Safety and Tolerability of Immune Globulin Intravenous in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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Background: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a common inflammatory neuropathy that can be progressive, stepwise progressive, or relapsing and remitting.

Objectives: To further evaluate the long-term safety and tolerability of immune globulin intravenous, 10% caprylate–chromatography purified immune globulin intravenous in CIDP.

Design: Randomized multicenter trial.

Setting: Hospitals and outpatient clinics.

Patients: Adults with CIDP (n=113).

Interventions: Immune globulin intravenous, 10% caprylate–chromatography purified (2 g/kg of body weight) or placebo was infused as a baseline loading dose, followed by a maintenance dose (1 g/kg) every 3 weeks for up to 24 weeks. Patients who responded were rerandomized into a double-blind extension phase of immune globulin intravenous, 10% caprylate–chromatography purified (1 g/kg) or placebo every 3 weeks for up to 24 weeks. Patients who relapsed during the extension phase were withdrawn from the study.

Main Outcome Measures: Additional analyses of safety and tolerability.

Results: Overall, 113 patients and 95 patients were exposed to immune globulin intravenous, 10% caprylate–chromatography purified and placebo, respectively. Exposure to immune globulin intravenous, 10% caprylate–chromatography purified was approximately twice that of placebo (1096 vs 575 infusions). Most maintenance dose courses were administered over 1 day in the immune globulin intravenous, 10% caprylate–chromatography purified (89.1% of 783 dose courses) and placebo (91.1% of 359 dose courses) groups. The most common drug-related adverse events (AEs) with immune globulin intravenous, 10% caprylate–chromatography purified were headache (4.0 per 100 infusions) and pyrexia (2.4 per 100 infusions). Five drug-related serious AEs (pulmonary embolism, pyrexia, vomiting, and 2 headache events) were reported in 3 patients (2.7%) exposed to immune globulin intravenous, 10% caprylate–chromatography purified. The incidence of drug-related serious AEs was higher after loading dose infusions than after maintenance dose infusions (4 AEs vs 1 AE). Age, weight, CIDP severity, and previous immune globulin intravenous exposure had no substantial effect on the percentage of patients with AEs, including serious AEs.

Conclusion: Data support a favorable safety and tolerability profile for administration of immune globulin intravenous, 10% caprylate–chromatography purified as CIDP maintenance therapy.

Trial Registration: clinicaltrials.gov Identifier NCT00220740.
after referred to as the ICE study) was to evaluate the long-term efficacy and safety of immune globulin intravenous, 10% caprylate–chromatography purified in CIDP. As one of the longest-duration and largest clinical trials of immune globulin intravenous for the treatment of CIDP, the study design permitted a rigorous assessment of the safety and tolerability of long-term (≤48 weeks) immune globulin intravenous, 10% caprylate–chromatography purified treatment. The objectives of this study were to provide additional insight into the safety and tolerability of long-term administration of immune globulin intravenous, 10% caprylate–chromatography purified to supplement primary published results of the ICE study.6

**METHODS**

Details on the study design, inclusion criteria, informed consent, and methods were reported in the publication of the primary efficacy analysis.6 As delineated in that article, this study was a randomized, double-blind, response-conditional (rescue), placebo-controlled trial. Adults with documented CIDP were randomized to receive immune globulin intravenous, 10% caprylate–chromatography purified or placebo (0.1% albumin). Patients received a baseline loading dose (2 g/kg of body weight) administered over 2 to 4 days, followed by a maintenance dose (1 g/kg) administered over 1 to 2 days every 3 weeks for up to 24 weeks. If the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score worsened by at least 1 point relative to baseline at any time between day 16 and week 24 or if the adjusted INCAT disability score did not change by week 6, the patient crossed over to receive the alternate (rescue) treatment. Patients who completed the first period or crossover (rescue) period and responded to therapy (INCAT disability score improved from baseline by ≥1 point and was maintained through week 24) were randomized to a 24-week double-blind extension phase. Patients were randomized to receive immune globulin intravenous, 10% caprylate–chromatography purified (1 g/kg) or placebo over 1 to 2 days every 3 weeks for up to 24 weeks. If a patient relapsed (adjusted INCAT disability score worsened from the extension baseline value by ≥1 point at any assessment), he or she was withdrawn from the study. The safety population included all patients who received at least 1 infusion of study medication. Safety data for the first period, crossover period, and extension phase were combined and summarized by treatment using descriptive statistics. Severity of AEs was classified as mild (usually transient in nature and generally not interfering with normal activities), moderate (sufficiently discomforting to interfere with normal activities), or severe (impairments preventing normal activities).

**RESULTS**

Data from each period or phase were pooled by treatment (immune globulin intravenous, 10% caprylate–chromatography purified or placebo) to provide a comprehensive assessment of the safety profile. Therefore, the safety population was composed of 113 patients exposed to immune globulin intravenous, 10% caprylate–chromatography purified and 95 patients exposed to placebo any time during the first period, crossover period, or extension phase.6 The mean (SD) exposure to immune globulin intravenous, 10% caprylate–chromatography purified (23.8 [16.4] weeks per patient) was approximately twice that with placebo (14.1 [12.0] weeks per patient), and 28 patients (24.8%) were exposed to immune globulin intravenous, 10% caprylate–chromatography purified for at least 36 weeks vs 5 patients (5.3%) to placebo. Most loading dose courses (administered at the start of the first and crossover periods) were given over 2 days in the immune globulin intravenous, 10% caprylate–chromatography purified group (90 of 104 courses [86.5%]) and in the placebo group (67 of 81 courses [82.7%]) (Figure, A). Most maintenance dose courses were administered over 1 day in the immune globulin intravenous, 10% caprylate–chromatography purified group (698 of 783 courses [89.1%]) and in the placebo group (327 of 359 courses [91.1%]) (Figure, B). Overall, 1210 of 1262 maintenance infusions (95.9%) were administered within 5 hours (overall mean, 2.7 hours).6

Interruptions of infusions because of AEs were rare (Table 1). Three patients in the immune globulin intravenous, 10% caprylate–chromatography purified group and 3 patients in the placebo group developed AEs that required interruption of 3 and 4 infusions, respectively, most of which occurred during administration of the loading dose. However, all infusions were restarted during the
same day and were completed without further interruption. Few patients withdrew from the study because of AEs. Three patients (2.7%) in the immune globulin intravenous, 10% caprylate–chromatography purified group and 2 patients in the placebo group (2.1%) were withdrawn from the study because of AEs. Among these, 1 patient in each group experienced an AE resulting in study withdrawal during the loading dose phase of treatment.

Drugs-related AEs were reported in 54.9% of 113 patients exposed to immune globulin intravenous, 10% caprylate–chromatography purified and in 16.8% of 95 patients exposed to placebo. Because of the greater exposure to immune globulin intravenous, 10% caprylate–chromatography purified vs placebo (1096 vs 575 infusions), the number of AEs per 100 infusions was calculated to correct for this difference. Using this analysis, a drug-related AE was reported during 17.7 of every 100 immune globulin intravenous, 10% caprylate–chromatography purified infusions and during 4.3 of every 100 placebo infusions. The most common drug-related AEs associated with immune globulin intravenous, 10% caprylate–chromatography purified and placebo were headache (4.0 and 1.2 events per 100 infusions, respectively), pyrexia (2.4 and 0.0 events per 100 infusions, respectively), hypertension (1.5 and 0.5 events per 100 infusions, respectively), influenza-like illness (1.2 and 0.0 events per 100 infusions, respectively), and chills (0.8 and 0.0 events per 100 infusions, respectively). Of 113 patients in the immune globulin intravenous, 10% caprylate–chromatography purified group, 33.6% experienced at least 1 mild drug-related AE, and 18.6% experienced at least 1 moderate drug-related AE (10.5% and 5.3%, respectively, for patients in the placebo group). The frequency of drug-related AEs during loading dose or maintenance dose administration was also compared. With immune globulin intravenous, 10% caprylate–chromatography purified, 46.7 drug-related AEs were reported per 100 infusions during loading dose courses, and 10.1 drug-related AEs were reported per 100 infusions during maintenance dose courses. Headache was the most commonly reported drug-related AE in patients exposed to immune globulin intravenous, 10% caprylate–chromatography purified during loading dose courses (26.9% of 104 patients) and during maintenance dose courses (6.9% of 101 patients). With placebo, 9.3 and 2.0 drug-related AEs per 100 infusions were reported during loading dose and maintenance dose courses, respectively.

Five drug-related serious AEs (moderate pyrexia, moderate vomiting, suspected but unconfirmed moderate pulmonary embolism, and 2 moderate headache events) were reported in 3 patients (2.7%) exposed to immune globulin intravenous, 10% caprylate–chromatography purified. The headaches occurred concurrently in a patient who experienced pyrexia and in a patient who experienced vomiting, both of whom were hospitalized. The case of suspected pulmonary embolism was reported in a patient with a history of this condition. This event resolved, and the patient completed the study. Compared with patients administered immune globulin intravenous, 10% caprylate–chromatography purified, a similar percentage of patients administered placebo experienced drug-related serious AEs: 4 placebo-related serious AEs (severe asthma, moderate cerebrovascular accident, moderate deep vein thrombosis, and mild asthma) were reported in 3 patients (3.2%). The incidence of drug-related serious AEs per infusion was higher after loading dose infusions than after maintenance dose infusions for immune globulin intravenous, 10% caprylate–chromatography purified (4 AEs vs 1 AE) and for placebo (3 AEs vs 1 AE). Most drug-related serious AEs (7 of 9 [77.8%]) occurred during the first period. Furthermore, of 9 drug-related serious AEs, 55.6% occurred within 1 day and 77.8% occurred within 3 days relative to the start of a study drug infusion.

Overall, most patients with an AE experienced the AE within 72 hours after infusion, which included 75 of 85 patients in the immune globulin intravenous, 10% caprylate–chromatography purified group and 20 of 45 patients in the placebo group. Similarly, most patients with a drug-related AE experienced the AE within 72 hours after infusion, which included 60 of 62 patients in the immune globulin intravenous, 10% caprylate–chromatography purified group and 13 of 16 patients in the placebo group. Furthermore, 3 of 6 patients in the immune globulin intravenous, 10% caprylate–chromatography purified group and 2 of 8 patients in the placebo group who experienced a serious AE did so within 72 hours after infusion.

Subanalyses were also conducted to determine potential differences in safety profiles based on select baseline demographics. Neither age, weight, previous immune globulin intravenous exposure, nor CIDP severity (baseline INCAT disability score) influenced the percentage of patients with AEs, including serious AEs (Table 2). There seemed to be a higher percentage of patients with AEs in the immune globulin intravenous, 10% caprylate–chromatography purified group who had less severe disease at baseline (INCAT disability score, ≤4) than those

<table>
<thead>
<tr>
<th>Patient</th>
<th>Period</th>
<th>Week</th>
<th>Day</th>
<th>Treatment</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>First</td>
<td>0</td>
<td>1</td>
<td>Drug</td>
<td>Moderate chest pain and moderate fever</td>
</tr>
<tr>
<td>2</td>
<td>First</td>
<td>0</td>
<td>1</td>
<td>Drug</td>
<td>Mild chronic bronchitis</td>
</tr>
<tr>
<td>3</td>
<td>First</td>
<td>0</td>
<td>1</td>
<td>Placebo</td>
<td>Severe asthma attack</td>
</tr>
<tr>
<td>4</td>
<td>First</td>
<td>0</td>
<td>3</td>
<td>Placebo</td>
<td>Mild vomiting and hospitalization for observation</td>
</tr>
<tr>
<td>5</td>
<td>First</td>
<td>0</td>
<td>1</td>
<td>Placebo</td>
<td>Mild bronchitis</td>
</tr>
<tr>
<td>6</td>
<td>First</td>
<td>6</td>
<td>1</td>
<td>Placebo</td>
<td>Moderate hypertension</td>
</tr>
<tr>
<td>7</td>
<td>First</td>
<td>6</td>
<td>1</td>
<td>Placebo</td>
<td>Moderate hypertension</td>
</tr>
<tr>
<td>8</td>
<td>Crossover</td>
<td>0</td>
<td>1</td>
<td>Drug</td>
<td>Moderate hypertension</td>
</tr>
</tbody>
</table>

Table 1. Adverse Events Resulting in Interruption of Infusion

*Drug is immune globulin intravenous, 10% caprylate–chromatography purified.*
who had more severe disease at baseline (P = .04, Fisher exact test). However, no difference in disease severity at baseline for immune globulin intravenous, 10% caprylate–chromatography purified–treated subjects was demonstrated for drug-related AEs (P = .11, Fisher exact test) or for serious AEs (P = .33, Fisher exact test).

Administration of immune globulin intravenous continues to have an important role in the treatment of autoimmune neuromuscular disorders. The ICE study is one of the largest and longest-duration trials to date of immune globulin intravenous in CIDP. The trial was designed not only to examine the benefits of immune globulin intravenous, 10% caprylate–chromatography purified–treated subjects was demonstrated for drug-related AEs (P = .11, Fisher exact test) or for serious AEs (P = .33, Fisher exact test).

### Table 2. Safety Summary by Select Baseline Characteristics

<table>
<thead>
<tr>
<th>Variablea</th>
<th>Patients With AEs</th>
<th>Patients With Drug-Related AEs</th>
<th>Patients With Serious AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug (n=113)</td>
<td>85 (75.2)</td>
<td>62 (54.9)</td>
<td>6 (5.3)</td>
</tr>
<tr>
<td>Placebo (n=95)</td>
<td>45 (47.4)</td>
<td>16 (16.8)</td>
<td>8 (8.4)</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug (n=84)</td>
<td>63 (75.0)</td>
<td>47 (56.0)</td>
<td>4 (4.8)</td>
</tr>
<tr>
<td>Placebo (n=67)</td>
<td>31 (46.3)</td>
<td>10 (14.9)</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>≥65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug (n=29)</td>
<td>22 (75.9)</td>
<td>15 (51.7)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Placebo (n=28)</td>
<td>14 (50.0)</td>
<td>6 (21.4)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td><strong>Previous Immune Globulin Intravenous Exposure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug (n=81)</td>
<td>61 (75.3)</td>
<td>44 (54.3)</td>
<td>5 (6.2)</td>
</tr>
<tr>
<td>Placebo (n=75)</td>
<td>36 (48.0)</td>
<td>12 (16.0)</td>
<td>5 (6.7)</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug (n=32)</td>
<td>24 (75.0)</td>
<td>18 (56.2)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Placebo (n=20)</td>
<td>9 (45.0)</td>
<td>4 (20.0)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td><strong>CIDP Severity, Baseline INCAT Disability Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug (n=76)</td>
<td>62 (81.6)</td>
<td>46 (60.5)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Placebo (n=66)</td>
<td>31 (47.0)</td>
<td>11 (16.7)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>≥5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug (n=37)</td>
<td>23 (62.2)</td>
<td>16 (43.2)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Placebo (n=29)</td>
<td>14 (48.3)</td>
<td>5 (17.2)</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug (n=66)</td>
<td>48 (72.7)</td>
<td>35 (53.0)</td>
<td>4 (6.1)</td>
</tr>
<tr>
<td>Placebo (n=54)</td>
<td>25 (46.3)</td>
<td>8 (14.8)</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td>≥80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug (n=47)</td>
<td>37 (78.7)</td>
<td>27 (57.4)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Placebo (n=41)</td>
<td>20 (48.8)</td>
<td>8 (19.5)</td>
<td>4 (9.8)</td>
</tr>
</tbody>
</table>

Abbreviations: AEs, adverse events; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; INCAT, Inflammatory Neuropathy Cause and Treatment. aDrug is immune globulin intravenous, 10% caprylate–chromatography purified.

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chromatography purified can be infused at higher doses and over shorter time frames than has been observed in the customary clinical practice of infusing 2 g/kg over 5 days (daily dose, 0.4 g/kg).

Even after long-term administration (every 3 weeks for up to 48 weeks) with immune globulin intravenous, 10% caprylate–chromatography purified (1 g/kg), the incidence of drug-related AEs and serious AEs per 100 infusions and interruptions in infusions was low, as was the incidence observed with placebo. There were also no apparent differences between groups when compared by baseline characteristics such as patient age, weight, baseline CIDP severity, or previous immune globulin intravenous exposure. The most common AEs (regardless of causality) and drug-related AEs were those frequently reported by patients in other investigations involving immune globulin intravenous; serious AEs occurred slightly more often in the placebo group than in the immune globulin intravenous, 10% caprylate–chromatography purified group, and the type of serious AE was similar in both groups. Furthermore, in a Cochrane review evaluating immune globulin intravenous vs placebo in CIDP, which included the ICE study data, the relative risk of serious AE development was not significantly different between immune globulin intravenous and placebo (relative risk, 0.82; 95% confidence interval, 0.36-1.87).

A review of the literature disclosed a lack of substantial prospective detailed information about specific AEs associated with administration of immune globulin intravenous in patients with CIDP. Besides the ICE study, 2 other randomized controlled trials have provided detailed information about AEs. Hughes et al reported AEs in 18 of 30 courses of immune globulin intravenous (2 mg/kg administered over 1-2 days) in a randomized controlled trial of immune globulin intravenous vs oral prednisolone in 32 patients with CIDP. Headache was the most common immune globulin intravenous AE and was reported in 10 courses (33%). In addition, indigestion, fever, rash, and hypotension were reported during 20%, 17%, 6%, and 3% of immune globulin intravenous courses, respectively. None of these AEs were significantly more common in the immune globulin intravenous group compared with the plasma exchange group.

In summary, immune globulin intravenous, 10% caprylate–chromatography purified infused every 3 weeks for up to 48 weeks is safe and well tolerated in patients with CIDP. Data from this large prospective trial support the conclusion that immune globulin intravenous, 10% caprylate–chromatography purified can be safely administered over 1 to 2 days, depending on the dose given. A shorter administration schedule does not seem to increase the risk of immune globulin intravenous, 10% caprylate–chromatography purified–related AEs and should lead to substantial cost savings for inpatient and outpatient infusions.

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between serum 25-hydroxyvitamin D3 level and performance on psychometric
in relation to serum parathyroid hormone and serum 25-hydroxyvitamin D lev-
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Correction

Error in Abstract. In the Original Contribution titled “Safety and Tolerance of Immune Globulin Intrave-
nous in Chronic Inflammatory Demyelinating Polyra-
diculoneuropathy,” by Donofrio et al, published in the
September issue of the Archives (2010;67[9]:1082-
1088), the n value reported in the structured abstract was
incorrect. The patients entry on page 1082 should have
read as follows: Patients: Adults with CIDP (n=117).