

Systematic Review

e Anti-Tumor Necrosis Factor Antagonists in the Treatment of Low Back Pain and Radiculopathy: A Systematic Review and Meta-analysis

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Background: Low back pain, with or without radiculopathy, is an important cause of disability and economic expenditure. However, many patients are not achieving optimal pain control with existing medications. Tumor necrosis factor antagonists (anti-TNF α) could be an alternative drug treatment.

Objectives: Systematic review the efficacy and safety of anti-TNF α in the treatment of low back pain with or without radiculopathy.

Study Design: Inclusion criteria were observational studies with safety as an outcome, and randomized or nonrandomized controlled trial (RCT) studies on efficacy and/or safety of anti-TNF α drugs on low back pain. Exclusion criteria included patients with auto-immune conditions or osteoporosis.

Results: Studies were assessed independently by 2 authors regarding inclusion/exclusion criteria, risk of bias, clinical relevance, quality, and strength of evidence (GRADE approach). Of the 1,179 studies retrieved, all duplicates were excluded and then the inclusion/exclusion criteria was applied. One observational study (n = 143) and 11 RCTs remained (n = 539): 8 for etanercept (n = 304), one for adalimumab (n = 61), one for adalimumab and etanercept (n = 60), one for infliximab (n = 40) and one for REN-1654 (n = 74). Only 3 etanercept and 2 adalimumab studies showed statistically significant pain relief when compared to placebo. There was no difference in the overall incidence of adverse effects when comparing anti-TNF- α and placebo.

Limitations: Despite the statistically significant effect, this meta-analysis has important limitations, such as high heterogeneity and high use of outcome imputation.

Conclusions: There is low evidence that epidural etanercept has a low-to-moderate effect size when compared to placebo for pain due to discogenic lumbar radiculopathy (5 studies, n=185), with a standardized mean difference = -0.43 (95% confidence interval [CI] -0.84 to -0.02).

There is moderate evidence that epidural etanercept does not have a higher adverse effects incidence rate when compared to placebo for discogenic lumbar radiculopathy (5 studies, n = 185) with a relative risk (RR) = 0.84 (95% CI 0.53 to 1.34).

There is moderate evidence that anti-TNF α does not have a higher adverse effects incidence rate when compared to placebo for low back pain (10 studies, n= 343) with an RR = 0.93 (95% CI 0.56 to 1.55).

We strongly suggest that anti-TNF α continue to be studied in experimental settings for the treatment of low back pain. We cannot currently recommend this therapy in clinical practice. New research could shed some light on the efficacy of anti-TNF α and change this recommendation in the future.

Key words: Low back pain, systematic review, meta-analysis, tumor necrosis factor-alpha, TNF, biologics, tumor necrosis factor-alpha antagonists, anti-TNF, etanercept, adalimumab, discogenic lumbar radiculopathy, sciatica.

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Low back pain (LBP), with or without radiculopathy, is an important cause of disability and economic expenditure (1-5). In fact, a recent study published by the US Burden of Disease Collaborators showed that in 2010 low back pain was the disease with the largest “years lived with disability”, and responsible for the third largest “disability-adjusted life year” in the US(6). Evidence suggests these numbers are rising, since Freburger et al showed that chronic impairing LBP has presented an alarming increase, with prevalence in a single state in the US rising from 3.9% in 1992 to 10.2% in 2006 (7).

The costs associated with LBP in the US exceeds \$100 billion per year (8), with patients with severe pain incurring significantly higher costs than other patients (9,10). Expenditures also show an important growth tendency, not only due to the higher prevalence of LBP, but also by an increased cost per capita (11). Martin et al (11) showed that in an 8-year period, mean expenditure per patient with spinal pain (LBP plus neck pain) had a 65% increase (11).

Most cases of LBP resolve during the first 6-8 weeks (10,12-17). However, a systematic review showed that in primary care settings, the median (range) proportion of patients with poor outcome was 11% (2-20%) at 3 to 6 months, and 21% (7-42%) at one year (17).

Current treatments

Possible treatments include drugs, surgery and minimally invasive procedures (18). Guidelines usually elect painkillers and nonsteroidal anti-inflammatory drugs (NSAIDs) as the first line of treatment (18). However, there is only limited evidence of the therapeutic effectiveness and cost effectiveness of those drugs for low back pain with or without radiculopathy (19-23). Contrary to most guidelines' recommendations, Ivanova et al (24) found that opioids were the most prescribed drug for patients with low back pain (18,24). Unfortunately, opioids also lack evidence of therapeutic effectiveness and cost-effectiveness, and are associated with important adverse effects, tolerability, and potential misuse/abuse (25-31).

Fusion surgery showed consistent evidence of clinically meaningful improvement in degenerative disc disease (32), whereas total disc replacement did not (33). On the other hand, surgery for radiculopathy due to a herniated disc seems to have only a short-term effect (34). There is a paucity of cost-effectiveness data regarding surgery in low back pain (23).

Several systematic reviews show that transforaminal,

interlaminar, and caudal epidural injections with steroids plus local anesthetics present good evidence of effectiveness for radiculopathy secondary to disc herniation (35-37). Manchikanti et al (38) showed that caudal epidural steroid injections were associated with a cost utility of less than \$2,200 per one quality-adjusted life year (QALY). Comparatively, the United Kingdom's National Institute for Health and Care Excellence defines cost effective as those interventions with an incremental cost-effectiveness ratio of less than £20,000 per QALY (38).

Novel treatments are being researched. Recent literature linked tumor necrosis factor alpha (TNF- α) to several sources of low back pain and thus, could be a new target for therapy.

Pathophysiology of low back pain

Diagnosing the cause of LBP is challenging. Many etiologies, such as disc disease, facet arthropathy, spinal stenosis, and myofascial injuries overlap and present similarly. This may be explained by the similar pathways wherein they intersect and relay pain.

TNF- α may promote facetogenic pain. In joints, nociceptive pain occurs with the activation and sensitization of “insensitive” neurons, possibly through TNF- α and interleukin (IL)-1 (39). TNF- α , IL-1 and nerve growth factor (NGF) promote inflammation, activation of chemokines, and up-regulation of several receptors (40,41). These neuron modifications favor ectopic discharges, perceived as pain, as well as promote modifications at the dorsal root ganglia, resulting in chronic, persistent pain (39,42).

TNF- α may have a role in discogenic radiculopathy symptoms, since evidence shows they are caused not only by mechanical compression but also by chemical exposure of factors contained in the nucleus pulposus (43-45). TNF- α and nucleus pulposus injection causes similar effects to annular rupture and discogenic irritation in animal models (46,47), which can be inhibited by anti-TNF- α (48-50). Thus, it is hypothesized that TNF- α has a central role in the pathophysiology of radiculopathy. Similar to discogenic radiculopathy pain, pain originating from spinal stenosis has its roots in neural compression (51). Since studies show the association between neuronal harming, dorsal root ganglia sensitization, and both TNF- α (42,52) and NGF (41,53), it is hypothesized that these cytokines are also important in promoting pain in spinal stenosis.

Rationale for using anti-TNF- α

Using anti-TNF- α has been proven effective in control-

ling different rheumatologic diseases (e.g., rheumatoid arthritis and ankylosing spondylitis) (54). Moreover, several studies have linked TNF- α with different causes of low back pain (39-53,55-60). Despite their efficacy in rheumatology, however, TNF- α inhibitors also showed an increased risk for adverse effects, including upper respiratory tract infection, headache, nausea, and in some cases, demyelinating disease (61). Nevertheless, the success of anti-TNF- α on rheumatologic diseases and the recent discoveries on the pathophysiology of low back pain stimulated research on anti-TNF- α for low back pain. To our knowledge, there is no systematic review of this subject.

Objective

The objective of this systematic review is to study the efficacy and safety of anti-TNF- α in the treatment of low back pain with or without radiculopathy.

METHODS

This systematic review was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (62), the Cochrane Back Review Group (CBRG) (63,64), and other guidelines (65,66). This research has 2 parallel systematic reviews: anti-NGF in the treatment of low back pain (67) and the present study.

The objective of the present systematic review is to assess whether the use of anti-TNF- α is efficacious and/or safe for the treatment of low back pain with or without radiculopathy.

Eligibility Criteria

Types of Studies

The following study designs were included:

- Randomized controlled trials (RCTs)
- Nonrandomized controlled trials
- Observational studies which had safety as an outcome.

Studies were included if they were published or unpublished. The only outcome assessed on observational studies was safety.

Types of Participants

Participants were adults aged at least 18 with low back pain (e.g., radicular and nonradicular low back pain, discogenic low back pain, lumbar spondylosis, etc) of any duration.

Types of Intervention

Interventions were the use of anti-NGF (tanezumab or fulranumab or others) and/or anti-TNF- α (etanercept, adalimumab, golimumab, certolizumab pegol, infliximab or others) drugs alone or combined with other co-interventions by any route of administration. Solely anti-TNF- α studies will be shown on Results in the present article (Fig. 1). For anti-NGF studies, please review our parallel study (67).

Types of Outcome Measures

Primary outcome: pain relief (using any score or scale).

Secondary outcome: functional improvement (using any score or scale) and adverse effects (number of patients with adverse effects).

Exclusion Criteria

Studies were excluded if:

- Participants had auto-immune conditions, such as ankylosing spondylitis, psoriatic arthritis, or rheumatoid arthritis
- The study included osteoporosis as an inclusion criteria
- The study included bone mass index as a primary outcome
- Studies analyzing only the osteogenic effects of anti-TNF- α and not pain control.

Literature Search

The search was conducted from September 2012 through October 2012 with no language or date restrictions in the following databases:

- Medline (via PubMed): www.pubmed.com
- EMBASE: www.embase.com
- Cochrane Library: www.thecochranelibrary.com
- National Institute for Health's ClinicalTrials.gov database: www.clinicaltrials.gov
- Hand search of theses, annals of congresses and meetings (i.e. American Pain Society Annual Scientific Meeting, American College of Rheumatology/ Association of Rheumatology Health Professionals Annual Scientific Meeting), references and contact with experts in the field. A hand search was conducted until September 2013.

Search Strategy

The same keywords were used while searching all databases and trial registries, respecting their differences (e.g., Emtree terms and MeSH terms were

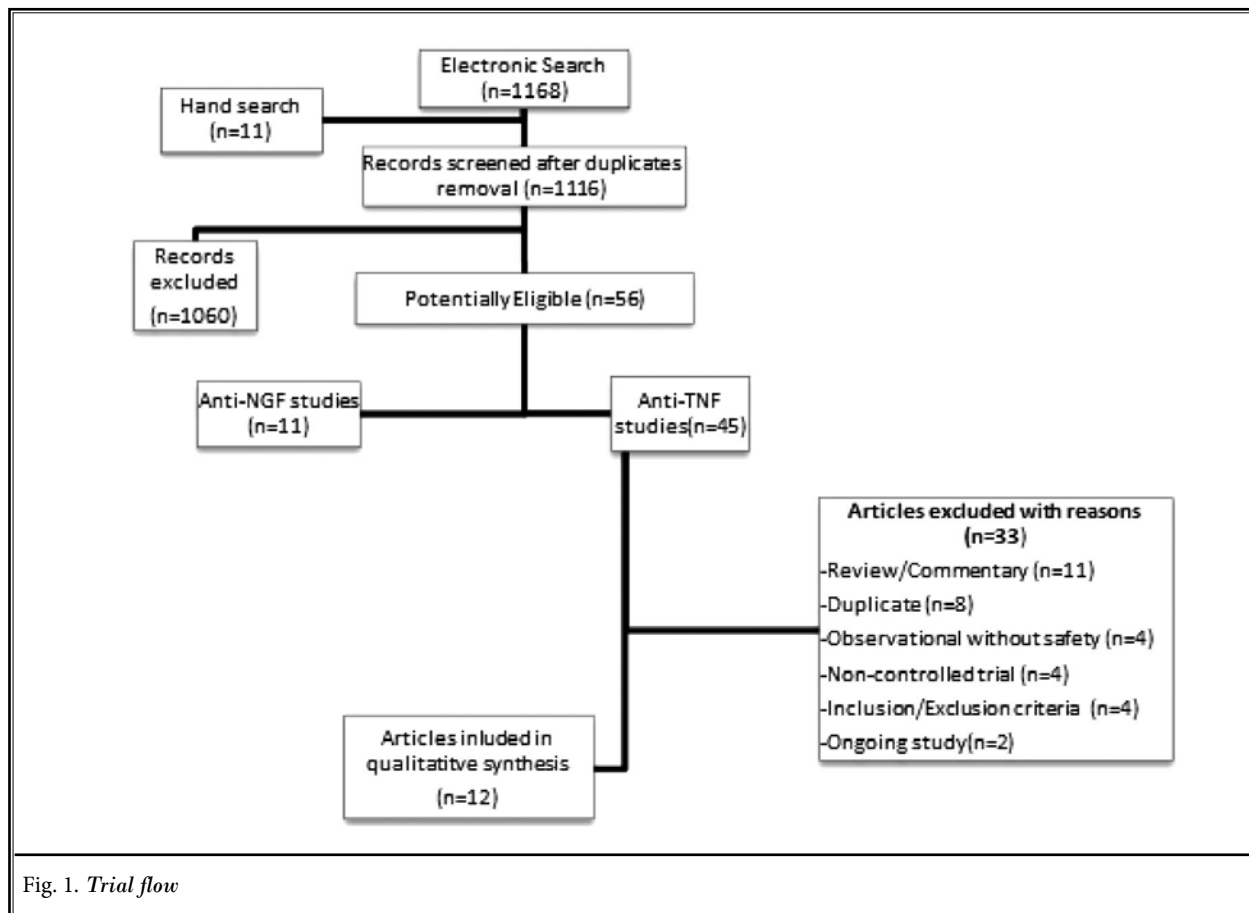


Fig. 1. Trial flow

mapped in Embase and Medline, respectively).

The keywords were "monoclonal antibodies," "nerve growth factor," "tumor necrosis factor," "etanercept," "infliximab," "adalimumab," "certolizumab," "golimumab," "tanezumab," "fulranumab," "anti-tnf," "anti-NGF," "sciatica," "back pain," and "spine."

Data Extraction

Data for each study were extracted independently by 2 authors. Disagreements were resolved by consensus. If no consensus was achieved, a third author was consulted.

All studies had their titles and abstracts analyzed according to the inclusion and exclusion criteria. If an article seemed to be eligible, or if its eligibility was unclear, the full text was extracted. All studies that had their full text assessed are described in the Results section.

Any missing data were clarified by contacting the authors directly.

Validity Assessment

Two authors performed the validity assessment in

an unblinded manner. If no consensus was achieved, a third author was consulted.

Risk of bias for randomized studies was assessed using the CBRG criteria (63) (Table 1). A subjective evaluation was performed for nonrandomized studies. Randomized studies that scored > 6 on the CBRG criteria were defined as having a low risk of bias. Studies were not excluded based on the risk of bias.

Clinical relevance was defined using CBRG criteria (63,68) (Table 2). No cutoff value was defined. Studies were not excluded based on their clinical relevance.

Quality of evidence

The quality of evidence for pain reduction, functional improvement, and safety was evaluated using the GRADE approach and the GRADEprofiler software (Cochrane Back Review Group, Institute for Work & Health, Toronto, Ontario, Canada), as recommended by the CBRG (63,69). In this approach, evidence for each outcome is assessed on 5 domains: limitations of the study design, inconsistency, indirectness (inability to

Table 1. Risk of bias.

Question	Answer (1/0/0)
1. Was the method of randomization adequate?	Yes/No/Unsure
2. Was the treatment allocation concealed?	Yes/No/Unsure
3. Was the patient blinded to the intervention?	Yes/No/Unsure
4. Was the care provider blinded to intervention?	Yes/No/Unsure
5. Was the outcome assessor blinded to the intervention?	Yes/No/Unsure
6. Was the drop-out rate described and acceptable?	Yes/No/Unsure
7. Were all randomized participants analyzed in the group to which they were allocated?	Yes/No/Unsure
8. Are reports of the study free of suggestion of selective outcome reporting?	Yes/No/Unsure
9. Were the groups similar at baseline for the most important prognostic indicators?	Yes/No/Unsure
10. Were co-interventions avoided or similar?	Yes/No/Unsure
11. Was the compliance acceptable in all groups?	Yes/No/Unsure
12. Was outcome assessment timing similar in all groups?	Yes/No/Unsure

Adapted from Furlan AD, et al; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila, Pa: 1976) 2009; 34:1929-1941.* (63)

Table 2. Clinical relevance.

Question	Answer (1/0/0)
1. Are the patients described in detail so that you can decide whether they are comparable to those that you see in your practice?	Yes/No/Unsure
2. Are the interventions and treatment settings described well enough so that you can provide the same for your patients?	Yes/No/Unsure
3. Were all clinically relevant outcomes measured and reported?	Yes/No/Unsure
4. Is the size of the effect clinically important?	Yes/No/Unsure
5. Are the likely treatment benefits worth the potential adverse effects?	Yes/No/Unsure

Adapted from Furlan AD, et al; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976) 2009; 34:1929-1941*(63,68).

generalize), imprecision (insufficient or imprecise data) of results, and publication. Two authors evaluated this independently in an unblinded manner. If no consensus was reached, a third author was consulted.

Strength of recommendation was evaluated for the same outcomes, using the GRADE guidelines (70). Each outcome was classified in one of 4 categories: strong for, weak for, weak against, and strong against.

Quantitative data analysis

Pooled intervention was calculated as a weighted average of intervention effects estimated in the individual studies using a random-effects model for all outcomes. Primary outcome (changes from baseline values in pain score for low back pain) as well as functional improvement (changes from baseline values in disability score for low back pain) were analyzed using the standardized mean difference (SMD) meta-analyses

as reported scales were different across the studies. For those continuous outcomes, a 95% confidence interval (CI) was estimated using the inverse variance and random-effects model. In case a 95% CI was reported instead of the standard deviation (SD), the SD was obtained according to the method described in the Cochrane Handbook (71). If no measure of dispersion was reported for the main outcome (mean change from baseline), the SD was imputed using the value from the final assessment. For instance, if the SD was not reported for the mean change of pain from baseline to 4 weeks, then the SD of pain assessment at 4 weeks was used. When the mean and the SD were only reported for individual dosages, a weighted average of the intervention group was calculated.

An effect size of etanercept by dosing was performed following these steps: Patients who received the specified dose were included in the active arm

(placebo arm remained unaltered); effect sizes (mean, 95% CI) were calculated for each pooled dose level; mean and 95% CI for each pooled dose effect size were represented in a box plot.

Adverse effects were analyzed as a binary outcome and risk difference and its 95% CI was assessed using the Mantel-Haenszel method.

The homogeneity between articles was evaluated with the Chi-square and I² tests and considered I² > 30% as evidence of heterogeneity.

The software used for the analysis was Review Manager (RevMan) version 5.0 (The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Trial flow

The electronic search retrieved 1,168 studies and the hand search retrieved 11 results. After excluding duplicates and articles based on title and abstract, we found 56 potentially eligible studies (Fig.1). Of those, 45 were anti-TNF- α studies and 11 were anti-NGF, analyzed in a parallel systematic review (67). There was no study with both anti-TNF- α and anti-NGF drugs. Consensus was reached between the 2 authors on all occasions.

Among the 45 anti-TNF- α studies, 33 were excluded; 11 were reviews or commentaries (44,46,72-80); 8 were duplicates (81-88); 4 were observational studies that did not have safety as an outcome (89-92); 4 were noncontrolled clinical trials (93-96); 4 did not meet other inclusion/exclusion criteria (97-100); 2 were ongoing studies (101,102). A total of 12 studies were included in the qualitative synthesis(103-114).

Study Characteristics

Twelve studies were analyzed with a qualitative synthesis (Tables 3-4) and except for the study by Tobinick et al (113) which was an observational study, all were randomized controlled trials (Table 3). Information could not be obtained regarding the study by Carragee et al (103).

The mean age of the patients ranged from 39.3 to 66.0 years. The gender distribution varied across the studies, although the study by Okoro et al (112) was the only one that had a female majority. Most studies included patients with subacute or subacute-to-chronic pain, with the studies by Cohen et al (103) and Tobinick et al (113) performing as outliers (pain duration of 63 and 116 months, respectively). Except the study by Kume et al (110), which used ETN and ADA, all studies

used a single anti-TNF- α drug. Information regarding disability assessment and concomitant use of other pain medications was often not reported.

The safety of anti-TNF- α was assessed on all studies except for Carragee et al (103), since data could not be obtained. Of 608 patients, 80 showed adverse effects (AEs), most of them classified by the authors as minor. AE severity classification varied across studies; Freeman et al (114) had the most strict criteria, defining pain worsening and headache as severe. There was no significant difference on AEs when comparing anti-TNF- α with placebo or steroids. Eleven serious AEs were reported, only one of them outside the study by Freeman et al (114): a nonfatal digestive tract hemorrhage in the study by Genevay et al (107), which happened to a 59-year-old woman who had been on nonsteroidal anti-inflammatory drugs for 6 weeks at the time of the study.

Among 10 RCTs whose data were available (n = 465), 5 (n = 185) showed that anti-TNF- α therapy had statistically significant pain relief compared to placebo for low back pain (105,107,110,111,114).

Epidural interventions

Six RCTs (n = 313) had epidural as the route of administration: Kume et al (109,110) used caudal injections; while Freeman et al (114), Cohen et al (105, 106) and Ohtori et al (111) used transforaminal injections. All epidural interventions used etanercept as the study drug. Moreover, Kume et al (110) also used adalimumab in a parallel arm. ETN dosage varied from 0.5 mg in Freeman et al (114) to 25 mg in Kume et al (110). Cause for pain was discogenic lumbar radiculopathy in all studies (105,106,109,110,114), except for Ohtori et al (111), which studied lumbar spinal stenosis. Patients' baseline characteristics varied across studies. Cohen et al (105,106) had more young and male patients, perhaps due to its military setting. Freeman et al (114) had the lowest back pain ratings at baseline.

Among RCTs of discogenic lumbar radiculopathy (DLR), only Cohen et al (105) and Freeman et al (114) showed a difference from placebo. Studies were heterogeneous regarding patients' characteristics at baseline.

Subcutaneous interventions

Two RCTs (n = 76) and one observational study (n = 143) were in this category. Genevay et al (107) analyzed subcutaneous ADA, whereas Okoro et al (112) and Tobinick et al (113) performed subcutaneous etanercept in the perispinal area. Tobinick et al (113) performed a retrospective study of discogenic nonradicular low back pain.

Anti-Tumor Necrosis Factor Antagonists in the Treatment of Low Back Pain

Table 3. Study characteristics at baseline in mean + SD, except for use of pain medication or if stated otherwise, organized by route of administration of anti-TNF- α .

	Sample Size (total = 682)	Age (years)	Gender	Back pain (0-10)	Leg Pain (0-10)	Duration of pain (months)	Disability	Use of pain medication (%)
Epidural Total = 313								
Cohen et al 2009 (105)	n = 24	41-46‡	M = 70%, F = 30%	VAS = 6.08 (\pm 1.94)	VAS = 6.78(\pm 1.68)	4.3 (\pm 2.9)	ODI = 39.7 (\pm 15.06)	N.R.
Cohen et al 2012 (106)	n = 84	42.3 (\pm 10.8)	M = 70.3%, F = 26.7%	NRS = 5.35 (\pm 2.53)	NRS = 6.21 (\pm 1.90)	2.7 (\pm 1.74)	ODI = 41.86 (\pm 16.48)	Opioid therapy = 41.7%
Freeman et al 2013 (114)	n = 37	47.22 \pm 12.06	M = 64.9, F = 35.1	NRS = 4.41 (\pm 1.89)	NRS = 5.89 (\pm 0.92)	1.43 \pm (1.67)	ODI = 35.12 (\pm 14.11)	N.R.
Kume et al 2008 (109)	n = 28	54.0 (N.R.)	M = 62.4%, F = 37.6%	VAS = 7.91 (N.R.)*	N.R.*	1.91 (N.R.)	N.R.	N.R.
Kume et al 2009 (110)	n = 60	52.6 (N.R)	M = 65%, F = 35%	VAS = 8.03 (\pm 1.80)*	N.R.*	1.80 (N.R)	N.R.	N.R.
Ohtori et al 2012 (112)	n = 80	66 (\pm 5.32)	M = 50%, F = 50%	VAS = 7.7 (\pm 2.0)	VAS = 6.45 (\pm 1.51)	2.4 (N.R.)	ODI = 39 (\pm 7.6)	NSAID = 86.2%
Intradiscal Total = 36								
Cohen et al 2007 (104)	n = 36	39.3 (\pm 11.4)	M = 78%, F = 22%	VAS = 5.83 (N.R.) \leftrightarrow	N.A.	63.6 (\pm 50.4)	N.R.	Opioid use = 43%
Intravenous Total = 40								
Korhonen et al 2005 (108) †	n = 40	40.7 (\pm 8.4)	M = 60%, F = 40%	VAS = 5.6 (0-9.7)	VAS = 7.3 (3.0-9.9)	2.03 (0.66-3.4)	ODI = 48 (18-82)	N.R.
Per os Total = 74								
Carragee et al (103)	n = 74	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Subcutaneous Total = 219								
Genevay et al 2010 (107)	n = 61	52.08 (\pm 12.98)	M = 58%, F = 42%	VAS = 3.84 (\pm 3.14)	VAS = 7.34 (\pm 1.97)	3.55 (\pm 3.38)	ODI = 69.44 (\pm 12.01)	Course of steroid prior to treatment = 39%
Okoro et al 2010 (112)	n = 15	N.R.	M = 33.3%, F = 66.7%	VAS = 4.07 (\pm 2.49)	VAS = 8.06 (\pm 1.66)	N.R.	ODI = 52.12 (\pm 18.13)	N.R.
Tobinick et al 2004 (113)	n = 143	55.8 (\pm 14.3)	M = 51.7%, F = 48.3%	7.09 (\pm 1.94)	N.R.	117 \pm 135.6	ODI = 42.8 (\pm 17.9)	N.R.

† = Median \pm range. ‡ = range of medians. \leftrightarrow = values estimated from the bar graph provided on the study. * = the study reported a combined pain level for low back pain and leg pain. N.R. = not reported. NSAID = nonsteroidal anti-inflammatory. ODI = Oswestry Disability Index. VAS = Visual analog scale

Genevay et al (107) was the only study using a subcutaneous route that showed a reduction in low back pain levels, comparing adalimumab to placebo. However, there was no difference in leg pain levels, which was the study's primary outcome.

Tobinick et al (113) assessed both chronic neck and low back disc-related pain. Data were not provided for different pain sites. Observational studies were only

assessed regarding AEs, which are further described in the section "Quantitative analysis." It was estimated that AE rates were not significantly different between low back and neck pain.

Intradiscal, intravenous and per os

Carragee et al (103), Cohen et al (104) and Korhonen et al (108) conducted the only RCTs in their cat-

Table 4. Study intervention and outcomes, by route of administration.

Author, year	Number of patients (total = 682)	Type of study	Condition	Intervention	Follow up length	Reported outcomes adjusted by covariance	Comment
Epidural Total=313							
Cohen et al 2009 (105)	n = 24 ETN=18 (6 for each group: 2, 4 or 6mg), PBO=6	RCT, dose-response	DLR	2 injections of ETN (EP) or PBO (EP), 2 w apart	6 mo	No	Leg and low-back pain were lower on ETN group at 1 mo. Disability and AEs did not differ among groups.
Cohen et al 2012 (106)	n = 84 ETN (4 mg) = 28, STE = 28, PBO = 28	RCT, multicenter	DLR	2 injections of ETN (EP) or STE (EP) or PBO (EP), 2 w apart	1 mo	Yes	No significant difference on pain at 1 mo between the groups. STE had a better functional improvement than ETN.
Freeman et al 2013 (114)	n = 37 ETN (0.5 mg) = 8, ETN (2.5 mg) = 10, ETN (12.5 mg) = 9, PBO = 10	RCT, multicenter	DLR	2 injections of ETN (EP) or PBO (EP), 2 w apart	6 mo	Yes	All ETN arms significantly reduced back pain. Only ETN (0.5mg) significantly reduced leg pain.
Kume et al 2008(109)	n = 28 ETN (25 mg) = 14, PBO = 14	RCT	DLR	Single injection of ETN (EP) or PBO (EP)	1 mo	Yes	No significant difference in any outcome.
Kume et al 2009 (110)	n = 60 ETN (25 mg) = 20, ADA (40 mg) = 20, PBO = 20	RCT	DLR	Single injection of ETN (EP) or ADA (EP) or PBO (EP)	1 mo	Yes	Pain was significantly lower at 1 month only in the ADA group. No difference on surgeries or AEs.
Ohtori et al 2012 (111)	n = 80 ETN (10 mg) = 40, STE = 40	RCT	LSS	Single injection of ETN (EP) or STE (EP)	4 wks	No	Leg pain significantly lower at 1, 2, and 4 w. Low back pain lower only at 1 and 2 w.
Intradiscal Total=36							
Cohen et al 2007 (104)	n = 36 ETN = 30 (6 for each group: 0.1, 0.25, 0.5, 0.75 and 1 mg); PBO = 6	RCT, dose-response	DLBP/DLR	Single dose of ETN (ID) or PBO (ID)	6 mo	No	No difference between groups in VAS, ODI or AEs.
Intravenous Total = 40							
Korhonen et al 2005 (108)	n = 40 INF (5mg/kg) = 21, PBO = 19	RCT	DLR	Single injection of INF (IV) or PBO (IV)	6 mo	Yes	No significant difference in any outcome.
Subcutaneous Total = 219							
Genevay et al 2010(107)	n = 61 ADA (40 mg) = 31, PBO = 30.	RCT, multicenter	DLR	2 injections of ADA (SC) or PBO (SC), 1 w apart	6 mo	Yes	Back pain was lower on ADA at week 6 and at almost all time points. PBO patients required more surgery. No difference on drug usage. Leg pain, ODI and SF-12v2 did not differ.
Okoro et al 2010 (112)	n = 15 ETN (25 mg) = 8, PBO = 7	RCT	DLR	Single injection of ETN (SC) or PBO (SC)	12 wks	No	No significant difference in any outcome at all time points.
Tobinick et al 2004 (113)	n = 143 ETN(25mg)	Observational	DLBP/ DCP	2.3 ± 0.7 injections of ETN (SC) 1.9 ± 1.16 w apart	1 mo	No	16 nonserious AEs which were resolved spontaneously.
Per os Total = 74							
Carragee et al 2006 (103)	n = 74 REN-1654 100 mg = 39, PBO = 35	RCT	LR	REN-1654 (PO) or PBO (PO)	3 wks	N.R.	No difference in average leg pain.

ADA = adalimumab. AEs = adverse effects. DLR = discogenic lumbar radiculopathy. DLBP = discogenic low back pain. DCP = discogenic cervical pain. ETN = etanercept. EP = epidural. GPE = Global Perceived Effect. ID = intradiscal. INF = infliximab. IV = intravenous. LSS = lumbar spinal stenosis. LR = lumbar radiculopathy. OBS = observational study. ODI = Oswestry Disability Index. PBO = placebo. RCT = randomized controlled trial. SC = subcutaneous. SF-12v2 = Short Form Health Questionnaire. STE = steroids. VAS = Visual analog scale

egory, per os, intradiscal, and intravenous, respectively. Carragee et al (103) studied the effects of REN-1654, a drug which was under development by Renovis and was discontinued due to its lack of efficacy.

Cohen et al (104) conducted a dose-response RCT using etanercept for discogenic low back pain with or without radiculopathy. As opposed to the other studies included in this systematic review, Cohen et al (104) studied patients with chronic pain, for a mean of 63.6 months.

Korhonen et al (108) injected intravenous infliximab for discogenic lumbar radiculopathy. None of those studies found a significant difference in any outcome.

Risk of Bias

Consensus was reached on all occasions. All the studies except Carragee et al (103) had a risk of bias scored ± 6 , defined by the CBRG as a low risk of bias (Tables 5, 6). Since several articles did not have enough

Table 5. Risk of bias

Author,year	Carragee et al (103)	Cohen et al, 2007	Cohen et al, 2009	Cohen et al, 2012	Freeman et al	Genevay et al, 2010	Korhonen et al, 2005	Kume et al, 2008	Kume et al, 2009	Ohtori et al, 2012	Okoro et al, 2010
1. Was the method of randomization adequate?	-	+	+	+	+	+	+	+	+	+	+
2. Was the treatment allocation concealed?	-	-	-	+	+	+	+	+	+	+	+
3. Was the patient blinded to the intervention?	-	+	+	+	+	+	+	+	+	+	+
4. Was the care provider blinded to the intervention?	-	+	+	+	+	+	+	+	+	+	+
5. Was the outcome assessor blinded to the intervention?	-	+	+	+	+	+	+	+	+	-	+
6. Was the drop-out rate described and acceptable?	-	+	+	+	+	+	+	+	+	+	-
7. Were all randomized participants analyzed in the group to which they were allocated?	-	+	+	+	-	+	+	+	+	-	-
8. Are reports of the study free of suggestion of selective outcome reporting?	-	-	+	-	+	+	-	-	-	-	-
9. Were the groups similar at baseline re: the most important prognostic indicators?	-	+	-	+	+	-	-	+	+	+	-
10. Were co-interventions avoided or similar?	-	+	-	+	-	-	-	-	-	-	-
11. Was the compliance acceptable in all groups?	-	+	+	+	+	-	-	+	+	+	-
12. Was outcome assessment timing similar in all groups?	-	+	+	+	+	-	+	+	+	+	+
Total	0	10	9	11	10	8	8	10	10	8	6

Adapted from Furlan AD, et al; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2009; 34:1929-1941.(63)

Table 6. *Clinical relevance.*

Author, year	A) Patient description	B) Description of interventions and treatment settings	C) Clinically relevant outcomes	D) Clinical importance	E) Benefits versus potential harms	Total Criteria Met
Carragee et al (103)	-	-	-	-	-	0/5
Cohen et al, 2007 (104)	-	+	+	-	+	3/5
Cohen et al, 2009 (105)	-	+	-	-	+	2/5
Cohen et al, 2012 (106)	-	+	+	-	+	3/5
Freeman et al, 2013 (114)	-	+	+	+	+	4/5
Genevay et al, 2010 (107)	+	-	-	-	+	2/5
Korhonen et al, 2005 (108) †	+	+	-	-	+	3/5
Kume et al, 2008 (109)	-	-	-	-	+	1/5
Kume et al, 2009 (110)	-	-	-	+	+	2/5
Ohtori et al, 2012 (111)	+	+	+	-	+	4/5
Okoro et al, 2010 (112)	-	-	-	-	+	1/5
Tobinick et al, 2004 (113)	-	+	+	-	-	2/5

Adapted from Furlan AD, et al; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2009; 34:1929-1941(63,68)

information for an adequate bias assessment, the respective authors were contacted via personal communication. Only in the Carragee et al (103) study could the author not be reached. Being a nonrandomized study, Tobinick et al (113) was analyzed in a subjective matter. Since it was a noncontrolled, nonrandomized, unblinded study, it was prone to selection and measurement bias.

Quantitative Data Synthesis (meta-analysis)

Pain Relief

High heterogeneity was present among the included RCTs. A meta-analysis for pain relief was only performed in the subgroup that had the highest number of RCTs, which was epidural etanercept for discogenic lumbar radiculopathy (DLR).

Epidural etanercept was more efficacious than placebo for low back pain due to discogenic lumbar radiculopathy (SMD = -0.43, 95% CI [-0.84 to -0.02], $P = 0.04$) as shown in Fig. 2. In a sensitivity analysis, the exclusion of Freeman et al (114) caused the largest reduction in effect size (Fig. 3).

Only Cohen et al (105, 106) reported SD of change from baseline pain. Other RCTs had their SD imputed from a main assessment time point, as described in 2.7-Quantitative data analysis. In addition, Freeman et al (114) only reported the main outcome in a line graph, from which outcome values were estimated.

Freeman et al (114) found that the lowest dose of etanercept (0.5 mg) was the most efficacious in reducing average low back pain at 6 weeks. The hypothesis of inverse dose-effect for epidural etanercept on DLR was done using a post-hoc analysis. Data from all epidural RCTs for DLR were pooled and analyzed according to etanercept dosing (Fig. 4).

Functional Improvement

A meta-analysis was not conducted since most studies did not report this data adequately.

Adverse Effects

A pooled analysis for AEs is shown in Fig. 5. The study by Ohtori et al (111) was not pooled since the control group used dexamethasone instead of a placebo. Tobinick et al (113) was excluded due to the absence of a control group. For Korhonen et al (108), data published elsewhere regarding a one-year follow-up period were used. Freeman et al (114) did not report a serious AE by treatment arm.

There was no difference on the incidence of AEs between anti-TNF- α agents and placebo (RR = 0.93, 95% CI [0.56 to 1.55]). The authors reported 10 serious AEs, the most important being a digestive tract hemorrhage in a 59-year-old woman who had been taking NSAIDs for 6 weeks at the time of the study by Genevay et al (107); and an irregular heartbeat during the study by Freeman et al (114). None were fatal.

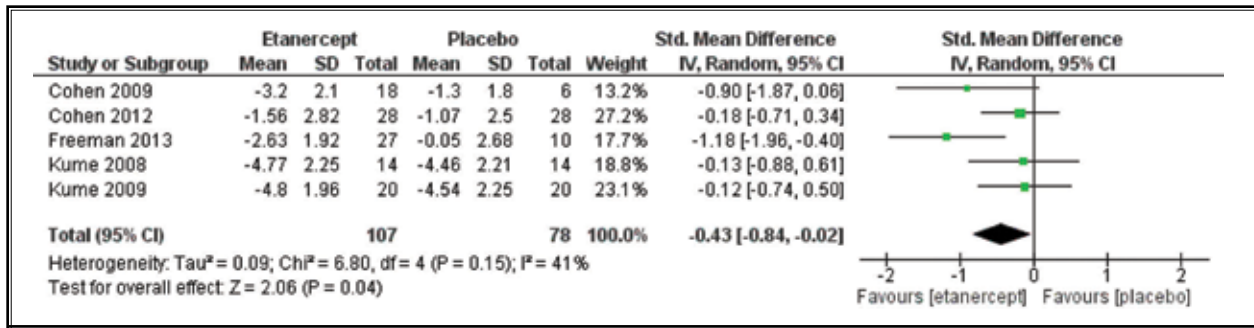


Fig. 2. Epidural etanercept vs placebo for low back pain.

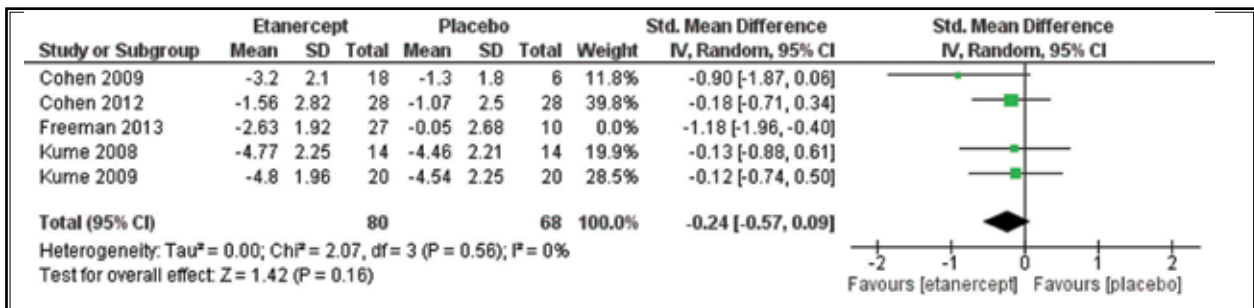


Fig. 3. Sensitivity analysis: epidural etanercept vs placebo for low back pain excluding Freeman et al.

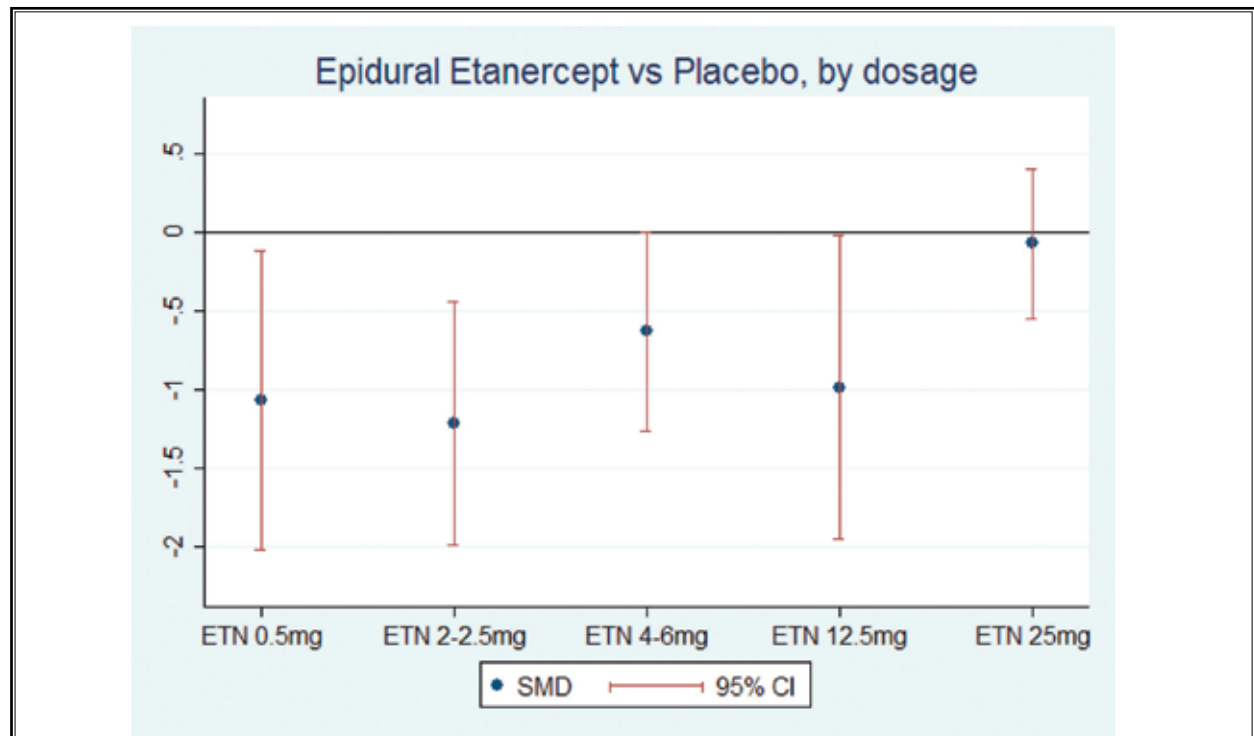


Fig. 4. Epidural etanercept vs placebo for DLR by dosage.

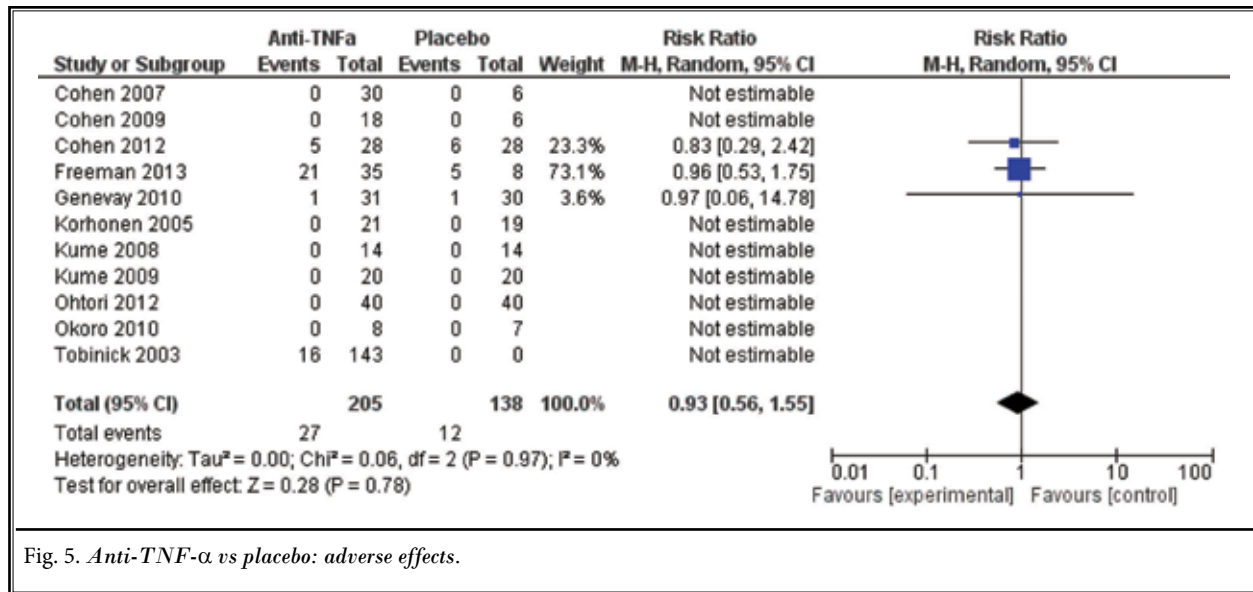


Fig. 5. Anti-TNF- α vs placebo: adverse effects.

Methodological Quality Assessment

There is low evidence that epidural etanercept has a low-to-moderate effect size when compared to placebo for pain due to discogenic lumbar radiculopathy (5 studies, $n = 185$), with a SMD = -0.43 (95% CI [-0.84 to -0.02]) (Tables 7, 8).

There is moderate evidence that epidural etanercept does not have higher incidence rate of adverse effects when compared to placebo for discogenic lumbar radiculopathy (5 studies, $n = 185$) with a RR = 0.84 (95% CI [0.53 to 1.34]).

There is moderate evidence that anti-TNF α does not have higher incidence rate of adverse effects when compared to placebo for low back pain (10 studies, $n = 343$) with a RR = 0.93 (95% CI [0.56 to 1.55]).

We strongly suggest that anti-TNF α continues to be studied in experimental setting for the treatment of low back pain. Despite the statistical significant effect, this meta-analysis has important limitations, as shown in Discussion session. Thus, in the present moment we cannot recommend this therapy in clinical practice. New research could shed some light on the efficacy of anti-TNF α and change this recommendation on a near future.

DISCUSSION

We found low evidence of the effect of etanercept for discogenic lumbar radiculopathy. Data regarding infliximab and adalimumab were not sufficient to conduct a meta-analysis.

However, a qualitative analysis of adalimumab showed promising results, since the 2 RCTs included showed efficacy over placebo. Genevay et al (107) showed an important reduction of low back pain with adalimumab. However, the main outcome, leg pain, did not show a statistically significant difference, nor did disability status. A 3-year follow-up analysis was published reporting a reduced need for back surgery by 61% of patients who received adalimumab compared to those who received a placebo (84). Patients underwent surgery at a median 2.3 months after study inclusion. Using data from Genevay et al (107), the median time after symptoms that patients underwent surgery was approximately 3.2 months. Since a recent systematic review showed that surgery for acute DLR may be only beneficial in the short term (34), perhaps the benefit of controlling pain in the first 3 months is a reduction in surgery rates, which could result in a cost-effective approach.

Freeman et al (114) found that an epidural injection of etanercept 0.5 mg was more efficacious than 2.5 mg and 12.5 mg injections for DLR. Moreover, they suggested an inverse dose-effect mechanism. This meta-analysis could not support this hypothesis. Even though the effect size of etanercept 25 mg seems smaller than the other dosages, overlap exists between the 95% CI of all dose levels (Fig. 4). Moreover, we could not find data in the literature to support the hypothesis of an inverse dose-effect mechanism of TNF- α antagonism. In fact, higher levels of TNF- α are associated with worse

Table 7. GRADE evidence profile for anti-TNF-α versus placebo for low back pain.

Quality Assessment Anti-TNF-α Versus Placebo for Low Back Pain							No. of Patients		Effect		Quality
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Anti-TNF-α	Control	Relative (95% CI)	Absolute	
Pain (follow-up median one month; measured with 0-10 scale; better indicated by lower values)											
10	RT	serious	serious	serious	serious	reporting bias	0	-	-	not pooled	⊗⊗⊗ very low
Adverse Effects (follow-up 1-6 months; assessed with cumulative incidence of adverse effects)											
10	RT	no serious risk of bias	not serious	not serious	serious ¹	none	27/205 (13.2%)	12/138 (8.7%)	RR 0.93 (0.56 to 1.55) ²	6 fewer per 1000 (from 38 fewer to 48 more)	⊗⊗⊗ moderate

RT = randomized trial. ¹ Only 2 of the 10 controlled studies adequately reported an event for this outcome

² RR= Relative Risk

Table 8. GRADE evidence profile for epidural etanercept versus placebo for discogenic lumbar radiculopathy.

Quality Assessment Epidural Etanercept Versus Placebo for DLR						No. of Patients		Effect		Quality
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Epidural Etanercept	Placebo	Relative (95% CI)	Absolute	
Pain (follow-up 1-6 months; measured with change from baseline pain; better indicated by lower values)										
5	RT	no serious	serious†	no serious	serious‡	107	78	-	SMD -0.43, 95% CI(-0.84, -0.02)	⊗⊗⊗ low
Adverse Effects (follow-up 1-6 months; assessed with cumulative incidence of adverse effects)										
5	RT	no serious	not serious	not serious	serious↔	21/107 (19.6%)	13/78 (16.7%)	RR 0.84 (0.53 to 1.34)	27 fewer per 1000 (from 78 fewer to 57 more)	⊗⊗⊗ moderate

RT = randomized trials† Only Freeman et al {need reference number} showed statistically significant change from placebo. Also, there was important heterogeneity in the analysis ($I^2 = 60\%$)

‡ Statistical significance was only found in Freeman et al (114)

↔ Among the 5 RCTs, only Freeman et al (114) and Cohen et al 2012(106) reported the event

outcomes in experimental studies on rheumatoid arthritis and joint pain (115,116). RCTs and observational studies with etanercept for rheumatology also did not show an inverse dose-effect (117,118).

To our knowledge, there are 2 ongoing RCTs on anti-TNF-α: a Finnish study on epidural adalimumab for discogenic radiculopathy (102), and a French study on intravenous infliximab for lumbar spinal stenosis (101).

In September 2013, a meta-analysis about biologics targeting TNF-α for sciatica was published by Williams et al (119). However, studies by Kume et al (109,110) and Carragee et al (103) were not included. Additionally, the study by Freeman et al (114) had not been published by that time. Williams et al (119) did not show a statistical significance for anti-TNF-α over placebo. There are important differences between both meta-analyses. Williams et al (119) pooled RCTs

with different drugs and routes of administration in a single analysis using a binomial outcome (overall global improvement). Among those studies, there was an RCT that used historical controls (96). We believe it is more appropriate to perform individual analysis for different drugs and routes of administration. Also, assessing pain with binomial outcomes may result in misinterpretation of the results.

Limitations

Sensitivity analysis showed that excluding Freeman et al (114), etanercept would have a small effect size over placebo for pain reduction (SMD=-0.24 95%CI[-0.57 to 0.09]). Freeman et al (114) had the lowest levels of low back pain at baseline (VAS=4.42 ± 1.89) and shorter pain duration (1.43 ± 1.67 months). Also, the placebo group had a mean difference of pain from

baseline of only -0.05 compared to -2.63 for those receiving etanercept, which could have led to an inflated effect size.

Important inconsistencies arise from other RCTs. Among epidural etanercept: while Cohen et al (104) found significant results for etanercept at one month, there was no difference from placebo at 3 and 6 months. Reasonable explanations include a limited effect duration and small power due to small sample size. Conversely, there were only 6 patients per study arm (2 mg, 4 mg, and 6 mg) as well as baseline differences across treatments, which could have resulted in a type-2 error. This hypothesis becomes stronger since Cohen et al (106) repeated the experiment with epidural injections of etanercept 4 mg in a multi-center trial with 28 patients by arm and failed to show any difference from placebo. Epidural etanercept RCTs had small sample sizes (median of 28, range = 18-37 patients in the etanercept arm). Therefore, there is a high risk of outliers causing type-1 and type-2 errors, especially for the dose-ranging studies with even smaller sample sizes for individual dosages. Dosing regimens were also highly heterogeneous, ranging from 0.5 mg-25 mg.

In a qualitative analysis, 2 out of 2 adalimumab RCTs showed efficacy over placebo, compared to 3 out of 8 for etanercept. Different dosing schemes could explain this difference. While the highest dose of etanercept was a single 25 mg injection (recommended dose for rheumatoid arthritis = 50 mg/week) (120), Adalimumab studies used a single injection of 40 mg (recommended dose for rheumatoid arthritis = 20 mg/week).

There is some evidence of publication bias, since data could not be obtained for one study (103).

Serious adverse events in anti-TNF- α therapy can be considered rare events (121), therefore small sample

sizes are an important limitation for the assessment of this outcome. Furthermore, the follow-up period may have been insufficient. Study follow-ups ranged up to 36 months, with 4 studies (n = 252 patients) reporting a follow-up of one month. Drug elimination time for etanercept and adalimumab are estimated to be 6 and 45 months respectively (61). By comparison, a recent systematic review of the safety of anti-TNF- α agents for rheumatoid arthritis had a follow-up of 12 - 64 weeks (121). Thus, the relatively small follow-up period assessed by our review may be an important limitation for safety assessment.

Although some data were obtained from the authors, not all necessary information could be obtained for a proper methodological evaluation. Standard deviation for the main outcome was imputed for 3 of the 5 RCTs. It is possible that the imputation led to under/overestimation of real effect sizes.

CONCLUSION

Anti-TNF- α appears to be a promising alternative in the treatment of low back pain, more specifically, epidural etanercept for DLR. However, more evidence is necessary in order to be accepted for use in clinical practice. Future RCTs should pursue larger sample sizes, fewer study arms, and a longer follow-up period. Observational studies should include a control group. Future meta-analyses would benefit if the RCTs published mean and standard deviation of outcomes, as well as a thorough description of statistical methods, so that a better quality of evidence can be obtained.

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