Anti-Nerve Growth Factor in the Treatment of Low Back Pain and Radiculopathy: A Systematic Review and a Meta-Analysis

Victor F. Leite, MD¹, Anna M. Buehler, PharmD, PhD¹, Omar El Abd, MD², Ramsin M. Benyamin, MD¹, Daniel C. Pimentel, MD, PhD¹, Janini Chen, PT¹, Wu Tu Hsing, MD, PhD¹, Danesh Mazloomdoost, MD⁶, and Joao E. D. Amadera, MD PhD¹

Background: Low back pain with or without radiculopathy is an important cause of disability and economic expenditure. However, many patients are not meeting optimal pain control through existing treatments. Recent studies have linked nerve growth factor (NGF) and the pathophysiology of persistent pain. Anti-NGF could be an alternative drug treatment for low back pain.

Objective: Systematically review the efficacy and safety of anti-NGF in the treatment of low back pain.

Methods: A systematic review of the literature with no language, date or publication status restriction, using Medline, EMBASE, Cochrane Library, and the clinicaltrials.gov database. Additional literature was retrieved by conferring with experts in the field or reviewing bibliographies and annals of meetings and congresses. Search terms included “monoclonal antibodies,” “nerve growth factor,” “anti-ngf,” “fulranumab,” “tanezumab,” “sciatica,” “back pain,” and “spine.”

Study Design: Inclusion criteria were observational studies with safety as an outcome and randomized or nonrandomized controlled trials studying the efficacy and/or the safety of anti-NGF drugs on low back pain. Exclusion criteria included patients with autoimmune conditions or osteoporosis. Studies were assessed independently by 2 authors regarding inclusion/exclusion criteria, risk of bias, clinical relevance, and quality of evidence (GRADE approach).

Results: 1,168 studies were retrieved. After excluding duplicates and applying the inclusion/exclusion criteria, 4 RCTs remained (n = 2,109): 2 for tanezumab, one for REGN475, and one for fulranumab. Only the tanezumab studies showed any significant difference over placebo (n = 1,563) for both pain relief and functional improvement.

Conclusions: There is very low evidence that systemically administered anti-NGF therapy has a small positive effect compared to placebo for both pain relief (standardized mean difference [SMD] = -0.29, 95% confidence interval [CI] -0.58 to 0.00) and functional improvement (SMD = -0.21, 95%CI -0.58 to -0.05) of low back pain. There was low evidence of adverse effects (AEs) compared to placebo and low evidence of neurological AEs than placebo (relative risk = 1.93, 95%CI 1.41 to 2.64). Tanezumab, as a specific anti-NGF treatment, showed low evidence of a small to moderate effect for pain relief of low back pain (SMD = -0.44, 95%CI -0.81 to -0.07); and low evidence of a small effect for functional improvement (SMD = -0.26, 95%CI -0.40 to -0.12) with systemic administration, although not clinically significant. Tanezumab and anti-NGFs overall had, respectively, moderate and low evidence of overall AEs and serious AEs and a higher risk of developing neurological AEs when compared with placebo.

Although anti-NGF, specifically tanezumab, showed a low-to-moderate effect on pain relief and functional improvement, it cannot be recommended for low back pain treatment. Without more research on the pathophysiology of anti-NGFs and adverse effects, its use is not safe in the overall population. However, as corroborated by the US Food and Drug Administration, this meta-analysis underscores a role for greater insight into anti-NGF therapy for painful conditions that are refractory to current drugs, such as oncologic pain, chronic pancreatitis, and phantom-limb pain. Given the pathophysiologic of axial pain involving inflammatory mediators and the adverse effects of systemic anti-NGF use, consideration of local therapies may warrant further exploration.

Key Words: back pain, anti-ngf, spine, sciatica, nerve growth factor, radiculopathy, treatment

From: ¹University of São Paulo, Brazil, ²Newton Wellesley Interventional Spine, LLC, Wellesley, MA, ³Millennium Pain Center, Bloomington, IL, ⁴University of Illinois, Urbana-Champaign, IL, ⁵Spine Center, São Paulo, Brazil, ⁶Pain Management Medicine, Lexington, KY

Address Correspondence: Joao E D Amadera, MD PhD
Head and Medical Director
Spine Center
Rua Abilio Soares, 250 1º andar
São Paulo, SP Brazil
CEP: 04005-000
Email: joao@fmusp.org.br

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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 LBP was the disease with the largest years lived with disability, and was responsible for the third highest disability-adjusted life-years in the US (6). Evidence suggests these numbers are rising, since Freburger et al (7) 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 a 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 + 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, during the first 6-8 weeks (10,12-17). However, a systemic review showed that in primary care settings, the median (range) proportion of patients with a poor outcome was 11% (2% - 20%) at 3 to 6 months, and 21% (7% - 42%) at one year (17).

Current Treatment

Possible treatments include drugs, surgery, and minimally invasive procedures (18). Guidelines usually elect painkillers and nonsteroidal anti-inflammatories (NSAIDs) as the first line of treatment (18). However, there is only limited evidence of the effectiveness and cost-effectiveness of those drugs for low back pain with or without radiculopathy (18-23). Contrary to most guidelines’ recommendations (18), Ivanova et al (24) found that opioids were the most prescribed drug for patients with low back pain. Unfortunately, opioids also lack evidence of effectiveness and cost-effectiveness, and are associated with important adverse effects, tolerability, and potential misuse/abuse (25-31). Invasive methods are also possible treatments. Several systematic reviews show that minimally invasive procedures, such as epidural injections, are effective and cost-effective for discogenic lumbar radiculopathy (32-35). Despite its efficacy, data suggest that an exaggerated number of spinal invasive procedures are being performed. Manchikanti et al (36) showed that from 2000 to 2008, Medicare receipts for spinal intervention-al techniques increased 107.8%. An audit performed by the US Department of Health and Human Services reported that in 2007 34% of transforminal epidural injection services did not meet Medicare requirements (37). Disc replacement surgery for degenerative disc disease did not show significant clinical improvements (38). On the other hand, surgery for radiculopathy due to a herniated disc seems to have an effect only in the short-term (39). However, there is not enough evidence to affirm that surgery is a cost-effective treatment for LBP (23). Thus, several current treatments lack effectiveness and cost-effectiveness, whereas others are highly misindicated. A high number of biologics are now being tested for diverse painful conditions (40-44). Nerve growth factor (NGF) antagonists (anti-NGF) have already been tested in phase-2 and phase-3 trials and a systematic review is needed in order to assess evidence.

NGF and Low Back Pain

NGF is a neurotrophic factor associated with pain signaling (45). NGF is released when there is tissue inflammation or nerve damage (46) and has an important role in the origin of hypersensitivity and persistent pain through several pathways. There is direct action on nociceptive neurons by causing rapid posttranslational changes in the diverse cation channels (47), and indirect action by activating mast cells, consequently releasing histamine, leukotrienes, and other inflammatory cytokines (47-49). Retrograde NGF axonal transport to the dorsal root ganglion up-regulates protein receptors that sensitize both the sensory nerve and more central second-order neurons, originating persistant pain (45). NGF is also involved in the regulation of inflammatory mediators such as Bradykinin, substance P, and calcitonin gene-related peptides, as well as the activation of inflammatory cells such as neutrophils (47,50).

There is a large body of evidence linking NGF to inflammatory, visceral, and neuropathic pain (45,51-62). Animal studies on rats demonstrate the efficacy of anti-NGF therapy for inflammatory pain (54,63,64). In animal models of bone cancer pain, anti-NGF was superior to high doses of morphine (62). In addition, NGF plays a role in the evolution of persistent pain, which suggests anti-NGF could be a viable treatment for chronic pain (52,61,62). Clinical trials have been conducted showing pain reduction on osteoarthritis and interstitial cystitis (65,66).

Despite the evidence of its efficacy in clinical studies, anti-NGF has had some controversy due to adverse effects. In 2010, the US Food and Drug Administration (FDA) put a hold on anti-NGF studies due to several cases of osteonecrosis in osteoarthritis patients receiv-
ing anti-NGF therapy through studies by Janssen, Pfizer, and Regeneron/Sanofi (67). In March 2012, after reviewing the data from the sponsors, a meeting of the FDA’s Arthritis Advisory Committee voted to resume the interrupted clinical studies with anti-NGF for conditions in which there are no agents with demonstrated analgesic efficacy, such as interstitial cystitis or pancreatitis (67). Given the existing potential for anti-NGF treatment and a need for novel therapies for low back pain, a systematic review of anti-NGF is needed to identify research achievements and gaps.

The objective of this systematic review is to study the efficacy and safety of anti-NGF on LBP.

**Methods**

This systematic review was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (19), the Cochrane Back Review Group (CBRG) (20,21) and other guidelines (22,23). This research contains 2 parallel systematic reviews: anti-TNF-α in the treatment of LBP (68) and the present study.

The objective of the present study is to systematic review whether the use of anti-NGF is efficacious and/or safe for the treatment of low back pain.

**Eligibility Criteria**

**Types of Studies**

The following study designs were included: Randomized controlled trials (RCTs) Nonrandomized controlled trials Observational studies with safety as an outcome.

Studies were included regardless of their publication status. Observational studies were only assessed for safety outcomes.

**Types of Participants**

Participants were adults of at least 18 years of age with LBP (e.g., radicular and nonradicular LBP, discogenic LBP, lumbar spondylosis) of any duration.

**Types of Intervention**

Interventions were the use of anti-NGF (tanezumab [TNZ] or fulranumab or others) and/or anti-TNF-α (etanercept, adalimumab, golimumab, certolizumab pegol, infliximab, or others) alone or combined with other co-interventions by any route of administration.

In the present systematic review, only anti-NGF studies will be shown in the results (Fig. 1). For anti-TNF-α studies, please review the parallel systematic review (68).

**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 autoimmune conditions, such as ankylosing spondylitis, psoriatic arthritis, or rheumatoid arthritis Study included osteoporosis as an inclusion criteria Study included bone mass index as a primary outcome Studies analyzing only the osteogenic effects of anti-TNF 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:


**Search Strategy**

The same keywords were used in all databases and trial registries, respecting their differences (e.g., Emrree terms and MeSH terms were 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-tfn,” “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 (69) (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 (69,70) (Table 2). No cutoff value was defined. Studies were not excluded based on their clinical relevance.

Quality of evidence

Quality of evidence for pain reduction, functional improvement, and safety was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and the GRADE profiler software (Cochrane Back Review Group, Institute for Work & Health, Toronto, Ontario, Canada), as recommended by the CBRG (68,70). In this approach, evidence for each outcome is assessed in 5 domains: limitations

Table 1. Risk of bias.

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


Table 2. Clinical relevance.

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

of the study design, inconsistency, indirectness (inability to generalize), and imprecision (insufficient or imprecise data) of results and publication. Two authors conducted the evaluation independently in an unblinded manner. If no consensus was reached, a third author was consulted. The strength of recommendation was evaluated for the same outcomes, using the GRADE guidelines (72). Each outcome was classified in 1 of the 4 categories: strong for, weak for, weak against, 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. Since reported scales were different among the studies, primary outcomes (changes from baseline values in pain score for LBP), as well as functional improvement (changes from baseline values in disability score for LBP), were analyzed using a standardized mean difference (SMD) meta-analysis. For continuous outcomes, a 95% confidence interval (CI) was estimated using the inverse variance and random-effects model. Adverse effects were analyzed as a dichotomous outcome and risk ratio (RR) and its 95% CI was assessed using the Mantel-Haenszel method.

If studies had more than one anti-NGF arm (e.g., TNZ 5 mg vs. TNZ 10 mg vs. TNZ 20 mg versus placebo [PBO]), all the anti-NGF study arms were averaged in one single study arm (e.g., TNZ versus PBO), so that the final mean and standard deviation (SD) of the single anti-NGF arm was the weighted average of the multiple anti-NGF study arms. If the study did not report the SD of the groups, it was estimated from data reported in the primary study (i.e., mean values for intervention and control, and P-values that related to the differences between those means) (73). The estimation was performed so that one SD value was obtained for each anti-NGF arm (e.g., if the study had 3 TNZ arms, it would have 3 estimated SD). According to the recommendation of Higgins et al (74), the intermediate SD value was input to PBO. When exact P-values were not reported (e.g., P < 0.05), a conservative approach was used by taking the P value at the upper limit (e.g., for P < 0.05, it was estimated P = 0.05) (73).

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; the manual search retrieved 9 results. After excluding duplicates and articles based on title and abstract, 54 potentially eligible studies were found (Fig.1). Of those, 11 were anti-NGF and 43 were anti-TNF-α studies, analyzed in the parallel systematic review (CITATION). There was no study with both anti-TNF-α and anti-NGF drugs. Consensus was reached between the 2 authors on all occasions.

From the 11 anti-NGF studies, seven were excluded: three were duplicates (75-77), two were reviews or commentaries (78,79) and two were terminated early -- a Pfizer’s study (80) (due to the FDA-issued clinical hold on all anti-NGF studies on 2010) (81), and Sanofi-Aventis/Regeneron’s study on vertebral fracture pain due to low patient recruitment and enrollment (80).

A total of 4 studies were included on the qualitative synthesis (82-85), as shown in Table 3.

Study Characteristics

Four studies were analyzed on the qualitative synthesis (Tables 3 and 4), all of which were RCTs. All the studies were sponsored by pharmaceutical companies. Pfizer sponsored studies by Katz et al (82) and Kivitz et al (83); Johnson & Johnson sponsored the study by Sanga et al (85), and Regeneron sponsored an unpublished study (84). From the 4 studies, only the study by Katz et al (82) has been published in a peer-reviewed journal. The studies by Kivitz et al (83) and Sanga et al (85) were published only as conference abstracts, and the study by Regeneron (84) only as a protocol on the clinicaltrials.gov database. Therefore, the limited available data were supplemented by contacting the authors and accessing conference presentation files via an internet search.

All studies had patients with chronic nonradicular LBP, except the one from Regeneron (84), whose patients had lumbar radiculopathy. Across the studies, the average patient age was 51 years old and pain scores averaged 6.7 on an 11-point pain scale. These averages were similar across the studies. Only the studies by Katz et al (82) and Kivitz et al (83) reported pain duration, which was around 11 years.

Among the 4 RCTs, only TNZ studies showed statistically significant improvement on pain control and disability. The fulranumab study was terminated in October 2010 due to lack of efficacy (85).
Fig. 1. **Trial flow.**

Table 3. **Study characteristics at baseline.**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Number of patients (total = 2109)</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Back pain (0 - 10)</th>
<th>Leg Pain (0 - 10)</th>
<th>Duration of pain (years)</th>
<th>Function/Disability</th>
<th>Use of pain medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz, 2011 (81)</td>
<td>Total = 216 TNZ(IV) = 88, NPX = 88, PBO = 41</td>
<td>51.07 (± 14.73)</td>
<td>M = 51.6% F = 55.4%</td>
<td>aLBPI = 6.6 (± 1.4)</td>
<td>N.A.</td>
<td>10.77 (N.R.)</td>
<td>RMDQ = 2.6 (± 4.8)</td>
<td>N.R.</td>
</tr>
<tr>
<td>Kivitz, 2011 (82)</td>
<td>Total = 1347 TNZ(IV) = 822 NPX = 295, PBO = 230</td>
<td>51.7 (N.R)</td>
<td>M = 45.8% F = 54.2%</td>
<td>aLBPI = 6.68 (± 1.19)</td>
<td>N.A.</td>
<td>11.4 (N.R.)</td>
<td>RMDQ = 2.94 (± 2.86)</td>
<td>N.R.</td>
</tr>
<tr>
<td>Regeneron (83)</td>
<td>Total = 157 REGN475(SC) = 106 PBO = 51</td>
<td>N.R.</td>
<td>N.R.</td>
<td>N.R.</td>
<td>NNRS = 6.1 (± 1.35)</td>
<td>N.R.</td>
<td>N.R.</td>
<td>N.R.</td>
</tr>
<tr>
<td>Sanga, 2011 (84)</td>
<td>Total = 389 FUL(SC) = 311 PBO = 78</td>
<td>53.2 (± 12)</td>
<td>M = 54% F = 46%</td>
<td>APIS = 7.0 (± 1.24)</td>
<td>N.A.</td>
<td>N.R.</td>
<td>ODI = 35.3 (± 13.92)</td>
<td>Opioid use = 45%</td>
</tr>
</tbody>
</table>

aLBPI= average low back pain intensity. APIS= Average Pain Intensity Score (0-10 score in last 3 days). FUL= fulranumab. IV= intravenous. N.A.= not applicable. NPX= naproxen. N.R.= not reported. ODI= Oswetry Disability Index. PBO= placebo. REN= REN-1654. RMDQ= Roland Morris Disability Questionnaire. SC= subcutaneous. TNZ= tanezumab
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Consensus was reached on all occasions. We relied on the authors of the studies to obtain sufficient data for scoring the articles. The study by Regeneron (83) scored < 6, defined by the CBRG as a high risk of bias, mostly because adequate information to assess it could not be obtained.

Consensus for assessing clinical relevance was achieved on all occasions. The studies by Katz et al (82) and Kivitz et al (83) failed in Category B, description of intervention, since patients had to discontinue pain medication prior to baseline assessment and were only allowed acetaminophen up to 2000 mg/d. Therefore, they could have had more pain than in a clinical setting, and thus the study may have overestimated the effect of the anti-NGF therapy. The study by Kivitz et al (83) failed in Category A, patient description, since complete patient information (e.g., use of pain medication before and during the trial) could not be assessed. Sanga et al (85) failed in Category D, clinical importance, and Category E, risk-benefit analysis, due to a lack of efficacy data from the clinical trial. Information could not be obtained for the Regeneron (84) study.

Quantitative Data Synthesis (Meta-analysis)

Pain Relief

For the pain relief analysis, the study by Regeneron (84) was excluded due to a lack of data. The studies by Kivitz et al (83) and Katz et al (82) evaluated TNZ; Sanga et al (85) evaluated fulranumab (Tables 4-6). Katz et al (82) used a single intravenous injection of 200 µg/kg of TNZ, while Kivitz et al (83) used 3 arms of TNZ (5 mg versus 10 mg versus 20 mg) in an intravenous injection repeated after 8 weeks. Sanga et al (85) studied subcutaneous fulranumab in 4 different doses (1 mg versus 3 mg versus 6 mg + 3 mg versus 10 mg) every 4 weeks for a total of 12 weeks, in a total of 3 injections. When compared to PBO, all anti-NGF therapies combined (Fig. 2) had an average reduction of 0.29 SMD (95% CI, -0.58 to 0.00). According to Cohen’s rule of thumb for SMDs, 0.2 can be considered a small effect size, 0.5 a moderate effect, and 0.8 a large effect (86). Thus, our analysis showed a small effect for anti-NGF when compared to PBO for pain reduction. TNZ showed a small-to-moderate effect compared to PBO (SMD = -0.44, 95% CI [-0.81 to -0.07]).

Table 4. Study intervention and outcomes.

<table>
<thead>
<tr>
<th>Author, Year Study Type</th>
<th>Condition</th>
<th>Intervention</th>
<th>Number of patients (total = 2,109)</th>
<th>Length of follow-up</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz, 2011 (81) RCT</td>
<td>cLBP</td>
<td>Single TNZ 200 µg/kg (IV) or NPX (PO) or PBO</td>
<td>Total = 216 TNZ = 88 NPX = 88 PBO = 41</td>
<td>12 wk</td>
<td>TNZ had significant pain and RMDQ improvement from 4 w-12 w and 1 w-12 w, respectively. TNZ had more neurological AEs than NPX and PBO.</td>
</tr>
<tr>
<td>Kivitz, 2011 (82) RCT</td>
<td>cLBP</td>
<td>2 injections of TNZ 5, 10 or 20 mg (IV) 8 w apart vs NPX (PO) vs PBO</td>
<td>Total = 1347 TNZ 5 mg = 232 TNZ 10 mg = 295 TNZ 20 mg = 295 NPX = 295 PBO = 230</td>
<td>16 wk</td>
<td>TNZ 10 mg and 20 mg had significant pain reduction and RMDQ improvement vs PBO and NPX. TNZ had more neurological AEs than NPX and PBO.</td>
</tr>
<tr>
<td>Regeneron, 2010 (83) RCT</td>
<td>LR</td>
<td>Single injection of REGN475 0.1 or 0.3 mg (SC) or PBO (SC)</td>
<td>Total = 157 REGN475 0.1 mg = 53 REGN475 0.3 mg = 53 PBO = 51</td>
<td>12 wk</td>
<td>No significant difference on pain relief vs PBO. REGN475 had more neurological AEs.</td>
</tr>
<tr>
<td>Sanga, 2011 (84) RCT</td>
<td>cLBP</td>
<td>3 injections of FUL 1, 3, 6 + 3 or 10 mg (SC), 4 w apart or PBO (SC)</td>
<td>Total = 389 FUL 1 mg = 77 FUL 3 mg = 77 FUL 6+3 mg = 79; FUL 10 mg = 78</td>
<td>12 wk</td>
<td>No significant difference in pain relief or ODI. FUL presented more neurological AEs.</td>
</tr>
</tbody>
</table>

aLBPI= average low back pain intensity. AEs= adverse effects. cLBP= chronic low back pain. FUL= fulranumab. IV= intravenous. LR= lumbar radiculopathy. NPX= naproxen. N.A.= not applicable. N.R.= not reported. ODI= Oswetry Disability Index. PBO= placebo. PO= by mouth. RCT= randomized controlled trial. REN= REN-1654. RMDQ= Roland Morris Disability Questionnaire. SC= subcutaneous. TNZ=tanezumab. VAS= Visual analog scale.
Table 5. Risk of bias.

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<tbody>
<tr>
<td>1. Was the method of randomization adequate?</td>
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<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>2. Was the treatment allocation concealed?</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<td>3. Was the patient blinded to the intervention?</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
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<tr>
<td>4. Was the care provider blinded to intervention?</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5. Was the outcome assessor blinded to the intervention?</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>6. Was the drop-out rate described and acceptable?</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7. Were all randomized participants analyzed in the group to which they were allocated?</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>8. Are reports of the study free of suggestion of selective outcome reporting?</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9. Were the groups similar at baseline for the most important prognostic indicators?</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10. Were co-interventions avoided or similar?</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11. Was the compliance acceptable in all groups?</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>12. Was outcome assessment timing similar in all groups?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Total 7 10 4 10


Table 6. Clinical relevance.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>A) Patient description</th>
<th>B) Description of interventions and treatment settings</th>
<th>C) Clinically relevant outcomes</th>
<th>D) Clinical importance</th>
<th>E) Benefits versus potential harms</th>
<th>Total Criteria Met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz, 2011 (81)</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>4/5</td>
</tr>
<tr>
<td>Kivitz, 2011 (82)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>3/5</td>
</tr>
<tr>
<td>Regeneron (83)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0/5</td>
</tr>
<tr>
<td>Sanga, 2011 (84)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>3/5</td>
</tr>
</tbody>
</table>


Fig. 2. All anti-NGF therapies combined versus placebo: Change from baseline pain values.

Fig. 3. Tanezumab versus placebo: Change from baseline pain values.
Anti-Nerve Growth Factor in the Treatment of Low Back Pain and Radiculopathy

Functional improvement

Once again, the study by Regeneron (84) was not included due to the lack of data (Fig. 4). Anti-NGF showed a better functional improvement than placebo (SMD = 0.21, 95% Cl [0.37 to 0.05]). In a sub-group analysis (Fig. 5), TNZ also showed a small effect compared to PBO (SMD = 0.26, 95% Cl [-0.40 to -0.12]).

Adverse effects

All studies were included in the analysis of adverse events, except for Katz et al (82) since neither the intervention group nor the control group had any adverse effects.

Patients using anti-NGF drugs (Fig. 6) had an overall higher risk of developing any adverse effects when compared to PBO, although not statistically significant (RR = 1.13, 95% CI [0.98 to 1.29]). When stratifying by neurological adverse effects (e.g., headache, hyperesthesia, abnormal peripheral sensation, dizziness), anti-NGF therapy showed a higher RR (RR = 1.93; 95% CI [1.41 to 2.64]). Nevertheless, this did not result in a higher risk of a serious adverse effect for the patients using anti-NGF therapy (RR = 0.69, 95% CI [0.32 to 1.49]).

While TNZ did not show an increased risk for overall adverse effects (RR = 0.86, 95% CI [0.65 to 1.15]),
nor serious events compared to PBO, it did show an increased risk of neurological adverse effects (RR = 1.84, 95% CI [1.06 to 3.20]).

**Methodological Quality Assessment**

In summary (Table 7), there is very low evidence that systemic anti-NGF therapy has a small positive effect compared to PBO for both pain relief (SMD = -0.29, 95% CI [-0.58 to 0.00]) and functional improvement (SMD = -0.21, 95% CI [-0.37 to -0.05]) in LBP. There was low evidence that anti-NGF therapy had no superior incidence rate of overall adverse effects when compared to PBO. However there was low evidence that anti-NGF is associated with a higher risk of neurological adverse effects than PBO (RR = 1.93, 95% CI [1.41 to 2.64]). In a post-hoc evaluation of TNZ, there was low evidence of a small-to-moderate effect for pain relief for low back pain (SMD = -0.44, 95% CI [-0.81 to -0.07]); and low evidence of a small effect for functional improvement (SMD = -0.26, 95% CI [-0.40 to -0.12]) when compared to PBO. TNZ showed moderate evidence of a nonsuperior incidence rate for overall adverse effects (RR 1.13, 95% CI [0.98 to 1.29]) and serious adverse effects versus PBO. However, it showed a higher risk of developing neurological adverse effects (RR = 1.84, 95% CI [1.06 to 3.20]). Despite the relatively good results found in this meta-analysis, we are strongly against using anti-NGF drugs for LBP due to data found by the FDA.

**DISCUSSION**

Our systematic review and meta-analysis demonstrated that TNZ has a significant small-to-moderate effect on pain relief and a small effect on functional improvement. When we consider anti-NGF as a drug class, the results were decrease in magnitude of effect; this reduction was more significant for pain relief than for functional improvement. For both outcomes, considering anti-NGF as a drug class added heterogeneity on the pooled results, measured by the I2 statistics.

Our results could be compared with other studies investigating pharmacological interventions for the treatment of chronic nonspecific LBP. Kuijpers et al (19) demonstrated by meta-analysis that the use of NSAIDs...
and opioids had a larger effect on pain relief than anti-NGF drugs (SMD = -12.40, 95% CI [-15.53 to -9.26] and SMD = -0.54, 95% CI [-0.72 to -0.36]), respectively. On the other hand, they found no differences in pain relief using antidepressant drugs (SMD -0.02, 95% CI, [-0.26 to 0.22]).

As the evidence provided by Kuijpers et al (19) shows, the overall quality of evidence was low. Even though the included studies had a low risk of bias, the data were poorly reported, with important baseline characteristics not reported by the trials, scatter measurements of the data were not provided, and an inappropriate statistical analysis approach was taken. In this regard, information like duration of pain and use of concomitant medication were not homogeneously reported by the trials. Further, the length of the follow-up was different across the studies, ranging from 6 weeks by Katz et al (82) to 16 weeks by Kivitz et al (83). The treatment was also not similar in any of the included studies regarding drug dosage and the frequency of administration. All studies were supported by industry and just one of the studies was published as an original journal article. In the Kivitz et al (83) study, we had to estimate the SD for the treatment group. We also had to input the SD in the PBO group, which might have resulted in an overestimated SD and, consequently, an underestimated effect size. Moreover, the study by Katz et al (82) used a one-sided test with $\alpha = 0.1$ for the comparison of TNZ versus PBO. This could have led to an overestimation of the effect size on their study and in our meta-analysis.

Considering the safety of the interventions, our meta-analysis showed an increased risk for neurological adverse effects, with no statistical significance for
serious adverse effects or for any other adverse effects. Considering the small effect of anti-NGF on the investigated outcomes, the increased risk must be taken into account when weighed against the benefits.

Furthermore, we could not ignore the information that, in 2010, the FDA put anti-NGF studies on hold due to a high incidence of rapidly progressive osteoarthritis/osteonecrosis (RPOA/ON) in patients receiving those drugs for osteoarthritis pain (87). An independent adjudication supported by the FDA confirmed an association between anti-NGF and a higher incidence of RPOA/ON (88), based apparently on only one case of RPOA/ON that occurred out of 1,325 patients receiving anti-NGF for LBP (39). This event correlates with a dose-response as well as synergistic association with the concomitant use of NSAIDs. Nevertheless, in March 2012, the FDA’s Arthritis Advisory Committee stated that there was a role for the ongoing development of anti-NGF drugs for conditions where currently available pain therapies were inadequate (e.g., chronic pancreatitis, bone cancer pain), unless the patient was at a high risk for joint destruction (81,89). Furthermore, it was stated that new safety procedures should be taken in order to avoid new cases of RPOA/ON, such as a baseline radiograph of all the joints, pelvic magnetic resonance imaging and a central pathology and radiology analysis. Finally, the committee also determined that more experimental studies were needed to better understand the effects of NGF on vascular tissue. In July 2013, the FDA lifted their partial hold on tanezumab after nonclinical data were obtained (90). To our knowledge, studies with fulranumab and REGN475 are still halted.

Experimental studies link NGF to ischemia-induced neovascularization (45,91) and to cardiac repair following myocardial infarction (92). Until data obtained by the FDA are made available, it is not safe to recommend anti-NGF therapy for low back pain.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks (95% CI)</th>
<th>Relative effect</th>
<th>No. of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain relief</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Least mean change in VAS/NRS from baseline follow-up: 6-16 weeks</td>
<td>The mean pain relief in the intervention groups was 0.44 standard deviations lower than placebo (-0.81 to 0.07)</td>
<td>Small-to-moderate effect</td>
<td>1,181 (2 studies)</td>
<td>⊙○○○ low&lt;sup&gt;2,3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Functional improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODI/RMDQ follow-up: 6-16 weeks</td>
<td>The mean functional improvement in the intervention groups was 0.26 standard deviations lower than placebo (-0.40, -0.12)</td>
<td>Small effect</td>
<td>1,181 (2 studies)</td>
<td>⊙○○○ low&lt;sup&gt;2,3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adverse effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of adverse effects follow-up: median 16 weeks</td>
<td>RR 1.13 (0.98, 1.29)</td>
<td>RR 1.13</td>
<td>1,281 (2 studies)</td>
<td>⊙○○○ moderate&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CI: Confidence interval; RR: Risk ratio; GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
1 Visual Analog Scale / Numerical rating scale.
2 In the studies by Katz et al (81) and Kivitz et al (82), prior to baseline assessment, patients could only use rescue medications (acetaminophen up to 2000 g). This could result in higher baseline pain levels and a higher estimate effect of TNZ3. There were only 2 studies and both were sponsored, which makes the studies prone to publication bias.
4 According to Cohen’s conception for standardized mean differences, 0.2 is a small effect, 0.5 a moderate effect and 0.8 a large effect.
been studied, for either efficacy or safety profile. Given the pathophysiology of axial pain involving inflammatory mediators and the adverse effects of systemic anti-NGF use, consideration of local therapies may warrant further exploration.

**Conclusion**

In conclusion, although this meta-analysis does not support the use of anti-NGF drugs for the treatment of LBP, it contributes greater insights into anti-NGF therapy for other chronic painful conditions such as oncologic pain, chronic pancreatitis, and phantom-limb pain refractory to current drugs.

**Acknowledgements**

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