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Epidural administration of spinal nerves with the tumor necrosis factor-alpha inhibitor, etanercept, compared with dexamethasone for treatment of sciatica in patients with lumbar spinal stenosis: a prospective randomized study

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Abstract

Study Design. Prospective randomized trial.

Objective. To examine the effect of the tumor necrosis factor alpha (TNF-α) inhibitor, etanercept, on radicular pain by its epidural administration onto spinal nerves in patients with lumbar spinal stenosis.

Summary of Background Data. TNF-α is thought to play a crucial role in the radicular pain caused by lumbar disc herniation and spinal stenosis. Intravenous infusion of infliximab for sciatica has been examined in 2 studies; however, the results were equivocal.

Methods. Eighty patients with low back and radicular leg pain were investigated. We diagnosed the patients by physical examination, and X-ray and magnetic resonance imaging. In 40 patients we epidural administered 2.0 mL of lidocaine and 10 mg of etanercept onto the affected spinal nerve, and 2.0 mL of lidocaine and 3.3 mg of dexamethasone was used in 40 patients. Low back pain, leg pain, and leg numbness were evaluated using a visual analogue scale (VAS) and Oswestry Disability Index (ODI) score before and for 1 month after epidural administration.

Results. Low back pain, leg pain, and leg numbness in the two groups were not significantly different before epidural administration. Epidural administration of etanercept was more effective than dexamethasone for leg pain (3 days, 1, 2, and 4 weeks: $P < 0.05$), low back pain (3 days, 1 and 2 weeks: $P < 0.05$), and leg numbness (3 days, 1 and 2 weeks: $P < 0.05$). No adverse event was observed in either group.

Conclusion: Our results indicate that epidural administration of a TNF-α inhibitor onto the spinal nerve produced pain relief, but no adverse event. TNF-α inhibitors may be useful tools for

the treatment of radicular pain caused by spinal stenosis.

Key Words: TNF-alpha, inhibitor, etanercept, sciatica, spinal stenosis, pain

Mini abstract

Epidural administration of the TNF-α inhibitor, etanercept, onto spinal nerves in patients with lumbar spinal stenosis was more effective than similar application of dexamethasone for leg pain, low back pain, and leg numbness caused by spinal stenosis.

Key points

- We examined the effect of the TNF-α inhibitor, etanercept, on radicular pain by its epidural administration onto spinal nerves in patients with lumbar spinal stenosis, compared with application of dexamethasone.
- Epidural administration of etanercept was more effective than dexamethasone for leg pain, low back pain, and leg numbness.
- We did not observe any adverse event in either the etanercept or dexamethasone group.
- Epidural administration of a TNF-α inhibitor onto spinal nerves produced significant relief of pain caused by spinal stenosis.

Introduction

Radicular pain is a common symptom of lumbar disc herniation and spinal stenosis induced by mechanical compression and inflammation.[1,2] Cytokines generated at the inflammatory site produce associated pain.[3,4,5] Compression of the spinal nerve roots by lumbar spinal stenosis (LSS) is a major clinical problem associated with intermittent claudication, pain, numbness, and

lack of normal sensitivity.[6,7] It has been shown that compression of the spinal nerve roots may induce neurophysiologic dysfunction, degeneration, and reduced blood flow in nerve roots in both animal models and humans.[6,7]

Recently, cytokines such as interleukins 1, 6 (IL-1, IL-6), and tumor necrosis factor-alpha (TNF-α) have been strongly linked to radicular pain.[2,7,8] It has also been reported that IL-1, IL-6, and TNF-α are activated in dorsal root ganglia and Schwann cells in the spinal nerve roots following lumbar spinal stenosis, and that their expression is closely related to pain, motor nerve dysfunction and degeneration.[3,7]

In animal models, the TNF-α inhibitors, infliximab (intravenous injection) and etanercept (subcutaneous injection), have prevented a nucleus pulposus-induced reduction of nerve conduction velocity and also seemed to limit nerve fiber injury, intracapillary thrombus formation, and intraneural edema.[9] In the clinic, inhibition of TNF-α has become a common modality for treating rheumatoid disease. It has been reported that a single intravenous infusion of infliximab was effective in treating sciatic pain caused by lumbar disc herniation.[10] On the other hand, intravenous infusion of infliximab was compared to a placebo by a Finnish group that conducted the first randomized controlled trial of this inhibitor. The results were disappointing.[11,12]

Cohen et al. have reported a preclinical safety study of transforaminal epidural etanercept for the treatment of sciatica caused by disc herniation in 24 patients. They found effectiveness was dependent on the dose of etanercept (4 groups).[13] In the clinical arm of the study, significant improvements in leg and back pain were collectively noted for the etanercept-treated patients one month after treatment, but not for patients in the saline-treated group.[13] However, the number of patients in their study was small, and the sciatica caused by lumbar disc herniation.

The purpose of the current study was to examine the effect on radicular pain of epidural administration of the TNF-α inhibitor, etanercept, onto spinal nerves in patients with lumbar spinal stenosis. We compared application of the TNF-α inhibitor, etanercept, with application of dexamethasone for the treatment of pain.

Methods

The ethics committee of our institution approved the protocol for the human procedures used in this study and informed written consent was obtained from each subject.

Patients

Patients had low back and leg pain, continuing for at least 1 month. Patients who had previously undergone spinal surgery were excluded from the study. We also excluded patients with spinal tumor, infection, or trauma. Patients were diagnosed with lumbar spinal stenosis on X-ray and magnetic resonance imaging (MRI) and by physical examination. Diagnosis by X-ray was spondylosis and spondylolisthesis (more than 3 mm of anterior slip in a normal position). The degree of spinal stenosis varied from slight to severe. MRI showed central stenosis, stenosis of the lateral recess, and foraminal stenosis. We measured degree of stenosis in case of stenosis of the lateral recess and central stenosis and classified it as: >0% to ≤30%, slight stenosis; >30% to ≤70%, moderate stenosis; >70% to ≤100%, severe stenosis. Most patients diagnosed as having stenosis of the lateral recess fell into the category of slight stenosis in the current study. Details are shown in Table 1 and 2. Patients who showed monoradiculopathy were evaluated. Patients who showed cauda equine syndrome, or polyradiculopathies were excluded from the current study. If a single affected spinal nerve was found using imaging and physical examination, spinal

infiltration was performed to confirm the finding. Patients were allowed nonsteroidal anti-inflammatory drugs (NSAIDs) to control low back pain and leg pain.

Epidural administration

The patients were divided randomly into 2 groups. The patients were randomized according to the minimization method for injection using etanercept or injection using dexamethasone.[14] We employed sex and age as stratification factors.

Patients received a single epidural administration (2.0 mL of lidocaine and 10 mg of etanercept, etanercept group; n = 40) or a single epidural administration (2.0 mL of lidocaine and 3.3 mg of dexamethasone, dexamethasone group; n = 40). Both groups received 1.5 mL of 1% lidocaine solution into the skin. Then a 22-gauge spinal-nerve-block needle was advanced obliquely to the corresponding spinal nerve under fluoroscopic control and 0.5 mL of the contrast medium Iotorolan (Schering AG, Berlin, Germany) was injected to confirm the position of the spinal nerve. Subsequently unilateral epidural administration of lidocaine and the agent (2.0 mL of lidocaine and 10 mg of etanercept, or 2.0 mL of lidocaine and 3.3 mg of dexamethasone) was performed.

Pain scores

We evaluated the change in low back and leg pain before and after epidural administration. To evaluate pain, the visual analogue scale (VAS) score (0, no pain; 10, worst pain) was recorded before and 30 minutes, 3 days, 1 week, 2 weeks, and 4 weeks after epidural administration. Oswestry Disability Index (ODI) scores were recorded before and 4 weeks after epidural administration.

Subjective Outcomes

At 4 weeks after injection, patients were asked to choose one of the following responses regarding their satisfaction with the treatment: (1) treatment met my expectations; (2) I did not improve as much as I had hoped, but I would undergo the same treatment for the same outcome; (3) treatment helped, but I would not undergo the same treatment for the same outcome; or (4) I am the same as or worse than I was before the treatment.

Complications

Deep or superficial infection including respiratory infection in both groups was evaluated. Spinal nerve injury (motor palsy or sensory disturbance) or other complications in both groups were also evaluated.

Statistical Analysis

Data were compared using a Kruskal–Wallis test to compare pain scales between the two groups, a one-way ANOVA with post hoc comparisons for age, symptom duration, and follow-up; and Fisher's test was used for dichotomous/categorical variables. $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics of patients in both the etanercept and dexamethasone groups are shown in Table 1. There was no significant difference in VAS score (leg pain, low back pain, leg numbness) and ODI score between the 2 groups ($P > 0.05$). There was no significant difference

in the number of the patients who used NSAIDs between the 2 groups ($P > 0.05$). Affected spinal nerves were mainly in L5 spinal nerves in both groups.

In both groups, treatment was significantly effective in attenuating leg pain, leg numbness, and low back pain 30 min after injection ($P < 0.05$) (Figures 1, 2, and 3). For leg pain in both groups, treatment was significantly effective in attenuating the pain during the 4 weeks of testing ($P < 0.05$) (Figure 1). VAS scores of leg pain in the etanercept group were significantly lower than those in the dexamethasone group at 3 days, and 1, 2, and 4 weeks ($P < 0.05$) (Figure 1).

For leg numbness, treatment was significantly effective in attenuating the pain during the 4 weeks in both groups ($P < 0.05$) (Figure 2). VAS scores of leg numbness in the etanercept group were significantly lower than those in the dexamethasone group at 3 days, and 1, and 2 weeks ($P < 0.05$) (Figure 2).

Both epidural administrations were effective for low back pain (VAS) in both group during the 4 weeks ($P<0.05$) (Figure 3). VAS scores of low back pain in the etanercept group were significantly lower than those in the dexamethasone group at 3 days, and 1, and 2 weeks ($P < 0.05$) (Figure 3).

There was no significant difference in ODI scores before epidural administration between the groups ($P > 0.05$). The average ODI score decreased at 4 weeks, and there was significant improvement in both groups compared with before epidural administration ($P < 0.05$) (Table 1 and 3). However, there was no significant difference in ODI score between the etanercept and dexamethasone groups at 4 weeks ($P > 0.05$) (Table 3).

Details of subjective outcomes 4 weeks after injection are presented in Table 4. Subjective outcomes for most patients in both groups were good or fair; however, 6 patients in the etanercept group and 11 patients in the dexamethasone group reported an unexpected or poor

outcome.

Complications

Table 5 shows complications, from injection through 4 weeks of follow-up. There was no respiratory infection, deep, or superficial infection in either group. There was no spinal nerve injury or other complications in either group.

Discussion

In the current study, results indicate that single epidural administration of a TNF-α inhibitor onto the spinal nerve produced significantly more pain relief than application of dexamethasone, and produced no adverse event. TNF-α may mediate the radicular pain caused by spinal stenosis in humans.

It has also been reported that TNF-α is activated in dorsal root ganglia and Schwann cells in the spinal nerve roots following lumbar spinal stenosis, and is closely related to pain.[3,7] In human studies, the concentration of TNF-α has been found to be high in synovium in facet joints in lumbar spinal stenosis patients compared with lumbar disc herniation patients, thus suggesting that TNF-α in degenerated facet joints may be related to the cause of pain in degenerative lumbar disorders.[15]

Recently, two types of TNF-α inhibitors, infliximab and etanercept, have been used to treat radicular leg pain in animal and human studies. Intraperitoneal injection of infliximab prevents nucleus pulposus-induced histologic changes in the rat DRG.[16] Treatment with infliximab significantly reduced pain-related behavior in rats.[4] Etanercept prevented nerve degeneration.[9] It has recently been reported that intravenous injection of infliximab is clinically effective in

treating sciatic pain caused by lumbar disc herniation.[10] On the other hand, the effect of intravenous injection of infliximab was examined in a randomized controlled trial, and found not to be effective.[11,12] These studies in animal models and in humans are controversial, and the effect of direct application of TNF-α inhibitor onto damaged nerves including those found in spinal stenosis has not been fully explored.

Several authors have reported that the effects of direct application of a TNF-α inhibitor onto spinal nerves affected disc herniation in animals and humans. Norimoto et al. have reported that nucleus pulposus application onto crushed sciatic nerves produced mechanical allodynia; however, epidural administration of a TNF-α inhibitor (etanercept) onto the sciatic nerve did not suppress pain-related behavior.[17] Cohen et al. have reported a study in which 24 patients with subacute lumbosacral radiculopathy caused by disc herniation were randomly assigned to receive two transforaminal epidural injections of 2, 4, or 6 mg of etanercept, and significant improvements in leg and back pain were noted for the etanercept-treated patients, but not for the saline-treated control group, at one month after treatment. No adverse event was reported.[13] In the current study, we showed that epidural administration of a TNF-α inhibitor onto spinal nerves relieved pain caused by spinal stenosis. We concluded that TNF-α may play a crucial role in pain caused by both lumbar disc herniation and spinal stenosis. VAS scores of low back pain in the etanercept group were significantly lower than those in the dexamethasone group during a 2-week follow-up. However, there was no significant difference in ODI scores between the etanercept and dexamethasone groups at 4 weeks. In this regard, single application of 10 mg of etanercept had a relatively short term effect for low back pain.

In the current study, we compared lidocaine+etanercept with lidocaine+dexamethasone. The efficacy of steroids for nerve root injection has been reported. Fifty-five patients who were

deemed to be surgical candidates were treated and randomized to receive either a selective nerve root injection of betamethasone 6 mg with bupivacaine or a selective nerve root injection of bupivacaine alone. This study showed that 67% of patients in the group receiving both local anesthetic and steroid avoided the need for surgical intervention, compared with 28% in the group receiving local anesthetic alone.[18] A systematic review of therapeutic lumbar transforaminal epidural steroid therapy has shown that the indicated evidence for transforaminal lumbar epidural steroid injections is both short- and long-term pain relief compared with local anesthetic alone.[19] In the current study, we showed that application of etanercept produced significantly more pain relief than application of dexamethasone alone. We did not examine a lidocaine only group; however, etanercept is probably more effective for pain than application of lidocaine alone by analogy with the previous studies.

It is not clear whether systemic or direct administration of the inhibitor is the most effective route. In previous reports, intravenous injection of infliximab was effective or ineffective in treating sciatic pain caused by lumbar disc herniation[10,11,12] TNF-α is mainly expressed around or in the disc tissue, where blood supply is generally considered to be insufficient. Therefore we believe that the supply of TNF-α inhibitors is insufficient in case of systemic administration. It is also known that TNF-α inhibitors can have adverse effects when administered in high doses systemically.[18] It is not known if these effects occur after direct administration to nerve; however, both Cohen's study and the current study demonstrated the safety of direct application of the TNF-α inhibitor, etanercept, onto spinal nerves.

Limitations of the current study include its small size and prospective nature, and a short follow-up period of only 4 weeks. Second, as mentioned above, we did not examine a lidocaine only group; the only dose of etanercept used was 10 mg. Third, there are no evidence or dose

comparison studies that suggest that 10 mg of etanercept is equivalent to 3.3 mg of dexamethasone, and most patients also used NSAIDs. Fourth, we did not show any difference in pain based on ODI, because etanercept had a short-term effect for low back pain. Further study using different doses, multiple applications, or different tools for evaluation are required to clarify these points.

In summary, based on VAS scale scores, epidural administration of the TNF-α inhibitor, etanercept, onto spinal nerves, reduced low back pain, leg pain, and leg numbness caused by spinal stenosis. We did not observe any adverse event in the etanercept administration group. TNF-α inhibitors may therefore be useful tools for the treatment of radicular pain caused by spinal stenosis.

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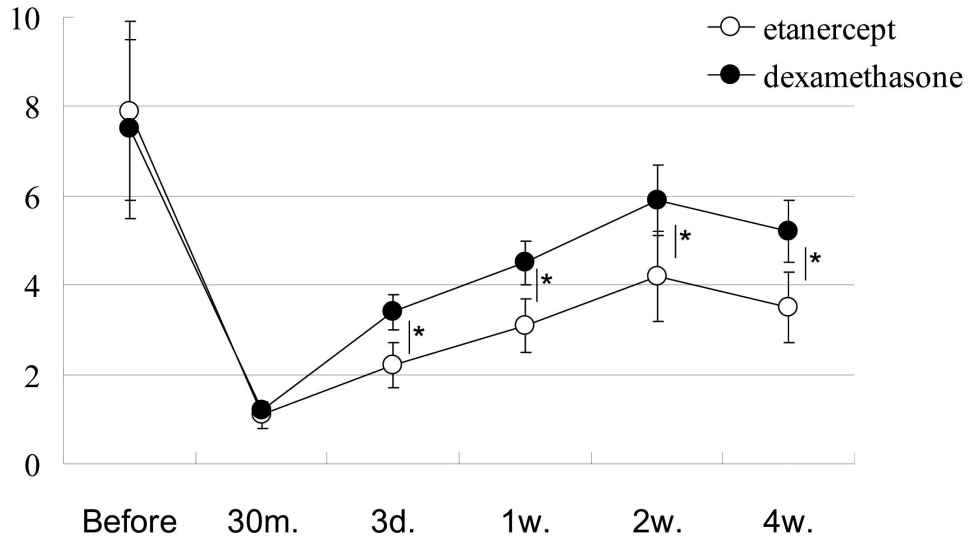
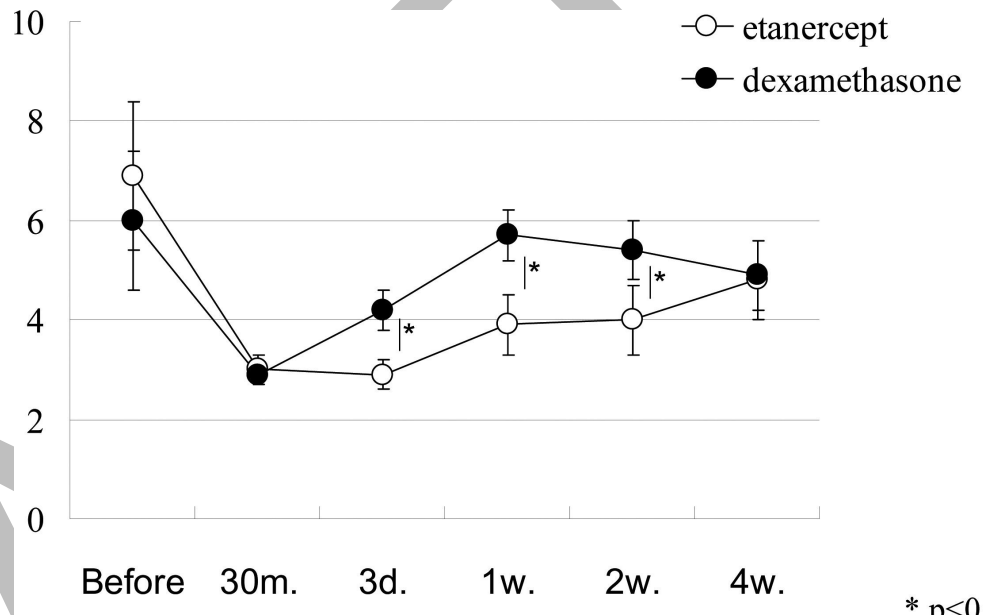


* p<0.05

Figure 1.

Time course of leg pain (VAS). White circles indicate etanercept group and black circles indicate dexamethasone group.



* p<0.05

Figure 2

Time course of leg numbness (VAS). White circles indicate etanercept group and black circles indicate dexamethasone group.

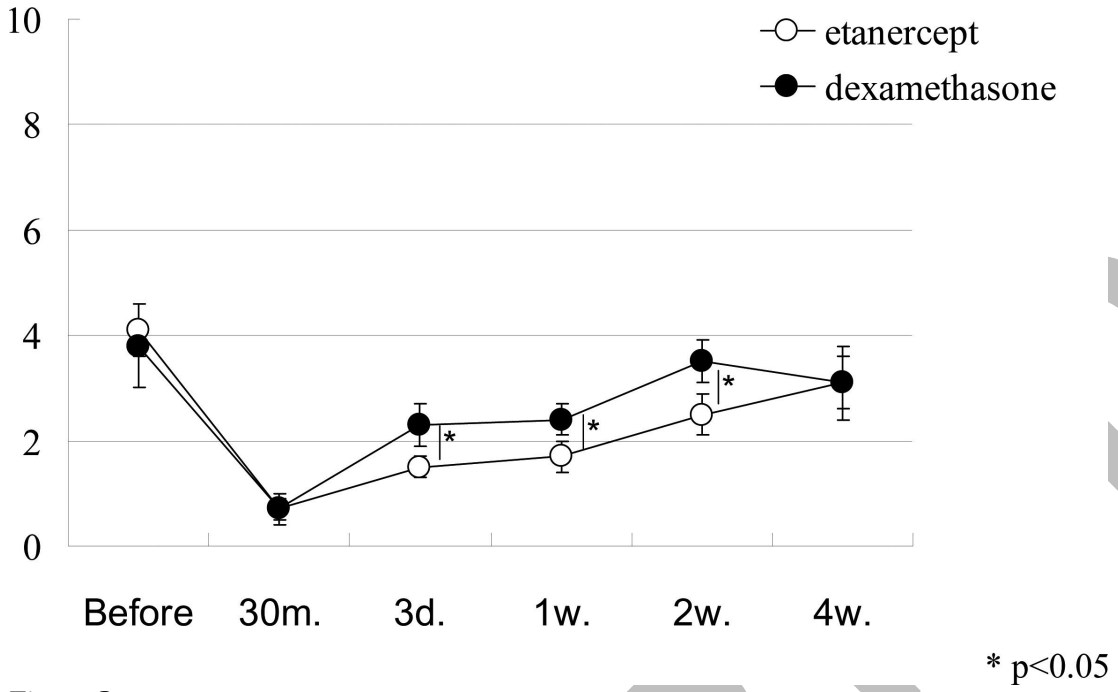


Figure 3

Time course of low back pain (VAS). White circles indicate etanercept group and black circles indicate dexamethasone group.

Table 1 Demographic Characteristics			
	etanercept	**dexamethasone**	**Statistical analysis**
Number of patients	40	40	N.S.
Sex	Male: 22 Female: 18	Male: 18 Female: 22	N.S.
Age mean range (range), years	65 ± 5.5 (50-80)	67 ± 5.0 (49-79)	N.S.
Symptom duration, mean (range), months	2.5 (1-12)	2.3 (1-12)	N.S.
Use of NSAIDs (10mg of Meloxicam/day)	35	34	N.S.
Use of oral steroid	0	0	N.S.
Pain score before infiltration			
Leg pain			
Visual Analogue Scale (VAS)	7.9 ± 2.0	7.5 ± 2.0	N.S.
Leg numbness			
Visual Analogue Scale (VAS)	6.9 ± 1.5	6.0 ± 1.4	N.S.
Low back pain			
Visual Analogue Scale (VAS)	4.1 ± 0.5	3.8 ± 0.8	N.S.
Oswestry Disability Index（ODI）	38 ± 8.2	40 ± 7.0	N.S.
Affected spinal nerve	L4: 5 L5:24 S1:11	L4: 7 L5: 24 S1: 9	N.S.

Table 2 X-ray and MR-imaging evaluation, and affected spinal nerve			
	etanercept	**dexamethasone**	**Statistical analysis**
Number of patients	40	40	N.S.
X ray evaluation			N.S.
Spondylosis	26	24	N.S.
Spondylolisthesis	14	16	N.S.
MRI evaluation			
Central stenosis			
>0% ≤30%; slight stenosis	20	18	N.S.
>30% ≤70%; moderate stenosis	11	10	N.S.
>70% ≤100%; severe stenosis	5	6	N.S.
Foraminal stenosis	4	6	N.S.
Affected spinal nerve	L4: 5 L5:24 S1:11	L4: 7 L5: 24 S1: 9	N.S.

Table 3 Pain score 4 weeks after epidural administration			
	etanercept	**dexamethasone**	**Statistical analysis**
Leg pain			
Visual Analogue Scale (VAS)	3.5 ± 0.8	5.2 ± 0.7	P=0.026
Leg numbness			
Visual Analogue Scale (VAS)	4.8 ± 0.8	4.9 ± 0.7	N.S.
Low back pain			
Visual Analogue Scale (VAS)	3.1 ± 0.5	3.1 ± 0.7	N.S.
Oswestry Disability Index （ODI）	28 ± 6.2	30 ± 6.0	N.S.

Table 4 Subjective Outcomes (Number of patients)		
	etanercept	**dexamethasone**
	Number of patients	Number of patients
1) Treatment met my expectations	22	17
2) I did not improve as much as I had hoped, but I would undergo the same treatment for the same outcome	12	12
3) Treatment helped, but I would not undergo the same treatment for the same outcome	3	6
4) I am the same as or worse than I was before the treatment	3	5

Table 5 Complications			
	etanercept	**dexamethasone**	**Statistical analysis**
Number of patients			
Deep Infection	0	0	N.S.
Superficial Infection	0	0	N.S.
Hematoma	0	0	N.S.
Spinal nerve injury	0	0	N.S.
The others	0	0	N.S.