Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial

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Summary

Background Short-term studies suggest that intravenous immunoglobulin might reduce disability caused by chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) but long-term effects have not been shown. We aimed to establish whether 10% caprylate-chromatography purified immune globulin intravenous (IGIV-C) has short-term and long-term benefit in patients with CIDP.

Methods 117 patients with CIDP who met specific neurophysiological inflammatory neuropathy cause and treatment (INCAT) criteria participated in a randomised, double-blind, placebo-controlled, response-conditional crossover trial. IGIV-C (Gamunex) or placebo was given every 3 weeks for up to 24 weeks in an initial treatment period, and patients who did not show an improvement in INCAT disability score of 1 point or more received the alternate treatment in a crossover period. The primary outcome was the percentage of patients who had maintained an improvement from baseline in adjusted INCAT disability score of 1 point or more through to week 24. Patients who showed an improvement and completed 24 weeks of treatment were eligible to be randomly re-assigned in a blinded 24-week extension phase. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00220740.

Findings During the first period, 32 of 59 (54%) patients treated with IGIV-C and 12 of 58 (21%) patients who received placebo had an improvement in adjusted INCAT disability score that was maintained through to week 24 (treatment difference 33·5%, 95% CI 15·4–51·7; p=0·0002). Improvements from baseline to endpoint were also recorded for grip strength in the dominant hand (treatment difference 10·9 kPa, 4·6–17·2; p=0·0008) and the non-dominant hand (8·6 kPa, 2·6–14·6; p=0·005). Results were similar during the crossover period. During the extension phase, participants who continued to receive IGIV-C had a longer time to relapse than did patients treated with placebo (p=0·011). The incidence of serious adverse events per infusion was 0·8% (9/1096) with IGIV-C versus 1·9% (11/575) with placebo. The most common adverse events with IGIV-C were headache, pyrexia, and hypertension.

Interpretation This study, the largest reported trial of any CIDP treatment, shows the short-term and long-term efficacy and safety of IGIV-C and supports use of IGIV-C as a therapy for CIDP.

Introduction

Since its first description,[1,2] chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) has become recognised as an important cause of peripheral neuropathy.[3–6] CIDP is a progressive or relapsing disease with a worldwide prevalence of 2–7 individuals per 100 000.[7,8] Its course is variable, but in a population-based study in southeast England, 54% of patients had been severely disabled by their illness at some stage and 13% were still severely disabled at the time of prevalence assessment.[7] Because CIDP has an inflammatory pathology, resembles experimental autoimmune neuritis, shows some evidence of a response against peripheral nerve glycolipid and protein antigens, and has a good response to immunomodulatory treatment, it is likely to be an autoimmune disease.[6,9]

Randomised trials suggest that corticosteroids, plasma exchange, and intravenous immunoglobulin (IVIg) reduce impairment at least temporarily.[10–12] Corticosteroids and IVIg are both used as first-line treatment options; however, a risk of long-term adverse effects is the main disadvantage of corticosteroids, and expense can be a concern with IVIg.[5] In three of four small, short-term clinical trials in patients treated de novo, IVIg was more efficacious than placebo,[13–16] and a meta-analysis showed significant short-term reduction in disability and improvement in strength.[12] These data suggested that IVIg is beneficial in the short-term treatment of CIDP. However, there are insufficient data on longer-term effects for licensing of IVIg in most countries. The IGIV-C CIDP efficacy (ICE) study was designed to compare the long-term efficacy and safety of immune globulin intravenous, 10% caprylate-chromatography purified (IGIV-C) with

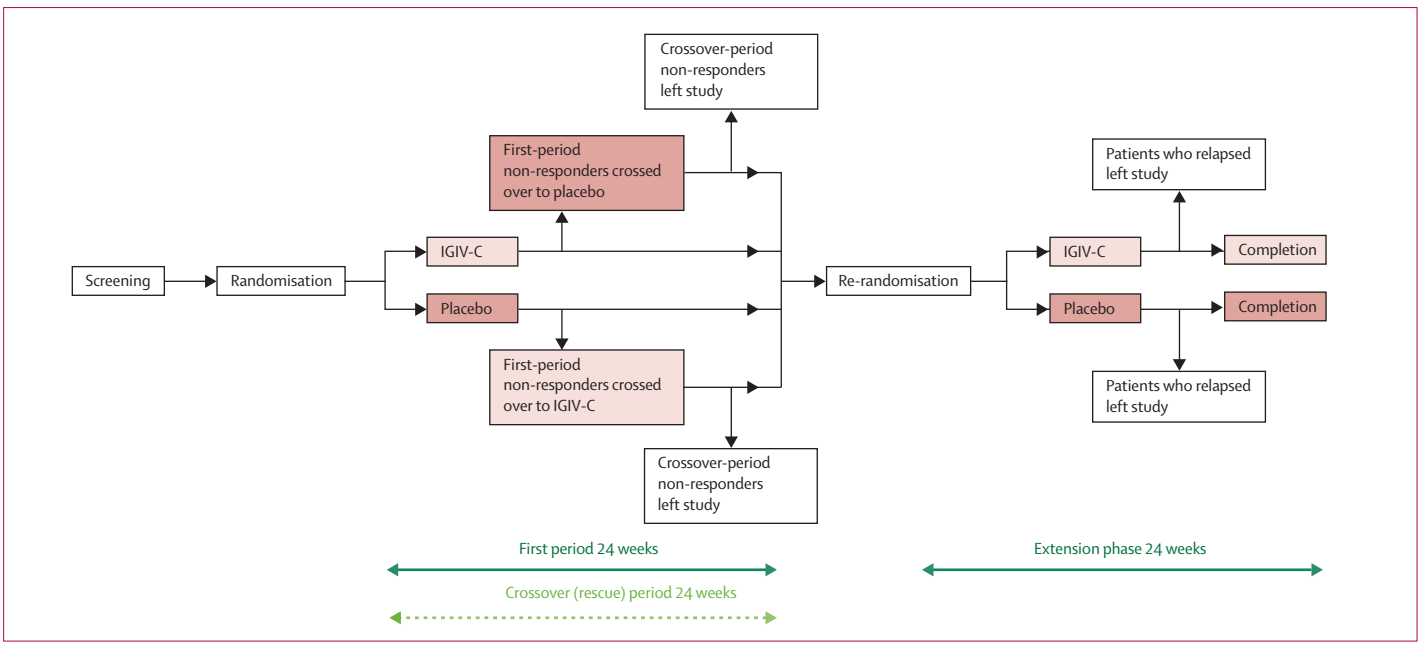


Figure 1: **Study design**
After a screening period of ≤10 days, eligible patients were randomly assigned to receive either IGIV-C or placebo for up to 24 weeks. If the adjusted INCAT disability score worsened by ≥1 point relative to baseline at any time between day 16 and week 24, if the adjusted INCAT score remained unchanged from baseline until week 6, or if the score improved but returned to baseline or lower than baseline at any time from week 6 up to and including week 24, the patient crossed over to receive the alternate (rescue) treatment for up to 24 weeks (broken line). Patients who were first-period adjusted-INCAT responders were eligible to be randomly re-assigned to IGIV-C or placebo in a double-blind extension phase for an additional 24 weeks. If the adjusted INCAT score worsened from the extension baseline value by ≥1 point at any assessment, the patient was judged to have relapsed and was withdrawn from the study.

that of placebo in the treatment of CIDP and to support efforts to license IGIV-C. Compared with the IVIg solvent and detergent process, the manufacture of IGIV-C requires substantially fewer steps, has a 70% shorter processing time, yields 50% more IgG, and produces a purer final product.[17] We used a unique response-conditional crossover design to provide rescue treatment if needed, and patients who showed an improvement in inflammatory neuropathy cause and treatment (INCAT) disability score during treatment were re-randomised into a 24-week extension phase.

Methods

Patients

Patients 18 years of age or older were recruited between April, 2004, and June, 2005, from 33 centres in Europe, North America, South America, and Israel. Eligible patients had a diagnosis of CIDP, progressive or relapsing motor and sensory dysfunction of at least one limb resulting from neuropathy over the 2 months before study entry, and significant disability as defined by an overall INCAT disability score[18] of 2–9. An INCAT disability score of 2 had to be exclusively from leg disability to be eligible. Exclusion criteria were: treatment with steroids (>10 mg/day prednisolone or equivalent), IVIg, or plasma exchange in the 3 months before study entry; use of fish-oil supplements in the previous month (omega-3 fatty acids have been reported to have anti-inflammatory properties); treatment with other immunomodulatory or immunosuppressive agents (interferon or azathioprine) in the previous 6 months; myelopathy or evidence of central demyelination; persistent neurological deficits from stroke, CNS trauma, or peripheral neuropathy from other causes (eg, diabetes mellitus, IgM paraproteinaemia, or uraemic, toxic, or familial neuropathy); a motor syndrome that fulfilled criteria for multifocal motor neuropathy with conduction block (ie, upper limb motor weakness without sensory deficit and with a 50% decrease in action potential amplitude or area on proximal compared with distal stimulation in motor nerves); and evidence of systemic disease that might cause neuropathy. The study was approved by the institutional review boards and ethics committees of all participating centres, and all patients provided written informed consent.

Procedures

The study design included a first period, a response-conditional crossover (rescue) period, and an extension phase (figure 1). After a screening period of up to 10 days, eligible patients were randomly assigned in a 1:1 ratio to receive either IGIV-C (Gamunex, Talecris Biotherapeutics, Research Triangle Park, NC, USA) or placebo (0·1% albumin). Albumin was selected as the placebo because of its similar appearance to IVIg. Patients received a baseline loading dose of 2 g/kg over 2–4 days and then a maintenance infusion of 1 g/kg over 1–2 days every 3 weeks for up to 24 weeks (first period, figure 1).

Functional disability was assessed with an adjusted INCAT disability score at prespecified intervals (day 16 of treatment, and every 3 weeks for up to 24 weeks). The adjusted score is 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, because these changes were not judged by regulatory agencies to be clinically significant in all patients. However, all other 1-point steps in either the arm or the leg scale represented clinically meaningful changes in disability. Patients crossed over to the alternate treatment (crossover period, figure 1) if they were judged to be first-period adjusted-INCAT non-responders—ie, if their adjusted INCAT disability score deteriorated by 1 point or more at any visit after the first infusion of study drug, if their score was stable until week 6, or if their score improved but returned to baseline or lower than baseline at any time at week 6 or afterwards, up to and including week 24.

Patients in the crossover period received the alternate treatment according to the same treatment schedule as was used in the first period. Those who maintained an improvement in the adjusted INCAT score of 1 point or greater at all study visits from week 3 after crossover remained in the crossover period for 24 weeks. Those who failed to improve by week 3 after crossover, or who improved but subsequently returned to baseline or had a score below baseline, discontinued the study and did not enter the extension period. Participants who completed the first period or crossover period and whose INCAT disability score was consistently 1 point or more greater than baseline were eligible for inclusion in a 24-week, double-blind extension phase (figure 1). Eligible participants were randomly re-assigned in a 1:1 ratio to receive 1 g/kg IGIV-C or placebo over 1–2 days every 3 weeks for up to 24 weeks (no loading dose was given), and the adjusted INCAT disability score was assessed every 3 weeks during this period. Table 1 shows that the final re-assignment was not exactly 1:1 because re-assignment was done at each study site rather than centrally. If the score worsened from the extension baseline value by 1 point or more at any assessment, the patient was judged to have relapsed, was withdrawn from the study, and was treated at the discretion of his or her physician.

The blinded, response-conditional crossover period was designed to provide rescue therapy for patients who were first-period adjusted-INCAT non-responders (ie, had not shown and maintained an improvement during the first period). Because an aim of the trial was to support licensing efforts in various countries, a placebo-controlled trial was required by regulatory authorities. However, the long-term use of placebo was not generally tolerable to study investigators or patients because there is evidence that IVIg and other treatments are efficacious, although they are not approved for treatment of CIDP. Early rescue therapy at the first sign of deterioration allowed inclusion of a placebo arm to meet regulatory requirements and to minimise ethical concerns about treatment with placebo.

Outcome measures were selected on the basis of published trials in patients with CIDP and clinimetric reports of outcome measures. The primary efficacy variable was the percentage of adjusted-INCAT responders in the IGIV-C or placebo groups in the first period—ie, patients who showed an improvement from baseline of 1 point or more in the adjusted INCAT disability score (excluding a change between 0 and 1 in the upper limb score) that was maintained through to the final measurement in week 24. During the first period, the primary endpoint (ie, percentage of first-period adjusted-INCAT responders) was assessed at week 24 of treatment and included all patients who completed the first period without crossing over and maintained improvement of 1 point or more through to week 24. For the primary endpoint, any patient who crossed over to alternate (rescue) treatment or withdrew from the study during the first period was categorised as a first-period adjusted-INCAT non-responder. During the crossover period, the endpoint was measured at week 24 after time of crossover for patients who completed the crossover period or as the last assessment for patients who withdrew from the study. Information about response to treatments for CIDP before entry into the trial was not collected.

There were three secondary efficacy outcomes: mean change from baseline in maximum grip strength at endpoint during the first period, as assessed by a Martin Vigorimeter;[19] mean change from baseline in the compound muscle action potential amplitude after stimulation of the most severely affected motor nerve at the proximal site at endpoint during the first period; and time to relapse for patients who were first-period adjusted-INCAT responders or crossover-period adjusted-INCAT responders to IGIV-C and who entered the extension phase. Relapse during the extension phase was defined as worsening of adjusted INCAT disability score by 1 point or more from the extension baseline value. All nerve conduction tracings were analysed in a central neurology laboratory. The most severely affected nerve was identified at baseline during testing of the ulnar, median, peroneal, and tibial nerves; if the most severely affected motor nerve could not be distinguished at baseline, the nerve selected for analysis was the first nerve in this list that had been one of the three tested to meet the INCAT neurophysiology diagnostic criteria at screening.

Exploratory outcome measures included change from baseline to endpoint during the first period in the Medical Research Council (MRC) sum score[20] and the INCAT sensory sum (ISS) score.[21] Other exploratory outcome measures were change from baseline during the crossover period (time of crossover to endpoint) and change from baseline during the extension phase (time of extension entry to endpoint) for MRC sum score, ISS score, grip strength, and amplitude of the compound muscle action potential of the most severely affected motor nerve. All centres participated in two training sessions on uniform assessment of outcome measures.

Clinical laboratory data were obtained during the screening period, at baseline, and every 3 weeks during the first period, crossover period, and extension phase. Vital signs were measured before, during, and immediately after all infusions. All adverse events were recorded during the study and classified according to the investigators' assessment of severity and causal relation to treatment. An adverse event was judged to be serious if it was fatal, was life threatening, caused persistent or significant disability or incapacity, necessitated admission to hospital, was a congenital anomaly or birth defect, or was judged by an investigator to be an important medical event.

Patients were randomly assigned to receive IGIV-C or placebo at baseline after the confirmation of patient eligibility. Computer-generated random codes and treatment assignments were prepared by an independent group within the sponsor hierarchy and were distributed by the sponsor to the unblinded pharmacist at each centre. Eight randomisation numbers, in four blocks of two random numbers each, were initially assigned to each centre (block size was not disclosed to the centres). If a centre required additional random numbers, it received a set of eight numbers. The same procedure was used to generate separate random codes to assign patients to placebo or IGIV-C in the extension phase. During the study, unblinded monitors checked the drug batch log to ensure that the study medication was prepared and given as assigned. All other study team members were blinded to patient treatment during the study.

Statistical analysis

Efficacy data were assessed for the intention-to-treat population, defined as all randomised patients. The primary efficacy outcome—the difference between the treatment groups in proportions of patients who were first-period adjusted-INCAT non-responders—was evaluated with a χ^2 test (α=0·05, two sided). On this basis, a sample of 49 patients per group was required to provide 80% statistical power to detect a difference, according to an assumed response rate of 15% in the placebo group and 40% in the IGIV-C group. To allow for a dropout rate of 10%, we aimed to enrol 55 patients per treatment group.

For the change from baseline in adjusted INCAT disability score, grip strength, amplitude of action potentials in the most severely affected motor nerve, and the exploratory efficacy endpoints, a last-observation carried forward approach was used and treatment differences were compared by analyses of covariance adjusted for geographic region and baseline measurement. Kaplan-Meier estimates and the log-rank test were used to compare the treatment difference for time to relapse during the extension period. We used descriptive statistics for adverse events, which were recorded for all patients who received study medication. SAS version 8.2 was used for all statistical analyses.

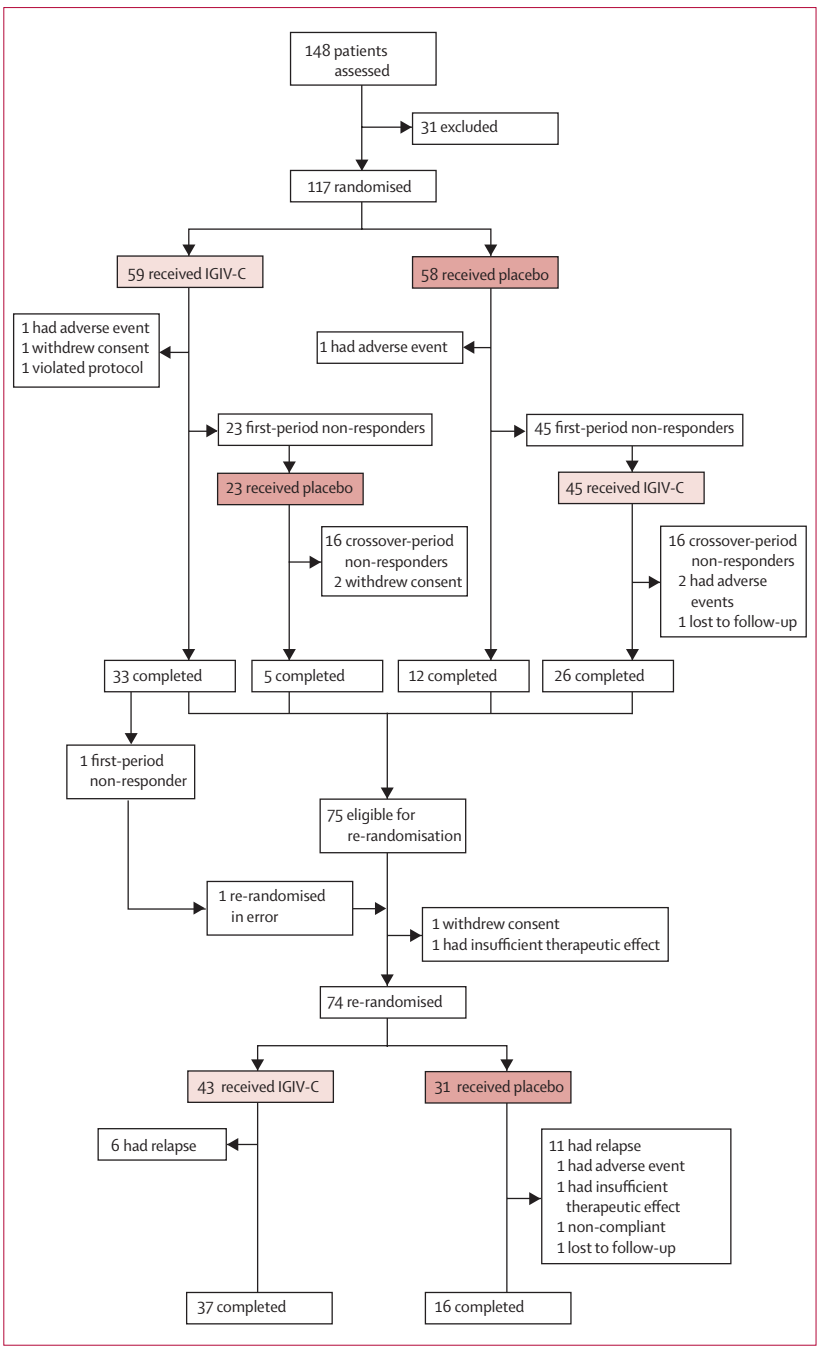


Figure 2: **Trial profile**

This trial is registered with ClinicalTrials.gov, number NCT00220740.

Role of the funding source

The study sponsors designed the trial, interpreted the data, and provided editorial support for preparation of the manuscript in consultation with the steering committee. Data management and statistical analysis were done by StatWorks (Research Triangle Park, NC,

USA). The steering committee had full access to all the data and made the final decision to submit the manuscript for publication.

Results

Figure 2 shows the trial profile. 30 of the 31 patients who were not randomised had failed to meet inclusion criteria; the other was lost to follow-up during screening. Baseline INCAT disability scores, grip strengths, MRC sum scores, and ISS scores were similar in the IGIV-C and placebo groups (table 1). During the first period, 32 patients (54%) who received IGIV-C were adjusted-INCAT responders (ie, showed and maintained an increase in adjusted INCAT score of 1 point or more) compared with 12 patients (21%) who received placebo (33·5% difference, 95% CI 15·4–51·7; p=0·0002). A multiple regression analysis showed that treatment outcome was not affected by sex (p=0·977), time to CIDP diagnosis (p=0·379), or compound muscle action potential amplitude (p=0·536). One patient in the IGIV-C group showed an initial improvement from baseline and completed the period but was judged to be a first-period adjusted-INCAT non-responder because their adjusted INCAT score decreased to baseline at the final assessment of the first period. Four patients, all randomised to receive IGIV-C, who should have crossed over during the first period because their adjusted INCAT score was stable at week 6 or later, continued in the first period and all improved, maintained the improvement, and completed the 24-week treatment. A sensitivity analysis, by classification of these four patients as adjusted-INCAT non-responders, gave similar results (26·8% difference between treatment groups, 8·6–44·9; p=0·002). Most patients who did not complete the first period had crossed over to the alternate treatment: 23 of 26 (88%) patients in the IGIV-C group and 45 of 46 (98%) patients in the placebo group.

We tested in a subanalysis whether previous exposure to IVIg might have biased the response. 12 of 20 (60%) patients in the IGIV-C group who had previous IVIg exposure were first-period adjusted-INCAT responders compared with 0 of 12 (0%) in the placebo group (p=0·0006). Similarly, 20 of 39 (51%) patients in the IGIV-C group who had not previously received IVIg were first-period adjusted-INCAT responders compared with 12 of 46 (26%) patients in the placebo group (p=0·024). In an additional subanalysis, 16 of 59 (27%) patients who received IGIV-C were first-period adjusted-INCAT responders with an improvement of 2 points or more at week 24, compared with eight of 58 (14%) patients in the placebo group (p=0·074). Table 2 shows differences between the treatment groups for secondary and exploratory efficacy outcomes. Patients in the IGIV-C group had significantly greater improvement from baseline grip strength than did those in the placebo group for both the dominant hand and non-dominant hand, and improvements in MRC sum score and ISS score were greater with IGIV-C than with placebo during the first period. The proximally evoked compound muscle action potential of the most severely affected motor nerve was slightly greater with IGIV-C treatment than with placebo, although this improvement was not statistically significant.

	IGIV-C (n=59)	Placebo (n=58)
Sex		
Male	31 (53%)	46 (79%)
Female	28 (47%)	12 (21%)
Age (years)		
Mean	50 (17)	53 (16)
Range	19–79	18–83
Ethnic origin		
White	55 (93%)	52 (90%)
Black	0	1 (2%)
Hispanic	3 (5%)	5 (9%)
Other	1 (2%)	0
Previous IVIg treatment	20 (34%)	12 (21%)
Time since first CIDP symptoms (years)	5·8 (7·4)	4·8 (4·9)
Time since CIDP diagnosis (years)	2·4 (3·7)	1·8 (2·9)
Baseline INCAT disability score	4·2 (1·4)	4·1 (1·5)
Baseline amplitude (mV)*	1·29 (1·39)	1·82 (1·99)
Baseline grip strength (kPa)		
Dominant hand	48·2 (23·6)†	52·1 (23·3)
Non-dominant hand	47·0 (25·1)‡	50·2 (22·8)
Baseline MRC sum score	49·3 (6·9)	50·0 (7·2)
Baseline ISS score	7·8 (4·9)†	7·9 (4·9)†

Data are number (%) or mean (SD) unless otherwise indicated. *Baseline action potential amplitude of the most severely affected motor nerve at most proximal site. †n=57. ‡n=58.

Table 1: **First-period demographics and baseline characteristics**

There were no differences between the IGIV-C and placebo groups in the mean time since first CIDP symptoms (4·6 [SD 4·2] *vs* 5·9 [8·6] years), mean time since CIDP diagnosis (2·03 [3·0] *vs* 2·03 [3·7] years), and mean INCAT disability scores (4·3 [1·5] *vs* 4·2 [1·4]). During the crossover period, adjusted INCAT disability score improved by at least 1 point in 26 of 45 patients (58%) treated with IGIV-C and five of 23 patients (22%) treated with placebo (p=0·005). Most patients who left the study during the crossover period did so because their adjusted INCAT disability scores showed no improvement (figure 2). Patients who were switched from placebo to IGIV-C had significantly greater mean improvements from baseline in adjusted INCAT disability score, grip strength in both the dominant hand and the non-dominant hand, and MRC sum score compared with patients who switched from IGIV-C to placebo (table 2). Improvements from baseline in the proximally evoked compound muscle action potential amplitude of the most severely affected motor nerve and in ISS score were slightly greater with IGIV-C treatment than with placebo, although this difference was not statistically significant.

56 of 58 patients who were adjusted-INCAT responders during treatment with IGIV-C and 17 of 17 patients who

	First period				Crossover (rescue) period				Extension phase			
	Change from baseline* Mean (SD)		LSM difference† (95% CI)	p†	Change from baseline* Mean (SD)		LSM difference† (95% CI)	p†	Change from baseline* Mean (SD)		LSM difference† (95% CI)	p†
	IGIV-C (n=59)	Placebo (n=58)			IGIV-C (n=45)	Placebo (n=23)			IGIV-C (n=31)	Placebo (n=26)		
Adjusted INCAT disability score	−1·1 (1·8)	−0·3 (1·3)	−0·7 (−1·3 to −0·2)	0·010	−1·2 (1·5)	−0·3 (1·8)	−0·9 (−1·7 to −0·1)	0·022	0·1 (0·7)	0·4 (1·7)	−0·5 (−1·2 to 0·2)	0·181
Amplitude (mV)‡	0·69 (1·86)	0·47 (2·29)	0·24 (−0·53 to 1·00)	0·542	0·28 (1·71)§	−0·23 (0·82)¶	0·49 (−0·32 to 1·30)	0·230	0·01 (1·63)‖	−0·51 (1·84)**	0·78 (−0·07 to 1·64)	0·072
Grip strength (kPa)												
Dominant hand	13·2 (19·3)††	1·5 (15·6)	10·9 (4·6 to 17·2)	0·0008	15·5 (26·8)	−1·0 (11·7)	16·1 (4·5 to 27·7)	0·007	−0·8 (11·3)	−3·9 (20·9)	4·3 (−5·0 to 13·6)	0·353
Non-dominant hand	13·3 (17·4)‡‡	4·3 (14·9)	8·6 (2·6 to 14·6)	0·005	14·6 (23·1)	−2·9 (11·6)	17·6 (7·0 to 28·1)	0·001	−0·3 (11·0)	−5·6 (22·7)§§	5·8 (−4·1 to 15·7)	0·247
MRC sum score	3·3 (5·6)	0·2 (4·5)	3·1 (1·3 to 4·9)	0·001	4·4 (6·5)	−0·6 (5·4)	4·7 (1·6 to 7·8)	0·004	0·8 (4·1)	−1·0 (4·4)	2·0 (−0·3 to 4·3)	0·081
ISS score	−1·2 (3·4)††	0·2 (3·9)††	−1·5 (−2·7 to −0·2)	0·021	−1·7 (3·8)	−0·5 (3·1)	−0·6 (−2·4 to 1·2)	0·499	−0·5 (4·0)¶¶	0·2 (2·6)	−0·4 (−2·3 to 1·5)	0·667

*Baseline refers to the last measurement before the start of treatment during each indicated period. †Least squares mean (LSM) and p values were obtained from the analysis of covariance model with change from baseline as the dependent variable, treatment and region as factors, and the baseline value as the covariate. ‡Amplitude of the most severely affected motor nerve at the most proximal site. §n=44. ¶n=20. ‖n=29. **n=24. ††n=57. ‡‡n=58. §§n=25. ¶¶n=30.

Table 2: **Efficacy of IGIV-C versus placebo in patients with CIDP**

were adjusted-INCAT responders during treatment with placebo during the first or crossover phases were randomly re-assigned into the extension phase. One patient treated with IGIV-C who was identified as a first-period adjusted-INCAT non-responder entered the extension phase and was re-randomised to the placebo group in error. Thus, 74 patients were re-randomised during the extension phase (figure 2). The main reason for discontinuation of the extension phase by patients was CIDP symptom relapse (ie, worsening of adjusted INCAT disability score by 1 point or more from extension baseline value), which occurred in six (14%) patients treated with IGIV-C and 11 (35%) patients treated with placebo (p=0·011 for difference between groups).

For the efficacy analyses during the extension phase, we assessed the 57 patients who received IGIV-C and were first-period or crossover-period adjusted-INCAT responders: 31 of these patients were randomly re-assigned to IGIV-C and 26 were randomly assigned to placebo. Mean baseline adjusted INCAT disability score was similar in these two groups (2·3 [SD 1·5] *vs* 2·7 [1·6], respectively). Treatment with IGIV-C during the extension phase generally maintained or slightly improved several efficacy outcome measures versus baseline values at re-randomisation, but the differences versus placebo were not significant (table 2). However, patients who continued to receive IGIV-C during the extension phase had a significantly longer time to relapse than did patients who were treated with placebo during the extension phase (p=0·011; figure 3). The probability of relapse was 13% with IGIV-C treatment compared with 45% with placebo treatment (hazard ratio=0·19, 95% CI 0·05–0·70).

Few patients left the study because of adverse events: one (2%) patient from each treatment group during the first period; two (4%) patients treated with IGIV-C during the crossover period; and one (3%) patient treated with placebo during the extension phase. Safety data from each period were pooled to provide a complete picture of the adverse event profile, and the safety population consisted of 113 patients exposed to IGIV-C and 95 patients exposed to placebo. The drug exposure rate with IGIV-C was almost twice that of placebo (1096 *vs* 575 infusions). Most loading-dose infusions, which were given at the start of the first period or crossover period, were given over

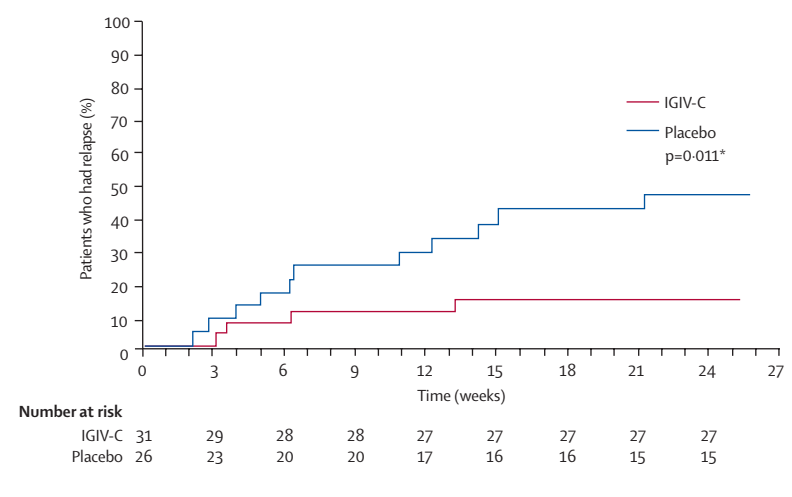


Figure 3: **Time to relapse**
Data shown pertain to the subset of patients who received IGIV-C and were first-period adjusted-INCAT responders (showed and maintained an improvement of ≥1 point relative to baseline). These patients were followed for time to relapse (ie, a decrease in adjusted INCAT score of ≥1 point that was not attributed to a change of 0 to 1 in the upper extremities) during the extension phase. The patient who was enrolled in the extension phase in error was not included in the analysis. *p for difference between groups.

	IGIV-C (n=113)			Placebo (n=95)		
	Patients	Adverse events	Frequency*	Patients	Adverse events	Frequency*
Any adverse event	85 (75%)	377	34·4%	45 (47)	120	20·9%
Headache	36 (32%)	57	5·2%	8 (8)	15	2·6%
Pyrexia	15 (13%)	27	2·5%	0	0	0·0%
Hypertension	10 (9%)	20	1·8%	4 (4)	6	1·0%
Asthenia	9 (8%)	10	0·9%	3 (3)	4	0·7%
Chills	9 (8%)	10	0·9%	0	0	0·0%
Back pain	9 (8%)	10	0·9%	3 (3)	3	0·5%
Rash	8 (7%)	13	1·2%	1 (1)	1	0·2%
Arthralgia	8 (7%)	11	1·0%	1 (1)	1	0·2%
Nausea	7 (6%)	9	0·8%	3 (3)	3	0·5%
Dizziness	7 (6%)	3	0·6%	1 (1)	1	0·2%
Influenza	6 (5%)	6	0·5%	2 (2)	2	0·3%

*Percentage of adverse events in the safety population divided by total number of infusions in group (1096 for IGIV-C group and 575 for placebo group).

Table 3: **Adverse events reported in ≥5% of patients in a treatment group, irrespective of causality**

2 days: 179 of 227 (79%) infusions in the IGIV-C group and 133 of 182 (73%) infusions in the placebo group. Most maintenance-dose infusions were given over 1 day in both the IGIV-C group (695 of 869 [80%] infusions) and the placebo group (326 of 393 [83%] infusions), overall 1210 of 1262 (96%) maintenance infusions were given within 5 h (overall mean, 2·7 h).

To correct for the difference in drug exposure between the treatment groups, the number of adverse events per infusion was calculated (table 3). Headache, pyrexia, and hypertension were the most common adverse events reported by investigators for IGIV-C-treated patients. Adverse events judged by the investigator to relate to the study medication were reported in 62 of 113 (55%) patients treated with IGIV-C and 16 of 95 (17%) patients treated with placebo. Most adverse events in the IGIV-C group were mild and the most common drug-related events were headache (44 of 1096 [4·0%] infusions) and pyrexia (26 of 1096 [2·4%] infusions). In the placebo group, headache was reported for seven of 575 (1·2%) infusions, with no reports of pyrexia. Serious adverse events were reported for six of 113 (5%) patients who were being treated with IGIV-C (9/1096 infusions, 0·8%) and eight of 95 (8%) patients who were receiving placebo (11/595 infusions, 1·9%). Except for one case each of moderate bronchopneumonia and severe relapse of CIDP symptoms, all serious adverse events resolved by the end of the study. One patient who had been treated with two infusions of IGIV-C during the first period and had crossed over (25 days after the last infusion of IGIV-C) to placebo developed fatal sepsis: 14 days after the last placebo infusion during the crossover period, this patient had withdrawn from the study owing to an insufficient therapeutic effect, and sepsis developed about 6 weeks after withdrawal from the study. Neither the preceding relapse of CIDP symptoms nor the development of sepsis was judged by the investigator to be drug related.

Discussion

Intravenous immunoglobulin has been used as a treatment of CIDP for many years, either alone or in conjunction with corticosteroids or other immunosuppressive agents. However, before this study, evidence for the efficacy of IVIg had been limited to a few controlled studies with a small sample size and short duration of assessment (≤6 weeks). Only five published randomised controlled trials have assessed the efficacy of IVIg versus placebo.[13,15,16,22,23] A meta-analysis[12] that included four of these randomised trials (N=113) showed that a significantly greater proportion of patients with CIDP who received IVIg improved within 1 month of treatment compared with patients who received placebo. To assess whether the improvement was clinically meaningful, data were collated from three trials in which a Rankin score was used or could be deduced; significantly more patients treated with IVIg improved by at least 1 point compared with patients who received placebo. The researchers concluded that IVIg improved CIDP disability for at least 2–6 weeks compared with placebo and that the efficacy of IVIg was similar to that of oral prednisolone and that of plasma exchange.

Our study confirms that the short-term improvement in adjusted INCAT disability score in response to IVIg is significantly greater than that to placebo. Grip strength, MRC sum score, and ISS score also improved significantly. Investigation of the relations and sensitivity among these scales is ongoing and will be the subject of a separate manuscript. This study did not show a significant improvement in the amplitude of the compound muscle action potential of the most severely affected motor nerve at endpoint during the first period of the study. Routine electrophysiology might not be sufficiently sensitive to capture clinically meaningful changes in the remyelination and regeneration of axons when there is already advanced axonal loss.[24] On the basis of published reports that were reviewed before the study protocol was developed,[13–16,23] the rate of improvement during treatment with placebo in our study was predicted to be 15%. The actual rate was 20%, which is close to the predicted value. Why this rate should be so high across all these studies is unknown, but possible explanations are fluctuations in the course of the disease or a placebo effect arising from participation in a clinical trial and increased medical attention.

The results from the first period of this study were validated during the response-conditional crossover (rescue) period, even though the sample size was smaller in the crossover period. The percentage of patients who were crossover-period adjusted-INCAT responders was similar to the results of the primary efficacy outcome. The extension phase of the trial showed the long-term efficacy of IGIV-C maintenance therapy given every 3 weeks in patients with CIDP. This part of the study was

designed to assess whether patients who had shown an improvement in response to IGIV-C were able to maintain treatment benefit when assigned to IGIV-C therapy or to withdrawal of active treatment. Withdrawal of therapy (ie, re-randomisation to placebo) increased the risk of CIDP relapse. Of the patients who received IGIV-C and were first-period or crossover-period responders, those who continued to receive IGIV-C during the extension phase were free of relapse for significantly longer than were those who received placebo. These results suggest that maintenance therapy with IGIV-C every 3 weeks might prevent relapse and provide long-term benefits to patients with CIDP.

The frequency of adverse events per infusion was low with IGIV-C and did not differ greatly from the frequency with placebo. These results are consistent with or better than those reported in other IVIg studies.[12,25] The incidence of serious adverse events in the IGIV-C group was also low and similar to placebo, even with the long-term administration (every 3 weeks for up to 48 weeks) of high-dose IGIV-C (1 g/kg). Thus, IGIV-C was well tolerated, particularly in light of the short duration of infusion for both the loading and the maintenance doses. Most infusions of IGIV-C were given over 2 days for the 2 g/kg loading doses and 1 day for the 1 g/kg maintenance doses. In previous studies and routine clinical practice, IVIg has often been administered over 5 days in a daily dose of 0·4 g/kg per day.[13,16,22,23] Our results show that 1–2 g/kg of IGIV-C can be safely given over a more convenient, shorter time frame of 1–2 days. This would also result in large cost savings for inpatient and outpatient infusions.

In conclusion, the ICE trial has shown that IGIV-C is more efficacious than placebo. The study was designed to answer clinical questions and to address regulatory requirements, because a well-controlled study of this size and duration to assess the benefits of IVIg therapy had not been published previously. Short-term and long-term improvements in disability as assessed by the INCAT scale were supported by significant improvements in objective clinical measures of grip strength, MRC sum score, and ISS score. Improvement in these secondary and exploratory outcome measures is important, because stronger grip strength and a higher MRC score translate into better functionality for patients.[26] The results also showed the prolonged benefits of IVIg maintenance therapy for patients who improve in response to initial IVIg therapy. The additional evidence for short-term efficacy and first evidence of longer-term benefit provided by this trial strengthen the case for use of IVIg as a first-line initial and maintenance treatment for CIDP,[5] which is likely to affect the care of patients with this disease wherever IVIg is available.

Contributors

RACH, PD, VB, MCD, H-PH, NL, ISJM, and PAvD were members of the ICE Study Steering Committee for Talecris Biotherapeutics. RACH, VB, MCD, H-PH, NL, ISJM, and PAvD participated in study design and the evaluation of study results. CD and KH helped design the trial, interpreted the data, and provided statistical support. CD, KH, NL, and ISJM suggested additional analyses. ISJM supplied training to all participating centres to standardise the use of outcome measures. RACH and PD contributed to development of the first draft and subsequent revisions of the manuscript. All authors critically reviewed and approved the final manuscript.

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Conflicts of interest

CD and KH are employees of Talecris Biotherapeutics. PD, VB, MCD, H-PH, NL, ISJM, and PAvD received honoraria for participation on the ICE Study Steering Committee. RACH has received hospitality and his department has received consultancy fees from Talecris Biotherapeutics. H-PH has received honoraria from Talecris Biotherapeutics for speaking at scientific symposia and for serving on a steering committee.

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