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# SPINE SECTION

## *Original Research Articles*

# Single Intradiscal Administration of the Tumor Necrosis Factor-Alpha Inhibitor, Etanercept, for Patients with Discogenic Low Back Pain

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### Abstract

**Objective. To examine the analgesic effect of intradiscal administration of a tumor necrosis factor-αα (TNF-α) inhibitor in patients with discogenic low back pain (LBP).**

**Design. Prospective, randomized study.**

**Setting. Department of Orthopaedic Surgery, Chiba (Japan) University Hospital.**

**Subjects. Seventy-seven patients diagnosed with discogenic LBP.**

**Methods. Discogenic LBP patients were randomly assigned to the etanercept (n = 38; bupivacaine [2 mL] with etanercept [10 mg]) or control (n = 39; bupivacaine [2 mL]) groups. Patients received a single intradiscal injection. Numerical rating scale (NRS) scores for LBP at baseline, 1 day, and 1, 2, 4, and 8 weeks after the injection were recorded. The Oswestry disability index (ODI) scores at baseline and at 4 and 8 weeks after injection were evaluated. Postinjection complications were recorded and evaluated.**

**Results. In the etanercept group, the NRS scores were significantly lower than in the control group at every time point after the injection for 8 weeks ($P < 0.05$). Similarly, 4 weeks after the injection, the ODI score was lower in the etanercept group than in the control group ($P < 0.05$). However, the ODI scores were not significantly different at 8 weeks. Complications were not observed.**

**Conclusions. Single intradiscal administration of a TNF-α inhibitor can alleviate intractable discogenic LBP for up to 8 weeks. TNF-α may be involved in discogenic pain pathogenesis. This procedure is a novel potential treatment; longer-term effectiveness trials are required in the future.**

**Key Words. Prospective Randomized Study; Discogenic Low Back Pain; Tumor Necrosis Factor-Alpha; Etanercept; Intradiscal Administration; Inflammatory Cytokines**

### Introduction

Low back pain (LBP) originates from several sources, including nerves, muscles, facet joints, and the degeneration of intervertebral discs (IVDs) [1]. Discogenic LBP is

regarded by some as a leading cause of chronic LBP [2–6]. This condition is diagnosed on the basis of reproduction of the patient's pain following disc stimulation, otherwise known as discography [7–11]. However, to date, no treatment has been rigorously shown to be effective for lumbar discogenic pain. Some basic and clinical science studies implicate tumor necrosis factor-alpha (TNF-α) as a possible mediator of discogenic pain [4,12–15]. This invites the possibility of using intradiscal injections of TNF-α inhibitors, such as etanercept, for the treatment of discogenic LBP. One previous study explored this possibility, but did not find more than a placebo effect [16]. However, that study used small doses of etanercept (0.1–1.5 mg), which may have been insufficient. This study was, therefore, undertaken to test if this might be the case. We assessed the pain-relieving effect, effective duration, and adverse events associated with single intradiscal injections of etanercept (10 mg) in patients with discogenic LBP.

## Methods

The ethics committee of Chiba University approved the protocol for the human procedures used in this study, and informed written consent was obtained from each patient.

### *Patients*

The study was conducted in a Chiba (Japan) University hospital that sees approximately 3,000 chronic LBP patients/year. The patients included in this study were recruited from this source population if they met the inclusion criteria: (1) LBP that was refractory to conservative treatment, including medication and rehabilitation; (2) numerical rating scale (NRS) score >4 (0, no pain; 10, worst pain) at the baseline assessment; (3) Oswestry disability index (ODI) >30% at the baseline assessment; (4) magnetic resonance imaging (MRI) of the degenerative IVDs allowed classification according to the Pfirrmann classification [17] (patients with Grades III–V IVD degeneration were included, but their IVD degeneration was limited up to 2 levels); and (5) neurological abnormalities were absent, including pain or numbness in both lower extremities [18–20]. The exclusion criteria were postoperative pain, spinal tumors, malignancies, infections, trauma, or other neurological or psychiatric diseases. Patients were allowed to use nonsteroidal anti-inflammatory drugs (NSAIDs), if these drugs had been prescribed before the injection, with no allowance for adjusting the dosage during the study period.

The physical criterion for diagnosing discogenic LBP was pain exacerbation caused by forward flexion. Additionally, pain-provocation discography was performed using a nonionic contrast agent (iohexol, Daiichi-Sankyo, Tokyo, Japan) to confirm the pain as being IVD-dependent [21,22]. In patients with two degenerated IVDs, discography was performed simultaneously for both IVDs; the IVD diagnosed with the stronger pain was considered the origin.

### *Intervention: Direct Intradiscal Administration (Discography and Discoblock) Procedure*

Intradiscal injections were performed as previously reported [11]. With the patient in a lateral decubitus position, 5 mL of 1% xylocaine (AstraZeneca, Osaka, Japan) was injected along the needle course from the skin to the IVD. A 22-gauge discography needle was advanced obliquely into the corresponding IVD, under fluoroscopic guidance (Figure 1). The needle position was confirmed to determine whether the tip had reached the center of the nucleus pulposus, based on the antero-posterior and lateral views. Subsequently, intradiscal injection of iohexol was performed to determine the pain provocation. After the procedure, we injected 1% xylocaine (1 mL) into the disc to confirm pain relief in each subject. Finally, 76 patients were identified for inclusion in this study.

Two or more weeks after the discography procedure, the 77 patients were randomly assigned to either the etanercept group (n = 38) or the control group (n = 39). The etanercept group received 2 mL of bupivacaine (0.5% bupivacaine, 2 mL, AstraZeneca, Osaka, Japan) and 10 mg of etanercept (Takeda Pharmaceutical, Osaka, Japan), whereas the control group received only 2 mL of bupivacaine. All patients were blinded to the treatment they received (single blind). Diagnostic discography and the therapeutic intradiscal injections were performed by three physicians with sufficient experience with the procedure.

### *Outcome Measurements (Pain Evaluations)*

We evaluated LBP before and after the injections. To evaluate pain, the NRS scores were recorded at

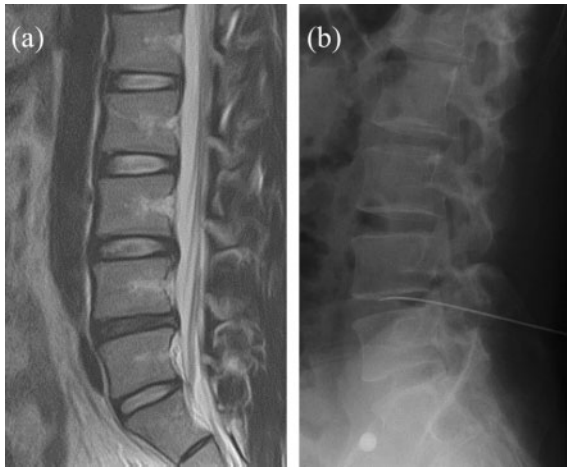


**Figure 1** Representative radiological images. (a) MRI of a degenerative disc, limited to a single level. (b) After positive discography findings, performed using a contrast agent, intradiscal injection was performed under fluoroscopic guidance.

baseline, and at 1 day, and 1, 2, 4, and 8 weeks after the intradiscal injections. Additionally, the ODI scores were determined at baseline and at 4 and 8 weeks after the injections. A successful outcome, after intradiscal injection, was defined as a statistical improvement in the NRS and ODI scores in the etanercept group, compared with the control group, at each time point [23]. The pain evaluation data from the patients were collected by trained medical staff (nurses and medical assistants, not the physician who performed the injection). The pain data were assessed by investigators blinded to the identity and treatment assignment of the patients.

*Adverse Events*

Potential adverse events included superficial or deep infections, respiratory tract infections, hematomas, and nerve injuries.

*Statistical Analysis*

Data were analyzed using a Mann-Whitney *U*-test to compare scores between the groups; a one-way analysis of variance was also performed with post hoc comparisons for age, symptom duration, and follow-up. For all statistical analyses, $P$ values $< 0.05$ were considered statistically significant.

## Results

We excluded some patients with insufficient follow-up in each group. At the study's termination, both groups contained 30 patients, each of whom was definitively evaluated (Figure 2). Table 1 shows the patients' demographic characteristics. The etanercept group included 15 men and 15 women (mean age, 62.8 years), whereas the control group included 12 men and 18 women (mean age, 59.7 years). NSAIDs were used by 8 patients in the etanercept group and by 10 patients in the control group.

Degenerative IVDs were classified as follows (etanercept, control): Grade III (1, 2), Grade IV (16, 18), and

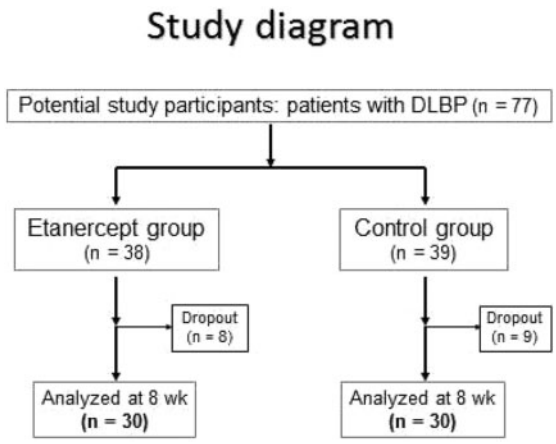


**Figure 2** Seventy-seven patients with discogenic low back pain (DLBP) were included in this study. Ultimately, both groups consisted of 30 evaluable patients.

**Table 1** Patient baseline demographic characteristics

| | Etanercept Group | Control Group | Statistical Analysis |
|---|---|---|---|
| Patients, n | 30 | 30 | |
| Sex | | | |
| Men | 15 | 12 | |
| Women | 15 | 18 | |
| Age, years (range) | 62.8 (32–80) | 59.7 (23–74) | N.S. |
| Patients using NSAIDs, n | 8 | 10 | N.S. |
| Pain score before injection | | | |
| Low back pain | | | |
| Numerical rating scale score | 8.54 | 8.28 | N.S. |
| Oswestry disability index score | 58.1 | 56.3 | N.S. |
| Disc level | | | |
| L3/4 | 5 | 5 | |
| L4/5 | 22 | 21 | |
| L5/S1 | 3 | 4 | |
| Pfirrmann classification | | | |
| Grade 3 | 1 | 2 | |
| Grade 4 | 16 | 18 | |
| Grade 5 | 13 | 10 | |

NSAIDs, nonsteroidal anti-inflammatory drugs.

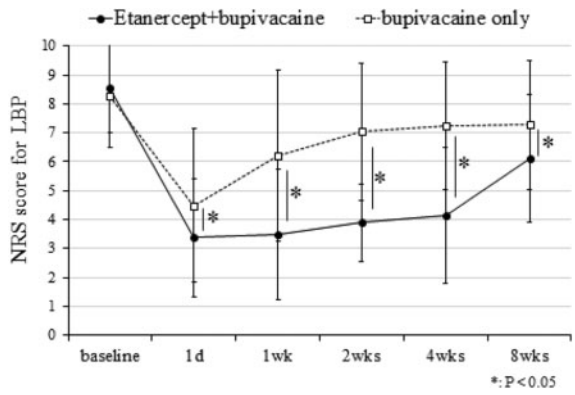


**Figure 3** NRS scoring for LBP. Error bars represent standard deviations.

**Table 2** Distribution of NRS pain scores in the control and treatment groups, at each time point

| NRS | Etanercept Group | | | Control Group | | |
|---|---|---|---|---|---|---|
| score | Baseline | 4 wks | 8 wks | Baseline | 4 wks | 8 wks |
| **0** | 0 | 1 | 0 | 0 | 0 | 0 |
| **1** | 0 | 2 | 0 | 0 | 0 | 0 |
| **2** | 0 | 0 | 2 | 0 | 1 | 1 |
| **3** | 0 | 6 | 1 | 0 | 2 | 2 |
| **4** | 1 | 5 | 0 | 1 | 2 | 0 |
| **5** | 0 | 12 | 8 | 1 | 3 | 5 |
| **6** | 0 | 4 | 6 | 2 | 2 | 2 |
| **7** | 7 | 0 | 7 | 1 | 1 | 1 |
| **8** | 6 | 0 | 6 | 11 | 6 | 5 |
| **9** | 6 | 0 | 0 | 8 | 11 | 14 |
| **10** | 10 | 0 | 0 | 6 | 2 | 0 |
| Total | 30 | 30 | 30 | 30 | 30 | 30 |

Grade V (13, 10). The affected degenerative disc level was primarily L4/5 in both groups.

*Low Back Pain*

Figure 3 shows the progress of the LBP NRS scores. In both groups, the intradiscal injection had a significant effect for at least 1 week. Starting within a week after the injection, the pain scores for both groups gradually increased. Pain relief was significantly greater in the etanercept group than in the control group, with the NRS scores being significantly lower in the etanercept group than in the control group at 1 day and at 1, 2, 4, and 8 weeks ($P < 0.05$). Table 2 shows the distribution of NRS scores, at each postinjection time point, for both groups of patients. Table 3 shows the number of patients who showed improvement and the number with worse pain 4 and 8 weeks after intradiscal injection. At 4 weeks, the proportion of patients who achieved at least 50% relief of their back pain was significantly greater (57%; 95% confidence intervals: 39–75%) in the group treated with etanercept than in the control group (23%; 8–38%). By 8 weeks, however, this difference disappeared, with only 23% and 20% of patients in the two groups, respectively, maintaining 50% relief.

**Table 3** The number of patients that showed improvement and the numbers with worsened symptoms after intradiscal injection in the Etanercept and Control groups at 4 and 8 weeks. (Improvement rates are rounded)

| | Etanercept Group | | Control Group | |
|---|---|---|---|---|
| | 4 wks | 8 wks | 4 wks | 8 wks |
| 100% | 1 | 0 | 0 | 0 |
| 90% | 2 | 0 | 0 | 0 |
| 80% | 0 | 0 | 1 | 1 |
| 70% | 3 | 1 | 1 | 1 |
| 60% | 7 | 2 | 2 | 1 |
| 50% | 4 | 3 | 3 | 3 |
| 40% | 6 | 4 | 2 | 3 |
| 30% | 6 | 7 | 1 | 1 |
| 20% | 0 | 6 | 0 | 1 |
| 10% | 0 | 1 | 2 | 2 |
| 0% | 0 | 4 | 10 | 9 |
| Worse | 1 | 2 | 8 | 8 |
| Total | 30 | 30 | 30 | 30 |

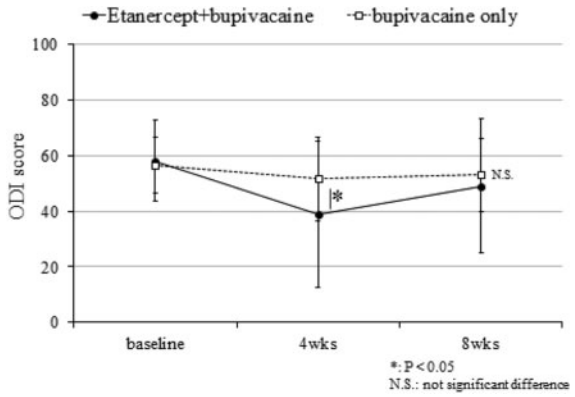


**Figure 4** ODI scoring for LBP. Error bars represent standard deviations.

Figure 4 shows the ODI scores throughout the study period. There were no significant differences in the baseline ODI scores between the groups, but there was a significant difference between the groups at 4 weeks ($P < 0.05$); a significant difference was not observed at 8 weeks.

*Incidence of Adverse Events*

There were no signs of infection, including respiratory tract infections, in either group. There were no other

complications, such as local hematomas, systemic inflammatory reactions, or spinal nerve injuries, in either group.

## Discussion

The findings of this study indicated that, compared with the administration of bupivacaine alone, intradiscal injection of bupivacaine and etanercept had a significantly greater analgesic effect in patients with discogenic LBP. These effects were evidenced by the improved NRS throughout the 8 weeks and the improved ODI scores for 4 weeks. However, although 57% of patients treated with etanercept experienced a clinically significant reduction in pain for 4 weeks, this effect was extinguished by 8 weeks; at which time the proportion of patients with significant relief of pain was low, and statistically equivalent to that of the control group.

A pathologic IVD is thought to be a significant contributor to LBP. However, the pathophysiology of discogenic LBP remains largely unknown [24,25]. Some reports have suggested that the presence of sensory nerve fibers in the deeper layer of the annulus fibrosus and the production of inflammatory mediators in the degenerated nucleus pulposus lead to discogenic LBP in patients with degenerated IVDs [12,13]. Miyagi et al. [26] studied punctured and compressed coccygeal IVDs in rats, and reported that IVD degeneration can induce elevated levels of TNF-α. Similarly, Burke et al. [27] reported that IVDs from patients with discogenic LBP contained more inflammatory mediators than did IVDs from patients with IVD herniation. These reports strongly suggest an association between TNF-α and discogenic LBP.

One study reported that pain and ODI scores did not improve after multiple doses of intradiscal etanercept (maximum dose, 1.5 mg) [16]. Meanwhile, a basic science study [28] showed the effectiveness of intradiscal administration of etanercept (100 μg) in a rat IVD injury model; the dose corresponded to a 10–20 mg dose of etanercept in humans. Based on the findings of that study, we used a dose of 10 mg and obtained a definite pain relief effect in patients with discogenic LBP. The optimal dose and the option of continuous administration should be investigated in the future.

This study has some limitations. First, the follow-up period was limited to 8 weeks, and should be extended. A longer follow-up period is required to examine the pain-relieving effects and impact on IVDs in future studies. Second, the pathophysiology of discogenic LBP is controversial [29–34]. In the current study, we did not perform a facet block to confirm the pain generator, in all cases. Third, the current study was not performed in a double-blind manner, resulting in a potential for bias.

## Conclusion

Intradiscal injection of a TNF-α inhibitor into degenerative IVDs showed an analgesic effect throughout an 8-week follow-up and ODI improvements for 4 weeks in patients with discogenic LBP, without the development of any adverse events. These results suggest that TNF-α may be involved in the pathogenesis of discogenic pain. An intradiscal TNF-α inhibitor may be a novel treatment for discogenic LBP, but a therapy providing longer-term benefits needs to be found and evaluated.

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