Drugs 2005; 65 (9): 1283-1291
0012-6667/05/0009-1283/$39.95/0

Infliximab

In Ankylosing Spondylitis

Dean M. Robinson and *Gillian M. Keating*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Infliximab is a monoclonal antibody that binds to tumour necrosis factor-α and blocks its biological activity. It is approved for use in patients with rheumatoid arthritis, Crohn's disease and ankylosing spondylitis.

▲ In well designed, placebo-controlled trials of 12 or 24 weeks' duration in patients with active ankylosing spondylitis, more infliximab 5 mg/kg recipients achieved a response than placebo recipients according to Ankylosing Spondylitis Assessment Study 20% (61.2% vs 19.2%) or Bath Ankylosing Spondylitis Disease Activity Index 50% (53% vs 9%) criteria (primary endpoints).

▲ Infliximab was also superior to placebo in terms of various secondary clinical endpoints and in reducing spinal inflammation (as assessed by magnetic resonance imaging).

▲ Prolonged efficacy has been demonstrated in patients with ankylosing spondylitis who received infliximab for up to 3 years.

▲ Infliximab is generally well tolerated in patients with ankylosing spondylitis, with most adverse events being of mild-to-moderate severity.

Features and properties of infliximab (Remicade®)	
Indications	
Patients with rheumatoid arthritis, Crohn's disease and ankylosing spondylitis (the focus of this article)	
Mechanism of action	
Monoclonal antibody that binds to and neutralises soluble and transmembrane tumour necrosis factor-α	
Dosage and administration in patients with ankylosing spondylitis	
Dose	5 mg/kg
Route of administration	Intravenous infusion
Frequency of administration	Doses at weeks 0, 2 and 6 and then at 6-week (US) or 6- to 8-week (EU) intervals
Pharmacokinetic profile of infliximab 5 mg/kg in 192 patients with moderate-to-severe Crohn's disease after infusions at 0, 2 and 6 weeks, and then at 8-week intervals for 46 weeks	
Median peak plasma concentration	120 μg/mL
Median time to peak plasma concentration	14 days
Median elimination half-life	12.5 days
Adverse events	
Incidence ≥2-fold higher than placebo	Pharyngitis, elevated serum ALT and AST levels and rhinitis

Ankylosing spondylitis is one of five related spondyloarthropathies (ankylosing spondylitis, reactive arthritis, psoriatic arthritis, inflammatory bowel disease and undifferentiated spondyloarthropathies) that have a prevalence of 0.6–1.9%.[1] Ankylosing spondylitis is the most common subtype (prevalence 0.1–1.1%) and its primary manifestation is inflammatory back pain,[1] with inflammation characteristically involving the sacroiliac joints.[2]

Therapy with NSAIDs is common (70–80% of patients) but efficacy is variable.[1] Corticosteroids and disease-modifying antirheumatic drugs (DMARDs), such as methotrexate and sulfasalazine, have demonstrated limited efficacy in treating the spinal manifestations of ankylosing spondylitis.

Infliximab (Remicade®)[1] is a monoclonal antibody that targets tumour necrosis factor (TNF)-α, a cytokine with multiple actions, including the mediation of inflammatory responses.[3] It has proven efficacy in the treatment of rheumatoid arthritis and Crohn's disease,[4] and the international ASAS (ASessments in Ankylosing Spondylitis) consensus statement recommends the use of anti-TNFα agents in ankylosing spondylitis;[5] this review focuses on the use of infliximab in the treatment of ankylosing spondylitis.

1. Pharmacodynamic Properties

The pharmacodynamic properties of infliximab have been reviewed in some detail previously;[4] therefore, only key properties relevant to therapy for ankylosing spondylitis are reviewed here.

The cytokine TNFα is implicated in ankylosing spondylitis, as shown by the overexpression of TNFα messenger RNA and protein[6] in the sacroiliac joint and the elevation of circulating levels of TNFα[7] in patients with ankylosing spondylitis.

TNFα induces expression of chemokines, endothelial adhesion molecules and other cytokines that recruit and activate leukocytes, promote the production of acute phase proteins and stimulate bone resorption by osteoclasts (reviewed by Keating and Perry[4]). Other proinflammatory cytokines, such as interleukin (IL)-1, are inhibited by TNFα neutralisation, suggesting that TNFα plays a central role in many immune-mediated diseases.[8]

- Infliximab is a chimeric IgG1κ monoclonal antibody, comprising human constant and murine variable regions, which binds to human TNFα with an association constant of 10^{10} mol/L^{-1}.[9] It neutralises both soluble and transmembrane TNFα and may also promote both lysis of TNF-producing cells and T-lymphocyte apoptosis.[4] Infliximab binding to TNFα does not promote its removal, but rather renders it inactive.[10]

- The cytokine response of T cells to infliximab therapy is ambiguous.[2,6,11,12] Data suggest that in patients with ankylosing spondylitis, infliximab 5 mg/kg increases the number of CD4+ and CD8+ cells expressing type 1 helper cytokines (interferon [IFN]-γ[6,12] and IL-2[12]); however, decreases in CD4+ and CD8+ cells positive for IFNγ have also been reported.[11] Whether this discrepancy is due to a time-dependent effect of infliximab treatment[2] or methodological differences[12] is unclear.

- Likewise, during treatment with infliximab 5 mg/kg, one study reported that the number of CD3+ cells (includes CD4+ and CD8+ cells) secreting TNFα increased,[6] while another reported a decrease in TNFα-secreting CD8+ cells.[11]

- Serum matrix metalloproteinase 3 (MMP-3) and macrophage colony-stimulating factor 1 (MCSF-1) have been identified as possible markers of ankylosing spondylitis disease activity.[13] In 41 patients with ankylosing spondylitis,[13] significant correlations were found between MCSF-1 ($r = 0.41$; $p =$

1 The use of trade names is for identification purposes only and does not imply endorsement.

0.004) or MMP-3 (r = 0.48; p = 0.0007) and a measure of disease severity, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[14] which assesses disease activity on the basis of fatigue, spinal pain, peripheral arthritis, enthesitis and morning stiffness.

- In 13 patients with ankylosing spondylitis receiving infliximab 3 mg/kg, significant declines in serum MMP-3 levels (p = 0.013) and BASDAI values (p = 0.00007), but not MCSF-1 levels, were observed.[13]
- However, recent data from 33 patients with ankylosing spondylitis suggests that serum MMP-3 levels may be more reflective of peripheral synovitis rather than axial or systemic inflammation.[15]

2. Pharmacokinetic Properties

This section focuses on the pharmacokinetics of infliximab when administered according to the regimen approved for use in patients with ankylosing spondylitis (intravenous infusion of infliximab 5 mg/kg at 0, 2 and 6 weeks, followed by infusions at 6-week[9] or 6- to 8-week[3] intervals) [see section 5].

Data are not available concerning the pharmacokinetics of infliximab in patients with ankylosing spondylitis; thus, this section discusses the pharmacokinetics of the approved regimen in patients with moderate-to-severe Crohn's disease. Data were obtained from the ACCENT (A Crohn's disease Clinical trial Evaluating infliximab in a New long-term Treatment regimen) I study,[16] supplemented by data from the prescribing information[3,9] and a trial in patients with rheumatoid arthritis.[17]

- In patients with Crohn's disease, administration of a single dose of intravenous infliximab 5 mg/kg was associated with a median maximum serum concentration (C_{max}) of 102 μg/mL, which was reached in a median time (t_{max}) of 0.084 days.[16] Infusion of infliximab 5 mg/kg at weeks 0, 2 and 6 and at 8-week intervals thereafter for 46 weeks led to slight accumulation of the drug in serum, with a median C_{max} of 120 μg/mL reached in a median t_{max} of 14 days.
- In patients receiving maintenance doses of infliximab 5 mg/kg at 8-week intervals, steady-state serum concentrations were reached after week 22.[16] The median preinfusion serum infliximab concentration was ≈2 μg/mL between weeks 22 and 54, while median postinfusion concentrations were 93 μg/mL at week 0, 111 μg/mL at week 22 and 99 μg/mL at week 46.[16]
- Infliximab distribution is confined mainly to the vascular compartment,[9] with a volume of distribution at steady-state of 70 mL/kg and a median distribution half-life of 3 days.[16]
- Although the pathways by which infliximab is eliminated have not been characterised, unchanged infliximab has not been detected in urine.[3,9] Infliximab had a median terminal elimination half-life of 12.5 days in patients with Crohn's disease who received infliximab 5 mg/kg at 8-week intervals (following doses at weeks 0, 2 and 6).[16] Median clearance was 5.2 mL/day/kg.
- Methotrexate seemed to reduce the clearance of infliximab from serum in patients with rheumatoid arthritis who received these drugs in combination.[17] This effect may be linked to a reduction in the immunogenicity of infliximab when administered in combination with methotrexate.

3. Therapeutic Efficacy

The efficacy of intravenous infliximab at the recommended dosage of 5 mg/kg[3,9] has been examined in patients with ankylosing spondylitis in two randomised, double-blind, placebo-controlled, multicentre trials of 12[18] and 24[19] weeks' duration. The 24-week, phase III ASSERT (Ankylosing Spondylitis Study for the Evaluation of Recombinant infliximab Therapy) trial included 279 patients[19] and the 12-week trial included 69 patients.[18] Patients in both trials had active disease (BASDAI score ≥4 and spinal pain score ≥4 on a

visual analogue scale [VAS] of 0–10).[18,19] Fully published[20] and preliminary[21] analyses of magnetic resonance imaging (MRI) data from these trials are also available.

The long-term use of infliximab was examined in extension studies of the 12-week trial in which placebo recipients switched to infliximab; fully published data are available for 1-,[22] 2-[23] and 3-year[24] extensions, while data after withdrawal at 3 years are available as an abstract.[25] Fully published data from noncomparative trials of infliximab[26-29] and a pharmacoeconomic analysis of infliximab[30] are also discussed briefly.

In ASSERT, patients received intravenous infusions of infliximab 5 mg/kg (n = 201) or placebo (n = 78) at 0, 2, 6, 12 and 18 weeks.[19] In the 12-week trial, patients received infliximab 5 mg/kg (n = 34) or placebo (n = 35) at 0, 2 and 6 weeks;[18] patients could then go on to receive infliximab 5 mg/kg at 6-week intervals for up to 3 years.[22-24] In both trials patients were screened for active and latent tuberculosis (TB).[18,19] Concomitant DMARDs, anti-TNF therapy other than infliximab and oral corticosteroids were not permitted.[18,19] Infliximab recipients in the 12-week trial had a mean disease duration of 16.4 years compared with 14.9 years in placebo recipients.[18] In ASSERT, median disease duration in infliximab and placebo recipients was 7.7 and 13.2 years.[19] Mean age was ≈40 years in both trials,[18,19] and men made up 81%[19] and 65%[18] of the study populations.

The primary efficacy endpoint in ASSERT was the proportion of patients achieving a 20% response according to ASAS criteria, at week 24 ($ASAS_{20}$).[19] These criteria are defined as an improvement from baseline of ≥20% and an absolute improvement of ≥1 (on scale of 0–10) in three of four domains, with no worsening in the fourth domain. These domains were inflammation (assessed from early morning stiffness questions in BASDAI), function (assessed using the Bath Ankylosing Spondylitis Functional Index [BASFI;[31] 10 specific questions on daily functions]), patient perception of spinal pain (assessed using a VAS) and patient global assessment.[32] In the 12-week trial the primary efficacy endpoint was a 50% improvement in BASDAI ($BASDAI_{50}$) between baseline and week 12, assessed on an intent-to-treat (ITT) basis.[18]

Secondary endpoints in the two trials included the proportion of patients achieving $BASDAI_{50}$,[19] $ASAS_{20}$,[18] absolute scores from BASDAI, BASFI and the Bath Ankylosing Spondylitis Metrology Index (BASMI; a clinical measurement of spinal mobility[33]),[18,19] health-related quality of life assessed by Short Form-36 (SF-36),[18,19] serum C-reactive protein (CRP) level[18,19] and erythrocyte sedimentation rate (ESR).[18]

- Infliximab was effective in the treatment of ankylosing spondylitis in both trials.[18,19] In ASSERT, $ASAS_{20}$ criteria were achieved by 61.2% of infliximab versus 19.2% ($p < 0.001$) of placebo recipients.[19] In the 12-week trial, 53% of infliximab versus 9% ($p < 0.0001$) of placebo recipients achieved $BASDAI_{50}$ (figure 1).[18]

- Improvements in disease state were relatively rapid. In infliximab recipients, ≈50% had achieved an $ASAS_{20}$ response[19] and 41% had achieved $BASDAI_{50}$[18] within 2 weeks of commencing therapy.

- Secondary endpoints also demonstrated improvement with infliximab but not placebo treatment in both trials.[18,19] In ASSERT, significantly ($p < 0.001$) greater improvements from baseline to 24 weeks occurred in infliximab versus placebo recipients in median BASDAI (−2.9 vs −0.4) and BASFI (−1.7 vs 0.0) scores, median percent change from baseline in CRP level (−68.7% vs 0.0%) and the median SF-36 physical component summary score (+10.2 vs +0.8), while the BASMI score also improved significantly (−1.0 vs 0.0; $p = 0.019$).[19] In addition, significantly ($p < 0.001$) more infliximab

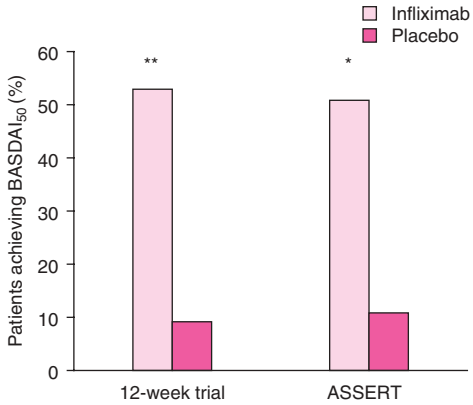

Fig. 1. Proportion of patients with active ankylosing spondylitis in randomised, double-blind, placebo-controlled, multicentre trials who achieved a 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index ($BASDAI_{50}$) with infliximab therapy. In a 12-week trial (n = 69)[18] and in the 24-week ASSERT (Ankylosing Spondylitis Study for the Evaluation of Recombinant infliximab Therapy) trial (n = 297),[19] patients received intravenous infusions of infliximab 5 mg/kg or placebo at 0, 2 and 6 weeks;[18,19] patients in ASSERT received additional infusions at 12 and 18 weeks.[19] $BASDAI_{50}$ was assessed at week 12[18] or 24[19] (secondary endpoint in ASSERT). * $p < 0.001$, ** $p < 0.0001$ vs placebo.

than placebo recipients achieved $BASDAI_{50}$ (figure 1) responses at 24 weeks.[19]

- In the 12-week trial, significantly ($p < 0.0001$) greater improvements in infliximab versus placebo recipients were reported in mean BASDAI (+3.2 vs +0.6) and BASFI (−2.1 vs +0.1) scores, median CRP level (−18 vs −3 mg/L), median ESR (−23 vs +4 mm/h) and the mean SF-36 physical component summary score (+15% vs −1.6%).[18] The BASMI score was also significantly improved (−0.9 vs +0.2 [estimated from a graph]; $p = 0.0023$). Moreover, significantly more infliximab than placebo recipients achieved $ASAS_{20}$ (84% vs 30% [estimated from a graph]; $p < 0.05$) responses at 12 weeks.[18]

- Infliximab reduced spinal inflammation, as assessed by MRI in 194 infliximab and 72 placebo recipients in ASSERT[21] and 9 infliximab and 11 placebo recipients in the 12-week trial.[20] The MRI data from ASSERT, independently assessed by two readers across 23 vertebral units using T1-weighted imaging with the contrast agent gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) and fat-saturated short tau inversion recovery sequences (STIR), showed a mean reduction from baseline in the spinal inflammation activity scores of 54% with infliximab versus 13% ($p < 0.001$) with placebo.[21]

- Data from the 12-week trial showed significantly greater improvements in acute lesion scores of 23 vertebral units with infliximab than with placebo, as determined by T1-weighted Gd-DTPA (+40% vs +6%; $p = 0.039$) and STIR (+60% vs −21%; $p < 0.001$) imaging.[20] There was no significant difference between infliximab and placebo recipients in the change in chronic lesion scores determined by T1-weighted sequences (+7% vs −35%).

- Prolonged infliximab efficacy has been demonstrated in patients from the 12-week trial[18] who went on to receive infliximab 5 mg/kg at 6-week intervals for up to 3 years.[22-24] Analysis (ITT) showed that 47% of patients who received infliximab throughout, and 51% of those who had switched to infliximab after receiving placebo during the initial 12-week trial, achieved the $BASDAI_{50}$ criteria at week 54.[22] In 54 patients who completed 54 weeks of the trial, mean BASDAI scores declined by 3.0 points ($p < 0.01$).[23]

- After 1 year of therapy, 52 patients elected to continue infliximab therapy until week 102, and 30 patients (ITT 43%; 58% of those electing to continue) achieved a $BASDAI_{50}$ score at week 102.[23] A third year of therapy was undertaken by 46 patients, and $BASDAI_{50}$ was achieved by 28 patients at year-end (ITT 41%; 61% of those continuing).[24]

- Within 3 months of withdrawal of infliximab after 3 years of therapy, clinical relapse occurred in 27 of 42 patients (64%) after a mean of 13.4 weeks of discontinuation.[25] The mean BASDAI score rose from 2.8 at withdrawal to 6.4 at relapse, while the mean serum CRP level rose from 2.1 to 15.0 mg/L and ESR rose from 11.3 to 36.4 mm/h.

- Results from three small (n = 21–50) 14-week to 12-month noncomparative studies[26,28,29] and a 52-

week extension[27] of the 14-week study[26] showed that most patients responded to infliximab therapy;[26,28,29] nonresponders had significantly lower mean CRP and TNFα (both $p < 0.01$) at baseline.[27] In these studies, patients with active ankylosing spondylitis received intravenous infliximab 5 mg/kg at 0, 2 and 6 weeks;[26,28,29] 8-weekly maintenance infusions continued after the initial loading period in the 12-month study[29] and in the 52-week extension.[27]

Pharmacoeconomic Considerations

The cost effectiveness of infliximab from a societal perspective was modelled over 1 year of treatment plus 1 year after withdrawal, using clinical data from the 12-week placebo-controlled trial,[18] and British resource consumption data.[30] Direct and indirect costs from the year 2002 and discount rates of 6% (costs) and 1.5% (utilities) were applied.

- The analysis indicated that infliximab treatment costs were partially offset by reductions in total disease costs when compared with placebo. The total 2-year cost in untreated patients was £25 126, while infliximab treatment costs of £14 100 and other costs of £17 240 resulted in a net increase of £6214 (discounted by 6%) in infliximab recipients. The total gain in quality-adjusted life-years (QALY) with infliximab versus no treatment was estimated to be 0.175 over 2 years, giving an incremental cost per QALY gained of £35 400. If a 3% discount rate (costs and utilities) was used, the increase in cost was £6624, the QALY gained was 0.174 and the incremental cost per QALY gained was £38 100.[30]

4. Tolerability

Adverse events associated with infliximab therapy have been reviewed recently.[34] This section therefore focuses on adverse events in placebo-controlled trials of intravenous infliximab 5 mg/kg in patients with ankylosing spondylitis (see section 3 for study details).[18,19] Results from extension studies[22-24] of the 12-week trial[18] and data on the induction of antinuclear antibodies (ANA)[22,29] and double-stranded DNA autoantibodies (dsDNAa)[22] [autoantibodies associated with systemic lupus erythematosus] in patients with ankylosing spondylitis are also included. In addition, the results of a 2-year study in patients with ankylosing spondylitis (n = 16) receiving infliximab 5 mg/kg at 0, 2 and 6 weeks and thereafter at 6- or 8-week intervals are also discussed.[35]

- Infliximab was generally well tolerated by patients with ankylosing spondylitis, with most adverse events being of mild-to-moderate severity.[18,19] In ASSERT, 72% of placebo and 82% of infliximab recipients experienced adverse events.[19]
- Upper respiratory tract infection (URTI) was the most frequently reported adverse event in both placebo-controlled trials,[18,19] with an incidence in ASSERT in infliximab and placebo recipients of 13.9% versus 14.7%.[19] In ASSERT, adverse events occurring in more that 5% of patients and affecting more than twice as many infliximab as placebo recipients included pharyngitis, elevated serum liver enzyme levels and rhinitis (see figure 2).[19]
- Serious adverse events with infliximab treatment were uncommon.[18,19] In the 12-week trial, three infliximab, but no placebo, recipients had serious adverse events (systemic TB, allergic granulomatosis of the lung, transient leukopenia) and were withdrawn from the trial.[18] The patient who developed TB did not undergo tuberculin skin testing prior to starting infliximab therapy.[18]
- In ASSERT, serious adverse events (including pneumonia with leukocytosis and ganglioneuroma) were reported in 3.5% infliximab recipients, none of which led to discontinuation of study medication, and 2.7% placebo recipients.[19] Both treatment groups experienced the same incidence of infusion reactions (2.7%).[19] After 24 weeks, 40.7% of infliximab and 9.2% of placebo recipients had devel-

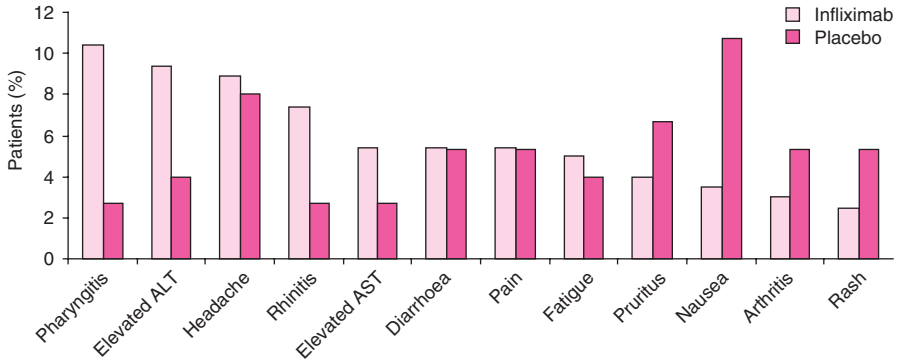

Fig. 2. Tolerability profile of infliximab in patients with active ankylosing spondylitis. Adverse events reported in ≥5% of either infliximab or placebo recipients by study end in the 24-week ASSERT (Ankylosing Spondylitis Study for the Evaluation of Recombinant infliximab Therapy) trial (n = 297).[19] Patients with ankylosing spondylitis received intravenous infusions of infliximab 5 mg/kg or placebo at 0, 2, 6, 12 and 18 weeks.

oped ANA while 12.7% of infliximab and none of the placebo recipients had developed dsDNAa titres.

- In the 2-year study,[35] ANA were induced in 73% of patients with ankylosing spondylitis receiving infliximab and dsDNAa were induced in 31% of infliximab recipients; however, all dsDNAa were of the IgM isotype and no symptoms or antibodies indicative of lupus were observed.[35]

- In the first extension phase of the 12-week trial (between weeks 13 and 54), the most commonly reported drug-related adverse events included liver function test (LFT) abnormalities (12% of patients), headache (9%), URTI (7%) and sinusitis (7%), with 9% of patients experiencing serious drug-related adverse events (including peripheral arthritis, hepatitis, LFT abnormalities and lupus-like rash).[22] Eight patients discontinued infliximab because of adverse events during this extension phase.[22]

- By week 54, 17 of 69 patients (25%) had ANA, although only three had musculoskeletal symptoms.[22] Four of 12 ANA-positive patients had slight-to-moderate elevations in dsDNAa titres, but no lupus symptoms.[22]

- In the second year of the extension phase, the most commonly occurring adverse events were URTI (17% of patients), rhinitis (13%) and herpes simplex infection (12%).[23] Two patients reported serious adverse events (infusion-related symptoms and musculoskeletal pain) that were possibly related to infliximab therapy, and three patients discontinued therapy because of adverse events.[23]

- In the third extension year, URTI (37%) and rhinitis (20%) continued to be the most common adverse events, along with diarrhoea (22%). Serious adverse events occurred in 13% of patients, but none were considered to be related to infliximab.[24]

5. Dosage and Administration

The recommended infliximab regimen in ankylosing spondylitis is an intravenous infusion of 5 mg/kg at weeks 0, 2 and 6 (administered over at least 2 hours) followed by maintenance infusions at 6-week intervals (US)[9] or 6- to 8-week intervals (Europe).[3]

Local prescribing information should be consulted for dosage reduction guidelines in patients experiencing toxicity, dosage recommendations in special populations, contraindications and precautions.

6. Infliximab in Ankylosing Spondylitis: Current Status

Infliximab is effective in the treatment of active ankylosing spondylitis. It is generally well tolerated, and improvements in disease state may be retained for up to 3 years with maintenance therapy.

Infliximab has been approved in the US for reducing signs and symptoms in patients with active ankylosing spondylitis[9] and in Europe for treatment in patients with severe axial ankylosing spondylitis and elevated serological markers of inflammatory activity who are unresponsive to conventional treatment.[3] In both the US and Europe, infliximab is also approved for the treatment of active Crohn's disease and rheumatoid arthritis.[3,9]

References

1. Sieper J, Braun J. Anti-TNF agents for the treatment of spondyloarthropathies. Expert Opin Emerg Drugs 2002; 7 (2): 235-46
2. Braun J, Sieper J. Biological therapies in the spondyloarthritides: the current state. Rheumatology (Oxford) 2004 Sep; 43 (9): 1072-84
3. European Agency for the Evaluation of Medicinal Products. Remicade [online]. Available from URL: www.emea.eu.int/humanndocs/Humans/EPAR/Remicade/Remicade.htm [Accessed 2005 Jan 10]
4. Keating GM, Perry CM. Infliximab: an updated review of its use in Crohn's disease and rheumatoid arthritis. Biodrugs 2002; 16 (2): 111-48
5. 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 Sep; 62 (9): 817-24
6. Braun J, Xiang J, Brandt J, et al. Treatment of spondyloarthropathies with antibodies against tumour necrosis factor α: first clinical and laboratory experiences. Ann Rheum Dis 2000; 59 Suppl. 1: i85-9
7. Gratacos J, Collado A, Filella X, et al. Serum cytokines (IL-6, TNF-α, IL-1β and IFN-γ) in ankylosing spondylitis: a close correlation between serum IL-6 and disease activity and severity. Br J Rheumatol 1994 Oct; 33 (10): 927-31
8. Zou JX, Braun J, Sieper J. Immunological basis for the use of TNFα-blocking agents in ankylosing spondylitis and immunological changes during treatment. Clin Exp Rheumatol 2002 Nov-Dec; 20 (6 Suppl. 28): S34-7
9. US Food and Drug Administration. Prescribing information: Remicade® (infliximab) for IV injection [online]. Available from URL: http://www.fda.gov/cder/foi/label/2004/103772_5077_lbl.pdf [Accessed 2005 Jan 10]
10. Wagner C, Mace K, deWoody K. Infliximab treatment benefits correlate with pharmacodynamic parameters in Crohn's disease patients. Digestion 1998; 59 Suppl. 3: 124-5
11. Zou J, Rudwaleit M, Brandt J, et al. Down-regulation of the nonspecific and antigen-specific T cell cytokine response in ankylosing spondylitis during treatment with infliximab. Arthritis Rheum 2003; 48 (3): 780-90
12. Baeten D, Vandooren B, De Rycke L, et al. Effect of infliximab treatment on T cell cytokine responses in spondylarthropathy: comment on the article by Zou et al. [letter]. Arthritis Rheum 2004; 50 (3): 1015-7
13. Yang C, Gu J, Rihl M, et al. Serum levels of matrix metalloproteinase 3 and macrophage colony-stimulating factor 1 correlate with disease activity in ankylosing spondylitis. Arthritis Rheum 2004 Oct; 51 (5): 691-9
14. Garrett S, Jenkinson T, Kennedy LG, et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994 Dec; 21 (12): 2286-91
15. Vandooren B, Kruithof E, Yu DT, et al. Involvement of matrix metalloproteinases and their inhibitors in peripheral synovitis and down-regulation by tumor necrosis factor α blockade in spondylarthropathy. Arthritis Rheum 2004 Sep; 50 (9): 2942-53
16. Boyle A, Tawadros R, Zhu Y, et al. Comparative pharmacokinetics of single and multiple-dose infliximab in Crohn's disease patients [abstract no. W1349]. Gastroenterology 2002 Apr; 122 Suppl. 1: A614-5. Plus poster presented at Digestive Disease Week and the 103rd Annual Meeting of the American Gastroenterological Association; 2002 May 19-23; San Francisco
17. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998 Sep; 41 (9): 1552-63
18. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 2002 Apr 6; 359: 1187-93
19. 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 2005 Feb; 52 (2): 582-91
20. Braun J, Baraliakos X, Golder W, et al. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. Arthritis Rheum 2003 Apr; 48 (4): 1126-36
21. Braun J, Landewé R, Hermann K-G, et al. The effect of infliximab therapy on spinal inflammation assessed by magnetic resonance imaging in a randomized, placebo-controlled trial of 279 patients with ankylosing spondylitis [abstract no. L21]. Presented at 68th Annual Meeting of the American College of Rheumatology; 2004 Oct 16-21; San Antonio [online]. Available from URL: http://www.rheumatology.org/annual/abstracts/search.asp [Accessed 2005 May 11]

22. 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 Aug; 48 (8): 2224-33

23. Braun J, Brandt J, Listing J, et al. Two year maintenance of efficacy and safety of infliximab in the treatment of ankylosing spondylitis. Ann Rheum Dis 2005 Feb; 64 (2): 229-34

24. Braun J, Baraliakos X, Brandt J, et al. Persistent clinical response to the anti-TNF-α antibody infliximab in patients with ankylosing spondylitis over 3 years. Rheumatology (Oxford) 2005 May; 44 (5): 670-6

25. Baraliakos X, Brandt J, Listing J, et al. Clinical response to withdrawal of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. Clin Exp Rheumatol 2004 Sep-Oct; 22 (5): 665

26. Stone M, Salonen D, Lax M, et al. Clinical and imaging correlates of response to treatment with infliximab in patients with ankylosing spondylitis. J Rheumatol 2001 Jul; 28: 1605-14

27. Stone MA, Payne U, Pacheco-Tena C, et al. Cytokine correlates of clinical response patterns to infliximab treatment of ankylosing spondylitis. Ann Rheum Dis 2004 Jan; 63 (1): 84-7

28. Breban M, Vignon E, Claudepierre P, et al. Efficacy of infliximab in refractory ankylosing spondylitis: results of a six-month open-label study. Rheumatology (Oxford) 2002 Nov; 41: 1280-5

29. Temekonidis TI, Alamanos Y, Nikas SN, et al. Infliximab therapy in patients with ankylosing spondylitis: an open label 12 month study. Ann Rheum Dis 2003 Dec; 62 (12): 1218-20

30. Kobelt G, Andlin-Sobocki P, Brophy S, et al. The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab (Remicade®). Rheumatology (Oxford) 2004 Sep; 43 (9): 1158-66

31. Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994 Dec; 21 (12): 2281-5

32. 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 Aug; 44 (8): 1876-86

33. Jenkinson TR, Mallorie PA, Whitelock HC, et al. Defining spinal mobility in ankylosing spondylitis (AS): the Bath AS Metrology Index. J Rheumatol 1994 Sep; 21 (9): 1694-8

34. Khanna D, McMahon M, Furst DE. Safety of tumour necrosis factor-α antagonists. Drug Saf 2004; 27 (5): 307-24

35. Ferraro-Peyret C, Coury F, Tebib JG, et al. Infliximab therapy in rheumatoid arthritis and ankylosing spondylitis-induced specific antinuclear and antiphospholipid autoantibodies without autoimmune clinical manifestations: a two-year prospective study. Arthritis Res Ther 2004; 6 (6): R535-43

Correspondence: *Dean M. Robinson,* Adis International Ltd, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz