Low-Dose Intravenous Immunoglobulin Treatment for Long-Standing Complex Regional Pain Syndrome
A Randomized Trial
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Background: Two small trials suggest that low-dose intravenous immunoglobulin (IVIg) may improve the symptoms of complex regional pain syndrome (CRPS), a rare posttraumatic pain condition.

Objective: To confirm the efficacy of low-dose IVIg compared with placebo in reducing pain during a 6-week period in adult patients who had CRPS from 1 to 5 years.

Design: 1:1 parallel, randomized, placebo-controlled, multicenter trial for 6 weeks, with an optional 6-week open extension. Patients were randomly assigned to 1 of 2 study groups between 27 August 2013 and 28 October 2015; the last patient completed follow-up on 21 March 2016. Patients, providers, researchers, and outcome assessors were blinded to treatment assignment. (ISRCTN42179756)

Setting: 7 secondary and tertiary care pain management centers in the United Kingdom.

Participants: 111 patients with moderate or severe CRPS of 1 to 5 years’ duration.

Intervention: IVIg, 0.5 g/kg of body weight, or visually indistinguishable placebo of 0.1% albumin in saline on days 1 and 22 after randomization.

Measurements: The primary outcome was 24-hour average pain intensity, measured daily between days 6 and 42, on an 11-point (0- to 10-point) rating scale. Secondary outcomes were pain interference and quality of life.

Results: The primary analysis sample consisted of 108 eligible patients, 103 of whom had outcome data. Mean (average) pain scores were 6.9 points (SD, 1.5) for placebo and 7.2 points (SD, 1.3) for IVIg. The adjusted difference in means was 0.27 (95% CI, −0.25 to 0.80; P = 0.30), which excluded the prespecified, clinically important difference of −1.2. No statistically significant differences in secondary outcomes were found between the groups. In the open extension, 12 of the 67 patients (18%) who received 2 IVIg infusions had pain reduction of at least 2 points compared with their baseline score. Two patients in the blinded phase (1 in the placebo and 1 in the IVIg group) and 4 in the open IVIg phase had serious events.

Limitations: Results do not apply to patients who have had CRPS for less than 1 year or more than 5 years and do not extend to full-dose treatment (for example, 2 g/kg). The study was inadequately powered to detect subgroup effects.

Conclusion: Low-dose immunoglobulin treatment for 6 weeks was not effective in relieving pain in patients with moderate to severe CRPS of 1 to 5 years’ duration.

Primary Funding Source: Medical Research Council/National Institute for Health Research Efficacy and Mechanism Evaluation Program, Pain Relief Foundation, and Biotest United Kingdom.
METHODS

Design Overview
In this parallel-group trial, patients with CRPS were randomly assigned in 1:1 allocation to receive either 2 infusions of IVlg, 0.5 g/kg of body weight, or placebo. All patients were offered an open-label extension of 2 IVlg infusions. Providers, researchers, and outcome assessors were blinded to treatment assignment. The East of England Welwyn committee gave ethics approval (reference: 12/EE/0164). Patients were provided with informational leaflets about the trial, and those interested in participating provided written informed consent. The study protocol has been published (10) and is available in Supplement 1 (available at Annals.org).

Setting and Participants
The study recruited patients from 7 secondary and tertiary care pain treatment centers in the United Kingdom; potential participants were identified from the internal databases of these study centers or were referred to the centers as new patients. To enhance recruitment, the study was promoted regularly throughout the United Kingdom in pain medicine journals, through letters to each specialist pain clinic, on social network sites, and within CRPS patient organizations.

Eligible participants were nonpregnant adults with moderate or severe CRPS (on the basis of the Budapest research criteria [3]). The CRPS severity cutoff was concealed and determined by a mean pain intensity score of 5 points or higher on an 11-point (0- to 10-point) numeric rating scale (NRS) recorded in the first 7 daily pain diary entries during screening, with no single entry below 4 points. A pain intensity score of 4 points is considered a cut point between mild and moderate pain (11). The Budapest research criteria, used by all the recruitment centers, require the presence of at least 1 regional sign in at least 2 of the following 4 diagnostic categories: sensory abnormalities, such as allodynia; swelling or sweating; color or temperature changes; and motor or trophic changes. The criteria also require the report of symptoms in all 4 categories. Patients with CRPS type I (without nerve injury) or II (with nerve injury) were eligible to participate. Eligible patients had CRPS for 1 to 5 years and no other pain that, in the study physician’s opinion, might interfere with their personal assessment of CRPS pain changes.

Before enrollment, patients received tricyclic antidepressants, gabapentinoids, and mild and strong opioids, as well as specialized pain physiotherapy, unless these treatments were refused or contraindicated. Patients with an implanted spinal cord stimulator were eligible if they met pain intensity criteria with the stimulator turned on. Participants continued their usual exercise and medication regimens. Further details regarding inclusion and exclusion criteria are provided in the study protocol (Supplement 1) (10).

After giving consent and being screened for eligibility, suitable patients completed a screening diary for 7 days, then were contacted by telephone to ascertain their diary values; those who met the pain eligibility criteria were randomly assigned to a study group 10 to 21 days after screening (that is, on day 0).

Randomization and Interventions
Participants were individually randomly assigned (1:1) to receive IVlg or placebo by site staff via an independent online system, using block randomization with randomly varying block sizes, stratified by study center. The intervention was blinded by preparation of the IVlg (0.5 g/kg) or placebo solution (0.1% albumin in normal saline) in bottles of identical appearance. Upon notification, nonblinded dispensing site pharmacists removed the bottle label indicating the trial group before dispensing the agents. All other study site staff, the trial manager or site monitor, the statistician, and the chief investigator remained blinded to the patients’ treatment assignments until database lock. No participants required emergency unblinding.

Blinded infusions were scheduled on days 1 and 22 after randomization. A predetermined time window around the infusion days provided flexibility (first infusion, up to 5 working days; second infusion, day 22 ± 1 day). The primary outcome period, days 6 to 42 after randomization, remained fixed and was thus independent of the actual infusion dates.

Patients who completed the blinded phase were offered open-label IVlg on days 43 and 64 after randomization. The dosages prescribed were within normal, weight-determined clinical limits (0.5 g/kg) for low-dose treatment.

Outcomes and Follow-up
The primary outcome measure was the average 24-hour pain intensity score on an 11-point NRS, with 0 designating “no pain” and 10 “pain as bad as you can imagine.” This outcome was measured daily from days 6 to 42, with this interval prespecified to exclude the period of early, unspecific, temporary pain increases, such as headaches (8). Secondary outcomes were pain interference, measured with the interference subscale of the Brief Pain Inventory (11-point NRS from 0 to 10 points), with higher scores indicating more interference (12), and quality of life (measured by the 5-level EuroQol 5-dimensional questionnaire [EQ-5D-5L]), where higher scores indicate a better quality of life (13). All other outcomes were exploratory.

Paper diaries documenting the participants’ average 24-hour pain intensity were self-administered from days 1 to 42 after randomization (an example diary is provided in Supplement 2, available at Annals.org). Patients who decided to have 2 open infusions after the blinded phase completed additional 24-hour diaries until day 84, then completed weekly pain diaries for 9 more weeks. The other patients completed weekly diaries for 3 weeks. Site staff contacted participants twice after each infusion to confirm their adherence to keeping the pain diaries and to document any adverse events.

At screening and day 43, patients completed questionnaires assessing their multidimensional pain experience. Multidimensional assessment tools were used, including those for pain interference, quality of life, and...
IVIg in Complex Regional Pain Syndrome

The sample size was based on the following assumptions from a pilot study (8): 122 participants were needed to detect a clinically meaningful difference, on a group level (15), in a pain score of 1.2 points on the NRS, determined by using a 2-sample t test assuming 5% statistical significance, 85% power, and a common SD of 2.2 (as in the previous study). Assuming 10% loss to follow-up and 5% nonadherence increased this number to 152 participants. We intended to collect 37 measurements of pain intensity (the primary outcome) per participant and to analyze the outcome by using a mixed-effects regression model. Therefore, the sample size was reduced on the basis of these extra measurements. From the pilot study (8), the correlation between a patient’s measures was assumed to be 0.7; hence, the multiplying factor was \([1 + (37 - 1) \times 0.7]/37 = 0.71\). Therefore, the total sample size required was calculated as \(152 \times 0.71 = 108\) participants (54 participants per study group).

All statistical analyses were conducted by using Stata, version 14 (StataCorp). The primary outcome was analyzed by using a random intercept mixed model (Stata: mixed) to establish any difference in pain scores between the IVIg and placebo groups after treatment. In detail, this model contained fixed effects for treatment and study center and assumed an exchangeable correlation structure among the 37 repeated outcome measurements for each patient. Modeling assumptions were checked: Level 1 and 2 residuals were checked for normality. The primary analysis sample was an intention-to-treat sample based on all randomly assigned, eligible patients. However, imputation was not performed; hence, 5 patients who supplied no outcome data did not contribute to this analysis.

The following sensitivity analyses were performed: a constrained longitudinal data analysis that modeled both the baseline and postrandomization pain scores as the outcome (16) and thus included 5 patients who did not contribute to the primary analysis, a fixed effect added to the mixed model for baseline pain score, a fixed effect added to the mixed model for disease duration, and an analysis that included patients who incorrectly gave consent to participate in the trial after not meeting the inclusion criteria.

Possible subgroup effects based on study center, disease duration, sex, allergy status, IgG plasma level, anxiety and depression, and CRPS type were investigated separately by using exploratory plots and fitting mixed models that included interaction terms between the factor and treatment. As a secondary analysis, we calculated the proportion of participants in each group who achieved 50% or 30% pain relief on the basis of the average pain level reported on days 6 to 42, compared with baseline pain (the average pain level recorded during the first 7 days of the screening period). Pain reduction of 30% represents a clinically meaningful effect on an individual level (17).

The secondary outcomes—Brief Pain Inventory interference scores and quality of life (EQ-5D-5L), as well as McGill Pain Questionnaire (Short Form) descriptor terms (18)—and limb temperature were analyzed by using linear regression models (Stata: regress) with covariates for treatment and study center.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of the LIPS (Low-Dose Immunoglobulin in Long-Standing Complex Regional Pain Syndrome) trial.

- Patients assessed for eligibility (n = 121)
  - Randomly assigned (n = 111)
    - Assigned to placebo group (n = 56)
      - Received placebo: 55
      - Did not receive placebo: 1
    - Assigned to IVIg group (n = 55)
      - Received IVIg: 54
      - Did not receive IVIg: 1
  - Lost to follow-up (supplied no outcome data) (n = 2)
  - Analyzed (n = 56)
- Excluded (n = 10)
  - No longer consenting: 4
  - Not contactable: 1
  - Ineligible pain scores: 1
  - Ineligible blood results: 2
  - Ineligible disease duration: 1
  - Ineligible Budapest criteria: 1

IVIg = intravenous immunoglobulin.
For participants who decided to receive both open infusions and had average pain relief of at least 30% or 2 NRS points from 6 to 20 days after their last open infusion, as compared with baseline, the time between the last open infusion and the first period in which average weekly pain equaled or exceeded baseline minus 1 NRS point was calculated as the IVIg effect duration. Because the study ended on day 148 (12 weeks after the second open infusion), later effects were not recorded.

A data monitoring committee had access to the unblinded data and monitored the progress of the trial in terms of safety and ethical issues. A blinded interim analysis was performed for safety after half the participants completed the trial. The stopping rule was based on detecting an effect in favor of placebo at the 5% significance level. The data monitoring committee reviewed the results of the analysis and recommended continuation of the trial.

This trial is registered with the ISRCTN registry (ISRCTN42179756).

Role of the Funding Source

This project was funded by the Efficacy and Mechanism Evaluation Program, a Medical Research Council and National Institute for Health Research partnership, and the Pain Relief Foundation Liverpool. Biotest United Kingdom Limited provided the active study medication at no cost. The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Patients

Between 27 August 2013 and 28 October 2015, 121 patients from 7 sites were screened for eligibility. Of these patients, 111 were randomly assigned to 1 of the 2 trial groups: 56 to the placebo group and 55 to the IVIg group. Three patients were randomly assigned in error: 2 had an average baseline pain score (during the first 7 days of screening) below 5 points, and 1 had CRPS for less than 12 months. These 3 patients (all randomly assigned to receive IVIg) were excluded from the primary analysis. Twelve patients withdrew from study medication before the end of the blinded phase (day 42). Of these patients, 2 (1 from the placebo group and 1 from the IVIg group) did not receive their first infusion and supplied no outcome pain data, and 3 (2 from the placebo group and 1 from the IVIg group) received their first infusion but also supplied no outcome pain data. The remaining 7 patients received their first infusion, and all completed their pain diaries for at least 2 weeks. Six of the 12 patients who withdrew indicated an adverse event as the reason for their withdrawal (3 from the placebo group and 3 from the IVIg group), 1 patient wished to pursue an alternative therapy, 2 patients stated problems with travel arrangements, and 3 patients gave no reason. The primary analysis sample included 108 patients, 56 in the placebo group and 52 in the IVIg group (Figure 1).

Baseline characteristics for these 108 patients are shown in Table 1. Balance was achieved for most variables, although there was a slight imbalance with regard to sex. Apart from 1 case of stable Crohn disease, participants had no severe or multiple concomitant autoimmune disorders (not shown in table).

There was no indication that patients were able to identify their treatments when assessed directly after the first infusion (Table 2) or after the second infusion (not shown in table); hence, we were satisfied that blinding was successful.

Primary Outcome

Of the 108 patients, 103 provided at least 14 daily pain intensity scores for the primary outcome between day 42. Of these patients, 111 were randomly assigned to 1 of the 2 trial groups: 56 to the placebo group and 55 to the IVIg group (ISRCTN42179756).

Table 1. Baseline Characteristics of Patients in the Primary Analysis Sample*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 56)</th>
<th>Low-Dose IVIg (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>41.0 (12.5)</td>
<td>43.7 (11.6)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 (25)</td>
<td>19 (37)</td>
</tr>
<tr>
<td>Female</td>
<td>42 (75)</td>
<td>33 (63)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>White</td>
<td>55 (98)</td>
<td>50 (96)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.5 (1.2)</td>
<td>2.3 (1.2)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>2.5 (1-4)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>CRPS type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I†</td>
<td>49 (88)</td>
<td>44 (85)</td>
</tr>
<tr>
<td>II‡</td>
<td>6 (11)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Undecided</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Limb involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 limb, n (%)</td>
<td>43 (77)</td>
<td>41 (79)</td>
</tr>
<tr>
<td>2, 3, and 4 limbs, respectively, n</td>
<td>10, 0, and 3</td>
<td>8, 2, and 1</td>
</tr>
<tr>
<td>Average baseline pain score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7.4 (1.1)</td>
<td>7.5 (1.0)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>7.4 (6.7-8.1)</td>
<td>7.6 (7.0-8.3)</td>
</tr>
<tr>
<td>Mean EQ-SD-5L score for quality of life (SD)</td>
<td>0.34 (0.28)</td>
<td>0.33 (0.27)</td>
</tr>
<tr>
<td>Mean Brief Pain Inventory pain interference score (SD)</td>
<td>7.32 (1.72)</td>
<td>7.47 (1.63)</td>
</tr>
<tr>
<td>Limb temperature§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean difference from nonaffected side (SD), °C</td>
<td>−0.75 (0.20)</td>
<td>−0.90 (0.24)</td>
</tr>
<tr>
<td>Patients with lower temperature in affected side, %</td>
<td>68</td>
<td>70</td>
</tr>
</tbody>
</table>

CRPS = complex regional pain syndrome; EQ-SD-5L = 5-level EuroQol 5-dimensional questionnaire; IQR = interquartile range; IVIg = intravenous immunoglobulin.

* Percentages may not sum to 100 due to rounding.
† Not associated with injury to a major nerve.
‡ Associated with injury to a major nerve.
§ Measured only in patients who had a healthy contralateral limb and could tolerate the procedure (47 patients in the placebo group and 46 patients in the IVIg group).
Table 2. Success of Blinding*

<table>
<thead>
<tr>
<th>Guess</th>
<th>Prescribed low-dose IVIg</th>
<th>Uncertain</th>
<th>Prescribed placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Low-Dose IVIg</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Prescribed low-dose IVIg</td>
<td>5 (9)</td>
<td>5 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncertain</td>
<td>44 (80)</td>
<td>35 (69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribed placebo</td>
<td>6 (11)</td>
<td>11 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>55 (100)</td>
<td>51 (101)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IVIg = intravenous immunoglobulin.
* Assessed directly after the first infusion by the 106 patients in the primary analysis sample who received it. One patient in each group did not receive the infusion. Values are numbers (percentages), which may not sum to 100 due to rounding.

Table 1 (available at Annals.org). The average pain scores during days 1 to 84, by study group, are shown in Figure 2.

Average pain scores per patient were very similar for each treatment group. The mean of the average scores was 6.9 points (SD, 1.5) for placebo and 7.2 points (SD, 1.3) for IVIg; the adjusted difference in means was 0.27 (95% CI, −0.25 to 0.80; P = 0.30). The CI excludes the clinically important difference of −1.2. The average pain scores during the primary outcome period (days 6 to 42) were fairly constant (Figure 2).

The treatment effect changed little when baseline pain was considered as an outcome in order to include the 5 patients without postrandomization data. It also changed little when the primary model was adjusted for average baseline pain and disease duration. Similarly, the results changed only minimally when we included the 3 patients who had been randomly assigned in error. One patient in the placebo group recorded very low pain scores (mean pain, 0.9 point from 37 measurements). Omitting this patient from the primary analysis reduced the overall treatment effect in favor of placebo by a third (0.17 [CI, −0.30 to 0.64]; P = 0.49).

No evidence was found of any subgroup effects based on disease duration (P = 0.164), sex (P = 0.76), allergy status (P = 0.49), low baseline IgG level (<10 mg/mL; P = 0.193), or Hospital Anxiety and Depression Scale subscores for anxiety (P = 0.37) and depression (P = 0.77) (Table 2 of Supplement 2, available at Annals.org). Weak evidence was found that treatment differs by CRPS type (P = 0.016), with a possible positive effect for patients with type II CRPS (n = 14; 3 patients with “undecided” CRPS type were omitted from this analysis). No statistical evidence was found for a difference in treatment effects among the 7 study sites (P = 0.68); however, we note that this study was not powered for these comparisons (Table 3 of Supplement 2, available at Annals.org).

After treatment, 69 patients (67%) had lower pain scores, and the number of patients with lower scores was similar in both groups: 35 of 53 (66%) in the placebo group and 34 of 50 (68%) in the IVIg group. Four patients—3 in the placebo group and 1 in the IVIg group—achieved 30% pain reduction. In addition to these 4 patients, 1 patient from the placebo group achieved 50% pain reduction.

Secondary Outcomes

At baseline, patients had a very low quality of life and high pain interference, consistent with reports for patients with persistent CRPS (Table 1) (5). The mean quality-of-life score at baseline (EQ-SD-5L) was around 0.33 in both groups. It increased slightly after treatment, to a mean score of 0.37 point (SD, 0.29) for the placebo group and 0.41 point (SD, 0.27) for the IVIg group. The adjusted difference in means was 0.03 (CI, −0.08 to 0.15; P = 0.58). The number of patients with a meaningful improvement—that is, 0.1 point or greater—was similar between groups: 20 of 51 (39%) in the placebo group and 18 of 43 (42%) in the IVIg group. At baseline, the mean score on the Brief Pain Inventory interference subscale was around 7.3 points in both groups; it decreased to 6.89 points (SD, 2.08) for the placebo group and 7.24 points (SD, 1.54) for the IVIg group, and the adjusted difference in means was 0.35 (CI, −0.43 to 1.13; P = 0.38).

Exploratory Outcomes and Open Extension

One patient in the IVIg group stopped receiving analgesic medication, whereas 1 patient in the placebo group, and 3 patients in the IVIg group started receiving it.

A summary of exploratory and open-extension outcomes is given in Tables 4, 5, and 6 of Supplement 2 (available at Annals.org).

Adverse Events

Harms from the study medication in the parallel phase are summarized in Table 3. Two serious adverse events occurred during the blinded phase. One patient receiving placebo had severe headaches and vomiting, and one patient in the IVIg group had severe headaches. Both patients required hospitalization but were discharged the next day and quickly recovered. Open-phase events are detailed in Supplement 2.

Discussion

In this phase 3 RCT, treatment with 2 low doses of IVIg (0.5 g/kg per dose) over 6 weeks had no clinically important effect on the intensity of patients’ pain. In the active group, no patient reported substantial pain reduction, which contrasts with results from previous, smaller studies. We conducted this trial to obtain definitive evidence for low-dose IVIg treatment on the basis of preliminary data indicating efficacy. Immunoglobulin treatment did not reduce pain or improve any of the secondary or exploratory outcomes. We found no predictive marker for a better treatment response among prespecified variables. The small pain reduction in the placebo group is consistent with recent meta-analysis data indicating that patients with persistent CRPS have a relatively stable natural course and only a small placebo effect in clinical trials (19). An English-language MEDLINE search of IVIg treatment for CRPS returned 5 primary reports: 2 case reports, one of which was on high-dose treatment in
acute CRPS (20, 21); our case series (9); our previous RCT (8); and our report on maintenance therapy in 2 patients (22) (overall, n = 25 cases). Each report indicated IVIg efficacy in CRPS. In addition, other authors have highlighted that they have been using IVIg successfully in their patients (23, 24), without providing details. It is not known why the results from the current RCT differ so markedly from those of these earlier studies. Small trials, particularly if associated with only a few primary events, are subject to biases, including selection and exaggeration. The importance of responder analysis to identify predictive factors for a response is evident; however, our results suggest that responders to low-dose IVIg are rare.

Our findings add to the negative evidence for the efficacy of anti-inflammatory treatments for persistent CRPS, including lenalidomide, infliximab, and intrathecal and oral steroids (25–28). Recent in vivo and in vitro studies suggest a role for functionally active, noninflammatory autoantibodies (29–31), indicating that patients might respond to immune therapies that either directly reduce autoantibody plasma levels or target lymphocytes (24, 32–35).

The strengths of our study include its multicenter nature; its sample size for a rare disorder (to our knowledge, this is the largest academic trial in persistent CRPS to date); its recruitment over a prespecified, relatively short period; its successful blinding; and its high level of patient adherence, which resulted in high-quality data, minimizing uncertainty (Table 1 of Supplement 2). The patient demographics were typical for this group, and active and comparator groups were well-balanced. The consistently negative primary and pre-defined secondary end points provide clear, definite evidence that this intervention is not effective in this group.

Limitations include the inapplicability of our data to groups of patients who have had CRPS for more than 5 years or less than 1 year, because these patients were excluded from our study.

Our results do not extend to treatment with full-dose IVIg, such as a 2-g/kg infusion. The use of albumin as a control treatment may have confounded treatment effects because of its possible activity in immune-mediated disorders (36). We chose a very low albumin concentration (0.1%), and the overall placebo response in this trial was low; we infer that our results were not

![Figure 2. Average pain score for each day, by trial group (days 1 to 84).](image)

Values on the y-axis reflect average 24-h scores of pain intensity on the numeric rating scale (0 = “no pain,” 10 = “pain as bad as you can imagine”). Patient numbers for the placebo and IVIg groups, respectively, by time point, are as follows: screening, n = 56 and 52; day 1, n = 49 and 44; day 6, n = 53 and 48; day 22, n = 48 and 45; day 43, n = 46 and 39; and day 84, n = 35 and 27. Screening started a maximum of 21 days before randomization (randomization = day 0). The primary efficacy analysis does not include 5 patients without outcome data. The dashed vertical line marks the end of the parallel, blinded trial. IVIg = intravenous immunoglobulin.

| Table 3. Harms Reported During the Blinded Phase of the Study* |
|-----------------|-----------------|
| **Adverse Event** | **Placebo** | **Low-Dose IVIg** |
|                  | (n = 56) | (n = 52) |
| Death            | -       | -       |
| Withdrawal from study medication because of adverse event | 3 (5) | 3 (6) |
| ≥1 adverse event | 40 (71) | 39 (75) |
| Patients with serious adverse events | 1 (2) | 1 (2) |
| Headache         | -       | 1 (2)   |
| Headache and vomiting | 1 (2) | - |

IVIg = intravenous immunoglobulin.
* Values are numbers (percentages).
substantially confounded by the use of albumin placebo. Our study was not powered to detect any subgroup effects.

In conclusion, in this RCT of 108 patients with CRPS of 1 to 5 years’ duration, once-repeated treatment with low-dose (0.5 g/kg) IVlg over 6 weeks did not reduce pain: No patient experienced more than 50% pain relief while receiving the drug, in contradistinction to results from earlier studies. Alternative analgesic technologies are needed to allow treatment of this often-devastating condition.

From University of Liverpool and The Walton Centre National Health Service (NHS) Foundation Trust, Liverpool; Institute of Psychiatry, Psychology and Neuroscience, Guy’s and St Thomas’ Hospital, and University College London, London; Modepharma Limited, Beckenham; Queen Elizabeth University Hospital, Glasgow; University West of England, Bristol; Swansea University, Swansea; Norfolk and Norwich University NHS Trust, Norwich; Cambridge University Hospitals, Cambridge; and University Hospitals of Leicester NHS Trust, Leicesters, United Kingdom.

Note: The corresponding author and the trial statistician had full access to all the data in the study, and the corresponding author was responsible for the final submission of the publication.

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