Infliximab in the treatment of ankylosing spondylitis

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Abstract: Ankylosing spondylitis (AS) is a chronic, progressive disease characterized by inflammation in the spine and sacroiliac joints which causes pain, stiffness and the potential for spinal ankylosis. It is associated with significant functional impairment. It is common and since onset is often in young people, the burden of disease is considerable. Conventional treatment including non-steroidal antiinflammatory drugs (NSAIDs) and physiotherapy have proven but limited efficacy in controlling symptoms and preventing progression of spinal manifestations. Infliximab, a chimeric monoclonal antibody which binds to and inhibits tumor necrosis factor alpha (TNFα), is highly effective in controlling disease activity in AS. In AS, infliximab 5 mg/kg body weight is usually given as an infusion at weeks 0, 2 and 6, and then every 6–8 weeks. When infliximab is used in combination with NSAIDs a rapid improvement in disease activity by at least 50% is seen in as many as 50% of AS patients. Infliximab has been shown to have ongoing efficacy for as long as regular infusions continue and is safe in the medium term. Magnetic resonance studies show major reductions in spinal inflammation during treatment with infliximab, however ongoing studies will assess if infliximab has disease modifying effect in AS.

Keywords: infliximab, ankylosing spondylitis, tumour necrosis factor inhibitors

Ankylosing spondylitis (AS) is a chronic systemic inflammatory arthropathy that primarily affects the axial skeleton. It is the prototype of the spondyloarthritides (SpA), a group of diseases which includes psoriatic arthritis, inflammatory bowel disease associated arthritis, reactive arthritis and undifferentiated spondyloarthritis. AS usually begins in adolescence or early adulthood, and is two to three times more common in men as in women (Khan 2002). The incidence varies with geographic location, affecting 0.1%–1.5% of the population (Boonen and van der Linden 2006). The major clinical features of AS are sacroiliitis and inflammatory back pain, the later characterized by insidious onset before the age of 45 years, and worsening with inactivity and improving with physical activity. This is associated with impaired spinal mobility, with restriction of flexion and extension of the lumbar spine and expansion of the chest. Other musculoskeletal features include peripheral arthritis and enthesitis (inflammation at the sites at which ligaments and tendons insert into bone). These features are reflected in the modified New York criteria used to establish a diagnosis of AS (Table 1), which also recognizes radiological evidence of sacroiliitis as the hallmark of AS (van der Linden et al 1984). Extra-articular manifestations can include constitutional symptoms, acute anterior uveitis (AAU), spinal osteoporosis and aortic valve incompetence. The course of AS is variable but can lead to severe functional impairment due to spinal fusion and hip joint involvement or from extra-spinal manifestations. AS is also associated with unemployment and significant financial cost (Ward 2002; Mau et al 2005; Boonen and van der Linden 2006).

The goals of management of AS are to relieve pain, stiffness and fatigue, maintain spinal mobility and posture and avoid disability. For over 5 decades the mainstay of
had abundant TNFα messenger RNA (Braun et al 1995) and that TNFα was elevated in the serum (Gratacos et al 1994; Toussirot et al 1994) and synovial tissue (Canete et al 1997) of patients with SpA justified pilot studies of infliximab therapy for AS. Open studies performed simultaneously in Ghent (Van den Bosch, Kruithof, Baeten, et al 2000) and Berlin (Brandt et al 2000) showed rapid and persistent reduction in symptoms of AS with infliximab therapy which were confirmed in further open label studies (Stone et al 2001; Maksymowych et al 2002; Breban et al 2002) and observational cohort studies (Brandt et al 2001; Temekonidis et al 2003) using infliximab in patients with active AS refractory to treatment with NSAIDs.

**Infliximab**

Infliximab is a chimeric IgG1κ monoclonal antibody, composed of human constant regions and the TNF-α-specific murine variable regions (Knight et al 1993). Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses. Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα, preventing association of TNFα with its receptors (Knight et al 1993). Cells expressing transmembrane TNFα bound by infliximab are lysed in vitro by both complement and cell mediated lysis (Scallon et al 1995). Infliximab inhibits the functional activity of TNFα in a wide variety of in vitro bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells (Siegel et al 1995). It is supplied as a sterile, white, lyophilized powder, reconstituted with sterile water for intravenous infusion, usually over 1–2 hours. In AS the conventional dose regimen is 5 mg/kg given initially at 0, 2 and 6 weeks, then every 6–8 weeks. Infliximab is licensed for use in adults; it has not been tested in children.

**Considerations relevant to understanding clinical trials in AS**

Interpreting clinical trials in AS requires an introduction to classification and outcome measures relevant in AS, including potential limitations. Entry criteria require a definite diagnosis of AS according to modified New York criterion (Table 1), thus all enrolled patients have radiological evidence of sacroilitis of at least grade 2 bilaterally (early sacroiliitis with minor sclerosis, limited erosions and joint space narrowing) or grade 3 unilaterally (definite sacroilitis with severe sclerosis, clear-cut erosions, joint space narrowing and some ankylosis). As sacroilitis often takes years to develop,
results from these trials can only be applied to patients with established, longstanding disease. Expert panels have acknowledged that this may exclude patients with early AS who may still benefit greatly from treatment with infliximab (Braun, Pham, et al 2003) and the development of diagnostic criteria which include MRI to identify patients with early disease remains an area of active research. For the purpose of enrolment most clinical trials define active disease as a Bath Ankylosing spondylitis activity index (BASDAI) of $>4$. Key outcome assessment instruments are outlined in Table 2.

Response to treatment is generally measured as absolute reduction of any one of the outcomes measures by a pre-defined amount (eg, a reduction in BASDAI of $\geq 2$) or as a percentage reduction of a composite score. The Assessments in Ankylosing Spondylitis (ASAS) Working Group has defined and validated a composite of disease activity and disability called ASAS 20 which requires an improvement of 20% or more and absolute improvement of more than 10 units on a 0–10 scale in the 3 of the 4 domains of patient global, pain, function and inflammation and no deterioration in the remaining domain (Anderson et al 2001). Although not specifically validated, many trials report proportions of patients reaching ASAS 50 or ASAS 70 (patients reaching a 50% or 70% improvement in the ASAS 20 domains).

**Pivotal controlled trials in the treatment of AS**

Braun et al conducted a 12-week, multi-center, randomized-controlled trial (RCT) of infliximab versus placebo in 70 patients with active AS (Braun et al 2002). The primary end point was a 50% reduction of disease activity (measured as BASDAI). Fifty-three percent of infliximab-treated patients achieved this end-point compared with 9% of placebo-treated patients, a highly statistically significant difference ($p < 0.001$). Improvement was rapid in the infliximab-treated group with 41% of patients having 50% improvement within 2 weeks. There were also similar improvements in function, spinal mobility and quality of life for the infliximab group. Infliximab-treated patients also had reduced use of NSAIDs and reductions in C-reactive protein (CRP) and erythrocyte sedimentation rate. Although infliximab was generally well tolerated, three patients had serious adverse events and were withdrawn from this short study. These included disseminated tuberculosis, high fever and lymphadenopathy with pulmonary infiltrates. Twenty of these patients enrolled at one centre had spinal magnetic resonance imaging (MRI) of the spine conducted at baseline and week 12, in part to evaluate a new scoring system (Braun, Baraliakos, et al 2003). Seventy-five percent of patients had active spinal lesions, defined as vertebral bone marrow edema and/or erosions, with a 40% improvement seen in the infliximab group and 6% in placebo group. Reduction in MRI evidence of spinal inflammation had a strong correlation with the observed clinical improvement in infliximab-treated patients. At the 12-week conclusion of this trial the 69 completing patients all received treatment with infliximab 5 mg/kg every 6 weeks and have been followed-up in an open extension trial, the results of which are discussed below.

A contemporaneous RCT included 40 patients with a variety of SpA and included 11 patients with AS and a total of 21 patients with axial disease (Van Den Bosch et al 2002). Similar reductions in BASDAI, BASFI and spinal pain were observed at 12 weeks in these patients.

The ASSERT trial is the largest placebo-controlled trial of infliximab for AS, randomizing 279 patients in multiple centres to placebo or infliximab 5 mg/kg at baseline 2, 6, 12 and 18 weeks (van der Heijde et al 2005). The primary end point was achievement of ASAS 20 at 6 months. The patients were typical of those with active AS, consisting of 80% men with a median age of 40 years and median disease duration of almost 9 years. At 24 weeks 61% of the infliximab group had achieved an ASAS 20 response, compared to 19% in the placebo arm ($p < 0.001$). Again patients receiving infliximab also showed improvement within 2 weeks, which was sustained through the study period. Significant improvements were observed in the all outcomes measured including disease activity (BASDAI), function (BASFI), mobility (BASMI), chest expansion and quality of life (physical component of SF-36). Although adverse events were common in both treatment groups (82.2% of patients receiving infliximab and 72.0% of patients receiving placebo) most were mild and did not mandate withdrawal from the trial. The commonest were infections (43% infliximab versus 36% placebo) and infusion reactions (11% infliximab versus 9.3% placebo). Seven patients (3.5%) in the infliximab group had severe adverse events, with the one withdrawal due to myelitis. MRI outcomes have also been evaluated in a sub-set of the patients enrolled in the ASSERT trial (Braun, Landewe et al 2006). A total of 266 patients had spinal MRI at baseline and 24 weeks, 194 in the infliximab group and 72 in the placebo group. About 80% of patients had at least one active spinal lesion on MRI at baseline. Images were scored according to a MRI activity score (Braun, Baraliakos, et al 2003), which assigns a score of 0–6 for vertebrae from C2 to S1 on the presence and extent of bone marrow edema and erosions to give a total score of 0–138. Compared to placebo, more
Table 2 Outcome measures commonly used in trials of therapy in ankylosing spondylitis

<table>
<thead>
<tr>
<th>Tool</th>
<th>Dimension measured</th>
<th>Definition</th>
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<tbody>
<tr>
<td>BASDAI</td>
<td>Disease activity</td>
<td>A composite index that includes questions on fatigue, axial pain, peripheral arthritis, enthesitis and severity and duration of stiffness, measured on a visual analogue scale (VAS) of 0–10.</td>
</tr>
<tr>
<td>BASFI</td>
<td>Function</td>
<td>A self-assessment instrument consisting of 8 questions regarding function in AS and two questions reflecting the patient’s ability to cope with everyday life, measure on a VAS.</td>
</tr>
<tr>
<td>BASMI</td>
<td>Mobility</td>
<td>A composite index of clinical measurement of mobility including tragus to wall, lumbar flexion, cervical rotation, lumbar side flexion and inter malleolar distance, each measured on a 0–3 scale.</td>
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<tr>
<td>ASAS 20</td>
<td></td>
<td>A composite of disease activity and disability, an improvement of 20% or more, and absolute improvement of 10 or more units on a scale of 0–100 scale in 3 or more of the following 4 domains; 1. Patient global assessment (by VAS global assessment) 2. Pain assessment (average of VAS total and nocturnal pain scores) 3. Function (represented by BASFI) 4. Inflammation (average of the BASDAI's last two VASs concerning morning stiffness, intensity and duration) and an absence of deterioration in the potential remaining domain (deterioration defined as 20% worsening).</td>
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Garrett et al 1994  
Calin et al 1994  
Jenkinson et al 1994  
Anderson et al 2001

patients in the infliximab group showed a reduction in inflammation score and patients in the infliximab group had a significantly greater improvement in total MRI Activity Scores from baseline to week 24 (5.0 ± 6.2, mean ± SD, median 2.7) than did patients in the placebo group (0.6 ± 3.4, median 0.0) (p < 0.001).

All of these RCTs required withdrawal of DMARDs. Oral corticosteroids were discontinued before screening, however patients were permitted to continue baseline dose of NSAIDs. This is in contrast to treatment of RA with infliximab, which requires concomitant treatment with methotrexate, in part to reduce the incidence of human antibodies against the chimeric
parts of the molecule (Human anti-chimera antibodies or HACA) (Moreland et al 1996). HACA are thought to be responsible for infusion reactions (Baert et al 2003). In a 30-week double-blind RCT patients treated with infliximab and low dose methotrexate had a similar low incidence of infusion reactions to patients treated with infliximab alone, although the incidence of HACA antibodies in each treatment group was not assessed (Marzo-Ortega et al 2005).

Open label extensions
Reports on the open-label extension of the pivotal RCTs of infliximab therapy for AS show a durability of response. In the extension of the original 3-month RCT, Braun et al reported that of the original 69 patients who received infliximab after the 12 week end point, 49 (71%) continued infliximab for 2 years (Braun, Brandt, et al 2005), 43 (62%) for 3 years (Braun, Baraliakos, Brandt, et al 2005) and 41 (59.4%) for 5 years (Baraliakos et al 2006). All improvements in disease activity were sustained and almost 60% of patients maintained an ASAS 50 over 3 years. Outcomes for 5 years were recently reported in abstract form, confirming a sustained response (Barakiakos et al 2006). During the 3-year follow-up up to 96% of patients had adverse events, although these were generally mild with only 11 patients discontinued therapy due to adverse events (Braun, Baraliakos, Brandt et al 2005). Although the long-term efficacy of infliximab has been demonstrated, unfortunately there is a rapid loss of response with discontinuation. Over 60% of patients who have previously had a sustained response to therapy relapse within 4 months of cessation of infliximab infusions (Baraliakos, Listing, Brandt, et al 2005). Fortunately all patients retreated responded with resumption of infusions.

Other outcomes
An important outcome measure in trials of therapy for AS is the ability to prevent radiographic progression. Improvement of active spinal lesions over short periods after treatment with infliximab has been demonstrated by MRI as already discussed but chronic spinal changes are better assessed by plain radiography (Wanders et al 2004). Comparison of patients treated for 2 years with infliximab with patients from an AS cohort followed-up for 2 years showed a small, non-significant reduction in radiological changes on lateral lumbar and cervical spine views in the infliximab treated group as measured with modified Stoke ankylosing spondylitis spine score (Baraliakos, Listing, Rudwaleit, et al 2005), despite older age, longer disease duration and higher level of radiographic damage at baseline. Although promising, larger studies over longer periods will be required to assess the disease modifying effects of infliximab.

Enthesitis is one of the most common extra-axial features of the SpA. Neither of the two major RCT enrolling patients with AS demonstrated significant reductions in enthesitis or swollen joint count in infliximab treated patients, perhaps because the prevalence of extra-axial inflammation was very low at baseline in both studies (Braun et al 2002, van der Heijde et al 2005). However a 12-week RCT of 40 patients with a variety of SpA randomized to receive infliximab at standard AS dose or placebo did show infliximab treatment was associated with a statistically significant reduction in peripheral joint pain and tenderness (Van Den Bosch et al 2002). Infliximab has also induced a rapid and complete clinical and ultrasonographic resolution of refractory, erosive calcaneal enthesis in two HLA-B27+ patients after induction treatment with infliximab 3 mg/kg (D’Agnostino et al 2002).

The incidence of AAU appears to be reduced during treatment with infliximab. Data on 397 patients enrolled in RCT of TNFα-inhibitors showed patients receiving placebo had a mean 15.6 flares of AAU/100 patient years compared to 3.4/100 patient years for infliximab treated patients (Braun, Baraliakos, Listing, et al 2005).

AS can occur in the context of psoriasis, which in itself is a potentially disabling condition. A Phase III RCT inpatients with moderately severe psoriasis showed infliximab monotherapy was highly effective in treating both skin and nail psoriasis (Reich et al 2005).

Osteoporosis leading to spinal fracture is a recognised late complication of AS (Khan 2002). Two recent studies have reported improvements in bone mineral density (BMD) in patients with AS treated with infliximab (Allali et al 2003; Marzo-Ortega et al 2005). Allali et al (2003) measured significant improvements in BMD at the spine (3.6%, \( p = 0.001 \)) and total hip (2.2%, \( p = 0.0012 \)) in 29 patients with SpA treated with infliximab for 6 months. A RCT comparing treatment with infliximab and methotrexate versus methotrexate alone in 42 patients with AS recorded a 1.9% increase in BMD at the hip (\( p = 0.04 \)) in the infliximab group after 30 weeks with non-significant increases in the femoral neck and spine (Marzo-Ortega et al 2005). In these studies approximately 20% of patients were taking systemic glucocorticoids but these were not discontinued.

Infliximab treatment of AS has impacts on socio-economic outcome measures. Over the relatively short 6-month period of an RCT, infliximab treatment was associated with reductions in work absenteeism and work disability (van der Heijde et al 2006). In the open label extension of the Braun study...
Dose

There are no formal dose finding studies for infliximab in AS. The 5 mg/kg dose was chosen as this dose is standard for patients with Crohn’s disease and on the basis of a small study which suggested 5 mg/kg was more effective than 3 mg/kg (Braun et al 2002). Indeed in a cohort of 30 patients with SpA with axial involvement treated 6-weekly with 3 mg/kg infliximab, two-thirds of patients required an increase in dose or reduction in interval to achieve or maintain a response (Sidiropoulos et al 2005). In a Canadian cohort including 8 patients treated for 1 year with 3 mg/kg infliximab every 8 weeks, these patients had maintenance of initial response but two patients required an increased dose of infliximab to sustain the response (Maksymowych et al 2002). In a pilot study of 21 patients with a variety of AS related SpA a dosage regimen of 5 mg/kg of infliximab every 14 weeks ultimately resulted in almost 80% of patients experiencing relapse of disease activity prior to the next infusion (Kruthof et al 2002). This suggests the 14-week interval was too long. A dosage regimen of 5 mg/kg every 8 weeks has shown sustained achievements of ASAS 50 after 1 year of treatment. Thus most patients will require a dose of 3–5 mg/kg given 6–8 weekly for an adequate and sustained clinical response although there may be a need to individualize dosage or interval based on response.

Safety

The major immunomodulating effect of infliximab on the immune system raises concerns about the risk of infection, autoantibodies and tumors. The infectious risk associated with infliximab has been systematically assessed in a cohort of 107 patients with SpA with observations extending over 191.5 patient years of treatment (Baeten et al 2003). Eight severe infections were observed, including two cases of reactivation of tuberculosis, three retropharyngeal abscesses, one episode of culture-negative sepsis-like syndrome and two procedure-related infections. Re-activation of tuberculosis was also reported in a previously discussed RCT (Braun et al 2002). The risk of reactivation of tuberculosis during treatment with infliximab is well documented. Of note, this often occurs within 12 weeks of commencement of therapy, with in excess of 50% of cases being extra-pulmonary, 25% disseminated and almost 50% requiring a biopsy for diagnosis (Keane et al 2001). Current guidelines recommend screening for active or latent tuberculosis when considering treatment with a TNFα-inhibitor and treatment of latent tuberculosis with prophylactic isoniazid for at least 2 months prior to commencement of infliximab, with completion of 6–9 months of isoniazid therapy (American Thoracic Society 2000; British Thoracic Society 2005). Patients treated with infliximab, and their physicians, should be aware of the increased risk of serious infection and prompt assessment of any symptoms which may suggest infection is warranted. Infliximab therapy is relatively contraindicated in situations associated with an increased risk of infection including: chronic leg ulceration, septic arthritis of a native joint within 12 months, sepsis of a prosthetic joint within 12 months or indefinitely if prostheses remains in situ, persistent or recurrent chest infections (eg, bronchiectasis), and presence of an indwelling urinary catheter (Braun, Pham, et al 2003).

Clinical trials have shown that infliximab may induce autoantibodies such as antinuclear antibodies (ANA) and anti dsDNA antibodies (Charles et al 2000). The occurrence of these antibodies during infliximab therapy for AS has not been systematically addressed. In one placebo-controlled trial enrolling patients with SpA, 17% were ANA positive and none dsDNA positive at baseline but after 34-weeks of infliximab therapy 89% were ANA positive and 17% dsDNA positive (Van Den Bosch et al 2002). No patients had any clinical evidence of lupus-like disease.

Asymptomatic elevation in liver transaminases are commonly observed during treatment with infliximab and rare cases of acute liver failure and autoimmune hepatitis have been reported (Infliximab Product Information, Centocor, Malvern PA). Cytopenias have also been observed, although casual association has not been established.

Other contraindications to infliximab therapy include pregnancy or inadequate contraception in a women of child-bearing potential, breastfeeding, history of lupus or multiple sclerosis, malignancy other than basal cell carcinoma and those treated more than 10 years previously (Braun, Pham, et al 2003)

Biological modulation

Although there are no studies of a pure AS cohort, there are data regarding the biological effects of infliximab therapy.
in patients with SpA. Patients with SpA appear to have Th2 polarization with decreased T-cell production of IFNγ and IL-2 and increased IL-10 (Yin et al 1999; Baeten, Kruithof, et al 2001; Baeten, Van Damme, et al 2001). Treatment with infliximab induced a rapid and sustained increase in T-cell synthesis of IFNγ and IL-2 and transient decrease in IL-10 production (Baeten, Kruithof, et al 2001) restoring Th1/Th2 balance. This data supports the hypothesis that infliximab reverses the anergic state of Th1 cells. At a tissue level repeated synovial biopsy has allowed an insight into histological changes in synovial pathology in peripheral joints in SpA patients with active synovitis after treatment with infliximab. After 12 weeks infliximab reduced synovial layer thickness, endothelial activation (E-selection or VCAM-1) and cellular infiltration by neutrophils, macrophages and T cells (Baeten, Kruithof, et al 2001; Kruithof et al 2005). Synovial levels of matrix metalloproteinase-3 (MMP-3) and tissue inhibitors of matrix metalloproteinases (TIMP) are also elevated in SpA synovium and treatment with infliximab rapidly downregulates synovial expression of MMP-3 and TIMP and serum MMP-3 (Vandooren et al 2004). Further analysis has shown that reduction in lining and sub-lining macrophages and reduced immature macrophages, sub-lining matrix MMP-3 and neutrophil infiltration are accurate early predictors of response to treatment, performing as well as changes in acute phase reactants (Kruithof et al 2006).

**Cost effectiveness**

As a recombinant biological agent, infliximab therapy is expensive. Despite the expense, cost-effectiveness modeling in two health-care systems suggest the clinical benefits and improvement in quality of life with infliximab lead to lower disease-associated costs than standard care (Kobelt et al 2004, 2006) and modeling for long-term therapy assuming progression of BASFI sees a further reduction in the cost per quality adjusted life year. Longer term data on disease progression of AS during treatment with infliximab is required to confirm this hypothetical data, in addition to measurements of savings in in-direct costs related to work disability and AS-related illness.

**Current indications**

A consensus statement developed by the ASAS working group gives clear recommendations, based on published literature and expert opinion, about the indication for anti-TNFα therapy in AS (Braun, Pham, et al 2003; Braun, Davis, et al 2006). For the initiation of therapy the recommendations are 1. A diagnosis of definitive AS based on the modified New York criteria; 2. Presence of active disease for at least 4 weeks defined by both a sustained BASDAI of at least 4 and expert opinion based on clinical features, acute phase reactants, and imaging modalities; 3. Presence of refractory disease defined by failure of at least two NSAIDs during a single 3-month period, failure of intra-articular steroids if indicated, and failure of sulfasalazine in patients with peripheral arthritis; 4. Application and implementation of the usual precautions and contraindications for biological therapy. Discontinuation is recommended if there is a failure to reach at least a 50% or 2-unit improvement (on a 0–10 scale) of the BASDAI at 6–12 weeks or if expert opinion suggests cessation. Most countries will develop local guidelines for therapy, which may be influenced by cost considerations as well as published literature. Retrospective analysis of major RCTs suggests that a response to therapy may be predicted by shorter disease duration and less functional disability (Rudwaleit, Listing, et al 2004) however the patients included in this analysis had very high disease activity at baseline and these conclusions may not be appropriate to generalize to a real-world treatment situation. A major problem in treatment of AS is the long delay between onset of symptoms and diagnosis (Khan 2002). This is of particular relevance when response to infliximab therapy may be improved when therapy is commenced early. Rudwaleit, van der Heijde et al (2004) have proposed a clinical algorithm based on the presence of inflammatory back pain and assigning likelihood ratios for diagnosis based on the presence of other features of SpA. The presence of inflammatory back pain and two or three other features of SpA (including enthesitis, alternating buttock pain, peripheral arthritis, dactylitis, AAU, psoriasis, family history of SpA and response to NSAIDs) gave a positive test probability of over 90% for the diagnosis of early SpA. Further clinical trials of infliximab in patients with probable early AS will be necessary to confirm therapy is appropriate for these patients but a clinical and perhaps radiological benefit seems highly probable.

The advent of infliximab has dramatically increased the therapeutic options for people affected by AS. Infliximab is highly effective in treating active AS refractory to NSAIDs and some available radiological data suggest a disease modifying effect. Limitations of therapy include potential side effects, particularly serious infection, the cost and the undetermined benefit in early disease. The cost
effectiveness of long-term infliximab therapy remains to be determined.

References


Grainger and Harrison, 64:1462–6.


