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The Treatment of Disc Herniation-Induced Sciatica With Infliximab

Results of a Randomized, Controlled, 3-Month Follow-up Study

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Study Design. A randomized controlled trial.

Objectives. To evaluate the efficacy of infliximab, a monoclonal antibody against tumor necrosis factor (TNF)-α in a randomized controlled setting.

Summary of Background Data. Recently, we obtained encouraging results in an open-label study of infliximab in patients with disc herniation-induced sciatica. Furthermore, the results of experimental studies support the use of infliximab in sciatica. Therefore, we initiated a randomized, controlled trial (FIRST II, Finnish Infliximab Related STudy) to confirm the efficacy of a single infusion of infliximab for sciatic pain.

Methods. Inclusion criteria were unilateral moderate to severe sciatic pain with an MRI-confirmed disc herniation concordant with the symptoms and signs of radicular pain. Patients had to be candidates for discectomy, as evaluated by an independent orthopedic surgeon. Forty patients were allocated to a single intravenous infusion of either infliximab 5 mg/kg or placebo. Assessments at baseline and various time points included clinical examination with measurement of straight leg raising restriction; questionnaires related to subjective symptoms (leg and back pain by 100-mm visual analog scale, Oswestry disability); sick leaves; number of discectomies; and adverse effects possibly related to treatment. The primary endpoint was a reduction in leg pain from baseline to 12 weeks, which was analyzed using a Mann-Whitney U test and repeated-measures analysis.

Results. A significant reduction in leg pain was observed in both groups, with no significant difference between treatment regimens. Similar efficacy was observed between treatment groups for secondary endpoints. Seven patients in each group required surgery. No adverse effects related to treatment were encountered.

Conclusions. The results of this randomized trial do not support the use of infliximab for lumbar radicular pain in patients with disc herniation-induced sciatica.

Key words: lumbar radicular pain, sciatica, disc herniation, cytokine, TNF, infliximab, randomized controlled trial. **Spine 2005;30:2724–2728**

Sciatic pain is defined as radicular pain radiating from the back into the dermatome of the affected nerve root along the femoral or sciatic nerve trunk.[1] The most common cause is herniation of the intervertebral disc, which typically compresses either an L5 or S1 nerve root with pain radiation below the knee of the ipsilateral leg. Surgery is commonly regarded as the only effective treatment modality for sciatica.[2,3]

Knowledge of the pathophysiology of sciatica has increased during the last decade, and it is now understood that, in addition to mechanical compression, an inflammatory component is involved in the pathophysiology of sciatica.[4–6] Recently, the pivotal role of tumor necrosis factor (TNF)-α in nucleus pulposus-induced nerve root damage was revealed.[7,8] In Europe, infliximab, a chimeric monoclonal antibody against TNF-α, is indicated for use in patients with rheumatoid arthritis, ankylosing spondylitis, and Crohn's disease. Our preliminary open-label study suggested that infliximab is effective in herniated nucleus pulposus-induced sciatica.[9] Ten patients with disc herniation confirmed by magnetic resonance imaging (MRI) and acute or subacute (*i.e.*, lasting 2–12 weeks) sciatic pain concordant with radiologic findings received a single intravenous infusion of infliximab 3 mg/kg. Three hours after the initiation of the infusion, the mean leg pain had decreased by 49% from pretreatment values and by 66% at 1 week. At the 3-month assessment, 9 patients were free of symptoms, and no adverse events attributed to treatment were observed. This treatment effect warranted further study in a randomized controlled trial, called FIRST II (Finnish Infliximab Related STudy), to confirm the efficacy of infliximab in sciatica.

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■ Patients and Methods

Patients. Patients were recruited at two Finnish centers, Oulu University Hospital and ORTON Orthopedic Hospital, Helsinki. Centocor B.V. (Leiden, The Netherlands) funded the trial and provided the study agent. The study was approved by the Oulu University Hospital ethics committee. Before any study procedures were performed, patients signed an informed consent.

To be eligible for enrollment in this trial, patients (at least 18 years of age) had to be candidates for discectomy according to the Agency for Health Care Policy and Research rules.[10] An orthopedic surgeon, independent to the study and blinded to treatment, confirmed eligibility for surgery at baseline and assessed the need for surgery during follow-up on the basis of the patient's condition and the imaging findings. Patients had to display a disc herniation on MRI concordant with related clinical signs and symptoms of radicular pain, with a duration of symptoms ranging from 2 to 12 weeks and neural entrapment (straight leg raising [SLR] $\leq 60°$) with either a short-term (2–4 weeks) severe or long-term (4–12 weeks) moderate leg pain. Patients also had to be receiving nonsteroidal anti-inflammatory agents at the recommended minimum dose for at least 2 weeks before study entry.

Exclusion criteria included the need for emergency surgery; history of back surgery; ongoing pregnancy; serious infections in the previous 3 months; active or latent tuberculosis; documented human immunodeficiency virus infection; active hepatitis; current severe, progressive or uncontrolled comorbidities (*e.g.*, hepatic, neurologic, or cerebral disease including demyelinating diseases such as multiple sclerosis); prior use of infliximab; prior use of human/murine recombinant products; treatment with any other therapeutic agent targeted at reducing TNF-α (*e.g.*, pentoxifylline, thalidomide, etanercept) or any systemic immunosuppressants within the previous 3 months; concomitant congestive heart failure; known recent substance abuse; presence of a transplanted organ; history of lymphoproliferative disease; and malignancy within the past 5 years.

Methods. Patients were informed of the possible side effects of infliximab and were screened for tuberculosis (which included a detailed disease and exposure history, a tuberculin test, and a chest radiograph), infections (which included laboratory evaluations of hemoglobin and leukocyte counts, erythrocyte sedimentation rate [ESR], and C-reactive protein [CRP]), and concurrent hepatic disease(s) (which included an evaluation of liver transaminases [ALT, AST] and bilirubin). The clinical examination included a medical history that collected demographic data, concomitant medication(s), and both general (vital signs) and disease-specific information (SLR, lumbar flexion, side bending, tendon reflexes, manual motor and sensory testing). Patient-recorded subjective symptom assessments included the 100-mm Visual Analog Scale for leg and back pain, the Oswestry back-related disability index, and the number of sick leave days due to the current sciatic episode.

After eligibility was confirmed and signed informed consent was obtained, patients were allocated to treatment groups using random number tables with a random variation of block sizes of four and six at both centers. A pharmacist prepared the intravenous (IV) solutions approximately 1 hour before the scheduled infusion. Patients received a single IV infusion of either infliximab 5 mg/kg or placebo (saline) over a 2-hour period, with vital sign assessments conducted throughout the infusion. Leg and back pain was assessed 3 hours after the initiation of the infusion and by phone on day 1 after the infusion. The clinical examination was repeated after the cessation of the infusion. Follow-up assessments (including clinical examinations and subjective symptom assessments) were performed at 1 week, 2 weeks, 1 month, and 3 months after the infusion. Additionally, the occurrence of side effects and the number of discectomies were monitored and recorded.

Statistics. The primary endpoint was the reduction of leg pain through 12 weeks, as measured by the 100-mm Visual Analog Scale, for infliximab-treated patients compared with placebo-treated patients. Secondary endpoints included between-group comparisons of back pain reduction, Oswestry disability, improvement of SLR restriction, differences in the number of days on sick leave, and the number of discectomies. The change in leg and back pain from baseline to 12 weeks was truncated to zero (0%) for patients who had undergone discectomies. To asses the impact of the truncation to zero, a secondary analysis was performed using the last-value-carried-forward method in which postsurgery data were replaced by the last available score before the discectomy. The decision to perform both analyses was made before unblinding of the trial and before starting the data analyses. This approach was also used for Oswestry disability and SLR restriction.

The differences between continuous variables were compared with the Mann-Whitney U test or Student's t test for normally distributed variables (age, height, weight, and duration of symptoms). A Fisher's exact test or χ^2 test was used for categorical variables. A higher reduction in patients receiving a single infusion of infliximab reaching statistical significance with a two-sided P value of <0.05 would have established the efficacy of infliximab. Leg and back pain, Oswestry disability, and SLR restriction were also analyzed using repeated-measures analysis with a general linear mixed model with fixed times and covariates, including the baseline value of the variable of interest. In these analyses, last-value-carried-forward method was applied for postoperative values. All analyses were performed on an intention-to-treat basis.

■ Results

Patients

Patients were recruited between December 2002 and November 2003. Of the 97 patients screened at the two centers, 56 were excluded and 41 were randomized to either treatment group. One patient had abnormal liver function tests and was excluded after randomization but before receiving an infusion. In the final study population, 21 of 40 patients were allocated to the infliximab group and 19 to the placebo group (Figure 1; Table 1). The mean age and gender distribution of the excluded patients was similar to the baseline characteristics of the final study population described in Table 1. Twenty-one patients received infusions at the Oulu University Hospital and 19 at ORTON Orthopedic Hospital in Helsinki. At baseline, there were no significant differences between the two treatment groups. However, before the infusion, patients in the placebo group had a higher degree of SLR restriction compared with the infliximab group (35° *vs.* 45° respectively; $P = 0.018$), although subjective symptoms were similar between groups (Table 1).Two patients in the infliximab group had an SLR value outside the inclusion

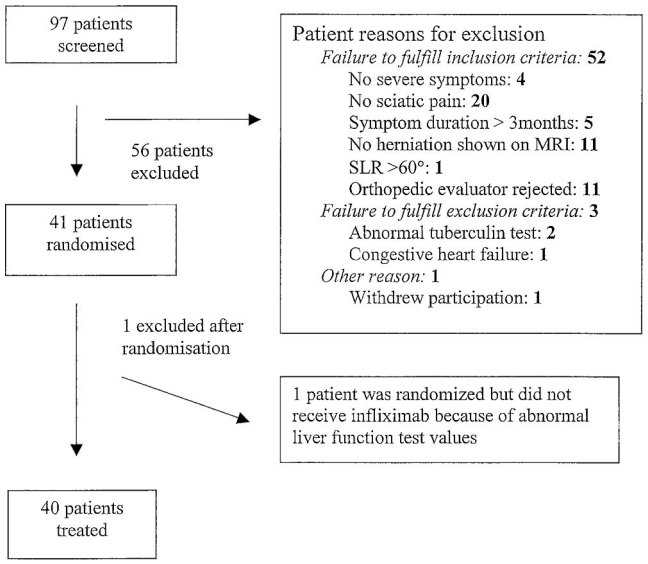

Figure 1. Patient flow-chart.

Table 1. Baseline Characteristics of the Study Population Prior to Infusion of Study Agent

	Infliximab (N = 21)	Placebo (N = 19)	All (N = 40)
Age (yr)*	42.0 (±8.4)	39.4 (±8.4)	40.7 (±8.4)
Male (%)	13 (62)	11 (58)	24 (60)
Race (%)			
White	21 (100)	17 (89)	38 (95)
Asian	0 (0)	2 (11)	2 (5)
Weight (kg)*	80.8 (±19.2)	76.3 (±16.5)	78.7 (±17.9)
Height (cm)*	176 (±8.3)	174 (±11.1)	175 (±9.7)
Body mass index (kg/m^2)*	25.9 (±4.8)	25.1 (±3.6)	25.5 (±4.2)
Symptom duration (days)†	58 (25–102)	63 (20–87)	61 (20–102)
No. of previous sciatica episodes (%)			
0	11 (52)	8 (42)	19 (48)
1	8 (38)	7 (37)	15 (38)
2 or more	2 (10)	4 (21)	6 (15)
Herniation level (%)			
L3–L4	0 (0)	1 (5)	1 (3)
L4–L5	12 (57)	5 (26)	17 (43)
L5–S1	9 (43)	13 (68)	22 (55)
Leg pain (mm)†	73 (32–93)	73 (30–99)	73 (30–99)
Back pain (mm)†	33 (0–86)	60 (2–97)	56 (0–97)
Oswestry disability (%)†	45 (18–70)	48 (18–82)	48 (18–82)
Straight leg raising (SLR) (°)†‡	45 (15–70)	35 (20–60)	40 (15–70)
Sensory defect (%)			
Medial leg	3 (14)	1 (5)	4 (10)
Lateral leg and dorsum of the foot	7 (33)	6 (32)	13 (33)
Lateral foot	10 (48)	12 (63)	22 (55)
Muscle weakness (%)			
Ankle dorsiflexion	2 (10)	3 (16)	5 (13)
Hallux extension	5 (24)	4 (21)	9 (23)
Ankle plantarflexion	7 (33)	6 (32)	13 (33)
Abnormal Achilles reflex (%)	8 (38)	9 (47)	17 (43)
Sick leave (days)†	20 (3–77)	24 (3–86)	24 (3–86)

*Mean (±SD).
†Median (range).
‡$P = 0.018$.

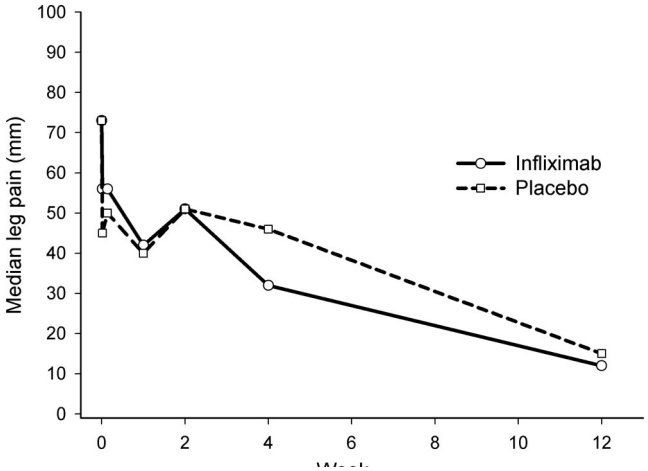

Figure 2. Patient-reported leg pain (visual analog scale; —— infliximab; - - - - placebo; $P = 0.82$).

criteria (65° [n = 1] and 70° [n = 1]) and 1 patient in the infliximab group had a symptom duration of 14 weeks; these inclusion criteria violations were regarded as minor. All patients adhered to the study visit schedule.

Efficacy

By week 12, the median reduction of leg pain was 43 mm in the infliximab group (range, 0–90 mm) and 50 mm in the placebo group (range, 0–89 mm). When the overall change was truncated to zero in the cases requiring discectomies ($P = 0.77$), the treatment difference (infliximab *vs.* placebo) was −7 mm (95% confidence interval [CI], −21 to 31 mm). By week 12, the reduction in back pain was 12 mm (range, −26 to 82 mm) in the infliximab group and 4 (range, −9 to 89 mm) in the placebo group ($P = 0.93$), and the treatment difference was 8 mm (95% CI, −19 to 16). When the last-value-carried forward method was used, the differences were even closer to the null hypothesis (data not shown). The null hypothesis was also supported by the results of the repeated-measures analysis for leg pain ($P = 0.82$, Figure 2), back pain ($P = 0.98$, Figure 3), Oswestry disability ($P = 0.37$,

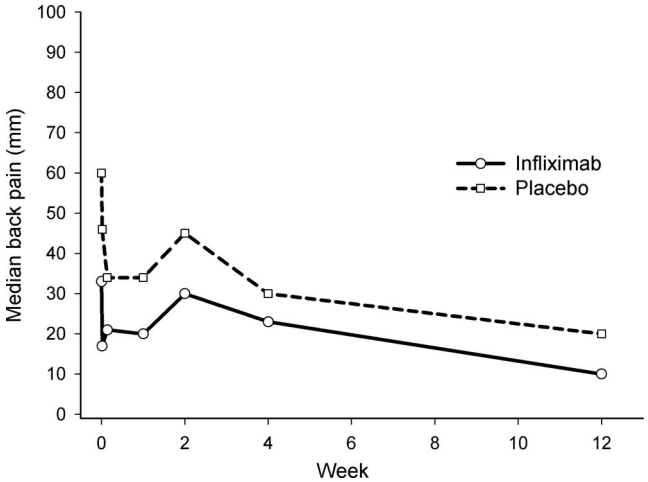

Figure 3. Patient-reported back pain (visual analog scale;—— infliximab; - - - - placebo; $P = 0.98$).

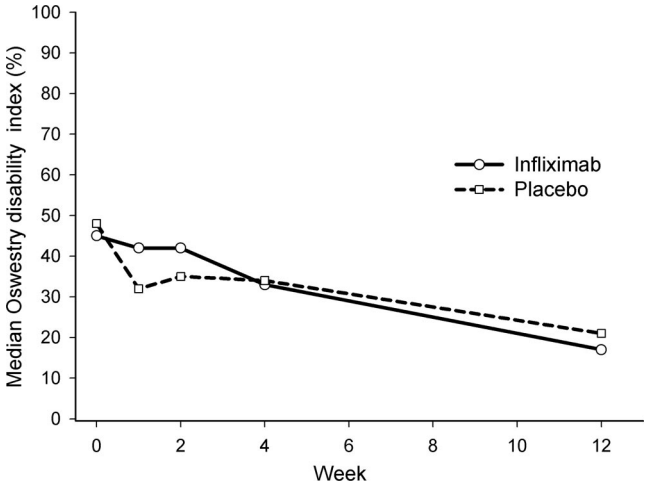

Figure 4. Oswestry disability index (——infliximab; - - - - placebo; $P = 0.37$).

Figure 4), and SLR restriction ($P = 0.51$, Figure 5). The median cumulative sick leave was 28 days (range, 0–106 days) in the infliximab group and 25 days (range, 0–91 days) in the placebo group ($P = 0.91$). The number of discectomies performed by week 12 was similar between treatment groups: 7of 21 (33%) in the infliximab group and 7 of 19 (37%) in the placebo group ($P = 1.00$). However, there were significant differences in the number of discectomies between the two treatment centers; 10 of 19 (53%) patients in ORTON Orthopedic Hospital in Helsinki and 4 of 21 (19%) patients in Oulu University Hospital required back surgery by week 12 ($P = 0.046$). In one surgical case, no herniation was detected despite the orthopedic surgeon's interpretation of a herniation on magnetic resonance imaging. This patient, however, had complete relief of her sciatic pain after surgery.

Adverse Events

There were no treatment-related adverse events encountered either during or immediately after treatment, or at any follow-up visit thereafter.

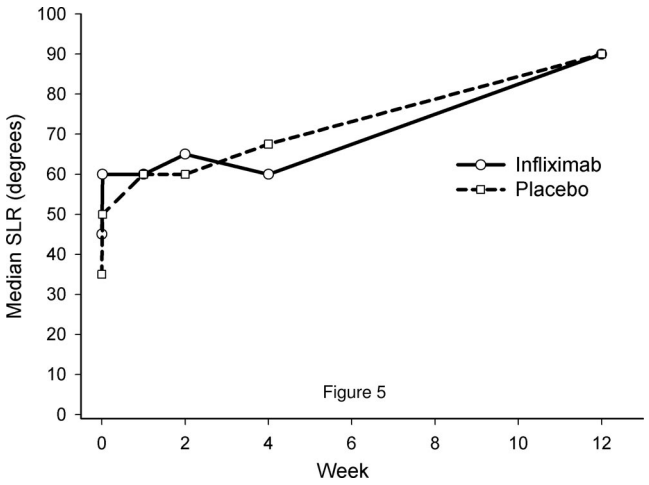

Figure 5. Straight leg raising (SLR) restriction (°; ——infliximab; - - - - placebo; $P = 0.51$).

■ Discussion

This is the first report of a randomized controlled trial evaluating the efficacy of an anti-TNF-α treatment in disc herniation-induced sciatica. Although our preliminary open-label results were very encouraging,[9] and the results were replicated in another open-label study using the soluble receptor TNF-α antagonist, etanercept,[11] the results of the present trial do not support the use of a single infusion of infliximab 5 mg/kg to treat moderate to severe disc herniation-induced sciatica.

Our negative results are disappointing as anti-TNF-α treatment was expected to be effective for the treatment of sciatica.[12] This expectation was justified as TNF-α produced by the nucleus pulposus cells appeared to be intimately involved with the basic pathophysiologic events leading to both nerve root dysfunction and pain. The pharmacologic inhibition of TNF-α was considered to be potentially effective in disc herniation-induced sciatica[7,13] and the therapeutic effects observed in open-label trials[9,11] were similar to those observed in animal models. Etanercept, reversed nucleus pulposus-induced nerve conduction block, and nerve root edema in a porcine model,[8] and neutralizing TNF-α antibodies prevented partially abnormal nociresponses caused by the application of nucleus pulposus on rat nerve roots.[14]

There are various explanations for these conflicting results. Beyond the placebo effect, it is reasonable to assume that sciatic pain syndrome due to disc herniation encompasses various stages with respect to the timing of the disease, *i.e.*, the chronicity of the condition. Pain is always centrally perceived and modulated, and the complexity increases in chronic pain syndromes. However, the patients in the current randomized trial had similar symptom duration as in the open-label trial. Therefore, the chronicity of sciatica is not a plausible explanation for the unforeseen results. Anatomic variations with respect to herniation size and diameter of the spinal canal in these two populations may partly explain the differences. All patients in the randomized clinical trial were established candidates for discectomy (with the exception of the 1 patient in whom no herniation was detected during surgery), whereas patients did not always fulfill the criteria for discectomy and symptoms were less severe in the open-label trial.

Another plausible explanation is a powerful placebo effect. Intravenous saline was remarkably effective in decreasing leg pain. It is hard to conceive that saline has any physiologic action beyond the placebo effect. It has, however, been suggested that placebo analgesia involves both higher-order cognitive networks and endogenous opioid systems. Positron emission tomography has confirmed that both opioid and placebo analgesia are associated with increased activity in the rostral anterior cingulated cortex, indicating a similar neural mechanism in placebo and opioid analgesia.[15]

We emphasize that the results of this randomized controlled trial do not absolutely indicate that the previous

theoretical framework for anti-TNF-α therapy should be ignored. However, based on the results of the current study, the routine clinical use of TNF-α antagonists in disc herniation-induced sciatica cannot be recommended. Clearly, additional research is required to define the possible beneficial scope of anti-TNF-α therapy in the treatment of sciatic pain syndrome due to disc herniation.

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■ Key Points

- This is the first report of a randomized controlled trial evaluating the efficacy of an anti-TNF-α treatment in disc herniation-induced sciatica.
- No differences between the treatment regimens were observed in the primary endpoint, the reduction of leg pain through 12 weeks. A significant reduction in leg pain was observed in both infliximab and saline groups.
- Similarly, no differences were observed in the secondary outcomes (reduction of back pain and Oswestry disability, improvement of straight leg restriction, differences in the number of days on sick leave, and the number of discectomies).

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