

# The anti-TNF revolution in ankylosing spondylitis

*Patients with severe disease now have access to promising new drugs*

---

To have lived through a revolution, to have seen a new birth of science, a new dispensation of health . . . is not given to every generation.

— William Osler (1913)

---

Driven by evidence from well designed clinical trials, infliximab, a monoclonal antibody that targets tumour necrosis factor alpha (TNF- $\alpha$ ), was recently listed on the Pharmaceutical Benefits Scheme (PBS) for treatment of ankylosing spondylitis.<sup>1</sup> This is welcome news for patients with a disorder for which, until now, there have been few effective therapeutic options.

Ankylosing spondylitis affects about 0.5%–1.0% of the population and typically begins between the ages of 15 and 40 years. It causes painful stiffness of the spine, progressive disability and loss of independence during the prime productive years. About 70% of patients go on to develop bony fusion of the spine, and the mortality rate for people with the condition is 1.5–4 times higher than that of the general population.<sup>2</sup>

To date, the treatment of ankylosing spondylitis has been unsatisfactory. Rheumatologists have combined physiotherapy and non-steroidal anti-inflammatory drugs, with the modest goal of relieving pain and stiffness, but such therapies do not alter the underlying disease process. Drugs that modify the disease process and prevent joint damage in rheumatoid arthritis (eg, corticosteroids, methotrexate and leflunomide) are of marginal benefit in ankylosing spondylitis. Randomised controlled trials have shown that sulfasalazine is of some benefit in ankylosing spondylitis, but only for peripheral joint involvement.<sup>3</sup> Clearly, novel approaches for treating ankylosing spondylitis have been long overdue.

Over the past decade, advances in basic medical research have seen the emergence of biological response modifiers that target critical mediators of the inflammatory response, such as TNF- $\alpha$ . Since August 2003, three biological agents that inhibit TNF- $\alpha$  have been listed on the PBS for severe rheumatoid arthritis: infliximab and adalimumab (monoclonal antibodies directed against TNF- $\alpha$ ), and etanercept (a soluble receptor that acts as a “decoy receptor” for TNF- $\alpha$ ).

In 1995, it was recognised that TNF- $\alpha$  occurs in high concentrations in inflamed sacroiliac joints in patients with ankylosing spondylitis,<sup>4</sup> thus identifying TNF- $\alpha$  as an important target for development of therapeutic agents. In the same year, international experts in ankylosing spondylitis established the Assessments in Ankylosing Spondylitis (ASAS) working group. This group included clinical epidemiologists, representatives of the pharmaceutical industry, and individuals with ankylosing spondylitis. The first goal of the ASAS group was to select and test the validity of a set of standardised clinical, serological and radiographic endpoints for clinical research and routine practice. Otherwise, rheumatologists were faced with the real possibility that new therapies would emerge from basic research but fail to find their rightful place in

the treatment of patients with ankylosing spondylitis because the available tools to measure efficacy were too insensitive.

By consensus, the following domains were selected to assess the efficacy of disease-controlling therapy: functional capacity, pain, spinal mobility, patient global assessment, spinal stiffness, peripheral joint swelling, erythrocyte sedimentation rate, spine and hip x-rays, fatigue and enthesitis (inflammation at sites of ligament, tendon or joint capsule insertion into bone).<sup>5</sup> These endpoints are now used almost uniformly in studies of anti-TNF therapy in ankylosing spondylitis. Another outcome measure to emerge from the ASAS group was the “ASAS-20”, representing a 20% improvement in a composite score of efficacy.<sup>6</sup> Recently, the group released a consensus statement for selection of appropriate candidates for treatment with anti-TNF therapy.<sup>7</sup> This statement formed the basis of the current PBS restrictions on the use of infliximab in ankylosing spondylitis.

Early data to emerge from uncontrolled studies of anti-TNF therapy in ankylosing spondylitis paved the way for randomised controlled trials. In a 3-month clinical trial, 18 of 34 patients (53%) treated with infliximab met the predefined response criterion, compared with 3 of 35 (9%) patients receiving placebo.<sup>8</sup> There was significant improvement in almost all outcome measures, including quality-of-life and functional measures. These improvements persisted during an open-label extension study in which all participants were given infliximab for an additional 42 weeks.<sup>9</sup>

In the largest anti-TNF randomised controlled study to date, 277 patients with ankylosing spondylitis received either etanercept or placebo.<sup>10</sup> At 24 weeks, 59% of the etanercept group and 28% of the placebo group met the ASAS-20 criteria for response. Although the mean disease duration among participants in the study was over 10 years, there were significant improvements in seemingly irreversible measures of spinal mobility.

Anti-TNF therapy is not without risk. Importantly, most side effects of anti-TNF therapy did not emerge from randomised controlled trials but from post-marketing reports. Mild injection-site reactions occur in 10%–35% of patients using the subcutaneous formulations (etanercept and adalimumab), while infusion reactions can occur with the intravenous preparation (infliximab). The risk of reactivation of latent tuberculosis is well recognised. Thus, patients must be screened with a chest x-ray and Mantoux test before initiation of anti-TNF therapy. As TNF is important in preventing dissemination of intracellular organisms, anti-TNF therapy increases the risk of *Aspergillus*, *Listeria* and *Cryptococcus* infections, and live vaccinations are contraindicated.

To date, post-marketing surveys have not shown an increase in risk of malignancy from anti-TNF therapy. There have been case reports of anti-TNF therapy being associated with autoimmune disorders, demyelination (optic neuritis and multiple sclerosis), exacerbation of cardiac failure, and abnormal liver function tests. However, the absolute risk of developing these complications after anti-TNF therapy is yet to be defined.

In order to claim that anti-TNF therapy truly modifies the disease, researchers need to demonstrate that the treatment can

slow down or prevent bony fusion and ankylosis. To date, this has not been achieved. A major limiting factor has been the requirement for study participants to demonstrate unequivocal radiographic evidence of sacroiliitis. As this is a late clinical feature of the disease, patients with early ankylosing spondylitis have been excluded from anti-TNF studies. Yet it is this cohort that is most likely to respond to anti-TNF therapy and in whom disease modification may be most readily apparent. Recently, a novel algorithm-based protocol for identifying patients with early ankylosing spondylitis in general practice recommended magnetic resonance imaging of sacroiliac joints for all people with inflammatory back pain and HLA-B27 positivity.<sup>11</sup>

Anti-TNF therapy has revolutionised the way in which we think about ankylosing spondylitis. By approving anti-TNF therapy for people with severe ankylosing spondylitis, the PBS has allowed clinical investigators in Australia to remain at the front line of this revolution.

**Lionel Schachna**

Director, Austin Spondylitis Centre, Austin Health, Heidelberg, VIC  
schachna@unimelb.edu.au

- 1 Health Insurance Commission. Pharmaceutical Benefits Scheme. Infliximab – for active ankylosing spondylitis. Schedule restriction details. 2004. Available at: [www.hic.gov.au/providers/forms/pbs/mp/infliximab\\_as/schedule\\_restriction.htm](http://www.hic.gov.au/providers/forms/pbs/mp/infliximab_as/schedule_restriction.htm) (accessed Oct 2004).
- 2 Lehtinen K. Mortality and causes of death in 398 patients admitted to hospital with ankylosing spondylitis. *Ann Rheum Dis* 1993; 52: 174-176.

- 3 Clegg DO, Reda DJ, Abdellatif M. Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondylarthropathies: a Department of Veterans Affairs cooperative study. *Arthritis Rheum* 1999; 42: 2325-2329.
- 4 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 Rheum* 1995; 38: 499-505.
- 5 van der Heijde D, Calin A, Dougados M, et al. Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis. Progress report of the ASAS Working Group. Assessments in ankylosing spondylitis. *J Rheumatol* 1999; 26: 951-954.
- 6 Anderson JJ, Baron G, van der Heijde D, et al. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. *Arthritis Rheum* 2001; 44: 1876-1886.
- 7 Braun J, Pham T, Sieper J, et al. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2003; 62: 817-824.
- 8 Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002; 359: 1187-1193.
- 9 Braun J, Brandt J, Listing J, et al. Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month, randomized, placebo-controlled trial. *Arthritis Rheum* 2003; 48: 2224-2233.
- 10 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* 2003; 48: 3230-3236.
- 11 Rudwaleit M, van der Heijde D, Khan MA, et al. How to diagnose axial spondyloarthritis early. *Ann Rheum Dis* 2004; 63: 535-543. □