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Randomized, Double-blind, Placebo-controlled, Dose-response, and Preclinical Safety Study of Transforaminal Epidural Etanercept for the Treatment of Sciatica

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Background: **Recent evidence implicates the inflammatory cytokine tumor necrosis factor as a major cause of radiculopathy. Yet, whereas open-label studies with systemically delivered tumor necrosis factor inhibitors have yielded positive results, a placebo-controlled study failed to demonstrate efficacy. One variable that may have contributed to poor outcomes is low drug levels at the site of nerve inflammation. To date, no studies have evaluated the efficacy or safety of epidurally administered anti–tumor necrosis factor agents.**

Methods: **A double-blind, placebo-controlled, dose-response study was conducted to evaluate an epidural tumor necrosis factor inhibitor. Twenty-four patients with subacute lumbosacral radiculopathy were randomly assigned to receive two transforaminal epidural injections of 2, 4, or 6 mg of entanercept 2 weeks apart in successive groups of eight. In each group, two patients received epidural saline. A parallel epidural canine safety study was conducted using the same injection doses and paradigm as in the clinical study.**

Results: **The animal and human safety studies revealed no behavioral, neurologic, or histologic evidence of drug-related toxicity. In the clinical arm, significant improvements in leg and back pain were collectively noted for the etanercept-treated patients, but not for the saline group, one month after treatment. One patient in the saline group (17%), six patients in the 2-mg group (100%), and four patients each in the 4-mg and 6-mg groups (67%) reported at least 50% reduction in leg pain and a positive global perceived effect one month after treatment. Six months after treatment, the beneficial effects persisted in all but one patient.**

Conclusion: **Epidural entanercept holds promise as a treatment for lumbosacral radiculopathy.**

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LUMBAR radicular pain is a common cause of disability. Conservative therapies, such as drugs and physical therapy, have proven no more effective than natural history.[1] Surgery remains an option, but it is a major, irreversible undertaking. Moreover, whereas surgery can relieve acute pain, its long-term outcome may be no better than with conservative therapy.[2–4] An alternative to conservative therapy and surgery has been injection therapy, notably epidural injections of corticosteroids. Epidural injections, however, have proven to be effective for only a subset of patients.[5,6]

Two areas wherein great strides have been made are elucidating the mechanisms and delineating the optimal treatment of radiculopathy. In recent years, compelling evidence has emerged implicating tumor necrosis factor-α (TNF)[7–10] and, to a lesser extent, other inflammatory mediators[11] as mechanisms of radiculopathy. In degenerated human intervertebral discs, TNF is present in increased concentrations.[7] In preclinical models, the application of TNF to nerve roots produces neuropathological and behavioral changes consistent with experimental disc herniation.[8–10] Moreover, the preemptive application of TNF inhibitors just before nerve injury may prevent these histopathological and behavioral changes.[12,13] Yet, translating these findings to clinical practice has yielded less than auspicious results. Whereas uncontrolled studies evaluating systemic infliximab and etanercept to treat lumbosacral radiculopathy demonstrated long-lasting pain relief,[14,15] the only controlled study found no significant difference between treatment and control groups.[16]

One explanation for these paradoxical results is that systemic administration is less effective than local administration in blocking the deleterious cascade of TNF-induced cellular events. This hypothesis is supported directly by animal studies showing the antinociceptive effect of local TNF inhibition to be more potent and longer lasting than that observed with systemic administration,[17] and indirectly by a human study showing excellent outcomes in six soldiers with postamputation pain treated with perineural etanercept.[18]

The debate over the optimal treatment for radiculopathy is one of considerable complexity. However, the most recent evidence suggesting that the benefits of surgery may be less pronounced and more ephemeral than previously thought makes the development of alternative treatments critically important.[2–4] The conceptual appeal of transforaminal epidural administration is that injecting a drug around the affected nerve root(s) purportedly maximizes benefits while minimizing the risks associated with treatment.

Two factors predicate the safe and responsible conduct of a clinical trial involving a new agent: safety and *prima facie* effectiveness. First, before exposing large groups of patients to the potential risks of a new molecular entity, the safety and efficacy should be determined in smaller studies. In this regard, it is known that TNF blockers can have adverse effects when administered in high doses systemically.[19] It is not known if these effects occur with transforaminal administration.

Second, systematic preclinical evaluation of safety with formal histopathology is necessary for the development of drugs for neuraxial delivery.[20–22] As a minimum initial analysis, preclinical safety should be established in a validated model using the same route of delivery, with multiple boluses in the upper range of doses/concentrations that may be used in humans.[23] Therefore, the principal aims of this study were to provide initial evidence of safety and efficacy, which should serve as the foundation for a large, multicenter study.

Materials and Methods

Preclinical Safety Study

Animals. The concurrent animal study was undertaken according to protocols approved by the Institutional Animal Care and Use Committee, University of California, San Diego, California. Destination bred beagle male and female dogs (Marshall Farms, North Rose, NY) were acclimated, submitted to neurologic examinations and clinical chemistries, and entered into the study. Animals were maintained in individual runs with free access to water and dry chow.

Study Paradigm. Three male and three female dogs (12–15 kg) were anesthetized with propofol. After preparing the skin, a 19-gauge epidural Touhy needle was inserted at the L6-7 or L7-S1 interspace. A 22-gauge polyethylene catheter was then threaded 8–10 cm to approximate the L2-3 vertebral level. The animals were randomly assigned to receive an epidural injection of either 2 ml of normal saline (1M/1F) or 6 mg/2 ml etanercept (2M/2F) over 2 min. After 10 min elapsed, the catheter was withdrawn and the animals recovered. The same procedure was performed twice at 2-week intervals.

Study Observations. Before and after surgery, temperature and specific behavioral indices were recorded daily to assess the state of arousal, muscle tone, and motor coordination throughout the in-life phase of the study, as described elsewhere.[24] Before and 2 days after each injection, heart rate, tail arterial blood pressure, and a detailed neurologic examination consisting of spinal reflexes, sensory and pain responses, proprioception, gait and movement, cranial nerve function, and fundoscopic examination, were taken by a veterinarian unaware of treatment allocation.

Necropsy/Histopathology. Forty-eight hours after the last injection, blood and cisternal cerebrospinal fluid (CSF) samples were drawn for clinical assessment. The animals then underwent whole-body perfusion-fixation, after which detailed necropsies were performed. Nerve roots, dorsal root ganglia, and spinal cord with meninges were harvested in cervical, thoracic, and three lumbar blocks (cranial to injection site, level of catheter tip region, and caudal to injection site), along with intervertebral discs at the L2-3 spinal level. These blocks were paraffin-embedded, sectioned, and stained (hemtoxylin and eosin, Bielschowsky stain for myelin, glial fibrillary acidic protein for astrocytes, and neuronal N for neurons). All tissues were examined by a veterinary pathologist (JLR) without knowledge of treatment. At minimum, each neuraxial block was examined for dural inflammation and neuropil degeneration and necrosis.

Clinical Study

Permission to conduct this double-blind, placebo-controlled safety and efficacy study was granted by the Johns Hopkins Internal Review Board, Baltimore, Maryland, and all relevant medical and ethical committees at Walter Reed Army Medical Center, Washington, DC. The design and number of patients for this study was determined in conjunction with Department of Defense statisticians to optimize safety and evaluate future dosing regimens. No data exist for equianalgesic dose conversions between parenteral and epidural etanercept; as a result, dosing regimens were extrapolated from a previous controlled study evaluating intradiscal etanercept[25] and relevant parenteral:intrathecal:intradiscal ratios for other analgesics.[26,27] This study was submitted to the internal review board in April 2005 and approved in January 2006. All procedures and follow-up visits were conducted at Walter Reed between April 2006 and December 2007.

Before performing any procedures, all patients signed informed consent.

All patients were recruited and enrolled by an investigator blinded to treatment allocation. Inclusion criteria included lumbosacral radiculopathy for at least 2 months but less than 1 yr in duration, failure to respond to conservative therapy, magnetic resonance imaging (MRI) evidence of a herniated disc concordant with the patient's symptoms, and a normal leukocyte count within 30 days of the first injection. Exclusion criteria were severe spinal stenosis, grade II or higher spondylolisthesis, coagulopathy, pregnancy, contrast allergy, systemic infection, unstable medical or psychiatric condition, any condition known to be amenable to TNF inhibitors (*e.g.*, spondylarthropathy or Crohn disease), and age less than 18 yr or greater than 70 yr.

Subject Randomization. A research assistant randomized patients *via* secured, presealed envelopes to receive two transforaminal epidural injections at 2-week intervals of either etanercept (Enbrel, Immunex Corp., Seattle, WA) or saline in a 3:1 ratio. To ensure safety and assess dose-responsiveness, each successive set of eight patients comprised one treatment block. In block I, six patients were randomized to receive two injections of 2 mg of etanercept mixed in 2 ml of sterile water, and two patients received two injections of 2 ml of normal saline. In block II, 6 patients received two transforaminal epidural injections of 4 mg of etanercept and two patients received 2 ml of saline. In block III, 6 patients received two transforaminal epidural injections of 6 mg of etanercept and two patients received 2 ml of saline. Group I consisted of the six patients, each receiving 2 mg of etanercept. Groups II and III were composed of the 4-mg and 6-mg etanercept patients, respectively. The six combined patients who received saline injections comprised group 0. All injectate solutions were prepared in identical unlabeled 3-ml clear syringes, which ensured that the treating physician was blinded to the contents.

Before dose escalation, all patients in the preceding treatment group had to complete 1-month follow-up visits without any evidence of toxicity that could be attributed to the study drug. This included a comprehensive neurologic examination, repeat leukocyte count, and a comparison of the preinjection MRI to a repeat MRI by a blinded radiologist. In addition to being blinded to the injectate contents, patients were not informed which group they belonged to (fig. 1).

Injection Technique. All injections were performed under the supervision of a board-certified pain physician unaware of treatment allocation. The segmental level at which the injection was administered was chosen on the basis of a combination of symptomatology and radiologic findings. In patients with single-level pathology, one nerve root was targeted. In patients with less discrete symptoms (*i.e.*, dermatomal overlap or atypical pain referral) and/or multi-level pathology, two levels were injected with divided drug doses at the same volume (2 ml) per level.

Under sterile conditions, an ipsilateral oblique view was obtained with an image intensifier, such that the pedicle was placed approximately one-third of the way across the vertebral body. A 22-gauge, 5-inch spinal needle was then guided into the upper portion of the foramen using intermittent fluoroscopic guidance. Correct needle position was confirmed in anteroposterior, lateral, and oblique views. At each level, epidural and nerve root spread were confirmed by the injection of 1 ml of contrast medium.

After the procedure, patients were instructed to limit strenuous activities for 6 h postinjection and to then resume normal activities as tolerated. Two weeks after the first injection, all patients returned for a repeat procedure.

Before the first follow-up visit, no patient underwent any additional therapeutic interventions. Subjects were given instructions on how to increase or decrease their preprocedure analgesic medications based on their response to therapy. For patients with debilitating pain who required interval rescue analgesics, either a nonsteroidal antiinflammatory drug or tramadol was prescribed.

Outcomes Measures. Outcome data were obtained by an investigator blinded to the patient's treatment group. The primary outcome measure was a numerical rating scale leg pain score reflecting the average pain experienced by the patient for 10 days before follow-up. A positive categorical outcome was predefined as at least 50% reduction in leg pain coupled with a positive global perceived effect. Secondary outcome measures included Oswestry disability index score (version 2.0; MODEMS, Des Plaine, IL), numerical rating scale back pain score, reduction in analgesic medications (predefined as a 20% reduction in opioid use or complete cessation of nonopioid analgesics),[25] and global perceived effect. Previous studies have determined a 10-point reduction in Oswestry disability index score to be clinically significant.[3] A positive global perceived effect was defined as a positive response to the following 3 statements: (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/wouldn't recommend it to others.

Follow-up visits were performed for all patients 1-month after the second injection. If the patient obtained a positive categorical outcome obviating the need for further therapy, they were reevaluated at subsequent 3- and 6-month follow-up visits. All patients were unblinded 3 months after injection. Physician unblinding was done at 1 month in patients who obtained inadequate pain relief and at 3 months in those whose improvement obviated the need for interval interventions.

At their first follow-up visit, patients underwent a complete neurologic examination, a white blood cell count

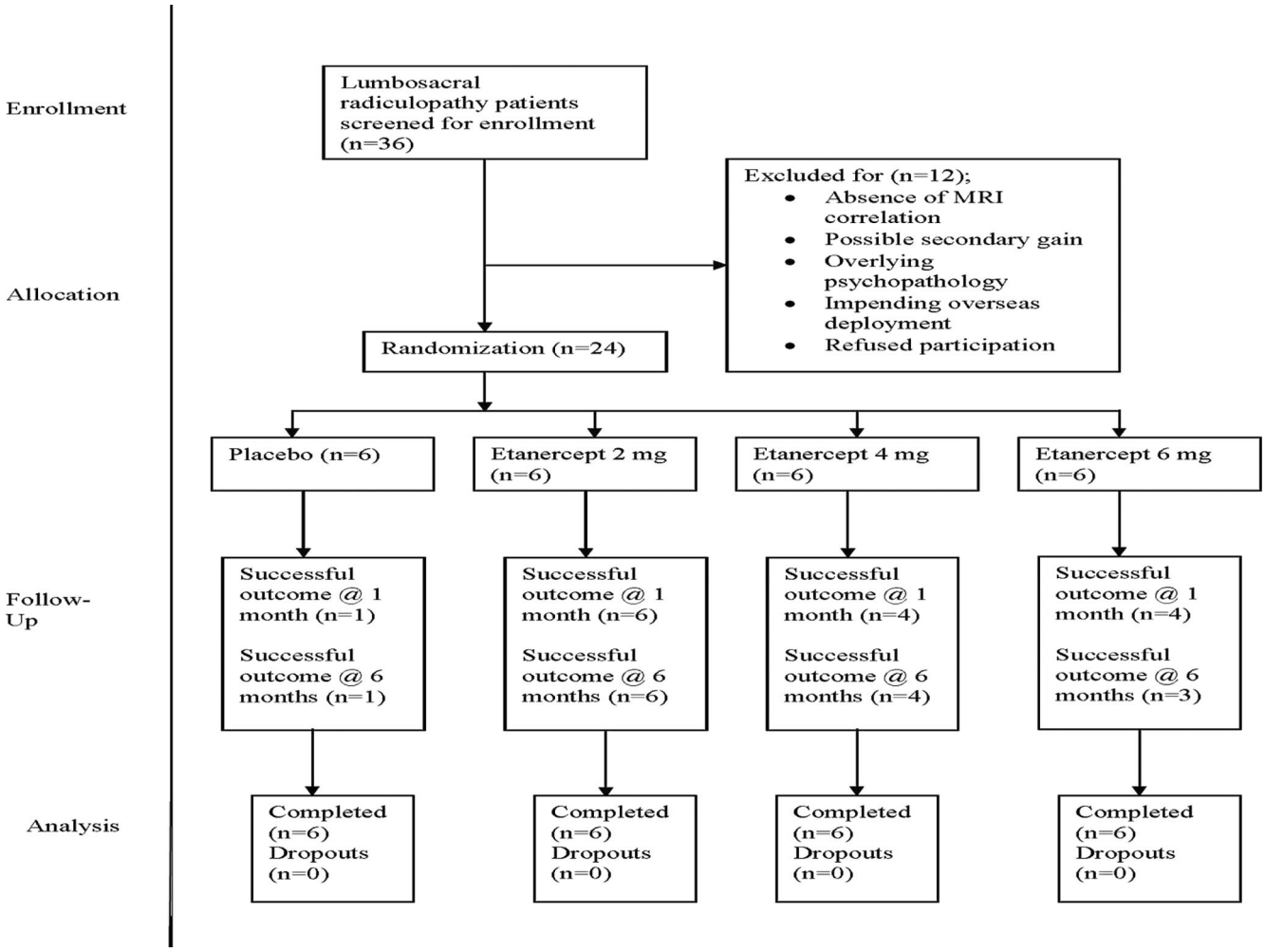

Fig. 1. CONSORT chart showing progression of subjects in study arms. MRI = magnetic resonance imaging.

to monitor possible side effects from etanercept, and a repeat MRI. In the first five study participants, the repeat MRI was done between 1 and 6 months after the injection series. Follow-up at each subsequent visit consisted of a brief history and neurologic exam.

Statistical Analysis

For each outcome variable, mean scores, median scores, and interquartile ranges (IQR) were calculated for each group. Percent reduction in pain scores was calculated from mean values. Baseline and posttreatment scores between groups were compared using Mann–Whitney U tests on a Minitab15 program (Minitab Inc, State College, PA). Within-group differences were compared using Wilcoxon Signed Rank Test. There were no dropouts, so an intention-to-treat analysis was completed. Subjects who declared their failure to benefit and sought escape treatment exited the study per protocol; therefore, between-group and within-group differences were not calculated beyond 1 month. The remainder of the subjects completed the study to determine of the duration of benefit.

Since this study was designed primarily as an exploratory study to test preliminary hypotheses rather than a definitive efficacy study, statistical adjustments for multiple comparisons were not deemed necessary. The proportions of patients who obtained at least 50% pain relief were calculated separately for each group and collectively for all etanercept patients at 1, 3, and 6 months. These outcomes were compared using 95% confidence intervals. $P \leq 0.05$ was considered statistically significant for all analyses.

Results

Preclinical Safety

All animals completed the two injection sequences. There were no behavioral signs of toxicity after either the first or second injection. Vital signs were in the normal range at all recorded intervals. Posttreatment mean cisternal CSF glucose and protein levels for test subjects that received etanercept were 72.5 ± 4.9 and 21.8 ± 5.9, respectively. Posttreatment mean cisternal CSF glucose and protein levels for test subjects that received saline were

Table 1. Summary of Day 16 (Sacrifice) Neurological Observations, Cisternal CSF/Blood Chemistry, and Lumbar Histopathology by Animal

					Day 16 CSF Chemistry			Day 16 Blood Chemistry			Histopathology Summary Summed Pathology Score†		
Dog	Sex	Weight, kg	Epid Tx	Neuro Observation	Glucose, mg/dL	Protein, mg/dL	WBC*	RBC	Hct	WBC*	Gross Observation	Lumbar Meningeal Inflammatiion	Lumbar Neuropil Degeneration/Necrosis
Population control‡			NA	NA	69 (66–72)	11 (10–12)	4 (1–36)	7 (6–8)	47 (45–50)	10 (9–11)	NA	NA	NA
517 6794	M	15.6	Saline	None	74	17	2	5.7	41	9.2	None	6.5	0
520 6791	F	10.2	Saline	None	69	128	33	3.8	27	4.8	Needle puncture	3	0
516 9348	M	15.6	Etanercept	None	70	16.2	1	5.6	38	8.4	None	0	0
516 9437	M	17.2	Etanercept	None	68	37	1	5.6	40	7.9	None	5.5	0
499 5970	F	11.8	Etanercept	None	85	15.7	2	5.7	41	6.8	None	6.5	0
503 1991	F	10.0	Etanercept	None	67	18.1	1	6.2	46	8.4	None	3	0

* Nucleated cell count. † A score represents the sum of assigned pathology scores for sites above, below, and at the catheter tip for lumbar meningeal inflammation and for lumbar neuropil degeneration/ necrosis, where each score could range from 0 (no lesion) to 12 (most severe lesion involving tissue above, below, and at the site of drug delivery). ‡ Control data showing mean and 25–75th quartiles for CSF and blood in 23 control (nontreated) beagles.

CSF = cerebrospinal fluid; Hct = hematocrit; RBC = red blood cell count; Tx = treatment; WBC = white blood cell count.

71.5 ± 3.5 mg/dL and 72.4 ± 78.2 mg/dL, respectively. The protein, white blood cell, and red blood cell counts were significantly higher for test subject 5206791 (received saline) due to modest blood contamination in the CSF sample (table 1). The neurologic examinations performed before and after each epidural injection by a veterinarian without knowledge of treatment allocation revealed no abnormal findings in any animal as revealed by: (1) spinal reflexes; (2) sensory and pain responses; (3) proprioception, gait, and movement; (4) cranial nerve function; or (5) retinal examination. At necropsy, there were no remarkable observations in the epidural space or peripheral tissues. The histologic findings are summarized below (see table 1; fig. 2).

Cervical Spinal Cord. There were no significant findings in any of the dogs.

Thoracic Spinal Cord. All animals had some degree of neutrophilic inflammation in the dura mater of the thoracic spinal cord. Dog 5206791 (saline) also had inflammation within the leptomeninges.

Lumbar Spinal Cord. All animals had some degree of inflammation in this level of the cord. Five of six animals had some degree of neutrophilic infiltration in the dura mater at the level of epidural injection. Similar findings were present in the dural blocks rostral and caudal to the injection site. In one saline-treated animal, a cleavage defect extending along a nerve root was observed, consistent with trauma secondary to needle insertion. The same dog had a tract of rarefaction, necrosis, and inflammation in the neuropil.

Dorsal Root Ganglion. The dorsal root ganglion from at least one level of the spinal cord was examined in all animals. One saline-treated animal had neutrophils infiltrating the perineural fibrous connective tissue surrounding the dorsal root ganglion. The ganglion was never breached by the inflammatory cells.

Spinal Nerves and Nerve Roots. Of the six animals, two (one saline, one etanercept) had some degree of inflammation in the perineural fibrous connective tissue that did not extend into the axons.

Cerebral Cortex, Cerebrum, Mesencephalon, Cerebellum, Brainstem, Eye, and Retina. There were no significant findings in any of the animals.

Lumbar Vertebra and Associated Intervertebral Discs. This tissue was evaluated in all dogs. Two animals (both etanercept) had mild neutrophilic infiltration of the overlying adipose tissue. None of the special stains of

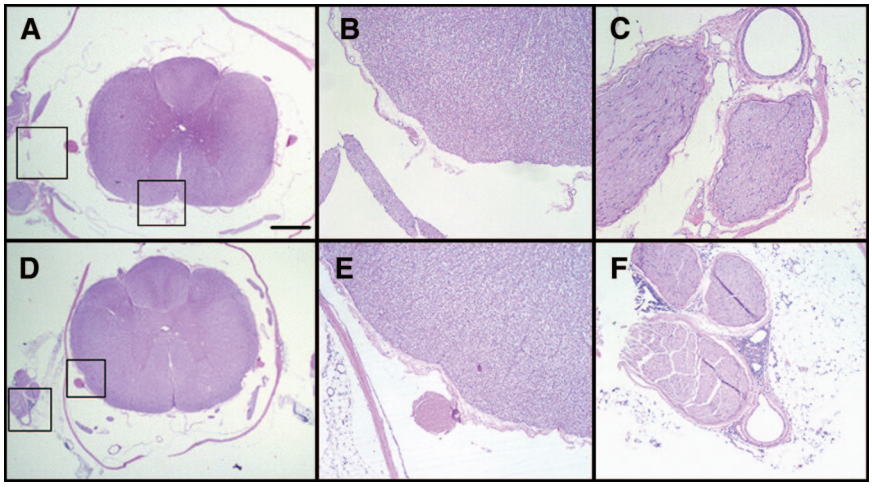

Fig. 2. Representative sections (*A* and *B*) (ba; 800 μM) and enlargements of the lateral white matter and meninges (*B* and *E* × 60) and middle and dorsal root ganglia/roots (*C* and *F* × 60) from the approximate spinal levels of drug delivery in an animal receiving epidural saline (*A, B, C*: dog 5176794; 2 ml of saline) or epidural etanercept (*D–F*: dog 5031911; 6 mg/2 ml). Box inserts in *A* and *D* show approximate areas from which the lower figures are enlarged. Sections are paraffin embedded and stained with hemtatoxylin and eosin.

Table 2. Baseline Demographic and Clinical Features Stratified by Treatment Group Among Patients Randomized to Transforaminal Epidural Injections with Either Normal Saline or Etanercept

		Etanercept		
	Group 0, Normal Saline	Group I, 2 mg	Group II, 4 mg	Group III, 6 mg
Number	6	6	6	6
Males	5	4	4	4
Females	1	2	2	2
Age, yr				
Median	46	46	41	43
IQR	29–63	41–69	33–45	38–48
Duration of pain, months				
Median	7	3	3	4
IQR	2–9	2–6	2–7	2–6
Segmental nerve treated				
L3	1			
L4		2	2	
L5	3	3	3	3
L3, L4				1
L4, L5	2	1		2
L5, S1			1	
Leg Pain NRS Score (0–10)				
Median	8	5	6	7
IQR	8–9	5–8	5–8	5–8
Back Pain NRS Score (0–10)				
Median	7	5	5	8
IQR	5–7	4–7	3–8	5–8
Oswestry Disability Score (0–100%)				
Median	53	33	35	37
IQR	34–61	22–52	19–49	29–57

IQR = interquartile range; NRS = numerical rating scale.

the spinal tissues proximal to the injection site demonstrated any abnormal findings.

Clinical Safety

No human subject reported any side effects from any injection at any dose of etanercept. No subject in any group exhibited a significant change in his white cell count, and there was no evidence of demyelination, arachnoiditis, necrosis, or other signs of neurotoxicity on posttreatment MRI. One patient in each treatment group, including saline, exhibited an increase in the size of their disc herniation. One patient each in the 4-mg and 6-mg etanercept groups demonstrated a decrease in the size of their symptomatic disc protrusion.

Clinical Symptoms

All subjects completed the protocol, with no dropouts occurring despite adequate pain relief and satisfaction. Before treatment, the four groups were comparable in most variables. The groups did not differ statistically with respect to gender-balance or age (table 2). The mean and median duration of symptoms in months was shorter in the collective etanercept patients ($P = 0.07$; mean 3.7, SD 2.2, median 3, IQR 2–6) compared to the control patients (mean 6.1, SD 2.9, median 7, IQR 2–9), although this was not significant for any single group. The three groups (I, II, and III) treated with etanercept did not differ from one another with respect to severity of leg pain before treatment. The severity of leg pain in the normal saline group (median 8, IQR 8–9) did not significantly differ from that of group III (median 7, IQR 5–8; $P = 0.2$) but was higher than that of groups I (median 5, IQR 4–6; $P = 0.053$) and II (median 6, IQR 5–8; $P = 0.03$). Collectively, the leg pain scores for all patients treated with etanercept were lower than those of patients treated with normal saline ($P = 0.02$). None of the groups differed with respect to severity of back pain, either individually or collectively. Disability scores were 33% higher in the normal saline group than in the collective etanercept groups ($P = 0.1$).

One month after treatment, the group treated with normal saline (group 0) experienced a 21% decrease in leg pain ($P = 0.25$) and an 18% diminution in back pain score ($P = 0.27$; table 3 and 4). This group showed less clinically relevant changes in disability scores, which declined 11% ($P = 0.46$). No patient in the saline group obtained complete relief of leg pain, but two reported at least 50% relief at 1 month. This relief persisted in one patient through their 6-month follow-up.

At 1 month, the collective etanercept group reported lower scores for the primary outcome measure, numerical rating scale leg pain, than the saline group, although this may have been related to the baseline difference in pain scores ($P < 0.01$; fig. 3). The mean decrease in leg pain scores for etanercept patients was 4.1 (SD 2.5), which favorably compares to the 2.2-point reduction in

Table 3. Numerical Rating Leg Pain Scores Stratified by Treatment Group and Time Point

		Etanercept			
	Placebo, n = 6	2 mg, n = 6	4 mg, n = 6	6 mg, n = 6	All, n = 6
Baseline					
Mean (SD, range)	8.2 (1.0; 7–10)	5.8 (1.8; 4–8)	6.3 (1.3; 5–8)	6.8 (1.7; 5–9)	6.3 (1.6; 4–9)
Median (IQR)	8 (8–9)	5 (4–6)	6 (5–8)	7 (5–8)	6 (5–8)
One month					
Mean (SD, range)	6.5 (2.4; 4–9)	1 (1.3; 0–3)*†	3 (2.9; 0–8)	3 (3.0; 1–7)	2.3 (2.5; 0–8)*†
Median (IQR)	6 (5–9)	1 (0–2)	2 (1–6)	3 (0–6)	1 (0–3)
Three months					
Mean (SD, range)	3‡	1.1 (0.8; 0–2)	0.5 (1.5; 0–2)	0.75 (1.2; 0–3)	0.8 (0.9; 0–3)
Median (IQR)	3‡	2 (1–4)	0 (0–1)	0 (0–1)	2 (0–2)
Six months					
Mean (SD, range)	4‡	1.4 (1.4; 0–3)	1.0 (2.0; 0–4)	0.5 (0.9; 0–1)	1.1 (1.5; 0–4)
Median (IQR)	4‡	1 (0–3)	0 (0–2)	0 (0–1)	0 (0–3)

* $P < 0.05$ compared with placebo group at 1 month. † $P < 0.05$ compared with baseline of the respective group. ‡ Data from one patient.
IQR = interquartile range.

the saline group (SD 2.1; $P = 0.15$). Group scores revealed an 83% improvement in leg pain from baseline in group I ($P = 0.04$), a 52% improvement in group II ($P = 0.08$), and a 56% decrease in group III ($P = 0.06$).

Mean back pain scores were lower 1 month after injection in the pooled etanercept patients than in those who received saline ($P = 0.01$). Mean differences between pre- and postinjection pain scores were also lower in the collective etanercept patients (3.2 [SD 2.1] *vs.* 1.3 [SD 1.8]; $P = 0.06$). Numerical rating scale scores for back pain at 1 month decreased 69% from baseline in groups I ($P = 0.04$) and II ($P = 0.06$) and 30% from preinjection values in group III ($P = 0.04$).

The average disability score for the collective etanercept patients was somewhat lower at 1 month follow-up than in the saline patients ($P = 0.11$), with the percentage drop being greatest in group II (35%; table 5). For those subjects remaining in the study, these scores continued to decline through 6-month follow-up. However, the mean decrease per subject was not significantly different between the combined etanercept (12.6, SD 13.5) and placebo patients (9.7, SD 10.9; $P = 0.78$). One month after injection, the average disability score decreased 26% in the pooled etanercept group ($P = 0.12$).

Among the six patients treated with 2 mg of etanercept, all (100%) experienced a successful categorical outcome (≥ 50% pain relief combined with a positive global perceived effect) lasting 6 months, with half obtaining complete pain relief. In the 4-mg group, four (67%) of six patients had a positive categorical outcome that persisted from the first to final follow-up. In the 6-mg group, two-thirds (n = 4) experienced a successful outcome 1 month after their injection series, with half of these achieving a pain-free state. By 6 months, three of the four patients continued to have a successful outcome. In contrast, only one subject (17%) in the control group experienced a positive outcome at 1 month, which lasted the duration of the study. The proportions of patients in the individual etanercept groups who obtained at least 50% relief of leg pain were not significantly greater than in the saline group (16%; 95% CI,

Table 4. Numerical Rating Back Pain Scores Stratified by Treatment Group and Time Point

		Etanercept			
	Placebo, n = 6	2 mg, n = 6	4 mg, n = 6	6 mg, n = 6	All, n = 18
Baseline					
Mean (SD, range)	6.6 (1.4; 5–8)	5.2 (1.4; 5–8)	5.4 (2.5; 3–9)	7.0 (1.7; 5–9)	5.9 (2.1; 3–9)
Median (IQR)	7 (5–7)	5 (4–7)	5 (3–8)	8 (5–8)	5 (4–8)
One month					
Mean (SD, range)	5.4 (2.0, 3–8)	1.6 (0.9; 1–3)*†	1.7 (1.6; 0–4)*	4.9 (1.6; 3–7)†	2.7 (2.1; 0–7)*†
Median (IQR)	5 (4–8)	2 (1–2)	2 (0–3)	4 (4–7)	2 (1–4)
Three months					
Mean (SD, range)	4‡	1.8 (1.3; 0–4)	0.8 (1.5; 0–3)	3.0 (1.2; 2–4)	1.8 (1.5; 0–4)
Median (IQR)	4‡	2 (1–3)	0 (0–2)	3 (2–4)	2 (0–2)
Six months					
Mean (SD, range)	4‡	4.8 (3.3; 2–9)	1.8 (2.2; 0–5)	2.7 (1.0; 2–4)	3.4 (2.8; 2–9)
Median (IQR)	4‡	4 (2–9)	1 (0–3)	3 (2–4)	3 (1–4)

* $P < 0.05$ compared with placebo group. † $P < 0.05$ compared with baseline of the respective group. ‡ Data from one patient.
IQR = interquartile range.

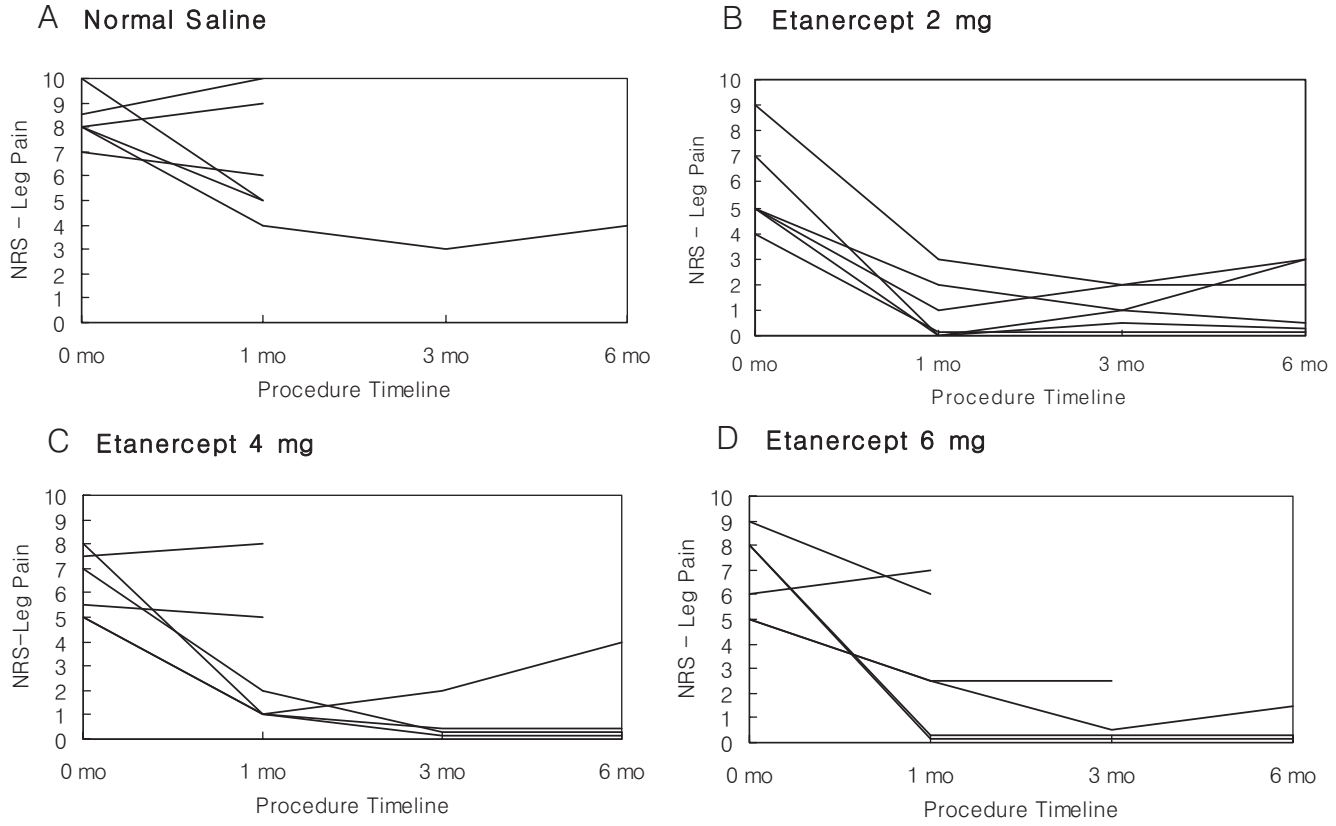

Fig. 3. (*A–D*) Line graphs demonstrating change in leg pain score for each treatment group during study course. Five patients in the saline group, 2 patients in the 4-mg etanercept group, and 3 patients in the 6-mg etanercept group who did not meet predetermined categorical success criteria exited the study before 6 months. NRS = numerical rating scale.

0–45%), but the combined proportion in all etanercept groups (78%; 95% CI, 59–97%) was significantly greater.

All etanercept patients except one who obtained at least 50% pain relief reported a positive global perceived effect at 1-month follow-up, and all but one reduced their medication intake. All seven patients with a positive outcome who were on opioids before treatment were able to discontinue their medications. Among the six etanercept patients in the military, five remained on active duty (table 6).

Discussion

The results of this study suggest that transforaminal epidural etanercept may someday prove to be a beneficial treatment in patients with lumbosacral radiculopathy. These preliminary results are consistent with animal

Table 5. Oswestry Disability Scores Stratified by Treatment Group and Time Point

		Etanercept			
	Placebo, n = 6	2 mg, n = 6	4 mg, n = 6	6 mg, n = 6	All, n = 18
Baseline					
Mean (SD, range)	48.7 (15.1; 24–64)	35.0 (14.6; 16–52)	34.7 (15.8; 16–56)	40.3 (14.2; 24–58)	36.7 (14.2; 16–58)
Median (IQR)	53 (34–61)	33 (22–52)	35 (19–49)	37 (29–57)	33 (24–52)
One month					
Mean (SD, range)	43.3 (11.4;26–58)	22.3 (16.6; 4–44)	23.5 (29.0; 1–72)	36.2 (14.9; 18–60)	27.3 (20.9; 1–72)
Median (IQR)	41 (37–55)	15 (12–43)	11 (2–51)	34 (24–50)	23 (11–44)
Three months					
Mean (SD, range)	22*	12.7 (14.0; 0–40)	7.3 (8.1; 2–18)	22.8 (15.2; 12–45)	14 (13.5; 0–45)
Median (IQR)	22*	9 (0–23)	6 (0–14)	17 (13–39)	11 (4–19)
Six months					
Mean (SD, range)	42*	33.0 (17.9; 14–66)	3.3 (4.3; 0–9)	8.7 (7.0; 2–16)	18.2 (18.8; 0–66)
Median (IQR)	42*	31 (20–42)	2 (0–7)	8 (1–16)	14 (3–31)

* Data from one patient.

IQR = interquartile range.

Table 6. Percentage of Subjects with a Positive Secondary Treatment Outcome Stratified by Treatment Group

		Etanercept		
	Group 0, Normal Saline	I, 2 mg	II, 4 mg	III, 6 mg
Percent positive medication reduction (baseline number)	5	6	5	6
1 month	40%, 1–79%	100%, 61–100%	60%, 21–99%	67%, 30–100%
3 months	20%, 0–52%	83%, 53–100%	60%, 21–99%	50%, 10–90%
6 months	20%, 0–52%	67%, 30–100%	60%, 21–99%	17%, 0–50%
Percent positive global perceived effect				
1 month	33%, 0–70%	100%, 61–100%	67%, 30–100%	67%, 30–100%
3 months	17%, 0–50%	100%, 61–100%	67%, 30–100%	50%, 10–90%
6 months	17%, 0–50%	100%, 61–100%	67%, 30–100%	50%, 10–90%
Maintained on active duty (baseline number) at 6 months	3, 67%, 30–100%	1, 100%, 61–100%	4, 75%, 41–100%	1, 100%, 61–100%
Proceeded to surgery at 12 months	17%, 0–50%	17%,* 0–50%	17%, 0–50%	17%, 0–50%

For medication reduction and global perceived effect, dropouts secondary to failure were carried over as "failures" at subsequent visits. 95% confidence intervals are listed with the proportions for each category.

* Underwent spinal fusion for persistent axial low back pain.

models demonstrating superiority of targeted local infiltration of cytokine inhibitors over systemic dosing[17] and inferred data suggesting epidural corticosteroids are more effective than parenteral administration.[28–31] In light of recent studies suggesting a transient nature to the benefit afforded by lumbar spine surgery,[2–4,32] the need to find a reliable intermediate-term bridge for natural resolution to occur takes on newfound urgency. Although our findings are auspicious, they should not be misconstrued as corroboration of efficacy or certification of safety.

Caveats to Clinical Study

Several concerns must be addressed to place these results in proper context. The first point involves the lack of a dose response. There are several possible explanations for this, which include a statistical anomaly stemming from the small sample size, diffusion of drug outside the area of pathology from excessive volume, ceiling effect secondary to receptor saturation, subclinical neurotoxicity manifesting as lack of efficacy, and lack of a true treatment effect. Recently, a randomized study comparing two doses of epidural methylprednisolone found the lower dose to provide slightly superior pain relief with fewer side effects.[33] Perhaps more relevant is an animal study by Quintao *et al.*[17] revealing no difference in efficacy or duration of antinociception between low-dose and high-dose (10-fold) perineural TNF inhibitor administration in an animal model of brachial plexus injury.

A second issue relates to sample size. A small sample-size was used in this study because it was designed, first and foremost, as a dose-finding study in which the potential toxicity of the agent tested was unknown. Consequently, it was impossible to conclusively prove that the particular doses tested were individually superior to placebo treatment. In fact, the appreciably worse baseline scores in the saline compared to the pooled etanercept group (*i.e.*, failed randomization) alone could explain the differences in improvement.

A final point relates to our primary outcome measure, which was based on a single global numerical rating score for the previous 10 days. Previously performed studies have demonstrated that one's recall of pain may be influenced by the current pain state.[34] Furthermore, many patients may not be able to adequately distinguish between leg pain, the primary outcome measure, and axial back pain, which is often referred into the leg.

Assertion of Safety

With regard to toxicity, this study provides *prima facie* evidence of the safety of eternacept when injected around an inflamed nerve root(s). The preclinical study showed no evidence of drug-related neurotoxicity at the highest dose used in the human study, with a recovery period of 16 days after the first injection. The assertion of clinical safety is based on the absence of neurologic or radiological changes in humans after multiple doses, and the absence of histopathology in a canine epidural model using equivalent injection volumes and drug doses delivered to an epidural volume conservatively estimated at one-third that of humans.[35] This model has been used to assess safety for a variety of agents developed for epidural delivery in humans.[36]

The safety data in patients suggest that transforaminal etanercept injections, in the dose and concentration ranges tested, should not be associated with immunosuppression or other side effects. Yet, because of the small number of patients studied, there remains a small chance that adverse effects could occur if transforaminal etanercept were used in a larger cohort. Studies that seek to assess clinical efficacy should heed this possibility and monitor patients for signs of toxicity.

Unanswered Questions

One important issue revolves around the disparity in baseline parameters between the control and etanercept groups. The possibility of baseline differences in clinical and demographic variables exists for all human trials, but it tends to be minimized by the large groups of patients needed to evaluate efficacy. The present study more closely mirrored a smaller phase I study; therefore, this collateral risk was magnified. In the randomized controlled Spine Patients Outcome Research Trial (SPORT) study comparing outcomes between surgical and nonsurgical treatment for herniated disc, those patients with lower baseline pain scores and disability were more likely to do better with less aggressive therapy.[3] The trend towards better outcomes in those patients with lower baseline pain scores has also been demonstrated for minimally invasive back pain treatments.[37] In addition, baseline differences in parameters can lead to discrepancies between actual and percent reduction in pain scores, since a 50% decrease from a higher baseline numerical rating scale score reflects a greater quantitative difference than the same percent decrease from a lower starting pain rating. Among the four patients with severe (≥ 8/10) radicular pain treated with epidural etanercept, three experienced sustained benefit throughout the study.

The final unanswered question centers on the duration of benefit. Discogenic radiculopathy tends to be a recurring phenomenon characterized by frequent bouts of remissions and exacerbations.[3,16,32] Although 13 of 18 patients achieved excellent relief lasting more than 6 months, the converse of this is that 28% of patients obtained only transient relief. One area that needs to be investigated is whether injecting agents with longer half-lives might prolong analgesia.

Whereas the results of this study indicate epidural TNF inhibitors may prove to someday be an effective treatment in patients with radiculopathy, the questions they raise are quantitatively similar to the ones they answer. Further areas for investigation include studies to definitively establish efficacy and further evaluate safety, ascertainment of whether or not the analgesic effects of TNF inhibitors are time-dependent (since inflammation plays a less prominent role in chronic than acute pain), and identification of the optimal candidates, drugs, dose ranges, and injection intervals for treatment. Although the authors are encouraged by the preliminary safety and efficacy data found in this report, we do not recommend the use of transforaminal etanercept for the treatment of back pain or radiculopathy at this time.

A brief hiatus occurred at the end of 2006, when the investigators were informed of the forthcoming publication rule requiring an investigational new drug application (IND) for human studies evaluating neuraxial medications not approved for epidural or intrathecal delivery. After correspondence with a member of the internal review board and the departments of anesthesiology and neurosurgery at Johns Hopkins School of Medicine and Walter Reed Army Medical Center, scientists at Amgen Corporation (Thousand Oaks, CA), the former Anesthesiology Consultant to the Surgeon General of the U.S. Army, researchers who had conducted neuraxial studies in animals using etanercept, Dr. James Eisenach, and a person at the U.S. Food and Drug Administration, the study was continued with the understanding that a concurrent animal safety study would be conducted and we would evaluate patients for radiological evidence of toxicity.

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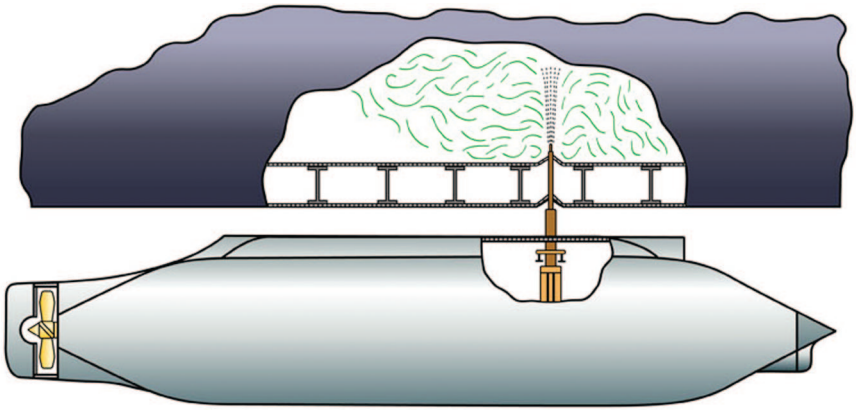
ANESTHESIOLOGY REFLECTIONS

Anesthetizing Enemy Sailors



In May of 1907, a Newton, Massachusetts resident named Carl M. Wheaton finished designing his "Means for Conducting Submarine Warfare." Wheaton's innovation connected "a submarine . . . to . . . a floating ship by driving a pin . . . through the bottom of the ship, and in subsequently injecting an anesthetic gas . . . to overcome and anesthetize the crew of the ship attacked. Preferably . . . the anesthetic [would be] injected into the engine or boiler room [rendering] . . . the ship helpless . . . [and possibly] enabling the ship to be captured practically without loss of life." Unfortunately, Wheaton himself suffered loss of life during the astonishing eight years that the U.S. Patent Office spent in evaluating his filing. Less than seven weeks after the U.S. Patent No. 1,131,761 was granted to Wheaton's administratrix, the transatlantic ocean liner *Lusitania* was sunk on May 7, 1915 by a single torpedo launched by submariners onboard Germany's *U-20*. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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