Chronic Inflammatory Demyelinating Polyradiculoneuropathy – An Overview of Intravenous Immunoglobulin Therapy

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Abstract

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a significant source of disability, and early diagnosis and immunomodulatory therapy administration are critical to minimise disease progression and axonal degeneration. Intravenous immunoglobulin (IVIg) therapy is considered to be a first-line treatment for CIDP. Comparative short- and long-term data of IVIg versus corticosteroids in CIDP patients are limited. Of the five published placebo-controlled studies in CIDP, four reported only on short-term improvements in disability (≤6 weeks). However, the IGIV CIDP Efficacy (ICE) study, the largest randomised, placebo-controlled CIDP study published to date (n=117), reported significant improvements in disability, functional impairment and quality of life with IVIg (Gamunex®) 1g/kg maintenance therapy every three weeks for up to 48 weeks. Furthermore, long-term IVIg administration was safe and well tolerated, particularly given the short duration of the infusions. Data suggest that a long-term scheduled maintenance regimen of IVIg in appropriate patients may provide substantial benefit and reduce the risk of CIDP relapse.

Keywords

10% caprylate/chromatography purified, chronic inflammatory demyelinating polyradiculoneuropathy, disability, Gamunex®, efficacy, immune globulin, inflammatory neuropathy cause and treatment, intravenous, safety

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a significant source of disability[1] and commonly presents as a progressive, symmetrical weakness in both proximal and distal muscles.[2] Underdiagnosis remains a concern, but the prevalence of CIDP worldwide is estimated to be up to eight individuals per 100,000 of the population[1,3–8] and it accounts for ~14% of cases of disabling peripheral neuropathies in individuals >65 years of age.[9] Long-term prognosis with CIDP is unpredictable in its early stages, and patients may experience a progressive or chronic relapsing course.[10] Due to the irreversible damage related to ongoing demyelination and secondary axonal loss in CIDP, early diagnosis and administration of immunomodulatory therapy is critical to minimise further disease progression and axonal degeneration.

Several therapies have been administered in the management of CIDP, with intravenous immunoglobulin (IVIg) therapy and corticosteroids considered first-line treatment options for sensorimotor CIDP.[11,12] Furthermore, guidelines recommend IVIg versus corticosteroids as first-line therapy for pure motor CIDP.[11] Although the immunomodulatory mechanism of action of IVIg in CIDP has not been fully elucidated, data from other diseases have suggested that IVIg may inhibit autoantibody production, modulate inflammatory mediators and adhesion molecules, induce blockade of Fc receptors (FcRs) on phagocytic cells, alter the activation, differentiation and effector functions of T cells and inhibit complement activation and prevention of membrane attack complex formation.[13,14]

Dosing and duration of IVIg therapy in clinical practice have previously been based on data from small clinical trials,[15,16] with initial treatment of a 2g/kg dose administered over two to five consecutive days.[11,12] Maintenance therapy has been recommended for consideration until the maximum benefit has been achieved and then a dose reduction to find the lowest effective dose.[12] However, specific dosing and duration guidelines for maintenance therapy have been lacking, and recommendations have varied from weekly to monthly intervals. Furthermore, long-term published data were limited to non-randomised trials.[17–19] In 2008, the IGIV CIDP Efficacy (ICE) study was published, which demonstrated the long-term benefit of IVIg 1g/kg every three weeks as maintenance therapy for CIDP.[20] This article will review the efficacy and safety data of IVIg in the treatment of CIDP.

IVIg versus Placebo

Five randomised, placebo-controlled trials have been published evaluating IVIg versus placebo in the treatment of CIDP,[15,16,20–22] and a Cochrane systematic review[23] evaluated the pooled data from these studies (n=235). A significantly higher percentage of patients treated with IVIg demonstrated an improvement in disability within six weeks of treatment initiation versus placebo (relative risk [RR] 2.40, 95% confidence interval [CI] 1.72–3.36), with a number needed to treat of three to observe an improvement in disability.[23] Four of the five studies evaluated only short-term improvement in disability (≤6 weeks).[15,16,21,22] However, the ICE study, the largest randomised, placebo-controlled

Table 1: Efficacy of Intravenous Immunoglobulin, 10% Caprylate/Chromatography Purified versus Placebo in Patients with Chronic Inflammatory Demyelinating Polyneuropathy

	First Period				Extension Phase			
	Change from Baseline, Mean ± SD				Change from Baseline[a] Mean ± SD			
Parameter	IGIV-C (n=59)	Placebo (n=58)	LSM Difference (95% CI)	p-value	IGIV-C (n=31)	Placebo (n=26)	LSM Difference (95% CI)	p-value
Adjusted INCAT disability score[20]	-1.1±1.8	-0.3±1.3	-0.7 (-1.3 to -0.2)	0.010	0.1±0.7	0.4±1.7	-0.5 (-1.2 to 0.2)	0.181
Grip strength, kPa[20]								
Dominant hand	13.2±19.3	1.5±15.6	10.9 (4.6–17.2)	0.0008	-0.8±11.3	-3.9±20.9	4.3 (-5 to 13.6)	0.353
Non-dominant hand	13.3±17.4	4.3±14.9	8.6 (2.6–14.6)	0.005	-0.3±11	-5.6±22.7	5.8 (-4.1 to 15.7)	0.247
MRC sum score[20]	3.3±5.6	0.2±4.5	3.1 (1.3–4.9)	0.001	0.8±4.1	-1±4.4	2 (-0.3 to 4.3)	0.081
ISS score[20]	-1.2±3.4	0.2±3.9	-1.5 (-2.7 to -0.2)	0.021	-0.5±4	0.2±2.6	-0.4 (-2.3 to 1.5)	0.667
Most severely affected motor nerve, excluding Erb's* point[24,b]	1.08±2.15[c]	0.46±2.03[c]	0.66 (-0.10, 1.41)	0.089				
Averaged CMAP amplitude of all motor nerves, mV[24,b]	0.75[c]	0.13[c]	0.62 (0.05, 1.2)	0.035				
Conduction block for all extremity motor nerves, %[24,b,d]	-4.91±16.51	1.44±12.79	-5.54 (-10.43, -0.64)	0.027				

SD = standard deviation; CI = confidence interval; CMAP = compound muscle action potential; IGIV-C = intravenous immunoglobulin , 10% caprylate/chromatography purified; INCAT = inflammatory neuropathy cause and treatment; ISS = INCAT sensory sum; LSM = least squares mean; MRC = Medical Research Council.
*a. Baseline refers to the last measurement before starting treatment during the extension phase; b. Data reported for first period only; c. Data are least squares mean; d. Conduction block was calculated as the reduction in amplitude from the most distal measurement site to the most proximal measurement site divided by the amplitude in the most distal measurement site and multiplied by 100. *Erb's point was excluded from consideration of most proximal site in conduction block calculation. Adapted with permission from Hughes et al., 2008.[20]*

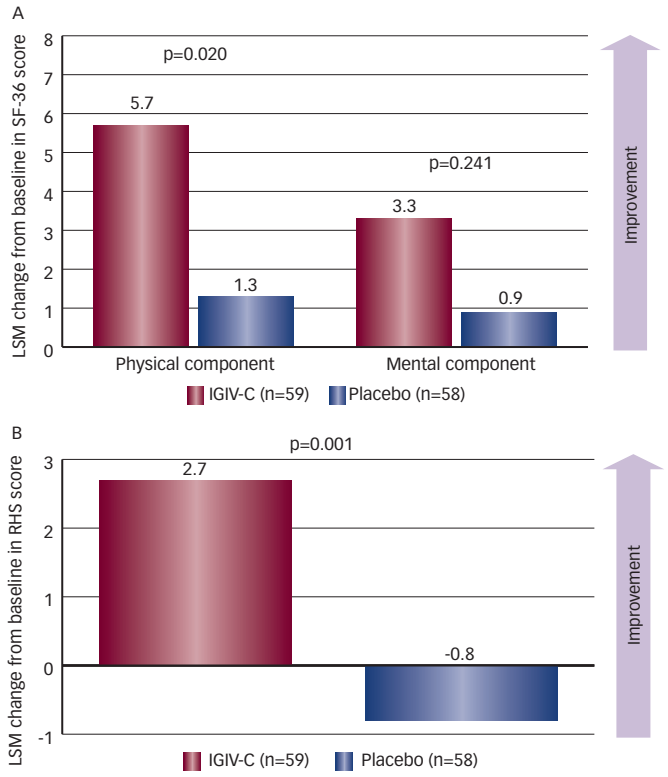
study in CIDP published to date, assessed the efficacy and safety of IVIg scheduled maintenance therapy for up to 48 weeks.[20,24,25]

The ICE Study

The ICE study was a randomised, double-blind, placebo-controlled trial that employed a unique study design.[20] The design included an initial 24-week period, a response-conditional cross-over period to provide rescue therapy if needed (24 weeks) and an additional 24-week re-randomised, blinded extension phase for patients who responded to study medication during the initial treatment period or the cross-over (rescue) period. A total of 117 adults with previously or newly diagnosed CIDP, progressive or relapsing motor and sensory dysfunction of at least one limb resulting from neuropathy over the two months before study entry and significant disability as defined by an inflammatory neuropathy cause and treatment (INCAT) disability score of 2–9 were treated with IVIg (human), 10% caprylate/chromatography purified (IGIV-C, Gamunex®, Talecris Biotherapeutics, Inc., Research Triangle Park, NC) or placebo. Patients received a baseline loading dose of 2g/kg over two to four days and then a maintenance infusion of 1g/kg over one to two days every three weeks for up to 24 weeks (first period). Patients whose adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) score did not improve from baseline by ≥1 point by week six or deteriorated at any visit crossed over to the alternative (rescue) therapy and were treated for up to 24 weeks (cross-over period). The primary efficacy end-point was the percentage of patients who responded to initial treatment (first period) without crossing over to rescue therapy. Patients who crossed over to rescue therapy were considered non-responders. Response was defined as ≥1-point improvement from baseline in the adjusted INCAT disability score to week 24. Patients who responded to initial treatment (primary end-point) or responded to rescue therapy (cross-over period) and completed 24 weeks of treatment were re-randomised to receive IGIV-C 1g/kg every three weeks or placebo in a double-blind 24-week extension phase. A goal of the extension phase was to determine whether initial clinical benefits of routinely scheduled IGIV-C therapy were maintained. During the extension phase, patients who relapsed (defined as ≥1-point worsening in extension-phase baseline-adjusted INCAT score) were discontinued from the study. A significantly greater percentage of patients treated with IGIV-C responded versus placebo (54 versus 21%, respectively; p=0.0002).[20] Of the 32 individuals who responded to IGIV-C, 41% improved after the first IGIV-C treatment course and 94% improved after the second IGIV-C treatment course.[26] However, some patients who responded continued to show improvement in disability (INCAT score) after the second treatment course. In fact, the mean time to maximal improvement in IGIV-C responders was 10.2 weeks (range 2.3–24 weeks), suggesting that treatment courses every three weeks beyond six weeks (i.e. two courses) could be beneficial and allow for maximal improvement in disability.[26]

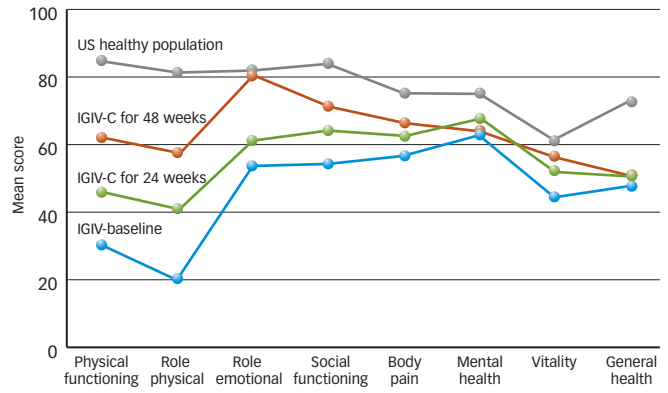
Treatment with IGIV-C significantly improved other measurements of clinical disability versus placebo, including hand-grip strength, Medical Research Council sum score and INCAT sensory sum score (see *Table 1*).[20] Improvements in electrophysiological parameters were also observed, including significant improvements in averaged motor

Figure 1: Improvements in Quality of Life



A: Larger improvements during the first period in Short Form-36® (SF-36) component summary scores were observed with intravenous immunoglobulin, 10% caprylate/chromatography purified (IGIV-C) versus placebo, with a greater difference observed in the physical component summary score (p=0.020). B: A significantly larger improvement from baseline in the Rotterdam Handicap Scale (RHS) scores was observed in patients treated with IGIV-C compared with patients treated with placebo (p=0.001). LSM = least squares mean. Reprinted with permission from Merkies et al., 2009.[25]

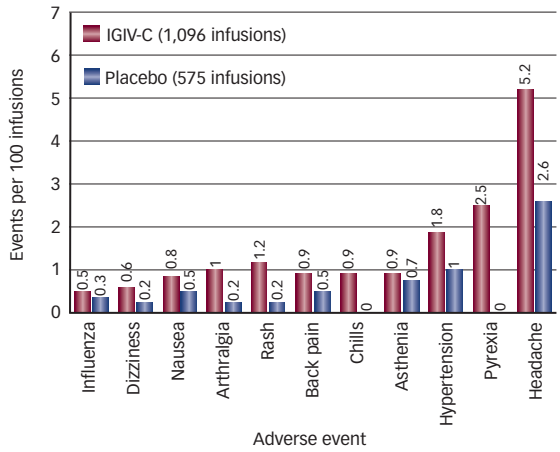
Figure 2: Trend in Quality of Life Improvements versus US Normative Values



Short Form-36® (SF-36) domain changes over time in patients treated with intravenous immunoglobulin, 10% caprylate/chromatography purified (IGIV-C) were compared with a sample of a healthy US population. A gradual improvement from baseline (blue) (n=58) with IGIV-C maintenance therapy every three weeks was observed after 24 weeks (green) (n=57) and 48 weeks (red) (n=27) in all mean SF-36 domain scores, with a trend towards US normative scores (grey) observed. Data from 2,474 healthy volunteers were used to calculate mean normal values.[26] Reprinted with permission from Merkies et al., 2009.[25]

amplitudes and conduction block (see *Table 1*).[24] In addition to improvements in disability and electrophysiological parameters, significant improvements in quality-of-life measures were demonstrated with IGIV-C versus placebo, notably in the physical component summary score of the Short Form-36® (SF-36) and the Rotterdam Handicap Scale score (see *Figure 1*).[25] Interestingly, a *post hoc* correlation analysis revealed that the baseline severity of the

Figure 3: Frequency of Adverse Events



Number of adverse events per 100 infusions reported in ≥5% of patients in any treatment group. Events per 100 infusions were calculated by taking the total number of adverse events in the group divided by the total number of infusions in the group (1,096 for the immunoglobulin intravenous, 10% caprylate/chromatography purified [IGIV-C] group and 575 for the placebo group) x 100. Data from Hughes et al., 2008.[20]

electrophysiological parameters did not predict response to IGIV-C treatment, suggesting that patients should not be excluded from receiving treatment based on the severity of abnormal nerve conduction findings.[27] The data were analysed for the subset of patients who had responded to IGIV-C during initial treatment (primary end-point) or rescue therapy and were re-randomised to the 24-week, double-blind extension phase: 31 patients were randomly re-assigned to continue IGIV-C therapy 1g/kg every three weeks and 26 patients were randomly assigned to be switched to placebo.[20] Continued treatment with IGIV-C every three weeks generally maintained or slightly improved several efficacy outcome measures from extension baseline values, whereas patients switched to placebo (withdrawal of IGIV-C) appeared to show a decline, with loss of the improvements initially gained with IGIV-C therapy (see *Table 1*). Patients who continued to receive IGIV-C had a significantly longer time to relapse than patients who received placebo (p=0.011), with a probability of relapse of 13% with IGIV-C compared with 45% with placebo (hazard ratio 0.19, 95% CI 0.05–0.70). In addition to long-term benefits in functional disability, when quality of life was assessed over the duration of the entire study (48 weeks), patients treated with IGIV-C maintenance therapy every three weeks experienced a gradual shift over time (up to 48 weeks) in all SF-36 domain scores towards US normative values (see *Figure 2*).[25] These results are consistent with a small open-label study (n=13) that evaluated IVIg as CIDP maintenance therapy over one year, in which general improvements from baseline in SF-36 scores also shifted towards normative values.[28]

Overall, IGIV-C 1g/kg every three weeks for up to 48 weeks was safe and well-tolerated in patients with CIDP, particularly given the short infusion duration for both loading and maintenance doses.[20] The majority of IGIV-C infusions were administered over two days for the 2g/kg loading doses (IGIV-C 79% of 227 infusions, placebo 73% of 182 infusions) and one day for the 1g/kg maintenance doses (IGIV-C 80% of 869 infusions, placebo 83% of 393 infusions). The safety data were pooled from each period (first period, cross-over period, extension phase) for the 113 patients exposed to IGIV-C and 95 patients exposed to placebo. Exposure to IGIV-C was approximately twice that of placebo (1,096 versus 575 infusions, respectively). To correct for the difference in drug exposure between the two treatment groups, the authors reported the number of adverse events per infusion. The frequency of adverse

events per infusion was low with IGIV-C and did not differ greatly versus placebo. Headache, pyrexia and hypertension were the most common adverse events reported for patients exposed to IGIV-C (see *Figure 3*). Serious adverse events were reported in 0.8 of every 100 IGIV-C infusions compared with 1.9 of every 100 placebo infusions.

IVIg versus Oral Corticosteroids

Comparative short- and long-term data of IVIg versus corticosteroids in patients with CIDP are limited. In a short-term, randomised, double-blind, cross-over (four-week wash-out period) trial, a single course of IVIg 2g/kg administered over one to two days was compared with oral prednisolone tapered from 60 to 10mg/day over six weeks.[29] For the 24 patients who completed both treatment periods, the INCAT disability score significantly improved from baseline for IVIg (0.71±1.27; p=0.012) to a slightly greater degree than prednisolone (0.58±0.93; p=0.005) after two weeks. There were also slightly larger non-significant improvements in other measures of disability (e.g. disability grade after six weeks) for IVIg versus prednisolone. Adverse events were reported for 18 of 30 IVIg courses (60%) and 11 of 27 prednisolone courses (41%), with no significant differences reported for headache, indigestion, fever, rash or hypotension. It is important to note that the trial was not designed or powered to determine equivalence, and the authors suggested that the results may have been biased against IVIg because eight patients did not complete the second arm of the trial.

IVIg versus Plasma Exchange

As plasmapheresis is time- and resource-intensive, requires especially trained staff, may result in rapid deterioration after treatment and is associated with the risk of haemodynamic adverse events,[30] it is generally not recommended as first-line therapy for CIDP.[12] One single-blind, cross-over study has been published comparing IVIg versus plasma exchange.[31] Patients received IVIg 0.4g/kg once a week for three weeks and then 0.2g/kg once a week for three weeks or plasma exchange twice weekly for three weeks and then once weekly for three weeks (duration of wash-out period between treatments varied). Thirteen of 20 patients completed the study. Improvement from baseline in the neuropathy disability score was observed with IVIg (36.1±32; p=0.006) and with plasma exchange (38.3±34.6; p<0.001). Significant improvements from baseline were also reported in mean summated compound muscle action potentials and weakness score for both IVIg and plasma exchange (p<0.002); however, no significant differences were observed between the two groups. During treatment with plasma exchange, two problems were reported with catheters and complications (e.g. light-headedness, nausea and rash) were quite common. No serious complications were reported with IVIg treatment.

Safety Considerations

Although IVIg has been considered one of the safest immunomodulatory agents available for long-term use in all ages in neurology,[32] rare serious adverse events can occur, including thromboembolic events, temporary renal impairment and allergic reactions.[23,33] Reassuringly, in a 2009 Cochrane review evaluating IVIg therapy versus placebo, the RR of development of serious adverse effects was not significantly different between IVIg and placebo (RR 0.82, 95% CI 0.36–1.87).[23] Overall, most adverse events reported for IVIg are mild and transient, and the most common events are typically related to administration (e.g. headache, rash or chills).[23] These events can generally be effectively managed by adjusting the infusion rate or administering anti-inflammatory/antihistamine prophylaxis.[34]

Pharmacoeconomics of IVIg

The pharmacoeconomics of IVIg is influenced by multiple factors, including the product cost, concentration administered, infusion time and duration of therapy. Data are limited, but one randomised, double-blind, cross-over trial published in 2003 compared the cost-effectiveness of a single dose of IVIg 2g/kg (n=12, involved a hospital stay) versus prednisolone (n=13, 60mg/day tapered to 10mg/day) in the treatment of CIDP.[35] The authors suggested that IVIg was more likely to be cost-effective versus prednisolone only if one quality-adjusted life year was valued at >€250,000 (2002 currency rates). However, this figure was based on a single-dose effect and short-term (six week) analysis and extrapolated to an annual gain. It did not address the potential long-term beneficial impact (IVIg as maintenance therapy) and long-term safety concerns (e.g. adverse events with corticosteroids) of the two therapies. Thus, further studies are needed to determine the cost-effectiveness of IVIg maintenance therapy in CIDP.

Conclusions

IVIg is considered a first-line therapy for the treatment of CIDP. The ICE study has provided strong support for the long-term benefits of IVIg therapy for disability and functional impairment and quality of life. Therefore, a long-term scheduled maintenance regimen of IVIg in appropriate patients with CIDP may provide substantial benefit and reduce the risk of disease relapse. Furthermore, high-dose IGIV-C can be safety administered over a more convenient, shorter time-frame (one to two days). Given the substantial limitations of currently published pharmacoeconomic data, robust adequately designed pharmaco-economic studies are warranted to determine the cost-effectiveness of long-term maintenance therapy in reducing the risk of CIDP relapse. ■

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