

Infliximab in Ankylosing Spondylitis: A Prospective Observational Inception Cohort Analysis of Efficacy and Safety

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ABSTRACT. Objective. Infliximab, a neutralizing antibody to tumor necrosis factor- α , appears to be effective therapy in ankylosing spondylitis (AS), although treatment is costly and serious infections are an increasing concern. We investigated the efficacy and tolerability of infliximab in a prospective observational inception cohort of patients with nonsteroidal antiinflammatory drug-refractory AS seen in both university and community based practice. We also used a lower dose, 3 mg/kg, than has been evaluated to date in AS.

Methods. We included all consecutive patients with AS starting infliximab therapy 3 mg/kg IV at 0, 2, and 6 weeks and q 2 months between April 2000 and October 2001. Data were systematically collected at baseline, 14 weeks, and 1 year, or at withdrawal, and included demographic characteristics, Bath AS indexes (BASDAI, BASFI, BASGI, BASMI), adverse events, and reasons for withdrawal. Laboratory measures included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum matrix metalloproteinases (MMP) 1 and 3, and serum human cartilage glycoprotein-39 (YKL-40). The first 6 consecutive patients were also studied by several magnetic resonance sequences, including dynamic MRI with gadolinium augmentation of affected joints. Maximal rate of augmentation was determined at baseline and 84 days. Analysis was by intention-to-treat.

Results. Twenty-one patients (m:f = 17:4), mean age 42.5 years (range 24–66), mean disease duration 13.8 years (range 3–26), were studied: 13 had active peripheral synovitis at baseline. Mean followup was 47.5 weeks (range 10–77). Four patients withdrew, 2 for serious adverse events (septic osteomyelitis and severe hypersensitivity after 3 and 2 infusions, respectively), one for lack of efficacy, and one lost to followup. Three patients required an increased dose to 5 mg/kg after 14 weeks. Efficacy data were available on 17 patients at 14 weeks; mean BASDAI improved significantly from baseline (6.2) to 14 weeks (2.8) ($p < 0.001$), with 10 patients (58.8%) showing at least 50% improvement (range 0–99.6%). Significant reduction in mean BASFI (43.4%; $p < 0.001$), BASGI (44%; $p = 0.001$), ESR (55%; $p < 0.001$), and CRP (63.5%; $p = 0.01$) was evident. Complete remission of peripheral joint disease was seen in 5 of 11 (45.4%) patients evaluated at 14 weeks and maximal rate of MRI defined gadolinium augmentation was significantly decreased ($p = 0.04$). Reductions in serum YKL-40 and MMP-1 and 3 were nonsignificant, but significant correlations were observed between changes in BASDAI, ESR, CRP, and changes in serum levels of MMP-3 and YKL-40 ($p < 0.005$ to $p < 0.05$). Followup data on 8 patients completing 1 year of therapy revealed continued efficacy at a dose of 3 mg/kg every 8 weeks.

Conclusion. Infliximab appears to be effective and well tolerated for both axial and peripheral joint disease in AS even at lower doses than those examined to date. Suppression of markers of cartilage degradation/turnover commensurate with reductions in clinical and laboratory measures of disease activity suggests that these markers should be further validated as surrogates for structural damage in AS. Controlled trials are warranted to further assess the potential of this agent in ameliorating structural damage. (J Rheumatol 2002;29:959–65)

Key Indexing Terms:

INFLIXIMAB
THERAPY

ANKYLOSING SPONDYLITIS
INCEPTION COHORT

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Submitted July 26, 2001; revision accepted November 14, 2001.

The treatment of ankylosing spondylitis (AS) has undergone little change since the advent of nonsteroidal antiinflammatory

tory drugs (NSAID) several decades ago. Despite the recent introduction of cyclooxygenase 2 (COX-2) selective inhibitors¹, this therapeutic approach is still primarily symptomatic and there is little evidence that these agents influence progression of structural damage or longterm functional outcomes. There have also been several uncontrolled and controlled studies of second-line agents traditionally used in the management of rheumatoid arthritis (RA)²⁻⁴. Some studies have reported limited efficacy with salazopyrin, particularly in patients with concomitant peripheral joint inflammation^{5,6}. There is no convincing evidence, however, that these therapies might be useful for the axial component of AS. There have thus been few therapeutic options for patients with AS refractory to NSAID, estimated to represent 25% of the total AS population⁷.

Considerable therapeutic optimism has been generated by the recent introduction of 2 therapies that specifically target the proinflammatory cytokine, tumor necrosis factor- α (TNF- α), a chimeric human/mouse monoclonal antibody (infliximab) and a divalent soluble TNF receptor p75 IgG Fc fusion protein (etanercept). This followed recognition that TNF- α was a pivotal cytokine in perpetuating synovial inflammation in RA. Computer tomography (CT) guided biopsies of the sacroiliac joint in patients with spondyloarthropathy (SpA) have also revealed the presence of TNF- α mRNA and protein in inflamed synovium⁸. Further, overexpression of TNF- α in mice carrying a related murine transgene containing a deletion in the 3' regulatory region that controls translation of TNF protein results in a form of spondylitis resembling human disease⁹. There have now been several uncontrolled studies describing significant efficacy following administration of infliximab in patients with SpA^{10,11}. A preliminary report also describes substantial efficacy in a double blinded placebo controlled study¹². All these studies used a dose of infliximab (5 mg/kg per infusion) that is higher than currently recommended for the treatment of RA (3 mg/kg per infusion).

This therapeutic approach carries significant longterm cost implications, and there is also emerging evidence that the incidence of serious infections, specifically tuberculosis, is a dose dependent phenomenon. We examined the efficacy and tolerability of infliximab in a prospective observational inception cohort of patients with NSAID refractory AS seen in both university and community based practice. A further objective was to evaluate the efficacy of a substantially lower dose of infliximab (3 mg/kg per infusion) than hitherto examined in patients with SpA. Finally, there is as yet no evidence that this therapeutic approach might actually modify the progression of structural joint damage, and we therefore also examined surrogate markers of articular cartilage turnover/breakdown, specifically serum matrix metalloproteinases (MMP) 1 and 3 and serum human cartilage glycoprotein-39 (YKL-40). YKL-40 mRNA is absent from normal articular cartilage but is abundant in cartilage from

patients with RA¹³. It appears to play a role in cartilage remodeling and has been implicated as a possible autoantigen in RA¹⁴.

MATERIALS AND METHODS

Patients and study protocol. We included all consecutive patients with AS seen by the Alberta Capital Health Region rheumatologists (5 university based, 7 community based) between April 2000 and October 2001. Infliximab was administered according to the described RA regime¹⁵, i.e., a dose of 3 mg/kg intravenously (IV) at baseline, 2 weeks, and 6 weeks and then every 8 weeks, over a period of 2 h in a specialized IV administration outpatient clinic at the University of Alberta Hospital. Patients fulfilled the modified New York criteria for AS and were judged by the referring rheumatologist to have active disease despite maximum and/or tolerated doses of NSAID. Concomitant second-line therapy as well as prednisone was allowed. There were no stipulations for concomitant therapy prior to initiation with infliximab. Data were systematically collected at baseline, 14 weeks, and 1 year, or at withdrawal, and included demographic characteristics, the Bath AS Disease Activity Index (BASDAI)¹⁶, the Bath AS Functional Index (BASFI)¹⁷, the Bath AS Global Index (BASGI)¹⁸, and the Bath AS Metrology Index (BASMI)¹⁹. A 66 swollen joint count was performed, together with routine blood tests, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). All patients had a chest radiograph and tuberculin test at baseline. The first 6 consecutive patients had magnetic resonance imaging (MRI) studies, which included fat suppression sequences and dynamic imaging with gadolinium augmentation at baseline and 14 weeks. Patients were excluded from receiving infliximab if they had a history of chronic or recurrent serious infection or malignancy, or if clinical and laboratory examination showed abnormalities of clinical relevance.

Withdrawal and adverse events. Prior to withdrawal for lack of efficacy, patients were permitted an increase in dose of infliximab to 5 mg/kg per infusion if, in the opinion of the attending rheumatologist, clinical response was not apparent by 14 weeks or if a clinical response had been initially observed at the lower dose and was subsequently considered inadequate. All adverse events were recorded as they occurred according to severity and relationship to infliximab therapy.

Laboratory assessment. Antinuclear antibodies (ANA) were measured at baseline, 14 weeks, and 1 year. A positive test was defined as a titer $\geq 1:40$. Anti-DNA antibodies were measured in ANA positive individuals using both the *Critihidia luciliae* (KallestadTM, BioRad) and Millipore Filter assays at baseline, 14 weeks, and 1 year. Total serum MMP-1 and 3 were measured by ELISA (Biotrak, Amersham Pharmacia, Piscataway, NJ, USA). Human cartilage glycoprotein-39 (YKL-40) was also measured by ELISA (Metra Biosystems, Mountain View, CA, USA). These assessments were performed at baseline and at 14 weeks.

MRI scans were performed on 6 patients using a 1.5 Tesla magnet (Siemens Symphony) as described²⁰. Sequences included T1, T2 with fat saturation, and dynamic MRI with gadolinium augmentation (dMRI). Unilateral scans were performed on 4 knees and one ankle. Bilateral sacroiliac joints were scanned in one patient. Maximal rate (speed) of gadolinium augmentation was calculated for 3 regions of synovium per joint as described²⁰. Identical areas of synovium were analyzed on each baseline and followup scan.

The average maximal rate of augmentation per joint was then calculated. STIR sequences were visually assessed for presence and severity of joint effusion, synovial thickening, enthesopathy, bone erosion, bone marrow edema, hyaline cartilage changes, and periarticular inflammation. Patients returned for followup MRI at Day 84.

Statistical analysis. Wilcoxon's rank-sum test was used to determine the significance of the differences in mean values of outcome measures. Analysis was by intention-to-treat and Pearson correlations were computed between changes in disease activity and changes in serum levels of markers of articular cartilage degradation/turnover. All tests were 2 sided and $p < 0.05$ was considered statistically significant.

RESULTS

Twenty-one patients with AS in the Alberta Capital Health Region received at least one infusion with infliximab during the period of the special access program in Canada. Of these, 17 were men and 4 were women, mean age was 42.5 years (range 24–66) and mean disease duration was 13.8 years (range 3–26). Twenty were B27 positive (95.2%). Thirteen had active peripheral synovitis at enrolment [mean swollen joint count 2.2 (range 2–7)] and 5 were undergoing concomitant therapy with second-line agents [5 methotrexate (MTX), one salazopyrin] that had been stable for at least one year prior to therapy. Three had concomitant Crohn's disease, one had Reiter's, and 2 had psoriasis. At baseline most patients had active disease, as defined by a BASDAI score ≥ 4 , with a mean BASDAI of 6.3 (range 3.7–8.0) and mean CRP of 68.1 mg/l (range 0.5–175). Patients had significant impairment of function (mean BASFI 6.1, range 1.7–8.9).

Mean followup by October 2001 was 47.5 weeks (range 10–77) and 4 patients withdrew during the followup period, one for lack of efficacy, one lost to followup, and 2 for severe adverse events. One patient developed septic osteomyelitis of the talus with *Staphylococcus aureus* following the 3rd infusion of infliximab, and the second developed a severe hypersensitivity reaction after the 2nd dose of infliximab. This latter consisted of acute severe joint pains associated with intense itching. This patient had not been taking concomitant MTX therapy. Three patients required a dose increase to 5 mg/kg after 14 weeks, 2 after initially responding to the 3 mg/kg dose and one for lack of efficacy from the outset (no change in BASDAI and increase in swollen joint count at 14 weeks), even though improvement was evident on dMRI of this patient's knee (data not shown). This patient has had a further increase in dose to 6 mg/kg q 4 weeks for lack of efficacy after initially responding to 5 mg/kg (followup of 68 weeks). MTX therapy was also instituted in 2 patients after 14 weeks of infliximab therapy after inadequate responses at 3 mg/kg. Three patients reported discontinuing NSAID.

Efficacy data were available on 17 patients at 14 weeks. Mean BASDAI improved significantly from baseline, the mean value at 14 weeks being 2.8 ($p < 0.001$) (Table 1). Ten (58.8%) patients showed at least 50% improvement (range 0–99.6%). Two patients showed no improvement ($< 5\%$ decrease in BASDAI). Significant reductions in the means for the BASFI, BASGI, ESR, and CRP were also evident (Table 1). Axial pain (item 2 of the BASDAI) decreased from a mean of 7.8 to 3.0 by 14 weeks ($p < 0.001$). Reductions in swollen joint count did not achieve statistical significance, although 5 of 11 patients (45.4%) evaluated at 14 weeks had complete clinical resolution of peripheral synovitis. The patient who experienced an exacerbation subsequently responded to a higher dose of infliximab and the institution of MTX therapy.

Efficacy data were available on 8 patients after 1 year. Therapeutic responses observed at 14 weeks were maintained at 1 year (mean BASDAI 2.9, mean BASFI 3.3, mean BASGI 2.9). Six patients continue to receive 3 mg/kg q 8 weeks after a mean followup of 71.2 weeks (range 60–77). One patient continues taking 5 mg/kg (followup of 64 weeks) and one continues at 6 mg/kg q 4 weeks (followup 68 weeks). There were no withdrawals after 14 weeks and we did not record any further significant adverse events.

Five (23.8%) patients were ANA positive at baseline. No additional patients became ANA positive at 14 weeks or 1 year and no patient has developed anti-DNA antibodies.

The changes seen in ELISA for serum YKL-40, MMP-1, and MMP-3 were not significant (Table 1), although substantial reductions in serum levels were noted in several patients. Further analysis revealed significant correlations between reductions in the BASDAI, BASFI, ESR, and CRP and reductions in serum levels of MMP-3 and YKL-40 (Figure 1, Table 2).

The MRI protocol was successfully completed in 6 patients. A 29-year-old woman with late stage disease of the sacroiliac joints had focal areas of bony ankylosis. Although the scan revealed subtle evidence of active disease, none of the observed abnormalities altered after therapy. The 5 patients scanned with peripheral joint disease had marked improvement or resolution of effusion after therapy (Figure 2). Synovial thickening in the knees that was severe in 3 patients underwent marked improvement after treatment, as did periarticular inflammation in all 4 cases. Bone marrow edema was observed on baseline MRI in only 3 patients, but this had resolved in all 3 joints at followup. Damage to patellar hyaline cartilage was observed in 2 knees and this was the only measure that did not undergo any improvement.

Maximal rate of synovial augmentation was determined by analyzing 3 regions of interest on each MRI scan at baseline and at 14 weeks after the start of infliximab therapy. A total of 5 joints were examined, including 4 knees and one ankle. A significantly decreased maximal rate of synovial augmentation was noted following infliximab therapy (Table 1). Marked consistency was noted in the maximal rate of augmentation within the 3 regions of interest examined per joint with respect to degree, shape of slope, and response to treatment (data not shown). Assessment of other MRI outcome variables (e.g., magnitude of augmentation, time to plateau) was not considered reliable due to technical difficulty in defining the point of maximal augmentation and considerable variation between regions of interest within the same joint.

DISCUSSION

The results of this study indicate that infliximab is effective and well tolerated for both axial and peripheral joint disease in patients with AS referred from both university and

Table 1. Mean change in clinical and laboratory outcome measures in all patients with AS receiving infliximab at 14 weeks' followup. Data are mean \pm SD.

Outcome Measure	Baseline	14 Weeks	Change	p
BASDAI	6.2 \pm 1.4	2.8 \pm 2.2	-3.4 \pm 2.3	< 0.001
BASFI	6.1 \pm 2.0	3.4 \pm 2.2	-2.6 \pm 2.1	< 0.001
BASGI	7.1 \pm 1.7	4.0 \pm 2.4	-3.1 \pm 2.6	0.001
BASMI	3.6 \pm 2.5	2.9 \pm 2.8	-0.6 \pm 1.1	0.09
Swollen joint count*	2.7 \pm 2.4	1.2 \pm 3.0	-1.6 \pm 2.6	0.08
ESR	34.9 \pm 16.0	15.7 \pm 14.2	-19.3 \pm 16.9	< 0.001
CRP	75.5 \pm 61.8	27.6 \pm 52.6	-47.9 \pm 63.5	0.01
Hemoglobin	123.1 \pm 23.1	138.9 \pm 20.1	+15.8 \pm 16.3	0.002
Serum MMP-1*	10.53 \pm 7.6	6.74 \pm 3.6	-3.79 \pm 5.4	0.06
Serum MMP-3*	274.4 \pm 201.5	168.1 \pm 232.8	-106.4 \pm 220.8	0.16
Serum YKL-40*	207.3 \pm 158	213 \pm 243.8	+6 \pm 140.2	0.9
Maximal rate of gadolinium augmentation** (% increase per second over baseline value)	4.5 \pm 2.6	1.3 \pm 0.8	-3.2 \pm 2.2	0.04

* Data from 11 patients. ** Data from 5 patients.

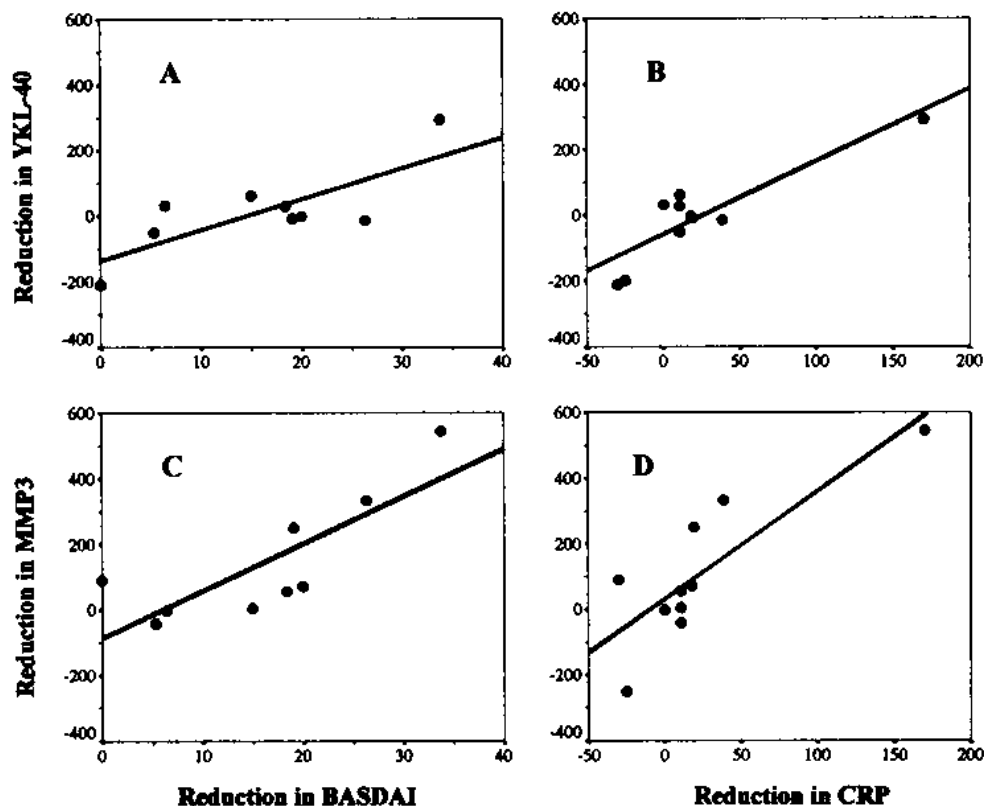


Figure 1. Regression line plotting correlation between the reduction in serum level of YKL-40 versus reduction in BASDAI score (A) and serum CRP (B); and reduction in serum level of MMP-3 versus reduction in BASDAI score (C) and serum CRP (D) in patients with AS after 14 weeks of therapy with infliximab.

community based practice. Hypersensitivity was not a concern despite a minority of patients who were taking concomitant MTX. Further, substantial efficacy was observed in doses currently recommended for the treatment of RA and substantially less than has been evaluated in SpA

to date. Suppression of markers of articular cartilage turnover/degradation, although not statistically significant for the entire cohort, correlated significantly with reduction in clinical and laboratory measures of disease activity, suggesting that they should be further validated as surro-

Table 2. Correlations between changes in measures of AS disease activity/function and changes in serum levels of YKL-40, MMP-1, and MMP-3 after 14 weeks of infliximab therapy.

	YKL-40	MMP-1	MMP-3
BASDAI	0.77*	0.23	0.80**
BASFI	0.70*	0.02	0.71*
BASGI	0.40	-0.11	0.72*
ESR	0.76*	-0.13	0.64*
CRP	0.88***	0.05	0.83***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$.

gates for structural damage in AS. Nevertheless, the occurrence of severe adverse events highlights the importance of systematic, prospective, continued surveillance of this and similar therapies and, in particular, heightened vigilance for the possibility of serious infections.

The population studied was fairly typical of patients seen in routine clinical practice, with the exception that considerably more patients had active peripheral synovitis and were undergoing concomitant therapy with MTX. This could reflect a selection bias in that disease activity is more difficult to discern in patients with purely axial compared to those with concomitant peripheral synovitis. Consequently,

one might expect that such patients would be more readily referred for costly therapy of limited availability. In addition, although the mean baseline value for the BASDAI was very similar to that noted in previous reports evaluating infliximab in SpA, it has not been shown that the BASDAI reliably discriminates between inflammatory and noninflammatory causes of back pain, and it is therefore still of questionable value as an inclusion criterion for selecting patients with active disease for clinical trials. This contrasts with the more reliable requirement for a specified number of swollen joints for inclusion in clinical trials of RA. Selecting patients with purely axial forms of disease for therapy with infliximab may be facilitated by dMRI with gadolinium augmentation showing enhancement indicative of active disease. This approach requires further study and validation.

The efficacy data noted in this cohort were rather similar to those reported in both uncontrolled and controlled trials¹⁰⁻¹² with improvement in disease activity of at least 50% in a majority of patients by 14 weeks, although some patients required an increase in dose from 3 to 5 mg/kg after 14 weeks, which resembles our findings in an inception cohort of RA patients receiving infliximab in the Alberta Capital Health Region (unpublished observations). However, this degree of efficacy was noted with a lower

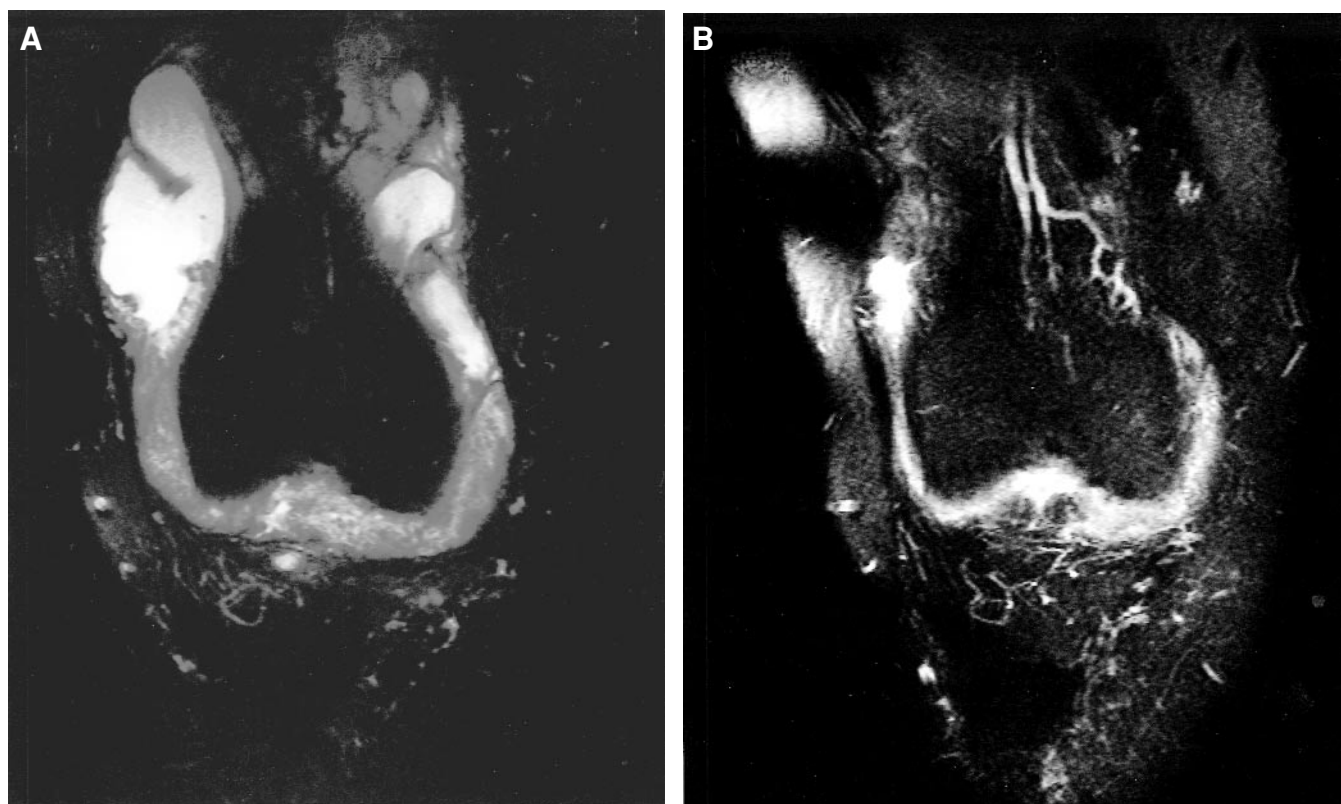


Figure 2. MRI of a 60-year-old woman with a 26 year history of AS and bilateral knee synovitis unresponsive to intraarticular steroids. A. Coronal T2 TSE with fat saturation (TR 4000, TE 96 ms) at the level of the trochlear groove — pretreatment baseline. This anterior image shows extensive synovial thickening along the medial, lateral, and anterior borders of the femoral condyles. A very large joint effusion fills the medial and lateral reflections and suprapatellar bursa. B. Coronal T2 TSE with fat saturation, identical location — posttreatment. Synovial thickening has dramatically improved and effusion has almost resolved.

dose of infliximab than used in other published trials of SpA and clearly supports the practice of initiating therapy in AS with the same dosing regime as currently recommended for RA. The occurrence of 2 serious adverse events, one being septic osteomyelitis and the other a severe hypersensitivity reaction, reinforces the prudence of this approach. Additional reports in SpA and RA have also raised concerns regarding serious chronic infections, specifically tuberculosis, that appear to be dose related²¹. Two cases of tuberculosis were noted shortly after initiation of infliximab therapy in a recent controlled evaluation in AS¹².

One report documented a high incidence of ANA in patients receiving infliximab for SpA²². Prospective histopathological and immunohistochemical evaluation of synovial biopsies in these patients also revealed progressive B cell infiltration that was not observed in patients with RA. In contrast, none of our patients developed ANA during therapy and none had anti-DNA antibodies. This may reflect the use of lower doses of infliximab, although this requires further followup.

Dynamic MRI with gadolinium augmentation is currently being evaluated as an outcome tool for assessing the degree of synovial inflammation in patients with RA²³. It has also been shown to be useful in detecting early sacroiliitis and revealed responsiveness to change in patients receiving CT guided cortisone injections for treatment of active sacroiliitis²⁴. We have described the value of this technique in detecting significant amelioration of peripheral synovitis in SpA patients treated with pamidronate²⁰. This report confirms the sensitivity of this method for confirming significant improvement of disease activity in patients receiving infliximab. Of several MRI outcome measures examined in this study, the maximal rate of gadolinium augmentation was associated with the highest degree of consistency between different regions of interest within the same joint and led to the least problems in interpretation²⁵. This measure should be further validated as an outcome tool for clinical trials in both AS and RA.

Infliximab appears to be as efficacious for AS in routine clinical practice as observed in clinical trials. It seems appropriate, however, to initiate therapy with the dose currently recommended for the treatment of RA, 3 mg/kg. In view of the costs, there should be further work evaluating more stringent selection criteria for treatment, incorporating not only clinical measures but also perhaps MR and serum markers of articular cartilage degradation/turnover. Further controlled trials are warranted to assess the potential of this agent to ameliorate structural damage.

REFERENCES

1. Dougados M, Behier JM, Jolchine I, et al. Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal anti-inflammatory drug. *Arthritis Rheum* 2001;44:180-5.
2. Ostendorf B, Specker C, Schneider M. Methotrexate lacks

efficacy in the treatment of severe ankylosing spondylitis compared with rheumatoid and psoriatic arthritis. *J Clin Rheumatol* 1998;4:129-36.

3. Steven MM, Morrison M, Sturrock RD. Penicillamine in ankylosing spondylitis: a double blind placebo controlled trial. *J Rheumatol* 1985;12:735-7.
4. Creemers MCW, van Riel PLCM, Franssen JAM, van de Putte LBA, Gribnau FWJ. Second-line treatment in seronegative spondyloarthropathies. *Semin Arthritis Rheum* 1994;24:71-81.
5. Dougados M, van der Linden S, Leirisalo-Repo M, et al. Sulfasalazine in the treatment of spondyloarthropathy: A randomized, multicentre, double-blind, placebo-controlled study. *Arthritis Rheum* 1995;38:618-27.
6. Clegg DO, Reda DJ, Weisman MH, et al. Comparison of sulphasalazine and placebo in the treatment of ankylosing spondylitis. *Arthritis Rheum* 1996;39:2004-12.
7. Amor B, Dougados M, Khan, MA. Management of refractory ankylosing spondylitis and related spondyloarthropathies. *Rheum Dis Clin North Am* 1995;21:117-28.
8. 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.
9. Crew MD, Effros RB, Walford RL, Zeller E, Cheroutre H, Brahn E. Transgenic mice expressing a truncated *Peromyscus leucopus* TNF- α gene manifest an arthritis resembling ankylosing spondylitis. *J Interferon Cytokine Res* 1998;18:219-25.
10. Van den Bosch F, Kruijthof E, Baeten D, De Keyser F, Mielants H, Veys EM. Effects of loading dose regimen of three infusions of chimeric monoclonal antibody to tumor necrosis factor α (infliximab) in spondyloarthropathy: an open pilot study. *Ann Rheum Dis* 2000;59:428-33.
11. Brandt J, Haibel H, Cornely D, et al. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor α monoclonal antibody infliximab. *Arthritis Rheum* 2000;43:1346-52.
12. Brandt J, Alten R, Burmester G, et al. Three months results of a double-blind placebo controlled phase III trial of infliximab in active ankylosing spondylitis [abstract]. *Ann Rheum Dis* 2001;60 Suppl 1:61.
13. Hakala BE, White C, Recklies AD. Human cartilage gp-39, a major secretory product of articular chondrocytes and synovial cells, is a mammalian member of a chitinase protein family. *J Biol Chem* 1993;268:25803-10.
14. Baeten D, Boots AMH, Steenbakkers PGA, et al. Human cartilage gp-39+, CD16+ monocytes in peripheral blood and synovium: Correlation with joint destruction in rheumatoid arthritis. *Arthritis Rheum* 2000;43:1233-43.
15. Maini R, St. Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumor necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;354:1932-9.
16. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gasford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: The Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;21:2286-91.
17. 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;21:2281-5.
18. Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Global Score (BAS-G). *Br J Rheumatol* 1996;35:66-71.
19. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. *J Rheumatol* 1994;21:1694-8.

20. Maksymowych WP, Lambert R, Jhangri GS, et al. Clinical and radiological amelioration of refractory peripheral spondyloarthritis by pulse intravenous pamidronate therapy. *J Rheumatol* 2001;28:144-55.
21. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor α -neutralizing agent. *N Engl J Med* 2001;345:1098-104.
22. Baeten D, Kruithof E, van den Bosch F, et al. Immunomodulatory effects of anti-tumor necrosis factor α therapy on synovium in spondyloarthropathy: histologic findings in eight patients from an open-label pilot study. *Arthritis Rheum* 2001;44:186-95.
23. Ostergaard M, Klarlund M, Lassere M, et al. Interreader agreement in the assessment of magnetic resonance images of rheumatoid arthritis wrist and finger joints — an international multicenter study. *J Rheumatol* 2001;28:1143-50.
24. Braun J, Bollow M, Seyrekbasan F, et al. Computed tomography guided corticosteroid injection of the sacroiliac joint in patients with spondyloarthropathy with sacroiliitis: Clinical outcome and followup by dynamic magnetic resonance imaging. *J Rheumatol* 1996;23:659-64.
25. Verstraete KL, De Deene Y, Roels H, Dierick A, Uyttendaele D, Kkinnen M. Benign and malignant musculoskeletal lesions: Dynamic contrast-enhanced MR imaging — parametric “first-pass” images depict tissue vascularization and perfusion. *Radiology* 1994;192:835-43.