Treatment of Refractory Inflammatory Monoarthritis in Ankylosing Spondylitis by Intraarticular Injection of Infliximab

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ABSTRACT. ***Objective.*** We describe a series of cases to evaluate the effect of intraarticular infliximab in patients with ankylosing spondylitis (AS) with treatment-resistant arthritis, and to consider whether longterm treatment with intravenous infliximab could be avoided in these patients.

Methods. Three patients, fulfilling the New York criteria for AS, had relapsing arthritis of the knee, despite nonsteroidal antiinflammatory drugs, sulfasalazine, and multiple intraarticular (IA) injections of corticosteroids. Since the axial disease or other locomotor manifestations did not justify administration of systemic tumor necrosis factor-α (TNF-α) blocking agents, an IA injection of 100 mg infliximab was administered. The primary endpoint was to examine the efficacy and safety of IA injection of infliximab in AS patients with therapy-refractory arthritis. Before and 4 weeks after IA injection the following variables were evaluated: degree of swelling and tenderness of the affected joint, number of cells/mm^3 after joint fluid examination, Bath Ankylosing Spondylitis Disease Activity Index, erythrocyte sedimentation rate, and C-reactive protein. In all 3 cases magnetic resonance imaging (MRI) was performed before injection and 4 weeks after injection.

Results. Clinical and biological variables and the MRI findings clearly improved. Remission of the peripheral arthritis was maintained up to 4 months in the first patient and up to 3 months in both others. No important side effects were noted.

Conclusion. We observed a beneficial effect of IA infliximab in refractory arthritis in patients with AS. This procedure could be considered an effective and safe treatment for therapy of refractory monoarthritis in AS and an alternative for parenteral TNF-blocking therapy. (J Rheumatol 2006;33:82–5; First Release: Nov 15, 2005)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS INFLIXIMAB INTRAARTICULAR

Several observations strongly implicate tumor necrosis factor-α (TNF-α) in the pathogenesis of ankylosing spondylitis (AS) and suggest the therapeutic potential of anti-TNF-α agents in this rheumatic disorder. Significantly higher TNF-α serum levels have been found in patients with AS versus patients with noninflammatory low back pain, although the cytokine concentration did not correlate with laboratory or clinical measures of disease activity[1]. High amounts of TNF-α messenger RNA[2] were detected in sacroiliac joint biopsy specimens from patients with AS. Randomized placebo controlled studies with infliximab in patients with AS[3] and other forms of spondyloarthropathy (SpA)[4] have demonstrated the effectiveness of this drug (at a dosage of 5 mg/kg every 6 or 8 weeks) based on clinical and biological variables. Clinical improvement in all disease variables, including axial inflammation, peripheral enthesitis, and peripheral arthritis, was significant, and this effect was maintained for more than one year[5,6]. Recently, however, it was shown that stopping infliximab infusions resulted in relapse of disease in most patients[7]; thus it can be concluded that TNF-α-blocking agents in AS will probably be necessary for many years or even permanently.

In a number of patients with AS, peripheral arthritis can be the dominant manifestation, without significant axial disease. This peripheral arthritis can be successfully treated with nonsteroidal antiinflammatory drugs (NSAID) or with intraarticular (IA) injections of corticosteroids, but in some cases the arthritis is refractory to treatment and symptoms persist.

In a previous study in 5 patients, IA infliximab was found to be effective and safe in patients with rheumatoid arthritis (RA) with refractory arthritis[8].

We describe a series of cases in order to evaluate the effect of IA infliximab in patients with AS with treatment-resistant arthritis, and to consider if longterm treatment with intravenous infliximab could be avoided in these patients.

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Accepted for publication September 20, 2005.

MATERIALS AND METHODS

Three patients fulfilling the New York criteria for AS[9] with persistent arthritis of the knee were studied. All 3 patients were being treated with NSAID, sulfasalazine (SSZ) [in 2 cases methotrexate (MTX) was temporarily administered], and multiple IA injections of corticosteroids. Nevertheless their arthritis relapsed and persisted, together with increased inflammatory serum measures and increased disease activity index measures (Bath Ankylosing Spondylitis Disease Activity Index, BASDAI > 4).

Since their axial disease or other locomotor manifestations did not indicate administration of systemic TNF-α-blocking agents, IA injection of 100 mg infliximab was administered. The primary endpoint was to examine the efficacy and safety of IA injection of infliximab in patients with AS with therapy-refractory arthritis. Current treatment with NSAID and SSZ was maintained.

Patients with a history of chronic infectious disease, positive tuberculin skin test, abnormal chest radiograph, or family history for tuberculosis were excluded from the study. Each patient had a complete physical and laboratory evaluation before and 4 weeks after IA injection. The following variables were evaluated before and 4 weeks after IA injection: degree of swelling and tenderness of the affected joint (no swelling or pain 0, mild 1, moderate 2, severe 3), the number of cells/mm^3 after joint fluid examination (in case synovitis was clinically present), BASDAI (1–10 scale), erythrocyte sedimentation rate (ESR, mm/h), and C-reactive protein (CRP, mg/dl). In all 3 cases magnetic resonance imaging (MRI, contrast enhanced T1 weighted scan with fat suppression) was performed before and 4 weeks after IA injection.

The 3 patients gave informed consent for this treatment, and approval was obtained from the ethics committee at St. Augustinus Hospital.

RESULTS

Case Reports

Patient 1 is a 27-year-old woman who presented in 2001 with inflammatory low back pain and swelling of the right knee. She had no other complaints. On clinical examination decreased lumbar mobility (Schober index 10/11 cm) and evident monosynovitis of the right knee were found. Laboratory findings revealed an increased CRP (2.74 mg/dl) and ESR (30 mm/h). Rheumatoid factor and antinuclear antibodies were negative. She was HLA-B27-positive. Radiography of the sacroiliac joints showed bilateral stage 2 sacroiliitis, and the diagnosis of AS was made. She was treated with NSAID for several months and an IA corticosteroid injection was given in the right knee. Her inflammatory back pain subsided, but the inflammatory monosynovitis of her right knee [white blood cell-synovial fluid (WBC-syn) 5165/mm^3] reappeared regularly. At this time SSZ 3 g daily was started. Since monosynovitis persisted under this treatment, SSZ was stopped and MTX 10 mg weekly was started. The synovitis of the right knee relapsed frequently under this treatment, even after MTX dose was increased to 15 mg weekly. After one year MTX was stopped and SSZ restarted. In the following months synovitis of her right knee relapsed and corticosteroid injections were needed sometimes 2 or 3 times a month.

Patient 2 is a 24-year-old man with inflammatory low back pain since early 2004. His lumbar mobility (Schober index 10/12.5 cm) was decreased, laboratory findings showed an elevated CRP (2.44 mg/dl), and radiography showed bilateral sacroiliitis, stage 2. He was first treated with NSAID. In June 2004 he developed monosynovitis of the right knee. SSZ 2.5 g daily was started. Several IA corticosteroid injections were given, but since the synovitis persisted, MTX up to 15 mg weekly was added. Despite combination therapy the inflammatory (WBC-syn 10,000/mm^3) monosynovitis of his right knee persisted and needle aspiration and drainage followed by corticosteroid injection was needed almost weekly.

Patient 3 is a 48-year-old man in whom AS diagnosis was made in 2001 based on clinical findings of decreased lumbar mobility (Schober index 10/12 cm) and synovitis of the right knee and left wrist; on laboratory results (CRP 2.1 mg/dl); and on radiographic findings (sacroiliitis stage 3–4). He was successfully treated with NSAID and SSZ 2 g daily until October 2004. Then he developed a very refractory monosynovitis of the right knee. In a period of 4 months several IA corticosteroid injections were needed (required weekly during one month) without result (WBC-syn 20,760/mm^3).

In these 3 patients very tender swelling of the knee with decreased mobility refractory to treatment was seen. Laboratory investigation showed elevated inflammatory serum variables. Before treatment in all 3 cases MRI showed a large amount of synovial fluid and a marked proliferation and thickening of synovial membrane (Figure 1); in Patient 2 also 2 small focal bone lesions were noted and in Patient 3 more extensive damage to the cartilage was seen. Radiographs were read by independent radiologists who received only information about diagnosis of AS. The BASDAI was significantly increased in all 3 cases (Table 1).

At this time we decided to give these 3 patients IA infliximab 100 mg in one injection after local anesthesia. The patients were reevaluated after 4 weeks. All 3 felt generally much better. No adverse reactions were noted. The arthritis of the knees had completely subsided (no pain and no swelling) and the mobility was restored. The inflammatory serum variables normalized (Table 1). Knee MRI revealed a decrease in synovial thickening and in intraarticular fluid (Figure 2). The BASDAI score decreased significantly (Table 1).

DISCUSSION

TNF-α-blocking agents, and especially infliximab given intravenously, have a rapid effect and significantly improve all clinical variables, including axial inflammation, peripheral enthesitis, and peripheral arthritis[3,4].

By performing needle arthroscopy before and after infliximab treatment, Baeten, *et al* demonstrated that the clinical benefit is paralleled by restoration of immunological alterations such as impaired Th1 cytokine profile, expression of vascular cell adhesion molecule-1 in the synovial membrane, the infiltration by CD163-positive macrophages, and high HLA-DR expression in the synovium[10,11].

A considerable number of patients with AS can be suc-

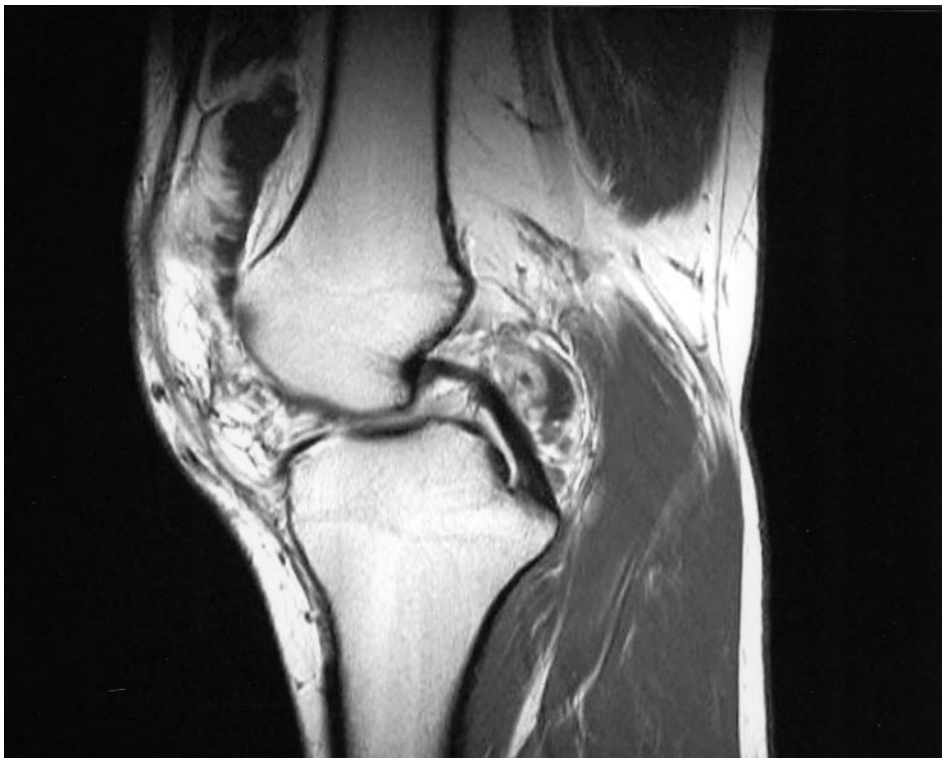

Figure 1. Contrast enhanced T1 weighted sagittal MRI scan without fat suppression reveals diffuse enhancing synovial thickening and fluid collection.

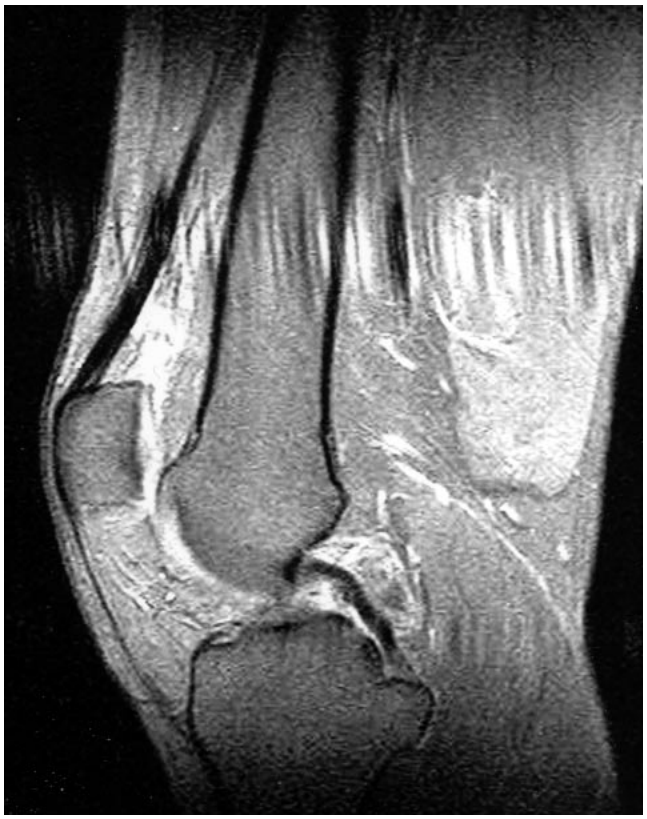

Figure 2. T1 weighted sagittal MRI scan with fat suppression shows decrease of synovial enhancement and thickening and fluid collection, after IA infliximab administration.

Table 1. Clinical, biological, and radiological data before and after intraarticular injection of infliximab in 3 patients.

	Before Injection			After Injection		
	P1	P2	P3	P1	P2	P3
Degree of swelling in the joint (0–3)	3	3	3	0	0	1
Degree of tenderness of the joint (0–3)	3	3	2	1	0	0
BASDAI score	7.6	8.8	6.7	0.8	3.3	1.7
Erythrocyte sedimentation rate, mm/h	30	6	2	18	2	2
C-reactive protein, mg/dl	2.74	2.44	1.5	1	0.1	0.6
MRI right knee						
Intraarticular fluid	+++	+++	+++	+/–	+	+
Synovial thickening	+++	+++	+	+	+/–	+
Synovial fluid total WBC, cells/mm^3	5,165	10,000	20,760	ND	ND	ND
Polymorphonuclear cells, %	69	41	74	ND	ND	ND
Lymphocytes, %	6	ND	14	ND	ND	ND
Macrophages, %	25	ND	12	ND	ND	ND

P: patient; WBC: white blood cell count; ND: not done.

cessfully treated with conventional agents, such as NSAID and sulfasalazine. Since infliximab treatment is expensive and since different side effects, mostly infectious, have been reported, these patients should not be treated by TNF-α blockers. Moreover, it was reported that in almost all AS

patients in which infliximab treatment was stopped, a relapse of disease occurred[7], meaning that this treatment should probably be given permanently. Some patients with AS have relatively minimal axial inflammatory manifestations that can be controlled by classical NSAID, but these patients may suffer from therapy-resistant peripheral arthritis, causing important inflammatory pain and disability.

The efficacy of IA infliximab injection was demonstrated in 2 studies with, respectively, 3[12] and 5 patients with RA[8]. In 5 patients with axial AS, IA injection with infliximab in the sacroiliac joint was effective[13]. In further case reports concerning different pathologies, the use of IA infliximab is also mentioned, with variable success[14-16].

In our 3 patients with AS and therapy-resistant monoarthritis of the knee, IA injection of 100 mg infliximab clearly improved their clinical manifestations, biological inflammatory variables, and MRI findings. IA injection of infliximab also resulted in systemic improvement, with a significant reduction of the BASDAI and serum inflammatory variables. Remission of peripheral arthritis was maintained up to 4 months in the first patient and up to 3 months in the 2 others. No significant side effects were noted.

Our report demonstrates the beneficial effect of IA infliximab in refractory arthritis in patients with AS and confirms results of a recently published case report[14].

This procedure could be considered an effective and safe treatment for therapy of refractory monoarthritis in patients with AS and an alternative for parenteral TNF-blocking therapy.

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