Intravenous immune globulin for the treatment of chronic inflammatory demyelinating polyradiculopathy (ICE Study): a randomized, placebo-controlled trial

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At the time of this trial, corticosteroids, plasma exchange, and intravenous immunoglobulin (IVIg) had been shown to reduce physical impairment in chronic inflammatory demyelinating polyradiculopathy (CIDP), though corticosteroids and IVIg were considered first line. Notably, smaller trials had shown significant efficacy of IVIg for the short-term management of CIDP, an important consideration given the disadvantages inherent to long-term corticosteroid treatment. However, there was insufficient data to support the long-term use of IVIg for CIDP, so the goal of this study was to compare the long-term efficacy and safety of IVIg to placebo for CIDP management. Here, a 10% caprylate-chromatography purified form of IVIg was used, named IGIV-C, given its ease of manufacturing, its higher yield of IgG, and its purer final product.

Experimental design and statistics: This study was designed as randomized, placebo-controlled trial, with an additional response-conditional crossover design. Eligible patients included those ≥18yrs of age with CIDP and significant disability from a relapsing or progressive motor/sensory dysfunction of ≥1 limb over the 2 months prior to study entry. Exclusion criteria are below[1]. The study consisted of three phases: a first period (24wks), a cross-over period (24wks), and an extension phase (24wks, **Figure 1**). This cross-over design allowed for "rescue" treatment for first period non-responders, as IVIg was known to be better (at least in the short term) than placebo prior to this study. However, a placebo arm was needed to support licensing efforts the use of the IGIV-C formulation. Regardless, in the first period, eligible patients were randomly assigned to receive either IVIg (2g/kg for 2-4d, then 1g/kg every 3wks for 24wks) or placebo (albumin). Functional disability was assessed at select intervals using an adjusted INCAT disability score[2]. Any patient who was deemed a non-responder, per specified INCAT score criteria, in this first period crossed over to the alternate treatment group for the cross-over period. Any patient who failed to improve by week 3 of the cross-over period then discontinued the study. Thereafter, all patients who were responders (per INCAT score criteria) in the first period and those who completed the cross-over period were eligible for re-randomization to either IVIg or placebo for the final extension phase. During the extension phase, IVIg was administered at 1g/kg every 3 wks and INCAT scores were assessed every 3wks. If any patient worsened from their baseline during the extension phase, they were withdrawn due to a presumed relapse. The primary efficacy outcomes were the % of first period INCAT responders in the IVIg and placebo groups, assessed at wk 24, excluding patients who crossed over. The same endpoint was measured at the end of the cross-over period. Secondary efficacy outcomes in each treatment group included change in grip strength and CMAPs of the most affected motor nerve at the end of the first period, and time to relapse in patients who entered the extension phase. Statistically, primary and secondary efficacy outcomes were measured via Chi-Square analyses, analysis of covariance (grip strength, CMAPs), or Kaplan Meier curves (time to relapse).

Results: A total of 117 patients were randomized into the first period of the study (59 to IVIg; 58 to placebo). Baseline patient characteristics were generally similar between the treatment groups (**Table 1**). In terms of the primary outcome, 54% of patients in the IVIg group vs. 21% in the placebo group were responders by wk 24 of the first period ($p = 0.0002$). Similarly, 58% of patients treated with IVIG vs. 22% of those treated with placebo during the cross-over period showed INCAT score improvement at wk 24 ($p = 0.005$). Further, in terms of secondary outcomes, improvement in grip strength by wk 24 of the first period was significantly greater in the IVIg vs. placebo group ($p = 0.008$, **Table 2**), and CMAPs of the most affected nerves were also higher in the IVIg vs. the placebo group, though differences did not reach statistical significance. Finally, in

[1] Exclusion criteria: treatment with steroids, IVIG, or PLEX in previous 3 months, use immunomodulatory agents in previous 6 months, myelopathy or deficits from other CNS/PNS disease, other peripheral or motor neuropathy, other systemic disease that could cause neuropathy

[2] INCAT disability scores for CIDP score arm and leg disability, with a score of 0-5 each for arms and legs; 0 = no disability, 5 = inability to use arms/wheelchair bound.

the extension phase, 74 patients were re-randomized to IVIg (n = 43) or placebo (n = 31), and during this phase, the probability of relapse was much lower with IVIg (13%) vs. placebo (45%, see **Figure 3**). Major adverse events of IVIg are summarized in **Table 3**, and mostly included headache and pyrexia.

Conclusions: Overall, this study confirmed the short-term efficacy of IVIg (namely IGIV-C) for the treatment of CIDP, and the results of the study validated the utility of IVIg for CIDP via the cross-over design of the study: a greater percentage of patients who crossed over into the IVIg group showed functional improvement as compared to those who crossed over into the placebo group. Further, results from the extension phase of the study suggested that IVIg provides a sustained benefit for CIDP, as the relapse rate was higher in the patients who were initially treated with IVIg in the first period or cross-over period, and then later treated with placebo after re-randomization during the extension phase. As the adverse event profile of IVIg was mild, this study provided sufficient support for the first line use of IVIg as maintenance therapy (at a dose of 1g/kg q3wks) for CIDP.

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