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Letters to the Editor

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Immunoglobulin maintenance therapy in long-standing complex regional pain syndrome, an open study

Sir, Complex regional pain syndrome (CRPS) is a post-traumatic limb pain associated with limb-confined sensory, autonomic, motor, skin and bone changes. Its causes are unknown, although recent studies have suggested an autoimmune contribution [1]. We previously reported success of repeated, pain-contingent, low-dose i.v. immunoglobulin treatments in reducing pain in one patient with severe intractable CRPS [2] and in a small, randomized controlled trial (RCT) we found that a single dose of IVIG reduced pain in patients with 6–30 months CRPS duration [3], but the duration of these effects was variable. To support the development of larger trials we investigated the potential long-term efficacy and cost-effectiveness of immunoglobulin treatment.

Between August 2010 and September 2011 we conducted an open, single-centre, proof-of-concept trial (ISRCTN63226217) of immunoglobulin maintenance treatment. Phone follow-up was until 12 months after the final infusion. Eligible patients were 5/12 participants in our earlier RCT, with two or more points less pain after IVIG vs placebo in the RCT [11-point (0–10) numerical rating scale (NRS)] [4], IVIG responders, who now had an on-going pain intensity of NRS 5 or higher. Following ethics approval (University College London/University College London Hospital) and written informed consent, we confirmed Budapest clinical criteria [5] and administered a single dose of 1 g/kg IVIG (the priming dose). In choosing this dose we explored whether doubling the previously applied dose of 0.5 g/kg would achieve additional pain relief. For safety reasons we stipulated that the i.v. treatment dose would revert to 0.5 g/kg should treatment of the first two patients with the 1 g/kg dose result in no better pain relief. Patients receiving important pain relief (>30%) were then trained to self-administer weekly one-quarter of their initial IVIG dose using a s.c. immunoglobulin (16% concentration) at home. Treatment with s.c. immunoglobulin is a patient-preferred treatment option that achieves high trough levels [6]. To gauge the lowest effective maintenance dose we halved the s.c. doses after both 6 and 9 months and reinstated the previous dose if this caused an increase in pain. Patients recorded their average daily pain intensities, quality of life and functional outcomes (Table 1; supplementary Table S1, available at Rheumatology Online). We also measured stimulus-evoked pain with a quantitative sensory test (QST). In accordance with published guidelines, patients were supported by an occupational therapist and a psychologist [7]. Information on the power analysis and statistical analysis is available as supplementary data at Rheumatology Online.

No patient had received immunoglobulin since RCT participation. One patient declined participation and another had developed neoplastic disease and was excluded. Between August 2010 and May 2011 we enrolled three earlier RCT participants. After a protocol change we approached additional patients seen at the study centre over the past 4 years to achieve the required number of four s.c. immunoglobulin-treated patients (supplementary data, power analysis and statistical analysis plan available at Rheumatology Online) and we enrolled one patient in May 2011; however, we stopped ongoing treatments in existing patients and enrolment of new patients in July 2011 after receipt of a post-marketing report of thromboembolic events associated with the s.c. immunoglobulin used (which has since been withdrawn from the UK market). Patients were permitted to use drugs they had remaining at home and the study was stopped thereafter.

Two of the treated patients passed the screening stage and received s.c. immunoglobulin treatment over 12 and 3 months, respectively (patient 1: 1 g/kg/4 weeks × 6 months, followed by 0.5 g/kg/4 weeks × 3 months, and 0.25 g/kg/4 weeks × 3 months; patient 3: 0.5 g/kg/4 weeks × 3 months; supplementary Fig. S1, available at Rheumatology Online). The treatment provided sustained pain reduction and improvements in function, quality of life and QST results (Table 1, supplementary Fig. S1 and supplementary Table S1, available at Rheumatology Online). At follow-up in September 2012, 12 months after their final infusion, these two patients had remained in remission. The other two patients experienced no important beneficial effects. Patients documented mild to moderate adverse reactions (Table 1). Cost-effectiveness calculations are provided in supplementary Table S2, available at Rheumatology Online.

This is, to our knowledge, the first report both of successful maintenance treatment with immunoglobulin and of induction of long-term remission in very long-standing CRPS. Our study was limited by the lack of a control group and its small size. Both responders had concomitant autoimmune diseases (Table 1), but we previously documented good (single-dose) IVIG efficacy in otherwise healthy patients [3]. Although we stopped the study early due to unexpected side effects reported with the drug in other patients (Methods section), similar reports have not emerged with other s.c. products; what renders the used product unique is unknown. We had previously observed no induction of remission in published [2] or unpublished cases, all treated
repeatedly in pain-contingent intervals. It is possible that maintenance of a certain IgG plasma level is required for long-lasting immune modulation, paralleling reports in other disorders [6]. Assuming ongoing pain relief, immunoglobulin treatment was cost effective in our two patients (supplementary Table S2, available at Rheumatology Online). Larger studies are now required to confirm and quantify both the pain-relieving and disease-modifying effects of immunoglobulin maintenance therapy in long-standing CRPS.

**Table 1** Patient demographics, disease characteristics and study outcomes

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex/affected limb(a)</td>
<td>F(b)/L</td>
<td>M(b)/LL</td>
<td>F(b)/U</td>
<td>M/L</td>
</tr>
<tr>
<td>CRPS duration, years</td>
<td>6</td>
<td>5.1</td>
<td>5.2</td>
<td>6.5</td>
</tr>
<tr>
<td>Initial treatment dose, g/kg</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Pain intensity(c)</td>
<td>(7.4); 3.1; 2.3; 2.5</td>
<td>(8.6); 8.2; N/A(^d); N/A(^d)</td>
<td>(6.1); 1.8; 0.3; 0.5</td>
<td>(5.4); 4.4; N/A(^d); N/A(^d)</td>
</tr>
<tr>
<td>EQ-5D(e)</td>
<td>(0.2); 0.6; 0.6</td>
<td>0.2; N/A(^d); N/A(^d)</td>
<td>(0.2); 0.6; 0.7</td>
<td>0.1; N/A(^d); N/A(^d)</td>
</tr>
<tr>
<td>Pain interference(f)</td>
<td>(7.7); 5.7; 1.6</td>
<td>7.1; N/A(^d); N/A(^d)</td>
<td>(6.1); 0; 0.2</td>
<td>7.1; N/A(^d); N/A(^d)</td>
</tr>
<tr>
<td>QST BNRS(g)</td>
<td>(7); 2; 2</td>
<td>(0); N/A(^d); 0</td>
<td>(5); N/A(^h); N/A(^h)</td>
<td>(10); N/A(^d); 7</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Headache, CRPS pain increase (\times) 4 days; moderate itching and swelling 25 cm around infusion sites (\times) 6 months</td>
<td>Headache (\times) 2 days</td>
<td>Headache (\times) 3 days</td>
<td>Mild shortness of breath (\times) 7 days without findings upon hospital admission</td>
</tr>
</tbody>
</table>

Patients’ ages ranged from 43 to 69 years. \(a\)Concomitant disorders: patient 1: psoriatic arthritis on MTX, with mild pain, not affecting the CRPS limb, gluten-sensitive enteropathy, pernicious anaemia; patient 2: smoker; patient 3: relapsing-remitting multiple sclerosis, Ehlers-Danlos II, long-standing pituitary microadenoma; patient 4: hypertension, rosacea; F, female; M, male. \(b\)Former participant in the earlier RCT; L, lower limb; LL, both lower limbs; U, upper limb. \(c\)Pain intensity recorded on an 11-point (0–10) numerical rating scale, with 0 = no pain and 10 = as bad as you can imagine [4]; the baseline value (average pain intensity over 14 days after enrolment) is in brackets, followed by the mean of the entries from the remainder of the trial period (11.5 months in patient 1, 2.5 months in patient 3) and the average pain intensity over the week prior to phone follow-up 12 months after the last s.c. infusion. \(d\)The patient was discharged after the IVIG treatment and did not receive s.c. treatment, therefore no additional data values are available. \(e\)EQ-5D: EuroQol score assessing quality of life in five domains (self-care, mobility, usual activities, pain and discomfort, anxiety/depression) at three levels (no problems, moderate/some problems, severe/extreme problems). The values given were taken at the day of enrolment (in brackets), day 14 after the priming infusion and at the end of the study. \(f\)Pain interference is the previous week’s average pain interference with seven activities of daily living, recorded on an 11-point (0–10) numerical rating scale, with 0 = no interference and 10 = complete interference. The values given were taken at the day of enrolment (in brackets), day 14 after the priming infusion and at the end of the study. \(g\)QST BNRS is the quantitative sensory testing brush allodynia pain score, with pain intensity on a 0/C150 10 numerical rating scale after five repeated gentle strokes with a soft brush over the painful area in 1 s intervals; additional QST results are available upon request from the corresponding author. The values given were taken at the day of enrolment (in brackets), day 14 after the priming infusion and at the end of the study. \(h\)This patient’s repeat QST results were not taken due to scheduling issues. N/A, not applicable.

**Rheumatology key message**

- Low-dose immunoglobulin maintenance treatment induced stable pain reduction in two patients with very long-standing CRPS.

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**Supplementary data**

Supplementary data are available at Rheumatology Online.
have been paid into institutional research funds. All other authors have declared no conflicts of interest.

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Takayasu arteritis in infancy

Sir, A 14-month-old girl was admitted acutely to the cardiac intensive care unit with pulmonary oedema secondary to severe acute aortic regurgitation and mitral regurgitation. She had complaints of persistent cough in the preceding 6 months, but had normal development and growth, including normal ophthalmological assessment, hearing and balance. Echocardiography indicated an inflammatory process, with initial suspicion of aortic root abscess. Urgent cardiac surgery was performed which involved mitral valve repair, aortic root homograft replacement and reimplantation of the left coronary artery. There was no frank pus around the aortic root. Blood cultures were sterile, the CRP was 27 mg/l (reference range <20 mg/l) and the ESR 35 mm/h (reference range <10 mm/h). Extensive infectious workup including syphilis serology and tuberculosis was negative. Histology of the aortic root revealed an inflammatory reaction with plasma cell infiltrate affecting the adventitia (Fig. 1A). The mitral valve leaflet demonstrated fragmented elastic laminae, fibroblast proliferation, increased vascularity and neovascularization with small blood vessels and mixed eosinophilic and plasma cell infiltrate. There was no histological evidence of acute bacterial endocarditis. Magnetic resonance angiography (MRA) and cardiac MRI confirmed the presence of large-vessel vasculitis affecting much of the aortic arch and its major branches, with arterial wall thickening and gadolinium uptake, luminal irregularity and patchy fusiform dilatation extending to the iliac bifurcation (Fig. 1B), confirming the diagnosis of Takayasu arteritis (TA). She was treated with daily oral prednisolone (2 mg/kg per day; with planned taper to 0.2 mg/kg over 4–6 months pending response), weekly s.c. MTX (15 mg/m² per week) and 5 mg/kg per day of aspirin as antiplatelet therapy. She made an excellent clinical recovery following her cardiac surgery and had prompt and complete normalization of her acute phase reactants. Three months later, she attended a routine outpatient appointment and was clinically in remission, with normal ESR and CRP. Two days later, however, she had an out-of-hospital cardiac arrest, requiring cardiopulmonary resuscitation for 30 min. She was transferred back to the cardiac intensive care unit, with recurrent episodes of unstable angina (severe pain and ST depression associated with bradycardia and apnoea). Emergency cardiac catheterization revealed severe stenosis of the reimplanted left coronary artery. Infliximab (6 mg/kg, at weeks 0, 2, 6 and four weekly thereafter) was added to her immunosuppressive therapy, and she received continuous i.v. unfractionated heparin, later converted to clopidogrel. One month after her cardiac arrest, she underwent successful left internal mammary artery bypass graft for stenotic left coronary artery disease. Again she made an excellent and rapid recovery. Five months later, however, she re-presented with transient ischaemic attacks with intermittent weakness affecting her right leg related to an occluded left carotid artery, which was not amenable to angioplasty or stenting. Warfarin was then added in place of clopidogrel, aiming for a therapeutic international normalized ratio of 2–3. MRA 22 months from initial presentation revealed a slender left common carotid and left subclavian artery, but no discrete focal narrowing. There was tapering of the infrarenal abdominal aorta and some stenosis of the superior mesenteric artery, although there were no areas of late gadolinium enhancement, and the aortic wall thickening had resolved. Twenty-four months from her initial presentation, she has been successfully weaned off.