

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

Nefyn H Williams,^{1,2*} Alison Jenkins,¹ Nia Goulden,¹ Zoe Hoare,¹ Dyfrig A Hughes,¹ Eifiona Wood,¹ Nadine E Foster,³ David A Walsh,⁴ Dawn Carnes,⁵ Valerie Sparkes,⁶ Elaine M Hay,³ John Isaacs,⁷ Kika Konstantinou,³ Dylan Morrissey,⁸ Jaro Karppinen,⁹ Stephane Genevay¹⁰ and Clare Wilkinson¹

¹School of Healthcare Sciences, Bangor University, Bangor, UK

²Betsi Cadwaladr University Health Board, Bangor, UK

³Research Institute of Primary Care and Health Sciences, Keele University, Keele, UK

⁴Arthritis Research UK Pain Centre Division of Rheumatology, Orthopaedics and Dermatology, University of Nottingham, Nottingham, UK

⁵Centre for Primary Care and Public Health, Bart's and the London School of Medicine and Dentistry, London, UK

⁶School of Healthcare Sciences, Cardiff University, Cardiff, UK

⁷National Institute for Health Research Newcastle Biomedical Research Centre, Newcastle University, Newcastle upon Tyne, UK

⁸Centre for Sports and Exercise Medicine, William Harvey Research Institute, Bart's and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

⁹Medical Research Centre Oulu, University of Oulu, Oulu, Finland

¹⁰Rheumatology Department, Geneva University Hospitals, Geneva, Switzerland

*Corresponding author nefyn.williams@bangor.ac.uk

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Scientific summary

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Scientific summary

Background

Sciatica is a severe leg pain usually caused by a ruptured intervertebral disc, the contents of which compress and irritate a lumbar nerve root. It is common, disabling and costly to the health service and to society. Current care pathways in the NHS typically involve the prescribing of analgesia by the patient's general practitioner (GP) and, if troublesome symptoms persist, referral for physiotherapy in community-based physiotherapy services, musculoskeletal interface services or secondary care spinal clinics. If pain persists, patients are referred for more invasive treatment, such as epidural corticosteroid injection, and 5–15% of patients eventually need disc surgery.

Sciatica caused by lumbar nerve root pain is usually caused by a prolapsed intervertebral disc, not only because of compression of the nerve root, but also as a result of the release of proinflammatory factors from the damaged disc, such as tumour necrosis factor alpha (TNF- α). Biological agents, such as the monoclonal antibodies infliximab (AbbVie, Maidenhead, UK) and adalimumab (Humira[®], AbbVie Ltd, Maidenhead, UK), bind specifically to TNF- α receptors and may have beneficial effects on the inflamed nerve root in sciatica. A network meta-analysis of different treatment strategies for sciatica found that biological agents had the highest probability of being best, but with wide confidence intervals. A meta-analysis of biological agents for sciatica compared with placebo combined six randomised controlled trials (RCTs) and one non-RCT, and found that biological agents resulted in reduced leg pain intensity in the short term and increased global effects in the medium term. However, these findings were no longer statistically significant when studies were restricted to RCTs. Although there was insufficient evidence to change practice from these reviews, there was sufficient evidence to suggest that a definitive RCT was warranted. This systematic review did not identify any economic evaluations. Although these treatments are costly, they may be cost-effective if they reduce the need for more expensive treatments such as disc surgery. In addition, when their patent expires, cheaper biosimilar drugs may be developed and used in their place. Adalimumab is administered by subcutaneous injection, but infliximab confers the additional expense of intravenous injection. We used adalimumab because of its ease of administration and, in order to provide a therapeutic effect lasting 1 month, two subcutaneous injections were given 2 weeks apart. In order to initiate a rapid response, we used the typical starting dosage when treating psoriasis or Crohn's disease of 80 mg followed by 40 mg.

Objectives

1. To evaluate the clinical effectiveness of subcutaneous injections of adalimumab plus physiotherapy compared with a placebo injection of 0.9% sodium chloride plus physiotherapy for patients with sciatica in whom first-line primary care treatment had failed. We planned to identify potential participants during primary care consultation, after referral to musculoskeletal service or following a practice database search.
The primary effectiveness outcome was sciatica-related health status using the Oswestry Disability Index (ODI). Secondary effectiveness outcomes included pain intensity, location, duration and anticipated trajectory; the risk of poor outcome; psychological measures including fear of movement, self-efficacy, anxiety and depression; employment status; and adverse effects.
2. To evaluate, from a health service and personal social care perspective, the cost-effectiveness of subcutaneous injections of adalimumab plus physiotherapy compared with a placebo injection of 0.9% sodium chloride plus physiotherapy for patients with sciatica in whom first-line primary care treatment had failed. The primary economic outcome was the incremental cost per quality-adjusted life-year (QALY) gained. QALYs would be estimated by administering the EuroQol-5 Dimensions, 5-level version (EQ-5D-5L) at each follow-up visit.

Methods

Design

Pragmatic, multicentre RCT with blinded participants and clinicians, and an outcome assessment and statistical analysis with concurrent economic evaluation and internal pilot.

Main centres

The RCT aimed to recruit from six sites overseen by five collaborating centres in North Wales, London, Keele, Nottingham and Cardiff.

Selection and withdrawal of subjects

Each collaborating centre would oversee a number of patient identification centres, which consisted of general medical practices and local musculoskeletal services. Patients would be identified in three ways:

1. by their GP
2. following a search of the general practice patient record database
3. after referral to local musculoskeletal services.

Research clinic

Patients were invited to participate by letter. Those who were interested were contacted by telephone and, if they fitted the inclusion criteria, were given an appointment in a research clinic run by a research physiotherapist. At this research clinic all potential participants were assessed by the research physiotherapist for eligibility. If eligible, participants had blood tests, tuberculosis screening, biological agents counselling and magnetic resonance imaging (MRI) to exclude serious spinal pathology. A second clinical assessment by the research physiotherapist 2–3 weeks later assessed if they were still eligible. If they were, informed consent was obtained for trial entry and randomisation.

Inclusion criteria

- Aged ≥ 18 years.
- Clinical features of sciatica.
- Leg pain worse or as bad as back pain.
- Unilateral leg pain approximating a dermatomal distribution (contralateral buttock pain permitted if it did not extend below the inferior gluteal margin).
- One of the following:
 - positive neural tension test, such as the straight-leg raise test restricted to $< 50^\circ$ by leg pain, positive femoral stretch test, muscle weakness or loss of tendon reflex affecting one myotome
 - loss of sensation in a dermatomal distribution.
- Persistent symptoms for at least 4 weeks and < 6 months despite first-line treatment in primary care.
- Moderate to high severity (score of ≥ 30 points) on the ODI.
- Female partners of sexually active male participants should use adequate contraceptives for at least 5 months after the last injection. Female participants should have a negative urine pregnancy test within 2 weeks prior to randomisation, unless they were post menopause or had had a sterilisation operation. Sexually active men of female participants must also use adequate contraceptive methods.

Exclusion criteria

- Unable to perform MRI.
- Serious spinal pathology.
- Incidental serious pathology identified by MRI.

- Neurological deficit involving muscle weakness requiring an urgent spinal surgery assessment (e.g. foot drop).
- Widespread pain throughout the body including the upper limb.
- Prior use of biological agents targeting TNF- α within the previous 6 months.
- Previous lumbar spinal surgery.
- Contraindications to adalimumab injection, including serious infection such as active or latent tuberculosis, transplanted organ, demyelinating disorders, malignancy, cardiac failure, low white cell count and pregnancy.
- Pregnancy or breastfeeding (women must not breastfeed for at least 5 months after the last adalimumab injection).
- Unable to communicate in English or Welsh.
- Unable or unwilling to give informed consent.

Randomisation

Randomisation was achieved by secure web access to the remote randomisation system at the North Wales Organisation for Randomised Trials in Health at Bangor University, and was performed by a dynamic adaptive randomisation algorithm to protect against subversion while ensuring that the trial maintained good balance to the allocation ratio of 1 : 1 both within each stratification variable and across the trial. Participants were stratified by (1) treatment centre and (2) presence of neurological signs (motor weakness or sensory loss).

Subcutaneous injections

All participants were randomised to receive two doses of subcutaneous injection 2 weeks apart in the posterior thigh. The intervention group received 80 mg of adalimumab followed by 40 mg. The control group received 0.9% sodium chloride in an equivalent volume to the intervention group.

Concurrent physiotherapy

Both groups received a concurrent course of physiotherapy provided over a period of 12 weeks. The number of sessions provided was determined by participant and therapist preference, and also response to treatment. We aimed to capture and describe these aspects of physiotherapy treatment as part of the trial.

Clinical management of persistent symptoms

Once the participants had completed their course of physiotherapy, if their symptoms had settled or were improving, no further intervention was organised. They were discharged to the care of their GP and followed up by the research team as described in this protocol. If troublesome symptoms persisted, then further treatment was planned as appropriate by referral to musculoskeletal interface clinics or secondary care specialists according to local arrangement in each of the centres.

Internal pilot trial

This aimed to rehearse the procedures and logistics to be undertaken in the main trial. It would assess the feasibility of the arrangements for delivering the interventions, recruitment rate and initial retention rate. The internal pilot was based on the first 50 participants recruited into the trial. The stopping criteria at the end of this internal pilot would be recruitment that failed to reach 80% of the planned recruitment rate target, dropouts up until the 6-week postal questionnaire assessment exceeding 20%, or more than one centre failing to commence recruitment.

Primary outcome

The primary clinical outcome was back pain-specific disability using the ODI, measured at 12 months. The primary economic outcome was the incremental cost per QALY gained, estimated by administering the EQ-5D-5L at each follow-up visit.

Outcome measures

Condition-specific outcomes

- Back pain-specific disability using the ODI.
- Leg pain-related functional disability using the leg pain version of the Roland–Morris Disability Questionnaire.
- Leg pain interference using the Sciatica Bothersomeness Index.
- Pain location using a pain manikin.

Generic outcomes

- Health utility using the EQ-5D-5L.
- Global assessment of change since baseline.

Psychological outcomes

- Anxiety and depression using the Hospital Anxiety and Depression Scale.

Use of health care and social care services

- Resource Use Questionnaire.

Process measures (potential predictors and mediators of outcome)

- Risk of persistent disabling pain (STarT Back screening tool).
- Pain trajectory (based on a single question).
- Pain Self-Efficacy Questionnaire.
- Fear avoidance beliefs (Tampa Scale of Kinesiophobia).

Follow-up

The outcomes would be collected at baseline, and after 6 weeks', 6 months' and 12 months' follow-up. The baseline was administered by research physiotherapists. We would send postal questionnaires at 6 weeks' and at 6 and 12 months' follow-up.

Statistics

Sample size

From the weighted mean difference in our previous meta-analysis, we found a relative improvement of 8 points in the ODI at 6 months' follow-up in the group receiving biological agents compared with placebo, with a standard deviation of 16 points, giving an effect size of 0.5. To detect a more conservative effect size of 0.4 with 90% power, with a significance level of 5% for a two-tailed *t*-test, a sample size of 133 in each treatment group would be needed. We aimed for a 90% return rate of the final questionnaires, but for a more conservative retention rate of 80%, 332 participants would need to be recruited.

Data analysis

All data were anonymised and coded so that data collection and statistical analysis would be blinded to treatment allocation and performed on a 'treatment as allocated' principle.

The main outcome variable would be the ODI measured at 12 months. A linear mixed-model approach for repeated measures would be used to assess the effects of time, group and time × group. Secondary continuous outcome variables would be assessed in a similar way, with the exception of time to referral for surgery, which would be assessed from trial entry (this is the date of second consent) using Kaplan–Meier

survival analyses and the log-rank test. Dichotomous variables would be explored using logistic regression. These analyses would be repeated using prespecified participant subgroups (including the presence of neurological deficit on entry to the trial and MRI findings).

Economic analysis

The health economic analysis would adopt the perspective of the NHS and personal social services and, additionally, indirect costs [e.g. time off work (secondary analysis)]. Costs would include those of treatment, tests, procedures and investigations, and contact with primary and secondary care services and personal social services. Resource use would be obtained from participants' self-reporting of resource use, captured by questionnaire administration. Unit cost data would be obtained from standard sources. The primary economic outcomes would be the incremental cost per QALY gained, estimated by administering the EQ-5D-5L at each follow-up point. Non-parametric bootstrapped 95% confidence intervals would be estimated (10,000 replicates). Total costs would be combined with QALYs to calculate incremental cost–utility ratios. Estimates of incremental cost-effectiveness ratios would be compared with the £20,000 to £30,000 per QALY threshold of cost-effectiveness, and a range of one-way sensitivity analyses would be conducted to assess the robustness of the analysis. Multivariate sensitivity analyses would be applied when interaction effects were suspected. The joint uncertainty in costs and benefits would be considered through the application of bootstrapping and the estimation of cost-effectiveness acceptability curves.

Results

Following initial delays finalising the trial contract with the funder, approvals were obtained with only small delays in the timetable. There were much longer delays negotiating subcontracts with sites. The contract negotiation in one site was never completed because of ongoing discussion about roles and responsibilities, and one site withdrew because the principal investigator had safety concerns of the initial dose. Only two sites recruited participants. In one site there were delays in recruiting from secondary care populations and delays in setting up primary care recruitment. In the other site, there were delays setting up the site, difficulties recruiting research physiotherapists and a poor rate of recruitment following the postal invitation to participate.

Although large numbers of invitations were sent to potential participants ($n = 1546$), there was a low rate of uptake with only 25 patients (2%) seen for an initial assessment, and eight patients (32%) were entered into the trial. Recruitment was improving just before the trial was closed, with five potential participants ready to be recruited within the following month.

Conclusions

The research question is still important to answer but, because of the lack of trial results, we cannot make any recommendations for future practice. The main failure was as a result of problems with contracts. Because of this, we were unable to complete the internal pilot study. There may be insufficient equipoise around the question of adalimumab for sciatica among patients and some clinicians, which could be addressed with qualitative research. The two-stage recruitment process was complicated and not feasible. We had planned to test other methods of primary care recruitment, but unfortunately the trial closed before we were able to do so.

A trial of biological therapy in patients with sciatica still needs to be done, but would require a clearer contracting process, qualitative research to ensure that patients would be willing to participate and simpler recruitment methods.

Trial registration

This trial is registered as ISRCTN14569274.

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