

## LETTER

## An n-of-one RCT for intravenous immunoglobulin G for inflammation in hereditary neuropathy with liability to pressure palsy (HNPP)

### BACKGROUND

Hereditary neuropathy with liability to pressure palsy (HNPP; tomaculous neuropathy) is a rare autosomal dominant disorder caused by a loss of function of the peripheral myelin protein 22 gene (*PMP22*; OMIM #601097) for which no curative treatment exists. Symptoms consist of recurrent painless episodes of focal sensory loss and muscle weakness, which are often provoked by nerve compression and resolve spontaneously within days to months.<sup>1</sup> In this report, we describe the case of a female patient with HNPP who initially presented with symptoms of a painful neuropathy which were successfully treated with intravenous immunoglobulin G (IVIg), and the results of a double-blind, placebo-controlled n-of-one trial to assess the effectiveness of IVIg in this patient.

In 2002, a 35-year-old female patient presented with a 15-month history of neuropathic pain in the right leg, and recurring episodes of weakness and sensory loss in the legs which resolved spontaneously after several weeks. Her medical and family history was unremarkable. Physical examination showed mild proximal weakness of the left leg (Medical Research Council (MRC) grade 4), severe weakness of the left foot extensors (MRC 0–2), hypoalgesia of the left hand and lower leg, and reduced tendon reflexes with absent Achilles reflexes. All additional investigations were normal, except electromyographic (EMG) studies which showed bilateral demyelinating conduction blocks at ulnar nerve compression sites, prolonged distal motor latencies of the ulnar, tibial, peroneal and median nerves, and absent F-waves in peroneal and right tibial nerves, consistent with HNPP, but also with definite electrodiagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) according to current European Federation of Neurological Societies/Peripheral Nerve Society guidelines.<sup>2</sup> A preliminary diagnosis of CIDP was made and a DNA test for suspected HNPP was ordered.

She was treated with IVIg (0.4 mg/kg/day) for 5 days followed by maintenance doses every 3 weeks, which led to improvements in muscle strength and resolution of pain. DNA analysis subsequently showed a deletion of 17p11.2 including the *PMP22* gene, and a definite diagnosis of HNPP was made, questioning the need for continued IVIg treatment. The patient consented to participate in a double-blind, placebo-controlled n-of-one trial to assess whether IVIg infusions led to a clinically meaningful reduction in pain and increase in muscle strength, and to establish whether maintenance treatment with IVIg was necessary. We provide a summary of this trial, and the full research report is available as online supplementary material 1.

### METHODS

During the 15-week n-of-one trial, IVIg (0.4 mg/kg) and placebo (0.9% saline) “trial” infusions (wrapped in tin foil for patient and investigator blinding) were administered in a random sequence which was generated by the dispensing hospital pharmacy. A week after each trial infusion, we offered an optional “rescue infusion” with the opposite treatment to ensure that potentially beneficial treatment would not be withheld for longer than a week. The interval between the last infusion (trial or rescue) and the next trial infusion was held constant at 3 weeks. Pain in the right leg and self-reported muscle strength of the left leg were scored three times per week on a 14 cm visual analogue scale (VAS; 0: ‘absence of pain’ or ‘paralysis’ to 14: ‘worst possible pain’ or ‘normal strength’). Clinically meaningful effects were defined as at least 30% reduction in pain compared with baseline,<sup>3</sup> and 30% increase in muscle strength. Side effects were also recorded.

IVIg and placebo scores across the first 7 days following trial infusions were compared to determine the effects on pain and muscle strength. We evaluated the course of pain and muscle strength over 3 weeks following IVIg infusions to assess the need for continued IVIg. Coefficients were calculated in SPSS V20, followed by Bayesian evaluation of informative hypotheses and calculation of Bayes factors using Bayesian evaluation of inequality constrained hypotheses for general statistical models (BIG),<sup>4</sup> with Bayes factors larger than 10 denoting strong support for a hypothesis.<sup>5</sup> Details of the analyses and the data archive are provided in online supplementary materials 2 and 3.

### RESULTS

The patient received four trial infusions (3 placebo, 1 IVIg) and requested three rescue infusions (all IVIg, after each placebo infusion). The trial’s timeline and VAS scores for pain and muscle strength are shown in [figure 1](#), demonstrating a beneficial effect of IVIg on both outcomes. Statistical testing showed strong support for the hypotheses that pain decreases (Bayes factor 63.74) and muscle strength increases (Bayes factor 61.51) more rapidly and to a clinically meaningful extent after IVIg compared with placebo. We also found strong support for the hypotheses that pain first decreases and then increases again (Bayes factor 13.78), and that muscle strength first increases and then decreases (Bayes factor 15.67) over 3 weeks following IVIg, which supported the need for continued IVIg infusions. No adverse effects were reported.

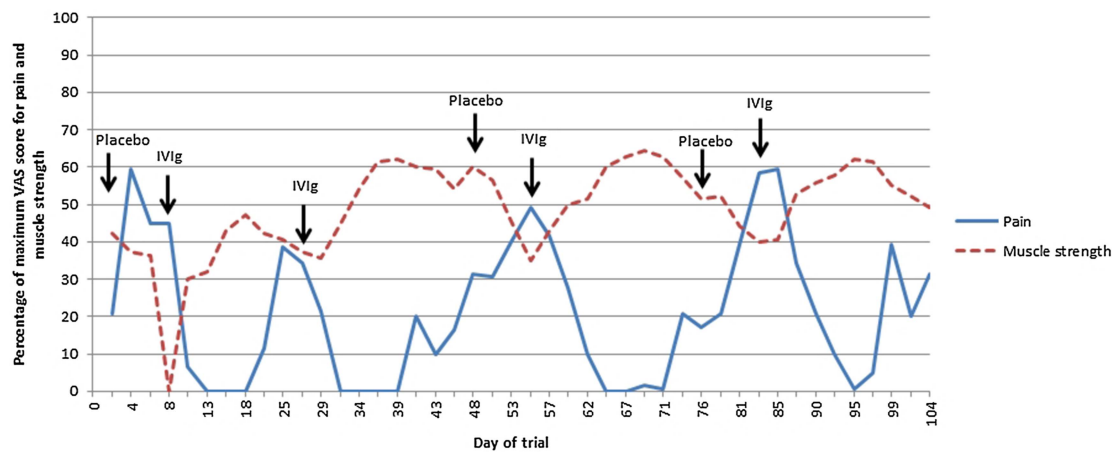
### Follow-up

During 12 years of follow-up, the interval for IVIg infusions was successfully increased to 5 weeks with a sustained clinical response. Follow-up EMGs (2003–2014) initially showed signs of demyelination (prolonged distal motor latencies and decreased nerve conduction times), but over the years became more consistent with stable axonal damage. The patient’s quality of life has remained stable.

### DISCUSSION

This case suggests that hereditary neuropathies may coexist with immune-mediated neuropathies. The conditions may be difficult to distinguish, because their clinical presentation may be similar, and electrophysiology or nerve biopsy studies can be unhelpful in establishing inflammatory demyelinating disease when demyelination is already present due to hereditary disease. Moreover, current diagnostic guidelines consider the presence of a hereditary demyelinating neuropathy as a diagnostic exclusion criterion for CIDP,<sup>2</sup> although several case reports for HNPP and other hereditary demyelinating neuropathies suggest otherwise.<sup>6–10</sup> Pain is atypical in hereditary neuropathies and its presence may therefore indicate coexisting inflammation. N-of-1 trials to assess the effects of immunomodulatory treatment may also help establish a diagnosis of coexisting inflammation and guide treatment for individual patients.<sup>11</sup>

In conclusion, this report suggests that some patients with hereditary neuropathies may have coexisting inflammation



**Figure 1** Trial timeline, administered infusions and VAS scores for pain and subjective muscle strength (IVIg, intravenous immunoglobulin G; VAS, visual analogue scale).

and demonstrates the importance of its timely recognition, because adequate immunomodulatory treatment can considerably improve patients' symptoms and quality of life.

Charlotte Vrinten,<sup>1,2</sup> Xin Gu,<sup>3</sup> Stephanie S Weinreich,<sup>1</sup> Mirjam H Schipper,<sup>4,5</sup> Judith Wessels,<sup>6</sup> Michel D Ferrari,<sup>4</sup> Herbert Hoijtink,<sup>3</sup> Jan J G M Verschuuren<sup>4</sup>

<sup>1</sup>Community Genetics, Department of Clinical Genetics, EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands

<sup>2</sup>Health Behaviour Research Centre, Department of Epidemiology and Public Health, University College London, London, UK

<sup>3</sup>Department of Methodology and Statistics, Utrecht University, Utrecht, The Netherlands

<sup>4</sup>Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

<sup>5</sup>Department of Neurology, Medical Centre Haaglanden, The Hague, The Netherlands

<sup>6</sup>Department of Clinical Pharmacology and Toxicology, Leiden University Medical Center, Leiden, The Netherlands

**Correspondence to** Charlotte Vrinten, Health Behaviour Research Centre, Department of Epidemiology and Public Health, University College London, Gower Street, London WC1E 6BT, UK; [c.vrinten@ucl.ac.uk](mailto:c.vrinten@ucl.ac.uk)

**Contributors** JJGMV, JW and MDF conceived the study and carried out the data collection. JJGMV, CV, SSW, HH and XG formulated the informative hypotheses which were evaluated by HH and XG. JJGMV and CV drafted the manuscript, with assistance from MHS. All authors commented on earlier versions of the manuscript and consented to submission of the final draft.

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**Data sharing statement** The data analyses and data archive for this study are made available as online supplementary materials 2 and 3.



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Charlotte Vrinten, Xin Gu, Stephanie S Weinreich, Mirjam H Schipper, Judith Wessels, Michel D Ferrari, Herbert Hoijtink and Jan J G M Verschuuren

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