EXPERT REVIEWS

Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy: the ICE trial

Expert Rev. Neurother. 9(6), 789–795 (2009)

Richard AC Hughes
Department of Clinical Neuroscience, Institute of Psychiatry, King's College London, London SE5 8AF, UK
Tel.:+ 44 207 848 5435
Fax: +44 207 848 5440
richard.a.hughes@kcl.ac.uk

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a potentially disabling autoimmune disease causing progressive or relapsing–remitting weakness with or without sensory loss. Previous small trials demonstrated short-term benefit from intravenous immunoglobulin (IVIg), and international guidelines recommend IVIg as an option. However, evidence had been insufficient to persuade authorities to approve IVIg for use in CIDP. This article aims to review the Immune Globulin Intravenous CIDP Efficacy (ICE) trial, which was a randomized, double-blind, placebo-controlled, response-conditional crossover trial of Gamunex® (intravenous immunoglobulin, 10% caprylate/chromatography purified). With 117 participants, it is the largest treatment trial ever conducted in CIDP. The results showed unequivocal short- and long-term benefit from IVIg in confirmation of previous reports. The trial also showed for the first time that continued IVIg infusion 1 g/kg every 3 weeks protected participants from relapse. Adverse events were mostly mild and serious adverse events were not more common with IVIg than with placebo. The results persuaded the US FDA and Health Canada to approve Gamunex for use in CIDP.

Keywords: chronic inflammatory demyelinating polyradiculoneuropathy • intravenous immunoglobulin • randomized, controlled trial

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an uncommon disease, usually causing relapsing and remitting or progressive weakness of the limbs with loss of the tendon reflexes and impairment of sensation. It affects people of all ages but is more common in the elderly and in men than women. In a recent epidemiological study in Italy, which used very strict diagnostic criteria [1], annual incidence was 0.36 and prevalence was 3.6 individuals per 100,000, respectively [2]. Other reports of prevalence have suggested estimates between 1.2 and 7.7 individuals per 100,000, but the diagnostic criteria and methods for capturing cases have varied so that there is no reliable evidence for variation between different geographical areas. There is no absolute diagnostic test, so that diagnosis depends on a combination of clinical and neurophysiological features. In particular, neurophysiological tests have to show evidence of demyelination consisting of slowing of motor nerve conduction, dispersion of the compound muscle action potential (CMAP) or partial conduction block. The criteria used in the Italian epidemiological study were originally derived for research purposes and were very strict [1]. Diagnostic criteria with less stringent neurophysiological criteria have been agreed upon by an international committee [3] and their use would be likely to identify more patients who would benefit from treatment.

The cause of CIDP is not known, but the histological appearances of active lesions resemble those of experimental autoimmune neuritis, showing endoneurial release of inflammatory mediators, deposition of complement, and infiltration by T cells and macrophage-associated demyelination. These appearances and the short-term responses to immunosuppression have led to the conclusion that CIDP is an autoimmune

 10.1586/ERN.09.30 ISSN 1473-7175

disease [4]. No single autoantigen has been discovered, but in 20% of patients there is evidence of antibodies to P0, the major peripheral nerve myelin glycoprotein. This protein is one of the antigens capable of inducing experimental autoimmune neuritis and is the target of the immune response in immunodeficient, nonobese diabetic mice with spontaneous inflammatory neuropathy [5–8].

Consensus guidelines from an international committee propose corticosteroids and intravenous immunoglobulin (IVIg) as first-line treatments with plasma exchange as an additional treatment option [3]. These treatments are not always adequate, and approximately 30% of patients are resistant to them [3]. Other immunosuppressive agents, such as azathioprine, methotrexate and cyclophosphamide, are often added, and the consensus view was that such treatments are justified [3], although there is no evidence from randomized controlled trials to support their use [9]. Despite treatment, 32% of patients were moderately or severely disabled on the prevalence day in the Italian epidemiological study [2].

Background & rationale of the ICE trial

The original rationales for using IVIg in CIDP were its multiple actions on the immune system: providing anti-idiotypic antibodies, blocking macrophage Fc receptors, inhibiting complement activity, and modulating central B- and T-cell function [10]. IVIg had been shown to be effective in the animal model of inflammatory neuropathy, experimental autoimmune neuritis, in two out of three studies [11–13]. Significant benefit from IVIg in CIDP had already been reported in two out of four placebo-controlled studies of altogether 113 patients [14–17]. A Cochrane review calculated a significantly higher relative rate of short-term improvement in disability (3.17, 95% CI: 1.74–5.75) [18]. However, none of the trials had addressed the issue of long-term benefit from IVIg and no IVIg product was licensed for use in CIDP, or any other neuromuscular disease, by the US FDA.

Study design

The Immune Globulin Intravenous CIDP Efficacy (ICE) trial was a randomized, double-blind, placebo-controlled, response-conditional crossover study of the IVIg product Gamunex® (immune globulin intravenous, 10% caprylate/chromatography purified [IGIV-C]; Talecris Biotherapeutics, Inc, Research Triangle Park, NC, USA) [19]. The participants had to have a diagnosis of CIDP made by a neurologist specialized/experienced in neuromuscular diseases with progressive or relapsing motor dysfunction of more than one limb for more than 2 months before trial entry. They had to meet the inflammatory neuropathy cause and treatment (INCAT) neurophysiological criteria for CIDP [20], confirmed by a central review committee. They were required to not be taking corticosteroids or only to be taking them in a dose not greater than the equivalent of prednisone 10 mg daily, and not to be taking IVIg or other immunotherapy. They had to have significant disability defined by an overall INCAT score of 2–9 (**Box 1**) [20]. If the INCAT disability score was only 2, the score had to be derived from leg disability only. During the initial period of the trial, participants received IGIV-C or placebo every 3 weeks for up to 24 weeks. In this period, participants who did not show an INCAT score improvement of 1 point within 6 weeks received the alternate treatment (response conditional crossover). The first dose was 2.0 g/kg and subsequent doses were 1.0 g/kg. The primary

Box 1. Inflammatory neuropathy cause and treatment disability score.

Arm disability

- Subjects were questioned and graded in their ability (not affected vs affected, but not prevented vs prevented) to do the following:
  - Do and undo zippers and buttons
  - Wash or brush hair
  - Use knife and fork together
  - Handle (pick up) small coins
- Classifications:
  - 0 = No upper limb problems
  - 1 = Minor symptoms, in one or both arms, not affecting the ability to perform any of the following functions: doing all zips and buttons; washing or brushing hair; using a knife and fork together; handling small coins
  - 2 = Disability, in one arm or both arms, affecting but not preventing any of the above mentioned functions
  - 3 = Disability, in one arm or both arms, preventing one or two of the above mentioned functions
  - 4 = Disability, in one arm or both arms, preventing three or all of the functions listed, but some purposeful movements still possible
  - 5 = Inability to use either arm for any purposeful movement

Leg disability

- Classifications:
  - 0 = Walking not affected
  - 1 = Walking affected, but walks independently outdoors
  - 2 = Usually uses unilateral support (stick, single crutch, one arm) to walk outdoors
  - 3 = Usually uses bilateral support (sticks, crutches, frame, two arms) to walk outdoors
  - 4 = Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps
  - 5 = Restricted to wheelchair, unable to stand and walk a few steps with help

The overall 10-point INCAT disability score was the sum of arm and leg disability

outcome was the percentage of participants who maintained an improvement from baseline in adjusted INCAT disability score of 1 point or more until week 24.

In an extension phase, participants who showed an improvement in the initial or crossover periods and completed 24 weeks of treatment were eligible to be randomly reassigned to IVIg or placebo for an additional 24 weeks.

Data analysis

Analysis was conducted by intention-to-treat. During the first period, responders were those who completed the 24 weeks without crossing over and maintained improvement of one adjusted INCAT disability score point or more until week 24. The adjusted score was identical to the INCAT disability score except for the exclusion of changes in upper limb function from 0 (normal) to 1 (minor symptoms) or from 1 to 0, which were not considered clinically important. For those participants who crossed over, responders were those who likewise maintained improvement of one adjusted INCAT disability score point or more until week 24, or until the last assessment in the case of earlier withdrawal. The difference between the treatment groups in proportions of nonresponders was evaluated with a χ^2 test ($\alpha = 0.05$, 2-sided).

Secondary efficacy outcomes in the first treatment period were mean change from baseline in maximum grip strength at end point and mean change from baseline in the CMAP amplitude after stimulation of the most severely affected motor nerve at the proximal site at end point. For these measures, the analysis used a last observation carried forward approach, and treatment differences were compared by analyses of covariance adjusted for geographic region and baseline measurement.

In the extension phase, the secondary efficacy outcome was time to relapse by 1 INCAT disability score point compared with the time of entry into the extension phase. Kaplan-Meier estimates and the log-rank test were used to compare the treatment differences for time to relapse.

Results

Efficacy

In total, 59 participants were initially randomized to receive IVIg and 58 to placebo. There were proportionally fewer men in the IVIg group (53%) compared with the placebo group (79%). The average ages were 53 years in the placebo and 50 years in the IVIg group, and other demographic features and measures of disability and impairment were well balanced.

The results are summarized in Table 1. During the first period, in the analysis of the primary outcome, 32 participants (54.2%) who received IVIg were responders compared with 12 participants (20.7%) who received placebo (difference 33.5%, 95% CI: 15.4–51.7; p = 0.0002). In support of this result, during the crossover period, the adjusted INCAT disability score improved by at least 1 point in 26 out of 45 patients (57.8%) treated with IVIg and in five out of 23 patients (21.7%) treated with placebo (p = 0.005). Some of the participants had received IVIg before entry into the trial. There were significantly more responders regardless of whether they had received IVIg in the past: among those who had received IVIg before, 12 out of 20 (60%) who received IVIg in the first treatment period responded compared with 0 out of 12 (0%) who received placebo (p = 0.0006); similarly, among those naive to IVIg, 20 out of 39 (51%) who received IVIg in the first treatment period responded compared with 12 out of 46 (26%) who received placebo (p = 0.024).

During the first treatment period, there was also a significant improvement in one of the secondary outcomes – grip strength of the dominant hand improved by 10.9 kPa (95% CI: 4.6–17.2) more in the IVIg than the placebo group (p = 0.0008) and in the non-dominant hand by 8.6 kPa (2.6–14.6; p = 0.005). There were no significant differences in the other secondary outcome measures, the mean change from baseline to end point in the CMAP amplitude after stimulation of the most severely affected motor nerve at the proximal site. However, in subsequent analyses, there was a significant improvement in the average of the mean change from baseline in the CMAP amplitude after stimulation of motor nerves [21]. There were also significantly greater improvements in the IVIg group than the placebo group in strength measured with the Medical Research Council sum score, in sensation measured with the INCAT sensory sum score and in the physical component summary score of the Short-Form 36 quality of life scale [19,22].

The extension phase tested 57 participants who received IVIg and responded to it during the initial or crossover periods: 31 were randomly reassigned to continue receiving IVIg and 26 were switched to placebo. For the third secondary outcome measure, the participants continuing to receive IVIg had a significantly

Table 1. Results of the Immune Globulin Intravenous CIDP Efficacy trial.

Period	Intravenous immunoglobulin	Placebo	Difference	p-value
First period response	32/59 (54.2%)	12/58 (20.7%)	33.5%	p = 0.0002
First period; dominant hand change in grip strength from baseline kPa. Mean (SD)	13.2 (19.3%)	1.5 (15.6%)	10.9 (95% CI: 4.6–17.2)	p = 0.0008
First period; non-dominant hand change in grip strength from baseline kPa. Mean (SD)	13.3 (17.4%)	4.3 (14.9%)	8.6 (95% CI: 2.6–14.6)	p = 0.005
Response conditional crossover (rescue) period response	26/45 (57.8%)	5/23 (21.7%)	36.0%	p = 0.005
Extension phase relapse	4/31 (12.9%)	11/26 (42.3%)	29.4%	p = 0.012

CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy; SD: Standard deviation.

longer time to relapse than those receiving placebo (p = 0.011). The probability of relapse was 13% on IVIg compared with 45% on placebo (hazard ratio = 0.19; 95% CI: 0.05–0.70).

Safety & tolerability

The safety population consisted of 113 participants exposed to IVIg and 95 patients exposed to placebo. Since on average the participants continued on IVIg much longer than placebo, there were 1096 IVIg and 575 placebo infusions. Most adverse events associated with IVIg were mild and the most common drug-related events were headache (4.0% of infusions vs 1.2% of placebo infusions) and pyrexia (2.4% of infusions versus none with placebo infusions). Serious adverse events were reported with 0.8% of IVIg and 1.9% of placebo infusions. Serious adverse events thought to be possibly drug related with IVIg occurred in three participants and were pulmonary embolism, pyrexia and headache, and headache and vomiting. Serious adverse events thought possibly drug-related with placebo also occurred in three participants and were asthma, stroke and deep vein thrombosis. With one exception, moderate bronchopneumonia in a participant who had received IVIg, serious adverse events resolved by the end of the trial: this serious adverse event was not considered related to the study drug. Of the 1096 IVIg infusions, 227 were given as loading doses and of the 575 placebo infusions, 182 were given as loading doses. A loading dose (2 g/kg) was given only at the first visit in the first treatment period or the response conditional crossover period. There was no loading dose in the extension period. The loading dose was to be given over 2–4 days depending on individual tolerability. More than 80% of the loading doses were given over 2 days (87% for IVIg and 83% for placebo) rather than the 5 days commonly used in practice. According to the protocol, the maintenance dose (1 g/kg) was to be administered over 1–2 days. More than 80% of maintenance infusions (89% for IVIg and 91% for placebo) were administered within 1 day.

Conclusion

The trial strongly endorsed the overall conclusion from previous trials, summarized in the earlier Cochrane review [18], that in the short term IVIg reduces disability and impairment in people with CIDP of moderate or greater severity. More importantly, it showed for the first time that continued treatment with IVIg every 3 weeks helps to maintain remission, because without such treatment patients are significantly more likely to relapse.

Fortunately, these benefits were achieved with a low rate of adverse events, and serious adverse events were not more frequent than with placebo infusions.

Expert commentary

The ICE trial sponsors were successful in recruiting 33 centers on four continents and in enrolling almost twice the number of participants achieved by any other trial of CIDP. This meant that the power of the study was adequate to detect clinically important effects. The trial design and conduct ensured that the results would have a low risk of bias. It had a placebo-controlled design in which the placebo infusions contained albumen so as to appear identical to the IVIg infusions. Allocation was concealed, and the participants and staff were blinded to the nature of the infusions, including during the crossover and extension phases. The staff of each center received training in data collection methods, and data collection was conducted under FDA Good Clinical Practice guidelines. Discontinuations owing to reasons other than nonresponse/relapse were low: five out of 59 on IVIg and four out of 58 on placebo in the initial treatment or response conditional crossover periods, and none out of 43 on IVIg and four out of 31 on placebo in the extension phase. Owing to the low risk of bias and the concordance with previous trial results, we can be confident that at least this IVIg product is efficacious in reducing disability in the short term and, if given every 3 weeks, in maintaining remission. The trial provided the strongest evidence available of the efficacy of IVIg in CIDP and led to the 2008 approval in the USA and Canada of IGIV-C for the treatment of CIDP to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.

The incidence of adverse events with this IVIg product was reassuringly low, but we should not lose sight of the fact that randomized controlled trials are usually too small or too short in duration to capture infrequent serious adverse events. Serious adverse events with different IVIg products are well recognized and include renal failure, stroke, exfoliative dermatitis and allergic reactions [23]. There is also a theoretical risk of transmitting infections with viral, prion or unknown infections, although the safety record in this respect of currently licensed preparations is excellent.

More research is needed to determine the best initial treatment. The alternatives are corticosteroids and plasma exchange. The trials comparing IVIg with these treatments were too small and too short to show equivalence to anything except the most important differences [20]. The inconvenience and limited availability of plasma exchange make it an unlikely choice. The convenience and simplicity of corticosteroids commend their use. Many experts prefer IVIg as the initial treatment because of the concern about the side effects of corticosteroids. In patients without contraindications to corticosteroids, other experts start corticosteroids but switch to IVIg in case of poor response or severe side effects. Corticosteroids may be inappropriate in patients with pure motor CIDP who have been reported to worsen with corticosteroids. Further trials to investigate the efficacy of corticosteroids and to compare them with IVIg are in progress. More research is also needed to discover the optimum dose and dose frequency. The 3-week dose frequency selected for this trial reflected the average half-life of IgG in the circulation; however, its half-life is variable and it is common experience that the dose interval has to be selected empirically on an individual basis.

The major drawback of IVIg, and one that stands in the way of it being regarded without question as the treatment of choice in CIDP, is its cost. The Medicare reimbursement rate for IVIg is US$67–70/g. At the higher rate, the cost of a 2.0 g/kg course for a 70 kg patient followed by 1.0 g/kg every 3 weeks for a year would be approximately US$88,000 in the USA. The principal competing treatment is corticosteroids, which are offered as an alternative initial and maintenance treatment option by an

international treatment guideline [3]. The one published cost–effectiveness comparison suggested that IVIg would only become cost effective compared with prednisolone if a quality-adjusted life year was valued at €250,000 [24]. However, this estimate was based on a short-term trial, and inclusion of the costs of the harmful long-term side effects of corticosteroids might dramatically alter this calculation. Further cost–effectiveness studies will be important in future research.

It is not clear how long treatment should be continued. If the fact that 55% of participants randomized to placebo in the extension phase during follow-up did not relapse is reflected in practice, then more than half of those with CIDP treated with IVIg every 3 weeks may enter remission and not need continued treatment. However, nearly half do, and it is good practice to reduce the dose of IVIg or withhold it periodically in patients who are on chronic treatment to determine whether they still need it. During the dose reduction or withdrawal phase, great care must be taken to observe the patient closely with serial observations of disability and impairment the same as or similar to those used in the ICE trial and to reinstitute treatment rapidly when its need has been demonstrated by objective deterioration. The judgments are difficult and require experience and trust between physician and patient.

A small but important practical point is that the ICE trial generally used a 2-day infusion period for infusing the loading dose of IVIg rather than the commonly used 5-day period, and a 1-day infusion period for the maintenance dose. The shorter treatment period allows worthwhile reductions in administration costs and is preferable to patients.

Future research is needed to discover biological tests for CIDP, which will allow its diagnosis without reliance on arbitrary clinical and neurophysiological criteria; to identify criteria which will identify responders to IVIg; to develop outcome measures with optimal biometric properties that are more responsive than those in current usage and allow accurate measurement of disease course in clinical practice and clinical trials; to investigate the optimal dose for inducing remission and similarly the optimal dose and dose interval for maintaining remission; and finally to develop non-toxic, less expensive and more convenient immunotherapies that reduce or avoid the need for IVIg.

Five-year view

My expectation is that within 5 years other IVIg products will be demonstrated to be efficacious in CIDP. The initial dose of 2.0 g/kg given over 2 days will likely remain, but we will have better information about the optimal maintenance frequency and dose of IVIg. The frequency is likely to be slightly longer than the 3 weeks used in the ICE trial, most commonly 4 weeks. However, both the dose and the frequency will be recognized as needing to be individualized, with rare patients needing as much as 2.0 g/kg weekly and most patients needing approximately 1.0 g/kg every 4 weeks. There is likely to be a move from intravenous to subcutaneous administration, which has already begun [25] and will be facilitated by the development of more concentrated subcutaneous immunoglobulin products. Owing to the multiple mechanisms of action of IVIg and likely multiple mechanisms of pathogenesis of CIDP, I do not anticipate that IVIg will be replaced by any component of it. The use of highly effective complement-inhibiting compounds, such as eculizumab, is of potential interest in view of the possible role of complement and complement-fixing antibodies in CIDP [26]. Although initial attempts to reduce the need for IVIg with low-dose methotrexate have been unsuccessful [27], I anticipate that further trials of larger doses of methotrexate or other agents such as azathioprine or alemtuzumab will be shown to be efficacious and will be used to reduce the need for IVIg once remission has been achieved with IVIg, corticosteroids or a combination of both [28]. In fact, the development of combination treatments with induction of remission by a combination of IVIg and other agents would be a very worthwhile topic of research. These advances will only be achieved with an international effort, which the Inflammatory Neuropathy Consortium seeks to provide [101].

Financial & competing interests disclosure

Richard Hughes has received hospitality, honoraria for speaking and consultancy fees from Talecris, the company which produces Gamunex, and was a member of the steering committee of the trial reviewed in this article. Professor Hughes has also acted as a consultant or received hospitality and honororia for speaking for the following other companies which produce IVIg: Baxter, CSL Behring, Kedrion, LFB and Octapharma. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing assistance was utilized in the production of this manuscript. The content of the paper was checked by staff employed by Talecris, the company which produces Gamunex which was the immunoglobulin product tested in the trial reviewed in this article.

Information resources

- Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. *JAMA* 291, 2367–2375 (2004).
- Eftimov F, Winer JB, Vermeulen M, de Haan, R, van Schaik I. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst. Rev.* (1), CD001797 (2009).
- Hughes RA, Donofrio P, Bril V *et al.* Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. *Lancet Neurol.* 7, 136–144 (2008).
- Köller H, Kieseier BC, Jander S, Hartung HP. Chronic inflammatory demyelinating polyneuropathy. *N. Engl. J. Med*. 352(13), 1343–1356 (2005).
- Joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy. *J. Peripher. Nerv. Syst*. 10, 220–228 (2005) Available at www.pnsociety.com/Guidelines_CIDP.pdf

Key issues

- The Immune Globulin Intravenous Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) Efficacy (ICE) trial randomized 117 participants with CIDP to immune globulin intravenous, 10% caprylate/chromatography purified or to placebo for 24 weeks and is the largest randomized controlled trial conducted in CIDP.
- During the first period, 32 out of 59 (54%) participants on intravenous immunoglobulin were responders compared with 12 out of 58 (21%) participants on placebo (difference 33.5%; p = 0.0002).
- During the response-conditional crossover period, 26 out of 45 participants (58%) on intravenous immunoglobulin (IVIg) and five out of 23 patients (22%) on placebo responded (p = 0.005).
- After 24 weeks, participants who had responded in the first or crossover periods were re-randomized: 31 were reassigned to IVIg and 26 were reassigned to placebo. The participants on IVIg had a significantly longer time to relapse than those on placebo (p = 0.011), and relapse occurred in 13% of 31 participants on IVIg compared with 45% of 26 on placebo.
- Adverse events were mostly mild and serious adverse events were not more common with IVIg than with placebo.
- The trial results endorse IVIg as a first-line treatment option for CIDP and led to the approval by the US FDA and Health Canada of Gamunex® for the treatment of CIDP to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 *Ad Hoc* Subcommittee of the American Academy of Neurology AIDS Task Force. Research criteria for the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). *Neurology* 41, 617–618 (1991).

• **The first and strictest set of diagnostic guidelines for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).**

2 Chiò A, Cocito D, Bottacchi E, Buffa *et al.* Idiopathic chronic inflammatory demyelinating polyneuropathy: an epidemiological study in Italy. *J. Neurol. Neurosurg. Psychiatry* 78, 1349–1353 (2007).

• **Most recent and most comprehensive high quality epidemiological study of CIDP.**

3 Joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. European Federation of Neurological Societies/ Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy. *J. Peripher. Nerv. Syst.* 10, 220–228 (2005).

•• **Consensus guidelines for diagnosis and management of CIDP.**

4 Köller H, Kieseier BC, Jander S, Hartung HP. Chronic inflammatory demyelinating polyneuropathy. *N. Engl. J. Med.* 352, 1343–1356 (2005).

• **Modern summary of the pathogenesis, diagnosis and management of CIDP.**

5 Salomon B, Rhee L, Bour-Jordan H *et al.* Development of spontaneous autoimmune peripheral polyneuropathy in B7–2-deficient NOD mice. *J. Exp. Med.* 194, 677–684 (2001).

6 Hughes RA, Allen D, Makowska A, Gregson NA. Pathogenesis of chronic inflammatory demyelinating polyradiculoneuropathy. *J. Peripher. Nerv. Syst.* 11, 30–46 (2006).

7 Yan WX, Archelos JJ, Hartung HP, Pollard JD. P0 protein is a target antigen in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann. Neurol.* 50, 286–292 (2001).

8 Sanvito L, Makowska A, Mahdi-Rogers M *et al.* Humoral and cellular immune responses to myelin protein peptides in chronic inflammatory demyelinating polyradiculoneuropathy. *J. Neurol. Neurosurg. Psychiatry* 80(3), 333–338 (2009).

9 Hughes RA, Swan AV, van Doorn PA. Cytotoxic drugs and interferons for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst. Rev.* 4, CD003280 (2004).

• **Cochrane systematic review of the evidence for immunosuppressive drugs in CIDP: an update is in press.**

10 Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. *JAMA* 291, 2367–2375 (2004).

• **Review of the evidence and mechanisms of action of intravenous immunoglobulin in neuromuscular disease.**

11 Enders U, Toyka KV, Hartung HP, Gold R. Failure of intravenous immunoglobulin (IVIg) therapy in experimental autoimmune neuritis (EAN) of the Lewis rat. *J. Neuroimmunol.* 76, 112–116 (1997).

12 Gabriel CM, Gregson NA, Redford EJ, Davies M, Smith K, Hughes RAC. Human immunoglobulin ameliorates rat experimental autoimmune neuritis (EAN). *Brain* 120, 1533–1540 (1997).

13 Lin HH, Spies JM, Lu JL, Pollard JD. Effective treatment of experimental autoimmune neuritis with human immunoglobulin. *J. Neurol. Sci.* 256, 61–67 (2007).

14 Vermeulen M, van Doorn PA, Brand A, Strengers PF, Jennekens FG, Busch HF. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study. *J. Neurol. Neurosurg. Psychiatry* 56, 36–39 (1993).

15 Hahn AF, Feasby TE. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy: a double-blind placebo-controlled crossover study. *Ann. Neurol.* 32, 294–295 (1992).

16 Mendell JR, Barohn RJ, Freimer ML *et al.* Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 56, 445–449 (2001).

17 Thompson N, Choudhary P, Hughes RA, Quinlivan RM. A novel trial design to study the effect of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. *J. Neurol.* 243, 280–285 (1996).

18 van Schaik I, Winer JB, De Haan R, Vermeulen M. Intravenous immunoglobulin for chronic inflammatory demyelinating

polyradiculoneuropathy. *Cochrane Database Syst. Rev.* 2, CD001797 (2002).

- **The Cochrane review on which the Immune Globulin Intravenous CIDP Efficacy (ICE) trial was based. This has been updated: see information resources.**

19 Hughes RA, Donofrio P, Bril V *et al.* Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. *Lancet Neurol.* 7, 136–144 (2008).

•• **The trial discussed in this report.**

20 Hughes RAC, Bensa S, Willison HJ *et al.* Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann. Neurol.* 50, 195–201 (2001).

21 Bril V, Katzberg H, Donofrio P *et al.* Electrophysiology in CIDP: results of a clinical treatment trial with IGIV. *Muscle Nerve* 39(4), 448–455 (2009).

- **More results from the ICE trial.**

22 Merkies ISJ, Bril V, Dalakas MC *et al.* Health-related quality-of-life improvements in CIDP with immune globulin IV 10%: The ICE Study. *Neurology* 72(15), 1337–1344 (2009).

- **More results from the ICE trial.**

23 Dalakas MC, Clark WM. Strokes, thromboembolic events, and IVIg: rare incidents blemish an excellent safety record. *Neurology* 60, 1736–1737 (2003).

- **Important reminder of rare serious adverse events with intravenous immunoglobulin.**

24 McCrone P, Chisholm D, Knapp M *et al.* Cost-utility analysis of intravenous immunoglobulin and prednisolone for chronic inflammatory demyelinating polyradiculoneuropathy. *Eur. J. Neurol.* 10, 687–694 (2003).

25 Koller H, Schroeter M, Feischen H, Hartung HP, Kieseier BC. Subcutaneous self-infusions of immunoglobulins as a potential therapeutic regimen in immune-mediated neuropathies. *J. Neurol.* 253, 1505–1506 (2006).

26 Rother RP, Rollins SA, Mojcik CF, Brodsky RA, Bell L. Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. *Nat. Biotechnol.* 25, 1256–1264 (2007).

27 RMC Trial Group. Randomised controlled trial of methotrexate for chronic inflammatory demyelinating polyradiculoneuropathy (RMC trial): a pilot, multicentre study. *Lancet Neurol.* 8, 158–164 (2009).

- **Largest trial of an immunosuppressant in CIDP did not show a significant beneficial effect.**

28 Hirst C, Raasch S, Llewelyn G, Robertson N. Remission of chronic inflammatory demyelinating polyneuropathy after alemtuzumab (Campath 1H). *J. Neurol. Neurosurg. Psychiatry* 77, 800–802 (2006).

Website

101 The International Inflammatory Neuropathy Consortium www.pnsociety.com/index.php?option=com_content&view=article&id=59&Itemid=103

Affiliation

- Richard AC Hughes, MD, FRCP, FMedSci
Professor, Department of Clinical Neuroscience, Institute of Psychiatry, King's College London, London SE5 8AF, UK
Tel.: +44 207 848 5435
Fax: +44 207 848 5440
richard.a.hughes@kcl.ac.uk