Single intradiscal injection of the interleukin-6 receptor antibody, tocilizumab, provides short-term improvement of discogenic low back pain.
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Abstract

Purpose: Inflammatory cytokines, such as interleukin (IL)-6, are gaining attention as etiologic factors associated with discogenic low back pain (LBP). This study evaluated the efficacy and associated adverse events of intradiscal injection of interleukin (IL)-6 receptor antibody (tocilizumab) in patients with discogenic LBP.

Methods: Thirty-two consecutive patients received intradiscal injections (2 mL) of 0.5% bupivacaine (control group). Thereafter, tocilizumab was intradiscally injected into another 31 consecutive patients, in addition to 1–2 mL of 0.5% bupivacaine (tocilizumab group). Prior to the treatment, the pain origin was confirmed in all subjects using pain provocation discography and confirming pain relief with 1 mL of 1% xylocaine. To evaluate the effect of tocilizumab injection, we compared the two groups before and after treatment using a numerical rating scale (NRS) and Oswestry disability index (ODI) scores. We also compared tocilizumab-induced pain relief with the grade of intervertebral disc (IVD) degeneration.

Results: At the final observation, 8 weeks after treatment, 30 cases were evaluable in each group. In the tocilizumab group, the NRS and ODI scores demonstrated significant improvements at 2 and 4 weeks post-treatment, respectively. IVD degeneration did not correlate with improved NRS scores in the tocilizumab group. Local infection (discitis) was observed in 1 patient in the tocilizumab group.

Conclusions: Intradiscal injection of tocilizumab demonstrated a short-term analgesic effect in patients with discogenic LBP. The present study revealed the clinical relevance of IL-6 to discogenic LBP. Further study is required to determine the long-term effects of intradiscal tocilizumab therapy.

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Key words
discogenic low back pain, interleukin-6, tocilizumab, intradiscal injection, case-control study
Introduction

Low back pain (LBP) is a common complaint among orthopedic patients, with a lifetime prevalence of up to 84% [1]. LBP is thought to originate from several sources, such as degenerated intervertebral discs (IVDs) [2], facet joints [3], and/or other structures [4]. Freemont et al. reported that nerve growth into the intervertebral disc was involved in the pathogenesis of chronic LBP [5], and other have reported that IVD abnormalities are related to the inflammation and axonal growth induced by inflammatory cytokines [6]. The expression of pain-related, proinflammatory mediators, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α, have been identified in degenerated IVDs, and may be related to discogenic LBP [6]. To alleviate discogenic LBP, intradiscal injections of anesthetic agents and/or steroids have been performed, but the effects remain controversial [7].

A previous study reported neither significant pain relief nor ODI score improvement after single intradiscal injections of the tumor necrosis factor-α inhibitor, etanercept (dose range, 0.1–1.5 mg), into discogenic LBP patients [8]. However, the etanercept doses (maximum, 1.5 mg) were lower than the dose used for treatment of rheumatoid arthritis (RA; 25 mg/week). Tocilizumab, which is a humanized, anti-IL-6 receptor monoclonal antibody that blocks IL-6 from binding to its receptor [9], has shown excellent therapeutic efficacy (prolonged pain relief) in patients with RA [10,11], which may be related to its clinically longer half-life. Ohtori et al. also reported that the epidural administration of tocilizumab into the spinal nerve reduced radicular pain [12], but there are no clinical reports describing the use of tocilizumab in patients with degenerative disc disease.

The current study assessed the pain-relieving effect, effective duration, and adverse events associated with intradiscal injection of tocilizumab in patients with discogenic LBP.

Materials and Methods

The ethics committee of our institution approved the protocol used in this study, and the patients provided written informed consent prior to participation in this study.

Beginning in December 2012, we enrolled 88 LBP patients, who were resistant to more than 3 months of conservative treatment. The inclusion criteria were: (1) patients with grades III–V IVD degeneration, according to their Pfirrmann classification following magnetic resonance imaging (MRI) [13], with the degeneration limited to 2 levels; (2) a numerical rating scale (NRS) score >4 (0, no pain; 10, worst pain); (3) an Oswestry disability index (ODI) score >30%, at baseline; and (4) absence of neurological abnormalities, including lower extremity pain or
numbness [14]. We excluded patients who had previous histories of lumbar surgery; spine or spinal cord tumors, infections, or trauma; and/or other neurologic or psychiatric disorders. Patients were allowed to take nonsteroidal anti-inflammatory drugs (NSAIDs) if they had been prescribed before the treatment, without a dosage change throughout the study period.

Discogenic LBP was diagnosed based on pain exacerbation during forward bending. Pain provocation discography was performed using the non-ionic contrast medium, iohexol (Daiichi-Sankyo, Tokyo, Japan), to determine the pain origin [15]. Intradiscal injections were performed as previously reported [16]. In the lateral decubitus position, 5 mL of 1% xylocaine (AstraZeneca, Osaka, Japan) was injected along the course of the needle from the skin to the IVD. A 22-gauge discography needle was advanced obliquely into the corresponding IVD under fluoroscopic guidance. The needle position was confirmed when the tip reached the center of the nucleus pulposus in the antero-posterior and lateral views. Subsequently, intradiscal injection of iohexol was performed to induce pain. After the procedure, we injected 1 mL of 1% xylocaine into the disc to confirm pain relief, in each patient. In patients with MRI evidence of 2 degenerated discs, discography was performed simultaneously for both IVDs; the IVD inducing the greater pain was selected for treatment.

The final analysis involved 63 patients (34 men, 29 women; average age, 58.2 years). Two or more weeks post-discography, intradiscal injection of bupivacaine (0.5% bupivacaine, 2 mL; AstraZeneca, Osaka, Japan), alone, was performed in 32 consecutive patients (control group). We also injected the offending discs with 40 mg of tocilizumab (Chugai Pharmaceutical, Tokyo, Japan) and 1–2 mL of 0.5% bupivacaine in the next 31 consecutive patients (tocilizumab group). This study was an open-label, single-institution, unblinded study (Fig. 1). Discography and intradiscal injections were performed by 3 physicians with sufficient experience with the procedure.

NRS scores were evaluated at baseline, 1 day, and 1, 2, 4, and 8 weeks after intradiscal injection. The ODI scores were also recorded at baseline, and at 4 and 8 weeks post-injection. We compared the time-course changes in NRS and ODI scores between the two groups [17]. To evaluate the influence of disc degeneration, we also compared the pain relief effect with tocilizumab, based on the grade of disc degeneration.

Any adverse events were recorded, including local infection, respiratory tract infection, hematoma, nerve injury, and/or any other possible side effects.

Data were analyzed using a Mann-Whitney $U$-test to compare scores between the groups and within the
Results

Thirty patients from each group were evaluable 8 weeks after treatment; 1 patient with discitis was excluded from the tocilizumab group, and 2 with insufficient follow-up were excluded from the control group (Fig. 1). The tocilizumab group included 20 men and 10 women (mean age, 60.6 years), and the control group comprised 12 men and 18 women (mean age, 59.7 years). The sex distribution was the only significant difference between the two groups (p = 0.038). NSAIDs were used by 26 subjects in the tocilizumab group and 25 in the control group (Table 1).

Fig. 2 shows that the NRS pain scores in both groups gradually increased over the 8 weeks following the initial pain relief. Pain relief was significantly greater in the tocilizumab group than that in the control group at 1 and 2 weeks, post-intervention (P < 0.05); however, significant differences were not noted at 4 and 8 weeks (Fig. 2).

Fig. 3 shows significantly lower ODI scores in the tocilizumab group than in the control group at 4 weeks, post-intervention (P < 0.05); however, no difference was seen at 8 weeks.

Differences were never observed between the NRS scores and the degree of disc degeneration in the tocilizumab group (Fig. 4).

One patient (non-compromised patient, no history of diabetes, malnutrition, or liver and kidney dysfunction) developed an infection after intradiscal tocilizumab injection, and complained of severe LBP on the day after the intradiscal injection. Clinical examination and MRI results revealed discitis, which was successfully treated with antibiotic administration, except for the residual LBP. No other complications, including local hematomas, systemic inflammatory reactions, or spinal nerve injuries, were observed.

Discussion

Previous reports have noted increased expression of proinflammatory cytokines in animals with injured IVDs and in humans with degenerated IVDs [18]. Other reports have indicated that overexpression of inflammatory cytokines, including IL-6, has been strongly linked with discogenic pain [19, 20]. Therefore, we speculated that inhibition of IL-6 overexpression might lead to pain relief. However, clinical reports on IL-6 inhibition for
Discogenic pain have not been previously published. The present study is the first to confirm improved NRS and ODI scores after intradiscal injection of tocilizumab, with an effect lasting 2–4 weeks.

Cohen et al. reported that the intradiscal injection of etanercept (maximum dose, 1.5 mg) was ineffective for patients with discogenic LBP [8]. However, their maximum dose injected was approximately 1/20 of that used clinically for RA treatment. On the other hand, the current study used 40 mg of tocilizumab, the maximum amount of intradiscal administration possible, and which is approximately half of the dose used for RA treatment.

Burke et al. reported that nucleus pulposus from patients suffering from painful degenerative disc disease release higher levels of IL-6 [19]. Significant differences were not observed at any time point, between the NRS scores and the degree of disc degeneration in the tocilizumab group. This may be due to the interaction of various inflammatory cytokines within the cytokine network [21]; the suppression of a single cytokine might provide only a transient effect. Further research is necessary to clarify the pathomechanism of discogenic pain on the basis of disc degeneration and inflammatory cytokines.

We experienced one case of discitis after tocilizumab administration among the 31 patients (3.0%). The incidence of discitis has previously been reported to be 0–4.9% in patients undergoing lumbar discography. Therefore, the incidence of discitis observed in this study was consistent with those reported in previous studies [22], and is likely not related to the intradiscal administration of tocilizumab.

In this study, we administered intradiscal bupivacaine, commonly used for the diagnosis and treatment of discogenic LBP [23], as an analgesic agent. Due to ethical considerations, a single administration of tocilizumab or saline was impossible. Although, several authors have reported a toxic effect of bupivacaine on IVD cells, based on in vitro studies [24], a radiologic and MRI study by Ohtori et al. failed to find evidence of accelerated disc degeneration within 5 years, in humans following a single intradiscal injection [25].

The present study has some limitations. First, the current study was not a randomized controlled trial; therefore, there was a potential for bias. Ideally, a randomized controlled trial and a dose-dependent outcomes trial should be conducted in the future. Second, we injected tocilizumab and bupivacaine into IVDs at the same time. To fully evaluate the pain-relieving effect of tocilizumab for discogenic pain, a study involving only the injection of tocilizumab is necessary, although it is ethically difficult. Third, more frequent evaluations of NRS and ODI scores may be required to reveal more detailed information on the intradiscal tocilizumab effect. Finally, a longer follow-up period is required to examine the pain-relieving effects and impact on IVDs in future studies.
In conclusion, intradiscal injection of tocilizumab demonstrated a short-term analgesic effect in patients with discogenic LBP, suggesting a clinical correlation between discogenic LBP and IL-6 expression. The clinical significance of this new therapy remains to be established. Further investigation into discogenic LBP pathology and an evaluation of its long-term pain relieving effect are required.

Disclosure

The authors report no conflicts of interest concerning the conduct and results of this study.
References


**Figure Legends**

**Fig. 1** Study flow diagram. The first subjects included 88 patients with low back pain (LBP) who were resistant to conservative treatment for >3 months. At the end of the study, 30 cases, in each group, were evaluable 8 weeks after intradiscal drug administration. IVD, intervertebral disc; MRI, magnetic resonance imaging

**Fig. 2** Changes in numerical rating scale scores for low back pain. The scores are significantly lower in the tocilizumab group than in the control group at weeks 1 and 2 (P < 0.05)

**Fig. 3** Oswestry disability index scores throughout the study period. There is a significant difference between the groups at 4 weeks (P < 0.05)

**Fig. 4** Correlation between the numerical rating scale score and the degree of disc degeneration in the tocilizumab group. No differences were observed at any time point
### Table 1. Patient demographic characteristics.

<table>
<thead>
<tr>
<th>Pfirrmann classification</th>
<th>Tocilizumab</th>
<th>Control</th>
<th>Statistical analysis between the groups</th>
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<tr>
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<td>Total</td>
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<td>Grade</td>
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<tr>
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<td>5</td>
<td>3</td>
</tr>
<tr>
<td>No. of patients</td>
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<td>17</td>
<td>13</td>
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<tr>
<td>Sex (male : female)</td>
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<td>12 : 5</td>
<td>8 : 5</td>
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<td>Age (range) (years)</td>
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<td>65.9</td>
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<td>No. of patients with 2 level disc degeneration</td>
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<td>No. using NSAIDs</td>
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<td>Pain score before injection</td>
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<td>8.4</td>
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<td>Oswestry disability Index</td>
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<td>56.3</td>
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<td>Affected disc level</td>
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N.S.: no significant difference between the groups

NSAIDs: nonsteroidal anti-inflammatory drugs
Study diagram

88 patients
with LBP who were resistant to conservative treatment for >3 months,
with IVD degeneration limited to 2 levels in MRI

63 patients diagnosed with discogenic LBP
<First procedure> <Second procedure>

Control group
(32 consecutive patients)

Dropout (n = 2)

Analyzed at 8 weeks
(n = 30)

Tocilizumab group
(31 consecutive patients)

Dropout (infection)
(n = 1)

Analyzed at 8 weeks
(n = 30)

Figure 1

~ Tocilizumab  • Control

Numerical rating scale score

Baseline 1 d 1 wk 2 wks 4 wks 8 wks

Time after intradiscal drug injection

Figure 2

*: P < 0.05, N.S.: not significant, compared with control
Figure 3

Figure 4