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Editorial

Intravenous immunoglobulin (IVIG) in the treatment of chronic demyelinating polyradiculoneuropathy

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Definition, diagnostic features, and prognosis of CIDP

CIDP is an acquired, demyelinating polyneuropathy, characterized by symmetric sensorimotor deficit, developing over at least 2 months. Weakness commonly predominates in distal muscles, but also occurs proximally and can affect facial muscles. The disease course is relapsing in two thirds of the patients and steadily or stepwise progressive in the others. Deep tendon reflexes are decreased or absent and, in most cases, spinal fluid protein is elevated (Dyck *et al.*, 1975 ; McCombe *et al.*, 1987 ; Barohn *et al.*, 1989). Electrodiagnostic features are focal motor conduction block or abnormal temporal dispersion in nerve segments, not prone to compression, prolongation of distal motor and F-wave latencies, absence of F-waves, and slowing of nerve conduction velocities. Various sets of electrodiagnostic criteria for primary demyelination have been proposed. Comparative studies have demonstrated that they are highly specific, but sensitivity is limited (Bromberg, 1991 ; Van den Bergh *et al.*, 2000). When the diagnosis remains doubtful, sural nerve biopsy can provide evidence of demyelination and remyelination. Because reported sensitivity levels are quite variable, its diagnostic value remains controversial (Barohn *et al.*, 1989 ; Molenaar *et al.*, 1998 ; Haq *et al.*, 2000).

CIDP is associated with significant longterm morbidity and disability and, in spite of treatment, a small percentage of patients may become totally dependent or die (Dyck *et al.*, 1975 ; McCombe *et al.*, 1987 ; Barohn *et al.*, 1989). The cause of CIDP remains poorly understood, but immune mechanisms seem to be implicated (van der Meché and van Doorn, 1995). A CIDP-like syndrome may be associated with other diseases, such as monoclonal gammopathy, diabetes, HIV infection, lupus erythematosus, malignancy. Currently, it is unknown whether the pathogenetic mechanisms underlying idiopathic and symptomatic CIDP are identical.

Treatment of CIDP

Because CIDP can be disabling and because an autoimmune origin appears likely, therapy with immunosuppressive and immunomodulating agents has been proposed. They include steroids, azathioprine, cyclophosphamide, cyclosporine, interferons, plasma exchange, and IVIG (Table 1).

Steroids and immunosuppression. Since the publication of successful treatment with steroids of a patient with recurrent CIDP by Austin (1958), efficacy of steroids has been reported in 65-95% of patients Dalakas and Engel, 1981 ; McCombe *et al.*, 1987 ; Barohn *et al.*, 1989). This was confirmed in an open, prospective, controlled trial of 28 patients (Dyck *et al.*, 1982). Improvement begins and reaches its maximum after a mean time interval of 2 and 6 months, respectively. Relapse occurs in up to 70% of patients after discontinuation of steroid therapy. A pilot study with pulsed high dose dexamethasone showed improvement in 7/10 patients with remission in 6 (Molenaar *et al.*, 1997). Longterm follow-up studies on efficacy and side-effects are not available, but approximately 25% of myasthenia patients were found to develop serious steroid-related side-effects (diabetes, arterial hypertension, gastric ulcers, osteoporosis and bone fractures, aseptic bone necrosis, cataract, proneness to infections, psychosis, etc.) within 4 years of treatment (Oosterhuis, 1984). Anecdotal reports exist on the efficacy of azathioprine (Pentland *et al.*, 1982 ; Dalakas and Engel, 1981 ; McCombe *et al.*, 1987), but an open, controlled trial failed to demonstrate additional improvement when azathioprine was added to steroids (Dyck *et al.*, 1985). Cyclophosphamide (Dalakas and Engel, 1981 ; McCombe *et al.*, 1987 ; Koski, 1994 ; Good *et al.*, 1998) and cyclosporine (Mahattanakul *et al.*, 1998 ; Barnett *et al.*, 1998) may also be beneficial, but randomised controlled trials have not been performed. These immunosuppressive agents may produce potentially serious side-effects (bone marrow suppression, hepatotoxicity, nephrotoxicity, hemorrhagic cystitis, gonadal damage, malignancy, etc.), rendering their routine use in CIDP problematic. Some patients have responded to interferon-alpha (Gorson *et al.*, 1998) and interferon-beta (Choudhari *et al.*, 1995) but a randomised controlled trial failed to demonstrate benefit in patients

refractory to other treatments (Hadden *et al.*, 1999). Two patients improved after treatment with mycophenolate (Mowzoon *et al.*, 2001).

Plasma exchange (PE). Evidence for the implication of humoural factors in CIDP pathogenesis led to the use of PE in a series of single or open trials after initial reports of a beneficial response in 1979 (Levy *et al.*, 1979 ; Server *et al.*, 1979). A randomised, double-blind, sham-exchange controlled trial demonstrated efficacy of PE in one third of 29 patients (Dyck *et al.*, 1986). A similar trial with cross-over design documented substantial improvement in 80% of 15 patients, starting within days following PE (Hahn *et al.*, 1996). Relapse occurred in two thirds of the responders, who all continued to improve on repeat PE treatment. PE is a relatively safe procedure, although thrombosis, bleeding, and septicemia occasionally occur, and improvement is rapid. However, the beneficial effect is usually transient, such that concurrent immunosuppression is often necessary. Also, PE is expensive and can be performed in specialised centres only.

Intravenous immunoglobulin (IVIG). Based on its efficacy in autoimmune thrombocytopenic purpura, intravenous infusions of fresh frozen plasma or with the immunoglobulin fraction thereof were successfully performed in a few patients (Maas *et al.*, 1981 ; Bush *et al.*, 1982). In an open study, Vermeulen *et al.* (1985) found a fast onset (within 8 days), significant improvement of muscle strength in 13/17 patients following intravenous fresh frozen plasma. In 9 patients, the effect was shortlasting (on average 3 weeks) and repeat treatments were required to prevent deterioration. These 9 patients responded equally well to IVIG (2g/kg), indicating that this was the effective component, and none became refractory during repeat treatment. Subsequent small, open studies provided further evidence for the efficacy of IVIG, but response rates have varied from 20-100% (Faed *et al.*, 1989 ; Cornblath *et al.*, 1991 ; Hoang-Xuan *et al.*, 1993 ; Nemni *et al.*, 1994). Lower response rates occurred in patients, who did not improve with other treatments. In a randomised, double-blind, cross-over, placebo-controlled trial with 7 patients, who had been on longterm IVIG treatment with continuing benefit, van Doorn *et al.* (1990) provided evidence for longterm efficacy in all patients. Unexpectedly, the same investigators found that benefit from IVIG (4/15 patients) and placebo (3/13 patients) was similar in the first double-blind, controlled trial with newly diagnosed, previously untreated patients (Vermeulen *et al.*, 1993). A low response rate to IVIG may be related to clinical features predictive of responsiveness. In an open study, van Doorn *et al.* (1991) found that 32/52 (62%) of patients improved after IVIG. The probability of improvement reached 93% in the presence of 5 factors : disease duration less than 1 year, progression of weakness until treatment, absence of discrepancy of weakness between arms and legs, areflexia in the arms, and > 20% slowing of motor conduction in the median nerve. Two large, randomised, double-blind, placebo-controlled trials have been conducted. Hahn *et al.* (1996) documented significant improvement in clinical and neurophysiological parameters and in disability scores in 19/30 (63%) patients treated with IVIG. In a randomised, double-blind, placebo-controlled trial, Mendell *et al.* (2001) documented improved strength in 76% of untreated CIDP patients and over one third improved by at least 1 functional grade on a disability scale. Longterm treatment was associated with stable improvement in several follow-up studies (van Doorn *et al.*, 1990 ; van der Meché and van Doorn, 1995 ; Choudhari and Hughes, 1995 ; Hahn *et al.*, 1996). From IVIG responders, 22% reached complete remission, whereas 66% needed repeat IVIG at 0.25-0.4g/kg every other week to maintain maximal improvement levels. After a mean follow-up time of 6.5 years, 18/30 responders (60%) were in remission, whereas the others continued to need intermittent IVIG (van der Meché and van Doorn, 1995). Further studies have shown that 79% of 90 patients responded to IVIG and that 85% of responders needed longterm treatment. IVIG treatment could be discontinued in 50 and 75% after 4 and 8.5 years, respectively (van der Meché, 2001).

Comparison between IVIG, PE, and steroids. A randomised, observer-blinded, cross-over study with 20 patients showed that PE and IVIG were equally effective in bringing about a large improvement, 'being equivalent to a change from a 50% bilateral pelvic and lower limb muscle weakness to no weakness' (Dyck *et al.*, 1994). For most patients, the effect of either PE or IVIG was short-lived and continued intermittent treatment with quite variable frequency and dosage was required to maintain high levels of functioning. The authors concluded that IVIG was preferable to PE because it is simple, less invasive, and because there is no need for expensive equipment and specialised health care personnel. Another randomised, double-blind, cross-over study with 32 patients compared a 6 week course of prednisolone (60 mg daily for 2 weeks) and IVIG (2g/kg) (Hughes *et al.*, 2001). Both treatments led to short-term improvement of disability and impairment, which was slightly but not significantly greater following IVIG than prednisolone. However, per protocol analysis revealed a marked trend towards more improvement with IVIG. Some patients did not require prolonged treatment after their first treatment course. The authors suggest that for those either IVIG or prednisolone are appropriate, whereas IVIG may be preferred for the others.

Table 1

Overview of therapeutic trials in CIDP.

Authors	Number of patients/Design	Treatment	Results
Dalakas and Engel, 1981	25/open	Steroids (100mg qd)	+ in most
	4/open	Azathioprine (3mg/kg qd)	+ in 3
	1/open	Cyclophosphamide (2mg/kg qd)	+
Dyck *et al*., 1982	28/open, randomised	Steroids (120mg qod) vs conventional treatment	+ (small)
Dyck *et al*., 1985	30/open, randomised	Azathioprine (2mg/kg qd) added to steroids	No additional +
Vermeulen *et al*., 1985	17/open	IVIG	+ in 13 (70%)
Dyck *et al*., 1986	29/double-blind, randomised	PE (n=15) vs sham (n=14)	+ in PE group
McCombe *et al*., 1987	76/open	Steroids	+ in 49 (65%)
	7/open	Azathioprine	+ in 4/7
	5/open	Cyclophosphamide	+ in 4/5
	13/open	PE	+ in 8 (61%)
Barohn *et al*., 1989	59/open	Steroids (+/- azathioprine/PE)	+ 56 (95%)
van Doorn *et al*., 1990	7/double-blind, randomised	IVIG vs placebo, cross-over	+ in 7 (known responders)
van Doorn *et al*., 1991	52/open	IVIG	+ in 32 (62%)
Vermeulen *et al*., 1993	28/double-blind, randomised	IVIG vs placebo	+ in 4/15 (IVIG) and 3/13 (placebo)
Koski, 1994	25/open	IV cyclophosphamide (+/-steroids)	+ in 20 (80%)
Dyck *et al*., 1994	20/observer-blinded, randomised	IVIG vs PE, cross-over	+ IVIG=PE
Choudhary and Hughes, 1995	33/open	PE	+ in 23
	21/open	IVIG	+ in 14
Hahn *et al*., 1996	18/double-blind, randomised	PE vs placebo, cross-over	+ in 12 (80%)
Hahn *et al*., 1996	30/double-blind, randomised	IVIG vs placebo, cross-over	+ in 19 (63%)
Molenaar *et al*., 1997	10/open	Pulsed dexamethasone	4 in 7 (70%)
Good *et al*., 1998	15/open	IV cyclophosphamide (+/-steroids)	+ in 11 (73%)
Mendell *et al*., 2001	53/double-blind, randomised	IVIG vs placebo	+ in 22/29 (76%)
Hughes *et al*., 2001	32/double-blind, randomised	IVIG vs steroids, cross-over	+ IVIG=PDN

Some patients who are unresponsive to steroids or PE may respond to IVIG and vice versa (Faed *et al.*, 1989 ; Cronblath *et al.*, 1991 ; van Doorn *et al.*, 1991 ; Choudhari and Hughes, 1995).

Conclusion

Randomised, blinded trials have established that steroids, PE, and IVIG are 3 efficacious treatment modalities for CIDP. At least two thirds of the patients respond to these treatments, but there are no criteria that predict to which treatment the individual patient will respond. Since CIDP is a chronic, disabling disorder, the goal is to select the most efficacious treatment for the individual patient. At present, IVIG represents the first line of treatment, because it is simple, improvement is rapid, and side-effects are minor in most cases. IVIG is expensive, but not more so than PE, which is much less practical because of the need for a specialised facility and which is more prone to side-effects. Steroids are easy to administer and are cheap, but improvement may take weeks or months. Furthermore, longterm use is associated with potentially serious side-effects. Cost-efficacy studies are needed, but the shortterm costs of IVIG may be balanced by the longterm healthcare costs related to steroid-induced complications. Steroids are contra-indicated in children and in patients with concurrent disorders, such as diabetes, gastric ulceration, osteoporosis, arterial hypertension, cataracts, etc. For patients who respond to a first course of treatment and do not need further treatment, either IVIG or steroids may be suitable.

If IVIG has led to initial improvement followed by secondary deterioration, optimal interval treatment needs to be determined in order to obtain stable, maximal improvement. For many patients, a treatment interval of 3 weeks is appropriate with doses varying between 0.4 and 1g/kg, but both the dose and the interval need to be tailored individually and adapted over time in order to maintain maximum function with the smallest effective dose and the largest possible time interval.

Patients who do not respond to IVIG should be treated with a second and if unresponsive again with a third treatment modality, because lack of response to one modality does not exclude responsiveness to other modalities. If a patient does not respond, or insufficiently so, to the 3 treatment modalities or if there are contra-indications, treatment with azathioprine, cyclophosphamide, cyclosporine, or interferons may be helpful.

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