A systematic review and meta-analysis of biological treatments targeting tumour necrosis factor α for sciatica

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ABSTRACT

Purpose. Systematic review comparing biological agents, targeting tumour necrosis factor α, for sciatica with placebo and alternative interventions.

Methods. We searched 21 electronic databases and bibliographies of included studies. We included randomised controlled trials (RCTs), non-RCTs and controlled observational studies of adults who had sciatica treated by biological agents compared with placebo or alternative interventions.

Results. We pooled the results of six studies (five RCTs and one non-RCT) in meta-analyses. Compared with placebo biological agents had: better global effects in the short term odds ratio (OR) 2.0 (95% CI 0.7 to 6.0), medium term OR 2.7 (95% CI 1.0 to 7.1) and long term OR 2.3 [95% CI 0.5 to 9.7); improved leg pain intensity in the short term weighted mean difference (WMD) -13.6 (95% CI -26.8 to -0.4), medium term WMD -7.0 (95% CI -15.4 to 1.5), but not long term WMD 0.2 (95% CI -20.3 to 20.8); improved Oswestry Disability Index (ODI) in the short term WMD -5.2 (95% CI -14.1 to 3.7), medium term WMD -8.2 (95% CI -14.4 to -2.0), and long term WMD -5.0 (95% CI -11.8 to 1.8). There was heterogeneity in the leg pain intensity and ODI results and improvements were no longer statistically significant when studies were restricted to RCTs. There was a reduction in the need for discectomy, which was not statistically significant, and no difference in the number of adverse effects.

Conclusions. There was insufficient evidence to change practice, but sufficient evidence to suggest that larger RCTs are needed.

Key words: sciatica, systematic review, meta-analysis, biological agents, tumour necrosis factor α

INTRODUCTION

Sciatica is a symptom defined as unilateral, well-localised leg pain, with a sharp, shooting or burning quality, that approximates to the dermatomal distribution of the sciatic nerve down the posterior lateral aspect of the leg, and normally radiates to the foot or ankle. It is often associated with numbness or paraesthesia in the same distribution [1]. Sciatica caused by lumbar nerve root pain usually arises from a prolapsed intervertebral disc [2], not only from compression of the nerve root [3], but also the release of pro-inflammatory factors from the damaged disc [4]. Sciatica is common [5], disabling [6-8] and costly to society [9]. Between 5-15% of patients with sciatica are treated with surgery [6,8], usually involving a lumbar discectomy. In the NHS in England in 2010/11 11,765 lumbar discectomies were performed [10].

Pro-inflammatory factors released from the prolapsed intervertebral disc include: phospholipase A2, prostaglandin E2, interleukin-1α (IL-1α), IL-1β, IL-6, nitric oxide and tumour necrosis factor α (TNFα). It has been suggested that TNFα is the cytokine of primary importance in the pathophysiology of sciatica [4]. Biological treatments targeting TNFα (etanercept, infliximab, adalimumab) are increasingly used in rheumatological practice to control inflammatory disease, and may be useful in sciatica [11]. A systematic review was conducted to ascertain the effectiveness of biological agents targeting TNFα for the treatment of sciatica, or lumbar nerve root pain, compared with placebo or alternative interventions. Outcomes included global effects, pain intensity, condition-specific outcome measures, adverse effects, work status and disc surgery

rates. Non-randomised and randomised controlled trials as well as controlled observational studies were included.

METHOD

This review used updated searches from a larger review evaluating the effectiveness and cost-effectiveness of all treatment strategies for sciatica [12], and was prepared in accordance with the PRISMA guidelines [13].

Literature search

The following databases were searched (from inception to February 2012) using strategies designed for each database: MEDLINE, EMBASE, CINAHL, AMED, British Nursing Index, Health Management Information Consortium, PsychINFO, Inspec, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, Health Technology Assessment database, NHS Economic Evaluation database, System for Information on Grey Literature, Science Citation Index, Social Science Citation Index, Index to Scientific and Technical proceedings, PEDro, BIOSIS, National Research Register, and other trial registries (n=7) available via the internet. An example of the search strategy for MEDLINE is presented in an appendix. No language restriction was used. The bibliographies of previous systematic reviews and included studies were screened to identify further relevant studies.

Included studies

The following study designs were included: randomised controlled trials (RCTs), non-RCTs and cohort studies with concurrent or historical controls. Studies with adults who had sciatica or lumbar nerve root pain diagnosed clinically or confirmed by imaging were eligible. Any biological agent targeting pro-inflammatory factors such as tumour necrosis factor-α compared with placebo or alternative interventions using any relevant patient based outcome measure were included.

Data extraction

Two reviewers independently screened the titles and abstracts for relevance. Full papers of potentially relevant studies were retrieved and assessed for inclusion, using the criteria reported above, by two independent reviewers. Data were extracted using predefined forms on a Microsoft Access database by one reviewer and checked for accuracy, against the original paper, by a second independent reviewer. Any disagreements were resolved by discussion or by a third reviewer if necessary.

Quality assessment

Quality assessment was undertaken by two independent reviewers with differences being resolved by consensus or by a third reviewer if necessary. We adapted a quality checklist [14,15] to be suitable for both RCTs and controlled observational studies of sciatica containing the criteria: external validity, selection bias and confounding, detection bias, performance bias, and attrition bias (Table 3).

Data analysis/synthesis

Pairwise meta-analyses were conducted for dichotomous and continuous outcomes. Continuous data were synthesised using final mean scores as weighted mean differences. Where mean values were unavailable but the medians were reported, these were used instead. Missing standard deviations (SDs) were derived using methods reported in the Cochrane Handbook [16], substituted with baseline values, or imputed using the weighted mean for each intervention category [17]. Studies were pooled using the random effects model [18] in Revman version 5; with between study heterogeneity examined using I^2 and Chi^2 statistics. Sensitivity analyses assessed the effect of substituting mean values with medians, using imputed SDs and excluding non-randomised studies.

RESULTS

The electronic searches identified 38443 references and a further 33 references were identified by hand searching, 954 papers were retrieved in full, 435 studies of sciatica were identified, nine of which evaluated biological agents (Figure 1).

Description of biological agents studies

We identified seven RCTs [19-26] one non-RCT [27,28] and one historical cohort study [29]. Two studies were reported in two separate publications each [23,24,27,28]. One non-RCT [27,28] and two RCTs [22-24] compared intravenous infusions of infliximab with placebo injections of saline. One RCT compared subcutaneous injection of etanercept with a placebo injection of saline [25], and another RCT compared three

different doses of an epidural injection of etanercept with each other and with an epidural saline injection [20]. One three-armed RCT compared epidural injections of etanercept with epidural injections of corticosteroid and with epidural injection of saline [26]. One RCT compared subcutaneous injections of adalimumab with placebo injections [21] (Table 1). One RCT compared epidural injections of autologous conditioned serum, rich in anti-inflammatory cytokines, compared with epidural injections of corticosteroid and local anaesthetic [19]. One historical cohort study compared sub-cutaneous injections of etanercept with intra-venous injections of corticosteroid [29] (Table 2).

The nine studies included 412 participants with mean ages between 39 and 54 years, with 40-80% men, five with acute [21-24,27-29], one with chronic [25] and three with acute and chronic symptom duration [19,20,26] (Tables 1 and 2). Three RCTs included patients with recurrent symptoms [21,23,24,29], but symptom recurrence was not reported in six studies [19,20,22,25,26,29]. Sciatica was confirmed by imaging in all studies and previous back surgery was excluded in five trials [22-28].

Most of the studies were RCTs (7/9 78%) and one was good quality [21]. Five reported an adequate method of random number generation [19,21-24], but only three documented a secure method of allocation concealment [21,25,26]. Three studies had moderately good external validity [21,26,29] (Table 3). Two RCTs reported medians rather than means [22-24]. Three RCTs did not report SDs [22-25], but were provided by

the authors in one RCT [25]. Imputed SDs were used in the meta-analyses for the remaining missing values [22-24].

Biological agent versus placebo

Global effect

Five studies reported a measure of global improvement (Table1). One poor quality non-RCT [27,28], two moderate quality [20,26] and one good quality RCT [21] were combined in meta-analyses at short term (4 to 6 weeks) and medium term (6 months) follow-up. One poor quality non-RCT [27,28] and one moderate quality RCT [23,24] were combined in a meta-analysis at long-term (12 months) follow-up. Combined odds ratios (ORs) were in favour of biological agents at all three time periods, but were only statistically significant at medium term follow-up. Indeed there was moderate heterogeneity at short (I^2=62%), medium (I^2=47%) and long term (I^2=47%) follow-up. ORs were 1.99 (95% CI 0.66 to 5.96) in the short term, 2.72 (95% CI 1.04 to 7.13) in the medium term and 2.26 (95% CI 0.53 to 9.73) in the long term (Figure 2). A sensitivity analysis excluding the non-RCT [27,28] only resulted in minimal changes to the summary OR and measurements of heterogeneity.

Leg pain intensity

Seven studies reported leg pain intensity measured with a visual analogue scale. One poor quality non-RCT [27,28], five moderate quality [20,22-25] and one good quality RCT [21] were combined in a meta-analysis at short term (4 to 6 weeks) follow-up and found a moderate weighted mean difference (WMD) of -13.63 units on a 0-100 visual

analogue scale (95% CI -26.84 to -0.41) in favour of biological agents. Five of these studies were combined in a meta-analysis at medium term (3 to 6 months) follow-up [21-25,27,28] and found a small WMD of -6.96 (95% CI -15.42 to 1.51) in favour of biological agents. One poor quality non-RCT [27,28] and one moderate quality RCT [23,24] were combined in a meta-analysis at long-term (12 months) follow-up and found no difference with a WMD of 0.18 (95% CI -20.39 to 20.75) (Figure 3). There was substantial heterogeneity at short (I^2=69%) and long term (I^2=86%), but not medium term, follow-up. A sensitivity analysis excluding the non-RCT [19,27] reduced the size of the WMDs and heterogeneity, so that the WMD at short term follow-up was no longer statistically significant. Excluding the two RCTs reporting medians [22-24] or the two RCTs with imputed SDs [22-24] had minimal effect at short and medium term follow-up. A funnel plot for publication bias did not appear to show asymmetry, but indicated a lack of large studies.

Oswestry Disability Index

Seven studies reported the Oswestry Disability Index. One poor quality non-RCT [27,28], four moderate quality [20,22-25] and one good quality RCT [21] were combined in a meta-analysis at short term (4 to 6 weeks) follow-up and found a WMD of -5.21 units (95% CI -14.09 to 3.68) on the ODI (range 0-100) in favour of biological agents. Five of these studies were combined in a meta-analysis at medium term (3 to 6 months) follow-up [21-25,27,28] and found a WMD of -8.16 (95% CI -14.36 to -1.96) in favour of biological agents. One poor quality non-RCT [27,28] and one moderate quality RCT [23,24] were combined in a meta-analysis at long-term (12 months) follow-up and found

a WMD of -4.99 (95% CI -11.78 to 1.80) in favour of biological agents (Figure 4). There was moderate heterogeneity at short (I^2=77%), medium (I^2=45%) and long term (I^2=61%) follow-up. A sensitivity analysis excluding the non-RCT [27,28] reduced the size of the WMDs so that the WMD at medium term follow-up was no longer statistically significant. Excluding the two RCTs reporting medians, for which we also imputed SDs [22-24], had minimal effect at short and medium term follow-up but increased the WMD at long term follow-up because only one non-RCT remained with a larger effect size [27,28]. The funnel plot for publication bias did not appear to show asymmetry, but indicated a lack of large studies.

Biological agent versus corticosteroid injection

Only three studies compared biological agents with an alternative treatment. One moderate quality RCT [19] compared epidural injection of autologous conditioned serum with epidural corticosteroid injection and found no statistically significant difference in mean overall pain intensity or mean ODI at short or medium term follow-up. One moderate quality RCT [26] compared epidural injection of etanercept with epidural corticosteroid injection and found no statistically significant difference in mean pain intensity, but a statistically significant improvement in ODI and global effects in favour of corticosteroid, in the short term (Figures 5 and 6). One poor quality historical cohort study [29] compared sub-cutaneous injections of etanercept with intra-venous injections of corticosteroid and found a statistically significant difference in global effects, mean leg pain intensity and ODI at short term follow-up (Figures 5-7).

Need for disc surgery

One poor quality non-RCT [27,28], three moderate quality [22-25] and one good quality RCT [21] were combined in a meta-analysis of the need for disc surgery. The combined odds ratio for needing disc surgery in those receiving biological agents compared with placebo was 0.54 (95% CI 0.26 to 1.14) with homogeneity amongst the effect sizes (I^2 =0%) (Figure 8). In addition, a poor quality cohort study [29] reported that one patient (10%) in the etanercept group and one (10%) in the intravenous corticosteroid group required disc surgery.

Employment outcomes

In one moderate quality RCT [23,24] there was a median of 42 days sick leave in the infliximab group compared with 25 days in the placebo group. In one good quality RCT [21] 16 patients (64%) in the adalimumab group returned to work by six months compared with 13 (42%) in the placebo group.

Adverse effects

There was no significant difference in the number of adverse events between infliximab, etanercept or adalimumab and placebo in one non-RCT and five RCTs when these were combined in a meta-analysis [21-28], and between epidural injections of etanercept or autologous conditioned serum compared with corticosteroid and local anaesthetic epidural injections in two RCTs [19,26] (Figure 9). Only one serious adverse effect of severe gastrointestinal haemorrhage was reported in a patient receiving adalimumab,

which was blamed upon concomitant administration of non-steroidal anti-inflammatory medication [21].

DISCUSSION

Summary of main findings

There was insufficient evidence for the efficacy of biological agents targeting TNFα compared with placebo. Meta-analyses found moderate and statistically significant improvements in global effects in the medium term, leg pain intensity in the short term and ODI in the medium term when all study types were included. However, there was moderate to substantial heterogeneity in the leg pain intensity and ODI results, and the meta-analysis results were no longer statistically significant when restricted to RCTs. There was a reduction in the need for disc surgery, which was not statistically significant and limited evidence for improved employment outcomes. There was no difference in the number of adverse effects. Only two studies comparing biological agents with an alternative treatment were identified. One was a RCT which, rather than testing a medicinal product, tested serum rich in anti-inflammatory cytokines; the other was a poor quality cohort study. They provided very limited evidence that a biological agent was superior to intra-venous corticosteroids, but not compared with epidural corticosteroid.

Strengths and limitations of the study

One of the strengths of this review was the extensive literature search that was undertaken to identify published, unpublished and grey literature. Observational studies

and non-randomised trials were included for completeness as some comparisons may not have been evaluated by RCTs. Observational studies can have better external validity than RCTs [30,31] and provide more generalisable findings, however the RCT is widely regarded as the design of choice when assessing the effectiveness of health care interventions [32] and we acknowledge the controversy over the inclusion of non-randomised evidence. In this review, priority was given to RCTs, and the quality of the studies noted. We also conducted a sensitivity analysis excluding non-randomised evidence.

Poor reporting and variation in the way the data were analysed meant that imputation or substitution of missing data was necessary in order for the meta-analyses to be as inclusive as possible. Omitting studies with missing SDs may induce bias in the summary effect estimate [33], and Furukawa, et al. [17] have shown that it is safe to borrow SDs from other studies. The use of imputed SDs was tested in a sensitivity analysis.

We identified heterogeneity in many of the meta-analyses performed. It was our intention to explore this heterogeneity with meta-regression, where ten or more studies were included in the meta-analysis, assessing the effect of study level co-variates such as: adequacy of randomisation procedure, allocation concealment, attrition rate and blinded outcome assessment. Unfortunately there were insufficient studies to do this.

Comparison with existing literature

This is the first systematic review of biological agents targeting TNFα for sciatica. It used updated searches from a larger systematic review examining all management strategies for sciatica, which included indirect comparisons of different management strategies synthesised in a mixed treatment comparison. This mixed treatment comparison (MTC) analysis found a significant improvement in leg pain intensity and condition-specific outcomes compared with inactive control when all studies were included; but when observational studies were excluded these findings were no longer statistically significant [12].

This systematic review focused on biological agents targeting TNFα. Other cytokines have also been implicated in the pathogenesis of sciatica (IL-1α, IL-1β, IL-6 etc.), but we did not identify any other comparator studies of biological agents targeting these alternative cytokines in sciatica. Other non-biological pharmacological agents may also influence cytokines. There has been one small RCT of one such agent; epidural clonidine compared with epidural corticosteroid [34]. The neurophysiology of nerve root pain has been complicated further by the discovery of the anti-inflammatory cytokine IL-10 [35], but agents manipulating this cytokine have yet to be tested in humans.

Implications for future research and clinical practice

There was insufficient evidence to recommend a change in clinical practice. There was heterogeneity in many of the meta-analyses and the improvements in outcome were statistically significant only when non-randomised studies were included. However,

these results provide sufficient evidence to suggest that further large RCTs are needed to establish the efficacy of biological agents targeting TNFα compared with placebo. There was a scarcity of RCTs comparing the effectiveness of biological agents with other treatments for sciatica; more are needed. Biological agents are expensive but may lead to cost savings if a reduction in disc surgery is confirmed; economic evaluations alongside RCTs are needed to assess this.

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REFERENCES

1. Deyo RA, Rainville J, Kent DL (1992) What can the history and physical examination tell us about low back pain? J Amer Med Assoc 268:760-765.

2. Weber H, Holme I, Amlie E (1993) The natural course of acute sciatica with nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroxicam. Spine 18:1433-1438.

3. Mixer WJ, Barr JS (1934) Rupture of the intervertebral disc with involvement of the spinal canal. N Engl J Med 211:210-215.

4. Goupille P, Jayson MI, Valat JP, Freemont AJ (1998) The role of inflammation in disc herniation-associated radiculopathy. Semin Arthritis Rheum 28:60-71.

5. Konstantinou K, Dunn KM (2008) Sciatica: Review of epidemiological studies and prevalence estimates. Spine 33:2464-2472.

6. Bush K, Cowan N, Katz DE, Gishen P (1992) The natural history of sciatica associated with disc pathology; a prospective study with clinical and independent radiological follow-up. Spine 18:1433-1438.

7. Tubach F, Beaute J, Leclerc A (2004) Natural history and prognostic indicators of sciatica. J Clin Epidemiol 57:174-179.

8. Weber H, Holme I, Amlie E (1993) The natural course of acute sciatica with nerve root symptoms in a double-blind placebo-controlled trial evaluating the effect of piroxicam. Spine 18:1433-1438.

9. van Tulder MW, Koes BW, Bouter LM (1995) A cost of illness study of back pain in the Netherlands. Pain 62:233-240.

10. The NHS Information Centre, Hospital Episode Statistics for England, Inpatient statistics, Total procedures and interventions 2010-11. http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=210. Accessed 23 August, 2012.

11. Cooper RG, Freemont AJ (2004) TNF-α blockade for herniated intervertebral disc-induced sciatica: a way forward at last? Rheum 43:119-121.

12. Lewis R, Williams NH, Matar HE, Din N, Fitzsimmons D, Phillips C, Jones M, Sutton A, Burton K, Nafees S, Hendry M, Rickard I, Chakraverty R, Wilkinson C (2011) The clinical effectiveness and cost effectiveness of management strategies for sciatica: systematic review and economic model. Health Technol Assess 15(39).

13. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. BMJ 339;b2535.

14. van Tulder MW, Furlan A, Bombardier C, Bouter L (2003) Editorial Board of the Cochrane Collaboration Back Review Group. Updated method guidelines for systematic reviews in the Cochrane collaboration back review group. Spine 28:1290-1299.

15. Effective Public Health Practice Project (2010) Quality assessment tool for quantitative studies. http://www.ephpp.ca/PDF/Quality%20Assessment%20Tool_2010_2.pdf. Accessed 23 August, 2012.

16. Higgins JPT, Deeks JJ (2008) Selecting studies and collecting data. In: Higgins JPT, Green S, (Eds) Cochrane handbook for systematic reviews of interventions. Wiley, Chichester (UK), pp 151-185

17. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N (2006) Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol 59:7-10.

18. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Controlled clinical trials 7:177-188.

19. Becker C, Heidersdorf S, Drewlo S, de Rodriguez SZ, Kramer J, Willburger RE (2007) Efficacy of epidural injections with autologous conditioned serum for lumbar radicular compression. Spine 32:1803-1808.

20. Cohen SP, Bogduk N, Dragovich A, Buckemaier III CC, Griffith S, Kurihara C, Raymond JL, Richter PJ, Williams N, Yaksh TL (2009) Randomized, double-blind, placebo-controlled, dose-response and preclinical safety study of transforaminal epidural etanercept for the treatment of sciatica. Anesthesiology 110:1116-1126.

21. Genevay S, Viatte S, Finckh A, Zufferey P, Balague F, Gabay C (2010) Adalimumab in severe and acute sciatica; a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 62:2339-2346.

22. Karppinen J, Korhonen T, Hammond A, Bowman C, Malmivaara A, Veeger N, Seitsalo S, Hurri H (2009) 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 1:9-13.

23. Korhonen T, Karppinen J, Paimela L, Malmivaara A, Lindgren K-A, Jarvinen S, Niirimaki J, Veeger N, Seitsalo S, Hurri H (2005) The treatment of disc herniation induced sciatica with infliximab; results of a randomized, controlled 3 month follow-up study. Spine 30:2724-2728.

24. Korhonen T, Karppinen J, Paimela L, , Malmivaara A, Lindgren K-A, Bowman C, Hammond A, Kirkham B, Jarvinen S, Niirimaki J, Veeger N, Haapea M, Torkki M, Tervonen O, Seitsalo S, Hurri H (2006) The treatment of disc herniation induced sciatica with infliximab; one year follow-up results of FIRST II, a randomised controlled trial. Spine 31:2759-2766.

25. Okoro T, Tafazal SI, Longworth S, Sell PJ (2010) Tumour necrosis factor α-blocking agent (etanercept); a triple blind randomized controlled trial of its use in treatment of sciatica. J Spinal Disord Tech 23:74-77.

26. Cohen SP, White RL, Kurihara C, Larkin TM, Chang A, Griffith SR, Gilligan C, Larkin R, Morlando B, Pasquina PF, Yaksh TL, Nguyen C (2012) Epidural steroids, etanercept, or saline in subacute sciatica: a multicenter randomized trial. Ann Intern Med 156:551-559.

27. Karppinen J, Korhonen T, Malmivaara A, Paimela L, Kyllonen E, Lindgren K-A, Rantanen P, Tervonen O, Niinimaki J, Seitsalo S, Hurri H (2003) Tumour necrosis factor-α monoclonal antibody, infliximab, used to manage severe sciatica. Spine 28:750-754.

28. Korhonen T, Karppinen J, Malmivaara A, Autio R, Niinimaki J, Paimela L, Kyllonen E, Lindgren K-A, Tervonen O, Seitsalo S, Hurri H (2004) Efficacy of infliximab for disc herniation induced sciatica; one year follow-up. *Spine* 29:2115-2119.

29. Genevay S, Stingelin S, Gabay C (2004) Efficacy of etanercept in the treatment of acute, severe sciatica: a pilot study. Ann Rheum Dis 63:1120-1123.
30. Turner RM, Spiegelhalter DJ, Smith GCS, Thompson SG (2009) Bias modelling in evidence synthesis. J R Stat Soc Ser A Stat Soc 172:21-47.
31. Eddy DM, Hasselblad V, Shachter R (1990) An introduction to Bayesian methods for Meta-analysis: The Confidence Profile Method. Medical Decision Making 10:15-23.
32. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG (2003) Evaluating non-randomised intervention studies. Health Technol Assess 7(27).
33. Wiebe N, Vandermeer B, Platt RW, Klassen TP, Moher D, Barrowman NJ (2006) A systematic review identifies a lack of standardization in methods for handling missing variance data. J Clin Epidemiol 59:342-353.
34. Burgher AM, Hoelzer BC, Schroeder DR, Wilson GA, Huntoon MA (2011) Transforaminal epidural clonidine versus corticosteroid for acute lumbosacral radiculopathy due to intervertebral disc herniation. Spine 36:E293-E300.
35. Milligan ED, Sloane EM, Langer SJ, Hughes TS, Jekich BM, Frank MG, Mahoney JH, Levkoff LH, Maier SF, Cruz PE, Flotte TR, Johnson KW, Mahoney MM, Chavez RA, Leinwand LA, Watkins LR. Repeated intrathecal injections of plasmid DNA encoding interleukin-10 produce prolonged reversal of neuropathic pain. Pain 2006;126(1-3):294-308.

APPENDIX MEDLINE (OVID) Search strategy

MEDLINE (OVID) 1950 to June week 1 2008 searched on 16-06-2008
Search updated on 04-12-2009 and on 01-02-2011

1. Sciatica/
2. (ischialg$ or sciatic$).ti,ab.
3. ((lumb$ or sacra$ or spin$) adj5 radicul$).ti,ab.
4. ((sciatic nerve or lumbar nerve or spinal nerve or sacral nerve) adj5 (irritation or inflammat$ or pain or neuropath$ or dysfunction$ or compressio$ or injur$ or traum$)).ti,ab
5. Intervertebral Disk Displacement/
6. ((intervertebral disk or intervertebral disc or lumbar disc or lumbar disk or lumbosacral disc or lumbosacral disk or lumbo-sacral disc or lumbo-sacral disk) adj5 (hernia$ or slip$ or prolapse or degeneration or fusion or sclerosis or rupture or distortion or fracture or displacement)).ti,ab.
7. ((lumbosacral nerve root or lumbo-sacral nerve root or lumbar nerve root) adj5 (irritat$ or inflammat$ or pain$ or neuropath$ or dysfunction$ or compressio$ or injur$ or traum$)).ti,ab.
8. ((refer$ or radiat$) adj5 (back or leg or foot)).ti,ab.
9. or/1-8
10. (treatment$ or therap$ or manag$ or surg$ or modalit$ or intervention$).ti,ab.
11. Bed rest/
12. (bed rest$ or activ$ or exercise$ or education$ or instruction$ or advice$).ti,ab.
13. Physical Therapy Modalities/
14. ((heat or hot or thermal or infra?red or ultrasound or ultrasonic or short-wave or physio$ or physical or exercise) adj5 (therap$ or treatm$)).ti,ab.
15. Transcutaneous Electric Nerve Stimulation/
16. (transcutaneous electric nerve stimulation or TENS).ti,ab.
17. Complementary Therapies/

18. Exp Musculoskeletal Manipulations/
19. Exp Acupuncture Therapy/
20. ((spina$ or chiropract$ or osteopath$ or physi$ or homeopath$ or acupunctur$ or musculo?skeletal or myofunctional) adj5 (massage or manipulat$ or therap$ or treatment$)).ti,ab.
21. Homeopathy/
22. homeopathy.ti,ab.
23. Herbal Medicine/
24. herbal medicine.ti,ab.
25. Orthotic Devices/
26. (braces or slings or splints or corset).ti,ab.
27. Traction/
28. traction.ti,ab.
29. Drug Therapy/
30. Exp Analgesics/
31. Anti-Inflammatory Agents, Non-Steroidal/
32. ((non-steroidal anti inflammatory or non-steroidal anti-inflammatory or non?narcotic or narcotic or opioid$ or opiate$) adj5 (drug$ or analges$)).ti,ab.
33. (paracetamol or acetaminophen).ti,ab.
34. (ibuprofen or aceclofenac or acemetacin or celecoxib or dexketoprofen or diclofenac sodium or etodolac or etoricoxib or fenbufen or fenoprofen or flurbiprofen or indometacin or indomethacin or ketoprofen or mefenamic acid or meloxicam or nabumetone or naproxen or piroxicam or sulindac or tenoxicam or tiaprofenic acid or azapropazone or biarison or acetaminophen or nimesulide or oxyphenbutazone or azapropazone or felbinac or alclofenac or nimesulid or etofenama or loxoprofen or phenylbutazone or valdecoxib or lornoxicam or etoricoxib).ti,ab.
35. (buprenorphine or butorphanol or codeine or dextromoramide or dextropropoxyphene or dihydromorphine or diphenoxylate or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or levorphanol or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or

oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or sufentanil or tilidine or tramadol).ti,ab.

36. Epidural Analgesia/
37. Epidural Injections/
38. ((intramuscular or intravenous or peri?neural$ or epidura$ or inject$) adj5 (cortico?steroid$ or steroid$ or ana?lgesic$ or chymopapain)).ti,ab.
39. (dexamethasone or hydrocortisone or prednisolone or methylprednisolone or prednisone or methylprednisone or triamcinolone).ti,ab.
40. Orthopedic Procedures/
41. Intervertebral Disk Chemolysis/
42. ((disc or disk) adj5 (chemolysis or chemonucleolysis)).ti,ab.
43. Vertebroplasty/
44. Diskectomy/
45. Neurosurgical Procedures/
46. Laminectomy/
47. Rhizotomy/
48. (discectomy or diskectomy or microdiscectomy or microdiskectomy or rhizotomy or sequestrectomy or vertebroplasty or nucleoplasty or laminectomy).ti,ab.
49. Surgical Decompression/
50. surgical decompression.ti,ab.
51. or/11-50
52. 9 and 51
53. limit 52 to human

Table 1 Characteristics of studies comparing biological agents with placebo

Study	Participants	Intervention	Control treatment	Length of follow-up	Outcomes
Korhonen, 2004 [27,28] Finland, Non-RCT	72 patients with nerve root pain confirmed by imaging. Data for TNF group only (no data for control group); mean duration 7.2 weeks; Mean age 39 years; 80% men	Intra-venous infusion of infliximab 3mg/Kg	Periradicular saline injection	12 months	Number of painless patients (>75% decrease from baseline leg pain score}; back and leg pain intensity (VAS); Oswestry Disability Index; number of sick leave days; clinical status, adverse effects
Korhonen, 2006 [23,24] Finland, RCT	41 patients with first or recurrent episode of nerve root pain confirmed by imaging; median duration 61 days; Mean age 41 years; 60% men	Intravenous infliximab 5mg/Kg	Intravenous saline injection	12 months	Number of painless patients (>75% decrease from baseline leg pain score}; back and leg pain intensity (VAS)[a,b]; Oswestry Disability Index[a,b]; RAND-36 health questionnaire; number sick leave days; number discectomies; clinical status, adverse effects
Karppinen, 2009 [22] Finland, RCT	15 patients with nerve root pain confirmed by imaging; disc hernaition at L3/4 or L4/5; mean duration 58 days; mean age 53 years; 67% men	Intravenous infliximab 5mg/Kg	Intravenous saline injection	6 months	Back and leg pain intensity (VAS)[a,b]; Oswestry Disability Index[a,b]; RAND-36 health questionnaire; number sick leave days; number discectomies; clinical status, adverse effects
Cohen, 2009 [20] USA, RCT	24 patients with nerve root pain confirmed by imaging; median duration 3-7 months; median age 41-46 years; 71% men	Transforaminal epidural injection etanercept: 2mg (Group 1) 4mg (Group 2) 6mg (Group 3)	Transforaminal epidural injection normal saline	6 months	Number with a positive outcome (>50% reduction in leg pain + global perceived effect [combination of pain, daily activities improved & satisfaction]); back and leg pain intensity (numerical rating scale)[c]; Oswestry Disability Index[c]; drug consumption;

					[Results from groups 1-3 combined for the meta-analysis]
Okoro, 2010 [25] UK, RCT	15 patients with nerve root pain confirmed by imaging for at least 24 weeks; Mean age not stated; 40% men	Subcutaneous injection of etanercept 25mg	Subcutaneous injection of saline	3 months	Leg pain intensity (VAS)[d]; Oswestry Disability Index[d]; modified somatic perception; modified Zung depression index; subjective walking distance; adverse effects
Genevay, 2010 [21] Switzerland, RCT	61 patients with first or recurrent episode of nerve root pain confirmed by imaging; mean duration 3.6 weeks; Mean age 49 years; 57% men	Subcutaneous injection of adalimumab 40mg x2	Subcutaneous injection of saline x2	6 months	Number of responders (>30% improvement from baseline leg or back pain score or Oswestry Disability Index}; back and leg pain intensity (VAS); Oswestry Disability Index, SF-12v2; drug consumption; number of discectomies; work status; adverse effects
Cohen, 2012 [26] USA, Germany, RCT	84 patients with nerve root pain confirmed by imaging; mean duration 2.7 months; mean age 42 years; 70% men	Transforaminal epidural injection etanercept 4mg+ local anaesthetic 0.5ml x2	Transforaminal epidural injection normal saline+ local anaesthetic 0.5ml x2	6 months (large proportion left study after 1 month)[e]	Positive categorical outcome (>50% decrease in leg pain + positive global perceived effect obviating the need for further treatment); back and leg pain intensity (NRS); Oswestry Disability Index; reduction in analgesic consumption

NRS Numeric Rating Scale; RCT Randomised Controlled Trial; SD Standard Deviation; SF-12 Short Form 12; TNF Tumour Necrosis Factor; VAS Visual Analogue Scale; [a]SD not reported, imputed from other studies in meta-analyses; [b]medians reported; [c]result from only a single patient in control group at 6 month follow-up; [d]mean leg pain intensity & SDs obtained from authors; [e]after 1 month participants who received no benefit exited the study to pursue other treatments

Table 2 Characteristics of studies comparing biological agents with alternative interventions

Study	Participants	Intervention	Control treatment	Length of follow-up	Outcomes
Biological agents vs Epidural steroid injection					
Becker et al , 2007 [19] Germany, RCT	84 patients with nerve root pain confirmed by imaging for at least 6 weeks; Mean age 54 years; 62% men	Epidural injection of Autologous Conditioned Serum (Group 1)	Epidural injection of steroid triamcinolone 5 mg or 10mg + local anaesthetic 1ml (Groups 2 & 3)	22 weeks	Overall pain intensity (VAS)[a]; Oswestry Disability Index, adverse effects [Results from groups 2 & 3 combined for the forest plot]
Cohen, 2012 [26] USA, Germany, RCT	84 patients with nerve root pain confirmed by imaging; mean duration 2.7 months; mean age 42 years; 70% men	Transforaminal epidural injection etanercept 4mg	Transforaminal epidural injection of steroid methyl prednisolone 60mg + local anaesthetic 0.5ml	6 months	Global perceived effect; back and leg pain intensity (NRS); Oswestry Disability Index; reduction in analgesic consumption
Biological agents vs Intravenous steroid					
Genevay, 2004 [29] Switzerland, HCS	20 patients with nerve root pain confirmed by imaging; mean duration 3.2 weeks; Mean age 47 years; 50% men	Subcutaneous injection of etanercept 25mg (anti-TNF alpha) x3	Intravenous injection of methylprednisolone 250mg x3	6 weeks	Numbers with a good clinical result (leg pain VAS <30 or Oswestry Disability Index <20); back and leg pain intensity (VAS); Oswestry Disability Index; Roland-Morris Questionnaire; number of discectomies

HCS Historical Cohort Study; RCT Randomised Controlled Trial; TNF Tumour Necrosis Factor; VAS Visual Analogue Scale; [a]results extracted from graphs

Table 3 Quality of included studies

Quality Checklist	Genevay et al, 2004 [29]	Korhonen et al, 2004 [27,28]	Korhonen et al, 2006 [23,24]	Becker et al, 2007 [19]	Karppinen et al, 2009 [22]	Cohen et al, 2009 [20]	Okoro et al, 2010 [25]	Genevay et al, 2010 [21]	Cohen et al, 2012 [26]
External Validity									
Are participants representative?	+/-	Unclear	Unclear	+/-	Unclear	Unclear	Unclear	+/-	+/-
Percentage who agreed to participate?	80-100%	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	<60%	80-100%
Staff & facilities representative?	+/-	+/-	+/-	+/-	+	+/-	+/-	+	+/-
Rating	Moderate	Weak	Weak	Weak	Weak	Weak	Weak	Moderate	Moderate
Selection Bias - Confounders									
Study design?	HCS	Non-RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Adequate method randomisation?	-	-	+	+	+	Unclear	Unclear	+	+
Adequate allocation concealment?	-	-	+/-	+/-	Unclear	+/-	+	+	+
Percentage relevant prognostic factors?	60-79%	<60%	60-79%	<60%	<60%	60-79%	<60%	80-100%	60-79%
Similar baseline prognostic factors?	+/-	Unclear	+	Unclear	Unclear	+/-	Unclear	+/-	+
Recruited from same population?	-	-	+	+	+	+	+	+	+
Recruited over same time period?	-	-	+	+	+	+	+	+	+
Analysis of co-variance or similar?	-	+	+	+	+	-	-	+	+
Co-interventions avoided or similar?	Unclear	Unclear	Unclear	+	Unclear	+	Unclear	+	+
Rating	Weak	Weak	Moderate	Moderate	Moderate	Moderate	Moderate	Strong	Strong
Detection Bias									
Valid outcome measurement?	+	+	+	+	+	+	+	+	+
Reliable outcome measurement?	+	+	+	+	+	+	+	+	+
Similar timing outcome assessment?	+	-	+	+	+	+	+	+	+
Outcome assessors blinded?	-	-	Unclear	+	Unclear	+	+	+	+
Data analyst blinded?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Rating	Weak	Weak	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Performance Bias									
Participants blinded?	-	-	+	+	Unclear	+	+	+	+
Clinicians blinded?	-	-	Unclear	-	Unclear	+	+	+	+
Blinding procedure tested?	NA	NA	Unclear	-	NA	Unclear	Unclear	Unclear	Unclear
Rating	Weak	Weak	Moderate	Moderate	Weak	Moderate	Moderate	Moderate	Moderate
Attrition Bias									
Similar characteristics drop-outs?	+	Unclear	+	+	Unclear	+	+	Unclear	Unclear
No differential drop-out?	-	Unclear	+	+	-	+	+	-	+
Percentage who completed the study?	80-100%	Unclear	80-100%	80-100%	80-100%	80-100%	80-100%	80-100%	<60%
Analysis according to treatment allocation?	+	+	+	+	+	+	+	+	+
Analysis included all allocated patients?	+	Unclear	+	+	+	+	+	+	-
Rating	Strong	Weak	Strong	Strong	Moderate	Strong	Strong	Moderate	Weak
Overall Rating	Weak	Weak	Moderate	Moderate	Moderate	Moderate	Moderate	Strong	Moderate

Key: + yes; - no; +/- partial; HCS historical cohort study; RCT randomised controlled trial

Figure Legends

Figure 1 **Systematic review flow chart**

Figure 2 **Summary of findings of global effects for studies comparing biological agents with placebo**

Figure 3 **Summary of findings of leg pain intensity for studies comparing biological agents with placebo**

Figure 4 **Summary of findings of Oswestry Disability Index for studies comparing biological agents with placebo**

Figure 5 **Summary of findings of global effects for a study comparing a biological agent with corticosteroid injection**

Figure 6 **Summary of findings of overall pain intensity for studies comparing biological agents with corticosteroid injection**

Figure 7 **Summary of findings of Oswestry Disability Index for studies comparing biological agents with corticosteroid injection**

Figure 8 **Summary of total numbers of discectomies in studies comparing biological agents with placebo**

Figure 9 **Summary of total numbers of adverse effects for studies comparing biological agents with placebo or corticosteroid injection**

Figure 1 Systematic review flow chart

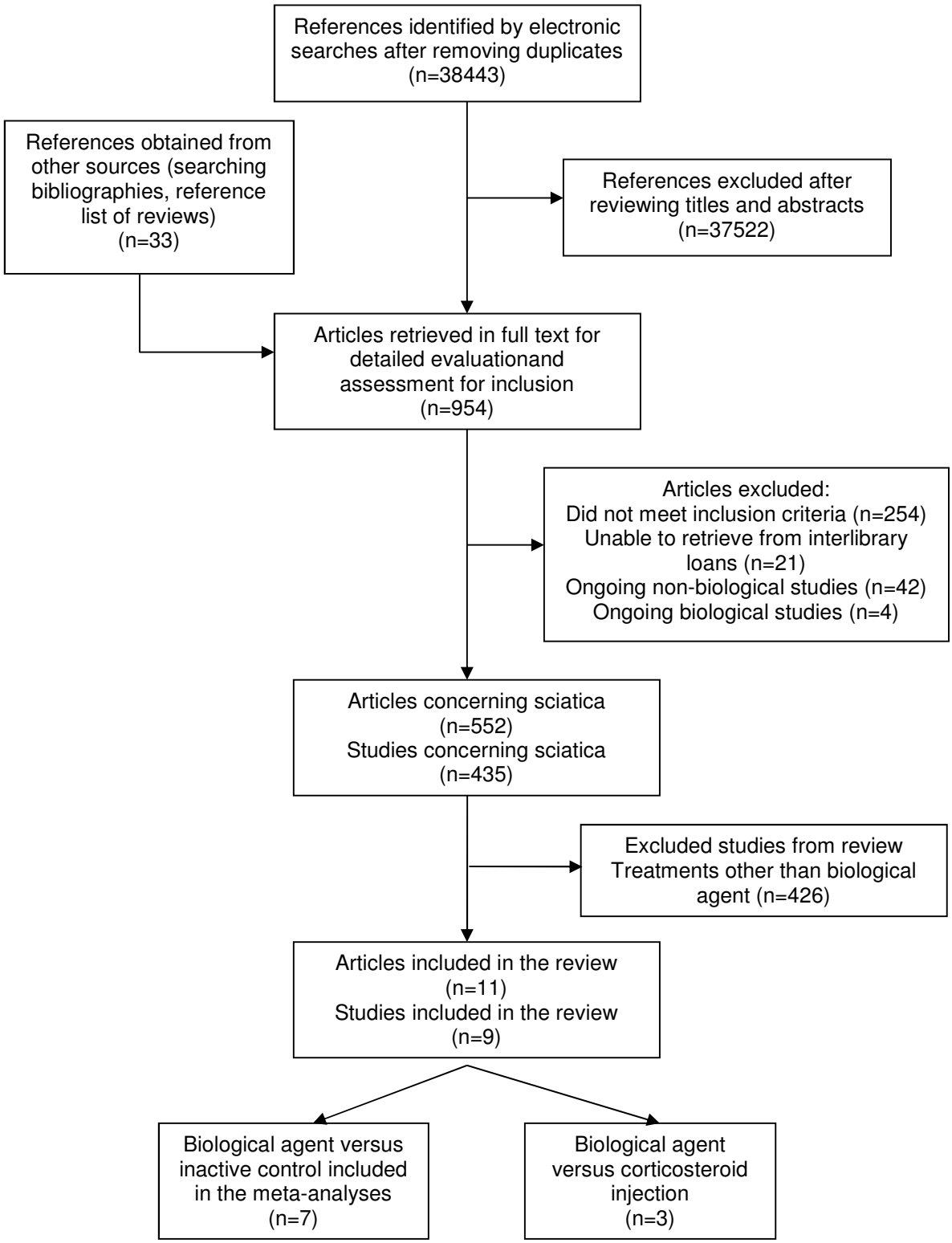

Figure 2 Summary of findings of global effects for studies comparing biological agents with placebo

Study or Subgroup	Biological agent Events	Total	Inactive control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.1.1 Short term follow-up							
Korhonen 2004 Non-RCT	7	10	17	62	23.8%	6.18 [1.43, 26.68]	2004
Cohen 2009 RCT	14	18	2	6	17.1%	7.00 [0.92, 53.23]	2009
Genevay 2010 RCT	22	31	21	30	29.2%	1.05 [0.35, 3.15]	2010
Cohen 2012 RCT	11	26	15	30	29.9%	0.73 [0.25, 2.11]	2012
Subtotal (95% CI)		**85**		**128**	**100.0%**	**1.99 [0.66, 5.96]**	
Total events	54		55				
Heterogeneity: Tau² = 0.76; Chi² = 7.96, df = 3 (P = 0.05); I² = 62%							
Test for overall effect: Z = 1.23 (P = 0.22)							
1.1.2 Medium term follow-up							
Korhonen 2004 Non-RCT	8	10	30	62	21.5%	4.27 [0.84, 21.72]	2004
Cohen 2009 RCT	13	18	1	6	12.6%	13.00 [1.20, 140.73]	2009
Genevay 2010 RCT	22	31	13	30	33.1%	3.20 [1.11, 9.22]	2010
Cohen 2012 RCT	10	26	12	30	32.7%	0.94 [0.32, 2.75]	2012
Subtotal (95% CI)		**85**		**128**	**100.0%**	**2.72 [1.04, 7.13]**	
Total events	53		56				
Heterogeneity: Tau² = 0.44; Chi² = 5.63, df = 3 (P = 0.13); I² = 47%							
Test for overall effect: Z = 2.03 (P = 0.04)							
1.1.3 Long term follow-up							
Korhonen 2004 Non-RCT	8	10	27	62	44.4%	5.19 [1.02, 26.43]	2004
Korhonen 2006 RCT	14	21	12	19	55.6%	1.17 [0.32, 4.28]	2006
Subtotal (95% CI)		**31**		**81**	**100.0%**	**2.26 [0.53, 9.73]**	
Total events	22		39				
Heterogeneity: Tau² = 0.56; Chi² = 1.98, df = 1 (P = 0.16); I² = 50%							
Test for overall effect: Z = 1.10 (P = 0.27)							

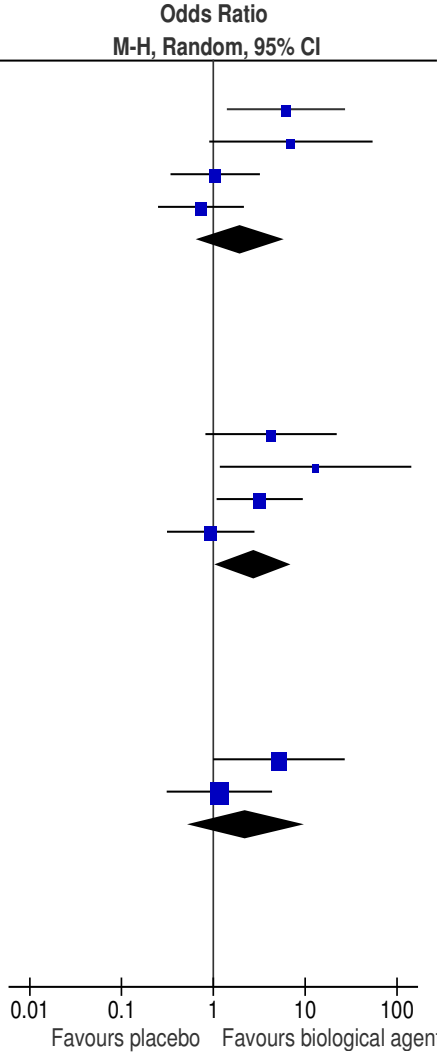

Figure 3 Summary of findings of leg pain intensity for studies comparing biological agents with placebo

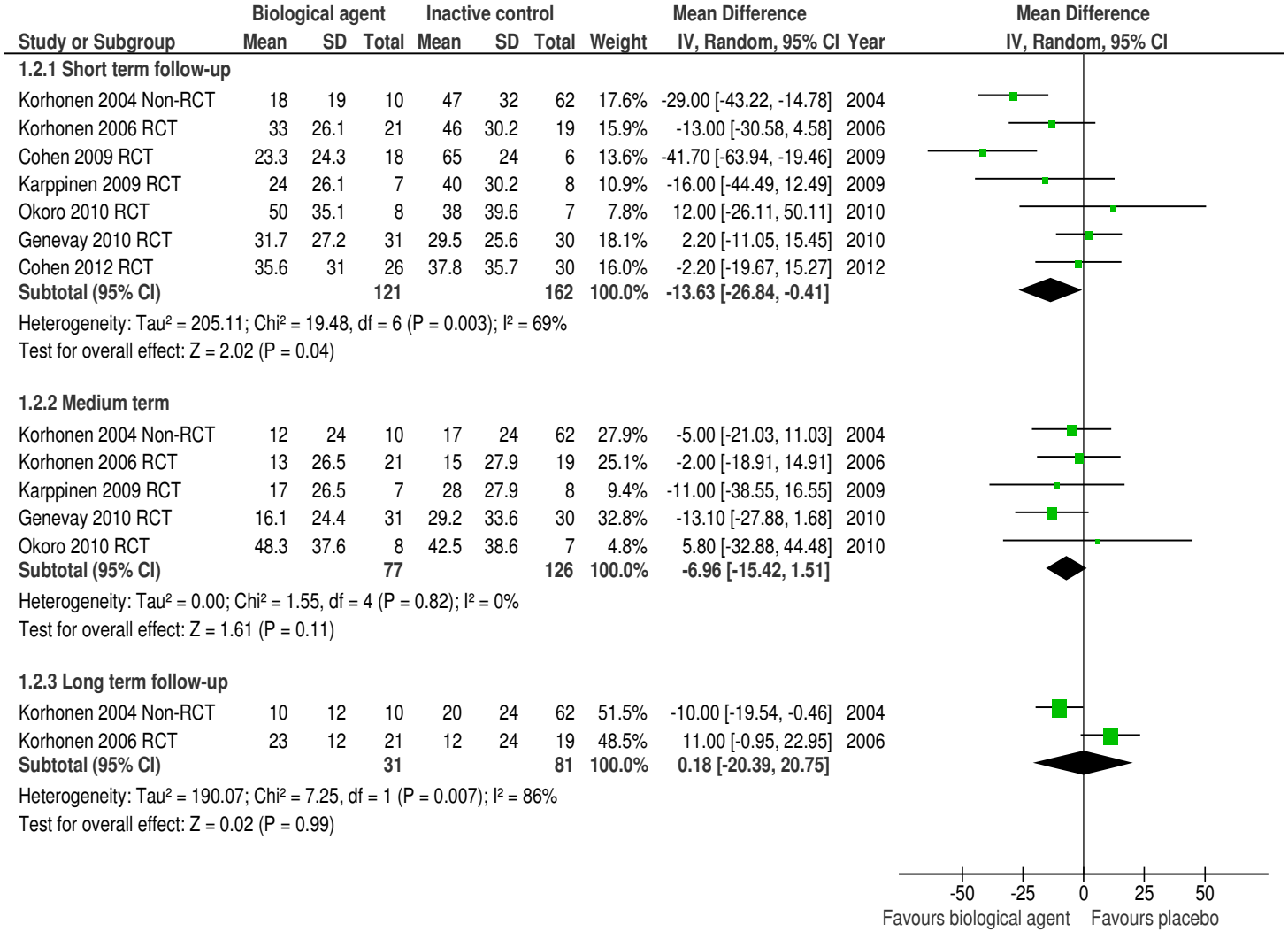

Figure 4 Summary of findings of Oswestry Disability Index for studies comparing biological agents with placebo

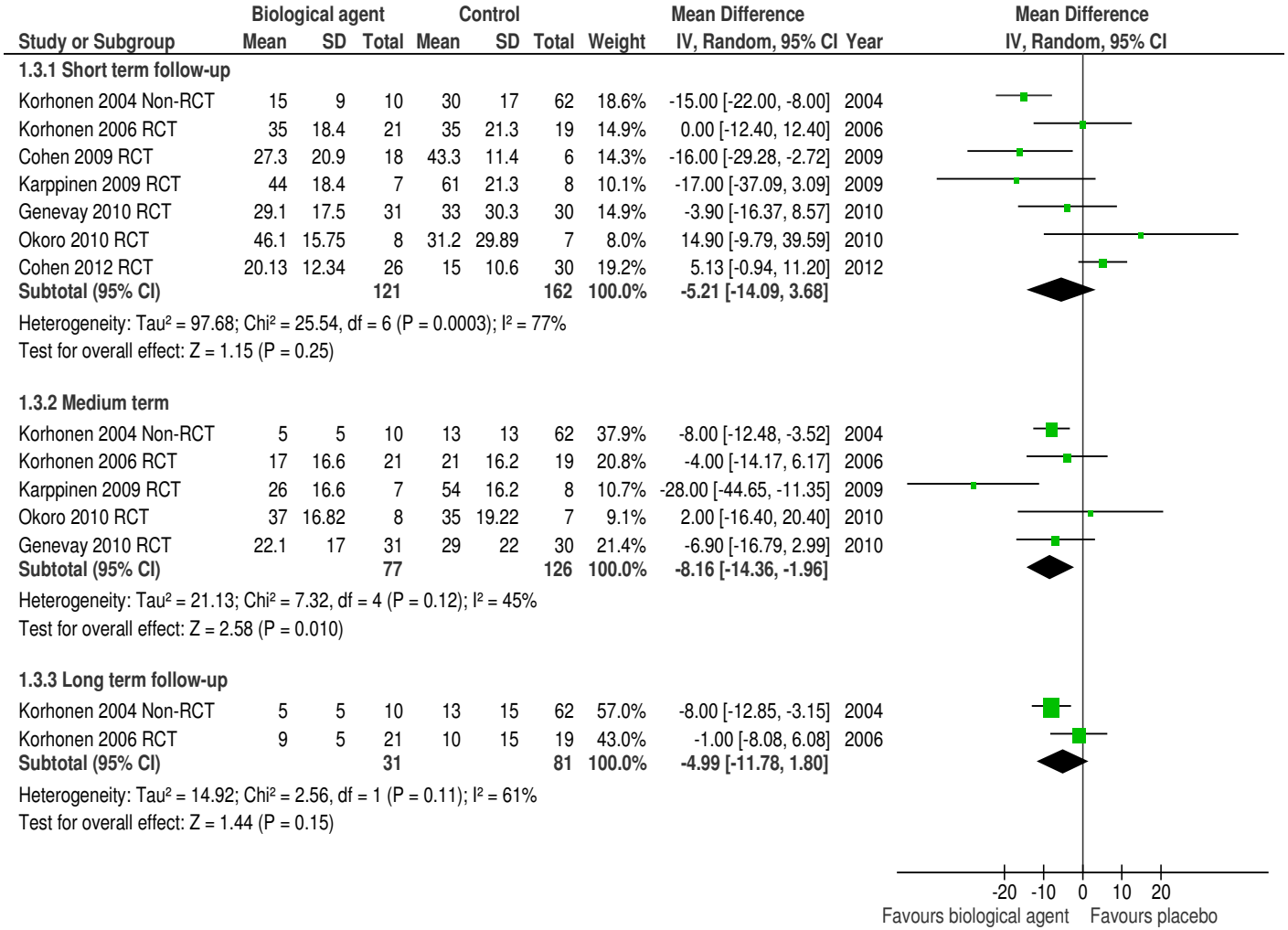

Figure 5 Summary of findings of overall pain intensity for studies comparing biological agents with corticosteroid injection

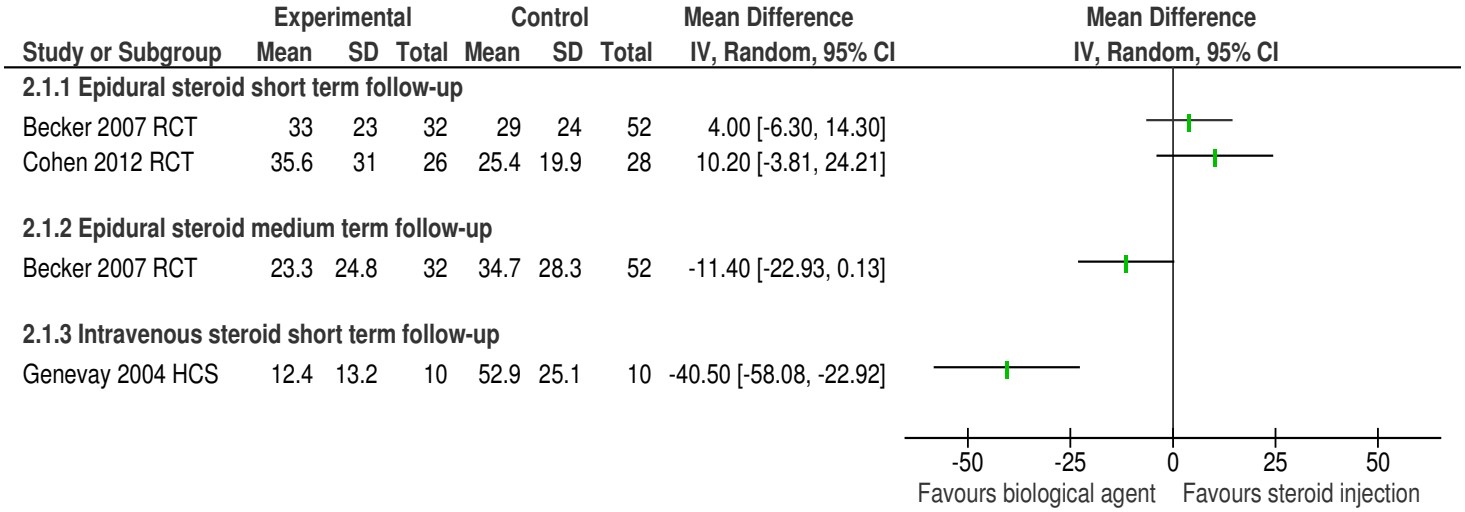

Figure 6 Summary of findings of Oswestry Disability Index for studies comparing biological agents with corticosteroid injection

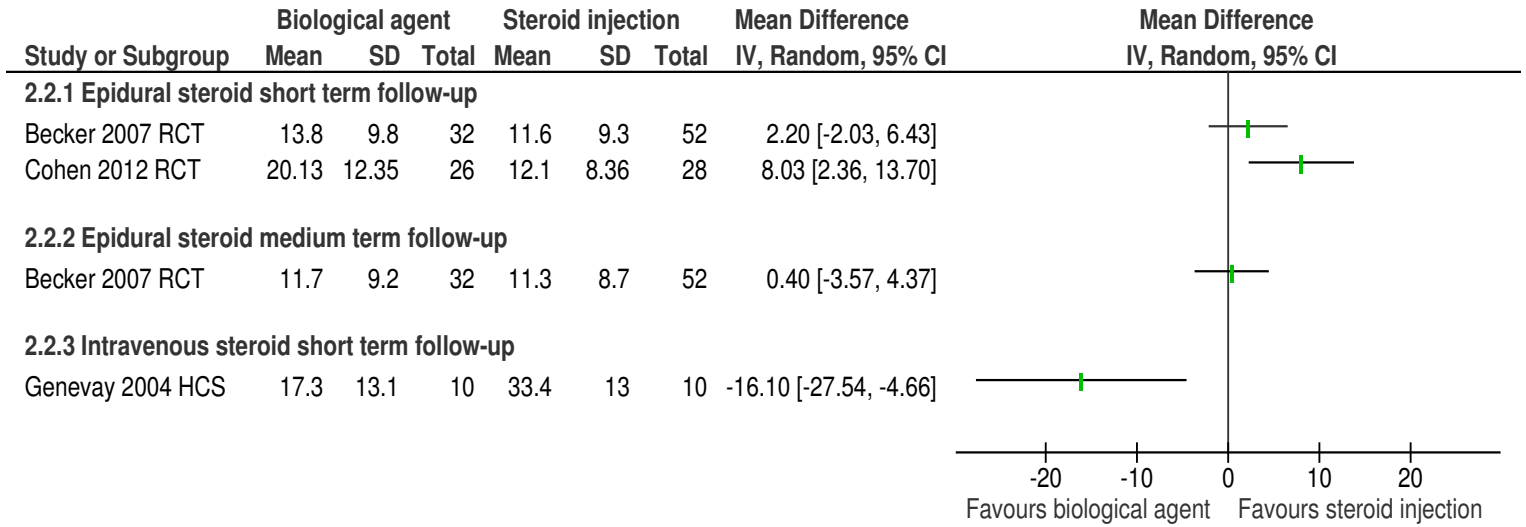

Figure 7 Summary of total numbers of discectomies in studies comparing biological agents with placebo

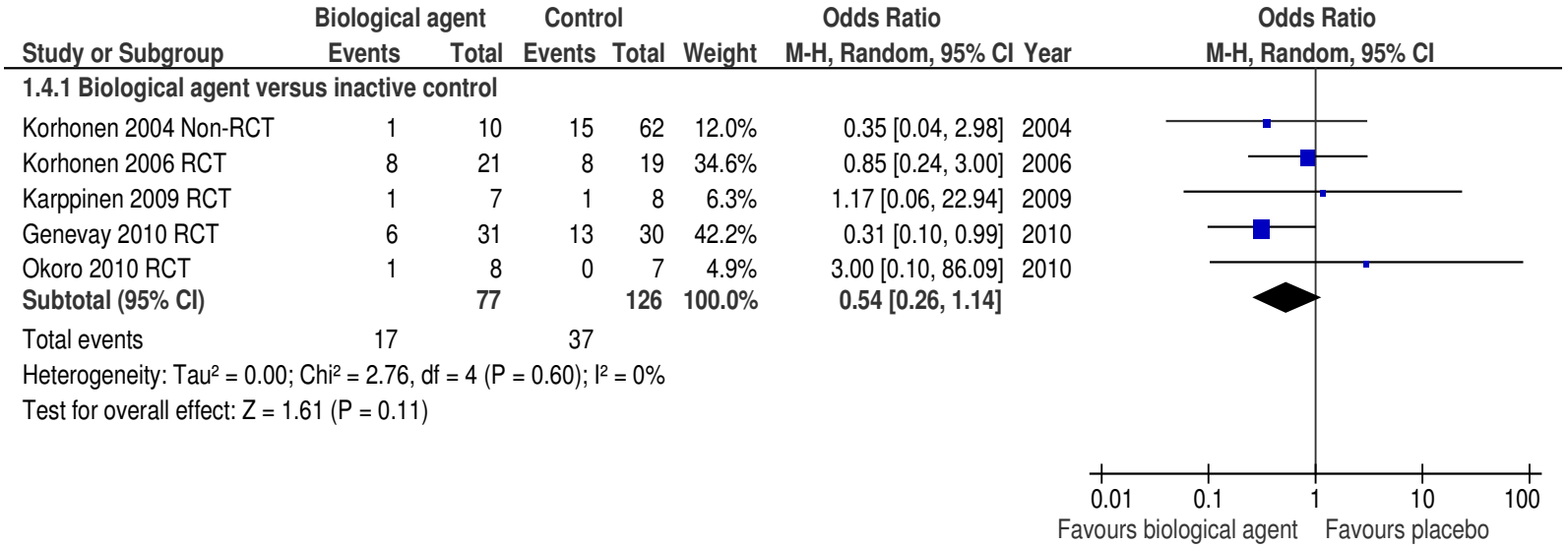

Figure 8 **Summary of total numbers of adverse effects for studies comparing biological agents with placebo or corticosteroid injection**