Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy
A double-blind, placebo-controlled, cross-over study

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Summary

Thirty patients with definite or probable chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) of chronic progressive (16 patients) or relapsing (14 patients) course were randomly assigned to receive intravenous immunoglobulin (IvIg) 0.4 g per kg body weight or a placebo treatment on 5 consecutive days in a double-blind, cross-over trial. Neurological function was monitored by serial quantitative assessments [neurological disability score (NDS); clinical grade (CG) and grip strength (GS) measurements] and by electrophysiological studies before and after each treatment period. Twenty-five patients completed both treatment periods. A comparison of the observed changes in clinical outcome measures revealed statistically significant differences in favour of IvIg, with (mean±SD) improvements in NDS by 24.4±5.4 points (P < 0.002) in CG by 1±0.3 points (P < 0.001) in GS by +6.3±1.7 kg (P < 0.005), whereas scores were unchanged or worse with placebo. A secondary two-group analysis of the first trial period included all 30 patients; 16 patients had been randomly assigned to IvIg and 14 to placebo treatments. Again significant differences in favour of IvIg were observed in all the clinical end-points: improvement in NDS was 35.6±25 points (P < 0.0001), in CG it was 1.3±1.9 points (P < 0.002) and in GS +9.8±7.7 kg (P < 0.001), whereas

all scores worsened with placebo. Of the 30 patients, 19 (63%) improved with IvIg treatments; nine out of 16 patients (56%) with chronic progressive CIDP, and 10 out of 14 patients (71%) with relapsing CIDP (differences were not statistically significant). A placebo response was seen in five patients. Comparison of paired electrophysiological measurements before and 4 weeks after IvIg treatments revealed statistically significant improvements in the summed motor conduction velocities (Σ MCV; P < –0.0001) and in the summed compound muscle action potentials (CMAP) evoked with proximal stimulation (Σ proximal CMAP, P < 0.03) of median, ulnar, peroneal and tibial nerves. Eight of nine IvIg responders with chronic progressive CIDP improved gradually to normal function with a single 5 day course of IvIg; in five of these, small doses of prednisone were prescribed during follow-up. In 10 IvIg responders with relapsing CIDP, improvement lasted a median 6 weeks (range 3–22 weeks) and was reproducible with open label treatments. All 10 patients have been maintained and stabilized with IvIg pulse therapy of 1 g per kg body weight or less, given as a single infusion prior to the expected relapse. A beneficial response to IvIg was found to be most likely in patients with acute relapse or with disease of one year or less. Patients with predominantly sensory signs did not improve.

Key words: chronic demyelinating polyneuropathy; CIDP; double-blind trial; conduction block; immunoglobulin, intravenous

Abbreviations: CG = clinical grade; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CMAP = compound muscle action potential; GBS = Guillain–Barré syndrome; GS = grip strength; NDS = neurological disability score; IvIg = intravenous immunoglobulin; NBL = neuroblastoma cell line

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy is an acquired paralytic illness associated with considerable long-term morbidity and disability (Dyck *et al.*, 1975; Barohn *et al.*, 1989). The disease may show either continuous or stepwise progression over months to years or may take a more fluctuating course (McCombe *et al.*, 1987). Spontaneous improvements are uncommon (Hughes *et al.*, 1992; Vermeulen *et al.*, 1993). The cause of CIDP is unknown. However, current evidence supports an auto-immune aetiology (*see* review in Hartung *et al.*, 1994). This concept forms the basis of the present therapeutic approaches, which are aimed at modulating the aberrant immune responses. Patients with CIDP often show improvement with a prescription of corticosteroids and/or of therapeutic plasma exchange. The utility of these treatments has been demonstrated in randomized controlled clinical trials (Dyck *et al.*, 1982, 1986; Hahn *et al.*, 1996). Despite their proven efficacy, both treatments have known disadvantages. The chronic course of the disease requires a long-term prescription of corticosteroids, which carries the risk of potentially serious side effects (Dyck, 1990). Plasma exchange, on the other hand, is a relatively safe procedure (Rodnitzky and Goeken, 1982) but its beneficial effect in CIDP is usually transient, reducing its use to adjuvant therapy (Pollard *et al.*, 1987; Hahn *et al.*, 1996). Moreover, plasma exchange is expensive, it can only be carried out in specialized centres and the repeated procedures require good vascular access (Shumak and Rock, 1984; Thornton and Griggs, 1994).

The report that some CIDP patients may derive substantial benefit from infusions with either freshly frozen plasma or gamma globulin (IvIg) was met with great interest (Vermeulen *et al.*, 1985). Several subsequent reports have documented that high dose IvIg can be an effective and safe treatment for selected patients with CIDP (Curro Dossi *et al.*, 1987; Faed *et al.*, 1989; van Doorn *et al.*, 1990*a*; Churchyard *et al.*, 1991; Cornblath *et al.*, 1991; Vedanarayanan *et al.*, 1991; Azulay *et al.*, 1992; Dyck *et al.*, 1994). However, in these studies the proportion of patients that was improved with IvIg therapy ranged from 20% to 100% and depended very much on patient selection. Moreover, most of these analyses had been retrospective, uncontrolled and non-blinded. The only prospective, double-blind, placebo-controlled study of IvIg in 28 unselected patients, did not show differences in the degree of improvement between IvIg and sham-treated patients (Vermeulen *et al.*, 1993). This failure to demonstrate benefit with IvIg contrasted very much with the previous experience and practice in open label treatments reported by the same investigators (van Doorn *et al.*, 1991). Thus, there is evidently a need for further critical evaluation of this treatment in CIDP and for a clearer definition of predictors of response (Thornton and Griggs, 1994; van Doorn, 1994).

In the following, we report observations derived from a prospective, double-blind, placebo-controlled, cross-over assessment of IvIg in 30 CIDP patients who had not been treated with IvIg before. We have found substantial benefit with this therapy in 19 out of 30 patient or 63% overall. Sustained improvement occurred in nine out of 16 patients (56%) with chronic progressive CIDP, whereas in chronic relapsing CIDP the therapeutic benefit, observed in 10 out of 14 patients (71%), was only temporary but reproducible. The latter patients were stabilized with long-term IvIg pulse therapy.

Methods

Patient selection

Patients were recruited prospectively between 1990 and 1994 at the neuromuscular clinics of London, Ontario and Calgary, Alberta; to enter the trial they had to fulfill the diagnostic criteria of definite (all four criteria) or probable (three of four criteria) CIDP (Ad Hoc Subcommittee, 1991). For newly diagnosed patients the neuropathy had to be continuously progressive for >8 weeks; cases with previously established diagnosis of chronic progressive or relapsing CIDP had to be either static or show recent deterioration. The diagnosis was reconsidered in each case and patients were carefully screened to rule out other diseases that could have produced the neuropathy. Such patients, including those with monoclonal gammopathy of unknown significance, were excluded. (Monoclonal paraproteins were determined by high resolution agarose gel serum and urine electrophoresis, Ig quantification and immunofixation techniques; localized myeloma was excluded by radiological skeletal survey.) Muscle weakness had to be severe enough to interfere with secure ambulation (NDS $\geqslant$ 40) and patients *must not* have been treated with IvIg before. Patients who had been treated previously with various other forms of immunomodulatory therapy were permitted to take part in the trial. However, they were not to receive any other treatment for their disease during the trial except low dose prednisone (<20 mg per day) if the prescription had been long term (>3 months) and if it was not altered before or during the trial. There was no overlap between this trial and a parallel study of therapeutic plasma exchange in CIDP (Hahn *et al.*, 1996). Patients or (in two cases) guardians signed an informed consent approved by the Ethics Review Board for Human Experimentation at each of the two institutions.

Study design

The study was designed as a double-blind, placebo-controlled, cross-over trial. The participating patients, the evaluating neurologist, the electromyographer and the nurses administering care and infusions were blinded to the nature of the treatment during the controlled portion of the trial. Only the study co-ordinator and the blood bank personnel were non-blinded.

The trial consisted of two identical 28-day periods

Table 1 *Clinical grading scale employed for functional assessments*

Grade	Definition
0	Normal
1	No disability; minor sensory signs or areflexia
2	Mild disability; ambulatory for >200 m; mild weakness in one or more limbs and sensory impairment
3	Moderate disability; ambulatory for >50 m without stick; moderate weakness MRC Grade 4 and sensory impairment
4	Severe disability; able to walk >10 m with support of stick; motor weakness MRC Grade 4 and sensory impairment
5	Requires support to walk 5 meters; marked motor and sensory signs
6	Cannot walk 5 m; able to stand unsupported and able to transfer to wheelchair; able to feed independently
7	Bedridden, severe quadriparesis; maximum strength MRC Grade 3
8	Respirator and/or severe quadriparesis; maximum strength MRC Grade 2
9	Respirator and quadriplegia
10	Dead

separated by a variable 'washout' period. Patients were randomly assigned to receive IvIg (Cutter Biological Products, Miles Inc.) in standard dose (*see* below) or placebo infusions (10% dextrose) on 5 consecutive days. To ensure that blinding was complete the infusions (IvIg as well as placebo) were delivered from the transfusion services in identical opaque 600 ml transfer packs fitted with a sampling site coupler (Fenwal Laboratories, Baxter Health Care Corporation, Deerfield, Ill., USA). Patients were monitored closely. The neurological function was assessed by the same blinded observer on days 1, 5, 21 and 28, with a quantitative NDS (modified from Dyck *et al.*, 1982), assignment of a CG and GS measurements. Electrophysiological measurements were made at the beginning and end of each treatment period. Since the disease course was expected to be variable, the following rules were predefined. Patients whose NDS changed <20 points from baseline during the first study phase were to be crossed over into the second arm on day 28. Patients found on day 28 to have improved by >20 points from baseline NDS were to be monitored and crossed over into the second phase when they had returned to their baseline score. Patients, who on day 21 were found to have deteriorated by >20 points in NDS, were to be crossed over prematurely into the second trial phase; they were designated as treatment failures. Extrapolating from the results of the previous neuropathy trials of Dyck *et al.* (1986) which had employed similar outcome measures, we predefined the criteria indicating improvement in the neuropathy as a change in the NDS of 20 points or greater and/or improvement by one CG or more. The code for individual patients was broken after completion of the second trial or at the time of trial analysis. Before the code was broken, study subjects and investigators were questioned regarding treatment effect and study phase

assignments. However, a formal analysis of blinding was not performed.

Neurological assessments

All patients were assessed by the same blinded observer. Tests included the measurements of an NDS (modified from Dyck *et al.*, 1982), comprised of the summed score of strength in 26 muscle groups; the summed score of sensation; assessment of the tendon reflexes (0 = normal, 1 = reduced, 2 = absent) and of tremor (0 = absent, 1 = present); dynamometer (Jamar™, TEC, Clifton, NJ, USA) (Mathiowetz, 1984) measurements of maximal hand grip (best of three) and assignment of a functional CG (Table 1). Each assessment was made and recorded independently; the earlier records were not made available to the evaluating neurologist until the trial period was completed. Inter-observer agreement was tested before the study began and was found to be very good. The NDS provides a reproducible quantitative assessment of a patient's neurological impairment. While some observer/patient bias may occur despite blinding, the validity of the method has been demonstrated (Dyck *et al.*, 1994).

Electrophysiological studies

A standardized set of electrophysiological measurements was made in the right arm and leg at the beginning and end of each treatment period, using conventional techniques with surface electrode recordings and monitoring of limb temperature. Tests included assessment of motor nerves: median, ulnar (four-point stimulation: wrist, distal and proximal to elbow, axilla), tibial and peroneal (three-point stimulation: ankle, fibular head, popliteal fossa) to determine motor response amplitude and duration following distal and proximal stimulation, terminal latencies, conduction velocities and F response latencies. Sensory nerves were also assessed: the median (II), ulnar (V) and sural nerves were stimulated antidromically to determine evoked sensory nerve action potential amplitudes and duration, distal latencies and conduction velocities. Needle electromyography of biceps, first dorsal interosseous, vastus medialis and peroneus brevis was carried out to evaluate the presence of fibrillation potentials and positive sharp waves, and the motor unit configuration and recruitment.

Nerve biopsy

A nerve biopsy was not an absolute requirement for participating in this trial. However, it had been performed in many study subjects as part of their diagnostic work up. Variably, the sural, superficial and deep peroneal nerves were biopsied near the ankle. A portion of each specimen was fixed in 2.5% buffered glutaraldehyde one part was processed for teased fibre studies and another part for embedding in epon according to standard techniques (Dyck *et al.*, 1993) to

Table 2 *Observations in the cross-over analysis (n = 25)*

Outcome measures	IvIg treatment		Sham treatment		Significance[+]
	Before	After	Before	After	
Neurological disability score	76.2±5.5	51.8±5.2	62.7±5.7	67.5±6.1	$P < 0.002$
Clinical grade	4.6±0.3	3.6±0.3	3.6±0.3	4.0±0.3	$P < 0.001$
Grip strength[*] (kg)	11.5±1.6	17.8±1.8	16.6±1.9	15.8±1.9	$P < 0.005$

Mean±SD. [*]Measured in 22 patients. [+]P values were obtained from ANOVAs repeated measures option and refer to differences in the effect of IvIg and sham treatments.

allow examination by light and electron microscopy. Teased fibres were analysed according to the classification of Dyck *at al.* (1993).

Laboratory studies

Cerebrospinal fluid, serum protein electrophoresis, serum and urine immune electrophoresis, IgA, IgM and IgG quantification, serum glucose, electrolytes, urea, creatinine, albumin, liver profile, glycosylated haemoglobin and radiological skeletal surveys were performed in most study subjects.

IvIg infusions

All infusions were given either on a hospital ward or in a special out-patient treatment centre with close monitoring for potential anaphylaxis or side effects. IvIg (Cutter Biological Products, Miles Inc; 5% human protein in 9–11% mannose) or placebo (10% dextrose) solutions were delivered from the institutional blood bank in identical opaque infusion bags (Fenwal transfer packs, *see* above). Intravenous Ig was prescribed at a dose of ~0.4 gm per kg body weight per infusion on 5 consecutive days. Each infusion was started with a test dose of 25 ml given over 30 min with cautious surveillance for possible anaphylaxis. The infusion was then continued at a rate of 125 ml h^{-1} with hourly monitoring of heart rate, blood pressure, body temperature and of side effects (e.g. headaches, nausea, etc.).

Statistical analysis

The two-period, double-blind, cross-over design was chosen because of its statistical efficiency. Moreover, in this design, each patient acted as his/her own control, enabling a more precise estimate of the treatment effect in the individual patient. However, the design assumes that effects of the first treatment would be 'washed out' by the time the second treatment begins. To address this concern, we also carried out a two-group analysis (active treatment versus sham) of only the first treatment phase. Power and sample size calculations were based on observations by Dyck *et al.* (1986) in a previous trial of CIDP. A sample size of 15 patients per group was large enough to detect differences in NDS of 20 points and greater at $\mu = 0.05$ with 80% power.

Baseline information was used to assess the response to IvIg in a subgroup analysis. As primary end points to measure treatment efficacy, we used the NDS, CG and GS measurements. As secondary end points we used selected electrophysiological measurements obtained from the study of the right arm and leg: the summed CMAPs of median, ulnar, tibial and peroneal nerves in response to proximal (Σ prox. CMAP) and distal stimulation (Σ dist. CMAP); the summed motor conduction velocities (Σ MCV), and the summed distal motor latencies (Σ DML) of median, ulnar, tibial and peroneal nerves.

All analysis was conducted in PC SAS, version 6.08. All P values reported are directly from PROC GLM, with the repeated measures option specified (SAS Institute Inc. User's Guide, 1990). For a secondary analysis in which we compared the electrophysiological measurements at baseline with those recorded 4 weeks after IvIg treatments we employed a paired Student's t test (data were normally distributed). A P value <0.05 was considered to be statistically significant. Unless stated otherwise, results are presented in the main text as mean±SD.

Results

Thirty patients, 19 female and 11 male, with a mean age of 52 years (range 9–79 years) were randomized for the trial. All patients had been shown by prior clinical and electrophysiological examinations to be suffering from an acquired demyelinating motor and sensory neuropathy of variable severity and duration (median 12 months; range 9 weeks to 21 years). At entry into the study they were considerably disabled (NDS = 77.5±27; CG = 4.4±1.8). The diagnosis of CIDP was confirmed by typical findings on electrophysiological examination (30 patients; median nerve motor conduction velocities = 26.6±9.8 m s^{-1}; findings of associated ongoing axonal degeneration and of axonal loss varied among recorded nerves and between subjects) on CSF examination (28 patients) and in nerve biopsies (23 patients). Thus a definite diagnosis of CIDP could be made in 21 patients (meeting all four criteria) while the diagnosis of CIDP was probable in the remainder (diagnosis confirmed by two of three laboratory criteria). The disease took a chronic progressive course in 16 patients and was chronic relapsing in 14 patients. Twelve of the 30 patients had received no prior treatments for CIDP, the others had previously been

Table 3 *Observations in the two-group, first phase analysis (n = 30)*

Outcome measures	IvIg treatment		Sham treatment		Significance[‡]
	Before	After	Before	After	
Clinical measures					
Neurological disability score	78.3±27.5	42.7±23.7	76.6±27.7	80.1±26.7	$P < 0.0001$
Clinical grade	4.6±1.9	3.3±1.9	4.2±1.9	4.7±1.9	$P < 0.002$
Grip strength[*] (kg)	8.7±6.9	18.5±8.5	16.0±9.9	15.3±9.2	$P < 0.001$
Electrophysiology[†]					
Σ MCV (m s^{-1})	98.7±43.1	114.0±45.1	108.3±43.9	95.1±35.9	$P < 0.0001$
Σ distal motor latency (ms)	33.9±13.9	30.0±15.1	27.6±15.3	28.8±15.4	$P < 0.04$
Σ distal motor amplitude (mV)	13.9±8.8	15.8±9.1	14.5±7.9	14.2±7.1	$P < 0.08$
Σ proximal motor amplitude (mV)	7.4±6.1	10.6±6.9	8.5±4.5	9.2±5.6	$P < 0.1$

Mean±SD. [*]Measured in 28 patients.[†]Only 23 complete electrophysiological measurements were available for analysis. [‡]P values were obtained from ANOVAs repeated measures option; and refer to differences in the effect of IvIg and sham treatments.

Table 4 *Electrophysiological measurements before and 4 weeks after IvIg treatments*

Electrophysiology	Before	After	Significance
Σ MCV (m s^{-1})	97.4±7.5	110.7±8.2	$P < 0.0001$
Σ distal motor latency (ms)	32.7±2.9	30.5±3.2	$P < 0.1$
Σ distal motor amplitude (mV)	14.7±1.6	15.8±1.6	$P < 0.1$
Σ proximal motor amplitude (mV)	8.1±1.2	10.2±1.2	$P < 0.03$

Mean±SE of the 22 complete data sets which were available; P values were obtained from the paired Student's t test comparing paired observations from each patient.

prescribed the following treatments, either alone or in various combinations; prednisone, ACTH, azathioprine, methotrexate, cyclophosphamide and plasma exchange. In some patients these treatments had intolerable or serious side-effects, requiring their prompt discontinuation. In general, patients disliked the effects of long-term immunosuppression and were keen to search for alternate therapies.

Observations with IvIg

Cross-over trial

The results of the cross-over trial are summarized in Table 2. Complete data for the two treatment periods were available for 25 patients. Two patients improved after the first treatment arm and continued to improve, so they were not crossed over. The code in these patients was broken at the time of data analysis; both had received active treatment in the first phase. One patient developed side effects resembling aseptic meningitis with the active IvIg treatment given during the first trial phase, this resulted in disclosing the code to the observer. Serial clinical and electrophysiological assessments of this patient documented unquestionable improvement which lasted 25 days, after which his function declined rapidly to baseline. He received a second infusion under blinded conditions, did not develop headaches and did improve to the same degree and for approximately the same duration. On breaking the code it was disclosed that both infusions had contained IvIg. The patient was therefore only included in the first phase analysis. He continued to respond favourably to IvIg pulse therapy given every 3 weeks. Two

other patients completed the full trial, they did not change with either treatment and did not return for the final assessment at 4 weeks. An analysis of the remaining 25 patients indicated that the clinical severity did not differ significantly beween subjects prior to active treatment or sham treatment; if anything, impairment on average was slightly greater prior to IvIg. Statistically significant improvements favouring IvIg treatments were noted in all end points and clinical outcome measures: in NDS by 24.4±5.4 points ($P < 0.002$); in CG by 1±0 point ($P < 0.001$); and in GS by +6.3±1.7 kg ($P < 0.005$), whereas, on average, all scores worsened slightly during sham treatments.

First phase analysis

In a secondary analysis we included all 30 patients and examined only the first phase of the trial; 16 patients had been randomly assigned to receive IvIg in the first phase and 14 patients to receive sham treatments. The results are summarized in Table 3. The severity of disease at entry into the study was comparable in the two groups, with the exception of GS measurements, which were considerably lower in the IvIg treated group. Once again, significant improvements were seen with IvIg treatments in all clinical end points: NDS improved by 35.6±25 points ($P < 0.0001$); CG by 1.3±1.9 points ($P < 0.002$); and GS by 9.8±7.7 kg ($P < 0.001$), whereas on average the sham treated group had worsened slightly.

Twenty-three complete electrophysiological data sets were

available from the first study phase for statistical analysis. The results of the statistical analysis are given in Table 3. At the end of the first trial phase statistically significant differences favouring IvIg treatments were observed in summed motor conduction velocities ($P < 0.0001$) and summed motor distal latencies ($P < 0.04$). Differences were also observed in the distal and proximal evoked CMAP but they did not reach statistical significance.

Subgroup analysis

When we analysed the patients individually using the predefined criteria for improvement (for details *see* Methods) we found a response to treatment in 19 out of 30 patients (63%); this had occurred in nine out of 16 patients with chronic progressive disease (56%) and in 10 out of 14 patients with chronic relapsing disease (71%) (the differences in response between the two groups were not statistically significant). A non-sustained placebo response was seen in five patients (17%). Four of these had been randomly assigned to the placebo in the first phase and of those, two showed a subsequent greater response with active treatment.

Patients with chronic progressive disease tended to be older (mean±SE of 63.5±3.1 years, range 36–79 years) and their disease was of shorter duration (median 4 months, range 9 weeks to 14 years). In contrast, patients with relapsing CIDP were younger (mean±SE of 37.5±5.3 years, range 9–76 years); and the duration of disease varied greatly (median 60 months, range 3 months to 21 years). Only five patients in the latter group had been recently diagnosed and had been symptomatic for <12 months. The remaining nine patients had been followed long term. They were studied during an acute relapse.

We also compared the electrophysiological measurements recorded at baseline with those recorded 4 weeks after IvIg treatment received in either the first or second trial phase (Table 4; complete paired data sets were available for 22 patients). Statistically significant improvements were observed in the summed motor conduction velocities ($P < 0.0001$) and in the summed proximal CMAP amplitudes ($P < 0.03$); the summed distal CMAP amplitudes and latencies were not significantly changed.

Observation during follow-up and with open label IvIg treatments

After completion of the controlled trial, follow-up was possible in all patients but one (for a mean±SE of 29.5±2.3 months, range 12–52 months).

The nine patients with chronic progressive CIDP who improved with IvIg, were given only a single 5-day course of infusions. Their neurological function was monitored by the same assessments, monthly where possible, over 1 year or else every 3 months for a mean follow-up of 25.0±2.2 months (mean±SE; range 12–37 months). All patients

showed gradual and continuous improvement: seven regained normal function; one is left with a partial foot drop and another with a mildly ataxic gait secondary to residual sensory deficits. Three patients had received IvIg infusion only. When the initial effect of IvIg appeared to have levelled off five patients were prescribed small doses of prednisone (≤25 mg per day, with a tapering schedule over several months). Their neurological function had improved so much that the expense of a second course of IvIg did not seem to be warranted. Only one patient was re-treated with IvIg upon secondary deterioration; benefit was again demonstrated on two occasions. However, since this patient was not stabilized and was still wheelchair bound, prednisone (50 mg per day with a tapering schedule over 6 months was added). The combined treatments resulted in a return to normal function.

During the blinded trial, 10 patients with chronic relapsing CIDP showed substantial and quantifiable improvements with IvIg treatments. However, the beneficial effects of IvIg were only temporary and lasted a median of 6 weeks (range 3–22 weeks). Upon relapse, we retested and confirmed the response with a second open label 5-day course of IvIg infusions; this also helped in determining the duration of the IvIg treatment effect for individual patients. Although the duration of the treatment benefit varied considerably it could be predicted fairly accurately for each patient. Nine patients were maintained on long term IvIg pulse therapy on this basis; it was given prior to the expected deterioration or at the very earliest sign of relapse. The dose of IvIg was titrated, as a rule to ≤1 mg per kg body weight, and was given by a single day infusion. By this approach, we sought to determine the minimal dose required to improve function to a normal or near normal level. This pulse therapy has been maintained for a mean±SE of 34.7±4 months (range 15–50 months) and it has lead to sustained and incremental improvements. Seven out of the 10 patients have received no other therapies, however, they require regular infusions to maintain full function. Small doses of prednisone (≤0.5 mg per kg) were added for the other three patients; the combined treatments have resulted in stabilization and full recovery in all three.

Patients who had not improved with IvIg were offered alternate therapies. Six out of these 11 patients (three with chronic progressive course and three with relapsing CIDP) improved with plasma exchange treatments and/or prednisone. Two of these recovered gradually to normal function within 12–18 months; the remainder were left with moderate disability caused by distal atrophy, weakness and sensory deficits, due to chronic axonal loss. Since both treatments were given simultaneously, the benefit of either alone could not be determined. A further five patients, with either slow or stepwise progressive disease, were refractory to treatments with either prednisone, azathioprine, methotrexate or oral cyclophosphamide, given alone or in combination. They were also not improved with trials of plasma exchange therapy. Of these, four patients had a predominantly sensory deficit and associated large amplitude action tremors.

Discussion

In this prospective, controlled and blinded assessment of IvIg in 30 CIDP patients who had not been previously treated with IvIg, we demonstrated therapeutic benefit in 19 patients (63%). At 4 weeks after a single 5 day course of IvIg infusions, significant improvement had occurred in all clinical end points; the mean change in NDS was 35.6 points ($P < 0.0001$) in CG 1.3 points ($P < 0.002$) and in GS +10 kg ($P < 0.001$). This analysis compared observations in 16 IvIg-treated versus 14 sham-treated patients of the first trial phase. Comparable improvement in neurological disability had been observed by Dyck *et al.* (1994) in 15 CIDP patients, who had received weekly single day IvIg infusions over a course of 6 weeks. This observer-blinded study was aimed to compare the beneficial effects of IvIg and plasma exchange treatments in the same patient. Patients had not been selected for their response to IvIg. However, approximately two-thirds had been previously treated. Our observations differ from the results of the only available prospective and controlled trial which followed a similar 5 day treatment design (Vermeulen *et al.*, 1993). Surprisingly, the latter trial did not show benefit with IvIg and failed to confirm the investigators' previous observations. In an earlier retrospective analysis of 52 CIDP patients treated with open label IvIg, van Doorn *et al.* (1991) reported therapeutic benefit in 32 patients (62%), a remarkably similar response rate to that observed in our patient sample. However, unlike us they found no correlation between disease course and response to treatment. In our sample, patients with chronic progressive CIDP were less likely to respond (56%, i.e. nine out of 16 patients) than those with chronic relapsing CIDP (71% i.e. 10 out of 14 patients). This may be due, in part, to the fact that in the former group the clinical features were more heterogenous, whereas, all 14 patients with chronic relapsing CIDP were randomized during an acute relapse or within less than a year of disease onset. The pretrial electrophysiological assessments in these patients had shown evidence of conduction block in motor fibres; this was partly reversed (at 4 weeks) by IvIg during both the blinded trial and with the subsequent open label treatments.

Therefore, it appeared that patients with acutely relapsing CIDP were very likely to respond to IvIg. The benefit was reproducible with subsequent infusions in all patients and they continued to improve with ongoing pulse therapy. These observations agree with the report of van Doorn *et al.* (1990*a*), which had confirmed in a double-blinded assessment that seven CIDP patients who were selected for their response to IvIg responded specifically and repeatedly to IvIg but not to placebo. In chronic progressive CIDP, IvIg treatment was more likely to benefit disease of duration $\leqslant 1$ year. However, this rule did not apply uniformly. In particular, patients with predominantly sensory deficits and large amplitude action tremor did not seem to respond. These characteristics were also present in the one refractory case in the small series reported by Nemni *et al.* (1994); they may identify a subgroup of patients who are not likely to benefit.

van der Meché *et al.* (1989) performed serial electrophysiological examinations in eight patients who were known to respond to freshly frozen plasma or high dose IvIg. After several courses of treatment, they observed a progressive increase in the CMAP recorded from the abductor pollicus brevis muscle with median nerve stimulation. Increases in CMAPs correlated with improvement in GS in five patients. In two patients, improvement in GS correlated with shortening of distal motor latencies. Both findings suggested reversal of conduction block. The electrophysiological recordings in the study of Faed *et al.* (1989) are difficult to interpret. Study intervals varied greatly among the nine patients, also changes were small and were not examined statistically. Other electrophysiological studies in a small number of adult patients and in children with CIDP treated with IvIg, remain in abstract form, where the data were only described, but not analysed statistically (Teasley *et al.*, 1990, 1991). The authors interpret their observations as being consistent with reversal of demyelination. The effects of IvIg treatment on selected electrophysiological measurements, i.e. summed CMAPs of median, ulnar and peroneal nerves and summed sensory nerve action potentials of median, ulnar and sural nerves, were examined and analysed in detail by Dyck *et al.* (1994). In that study, the authors compared the therapeutic benefit of IvIg and of plasma exchange treatments in the same CIDP patients. Statistically significant and comparable improvements in the summed CMAPs were shown at 6 weeks with either treatment and they were correlated with improvement in measured motor function. The treatment effects on other electrophysiological measurements were not mentioned. The authors consider reversal of conduction block as the most likely explanation for the rapid and impressive change in motor function. Our observations are essentially in agreement with these findings. In a comparable analysis of 22 patients we found that 4 weeks after high dose IvIg there was a statistically significant improvement in the summed motor conduction velocities and in the recorded summed CMAPs with proximal stimulation. Both changes indicate improvement in impulse conduction and reversal of conduction block, most likely due to remyelination (Feasby *et al.*, 1985). Myelin synthesis, growth rate and elongation of myelin sheaths have been shown to occur remarkably quickly (Hahn *et al.*, 1987), a finding consistent with the time course of improvements observed in CIDP.

In our study, patients reported subjective signs of improvement as early as the second or third infusion day. This was confirmed by the quantitative neurological assessments on trial day 5 in 12 of the 19 responders. Improvement progressed at a variable rate and maximal benefit was reached at a median of 6 weeks (range 3 weeks to 18 months). These observations are similar to those of van Doorn *et al.* (1991). The clinical and electrophysiological deficits seen in CIDP probably reflect a balance between continuously ongoing demyelination and remyelination. IvIg treatments may suppress or prevent demyelination, allowing ongoing remyelination to supervene.

In relapsing CIDP, the therapeutic benefit lasted a median of 6 weeks (range 3–22 weeks); in every case the duration of the beneficial effect was reproducible and predictable. With regularly scheduled single day IvIg pulse therapy, seven patients have been maintained for a mean of 3 years at a constant and fully functional level without added drug therapy. Four of them had previously been treated with long-term immunosuppressive drugs and were relieved that they no longer had to experience the side effects of these medications. However, so far, we have not been able to lengthen the treatment intervals or to discontinue the infusions. For logistical reasons (travel distance) and in an attempt to reduce infusion frequency, we added small to moderate doses of prednisone in three patients. After several weeks of combined therapy, we were able to phase out the IvIg infusions. All three patients were stabilized; they now have only minor neurological signs and lead an active and normal life. This outcome is remarkable, since all three had previously experienced severe fluctuations and long periods of nearly complete paralysis. The precise mechanism of action for either treatment is not known, but combining their use may provide synergistic benefits.

Now IvIg is being used for its immunomodulatory properties in an increasing number of diseases that are considered to be autoimmune disorders (Berkman *et al.*, 1990; NIH Consensus, 1990, Cherin *et al.*, 1991; Kaveri *et al.*, 1991; Dwyer; 1992; Levinson, 1992; van der Meché *et al.*, 1992; Hurez *et al.*, 1993; Thornton and Griggs, 1994; van der Meché 1994; van Doorn, 1994). Its application is relatively safe, but adverse effects have been observed with variable frequency (5–15%, usually <5%) including the potential for hypersensitivity and anaphylactic reactions. Other less severe side effects include fever, headache, myalgias, nausea, vomiting, vasomotor and cardiovascular manifestations and skin rashes (NIH Consensus, 1990; Miller *et al.*, 1992). In rare instances; symptoms may be more severe and resemble aseptic meningitis (Watson *et al.*, 1991). This complication may not re-occur with subsequent treatments (*see* Results). Aggravation of abnormal renal function and changes in blood viscosity, bearing the risk of cardiovascular and thromboembolic events, have to be kept in mind when treating elderly patients (Woodruff *et al.*, 1986; Schifferli *et al.*, 1991; Reinhart and Berchtold, 1992). All such potential problems have to be considered when advocating unsupervised treatments in the home of the patient as Dyck *et al.* (1994) suggested as a cost saving measure. Moreover, treatment efficacy for the various conditions for which IvIg has already been prescribed (haematological autoimmune disorders, myasthenia gravis, multiple sclerosis, connective tissue disorders, Crohn's disease, thyroid disorders of presumed immune aetiology, etc.) has not yet been proven and awaits more strict evaluation with double-blind, placebo-controlled assessments, as were used in our trial.

The precise mechanisms by which an infusion of high dose human polyspecific IgG exerts its immunomodulatory functions are not yet known. However, both early and short term interactions with various steps in the effector and amplification phase of the immune response, as well as more long-term effects on immunoregulation are being considered (*see* reviews by Dwyer, 1992; Hurez *et al.*, 1993; Kaveri *et al.*, 1994). The neutralization of circulating antibodies by idiotype–anti-idiotype interactions and the saturation and functional blockade of Fc receptors on macrophages by Ig probably play a major role in the beneficial effect of IvIg (Kimberly *et al.*, 1984; Clarkson *et al.*, 1986; Berchtold *et al.*, 1989; Rossi *et al.*, 1989). van Doorn *et al.* (1990*b*) provided evidence which suggests that such anti-idiotype–idiotype cross reactivity may play a role in the IvIg-induced improvement in CIDP. They had shown earlier that a proportion of sera from patients with Guillain–Barré syndrome (GBS) or CIDP contain anti-nerve antibodies that cross react *in vitro* with a selected neuroblastoma cell line (NBL). Anti-NBL antibody titres correlated with disease activity and they could no longer be detected after improvement with IvIg treatment (van Doorn *et al.*, 1987, 1988). In a more recent study van Doorn *et al.* (1990*b*) demonstrated that the *in vitro* inhibition of antibody binding was mediated by $F(ab')_2$ fragments of IvIg. This finding suggested that IvIg contains anti-idiotypic antibodies against determinants expressed on anti-NBL antibodies. Such anti-idiotypic antibodies with high affinity to anti-NBL antibodies were also found in sera from patients who had spontaneously recovered from GBS (Lundkvist *et al.*, 1993). Taken together these findings suggest that anti-idiotypic neutralization and suppression of auto-antibodies may contribute to the spontaneous as well as to the IvIg-induced recovery of these diseases. Other mechanisms may include: binding of IvIg to activated components of complement, thereby decreasing complement-mediated tissue damage and solubilization and clearance of circulating immune complexes (Basta *et al.*, 1989); functional modulation of T lymphocytes and modulation of the production of proinflammatory cytokines (Saoudi *et al.*, 1993) and anti-idiotypic antibodies contained in IvIg may also bind and down regulate B-cell receptors for antigen, thus decreasing auto-antibody production (Anderson, 1989). It is very likely that several of these mechanisms contribute to the observed short-term and long-term effects of IvIg.

Acknowledgements

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