005). TNF inhibitors should be avoided in patients with advanced heart failure, since large phase II and III trials with TNF-α antagonists have shown trends towards a worse prognosis in this population. TNF-α inhibitors are also associated with the formation of auto-antibodies, though these auto-antibodies are rarely associated with any specific clinical syndrome. Rare cases of aplastic anemia, pancytopenia, vasculitis, and demyelination have also been described with anti-TNF therapy (Desai and Furst 2006).

No head-to-head trials have been done between the TNF-α inhibitors; thus although all have been proven to have favorable treatment results, none have proven to be superior to each other. Because most available data are on the first FDA-approved TNF-inhibitor etanercept for treatment in ankylosing spondylitis, this paper will focus on this

medication. It is recognized that this focus has the limitation of collectively including only approximately 400 patients with limited study duration and methodology.

Clinical studies have proven the efficacy of etanercept for ankylosing spondylitis. Marzo-Ortega and colleagues preformed the first descriptive longitudinal clinical study on the use of subcutaneous etanercept in 10 spondyloarthropathy patients with active inflammatory spinal and peripheral joint involvement in 2001. Statistically significant improvement was seen in all clinical and functional variables. MRI data revealed regression or resolution of enthesal lesions, and absence of new lesions in 9 of the patients analyzed (Marzo-Ortega et al 2001). This study was limited by both the small number of patients as well as by the short 24-week duration of follow-up. This makes it difficult to make conclusions on long-term efficacy and safety.

Additional support for the use of etanercept in ankylosing spondylitis was provided by Gorman and colleagues. Forty patients with active ankylosing spondylitis were enrolled into a randomized, double-blind, placebo-controlled trial with an option of 6-month of open-label extension. The primary outcome measure was composite treatment response of 20% or greater improvement in at least three of the following: morning stiffness, nocturnal pain, BASFI, patient global assessment of disease activity, and score for joint swelling. At the end of a 4-month period 75% of the etanercept-treated patients had improved clinically, compared with 25% of the patients in the placebo group. Improvement was sustained over time (Gorman et al 2002). These marked changes that resulted from etanercept therapy were mostly subjective. The failure of improvement in the modified Schober's Index, the occiput-to-wall measurement, the Fatigue Severity Scale, and the counts and scores for tenderness in peripheral joints with etanercept therapy are important findings in this study.

The rapid onset of therapeutic relief was demonstrated by Calin and co-workers (Calin et al 2004). The efficacy of etanercept compared with placebo in 84 patients at 14 European centers over 12 weeks. The primary efficacy endpoint was an improvement of at least 20% in patient-reported symptoms, based on the multicomponent ASAS response criteria (ASAS 20). ASAS is a composite measure of improvement in ankylosing spondylitis symptoms that include total back pain, patient assessment of disease activity, inflammation, and physical function. Significantly more etanercept patients than placebo patients responded at the ASAS 20 level as early as week 2, and sustained differences were evident up to week 12. Etanercept was well tolerated. Most adverse events were mild to moderate; the only between-group difference was

injection site reactions, which occurred significantly more often in etanercept. However, this study was of short duration and thus long-term safety data cannot be inferred.

Etanercept has also been evaluated in a larger 24-week randomized, multicenter, double-blind, placebo-controlled study with open-label extension (Davis et al 2003). In the initial study 277 ankylosing spondylitis patients were randomized to receive etanercept or placebo. The primary endpoints were the proportions of patients achieving ASAS 20 criteria at 12 and 24 weeks. By week 12, 60% of the patients in the etanercept group were ASAS 20 responders compared with 27% of placebo-treated patients. Similar ASAS 20 responder rates were observed at the end of the 24-week assessment, 58% of etanercept patient compared with 23% of the placebo group. The etanercept group also had a significantly greater improvement in spinal mobility measures. No unexpected adverse effects or infections were observed.

Davis and colleagues performed a follow-up study to monitor extended efficacy and safety in patients with ankylosing spondylitis, and to determine efficacy in patients previously receiving placebo (Davis et al 2005). This study confirmed that ASAS responses to etanercept treatment were sustained for almost 2 years, with 74% of patients achieving an ASAS 20 response after 96 weeks of etanercept treatment.

Similar long-term efficacy results were demonstrated by Brandt and co-workers in a double-blind, placebo-controlled trial. In this 54-week open observational study, 26 ankylosing spondylitis patients received etanercept after several months of discontinuation following a 6-month randomized control trial with the same agent. All patients who developed high disease activity after cessation of etanercept, defined as a BASDAI and pain greater than or equal to four on a numerical rating scale, entered the study. Standard assessment tools, such as BASFI, were used. An intention-to-treat (ITT) and a completer analysis were performed. The results were compared with the baseline values of the open study. Out of the initial 30 patients, 26 (87%) were eligible for the open extension study after a mean of about 27 weeks. At week 54, 88% were still on treatment with etanercept. The ITT analysis showed that 58% (95% confidence interval 39%–74%) of the patients achieved a 50% improvement of BASDAI at week 54. According to the ASAS working group criteria, 31% were in partial remission at week 54. Function, metrology, and quality of life improved significantly. Only one patient had a serious adverse event (new onset of biopsy proven Crohn's) that resulted in discontinuation (Brandt et al 2005).

TNF-α is an essential cytokine in the innate immune response and defective host defense mechanisms may play a role in the pathogenesis of ankylosing spondylitis; thus there has been a concern of severe infectious complications with TNF-α blockade in spondyloarthropathy. The extent of the infectious complications with TNF-α inhibition can range from localized to disseminated. It appears that not only is the incidence of certain infections increased with anti-TNF-α therapy, but the ability to contain these infections is also impaired (Ellerin et al 2003). The extent of the infections ranges from localized to disseminated. Serious infections have included septic arthritis, infected prostheses, and a variety of opportunist infections (Giles and Bathon 2004). Reactivation of latent tuberculosis early after commencement of anti-TNF-α therapy and dissemination in a miliary fashion is a particular concern, and patients commencing anti-TNF-α therapy should have a screening chest X-ray and Mantoux test (Nash and Florin 2005). Isoniazid therapy for 9 months is indicated if anti-TNF-α therapy is deemed necessary and the Mantoux result is significantly positive (Ormerod 2004). Additionally, preliminary data suggest that anti-TNF-α therapy may be safe in chronic hepatitis C. However, TNF-α antagonists have resulted in re-activation of chronic hepatitis B if not given concurrently with antiviral therapy (Desai and Furst 2006).

TNF-α also has a role in immune regulation. Anti-TNF therapy use in patients with other inflammatory arthritides has suggested increases in demyelination and serious infection (Mohan et al 2001; Salliot et al 2007). These inflammatory conditions are associated with an increased risk of lymphoma. It is unclear whether this risk exists in ankylosing spondylitis (Askling et al 2006). Since variable rates of increased lymphoma risk have been described with anti-TNF therapy compared with the general population, long-term controlled and adequately powered follow-up studies are required to settle this issue. Solid tumors do not appear to be increased with anti-TNF therapy (Desai and Furst 2006). However, the existing clinical trial data are underpowered to assess long-term, serious adverse outcomes in ankylosing spondylitis patients. Data are also limited for use of anti-TNF therapy in pregnancy or lactation.

Conclusion

The current management approach to ankylosing spondylitis requires a combination of nonpharmacologic and pharmacologic treatment modalities. Appropriate and timely use of TNF-α antagonists is an additional option for patients with active ankylosing spondylitis who are inadequately controlled with conventional treatment. TNF-α inhibitor therapies have demonstrated rapid and consistent effectiveness in reducing the axial and peripheral symptoms of ankylosing spondylitis, and improving patient function and quality of life. There are data showing that TNF-α inhibition may also have a positive effect on anterior uveitis and cardiovascular disease seen in ankylosing spondylitis patients. Randomized, controlled trials are needed to further investigate anti-TNF therapy effect on other extra-articular aspects of ankylosing spondylitis. Additional studies are also needed to establish long-term safety, and determine whether these agents can halt disease progression in patients. Comparison studies between the three FDA-approved TNF inhibitors in ankylosing spondylitis patients will be helpful to determine if superiority exists, or if switching between biologics is of therapeutic value. Incorporation of pre-radiographic changes and MRI data will also be an important area of focus in the future for both defining interventional strategies and defining the entity of ankylosing spondylitis.

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