A randomised placebo-controlled Phase III multicentre trial: low-dose intravenous immunoglobulin treatment for long-standing complex regional pain syndrome (LIPS trial)

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Scientific summary

The LIPS trial

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Scientific summary

The text in the *Scientific summary* includes minor additions and formatting changes to the original text as published in Goebel A, Shenker N, Padfield N, Shoudrey K, McCabe C, Serpell M, *et al.* Low-dose intravenous immunoglobulin treatment for complex regional pain syndrome (LIPS): study protocol for a randomized controlled trial. *Trials* 2014;**15**:404.

Background

Complex regional pain syndrome (CRPS) is post-traumatic pain in a limb, and is associated with sensory, motor, autonomic, skin and bone changes. CRPS can resolve spontaneously, but if spontaneous resolution does not occur early, it is less likely to occur later. Many patients with CRPS have no effective method to relieve their ongoing pain. Those patients with CRPS of moderate to severe pain intensity were the target group for this study and report, on average, a very poor quality of life (QoL) and usually cannot work. Immunoglobulin treatment for chronic pain is a novel technology [Goebel A. Immunoglobulin responsive chronic pain. *J Clin Immunol* 2010;**30**(Suppl. 1):103–8]. In a first, open trial we found that low-dose intravenous immunoglobulin (IVIg) may be effective in reducing pain for some patients with CRPS ($n = 11$ participants; $n = 3$ had > 70% pain relief, $n = 2$ had > 25% < 70%, and $n = 6$ had 0–25% relief, following a variable number of low-dose infusion repeats). We later showed that, in one patient, repeat treatments provided reproducible effects. In a UK single-centre crossover randomised placebo controlled trial, a single, low-dose (0.5 g/kg) infusion of IVIg significantly reduced pain in patients with CRPS [$n = 13$, pain intensity on a validated 11-point Numeric Rating Scale (NRS) higher than 4 points (0 = no pain, 10 = pain as bad as you can imagine (Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, *et al.* Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005;**113**:9–19)]; these patients had the disease for between 0.5 and 2.5 years. The treatment difference was 1.55 NRS points [95% confidence interval (CI) 1.29 to 1.82 points; $p < 0.001$]. In a responder analysis (12 patients had received treatment), three patients had ≥ 50% less pain (4.5, 5 and 5 NRS points) after IVIg when compared with after saline treatment, and two patients had 29% and 31% less pain (2 and 2.5 NRS points less pain). One patient had 25% less pain (2 NRS points less pain) after saline than those patients having IVIg treatment. The average effect duration was 5 weeks. There was also a significant overall reduction of CRPS-related, non-painful symptoms and, in responders, improved sleep and global improvement, with few adverse events (headaches and pain increases for < 3 days). Post-infusion questionnaires showed successful blinding of patients and study doctors.

The above evidence provided proof of concept for the efficacy of low-dose immunoglobulin treatment for moderate and severe CRPS in reducing pain, with an advantageous side effect profile. The data also suggested that this treatment may improve QoL and pain interference. Because the numbers of treated patients were small, and most research was conducted in a single centre, it was important to confirm these findings in a larger group of patients and across several centres to gain confidence about both efficacy and affect size of this novel technology, and to demonstrate its generalisability.

Objectives

The primary objective was to gain, within 44 months, both definite proof of the clinical efficacy and a more confident estimate of the effect size of low-dose IVIg treatment to reduce pain in patients with moderate or severe CRPS.

Secondary objectives

To achieve better understanding of this technology, including:

- stability of effect with repeat administration
- factors predicting a beneficial response
- effects on additional outcome parameters including stimulus evoked pain, pain interference, QoL and short-term risk profile
- health economics evaluation
- creation of a bank of biological samples at the University of Liverpool for future CRPS serum autoantibody and serum substances research.

Methods (design/study population/participants/consent/randomisation/interventions/outcome measures)

We conducted a multicentre, randomised, double-blind, placebo-controlled, parallel group trial with an open extension across seven UK pain management centres. Patients were eligible if they had moderate or severe long-standing CRPS that they had experienced for up to 5 years. Participants were randomly allocated to receive 0.5 g/kg IVIg, the active intervention, or visually indistinguishable 0.1% albumin in saline placebo. Randomisation was initiated by study sites via an independent online randomisation system, and was 1 : 1 with varying block sizes, stratified by study centre. Participants, investigators and assessors were blinded to group assignment. The study drug/placebo was infused intravenously at the study centres on day 1 and day 22 after randomisation. The primary outcome was the 24-hour average pain intensity between day 6 and day 42, on an 11-point (0–10) NRS, compared between the groups. All patients who received an infusion and provided any outcome were included into the intention-to-treat analysis.

Results

A total of 111 patients were recruited and assigned between 27 August 2013 and 28 October 2015. Three patients were excluded because they had been inappropriately randomised, five patients were withdrawn from the primary analysis because they provided no outcomes and 103 patients were analysed for the primary outcome. The average pain score in the IVIg group was 0.27 units (95% CI –0.24 to 0.80 units) higher than in the placebo group. The 95% CI includes 0 and the corresponding *p*-value is relatively large ($p = 0.30$). Therefore, there is no significant evidence of a treatment effect at the 5% level and there was no significant difference between groups.

Limitations

Patients who had the disease for < 1 year and > 5 years were excluded from the study. Dosing was limited to a low-dose IVIg infusion at 0.5 g/kg. A second active arm with high-dose treatment would have been desirable.

Conclusions and recommendation for research

Low-dose immunoglobulin was not effective in relieving pain in patients with moderate to severe CRPS of 1–5 years' duration. Better drug treatments for long-standing CRPS are urgently required.

Trial registration

This trial is registered as ISRCTN42179756.

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This report

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