Biologic drugs as analgesics for the management of low back pain

Theodoros Dimitroulas [a,b], Tosin Lambe [c], George D Kitas [a,e], Rui V Duarte [d]

[a] Department of Rheumatology, Dudley Group NHS Foundation Trust, Dudley, UK
[b] Fourth Department of Internal Medicine, Hippokration Hospital, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece
[c] Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[d] Liverpool Reviews and Implementation Group, University of Liverpool, Liverpool, UK
[e] Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, University of Manchester, Manchester, UK

Corresponding author: Rui V Duarte, Liverpool Reviews and Implementation Group, University of Liverpool, Room 2.21 Whelan Building, Liverpool L69 3GB, UK

Email: rui.duarte@liverpool.ac.uk; Telephone: +44 (0)151 794 5726|

Funding sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest: The authors have no conflicts of interest to declare.

Disclaimer: Figure 1and accompanying description is original material and not reproduced from other sources

Running title: Biologic drugs for low back pain

Abstract

Objective: To discuss the current knowledge on the impact of commonly used biologic agents (i.e., anti-tumor necrosis factor alpha [anti-TNF-α] and anti-nerve growth factor [anti-NGF]) in the management of low back pain.

Methods: A narrative literature review of studies investigating the use of biologic agents for the management of low back pain was conducted. We searched MEDLINE and EMBASE for English language publications. A hand-search of reference lists of relevant studies was also performed

Results: Although some observational studies showed that inhibition of TNF-α reduced pain and improved function, randomised controlled trials and a meta-analysis failed to demonstrate superiority of anti-TNF-α over placebo in this regard. Anti-TNF-α however reduced the risk of having invasive procedures such as discectomy and radicular block. Conversely, controlled studies showed moderate pain reduction and mild functional improvement with anti-NGF administration, but the side-effect profile of anti-NGF was unfavorable compared to placebo.

Conclusions: Overall, anti-cytokine treatments have limited efficacy in patients with chronic low back pain. However, larger and better-designed studies may need to be performed in specific patient sub-populations. Low back pain is particularly disabling in younger patients. This group therefore represent a potential target population for investigating the effectiveness of anti-cytokine therapies, especially where other pharmacological and non-pharmacological management strategies have failed.

Keywords: anti-nerve growth factor, anti-tumour necrosis factor alpha, biologic drugs, low back pain

Introduction

Discomfort in the low back that is severe enough to limit activity can be broadly classed as low back pain (LBP) and it is the commonest health problem globally [1]. Thirty-nine percent of the general population will have at least one episode in their lifetime [2]. The condition is not often associated with serious or life-threatening conditions (~1%) [3]. The majority of the cases will resolve within three months, but some do become protracted, leading to significant morbidity and financial burden to patients and their carers, and places a disproportionately high demand on the overstretched healthcare systems worldwide.

LBP is often used interchangeably with the term sciatica although the later does not represent a specific diagnosis, it is a convenient way to refer to pain in the low back and/or radicular pain associated with disk herniation. Although herniated intervertebral disc-induced sciatica represents the most common mechanism for LBP [4][4], an important proportion of patients may also suffer from chronic pain originating from the lower back and radiating down to the leg which is neither related to intervertebral disc-related diseases (IVD) nor does it result from nerve-root compression [5]. These symptoms are attributable to referred pain from the lower back and account for a significant degree of disability in cases of various low back related conditions such as degenerative facet joint disease or foraminal stenosis. It is worth noting that imaging-based evidence of disc herniation may be found in asymptomatic patients underlying that no clear association between clinical presentation and identifiable pathology of the spine could be established in many cases of LBP [6]. Given the heterogeneous aetiology of symptoms, specific causes of chronic LBP particularly in the absence of IVD and/or radicular pain cannot always be elucidated, involving a complex interrelation between anatomic and functional abnormalities in the central nervous system, structural changes in the back such as degenerative spinal disease and vertebral joint overload due to atrophy or asymmetry of key stabilising muscles in the lumbar spine [7]. Such functional and skeletal

abnormalities amplified by psychological and social factors including negative emotions and beliefs, job dissatisfaction and unhelpful social support [8], account for the majority of cases of chronic LBP which is commonly characterised as "nonspecific", "idiopathic", "mechanical", "axial" or due to instability [9].

In the context of IVD, mechanical nerve root compression has long been considered as the major cause of disc-induced radicular pain [10]; recent experimental and clinical observations have however contradicted this purely mechanical hypothesis by suggesting a chemical element in the pathophysiology [11]. The introduction of nucleolus pulposus - the gelatinous core part of the intervertebral disc and the main component of IVD – into epidural space induces pain, electrophysiological abnormalities and nerve fibre degeneration even in the absence of mechanical stimuli (Olmarker's model) [12, 13]. Animal-model experiments have shown that nucleus pulposus exerts significant inflammatory properties resulting in the abnormal production of proinflammatory cytokines, amplification of inflammatory responses and recruitment of immune cells to the disc; processes that are highly involved in the generation of pain (Figure 1) [14, 15]. Advances in experimental and clinical research have led to the development of biologic agents targeting specific cytokines in pain potentiation and propagation in LBP. The commonest targets by far are Tumour Necrosis Factor (TNF), Nerve Growth Factor (NGF) and Interleukin-1 (IL-1). Both terms will be used here interchangeably in a broad and comprehensive manner.

TNF-alpha is an important inflammatory mediator that irritates and damages nerve roots. Endoneurial injection of TNF-alpha in rodents has been shown to cause vascular and histological nerve modifications that are similar to changes seen with extrusion of nucleus polposus [16, 17]. The involvement of TNF-alpha in disc herniation, nerve sensitisation and ingrowth is further supported by the preventive effects of TNF-alpha blockade in animal models of IVD [18, 19]. Local production of TNF-alpha is upregulated in degenerate and

herniated discs compared to non-degenerate IVD tissue, and highly sensitive methods have enabled the detection of the cytokine within nucleus pulposus, Schwann cells and epidural space [20]. These reports provided the rationale for clinical studies evaluating the efficacy of TNF-alpha inhibition for discogenic pain in humans [21, 22].

In rodents, increased concentrations of NGF and sensitisation of NGF receptors were observed in constricted sciatic nerve injury [23, 24]. Significant reduction in inflammatory processes, pain and hyperalgesia seen after the injection of anti-NGF subsequently confirmed a causal relationship between NGF and chronic constriction sciatic nerve injury [25], potentially, through the blockade of peripheral nociceptors [26]. The observed NGF and anti-NGF effects in the animal models were replicated in humans [27]. Here, upregulation of TNF and the production of IL-1 in degenerated or herniated discs, directly induce the expression of NGF in the inflamed tissue. Once expressed, NGF contributes to chronic neuronal stimulation primarily by binding to tyrosine kinase (TrKA) and p75NTR (75 kDa neurotrophin) receptors on sensory neurones, thereby causing post-translational changes in transient receptor potential vanilloid 1 (TRPV1). The interaction results in the depolarisation of ion channels that detect milieu acidity, which is ultimately perceived as pain. Additionally, NGF recruits other pro-inflammatory immune cells such as mast cells [28, 29] thereby exacerbating pain perception [30]. Details of these responses have been published elsewhere [31, 32].

Whilst clinical research on biologics specifically targeting TNF-alpha and NGF usually focus on systemic autoimmune disease and osteoarthritis respectively, the increasing incidence of LBP and the unmet need for adequate pain control have led to renewed interest in LBP. Accordingly, this review discusses the current knowledge on the use of anti-TNF and anti-NGF for the management of LBP.

[Insert Figure 1 here]

Methods

MEDLINE and EMBASE were extensively searched from inception up to March 2017, according to published guidance on narrative reviews [33]. A combination of both indexing and free-text terms were used, including chronic low back pain, sciatica, anti-TNF, anti-NGF and growth factors. Studies that evaluated the use of biologic agents for the management of chronic low back pain or sciatica were selected for inclusion. The search was restricted to articles published in English language. A hand search of the reference lists of studies meeting the inclusion criteria was also performed to identify other relevant papers. Where more than one paper from a single trial was identified, information from both papers were pooled and the latest version was cited.

Results

Anti-Tumour Necrosis Factor (TNF)-α Therapy

So far, only three anti-TNF medications have shown potential for being scaled-up into routine practice: These are infliximab, etanercept and adalimumab. Karppinen et al [34] treated 10 patients with a 2 to 12-week history of sciatica and magnetic resonance evidence of IVD with a single intravenous infusion of infliximab (3mg/kg) and achieved a significant reduction of radicular pain score within hours after the effusion (Table 1). The patients did not experience any side effects and were able to return to work at 4 weeks without undergoing any invasive procedure such as epidural steroid injections or surgery. A follow-up study re-assessing the same individuals at 6 and 12 months showed sustained clinical outcomes accompanied by a radiological improvement in repeated magnetic resonance in 9/10 patients while the remaining one required surgery [35]. Successful administration of infliximab has also been reported in case-reports and case series [36]. Another pilot study evaluated the efficacy of three etanercept subcutaneous injections (25mg every 3 days) in 10 patients with acute sciatica of recent onset – mean duration of symptoms 2.7 ± 1.8 weeks [37]. Leg and back pain visual analogue scores improved significantly in all patients on day 10 after treatment with one patient suffering a relapse at 3 weeks and treated surgically. In 9 patients beneficial effects were noted after 6 weeks. Perispinal delivery of etanercept has also been reported in 20 patients with improvement of pain and functional status but the heterogeneity of the

population including patients with history of spinal surgery and other methodological weaknesses limit the validity of the study [38].

Despite the encouraging findings of uncontrolled studies, some randomised controlled trials (RCTs) failed to provide robust evidence for the efficacy of biological agents targeting TNF-alpha in subjects suffering from IVD. A single infliximab infusion (5mg/kg) in 21 patients had no greater effect compared to 19 controls receiving placebo with regards to intensity of pain, function handicap, requirement for surgery or the resorption of disc herniation in magnetic resonance imaging over a 6-month period after the treatment [39]. In line with these observations epidural administration of etanercept (2 injections separated by 2 weeks) did not provide any advantage over epidural saline or steroids in patients with lumbosacral radiculopathy in triple blind RCTs [40]. On the other hand Freeman et al [41] demonstrated beneficial effects of transforaminal epidural etanercept (2 injections 2 weeks apart) in a placebo-controlled trial in 49 patients, observations which concur with previous reports in smaller cohorts [42]. A short course of subcutaneous adalimumab given early on severe acute sciatica decreased the requirement for back surgery in the adalimumab-treated group compared to the control cohort after a 3-year follow-up period [43, 44].

The inconsistent reports of controlled studies were confirmed in recently published systematic reviews and meta-analyses which showed that, compared to placebo or steroids, TNF-alpha inhibition was neither superior in controlling pain and alleviating symptoms nor did it increase the proportion of IVD patients returning to work [45, 46]. However, both reports demonstrated a reduction of the risk for discectomy in patients treated with biologic drugs highlighting that beyond anti-inflammatory, TNF-alpha antagonists may also have neuroprotective properties which promote the recovery rate of neurological abnormalities and the improvement of functional status.

[Insert Table 1 here]

Anti-Nerve Growth Factor (NGF) Therapy

The reassuring findings from preclinical studies were translated into a number of RCTs that aimed to assess the safety and efficacy of a humanised monoclonal antibody (mAb) against NGF (Table 2). Tanezumab, fulranumab and regeneron were the anti-NGFs that have been evaluated in a clinical trial. No study evaluating regeneron was included in this review because none has been published in a peer-reviewed journal.

In the first published phase II clinical trial of anti-NGF, 88 patients with chronic LBP received a single 200µg/kg of Tanezumab IV infusion at baseline and a matching daily oral placebo for the treatment duration of 12 weeks [50]. The second cohort of 88 patients received a single IV placebo at baseline and a 1000mg daily dose of oral naproxen. The last cohort of 41 patients received single IV placebo at baseline and daily oral placebos for the treatment duration. The primary outcome was mean change in LBP intensity score from baseline to 6 weeks. Katz et al [50] showed that the Tanezumab group had the greatest mean reduction in LBP intensity score. The intervention also significantly reduced participants Roland Morris Disability Questionnaire (RMDQ) and Patient's Global Assessment (PGA) score. Adverse event rates across the three cohorts were similar, and no serious adverse event was reported with Tanezumab.

Another published study reiterated the efficacy of anti-NGF. In the study, 1347 patients with a minimum 3-month history of chronic LBP were randomly assigned to treatment groups [51]. Of these, three cohorts of 232, 295 and 295 patients were treated with 5mg, 10mg and 20mg IV Tanezumab injection respectively at baseline and at eight weeks, all with matching daily oral placebo. Another cohort of 230 patients received two doses of IV placebo and daily oral placebo. The last cohort (295 patients) received two doses of IV placebo eight weeks apart with matching daily dose of naproxen (500mg). The lower doses and the long dose interval were due to anti-NGF's high affinity to bind specific targets and its long terminal half-life. The result at 16 weeks revealed that patients on 10mg and 20mg of the study drug had a greater reduction in LBP intensity compared with the placebo group and naproxen group. There was no significant difference between Tanezumab 5mg versus the placebo or naproxen group. Unlike Katz et al., the downside to Kivitiz et al. was that the incidence of adverse events was greater in patients who received Tanezumab. A noteworthy point was that there was no reported case of osteonecrosis or death. The achieved clinical outcomes were maintained in a follow-up open-label study of a subset of these patients.

One study however reported a contradictory finding. A five-arm placebo controlled RCT evaluated the efficacy of fulranumab, another form of anti-NGF, as an adjunctive therapy in patients with moderate-to-severe chronic LBP [52]. There were 88 patients in the placebo arm while 311 patients across four separate treatment groups received different strengths of the study medication. The first and second treatment group each had 77 patients who received 1mg and 3mg of subcutaneous fulranumab respectively every four weeks. Group 3 received a 6mg loading dose at baseline and subsequently received 3mg 4-weekly. 10mg was administered to the last group at similar intervals to the previous three groups. It was observed that fulranumab did not demonstrably reduce pain intensity compared to placebo at week 12.

A systematic review with meta-analysis reported that the overall evidence supporting the use of anti-NGF for reducing LBP intensity score, compared to placebo, was weak at best [53]. The meta-analysis component showed a small-to-moderate effect for pain relief and a small effect for functional improvement.

[Insert Table 2 here]

Discussion

The ability of biologic agents to inhibit/block crucial steps in the generation and propagation of nociceptive acute or chronic LBP means that this class of drugs could have a complementary role in the management of LBP where traditional interventions have failed to provide adequate relief for patients. Altough preclinical results have shown that anti-TNFs and anti-NGFs have the potential to revolutionise pain management, so far, clinical evidence has produced divergent results. In that respect it is also important to note that the two classes of biologic regimens have been tested in different subgroups of individuals suffering from sciatica: anti-TNFs have been predominantly tested in patients with acute or chronic sciatica accompanied by radicular pain whilst studies with mAbs against NGF recruited patients with chronic non-radicular LBP.

In the former group the superiority of anti-TNFs over placebo was confirmed in only one RCT. Other controlled trials did not demonstrate a statistically significant difference in clinical outcomes and systemic reviews and meta-analysis of RCTs, non-RCTs and observational controlled studies comparing TNF-inhibitors with placebo and other interventions did not provide sufficient evidence to recommend that these agents should be routinely used for sciatica [45, 46]. However they indicated a beneficial effect of anti-TNFs on leg pain intensity in short term and global effects on the medium term [45] as well as reduced risk ratio of discectomy or radicular block at medium term follow-up which however was not sustainable at long term follow-up [46]. A network meta-analysis of management strategies comparing the clinical effectiveness of different treatment strategies for sciatica (grouped into 18 treatment categories), including also economic evaluations suggested that biologic agents had the highest probability of being the best option but with very wide confidence intervals [55]. These observations clearly reflect the small number of trials and the lack of data, underscoring the necessity for larger and better-designed studies. To address this need a RCT was recently launched in United Kingdom to evaluate whether injections of adalimumab plus physiotherapy were more clinically and cost-effective than placebo plus physiotherapy for patients with sciatica but the study was prematurely terminated as a result of low recruitment due to operational issues and unwillingness of patients to participate [56].

With regards to nonspecific chronic LBP it appears the Tanezumab may be more effective in pain control (standarized mean difference [SMD] = -0.44, 95% confidence interval [CI] -0.81 to -0.07) and improvement of functional status (SMD = -0.26, 95%CI -0.40 to -0.12), however

when considering anti-NGFs as a drug class there was a decline in the magnitude of effect more significant for pain relief (SMD = -0.29, 95% CI -0.58 to 0.00) than for functional improvement (SMD = -0.21, 95%CI -0.37 to -0.05) of low back pain [53]. Despite a low to moderate effect of Tanezumab in pain relief and functional capacity the findings of this systemic review do not support the use of anti-NGFs for the management of chronic nonradicular LPB.

Collectively the outcomes of RCTs and other observational trials assessing the efficacy of biologic agents in chronic LPB have been rather disappointing demonstrating limited clinical value for patients suffering from this condition. However the overall quality of evidence in all systemic reviews was low because of the high heterogeneity of RCTs indentified in the meta-analyses associated with the small cohort sizes, the dosage and the route of administration of biologics, the duration of treatment or the length of follow-up. In addition, only one RCT [37] compared biologics with intravenous steroids providing limited evidence for the superiority of anti-TNFs but not compared with epidural steroid injections. Other common confounding issues in pain studies such as the input of psychological factors in lower response rates particularly in patients with longer duration of symptoms should be also taken into account in the interpretation of the findings. The evidence for changing practice in LBP associated or not with radicular pain is very low but biologics may have the potential to reduce pain particularly when other conservative treatment interventions have failed. Despite their cost, biologics may be proven a more cost-effective alternative compared to disc surgery and the high economic burden of anti-TNFs may be decreased with the initiation of biosimilars. Clearly further studies are warranted but they will require appropriate design and simple procedures to ensure both adequate recruitment rates and reliable outcomes.

More recent advances have identified that several inflammatory mediators (IL-1, IL-1β, IL-6, chemokines, prostaglandins) are upregulated in disc herniation tissue and/or the cerebrospinal fluid in patients with radicular pain and contribute to the irritation of nerve fibres suggesting that TNF-alpha might be only one piece of the puzzle [35]. Biologics with different mechanisms of action have been tried in patients with lumbar stenosis and chronic pain. For example, epidural application of tocilizumab – an anti-IL-6 receptor monoclonal antibody – onto the spinal nerve was more effective in alleviating pain than the application of dexamethasone [36]. Elucidating mechanisms of herniation of intervertebral disc-related nerve root pain remains a challenge, and future studies should also focus on the role of yet unexplored potential causes of pain persistence in a considerable fraction of patients. In a porcine model, a combination of TNF-alpha and interleukin-1 inhibition has been reported to

be more efficient in reducing the nucleus pulposus-induced effects on nerve conduction velocity than single inhibition [37], but dual cytokine inhibition is a largely untested intervention in humans. Targeting specific TNF-alpha-dependent responses that contribute to non-nociceptive pain such as immune cell recruiting processes, neovascularization and nerve ingrowth may represent a better approach than the complete blockage of cytokine signalling [12]. The utilisation of sensitive imaging modalities alongside functional measurement outcomes is also essential for the identification of structural changes following treatment with anti-cytokine agents.

Conclusion

Current medical and non-pharmaceutical interventions remain ineffective for patients with unresolved or recurrent low back pain, and there is an increasing need for improved treatments that may provide a better symptomatic pain relief. Novel insights into the cause and pathophysiology of lumbar pain and sciatica suggest that disc herniation leads to an injury-induced inflammation, which is the main driver of intraradicular inflammatory changes such as oedema and demyelination translated into clinical phenotype of radiculopathy. Amongst others TNF-α has an important role in the regulation of proinflammatory effects of nucleus pulposus contributing to the local vascular and inflammatory alterations characterising sciatica, but until today there is no robust proof for the analgesic effect of TNF-α inhibition in this condition. The delineation of molecular pathways driving acute and chronic sciatic pain and the deeper understanding of cytokine networks and inflammatory cells involved may identify novel therapeutic targets and enable a more favourable treatment outcome for these patients. In that respect, the launch of larger and better-designed studies may determine specific sub-groups of patients who may benefit from administration of TNF-α blockers or other classes of biologic regimens.

References

1 Dionne CE, Dunn KM, Croft PR. Does back pain prevalence really decrease with increasing age? A systematic review. *Age Ageing* 2006;35:229-34.

2 Hoyle M, Peters J, Crathorne L, Jones-Hughes T, Cooper C, Napier M, Hyde C. Cost-effectiveness of cetuximab, cetuximab plus irinotecan, and panitumumab for third and further lines of treatment for KRAS wild-type patients with metastatic colorectal cancer. *Value Health* 2013;16:288-96.

3 Henschke N, Maher CG, Ostelo RW, de Vet HC, Macaskill P, Irwig L. Red flags to screen for malignancy in patients with low-back pain. *Cochrane Database Syst Rev* 2013;(2):CD008686.

4 Luoma K, Riihimäki H, Luukkonen R, Raininko R, Viikari-Juntura E, Lamminen A. Low back pain in relation to lumbar disc degeneration. *Spine* 2000;25:487-92.

5 Golob AL, Wipf JE. Low back pain. *Med Clin North Am* 2014;98:405-28.

6 Brinjikji W, Luetmer PH, Comstock B, Bresnahan BW, Chen LE, Deyo RA, Halabi S, Turner JA, Avins AL, James K, Wald JT, Kallmes DF, Jarvik JG. Systematic literature review of imaging features of spinal degeneration in asymptomatic populations. *AJNR Am J Neuroradiol* 2015;36:811-6.

7 Russo M, Deckers K, Eldabe S, Kiesel K, Gilligan C, Vieceli J, Crosby P. Muscle Control and Non-specific Chronic Low Back Pain. Neuromodulation 2018;21:1-9.

8 National Guideline Centre (UK). Low Back Pain and Sciatica in Over 16s: Assessment and Management. London: National Institute for Health and Care Excellence, 2016.

9 Negrini S, Zaina F. The chimera of low back pain etiology: a clinical rehabilitation perspective. *Am J Phys Med Rehabil* 2013;92:93-7.

10 Shapiro IM, Risbud MV. The intervertebral disc: Springer 2014.

11 Valat J, Genevay S, Marty M, Rozenberg S, Koes B. Sciatica. *Best Pract Res Clin Rheumatol* 2010;24:241-52.

12 Olmarker K, Rydevik B, Nordborg C. Autologous nucleus pulposus induces neurophysiologic and histologic changes in porcine cauda equina nerve roots. *Spine* 1993;18:1425-32.

13 Byröd G, Rydevik B, Nordborg C, Olmarker K. Early effects of nucleus pulposus application on spinal nerve root morphology and function. *Eur Spine J* 1998;7:445-9.

14 Mulleman D, Mammou S, Griffoul I, Watier H, Goupille P. Pathophysiology of disk-related low back pain and sciatica. II. Evidence supporting treatment with TNF-α antagonists. *Joint Bone Spine* 2006;73:270-7.

15 Risbud MV, Shapiro IM. Role of cytokines in intervertebral disc degeneration: pain and disc content. *Nat Rev Rheumatol* 2014;10:44-56.

16 Igarashi T, Kikuchi S, Shubayev V, Myers RR. Exogenous tumor necrosis factor-alpha mimics nucleus pulposus-induced neuropathology: molecular, histologic, and behavioral comparisons in rats. *Spine* 2000;25:2975-80.

17 Murata Y, Onda A, Rydevik B, Takahashi I, Takahashi K, Olmarker K. Changes in pain behavior and histologic changes caused by application of tumor necrosis factor-alpha to the dorsal root ganglion in rats. *Spine* 2006;31:530-5.

18 Olmarker K, Rydevik B. Selective inhibition of tumor necrosis factor-α prevents nucleus pulposus-induced thrombus formation, intraneural edema, and reduction of nerve conduction velocity: possible implications for future pharmacologic treatment strategies of sciatica. *Spine* 2001;26:863-9.

19 Murata Y, Olmarker K, Takahashi I, Takahashi K, Rydevik B. Effects of selective tumor necrosis factor-alpha inhibition to pain-behavioral changes caused by nucleus pulposus-induced damage to the spinal nerve in rats. *Neurosci Lett* 2005;382:148-52.

20 Le Maitre CL, Hoyland JA, Freemont AJ. Catabolic cytokine expression in degenerate and herniated human intervertebral discs: IL-1β and TNFα expression profile. *Arthritis Res Ther* 2007;9:R77.

21 Cooper R, Freemont A. TNF-α blockade for herniated intervertebral disc-induced sciatica: a way forward at last? *Rheumatology* 2003;43:119-21.

22 Goupille P, Mulleman D, Paintaud G, Watier H, Valat JP. Can sciatica induced by disc herniation be treated with tumor necrosis factor α blockade? *Arthritis Rheum* 2007;56:3887-95.

23 Taniuchi M, Clark HB, Schweitzer JB, Johnson EM Jr. Expression of nerve growth factor receptors by Schwann cells of axotomized peripheral nerves: ultrastructural location, suppression by axonal contact, and binding properties. *J Neurosci* 1988;8:664-81.

24 Turner JE, Delaney RK, Johnson JE. Retinal ganglion cell response to axotomy and nerve growth factor antiserum treatment in the regenerating visual system of the goldfish (Carassius auratus): an in vivo and in vitro analysis. *Brain Res* 1981;204:283-94.

25 Doya H, Ohtori S, Fujitani M, Saito T, Hata K, Ino H, Takahashi K, Moriya H, Yamashita T. PR_191: C-Jun N-Terminal Kinase Activation in Dorsal Root Ganglion Contributes to Pain Hypersensitivity. *Arch Phys Med Rehabil* 2006;87:e37.

26 Ro L, Chen S, Tang L, Jacobs JM. Effect of NGF and anti-NGF on neuropathic pain in rats following chronic constriction injury of the sciatic nerve. *Pain* 1999;79:265-74.

27 Aoki Y, Nakajima A, Ohtori S, Takahashi H, Watanabe F, Sonobe M, Terajima F, Saito M, Takahashi K, Toyone T, Watanabe A, Nakajima T, Takazawa M, Nakagawa K. Increase of nerve growth factor levels in the human herniated intervertebral disc: can annular rupture trigger discogenic back pain. *Arthritis Res Ther* 2014;16:R159.

28 Kawamoto K, Aoki J, Tanaka A, Itakura A, Hosono H, Arai H, Kiso Y, Matsuda H. Nerve growth factor activates mast cells through the collaborative interaction with lysophosphatidylserine expressed on the membrane surface of activated platelets. *J Immunol* 2002;168:6412-9.

29 Petersen M, Heppelmann B, Koltzenburg M. Nerve growth factor regulates the expression of bradykinin binding sites on adult sensory neurons via the neurotrophin receptor p75. *Neuroscience* 1998;83:161-8.

30 Eibl JK, Strasser BC, Ross GM. Structural, biological, and pharmacological strategies for the inhibition of nerve growth factor. *Neurochem Int* 2012;61:1266-75.

31 Bannwarth B, Kostine M. Targeting nerve growth factor (NGF) for pain management: what does the future hold for NGF antagonists? *Drugs* 2014;74:619-26.

32 Suzuki M, Inage K, Sakuma Y, Orita S, Yamauchi K, Suzuki T, Suzuki M, Kubota G, Oikawa Y, Sainoh T, Sato J, Fujimoto K, Shiga Y, Abe K, Kanamoto H, Takahashi K, Ohtori S. Effect of administration of antibodies against nerve growth factor in a rat model of muscle injury. *Injury* 2016;47:609-12.

33 Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD. Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. *Rheumatol Int* 2011;31:1409-17.

34 Karppinen J, Korhonen T, Malmivaara A, Paimela L, Kyllönen E, Lindgren KA, Rantanen P, Tervonen O, Niinimäki J, Seitsalo S, Hurri H. Tumor necrosis factor-alpha monoclonal antibody, infliximab, used to manage severe sciatica. *Spine* 2003;28:750-3.

35 Korhonen T, Karppinen J, Malmivaara A, Autio R, Niinimäki J, Paimela L, Kyllönen E, Lindgren KA, Tervonen O, Seitsalo S, Hurri H. Efficacy of infliximab for disc herniation-induced sciatica: one-year follow-up. *Spine* 2004;29:2115-9.

36 Atcheson SG, Dymeck T. Rapid resolution of chronic sciatica with intravenous infliximab after failed epidural steroid injections. *Spine* 2004;29:E248-50.

37 Genevay S, Stingelin S, Gabay C. Efficacy of etanercept in the treatment of acute, severe sciatica: a pilot study. Ann Rheum Dis 2004;63:1120-3 doi:10.1136/ard.2003.016451 [doi].

38 Tobinick EL, Britschgi-Davoodifar S. Perispinal TNF-alpha inhibition for discogenic pain. *Swiss medical weekly* 2003;133:170-7.

39 Korhonen T, Karppinen J, Paimela L, Malmivaara A, Lindgren KA, Bowman C, Hammond A, Kirkham B, Järvinen S, Niinimäki J, Veeger N, Haapea M, Torkki M, Tervonen O, Seitsalo S, Hurri H. The treatment of disc-herniation-induced sciatica with infliximab: one-year follow-up results of FIRST II, a randomized controlled trial. *Spine* 2006;31:2759-66.

40 Cohen SP, White RL, Kurihara C, Larkin TM, Chang A, Griffith SR, Gilligan C, Larkin R, Morlando B, Pasquina PF, Yaksh TL, Nguyen C. Epidural Steroids, Etanercept, or Saline in Subacute Sciatica: A Multicenter, Randomized Trial. *Ann Intern Med* 2012;156:551-9.

41 Freeman BJ, Ludbrook GL, Hall S, Cousins M, Mitchell B, Jaros M, Wyand M, Gorman JR. Randomized, double-blind, placebo-controlled, trial of transforaminal epidural etanercept for the treatment of symptomatic lumbar disc herniation. *Spine* 2013;38:1986-94.

42 Cohen SP, Bogduk N, Dragovich A, Buckenmaier CC 3rd, Griffith S, Kurihara C, Raymond J, Richter PJ, Williams N, Yaksh TL. Randomized, double-blind, placebo-controlled, dose-response, and preclinical safety study of transforaminal epidural etanercept for the treatment of sciatica. *Anesthesiology* 2009;110:1116-26.

43 Genevay S, Viatte S, Finckh A, Zufferey P, Balagué F, Gabay C. Adalimumab in severe and acute sciatica: A multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2010;62:2339-46.

44 Genevay S, Finckh A, Zufferey P, Viatte S, Balagué F, Gabay C. Adalimumab in acute sciatica reduces the long-term need for surgery: a 3-year follow-up of a randomised double-blind placebo-controlled trial. *Ann Rheum Dis* 2012;71:560-2.

45 Williams NH, Lewis R, Din NU, Matar HE, Fitzsimmons D, Phillips CJ, Sutton A, Burton K, Hendry M, Nafees S, Wilkinson C. A systematic review and meta-analysis of biological treatments targeting tumour necrosis factor α for sciatica. Eur Spine J 2013;22:1921-35.

46 Wang YF, Chen PY, Chang W, Zhu FQ, Xu LL, Wang SL, Chang LY, Luo J, Liu GJ. Clinical significance of tumor necrosis factor-α inhibitors in the treatment of sciatica: A systematic review and meta-analysis. *PLoS One* 2014;9:e103147.

47 Okoro T, Tafazal SI, Longworth S, Sell PJ. Tumor necrosis alpha-blocking agent (etanercept): a triple blind randomized controlled trial of its use in treatment of sciatica. J *Spinal Disord Tech* 2010;23:74-7.

48 Ohtori S, Miyagi M, Eguchi Y, Inoue G, Orita S, Ochiai N, Kishida S, Kuniyoshi K, Nakamura J, Aoki Y, Ishikawa T, Arai G, Kamoda H, Suzuki M, Takaso M, Furuya T, Toyone T, Takahashi K. Epidural administration of spinal nerves with the tumor necrosis factor-alpha inhibitor, etanercept, compared with dexamethasone for treatment of sciatica in patients with lumbar spinal stenosis: a prospective randomized study. *Spine* 2012;37:439-44.

49 Karppinen J, Korhonen T, Hammond A, Bowman C, Malmivaara A, Seitsalo S, Hurr H. The efficacy of infliximab in sciatica induced by disc herniations located at L3/4 or L4/5: a small-scale randomized controlled trial. *Open Spine J* 2009;1:9-13.

50 Katz N, Borenstein DG, Birbara C, Bramson C, Nemeth MA, Smith MD, Brown MT. Efficacy and safety of tanezumab in the treatment of chronic low back pain. *Pain* 2011;152:2248-58.

51 Kivitz AJ, Gimbel JS, Bramson C, Nemeth MA, Keller DS, Brown MT, West CR, Verburg KM. Efficacy and safety of tanezumab versus naproxen in the treatment of chronic low back pain. *Pain* 2013;154:1009-21.

52 Sanga P, Polverejan E, Wang S, Kelly KM, Thipphawong J. Efficacy, Safety, and Tolerability of Fulranumab as an Adjunctive Therapy in Patients With Inadequately Controlled, Moderate-to-Severe Chronic Low Back Pain: A Randomized, Double-blind, Placebo-controlled, Dose-ranging, Dose-loading Phase II Study. *Clin Ther* 2016;38:1435-50.

53 Leite VF, Buehler AM, El Abd O, Benyamin RM, Pimentel DC, Chen J, Hsing WT, Mazloomdoost D, Amadera JE. Anti-nerve growth factor in the treatment of low back pain and radiculopathy: a systematic review and a meta-analysis. *Pain Physician* 2014;17:E45-60.

54 Lewis R, Williams N, Matar HE, Din N, Fitzsimmons D, Phillips C, Jones M, Sutton A, Burton K, Nafees S, Hendry M, Rickard I, Chakraverty R, Wilkinson C. The clinical effectiveness and cost-effectiveness of management strategies for sciatica: systematic review and economic model. *Health Technol Assess* 2011;15:1-578.

55 Williams NH, Jenkins A, Goulden N, Hoare Z, Hughes DA, Wood E, Foster NE, Walsh DA, Carnes D, Sparkes V, Hay EM, Isaacs J, Konstantinou K, Morrissey D, Karppinen J, Genevay S,

Wilkinson C. Subcutaneous Injection of Adalimumab Trial compared with Control (SCIATiC): a randomised controlled trial of adalimumab injection compared with placebo for patients receiving physiotherapy treatment for sciatica. *Health Technol Assess* 2017;21:1-180.