Anesthesiology 2007; 107:99–105

A Double-blind, Placebo-controlled, Dose–Response Pilot Study Evaluating Intradiscal Etanercept in Patients with Chronic Discogenic Low Back Pain or Lumbosacral Radiculopathy

Steven P. Cohen, M.D., Daniel Wenzell, M.D.,† Robert W. Hurley, M.D., Ph.D.,‡ Connie Kurihara, R.N.,§ Chester C. Buckenmaier III, M.D.,‖ Scott Griffith, M.D.,# Thomas M. Larkin, M.D.,** Erik Dahl, M.D.,†† Bennie J. Morlando, R.N.§*

Background: **In recent years, convincing evidence has emerged implicating tumor necrosis factor α as a causative factor in radiculopathy and discogenic back pain. But although preliminary open-label studies demonstrated promising results for the treatment of low back pain with tumor necrosis factor-α inhibitors, early optimism has been tainted by a controlled study showing no significant benefit in sciatica. To determine whether outcomes might be improved by a more direct route of administration, the authors evaluated escalating doses of intradiscal etanercept in 36 patients with chronic lumbosacral radiculopathy or discogenic low back pain.**

Methods: **A double-blind, placebo-controlled pilot study was conducted whereby six patients received 0.1, 0.25, 0.5, 0.75, 1.0, or 1.5 mg etanercept intradiscally in each pain-generating disc. In each escalating dose group of six patients, one received placebo. A neurologic examination and postprocedure leukocyte counts were performed in all patients at 1-month follow-up visits. In patients who experienced significant improvement in pain scores and function, follow-up visits were conducted 3 and 6 months after the procedure.**

Results: **At 1-month follow-up, no differences were found for pain scores or disability scores between or within groups for any dose range or subgroup of patients. Only eight patients remained in the study after 1 month and elected to forego further treatment. No complications were reported, and no differences were noted between preprocedure and postprocedure leukocyte counts.**

Conclusions: **Although no serious side effects were observed in this small study, a single low dose of intradiscal etanercept does not seem to be an effective treatment for chronic radicular or discogenic low back pain.**

IT would be difficult to overestimate the impact low back pain (LBP) has in industrialized countries. During the past half century, the prevalence of disabling LBP has surged dramatically in the Western world. The economic costs of LBP are astounding, exceeding by some estimates $50 billion per year in the United States alone.[1]

There are many sources of chronic LBP, with two of the most common being herniated disc[2] and internal disc disruption.[3,4] In recent years, compelling evidence has emerged implicating the inflammatory cytokine tumor necrosis factor α (TNF-α) as a major cause of radiculopathy, and to a lesser extent, discogenic LBP. Ozaktay *et al.*[5] showed that the application of inflammatory cytokines, present in degenerative and herniated disc tissue, results in sensitization of dorsal root neurons. In animal models, the exogenous application of TNF-α to nerve roots produces neuropathologic changes such as endoneurial edema, decreased conduction velocity, wallerian degeneration and demyelination, coupled with behavioral changes consistent with experimental disc herniation.[6,7] But when the TNF-α inhibitors infliximab and etanercept are administered at or just before disc herniation, both pathologic nerve root changes and spontaneous pain behavior are prevented.[8,9]

The evidence supporting a role for TNF-α in discogenic LBP is less robust but equally alluring. Weiler *et al.*[10] found the concentrations of TNF-α to be up to 10-fold higher in degenerated and herniated human lumbar discs removed during surgery than in control specimens examined at autopsy. In *in vitro* bovine discs, the application of low levels of TNF-α to nucleus pulposus induces protean degenerative changes comparable to that found in internal disc disruption.[11]

The results of these preclinical studies have led to multiple studies evaluating TNF-α inhibitors in radicular and discogenic LBP. In uncontrolled studies, both intravenous infliximab and subcutaneous etanercept were found to relieve both acute lumbar radiculopathy and chronic radicular and discogenic LBP.[12–15] However, in a more recent randomized, controlled study assessing the efficacy of a single intravenous infusion of infliximab in 40 patients with acute lumbosacral radiculopathy, Kor-

* COL S. Cohen, Associate Professor, Pain Management Division, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland; Anesthesia Service, Department of Surgery, Walter Reed Army Medical Center. † MAJ D. Wenzell, Department of Surgery, Madigan Army Medical Center, Tacoma, Washington (currently in Iraq). ‡ Assistant Professor, Pain Management Division, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland. § Anesthesia Service, Department of Surgery, Walter Reed Army Medical Center. ‖ LTC C. Buckenmaier, ** LTC (ret) T. Larkin, Anesthesia Service, Department of Surgery, # MAJ S. Griffith, Director, Pain Clinic, †† LTC E. Dahl, Department of Othopedic Surgery, Walter Reed Army Medical Center.

Received from the Department of Surgery, Anesthesia Service, Walter Reed Army Medical Center, Washington, D.C. Submitted for publication October 31, 2006. Accepted for publication January 9, 2007. Supported in part by the John P. Murtha Neuroscience and Pain Institute, Johnstown, Pennsylvania, and the US Department of the Army, Washington, D.C. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Address correspondence to Colonel Cohen: Johns Hopkins Division of Pain Management, 550 North Broadway, Suite 301, Baltimore, Maryland 21205. scohen40@jhmi.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue.

honen *et al.*[16] observed significant pain reductions in both treatment and control groups, with no differences noted between regimens.

Etanercept is a soluble p75 TNF-α receptor genetically fused with the Fc portion of immunoglobulin G. When etanercept binds to TNF with a longer half-life than the native receptor, it blocks its interaction with cell surface receptors. In an effort to reduce side effects, improve efficacy, and establish safety data for future studies, we undertook a double-blind, placebo-controlled, dose–response study evaluating escalating doses of intradiscal etanercept in the treatment of chronic radicular and discogenic LBP.

Materials and Methods

Permission to conduct this double-blind, placebo-controlled study was granted by all relevant Walter Reed Army Medical Center and US Department of Defense medical and ethical committees. All procedures were conducted at the Walter Reed Army Medical Center Pain Clinic, Washington, D.C., between January 2005 and August 2006. Before performing any procedures, all patients signed informed consent.

All discographies were done as screening procedures for intradiscal electrothermal therapy, percutaneous disc decompression, or open surgery. Inclusion criteria were based on the procedure for which patients were being screened. For intradiscal electrothermal therapy and percutaneous disc decompression, our selection criteria have previously been published.[17,18] Inclusion criteria for percutaneous intradiscal procedures included chronic low back and/or leg pain of more than 6 months' duration, lack of response to conservative therapy, age 60 yr or younger, disc height greater than 50% of normal, body mass index less than 30, and one or more discs with evidence of degenerative changes including loss of disc height, disc dessication, and endplate signal changes on T1- and T2-weighted magnetic resonance imaging. For percutaneous disc decompression, the main indication for discography was a small (< 6 mm) contained disc herniation causing concordant radicular symptoms.[18] No patient underwent discography solely for the purpose of intradiscal etanercept injection. The patients who underwent provocative discography as a presurgical screening test were being evaluated for total disc replacement or arthrodesis. Except for the restrictions on age, body mass index, and disc height, the inclusion criteria for these patients were similar to those for intradiscal treatments.

Exclusion criteria were symptomatic spinal stenosis, grade 2 or greater spondylolisthesis, inflammatory arthritis, untreated coagulopathy, malignancy, overt secondary gain issues, and an unstable medical or psychiatric condition that might preclude optimal therapy.[19] Psychiatrically unstable patients were ruled out as study candidates by prescreening Beck Depression Inventory scores (> 20) and historic examination (*e.g.*, questions targeting depression, post–traumatic stress disorder, and somatization disorder). As added exclusion criteria, all study patients had to have a normal complete blood cell count and negative antinuclear antibody and double-stranded DNA on prescreening laboratory testing.

Randomization

Potential study patients were randomly assigned by presealed envelopes to receive either intradiscal etanercept or saline in a 5:1 ratio. Randomization was deferred until discography was complete so that the desired ratio was maintained. In the event of a negative discography, the sealed envelope was returned to the research coordinator for redistribution to maintain the strict 5:1 etanercept:placebo ratio, which was mandated by the Department of Clinical Investigation. Both patients and physicians were blinded to the contents of the injectate.

To assess dose-responsiveness, each successive group of six patients comprised one treatment group. In group 1, five patients received 0.1 mg etanercept per positive discogram and one received saline. In group 2, five patients received 0.25 mg etanercept per positive discogram and one received saline. In group 3, five patients received 0.5 mg etanercept per positive discogram and one received saline. In group 4, five patients received 0.75 mg etanercept per positive discogram and one received saline. In group 5, five patients received 1.0 mg etanercept per positive discogram and one received saline. In group 6, five patients received 1.5 mg etanercept per positive discogram and one received saline. Before proceeding with dose escalation, all patients in the preceding treatment group had to complete their 1-month follow-up visits without evidence of toxicity that could be attributed to the study drug. The dosages of etanercept administered were chosen based on the 100:1 ratio used to calculate doses for intrathecal opioids and intradiscal antibiotics. In addition to being blinded to the injectate contents (*i.e.*, etanercept or placebo), patients were not informed about or informed as to which group they belonged to.

Discography and Disc Injection

Our technique and criteria for a positive discogram have been previously described.[20] A 22-gauge intravenous line was placed in all patients, and sedation with midazolam and fentanyl was administered if necessary. Subjects received 1 g cefazolin before the procedure. Discography was performed with the patient in the prone position on all suspected discs using a double-needle, extrapedicular approach. Discs were injected based on abnormal imaging studies and physical examination. Twenty-two gauge, 7-inch spinal needles were inserted into the center of the nucleus pulposus using

oblique, anteroposterior, and lateral fluoroscopic views. Criteria for a positive discogram included an abnormal radiographic appearance on both magnetic resonance imaging and discography, and concordant pain of 6 or greater out of 10 at 50 psi or less above opening pressure. At least one negative, adjacent control disc also had to be present for discography to be considered positive. Patients were blinded to the timing and level of disc stimulation.

All doses of etanercept (Enbrel; Immunex Corp., Seattle, WA) were reconstituted with 0.5 ml sterile water by a research nurse who maintained blinding. In the placebo group, patients received 0.5 ml saline. After determination of a positive discogram, the physician was given an unlabeled 1-ml syringe(s) whose contents were slowly injected into the positive disc(s). Subjects received one dose for each positive disc (*e.g.*, a patient with two positive discograms received one injection in each disc). After the study drug was administered, patients received 5 mg cefazolin per disc for infection prophylaxis.

Before the first follow-up visit, no patient underwent any additional therapeutic interventions. Subjects were given instructions about how to increase or decrease their preprocedure analgesic medications based on their response to therapy. For those patients who were not taking prediscography analgesics, a prescription for a nonsteroidal antiinflammatory drug (naproxen or celecoxib) was provided in the event that they experienced significant worsening of their pain.

Outcomes Measures

Data were obtained by a physician or investigator blinded to the patient's treatment group. The primary outcome measure was the visual analog scale (VAS) pain score, which reflected the average pain experienced by the patient for 10 days before follow-up. Secondary outcome measures included Oswestry Disability Index (ODI) score, reduction in analgesic medications (defined as any reduction in opioid use or complete cessation of nonopioid analgesics), and global perceived effect. A positive global perceived effect was defined as an affirmative response to the following three questions:

1. My pain has improved/worsened/stayed the same since my last visit.
2. The treatment I received improved/did not improve my ability to perform daily activities.
3. I am satisfied/not satisfied with the treatment I received and would recommend it to others.

Follow-up visits were performed in all patients 1 month after injection. If patients obtained a positive global perceived effect and significant ($>$ 20%) pain relief and/or functional improvement that obviated the need for further therapy, they were reevaluated 3 and 6 months after treatment. All patients were unblinded 3 months after injection.

Table 1. Demographic and Clinical Characteristics of Study Subjects

Age, mean (SE), yr	39.3 (1.9)
Sex	
Male	78%
Female	22%
Active duty status	63%
Location of symptoms	
Axial	58%
Radicular	42%
Opioid use	43%
Failed back surgical syndrome	17%
Duration of symptoms, mean (SE), yr	5.3 (0.7)
Leukocyte count, cells/mm^3	
Preprocedural	6.8 (0.3)
Postprocedural	7.1 (0.5)
Number of levels treated	
1	58%
2	36%
3	6%

Data are presented as percent unless otherwise specified.

Physician unblinding was done at 1 month in patients who obtained inadequate pain relief and desired further intervention. In those patients who obtained significant pain relief 1 month after disc injection, physician unblinding was done at 3-month follow-up.

At their first follow-up visit, all patients underwent a complete neurologic examination and a leukocyte count to monitor possible side effects from etanercept. Any patient who reported new neurologic symptoms or significantly increased pain received repeat magnetic resonance imaging. Dose escalation took place only after all subjects injected at the previous dose exhibited no evidence of drug-related toxicity.

Statistical analyses were performed using STATA version 9.2 (Statcorp, College Station, TX). The distribution of categorical variables in each group was compared using the Fisher exact test and logistic regression. Continuous variables were compared with analysis of variance and linear regression. Categorical data are reported by number of subjects and percentage. Continuous data are reported as mean and SE unless otherwise indicated. A P value less than 0.05 was considered statistically significant.

Results

Data were analyzed from 36 patients. No patient was lost to follow-up, and all subjects were present for their expected follow-up visits. Demographic (sex, age, military duty status) and clinical characteristics (previous back surgery, location of pain, duration of pain, number of levels treated, preprocedural leukocyte count, presence or absence of preprocedural opioid use) were similar among the different dosage groups including the placebo group ($P > 0.1$; table 1). Preprocedure VAS scores did not differ based on the sex or age of the study

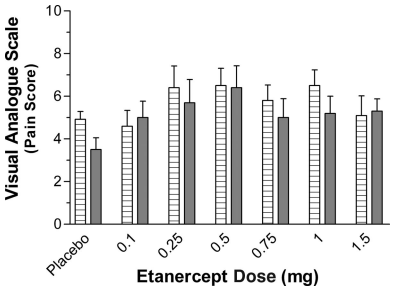

Fig. 1. Bar graph showing no relation between visual analog scale pain scores and etanercept dose. The *white bar* represents baseline values, and the *gray bar* indicates pain scores 1 month after injection (n = 5 per treatment group, 6 in placebo group).

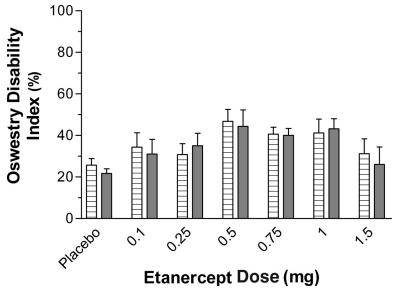

Fig. 2. Bar graph showing no relation between Oswestry Disability Index scores and etanercept dose. The *white bar* represents baseline values, and the *gray bar* indicates disability scores 1 month after injection.

participants, dosage group, presence of axial or radicular pain, duration of pain complaints, number of discs treated, active duty status, preprocedural opioid use, or previous back surgery ($P > 0.05$). Similarly, preprocedural ODI scores did not differ based on the same demographic and clinical variables with the exception of opioid use. The 40% of patients who were receiving opioid therapy at the time of enrollment in this study had significantly higher preprocedure ODI scores than those who were not taking opioid medications (43.4 ± 2.8 and 29.2 ± 2.8, respectively; $P < 0.01$).

Primary Outcome Measure

No difference in the primary outcome, VAS score at 1-month follow-up, was detected between or within dosage groups (fig. 1). Eight of the 36 subjects had greater than 20% pain relief and a positive global perceived effect and were hence followed up at 3 months. Three of the 8 patients were in the placebo group, 2 were in the 0.5-mg group, and 1 each was in the 0.1-, 0.75-, and 1-mg groups. The 3 placebo group subjects who experienced a successful outcome had a mean reduction in VAS score of 47% at 1 month. The 2 subjects in the 0.5-mg group who had a successful outcome had an average reduction in VAS score of 20%. The 3 subjects with a successful outcome at 1 month in the 0.1-, 0.75-, and 1-mg groups had VAS pain score reductions of 33%, 67%, and 43%, respectively. Three of the 8 subjects with a positive outcome at 1 month continued to have a successful outcome at 3 months. One subject each was in the placebo, 0.1-mg, and 0.75-mg groups. These subjects had reductions in 3-month VAS pain scores of 40%, 33%, and 71%, respectively. At their 6-month follow-up visits, the 2 patients in the placebo and 0.1-mg groups continued to obtain good pain relief, whereas the patient in the 0.75-mg group experienced a recurrence of his pain to baseline.

Secondary Outcome Measures

No differences existed between or within groups for ODI scores (fig. 2), global perceived effect scores (data not shown), leukocyte counts (fig. 3), or medication usage (data not shown) at the 1-month follow-up. Three- and 6-month data were collected for those patients with a positive response at 1 month. The 3 placebo group subjects who experienced a successful outcome had a mean reduction in ODI of 26% at 1 month. The 2 subjects in the 0.5-mg group who had a successful outcome both had ODI reductions of 32%. The 3 subjects with a successful outcome at 1 month in the 0.1-, 0.75-, and 1-mg groups reported reductions in ODI scores of 9%, 23%, and 11%, respectively. Three of the 8 subjects with a positive outcome at 1 month continued to have a successful outcome at 3 months. One subject each was in the placebo, 0.1-mg, and 0.75-mg groups. These 3 subjects had 3-month reductions in ODI scores of 19%, 0%, and 32%, respectively. At 6 months after the procedure, all experienced a return of their ODI score to baseline.

Analysis by Back Pain Classification, Predictive Factors, and Complications

Sex, age, location of pain (axial or radicular), number of levels treated, preprocedure opioid use, and military duty status were not associated with 1-month VAS scores when analyzed individually or when all covariates (including dosage of etanercept given) were controlled for using multivariate regression ($P > 0.05$; table 1). Among the 21 patients with discogenic LBP, 6 (29%) had a positive outcome at 1 month *versus* 2 of the 15 (13%)

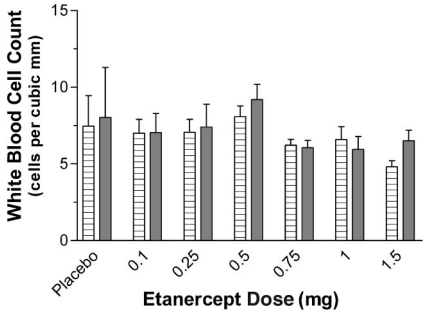

Fig. 3. Bar graph showing no significant change in mean leukocyte counts after intradiscal etanercept injections. The *white bar* represents baseline values, and the *gray bar* indicates leukocyte counts 1 month after injection.

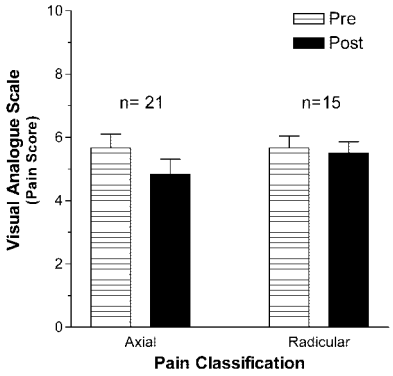

Fig. 4. Bar graph showing the preinjection and postinjection visual analog scale pain scores based on pain classification. Mean etanercept dose for patients with axial back pain: 0.53 mg (SE 0.12). Mean etanercept dose for patients with sciatica: 0.62 mg (SE 0.12).

with radicular symptoms ($P = 0.75$; figs. 4 and 5). However, duration of pain and the previous back surgery were positively associated with VAS scores, indicating the longer the patient experienced pain, the less likely a positive response would be obtained ($P = 0.05$ and $P = 0.01$, respectively; table 1). No variable was associated with 1-month ODI, global perceived effect, or change in medication consumption ($P > 0.05$; table 2).

Only one patient experienced a pain increase of greater than 20% at the 1-month follow-up (in the 1.5-mg group), and no patient experienced qualitatively new symptoms. These results were investigated by the intradiscal Enbrel study group and found to actually be an improvement over previously published data.[21] This patient and six others received repeat magnetic resonance imaging within 75 days of their intradiscal injection, with none exhibiting any significant interval changes.

Discussion

In the dose range examined in this study, the lack of efficacy of a one-time intradiscal injection of etanercept

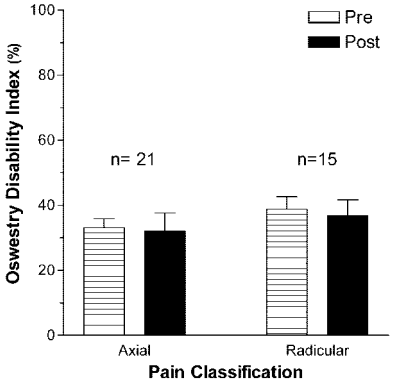

Fig. 5. Bar graph showing the preinjection and postinjection Oswestry Disability Index scores based on pain classification. Mean etanercept dose for patients with axial back pain: 0.53 mg (SE 0.12). Mean etanercept dose for patients with sciatica: 0.62 mg (SE 0.12).

Table 2. Demographic and Clinical Factors Associated with Outcome

	VAS*	ODI*	GPE†	Meds†
Sex	0.67	0.84	0.61	0.60
Age	0.50	0.96	0.22	0.22
Type of pain	0.40	0.61	0.27	0.88
Duration of pain	*0.05*	0.12	0.13	0.37
Levels treated	0.89	0.99	0.40	0.88
Duty status	0.32	0.36	0.50	0.14
Opioid use	0.32	0.11	0.83	0.42
FBSS	*0.01*	0.87	0.42	0.82
Dose	0.20	0.36	0.71	0.66

* *P* values determined from adjusted multivariate linear regression analysis. † *P* values determined from adjusted multivariate logistic regression analysis.

FBSS = failed back surgery syndrome; GPE = global perceived effect; ODI = Oswestry Disability Index score; VAS = visual analog scale pain score.

in patients with chronic LBP refractory to more conventional treatments seems unequivocal based on the results of this study. No dose of etanercept produced any appreciable benefit in any outcome measure for either chronic radicular or discogenic LBP patients. But the results of this double-blind, placebo-controlled pilot study are not uniformly negative. Because no subset of patients experienced any significant worsening pain, new neurologic symptoms, signs of toxicity, or evidence of anemia or immunosuppression, this suggests that toxicity, if present from low doses of intradiscal etanercept, is not common. Whether toxicity would be observed with repeated administration or larger doses remains unknown.

Several factors may have contributed to our negative results. First, preclinical and clinical studies involving TNF-α and its inhibitors have predominantly focused on acute LBP, where their role in the pathogenesis, prevention, and treatment of the condition is strong and irrefutable.[5–9,12,13] To minimize risk, our study focused on patients with chronic back pain for whom multimodal conventional treatments, including opioid and nonopioid analgesics, physical therapy, and a plethora of different therapeutic injections, had already failed. In almost all company-sponsored clinical trials, including those evaluating etanercept and infliximab for acute sciatica, these patients are usually excluded because of their well-known predisposition to treatment failure.[12,13,16] Most preclinical studies showing a preemptive effect for anti–TNF-α treatments administered the drugs before or at the time of injury.[6,8,9] For LBP treatment, duration of pain has been shown to predict treatment failure for a wide range of procedural interventions, including epidural steroid injections, decompression and fusion surgery, and lumbar facet joint radiofrequency denervation.[22–25]

A second reason for our findings may have been our route of administration and the conditions we treated. Whereas strong evidence exists to support the use of

epidural and intrathecal analgesics for spinal pain,[22,26] the preponderance of data do not support the use of intradiscal steroids or other analgesics for chronic LBP.[27,28] A substantial percentage (58%) of our subjects presented with predominantly axial LBP secondary to internal disc disruption, a condition notoriously difficult to treat.[29] Had intradiscal etanercept been efficacious in only one of the two subgroups (*i.e.*, radicular or discogenic LBP) of patients, this heterogeneity would function to reduce even further the already low power inherent in a dose-ranging study. Although retrospective studies by one research group have reported intermediate-term pain relief after subcutaneous injection of etanercept for discogenic spinal pain,[14,15] the evidence supporting its use in this condition is considerably less robust than for sciatica.

One small subset of patients with degenerative disc disease that might conceivably benefit from intradiscal anti–TNF-α is those with acute endplate fractures, which can lead to the introduction of cytokines into the disc.[4] Endplate fractures in and of themselves are not an indication for surgery or percutaneous intradiscal procedures. However, because no patient entered this protocol for the express purpose of being treated with intradiscal etanercept (*i.e.*, all patients underwent discography as part of their evaluation for either surgery or a percutaneous disc procedure), we did not target patients with acute endplate fractures.

A third reason for our negative outcomes may have been the single low doses administered, which were designed to optimize safety and assess dose-responsiveness. Etanercept and other anti–TNF-α drugs are clinically used for a wide range of conditions including rheumatoid arthritis, spondyloarthropathies, inflammatory bowel disease, and neuropathic pain—all disorders in which inflammation is purported to play a key role.[30] Although the dosages and dosing intervals vary widely between and within the assorted conditions studied, one common denominator is the need for multiple treatments spread out over short time intervals. In the clinical studies evaluating etanercept for sciatica and discogenic pain, subjects received either three 25-mg injections every 3 days or an average of 2.3 25-mg injections, respectively.[13,15] In contrast, the mean dose used in our patients was approximately one hundredth of what was used in these studies. Because no conversion data exist between subcutaneous and intradiscal etanercept dosages, we estimated our etanercept dosages based on extrapolated dose ratios for other analgesic agents (*e.g.*, 1:100 parenteral to intrathecal ratio for opioids, 1:100 parenteral to intradiscal ratio for antibiotics, and 1:1 intrathecal to intradiscal ratio for local anesthetics).[31–33] Therefore, the dosing scheme that we used may not have been sufficient. If escalating doses had been injected multiple times, it is possible that some pain relief or functional benefit might have eventually been observed, although the lack of any noticeable improvement at even the highest doses mitigates against this hypothesis.

The flip side of this argument is that higher doses of etanercept would almost inevitably result in a higher incidence of systemic side effects, which would have undermined our rationale for conducting this study. In a recent epidemiologic study, Cohen *et al.* [34] showed LBP to be the number one cause of medical evacuation from the theaters of combat in Iraq. Because TNF-α inhibitors are easy to administer and were shown in previous studies to provide almost immediate, long-lasting relief in a majority of LBP patients,[12,13] we originally proposed administering these drugs in high parenteral doses downrange at combat support hospitals. However, this proposal was rejected by the Department of the Army over concerns regarding toxicity, particularly immunosuppression at high, parenteral doses. In World War I, World War II, and the Korean conflict, infectious disease was the leading cause of morbidity and mortality.[35] Other potential toxic effects that might manifest with larger doses of intradiscal etanercept (especially in discs containing an incompetent annulus fibrosis whereby the injectate can freely extravasate into the epidural space) include massive nerve root inflammation and permanent injury to the cauda equina.

Finally, it is conceivable that unlike other antinociceptive medications such as steroids and opioids, only systemic administration of anti–TNF-α drugs may mitigate the physiologic and behavior changes associated with TNF-α. In a study by Kawakumi *et al.*,[36] the authors found that the local application of autologous nucleus pulposus to nerve roots in leukopenic rats produced neither mechanical allodynia nor reliably elevated levels of normal leukocytes, suggesting that the main contribution of TNF to pain may be mediated through circulating leukocytes. In a landmark study by Olmarker and Larsson,[6] local application of anti–TNF-α antibody to pig cauda equina only partially blocked the nucleus pulposus–induced reduction in nerve conduction velocity. The difference observed was not statistically significant compared with the control group, and significantly less than that noted after intravenous doxycycline administration, which by itself is a cytokine inhibitor. In the same study, the authors suggested that simultaneous blockade of other inflammatory mediators might be necessary to prevent the adverse nucleus pulposus–induced effects on nerve function.

The main upside of this study was the absence of any overt signs or laboratory evidence of adverse effects from a one-time, low-dose intradiscal etanercept injection. However, the absence of any clinical signs of neurotoxicity does not rule out subclinical toxicity, which may become relevant should higher doses be injected in or around neural structures in future studies.

In summary, the results of this small pilot study do not support a one-time, low-dose intradiscal injection of et-

anercept as a treatment for either chronic discogenic LBP or sciatica. Despite our neutral findings, the long-term safety data of intradiscal etanercept remains unknown. Both preclinical safety studies and more clinical outcome studies are needed before any further studies are undertaken evaluating intradiscal TNF-α inhibitors in LBP.

References

1. Nachemson A: Newest knowledge of low back pain. Clin Orthop Rel Res 1992; 279:8–20
2. Long DM, BenDebba M, Torgerson WS, Boyd RJ, Dawson EG, Hardy RW, Robertson JT, Sypert GW, Watts C: Persistent back pain and sciatica in the United States: Patient characteristics. J Spinal Disord 1996; 9:40–58
3. Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N: The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. Spine 1995; 20:1878–83
4. Cohen SP, Barna SA, Larkin TM, Palmer WE, Hecht AC, Stojanovic MP: Lumbar discography: A comprehensive review of outcome studies, diagnostic accuracy and principles. Reg Anesth Pain Med 2005; 30:163–83
5. Ozaktay AC, Cavanaugh JM, Asik I, DeLeo JA, Weinstein JA: Dorsal root sensitivity to interleukin-1 beta, interleukin-6 and tumor necrosis factor in rats. Eur Spine J 2002; 11:467–75
6. Olmarker K, Larsson K: Tumor necrosis factor (alpha) and nucleus-pulposus-induced nerve root injury. Spine 1998; 23:2538–44
7. Igarashi T, Kikuchi S, Shubayev V, Myers RR: Exogenous tumor necrosis factor-alpha mimics nucleus pulposus-induced neuropathology. Spine 2000; 25: 2975–80
8. Olmarker K, Nutu M, Storkson R: Changes in spontaneous behavior in rats exposed to experimental disc herniation are blocked by selective TNF-alpha inhibition. Spine 2003; 28:1635–42
9. Olmarker K, Rydevik B: Selective inhibition of tumor necrosis factor-alpha prevents nucleus pulposus-induced thrombus formation, intraneural edema, and reduction of nerve conduction velocity: Possible implications for future pharmacologic treatment strategies of sciatica. Spine 2001; 26:863–9
10. Weiler C, Nerlich AG, Bachmeier BE, Boos N: Expression and distribution of tumor necrosis factor alpha in human lumbar intervertebral discs: A study in surgical specimen and autopsy controls. Spine 2005; 30:44–53
11. Seguin CA, Pilliar RM, Roughley PJ, Kandel RA: Tumor necrosis factor-alpha modulates matrix production and catabolism in nucleus pulposus tissue. Spine 2005; 30:1940–8
12. Korhonen T, Karppinen J, Malmivaara A, Autio R, Niinimaki J, Paimela L, Kyllonen E, Lindgren KA, Tervonen O, Seitsalo S, Hurri H: Efficacy of infliximab for disc herniation-induced sciatica: One-year follow-up. Spine 2004; 29:2115–9
13. Genevay S, Stingelin S, Gabay C: Efficacy of etanercept in the treatment of acute, severe sciatica: A pilot study. Ann Rheum Dis 2004; 63:1120–3
14. Tobinick EL: Perispinal TNF-alpha inhibition for discogenic pain. Swiss Med Wkly 2003; 133:170–7
15. Tobinick E, Davoodifar F: Efficacy of etanercept delivered by perispinal administration for chronic back and/or neck disc-related pain: A study of clinical observations in 143 patients. Curr Res Med Opin 2004; 20:1075–85
16. Korhonen T, Karppinen J, Paimela L, Malmivaara A, Lindgren KA, Jarvinen S, Niinimaki J, Veeger N, Seitsalo S, Hurri H: The treatment of disc herniation-induced sciatica with infliximab: Results of a randomized, controlled, 3-month follow-up study. Spine 2005; 30:2724–8
17. Cohen SP, Larkin T, Abdi S, Chang A, Stojanovic M: Risk factors for failure and complications of intradiscal electrothermal therapy: A pilot study. Spine 2003; 28:1142–7
18. Cohen SP, Williams S, Kurihara C, Griffith S, Larkin TM: Nucleoplasty with or without intradiscal electrothermal therapy (IDET) as a treatment for lumbar herniated disc. J Spinal Disord Tech 2005; 18:S119–24
19. Carragee EJ, Tanner CM, Khurana S, Hayward C, Welsh J, Date E, Truong T, Rossi M, Hagle C: The rates of false-positive lumbar discography in select patients without low back symptoms. Spine 2000; 25:1373–80
20. Cohen SP, Larkin T, Fant GV, Oberfoell R, Stojanovic M: Does needle insertion site affect diskography results? A retrospective analysis. Spine 2002; 27:2279–83
21. Carragee EJ, Chen Y, Tanner CM, Hayward C, Rossi M, Hagle C: Can discography cause long-term back symptoms in previously asymptomatic subjects? Spine 2000; 25:1803–8
22. Benzon HT: Epidural steroid injections for low back pain and lumbosacral radiculopathy. Pain 1986; 24:277–95
23. Cohen SP, Hurley RW, Christo PJ, Winkley J, Mohiuddin MM, Stojanovic MP: Clinical predictors of success and failure for lumbar facet radiofrequency denervation. Clin J Pain 2007; 23:45–52
24. Dauch WA, Fasse A, Brucher K, Bauer BL: Predictors of treatment success after microsurgical operation of lumbar intervertebral disk displacement. Zentralbl Neurochir 1994; 55:144–55
25. Quigley MR, Bost J, Maroon JC, Elrifai A, Panahandeh M: Outcome after microdiscectomy: Results of a prospective single institutional study. Surg Neurol 1998; 49:263–7
26. Hassenbusch SJ, Portenoy RK, Cousins M, Buchser E, Deer TR, Du Pen SL, Eisenach J, Follett KA, Hildebrand KR, Krames ES, Levy RM, Palmer PP, Rathmell JP, Rauck RL, Staats PS, Stearns L, Willis KD: Polyanalgesic Consensus Conference 2003: An update on the management of pain by intraspinal drug delivery—report of an expert panel. J Pain Symptom Manage 2004; 27:540–63
27. Khot A, Bowditch M, Powell J, Sharp D: The use of intradiscal steroid therapy for lumbar spinal discogenic pain: A randomized controlled trial. Spine 2004; 29:833–6
28. Simmons JW, McMillin JN, Emery SF, Kimmich SJ: Intradiscal steroids: a prospective double-blind clinical trial. Spine 1992; 17 (suppl):S172–5
29. Carragee EJ: Persistent low back pain. N Engl J Med 2005; 352:891–8
30. Ellerin T, Rubin RH, Weinblatt ME: Infections and anti-tumor necrosis factor alpha therapy. Arthritis Rheum 2003; 48:3013–22
31. Kotilainen E, Muittari P, Kirvela O: Intradiscal glycerol or bupivacaine in the treatment of low back pain. Acta Neurochir (Wien) 1997; 139:541–5
32. Cousins MJ, Mather LE: Intrathecal and epidural administration of opioids. ANESTHESIOLOGY 1984; 61:276–310
33. Osti OL, Fraser RD, Vernon-Robers B: Discitis after discography: The role of prophylactic antibiotics. J Bone Joint Surg (Br) 1990; 72:271–4
34. Cohen SP, Griffith S, Larkin TM, Villena F, Larkin R: Presentation, diagnoses, mechanisms of injury, and treatment in soldiers injured in Operation Iraqi Freedom: An epidemiological study conducted at two military pain management centers. Anesth Analg 2005; 101:1098–103
35. Hoeffler DF, Melton LJ III: Changes in the distribution of navy and marine corps casualties from World War I through the Vietnam conflict. Mil Med 1981; 146:776–9
36. Kawakami M, Tamaki T, Matsumoto T, Kuribayashi K, Takenaka T, Shinozaki M: Role of leukocytes in radicular pain secondary to herniated nucleus pulposus. Clin Orthop Relat Res 2000; 376:268–77