

# Plasma-exchange therapy in chronic inflammatory demyelinating polyneuropathy

## A double-blind, sham-controlled, cross-over study

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### Summary

Eighteen patients with definite, untreated chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) of chronic progressive (nine patients) or relapsing course (nine patients) were randomized prospectively to receive 10 plasma-exchange (PE) or sham plasma-exchange (SPE) treatments over 4 weeks in a double-blind trial. After a wash-out period of 5 weeks or when they returned to baseline scores, patients were crossed over to the alternate treatments. Neurological function was assessed serially using a quantitative neurological disability score (NDS), a functional clinical grade (CG) and grip strength (GS) measurements. Electrophysiological studies were done at the beginning and end of each treatment. A primary 'intention to treat' analysis showed significant improvement with PE in all clinical outcome measures: NDS by 38 points,  $P < 0.001$ ; CG by 1.6 points,  $P < 0.001$ ; GS by +13 kg,  $P < 0.003$  and in selected electrophysiological measurements,  $\Sigma$  proximal CMAP,  $P < 0.01$ ;  $\Sigma$  motor conduction velocities,  $P < 0.006$ ;  $\Sigma$  distal motor latencies,  $P < 0.01$ . Fifteen patients completed

the trial and of those, 12 patients (80%) improved substantially with PE; i.e. five out of seven patients with chronic progressive course and seven out of eight patients with relapsing CIDP improved. There were three drop-outs: one patient lost venous access; one patient suffered a stroke and one patient left the trial to receive open treatment elsewhere. The improvement in motor functions correlated with the electrophysiological data, i.e. with improved motor conduction velocities and reversal of conduction block. Eight of 12 PE responders (66%) relapsed within 7–14 days after stopping PE. All improved with subsequent open label PE; all but two patients required long-term immunosuppressive drug therapy for stabilization. The PE non-responders improved with prednisone. We conclude that PE is a very effective adjuvant therapy for CIDP of both chronic progressive and relapsing course; concurrent immunosuppressive drug treatment is required. Exchange treatments should be given two to three times per week until improvement is established; the treatment frequency should then be tapered over several months.

**Keywords:** chronic demyelinating polyneuropathy; double-blind trial; plasma-exchange; conduction block; prednisone

**Abbreviations:** CG = clinical grade; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CIDP-MGUS = CIDP with monoclonal gammopathy of undetermined significance; CMAP = compound muscle action potential; GBS = Guillain-Barré syndrome; GS = grip strength; NDS = neurological disability score; PE = plasma-exchange; SPE = sham plasma-exchange

### Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy is an acquired peripheral nerve disease of presumed auto-immune aetiology (see recent review of Dyck *et al.*, 1993b). The diagnostic criteria and the natural history have been carefully set out (Dyck *et al.*, 1975; Prineas and McLeod,

1976; McCombe *et al.*, 1987; Barohn *et al.*, 1989; Ad Hoc Subcommittee, 1991; Simmons *et al.*, 1995) separating CIDP from the acute inflammatory demyelinating polyneuropathy or the Guillain-Barré syndrome (GBS). Recently a further differentiation of idiopathic CIDP from a variant form

associated with monoclonal gammopathy of undetermined significance (CIDP-MGUS) has been proposed based on retrospective analyses of large patient series (Gosselin *et al.*, 1991; Bromberg *et al.*, 1992; Simmons *et al.*, 1993, 1995).

Chronic inflammatory demyelinating polyradiculoneuropathy usually develops insidiously over weeks to months to years, causing fairly symmetrical motor and sensory deficits in the limbs and variable but often significant disability. The disease may begin at any age, even in early childhood (Sladky *et al.*, 1986) and the course may be either chronic progressive or relapsing with incremental residual deficits (Dyck *et al.*, 1975; McCombe *et al.*, 1987; Barohn *et al.*, 1989). During active phases of their disease patients often require assisted ambulation and may become wheelchair- or bed-bound. Despite modern therapy the condition may lead to considerable chronic morbidity, prompting a continuous search for improved treatments.

The cause of CIDP remains unknown. Clinical and laboratory evidence support the concept of an immunopathogenesis of both the acute and the chronic inflammatory demyelinating neuropathy [reviewed in Dyck *et al.* (1993b) and Hartung *et al.* (1995)]. Humoral and cell-mediated responses against a variety of myelin-derived autoantigens have been detected in some CIDP patients (Koski *et al.*, 1985; van Doorn *et al.*, 1987; Fredman *et al.*, 1991; Ilyas *et al.*, 1992; Khalili-Shirazi, 1992, 1993; Connolly *et al.*, 1993; Simone *et al.*, 1993). However, the findings are inconsistent and, so far, no predominant target epitope has been determined. More direct evidence for the importance of humoral factors in the pathogenesis of the disease has come from passive transfer experiments (Saida *et al.*, 1982; Heininger *et al.*, 1984; Pollard, 1987) and from early reports of repeated favourable responses to therapeutic PE in selected patients (Server *et al.*, 1979; Levy *et al.*, 1979; Toyka *et al.*, 1982; van Nunen *et al.*, 1982). The finding that sera of CIDP patients caused demyelination or functional peripheral nerve deficits with intraneural or systemic transfer provided a rationale for the use of PE in CIDP (Heininger *et al.*, 1984; Pollard, 1987). The response to PE was tested in several small groups of patients, yet the observations, often carefully documented, were derived from non-blinded assessments and were therefore subject to bias (Gross and Thomas, 1981; Pollard *et al.*, 1983; Donofrio *et al.*, 1985; Gibbels *et al.*, 1986). Moreover, patients were often treated simultaneously with immunosuppressive drugs that could have influenced the clinical response (Dyck *et al.*, 1982). A more rigorous approach was taken by Dyck and colleagues at the Mayo Clinic in a randomized, double-blind, sham apheresis-controlled study of 29 CIDP patients (Dyck *et al.*, 1986). A significant beneficial effect with PE was documented in one-third of non-selected patients (in five out of 15 patients in the controlled trial and in a further four patients of the sham group in the subsequent open trial). These important and critically derived observations underscored the utility of PE for CIDP (NIH Consensus, 1986). However, the Mayo Clinic trial did not provide information about predictors of response

or the optimal schedule for PE. Subjects were studied for only 3 weeks. Also, the length of their disease and previous treatments varied considerably and they received immunosuppressive drugs while being evaluated for PE.

In order to address these issues, we conducted a prospective, double-blind, sham apheresis-controlled, cross-over trial of PE in CIDP patients. The selection criteria for study subjects were deliberately very strictly defined (Ad Hoc Subcommittee, 1991). The disease had to be newly diagnosed, of short duration, not previously or concomitantly treated and confirmed by nerve biopsy. Patients with CIDP-MGUS were excluded. The assessment modalities and outcome measures were similar to the Mayo Clinic study to allow for comparison of the results. Our specific objectives were to define (i) the rate and magnitude of response, (ii) the predictors of response, (iii) the application of PE, and (iv) the role of corticosteroid therapy.

## Methods

### Patient selection

Patients were recruited prospectively between 1990 and 1994 at the participating centres throughout Canada; they had to fulfill the diagnostic criteria for definite CIDP (Ad Hoc Subcommittee, 1991) supported by CSF analysis, electrodiagnostic studies and a nerve biopsy. The neuropathy, of either chronic progressive or relapsing course, had to be newly diagnosed, not previously treated and had to be progressive for >8 weeks and <2 years (to avoid the inclusion of cases with neurological deficits secondary to axonal degeneration, that could not be expected to change during the study period). Muscle weakness had to be significant, interfering with secure ambulation (NDS  $\geq$  50). The patients had to be aged 18 years or older and gave informed consent to take part in the trial which had been approved by the institutional ethics review boards for human experimentation. Patients were carefully screened for diseases that could produce neuropathy and those with associated monoclonal gammopathy, HIV or hepatitis were excluded. (Monoclonal paraproteins were determined by high resolution agarose gel serum and urine electrophoresis, immunoglobulin quantification and immunofixation techniques. Localized myeloma was excluded by radiological skeletal survey.) Patients who were judged likely to encounter difficulties with antecubital venous access for serial apheresis were not allowed to participate (the hazards associated with jugular or subclavian vein access were considered unacceptable, in view of the SPE treatments). Prior to entry into the study all subjects had established disease with a stable or slowly progressive course.

### Study design

The study was designed as a double-blind, placebo-controlled, cross-over trial. The participating patients and evaluating

**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 m; 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

neurologist remained blinded throughout the entire trial; only the study coordinator and the PE personnel were non-blinded. The code was broken at the time of data analysis. A 'monitoring' neurologist served as backup to assure standard medical care, and was only made aware of the nature of the treatments in case of complications. The data were periodically reviewed by an independent safety oversight committee.

Patients were randomly assigned to either a series of PE or SPE. In phase I of the trial, 10 exchanges were given over 4 weeks: four in week 1, three in week 2, two in week 3 and one in week 4. This schedule was expected to remove >90% of circulating humoral factors such as putative auto-antibodies of either IgG for IgM class in the absence of resynthesis of autoantibodies (Buffaloe *et al.*, 1983). The patients were then monitored closely during a 5-week wash-out, after which they entered phase II of the trial and were crossed over to receive the alternate treatment (PE or SPE) with a subsequent similar wash-out. No other therapies were prescribed during the controlled trial. Function was assessed weekly by a quantitative NDS, a CG (Table 1), and GS measurements; electrophysiological studies were performed at the beginning and end of each of the two treatment periods. Allowance was made to shorten a treatment or wash-out phase in case of treatment failure or relapse (severe neurological deterioration by 3 CGs, as determined by two independent observers). Patients who continued to deteriorate to CG 8 were to be withdrawn and to be entered into the third and open phase of the trial. After completion of the two exchange treatment periods, patients who were still symptomatic were to enter phase III of the trial. In this phase prednisone was given over a 6-month period. The dose was 60 mg daily for 1 month and subsequent tapering of the prednisone daily

dose by 10 mg every month. Patients were also given the choice of receiving PE treatments twice weekly. Neurological function was monitored monthly and electrophysiological studies were performed at the beginning and end of phase III.

### Neurological assessments

Patients were assessed by the same blinded observer weekly during each of the treatment periods and at the beginning, middle and end of each wash-out period. Tests included the measurements of NDS (a summed score of strength in 26 muscle groups, of sensation and of reflexes, modified from Dyck, 1982; the NDS gives a reliable assessment of neurological impairment its validity has been demonstrated by Dyck *et al.*, 1994). We also used a dynamometer (Jamar TM, TEC, Clifton, NJ, USA) to measure maximal hand grip (GS, best of three; Mathiowetz *et al.*, 1984) and assigned a functional CG (Table 1).

### Electrophysiological studies

A standardized set of electrophysiological measurements was performed at the beginning and end of each treatment period using conventional techniques with surface stimulating and recording electrodes and careful monitoring of limb temperature. Median, ulnar (four-point stimulation: wrist, distal to elbow, proximal to elbow and axilla), tibial and peroneal (three-point stimulation: ankle, fibular head and popliteal fossa) motor nerve conduction was studied; the parameters evaluated included compound muscle action potential (CMAP) amplitudes evoked by proximal and distal stimulation, distal latencies, conduction velocities and F-wave latencies. Sural, median and ulnar antidromic sensory conduction studies were performed; parameters evaluated included sensory nerve action potential amplitudes, distal latencies and conduction velocities. All recordings were consistently performed in the right upper and lower limb to allow for comparison of serial studies. Concentric needle electromyography of biceps, first dorsal interosseous, vastus medialis and peroneus brevis was carried out and a semiquantitative assessment of fibrillation potentials and motor unit recruitment was made.

### Nerve biopsy

The left sural nerve was biopsied at the ankle. A portion of the specimen was fixed in 2.5% buffered glutaraldehyde, processed in part for teased fibre studies, and in part for embedding in epon according to standard techniques to allow examination by light and electron microscopy (Dyck *et al.*, 1993a). Teased fibres were analysed according to the classification of Dyck *et al.* (1993a). A demyelination index was calculated from the sum of percentages of fibres of category C, D and F. A portion of the nerve was mounted in O.C.T. compound, frozen in liquid nitrogen and stored

**Table 2** Clinical and electrophysiological outcome measures in PE versus SPE

Outcome measures	Plasma exchange		Sham exchange		Significance <sup>†</sup>
	Before	After	Before	After	
Clinical measure:					
Neurological disability score	73.3±5.3	35.3±4.5*	69.4±6.4	71.1±7.5	<i>P</i> < 0.001
Clinical grade	4.6±0.4	3.0±0.4*	4.3±0.4	4.7±0.5	<i>P</i> < 0.001
Grip strength (kg)	15.8±2.3	28.5±2.8	15.1±2.7	15.2±3.1	<i>P</i> < 0.003
Electrophysiological measure:					
Σ proximal CMAP (mV)	7.3±1.2	11.0±1.9	7.1±1.9	6.2±1.4	<i>P</i> < 0.01
Σ distal CMAP (mV)	15.0±2.0	17.3±2.6	12.7±2.3	12.2±1.7	<i>P</i> < 0.06
Σ motor conduction velocity (m s <sup>-1</sup> )	91.3±11.9	104.5±11.2	86.7±9.4	83.3±9.9	<i>P</i> < 0.006
Σ distal motor latency (ms)	34.7±5.5	29.1±2.9	35.3±4.7	37.7±5.1	<i>P</i> < 0.01

Mean±SD. \*Decreasing values for NDS and CG signify improvement; <sup>†</sup>*P* values were obtained from ANOVAs, repeated measures option, and refer to the differences between the effects of PE and SPE treatments.

at -70°C to be used for immunological studies (*see* Hahn *et al.*, 1996).

### Laboratory studies

Cerebrospinal fluid, serum protein electrophoresis, serum and urine immuno-electrophoresis, IgA, IgM and IgG quantification, immunofixation, serum glucose, electrolytes, albumin, liver profile, glycosylated haemoglobin and porphyrin screening were performed/measured for each subject as were a radiological skeletal survey and serology for HIV, hepatitis B and *Borrelia burgdorferi*.

### Apheresis procedure

Pheresis was performed from an antecubital venous access, using a continuous or intermittent cell separator (Cobe TPE, Cobe Spectra and the V-50 Haemonetics apheresis system). A curtain separated the apheresis equipment from the patient. The typical schedule prescribed was an exchange of 40–50 ml plasma per kg body weight per treatment. Blood was drawn and separated into cells and plasma; the cells were combined with reconstituted 5% human serum albumin and reinfused into the patient with normal saline. The anticoagulant acid citrate dextrose was used at a ratio of 1:20 and the replacement solution was supplemented selectively with calcium gluconate 3.75 mEq l<sup>-1</sup>. For SPE, blood was drawn and separated into cells and plasma, recombined and reinfused into the patient. The PE schedule was expected to remove >90 % of IgG and IgM antibodies in the absence of synthesis of new autoantibody (Buffaloe *et al.*, 1983). A sample of plasma from the first PE/SPE procedure was retained for future immunological assessments.

### Statistical considerations

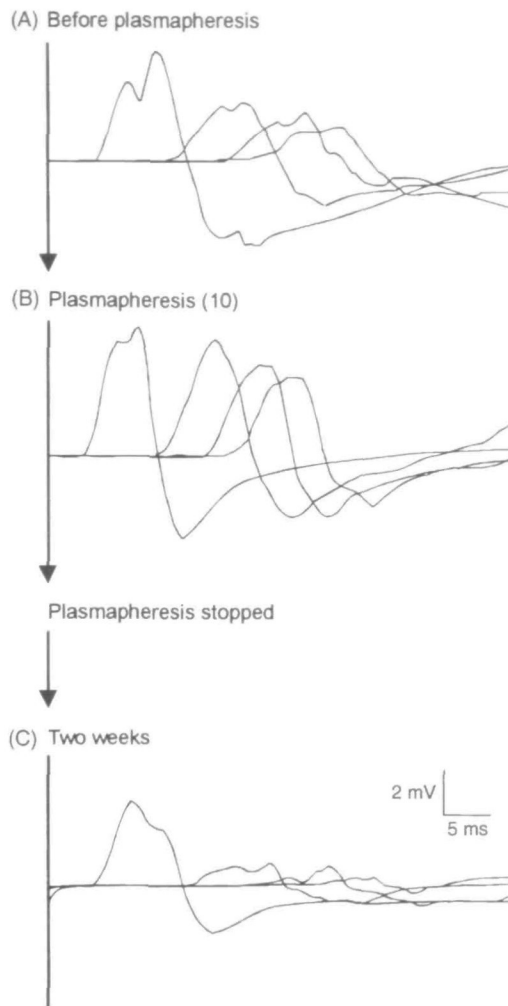
The two-period, double-blind, cross-over design was chosen because of its statistical efficiency. Moreover, in this design each patient acts as his/her own control; this gives a more precise estimate of the treatment effect in the individual

patient. Baseline information was then used in a secondary analysis aimed at determining predictors of response. As primary end-points to assess treatment efficacy, we used the NDS, CG, and GS measurements, and selected electrophysiological measurements: the summed CMAPs of median, ulnar, tibial and peroneal nerves in response to proximal (Σ proximal CMAP) and distal stimulation (Σ distal 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). A *P* value <0.05 was considered statistically significant. Unless stated otherwise results are presented as mean±SD.

### Results

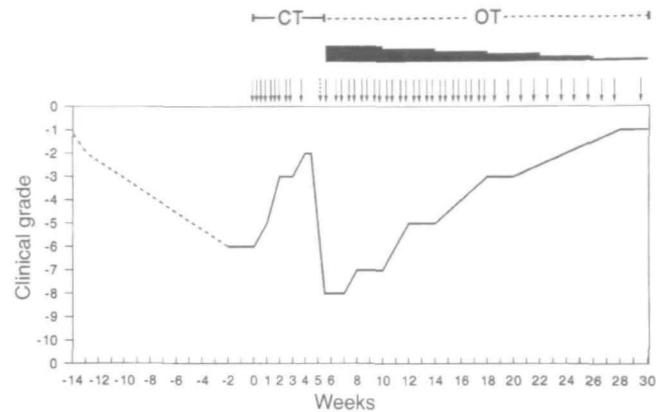
Eighteen patients, 13 men and five women, were randomized for the trial. Their acquired demyelinating neuropathy fulfilled the criteria of definite CIDP (Ad Hoc Subcommittee, 1991) and was of a mean duration of 4.5 months (range 3–18 months) with a chronic progressive (nine patients) or chronic relapsing (nine patients) course. (Three patients classified as chronic progressive CIDP improved substantially with PE; they then worsened again during wash-out and stabilized subsequently with PE plus immunosuppressive drugs; their relapse was considered to be treatment related.) Patients had not been treated prior to randomization. At entry into the study their neuropathy was severe (NDS = 77.0±4.3 points, CG 4.7±0.4) and interfered with ambulation (*see* Table 4). Evidence for ongoing demyelination was provided by the marked slowing of conduction velocities (mean median nerve motor conduction velocity 27.2±12.6 m s<sup>-1</sup>) and the nerve biopsy findings (*see* Table 3). Three patients did not complete the trial: one because of failed access for the second treatment arm (PE); one because of a stroke at the end of the first treatment arm (PE) and there was one drop-out during the first treatment series (SPE).



**Fig. 1** Representative ulnar motor conduction study from Patient 1 (A) prior to entry into the trial, (B) after completion of phase I (10 PE treatments in 4 weeks) and (C) after rebound relapse (recording from abductor digiti minimi and stimulating at the wrist, below elbow, above elbow and axilla). Note the reversal of conduction block, conduction slowing and dispersion of the recorded action potentials with PE, and the recurrence to an even greater degree during rebound relapse. Recording conditions were identical in the three sessions.

### Observations with PE

The observations made with PE versus SPE are summarized in Table 2. All patients were included in an intention to treat analysis. The mean values for the NDS, CG, GS and electrophysiological findings at entry into the respective treatment arms were comparable. With PE, significant improvement was found in all outcome measures: mean change in NDS, 38 points,  $P < 0.001$ ; in CG, 1.6 points,  $P < 0.001$ ; in GS, +13 kg  $P < 0.003$ . Analysis of the electrophysiological measurements revealed statistically significant improvement with PE in  $\Sigma$  proximal CMAP,  $P < 0.01$ ; in  $\Sigma$  MCV,  $P < 0.006$ ; in  $\Sigma$  DML,  $P < 0.01$ ; the change in  $\Sigma$  distal CMAP almost reached significance ( $P < 0.06$ ). All measures remained static or worsened during SPE.



**Fig. 2** Treatment responses in Patient 1 during the controlled trial (CT) and the open trial (OT). The patient had slowly deteriorated in the preceding months (hatched line) to a stable baseline. He was allocated to PE in phase one, received 10 PE treatments (arrows) over 4 weeks and improved quickly by 4 CG; he stabilized for only 6 days and deteriorated very rapidly within 3 days to his baseline score 6. He crossed over to SPE (hatched arrow). After one treatment he had reached CG 8. He was put into the open trial and received 60 mg prednisone daily by mouth (solid bar) plus PE twice weekly with subsequent tapering of PE. Gradual improvement was documented over the next 6 months (phase III).

Twelve of 15 patients (80%) who completed the controlled trial responded to PE with a substantial improvement in their neurological function (Table 3). The response was particularly impressive in six patients whose neurological dysfunction improved by  $>50$  points from baseline in  $\leq 4$  weeks. This corresponded to an amelioration of up to 5 CGs. First signs of improvement were usually noted 3–6 days after beginning the PE (i.e. after two to four treatments). Improvement continued steadily so that nine of the 12 patients, who responded favourably to PE had achieved secure ambulation by the end of 4 weeks. At this time they demonstrated only minor motor weakness and the deep tendon reflexes had often returned (Table 4). A corresponding improvement was seen in the electrophysiological testing (Table 3 and Fig. 1). One patient apparently improved spontaneously and two patients had not changed; one of these had shown a placebo response with non-sustained improvement during SPE.

On average, 3546 ml plasma was removed per treatment; a detailed record was kept on each procedure. The PE and SPE were well tolerated with the exception of the following two incidents. An 84-year-old man sustained a stroke after the ninth PE treatment. This occurred 1 day after an uncomplicated PE procedure and a clear relationship could not be established. His record showed that he had improved with PE, but he was not included in the secondary analysis. During phase III of the trial a 44-year-old, healthy man experienced an adverse reaction (hypotension and abdominal pain) within minutes of having been connected to the cell separator. He had undergone many previous PE procedures without side-effects. His symptoms were interpreted by the

**Table 3** Observations on individual patients at baseline and after PE in the controlled trial

No.	Age (years) /sex	CIDP type	CIDP duration months	MNCV (m s <sup>-1</sup> )	Biopsy (% fibre) DI/AD	CSF protein (mg l <sup>-1</sup> )	NDS before/ after PE (change)	CG before/ after PE (change)	Increase in grip after PE (kg)	Physiology after PE
1	56/M	ChrR	4	32	29.9/0.8	1194	90/25 (-65)	6/2 (-4)	+29	Improved
2	44/M	ChrR	4	38	32.5/3.1	735	76/27 (-49)	3/1 (-2)	+26	Improved
3	50/M	ChrPrg*	4	13	37.6/2.7	2526	120/21 (-99)	7/2 (-5)	+28	Improved
4	60/M	ChrPrg	5	47	11.0/11.0	1211	61/18 (-43)	4/2 (-2)	+9	Unchanged
5	48/F	ChrR	4	38	27.3/11.1	3140	82/DO	5/DO	DO	-
6	62/M	ChrPrg	3	29	85.8/0.9	1419	105/SI	7/SI	SI	Improved
7	74/M	ChrR	6	22	0/0	1596	85/63 (-22)	7/4 (-3)	-4	Unchanged
8	62/M	ChrPrg	3	17	80.8/12.1	3015	54/37 (-17)	3/3 (0)	+6.5	Improved
9	25/M	ChrR	18	43	47.4/0	3750	98/24 (-74)	(-4)	+25	Improved
10	40/M	ChrPrg	3	38	25.9/1.3	4003	106/28 (-78)	7/2 (-5)	+21	Improved
11	21/F	ChrR	5	26	20.3/0	1070	70/17 (-53)	3/2 (-1)	+23	Improved
12	41/F	ChrR	3	29	32.4/0	3990	66/20 (-46)	6/3 (-3)	+6	Improved
13	48/M	ChrPrg*	5	23	40.4/18	1460	67/25 (-42)	4/2 (-2)	+17	Improved
14	66/M	ChrPrg*	7	8	69.3/1.1	820	61/12 (-49)	3/1 (-2)	+15	Improved
15	61/F	ChrPrg	9	13	32.0/3.4	750	72/FA	3/FA	FA	-
16	19/F	ChrR	18	4	27.0/0	1001	50/52 (+2)	3/3 (0)	+6	Worse
17	68/M	ChrR	10	24	89.5/8.0	1360	106/21 (-85)	5/3 (-2)	+21	Improved
18	84/M	ChrPrg	5	46	29.0/19.0	1810	67/DO	6/DO	-	-

ChrR = chronic relapsing; ChrPrg = chronic progressive; DI = demyelination index of teased fibres C+D+F; AD = axonal degeneration; DO = drop-out; SI = spontaneous improvement; FA = failed access. \*Single relapse with D/C PE.

**Table 4** Functional state of each patient at baseline, their response to PE and other therapies and functional state at last follow-up

Patient	Baseline walking	First sign of response to PE	Weeks to improve by 1 CG	Weeks to secure walking	Rebound relapse after PE (days)	Response to prednisone ( $\pm$ PE)	Other drugs needed to stabilize	Walking at end of study*
1	Bed bound	2–3 days	<1	3	7	Yes	AZA	Normal
2	Walker	3–4 days	1	2	13	Yes	AZA, IvIg, Cyclo	Normal
3	Bed bound	2 days	<1	4	14	Yes	No	Normal
4	Walker	4–5 days	<1	3	No	Yes	No	Normal
5	Wheelchair	DO	–	–	–	Yes	AZA, IvIg	One cane
6	Bed bound	SI	6	11	–	–	No	Normal
7	Wheelchair	3–4 weeks	5	20	No	Yes	No	Normal
8	Two canes	None	6	6	No	Yes	–	Single cane
9	Wheelchair	3–4 days	<2	3	No	Yes	No	Normal
10	Bed bound	5–6 days	6	8	No	–	No	Normal
11	Single cane	5–6 days	2	2	9	Yes	AZA, Cyclo, IvIg	Normal
12	Wheelchair	5–6 days	<2	15	10	Yes	AZA, Cyclo	Normal
13	Single cane	3–4 days	<1	<1	13–15	No	Cyclo	Normal
14	Difficulty	3–4 days	<1	<1	40	†	Cyclo	Normal
15	Difficulty	FA	14	14	–	Yes	No	Normal
16	Difficulty	None	24	24	No	Yes	AZA, IvIg	Normal
17	Wheelchair	3–4 days	<1	5	10–15	Yes	AZA, Cyclo	One cane
18	Wheelchair	2 weeks	DO	Stroke	–	Yes	–	Walker

DO = drop-out; SI = spontaneous improvement; FA = failed access; AZA = azathioprine; Cyclo = cyclophosphamide; IvIg = i.v. immunoglobulin G. \*Observation time 1–4 years. †Declined drugs; on maintenance PE for 3 weeks, later cyclophosphamide.

attending personnel as an anaphylactic reaction and he was given an injection of diphenhydramine 50 mg i.v. and adrenaline 1:1000, 1 ml subcutaneously. Shortly thereafter he became diaphoretic and developed chest pain. An electrocardiogram showed changes of anterior inferior myocardial ischaemia. An emergency coronary angiogram showed an isolated thrombotic occlusion of the left anterior descending coronary artery associated with a mild localized stenosis but with no other evidence of coronary artery disease. The coronary circulation was restored by an angioplasty and he made a full recovery. While being observed in the coronary care unit, his neurological function deteriorated rapidly and he became quadriplegic, despite the prior and ongoing prescription of prednisone 60 mg daily for 8 weeks. He then responded favourably to treatment with i.v. immunoglobulin G.

### Treatment related relapses

Eight of the 12 patients (66%) who had improved subsequently relapsed after stopping PE; in seven the deterioration occurred 7–14 days after the last PE treatment. Six patients with apparently stable, chronically smouldering disease at randomization deteriorated rapidly over a few days and became more severely paralysed than they had been at entry into the study (Fig. 2). Deterioration occurred during the first wash-out in six patients. According to the predefined criteria, they were prematurely crossed over to receive the second treatment: one completed 10 sham treatments while

deteriorating slowly; one terminated the sham period after seven treatments because of a rapid deterioration to CG 6 and the other four patients received only 4, 3, 1 and 1 sham treatments, respectively. Their neurological function deteriorated so rapidly that within days they had reached CG 7–8. The deterioration was documented by two independent observers and confirmed by electrophysiological studies (Fig. 1); in accordance with the study protocol these patients were withdrawn from the controlled trial so that they could enter the third and open phase of the trial. Two patients who had received PE during the second controlled treatment arm relapsed during wash-out; one deteriorated rapidly within 14 days of the last PE and was entered into phase III, the other worsened much more gradually within 40 days of the last PE treatment. This patient declined corticosteroids and was maintained on PE every 3 weeks; cyclophosphamide 150 mg as a daily oral dose was added after 4 months and the frequency of PE was tapered. His condition stabilized so that he could return to his employment as an orderly. The condition of one patient with known relapsing CIDP deteriorated 100 days after the last PE; this was considered a spontaneous relapse.

### Observations during the open phase (III)

Fourteen patients were monitored monthly for 6 months while being treated with either prednisone alone (seven patients) or in combination with PE (seven patients). All patients improved, including the two patients who had not

responded to PE alone during the controlled trial. Those who had relapsed after the improvement with controlled PE treatments responded again promptly. After 6 months, 10 patients had almost completely recovered; only minimal neurological signs remained and they did not interfere with a normal life. One patient was left with a bilateral fixed partial foot drop requiring a single cane.

Four patients had a fluctuating course. They improved initially with prednisone and PE to almost normal function. However, upon reducing the frequency of PE, they promptly relapsed, in spite of having been medicated with high dose prednisone for >8 weeks. Azathioprine was added to the management without noticeable effect; they were later changed to cyclophosphamide (prescribed as a daily oral dose of 75–150 mg or as monthly i.v. pulse therapy at a dose of 12 mg per kg body weight) and their disease became stabilized. One patient with a very unstable course was treated with i.v. immunoglobulin G infusion pulse therapy after sustaining a complication with PE that precluded further treatments (*see* details above).

### Observation during long-term follow-up

Long-term follow-up of duration of  $33.9 \pm 3.5$  months (range 15–56 months) was possible in 16 patients. All except three patients maintained secure ambulation and they still have either a normal neurological examination or minor residual signs. Three patients remain with moderate distal weakness (MRC Grade 4 of 5) and walk with a single cane. Several relapses occurred in seven patients; in four patients these occurred when prednisone was tapered to a low dose. They improved each time the steroid was increased. Various other therapies were added (azathioprine, cyclophosphamide and human immunoglobulin G infusions) and all patients have been stabilized.

### Discussion

In this double-blind, controlled trial we were able to document significant benefit from therapeutic PE in 80% of prospectively enrolled, previously untreated patients with strictly defined CIDP of either static or progressive course. We demonstrated statistically significant improvement (by a mean of 38 points,  $P < 0.001$ ) in a quantitative NDS adapted from Dyck *et al.* (1982) that expresses the neurological status of the patient and correlates well with electrophysiological measurements that are not subject to observer or patient bias (Dyck *et al.*, 1994). The NDS has been used as a primary end-point to assess treatment efficacy in earlier neuropathy trials from the Mayo Clinic (Dyck *et al.*, 1986, 1991, 1992, 1994). This allows us to compare our results with those reported by Dyck *et al.* (1986). In our trial the magnitude of change in NDS and the response rate to PE was much higher (80% versus 33%) than that reported in the only previous controlled trial with unselected patient enrollment (Dyck *et al.*, 1986). The improvement with PE began within days

of commencing the treatments and progressed steadily so that nine out of 12 patients who responded favourably to PE had only minor residual dysfunction at the end of 4 weeks after receiving 10 PE treatments. The observed changes represented a very large biological effect, since the majority of patients were severely disabled at entry into the trial (Table 4). The striking differences in the outcome of the two trials may be explained in part by the much more vigorous PE scheduling in our study (10 versus six treatments) and the longer observation time. Also, and more likely, they could relate to our more strict selection of cases, in which the pathology was characterized by prominent but more readily reversible demyelination. The latter assumption is supported by our electrophysiological observations before and after PE, which demonstrated significant increases in the evoked compound motor amplitudes in response to proximal stimulation ( $\Sigma$  proximal CMAP,  $P < 0.01$ ), indicating reversal of conduction block (Fig. 1); significant reductions in distal motor latencies ( $\Sigma$  DML,  $P < 0.01$ ) and improvements in the motor conduction velocities ( $\Sigma$  MCV,  $P < 0.006$ ) were also seen. The changes indicate an improvement in the conduction in motor fibres as would be seen with remyelination, which can proceed with remarkable speed (Hahn *et al.*, 1987). The clinical and electrophysiological deficits seen in CIDP probably reflect a balance between continuously ongoing demyelination and remyelination (Feasby *et al.*, 1985). The observed rapid and impressive improvements with PE probably represent a shift in this balance towards remyelination with reversal of conduction block as illustrated in Fig. 1.

In a more recent study by Dyck *et al.* (1994) in which the authors compared the response to PE versus immunoglobulin infusions in CIDP patients, the rate and magnitude of response to PE was very similar to those in our study. However, in this Mayo Clinic trial only six out of 19 patients enrolled had not received prior immunotherapy. Several study patients had been treated earlier with PE and were known to respond. Therefore the assessment of PE in this cohort is not free of selection bias. Yet the remarkable agreement between the two studies of the measured treatment effect demonstrates the value of standardized evaluations and confirms the usefulness of PE in CIDP.

Our trial had been initiated and planned in collaboration with the Canadian Apheresis Group, a group that monitors and collects data on all apheresis procedures in Canada and keeps a specimen bank of samples taken from patients with a variety of disorders treated by PE. The objective of our study was to evaluate critically the use of PE in CIDP and to determine the optimal application of this expensive therapy. Patient selection criteria were therefore deliberately restrictive and no concurrent immunosuppressive medication was prescribed during the controlled portion of the trial; this was admittedly a somewhat artificial situation. Patients with associated diseases such as HIV infection, hepatitis and glomerulonephritis, and those associated with monoclonal paraproteins were excluded. Recent reports propose a



distinction between CIDP and CIDP-MGUS, which is based on differences in the natural history and response to therapy (Gosselin *et al.*, 1991; Bromberg *et al.*, 1992; Simmons *et al.*, 1993, 1995). However, circulating monoclonal paraproteins can be found in otherwise typical cases of idiopathic CIDP and such a strict separation may not be justified (Pollard *et al.*, 1983; Julien *et al.*, 1984; Cornblath *et al.*, 1991; Vallderiola *et al.*, 1993).

By chance, we enrolled an equal number of patients with chronic progressive and with chronic relapsing disease course. In the final analysis eight patients with relapsing disease and seven patients with chronic progressive disease could be evaluated. All but two (one in each group) showed substantial improvement with PE in all clinical outcome measures; 10 also had electrophysiological improvement. One patient with severe neurological deficits was found to have improved by 2 CGs prior to receiving PE in the second study phase. The further improvement during the active treatment may have been spontaneous. Spontaneous improvements have been observed in cases with subacute CIDP and monophasic course (Hughes *et al.*, 1992; Vermeulen, 1993). Whether such cases should be regarded as variant forms of GBS remains to be determined. Our patient had developed paralysis and severe sensory deficits with gradual continuous progression over 8 weeks to quadriplegia, but sparing the facial nerves and pulmonary function. The electrophysiological assessments indicated a severe demyelinating motor and sensory neuropathy. The nerve biopsy taken at 9 weeks, when examined by light and electron microscopy and by teased fibre analysis, showed severe and ongoing macrophage-associated demyelination and remyelination and only very rare endoneurial mononuclear inflammatory cells. The pathological changes reflected the chronic smouldering course of the disease.

In only one previous report was an attempt made to define the predictors of response to PE by careful analysis and correlation of clinical and pathological observations in five treated CIDP patients (Pollard *et al.*, 1983). The authors concluded that patients with chronic relapsing disease and electrophysiological and pathological findings of predominant demyelination are likely to respond to PE. By contrast, those with chronic progressive disease, with demyelination and associated axonal degeneration would probably not respond (Pollard, 1987). Our analysis of the 15 patients who had completed the blinded trial allowed us to define the predictors of response to PE more accurately. Among the eight patients with relapsing disease, seven showed substantial improvement in the original trial and with subsequent repeated treatments. The electrophysiological findings in all patients were consistent with a severe demyelinating neuropathy without evidence of axonal loss or ongoing axonal degeneration. The impression was confirmed in the pathological examination of the nerve biopsies. Examination of plastic-embedded cross-sections of the nerves by light and electron microscopy showed a near normal complement of myelinated nerve fibres (except for one case with severe

ongoing demyelination) and a variable number of randomly scattered axons that were ensheathed by disproportionately thin myelin, indicating prior de/remyelination. The acuity of the disease was much more accurately shown by the teased fibre analysis, which gave evidence for active primary demyelination and little or no axonal degeneration. In the one chronic relapsing case that did not improve, teased fibres gave a similar result. However, the examination of nerve sections showed evidence of much more chronic demyelination, with prominent onion bulb formation. This patient improved with prednisolone.

Among the seven patients with chronic progressive disease, five responded unequivocally to PE. One patient had shown spontaneous improvement prior to starting active treatment and was therefore discounted; the remaining patient (no. 7 in Table 3) showed a non-significant improvement. The electrophysiological and pathological measurements in this group were more variable. The degree of slowing of nerve conduction varied among cases and needle electromyography gave evidence of ongoing axonal degeneration. The pathology in nerve sections and in teased nerve fibres indicated a process of primary demyelination with associated axonal degeneration that varied in degree. In two cases the observed changes in the nerve biopsy correlated poorly with the degree of clinical symptoms, suggesting that the disease process was proximal and more prominent in nerve roots (Dyck *et al.*, 1975). The one case that did not respond to PE showed a remarkable degree of onion bulb formation and evidence of axonal loss. The pathological changes appeared very chronic and were inconsistent with the patient's claim that the disease had begun only 3 months before. The observed pathological features and the prominent peroneal motor deficit in this patient raised the possibility of hereditary motor and sensory neuropathy type I. However, there was no family history of neuropathy, and genomic DNA analysis did not reveal the common mutations. Both patients that failed to respond to PE improved subsequently with a prescription of corticosteroids, thus supporting the clinical impression that their disease was acquired and likely to have been immune mediated.

Given the foregoing observations, we conclude that a beneficial effect with PE may be expected in patients with either chronic relapsing or chronic progressive CIDP if the clinical, electrophysiological and histological features support primary demyelination and if chronic secondary axonal loss is not yet established, that is early in their disease course.

On planning the PE schedules for our trial we postulated that humoral factors, possibly auto-antibodies, might be important in the pathogenesis of CIDP (Pollard, 1987). The devised schedule for the apheresis procedures was aimed at removing ~90% of the putative pathogenetic factors from the circulation for at least 4 weeks (Buffaloe *et al.*, 1983). Since it was our objective to make a critical evaluation of the effect of PE on CIDP, no concurrent immunosuppressive medication was prescribed during the controlled trial. We anticipated that benefit from PE might only be temporary (Server *et al.*, 1979; Gross *et al.*, 1981; Toyka *et al.*, 1982)

and that only a portion of patients would respond to PE (Pollard *et al.*, 1983, Dyck *et al.*, 1986). Therefore, in a subsequent third and open phase of the trial we planned to assess in the same patient group the response to prednisone, a proven effective immunosuppressant in CIDP (Dyck *et al.*, 1982). In this part of the trial PE was optional. The intent was to determine (i) whether the combined treatments would provide added benefit and could stabilize patients and (ii) whether patients that received no benefit from PE would respond to prednisone.

We were aware of the so-called rebound phenomenon, a still unexplained worsening after PE, that is possibly caused by an overshooting synthesis of antibodies or other pathogenetic factors or by alterations in immunoregulatory mechanisms (Branda *et al.*, 1975; Heinger *et al.*, 1990; Dwyer *et al.*, 1992; Rudnicki *et al.*, 1992; Thornton and Griggs, 1994). However, we were surprised by the very rapid and profound deterioration in five patients, which occurred within a few days of stopping PE (illustrated in Fig. 2); another three patients deteriorated more slowly. Electrophysiological studies demonstrated profound conduction block, slowing of conduction velocities and dispersion of the recorded potentials (Fig. 1) indicating very active demyelination. At randomization all patients appeared to have slowly progressive or static disease. During the rebound relapse, five patients deteriorated so rapidly that their disease mimicked the time course and profile of GBS. All patients improved subsequently with maintenance PE and immunosuppressive drug therapy. However, on long-term follow-up, the five patients with rapid rebound continued to have a very active relapsing disease, suggesting the possibility that PE had a longer lasting effect on immunoregulation. This assumption remains speculative, since the overt disease prior to entry into the study had been of only short duration (3–5 months). The observations suggest that it may be important to prescribe concurrent immunosuppression while performing PE; they also stress the importance of a tapering schedule of PE. Only one patient in our series, who had become bedbound and completely helpless while deteriorating further with sham pheresis, improved and stabilized with PE alone. The remainder, even those who originally had not responded to PE, improved with corticosteroids. Four patients required the added prescription of cyclophosphamide (oral daily prescription or 1 monthly i.v. pulse therapy; detailed earlier). In long-term follow-up ( $33.9 \pm 3.5$  months) all patients appeared stable and they remain well or have only mild neurological deficits.

Our observations lead us to conclude that a favourable, often marked response to PE can be expected in most patients with CIDP, but that immunosuppressive drug treatment is often needed in the long-term. We have shown that the rapid and impressive improvement in neurological function is due to reversal of conduction block. Studies regarding the nature of humoral factors involved make use of plasma samples taken at various points during this trial (H.-P.Hartung, unpublished results). As guidelines for the PE schedule we recommend

(i) two to three apheresis procedures per week until improvement has occurred with (ii) subsequent tapering of the PE frequency. Immunosuppressive drug treatments have to be individualized according to the patient's response; prednisone appears to be an appropriate and effective drug in most patients, but occasionally cyclophosphamide may be necessary.

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