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Is Enbrel (Etanercept) Safe and Effective in Treating Patients With Sciatic Nerve Pain Resulting From Lumbar Disc Herniation or Spinal Stenosis?

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Is Enbrel (etanercept) safe and effective in treating patients with sciatic nerve pain resulting from lumbar disc herniation or spinal stenosis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not Enbrel (etanercept) is safe and effective in treating patients with sciatic nerve pain resulting from lumbar disc herniation or spinal stenosis.

STUDY DESIGN: Review of three English language primary randomized controlled trials from 2012-2013.

DATA SOURCES: One triple-blind, placebo-controlled randomized clinical trial, one double-blind, placebo-controlled randomized clinical trial, and one prospective randomized clinical trial were found using PubMed. These studies compared treatment with etanercept to treatment with saline and steroids (dexamethasone or methylprednisolone).

OUTCOMES MEASURED: Clinical outcomes of leg and back pain were measured using numeric pain rating scales, global perceived effect (GPE) surveys, and the oswestry disability index (ODI).

RESULTS: One triple-blind and one double-blind placebo controlled trial were reviewed, in addition to one prospective randomized trial. Cohen et al did not find any statistically significant differences in pain relief between the etanercept and saline groups, and subjects in the etanercept group did not experience any improvement in disability. Freeman et al found clinically and statistically significant improvements in leg and back pain as well as improvements in disability in the etanercept group when compared to placebo. Ohtori et al found that etanercept provided better pain relief and improvement in disability than dexamethasone. However, this difference was not statistically significant.

CONCLUSIONS: Based on the studies reviewed in this paper, the evidence is conflicting in determining whether or not etanercept is safe and effective in treating radiculopathy and sciatica resulting from lumbar herniation and spinal stenosis.

KEY WORDS: Sciatica, etanercept

INTRODUCTION: Lower back pain (LBP) affects millions of men and women despite demographic and socioeconomic differences. Lumbar radicular pain is the leading cause of disability worldwide[1]. Sciatic pain (sciatica) is a type of radicular nerve pain in which pain travels down the path of the sciatic nerve[2]. For many years, clinicians have searched for safer and more effective solutions to alleviate radiculopathy, as current therapies often fail to provide continuous and efficacious pain relief. Epidural injections seem to benefit only a subset of patients, and the effectiveness of invasive surgical therapies fails to supersede that of conservative treatments[3]. Recently, attention has shifted towards a new mechanism of LBP. Tumor necrosis factor alpha (TNF-α) and other mediators of inflammation are implicated with radicular pain and have become newly promising targets of pain management[3]. High concentrations of TNF-α have been noted in patients with disc degeneration, and preclinical trials have confirmed this suspicion by experimentally applying TNF to nerve roots of participants, finding that this produces sensations of pain consistent with that of a herniated disc[3]. Successful management of LBP is critical for improvement in overall quality of life for the 80% of Americans affected by low back pain at some point[1]. Annual care costs for these patients are estimated at $50 billion, making back pain the second most common complaint at physician visits[1]. In addition to the economic strain created by the cost of treatment and management, LBP heavily affects the work force, as it is one of the leading causes for work place absenteeism[1].

Most cases of LBP in those under 50 years of age are attributable to herniated discs, resulting in compression of the affected nerve root(s) and initiation of an inflammatory cascade that includes the release of cytokines and TNF-α[4]. The result is radicular pain: a distinct form of pain that travels down the leg, following the trajectory of the affected nerve root. Symptoms may include sharp, radiating pain down the back and/or leg that may be accompanied by numbness,

weakness, and diminished deep tendon reflexes[5]. Conventional treatments for radicular back pain are implemented in a step-wise fashion, beginning with non-pharmacological methods like chiropractic/osteopathic manipulation and physical therapy[6]. Medications such as non-steroidal anti-inflammatories (NSAIDs) may be used independently or as adjunctive therapy to the aforementioned methods[6]. Next, a trial of opioid analgesics, muscle relaxers, or epidural steroid injections may be indicated[6]. Surgical methods such as discectomies, disc replacements, and decompressive spinal fusion are reserved for recalcitrant cases of lumbar radiculopathy[6]. Current treatments may be effective in treating acute pain, but have mixed efficacy with regard to long-term pain management[4]. Enbrel (etanercept) may be used to inhibit the inflammatory mediator TNF- α, relieving radiculopathy and sciatica more effectively than conventional methods.

OBJECTIVE: The objective of this selective EBM review is to determine whether or not Enbrel (etanercept) is safe and effective in treating patients with sciatic nerve pain resulting from lumbar disc herniation or spinal stenosis.

METHODS: Two randomized controlled trials and one prospective randomized trial were selected for this review. These studies consisted of patients ages 18-80 with an established diagnosis of lumbosacral radiculopathy (continuous low back or leg pain for at least 4-6 weeks). All three studies encompassed wide demographic parameters, though two of the studies were predominantly male and one study was predominantly Caucasian. In all three studies, treatment and placebo groups were comparable with regard to age, race, and mean duration/severity of pain. Inclusion and exclusion criteria of all three studies were similar. These criteria, as well as study-specific demographics, can be found in Table 1. Each RCT studied the use of epidural or transforaminal etanercept. Patients received either bupivacaine or lidocaine injections prior to treatment. Comparison groups included epidural steroids (methylprednisone or dexamethasone)

and saline. Outcomes measured were reduction in radicular/sciatic nerve pain and safety (# of adverse events). Studies were required to be peer-reviewed, published, randomized controlled trials to meet the inclusion criteria for this review. Articles published prior to the year 2000 were excluded. All studies were retrieved through the PubMed database in 2015. Key words used in the data search were "sciatica" and "etanercept." All articles were published in English between the years of 2012-2013 and research was completed by the author of this review. Articles were selected based on relevance and the presence of patient oriented outcomes. Statistics reported in this review include relative benefit increase, absolute benefit increase, number needed to treat, relative risk increase, absolute risk increase, number needed to harm, and p-values.

Table 1: Demographics and Characteristics of studies included

Study	Type	#Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Cohen, 2012 (4)	RCT	84	18-70	Age 18-70; lumbosacral radiculopathy >4wks, <6mo; leg pain that ≥ as severe as back pain; failed conservative therapy; evidence of pathologic disc condition on MRI that matches sx	Persons w/ coagulopathy or systemic infection; unstable medical or psychiatric condition; previous spinal surgery or previous epidural steroid injection; allergy to contrast dye	0 dropouts, 46 "exit per study protocol"	Epidural injection of 4mg etanercept in 2mL of sterile water
Freeman, 2013 (7)	RCT	49	18-70	18-70y/o, good medical/ psychological health, capable of completing procedures; not breastfeeding, pregnant, or becoming pregnant; avg leg pain of 5/10 for at least 3-7d before randomization visit; dx of radicular pain b/w 6-26wks duration; pain in dermatomal distribution c/w involved nerve root; dx confirmed by CT/MRI w/in 6mo of screening visit; + straight leg, femoral stretch test; herniation affecting L3/4/5 or S1; -TB test; willingness to stabilize or decrease analgesic use	Hx of sciatica in currently affected leg; allergy to etanercept, oxycodone, hydrochloride, or contrast; BMI >35; major psychiatric d/o not controlled; abnormalities in AST/ALT or creatinine clearance <70mL/min; pain unrelated to disc herniation; polyradiculopathy; investigational drug received w/in 30d of screening; prior disc surgery; epidural steroids w/in 6mo of screening; worker's comp, disability, or litigation involvement; infection, malignancy, or demyelinating dz; use of anti-TNF w/in 1yr; severe stenosis; coagulopathy; psoriatic arthritis, AS, or RA; cyclophosphamide therapy; Wegener granulomatosis	4 d/c due to adverse events, 1 withdraw of consent, 1 protocol violation	Transforaminal epidural injection of etanercept (0.5mg, 2.5mg, or 12.5mg)
Ohtori, 2012 (2)	PRT	80	49-80	LBP/leg pain for ≥1mo; dx of spinal stenosis by X-Ray, MRI, and PE, confirmation by spinal infiltration	Previous spinal surgery; spinal tumor/infection/trauma; cauda equina syndrome or polyradiculopathies	0	Epidural injection of 10mg etanercept w/ 2.0mL of lidocaine

OUTCOMES MEASURED: Each RCT studied in this review used investigator and patient self-report measures to determine the efficacy and safety of etanercept. With regard to investigator measures, Cohen et al documented the number of subjects that required further intervention after treatment with etanercept vs. comparison[4]. Freeman et al documented the number adverse events with etanercept treatment vs. comparison (including worsening sciatica, headache, nausea, diarrhea, and constipation)[7]. All three studies used the oswestry disability index (ODI) and either a visual analog scale (VAS) or a numeric rating scale (NRS) as patient self-report measures for pain. Two studies used global perceived effect surveys (GPEs). Cohen et al obtained data through a physician or research nurse blinded to the treatment groups[4]. Leg pain, the primary outcome measured in this study, was determined by a NRS at 1 month post-injection (0= no pain, 10= worst pain) [4]. Secondary measures included a NRS for back pain, ODI (10 question survey assessing disability) and GPE (response to the following question: my pain has improved/worsened/stayed the same since my last visit) [4]. Freeman et al collected numerical leg/back pain data through daily subject study diaries that documented pain levels, medication use, and adverse events[7]. This study also employed ODI and GPE measures at 4 and 12 weeks post-injection[7]. Ohtori et al evaluated leg and back pain using a VAS (0= no pain, 10= worst pain) before the injection as well as 30 minutes, 3 days, 1 week, 2 weeks, and 4 weeks after injection[2]. In addition, ODI scores were measured prior to treatment and 4 weeks post-injection[2].

RESULTS: The 2012 Cohen et al study comparing epidural etanercept to methylprednisolone and saline was a triple-blind, placebo controlled RCT[4]. Eighty-four men and women ages 18-70 were enrolled in the study and 46 subjects exited "per protocol" (0 dropouts)[4]. This study was conducted at 3 United States military centers using outpatient pain clinic patients who were either veterans or military dependents[4]. Detailed inclusion and exclusion criteria are included in

Table 1. These criteria included a diagnosis of lumbosacral radiculopathy >4 weeks but < 6 months in duration, leg pain more than or as severe as back pain, and failed conservative therapy[4]. Excluded patients were those with coagulopathy or infection, due to the immunosuppressive properties of etanercept, and those with a contrast dye allergy, as contrast was used for identification of epidural uptake[4]. A research nurse stratified the participants into three groups using randomized, computer generated tables[4]. All groups received contrast dye, followed by 0.5mL of 0.5% bupivacaine and the assigned treatment: 60mg of methylprednisolone acetate in 0.5mL of saline (Group 1), 4mg of Enbrel (etanercept) in 2mL of normal saline (Group 2), or 2mL of normal saline (Group 3)[4]. This review focuses on comparing the effectiveness of etanercept (n = 26) and saline (n = 30). Each group received 2 injections, one at the beginning of the study, and another 2 weeks later. A NRS was used at baseline and 1 month after the second injection to assess leg and back pain. Compliance is considered to be 88% overall, as it was determined by the amount of patients who received both injections. Some patients refused a second injection due to lack symptom relief (n=5) or pain cessation less than expected (n=5)[4].

The mean baseline NRS scores for leg pain and back pain in the etanercept and saline groups can be seen in Table 2. After 1 month, mean NRS score for leg pain in the etancercept group was 3.56 vs. 3.78 in the saline group (omnibus p-value of 0.24) and mean NRS score for back pain in the etanercept group was 4.41 vs. 4.01 in the saline group (omnibus p-value of 0.40)[4]. Differences in pain between the two groups were -0.25 (p = 0.75) for leg pain and 0.40 (p = 0.56) for back pain[4]. With regard to the GPE, 57% of saline group subjects and 58% of etanercept group subjects were satisfied with the treatment[4]. There was no improvement in ODI scores at 1 month for the etanercept group[4]. Overall, 42.3% of subjects in the etanercept group,

vs. 50% of subjects in the saline group, reported successful treatment outcomes at 1 month.

Therefore, the resultant NNT is -12 (Table 3), indicating that, for every 12 patients treated with

etanercept instead of saline, one fewer patient will experience a reduction in back pain compared

to those treated with saline.

With regard to harm, 10.8% of patients in the saline group and 15.4% of patients in the

etanercept group experienced worsening pain, resulting in a NNH of 22. Therefore, for every 22

patients being treated with etanercept instead of saline, one additional patient will experience

worsening back pain (Table 4).

Table 2: Baseline and 1mo scores for leg and back pain and mean change in leg and back pain from Cohen et al data

	Baseline NRS (leg pain)	Baseline NRS (back pain)	1 month NRS (leg pain)	1 month NRS (back pain)	Mean change in leg pain	Mean change in back pain
Etanercept (n=26)	6.62 (1.66)	6.08 (2.51)	3.56 (2.35 to 4.72)	4.41 (3.37 to 5.44)	-2.98 (-4.41 to -1.55)	-1.56 (-2.83 to -0.28)
Saline (n=30)	6.31 (2.02)	4.75 (2.49)	3.78 (2.72 to 4.85)	4.01 (3.08 to 4.93)	-2.48 (-3.59 to -1.37)	-1.07 (-1.96 to -0.17)

Table 2 illustrates a between group difference (saline and etanercept) of -0.25 (p = 0.75) for leg pain and 0.40 (p = 0.56) for back pain 1 month after administration of the second injection. All CIs are 95%.

Table 3: Calculations for treatment from Cohen et al data

CER	EER	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
50%	42.3%	.154%	-7.7%	-12

Table 3 illustrates a NNT of -12, indicating that for every 12 patients treated with etanercept instead of saline, one fewer patient will experience a reduction in back pain.

Table 4: Calculations for harm from Cohen et al data

CER	EER	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)
10.8%	15.4%	42.6%	4.6%	22

Table 4 illustrates a NNH of 22, indicating that for every 22 patients treated with etanercept instead of saline, one additional patient will experience worsening back pain.

The 2013 Freeman et al study comparing etanercept to placebo was a double-blind,

placebo controlled RCT[7]. Fifty-one men and women between the ages of 18-70 years old were

enrolled and randomized, with 49 of those receiving the full treatment regimen, 43 of those

completing the study, and 37 of those meeting the criteria to be included in the PP population[7].

Therefore, 75.5% of all subjects who received full treatment were compliant (per protocol). Per

protocol (PP) patients were those who received 2 doses of medication with confirmed needle

placement and contrast flow during both injections[7]. These patients were also required to complete at least one pain assessment at 4 weeks post-injection[7]. This review evaluates the findings within the PP population, which included patients from 5 medical hospitals and 1 spinal clinic in Australia[7]. Detailed inclusion and exclusion criteria can be seen in Table 1. The criteria included patients with a diagnosis of lumbosacral back pain lasting 6-26 weeks, confirmed by radiology, and accompanied by an average pain score of at least 5 out of 10[7]. Patients with systemic or chronic infections, demyelinating disease, and known contrast dye allergies were excluded[7]. Subjects were randomized by a computer generated randomization schedule, and an investigational pharmacist prepared the treatments[7]. Clinicians preforming injections, reading films, and stratifying data were blinded[7]. Subjects received either etanercept (0.5mg, 2.5mg, or 12.5mg) or placebo[7]. Freeman et al did not specify the type of placebo used. This review focuses on comparing 0.5mg of etanercept to placebo. All patients received 2mL of 1% lidocaine intra-dermally as well as 2.0mL of contrast medium prior to receiving 2 transforaminal injections of either etanercept or placebo 2 weeks apart (one injection at 2 weeks, another at 4 weeks) [7].

Freeman et al used a NRS to evaluate changes in mean daily worst leg pain (WLP) from baseline to 4 weeks as the primary outcome measure[7]. Secondarily, changes in mean daily worst back pain (WBP), ODI, and GPE were evaluated[7]. Freeman et al found that 50% of the patients treated with 0.5mg of etanercept reported 100% reduction in daily WLP scores when evaluated 4 weeks after the second injection, while 0% of subjects in the placebo group experienced this treatment effect [7]. This finding was significant both clinically and statistically. This yields an ARR of 50%, meaning that patients treated with 0.5mg etanercept had a 50% absolute decrease in sciatic leg pain compared to placebo (Table 5). The group treated with 0.5mg etanercept also had a statistically significant decrease in WLP between baseline and 26 weeks. Patients treated

with etanercept 0.5mg experienced a 5.1 point decrease in WLP vs. a 1.9 point decrease in WLP

for placebo (p = 0.058) [7]. This clinical and statistical significance remained with WBP scores.

Two weeks after the first injection, >63% of subjects treated with 0.5mg etanercept, compared to

10% of patients treated with placebo, reported that they were "much improved" or "very much

improved" when evaluated by the ODI [7]. This yields a NNT of 2, meaning that for every 2

patients treated with 0.5mg of etanercept compared to placebo, one additional patient will have

clinically significant relief of leg and/or back pain (Table 6). Three months after the second

injection, ODI scores improved ≥10 points in the etanercept group, with disability reduced by

30% or more compared to placebo[7]. With regard to GPE, 63% of patients being treated with

0.5mg of etanercept rated their symptoms as "significantly improved," compared to 10% of

subjects being treated with placebo[7]. With regard to safety, both groups experienced similar rates

of adverse events (59% etanercept, 67% placebo), including continuing or worsening sciatica,

headache, nausea, diarrhea, and constipation (Table 7) [7]. The dosage of etanercept did not appear

to be related to the incidence of adverse effects.

Table 5: Calculations for prevention from Freeman et al data

CER	EER	Relative risk reduction (RRR)	Absolute risk reduction (ARR)	Number needed to treat (NNT)
0%	50%	50%	50%	2

Table 5 illustrates an ARR of 50%, meaning that patients treated with 0.5mg etanercept had a 50% absolute decrease in sciatic leg pain compared to placebo

Table 6: Calculations for treatment from Freeman et al data

CER	EER	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
10%	63%	5.3%	53%	2

Table 6 illustrates an NNT of 2, meaning that for every 2 patients treated with 0.5mg of etanercept compared to placebo, one additional patient will experience clinically significant relief of leg and back pain.

Table 7: Calculations for harm from Freeman et al data

CER	EER	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)
67%	59%	-.11%	-8%	-13

Table 7 illustrates a NNH of -13, meaning that for every 13 patients treated with 0.5mg of etanercept, one fewer patient will experience an adverse event such as sciatica, headache, nausea, diarrhea, or constipation.

The 2012 Ohtori et al study comparing epidural injection of etanercept to dexamethasone was a prospective randomized trial based in Japan (Chiba University Graduate School of Medicine)[2]. Eighty men and women, ages 49-80, were randomized using the minimization allocation method[2]. Compliance was not discussed, however, all 80 subjects provided ODI responses at 4 weeks post-injection without being lost to follow-up[2]. Detailed inclusion and exclusion criteria are in Table 1. Patients considered for inclusion had LBP/leg pain for at least 1 month with diagnosed lumbar stenosis clinically, by XRay/MRI, and with confirmation VIA spinal infiltration[2]. Patients with previous spinal surgery, trauma, cauda equine syndrome or polyradiculopathy were excluded, presumably because these anatomical and neurological variants pose a higher risk for complications[2]. All subjects received a 1.5mL intradermal injection of 1% lidocaine, followed by the respective treatment: either 2.0mL of lidocaine and 10mg of etanercept (n = 40) or 2.0mL of lidocaine and 3.3mg of dexamethasone (n = 40)[2]. Pain was evaluated using a VAS at baseline, then at 30 minutes, 3 days, 1, 2, and 4 weeks post-injection[2]. Patients also reported ODI scores at baseline and 4 weeks post-injection[2].

Ohtori et al found no statistically significant difference between groups in leg/back pain VAS scores or ODI scores ($p > 0.05$)[2]. However, both groups had statistically significant relief of leg pain up to 4 weeks post-injection ($p < 0.026$). Average leg pain scores were notably lower in the etanercept group than the dexamethasone group at 3 days, 1, 2, and 4 weeks post-injection ($p < 0.05$)[2]. VAS scores for LBP in the etanercept group were lower than dexamethasone scores at 3 days, 1 week, and 2 weeks post-injection ($p < 0.05$)[2]. Overall, 85% of patients in the etanercept group, compared to 73% of patients in the dexamethasone group, selected the answer "treatment met my expectations" or "I would undergo the same treatment for the same outcome" on the ODI survey at 4 weeks post-injection[2]. This yields a NNT of 9, meaning that for every 9

patients treated with 10mg of etanercept compared to dexamethasone, one additional patient will experience clinical improvement of sciatica (Table 8).

Table 8: Calculations for treatment using ODI scores from Ohtori et al

CER	EER	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
73%	85%	0.164%	12%	9

Table 8 illustrates a NNT of 9, meaning that for every 9 patients treated with 10mg of etanercept compared to dexamethasone, one additional patient will experience clinical improvement of sciatica.

Table 9: Improvement in leg pain

	IMPROVEMENT AT:				
	30 min	3 days	1 week	2 weeks	4 weeks
Etanercept	=	✓	✓	✓	✓
Dexamethasone	=				

✓ indicates superiority with regard to lower pain scores

= indicates equal efficacy with regard to lower pain scores

X indicates no improvement with regard to pain scores

Table 10: Improvement in back pain

	IMPROVEMENT AT:				
	30 min	3 days	1 week	2 weeks	4 weeks
Etanercept	=	✓	✓	✓	=
Dexamethasone	=				=

✓ indicates superiority with regard to lower pain scores

= indicates equal efficacy with regard to lower pain scores

X indicates no improvement with regard to pain scores

DISCUSSION: This review examines the use of etanercept compared to dexamethasone and saline in the management of spinal radiculopathy and sciatica. Cohen et al found no clinical or statistical significance in leg or back pain between patients treated with etanercept vs. saline, nor did the etanercept subjects report any improvement in disability. In fact, there was a 4.6% higher incidence of worsening pain in the etanercept group. Ohtori et al found that both of these treatments were safe and effective in providing significant pain relief up to 4 weeks post-injection, though etanercept provided better pain relief (Table 9, 10) and reduction in disability. These results were not statistically significant. Unlike the other two studies reviewed in this paper, Freeman et al did find a clinically and statistically significant difference in leg and back pain between groups, with half of the etanercept subjects experiencing 100% relief of leg pain after 1 month. This group also experienced a higher reduction in disability when compared to placebo. These studies failed to compare etanercept with non-invasive methods of treatment like

physical therapy. This review is limited by the lack of exclusion criteria used in the selection of studies. Differences in treatment effectiveness based on sex, race, and age are not addressed. The studies in this review were limited by small sample sizes, short follow-ups, reliance on patient self-report measures, and the use of injections on a set basis rather than as needed. Enbrel (etanercept) is indicated in the treatment of Rheumatoid Arthritis, Psoriasis/Psoriatic Arthritis, Ankylosing Spondylitis, and Juvenille Idiopathic Arthritis[8]. In 2012, Bonafede et al estimated the annual cost of etanercept to be $14,543.00[9]. It is unclear whether insurance will cover the cost of treatment for off-label indications like radiculopathy and sciatica. Etanercept is contraindicated in patients with sepsis and has US Boxed Warnings for Lymphoma and Tuberculosis[10].

CONCLUSION: Based on the studies reviewed in this paper, the evidence is conflicting in determining whether or not etanercept is safe and effective in treating radiculopathy and sciatica resulting from lumbar disc herniation and spinal stenosis. Of the 3 studies reviewed in this paper, only one was able to prove the efficacy and safety of etanercept with clinical and statistical significance. Future studies of epidural etanercept for spinal radiculopathy and sciatica could greatly benefit from a longer follow-up period. The clinical trials of etanercept used in this review failed to establish long-term efficacy: a major disadvantage of current conventional therapies and an ongoing area of investigation in the management of LBP. The NIH does not acknowledge any currently ongoing studies of etanercept in the treatment of radiculopathy and sciatica, but there are 56 clinical studies in progress which evaluate the use of etanercept in a multitude of other conditions. In further studies of etanercept, a comparison of low doses on an as needed basis may be most useful, given that the best results in this paper came from the lowest dose of epidural etanercept studied. In addition, efforts should be made to compare the efficacy of etanercept to other anti-TNF inhibitors, such as infliximab and adalimumab.

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