Chronic motor neuropathies: response to interferon-β1a after failure of conventional therapies

I S J Martina, P A van Doorn, P I M Schmitz, J Meulstee, F G A van der Meché

Abstract

***Objectives*—The effect of interferon-β1a (INF-β1a; Rebif®) was studied in patients with chronic motor neuropathies not improving after conventional treatments such as immunoglobulins, steroids, cyclophosphamide or plasma exchange.**

***Methods*—A prospective open study was performed with a duration of 6–12 months. Three patients with a multifocal motor neuropathy and one patient with a pure motor form of chronic inflammatory demyelinating polyneuropathy were enrolled. Three patients had anti-GM1 antibodies. Treatment consisted of subcutaneous injections of IBF-β1a (6 MIU), three times a week. Primary outcome was assessed at the level of disability using the nine hole peg test, the 10 metres walking test, and the modified Rankin scale. Secondary outcome was measured at the impairment level using a slightly modified MRC sumscore.**

***Results*—All patients showed a significant improvement on the modified MRC sumscore. The time required to walk 10 metres and to fulfil the nine hole peg test was also significantly reduced in the first 3 months in most patients. However, the translation of these results to functional improvement on the modified Rankin was only seen in two patients. There were no severe adverse events. Motor conduction blocks were partially restored in one patient only. Anti-GM1 antibody titres did not change.**

***Conclusion*—These findings indicate that severely affected patients with chronic motor neuropathies not responding to conventional therapies may improve when treated with INF-β1a. From this study it is suggested that INF-β1a should be administered in patients with chronic motor neuropathies for a period of up to 3 months before deciding to cease treatment. A controlled trial is necessary to confirm these findings.**

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Multifocal motor neuropathy is a chronic immune mediated demyelinating neuropathy.[1 2] Patients with multifocal motor neuropathy mostly have a stepwise progression of asymmetric muscle weakness and amyotrophy localised in the anatomical distribution areas of peripheral nerves. Sensory symptoms are generally not present. The electrophysiological hallmark of multifocal motor neuropathy is persistent conduction block. Most patients with this disease have high titre antibodies against the ganglioside GM1.[1 2] Clinically, multifocal motor neuropathy is also described as an asymmetric pure motor variant of chronic inflammatory demyelinating polyneuropathy with multifocal motor conduction blocks. Especially, during the evolution of multifocal motor neuropathy the multifocal character may gradually evolve in a more or less symmetric pattern, clinically resembling the motor form of chronic inflammatory demyelinating polyneuropathy. Pathological studies have also linked multifocal motor neuropathy with chronic inflammatory demyelinating polyneuropathy.[3 4]

The first line of treatment of patients with multifocal motor neuropathy constitutes high dosage of intravenous immunoglobulins (IVIg).[5 6] Initial reports suggested benefit from treatment with cyclophosphamide.[1 7] However, not all patients improve after these treatments. In the group of non-responders at least, there is a need for new treatment modalities. Such a new treatment might be interferon-β1a (IFN-β1a).

The main objective of this study was to investigate whether treatment with IFN-β1a resulted firstly in improvement at the level of disability and secondly at the impairment level in severely affected patients with chronic motor neuropathies not improving after conventional therapies such as IVIg, cyclophosphamide, steroids, or plasma exchange. Additionally, the influence of IFN-β1a on neurophysiological findings and anti-GM1 antibody titres was investigated.

Patients and methods

PATIENTS' CHARACTERISTICS (TABLE) AND THERAPY

Four patients entered this prospective open study. Three patients were diagnosed as having multifocal motor neuropathy based on the clinical and electrophysiological characteristics for multifocal motor neuropathy.[2] The fourth patient had a chronic symmetric pure motor neuropathy with rapidly evolving symptoms at onset in the lower limbs. This patient met the clinical, electrophysiological, and CSF criteria for the diagnosis of chronic inflammatory demyelinating polyneuropathy.[8] Immunofixation in this patient, however, showed an IgM-λ and an IgG-κ monoclonal gammopathy. Extended haematological investigation showed no other abnormalities.

Clinical data before onset of treatment with interferon-β1a (Rebif)

Patient	*Age/ sex*	*Diagnosis*	*Onset of symptoms*	*Initially affected motor nerves*	*Duration of illness(y)*	*Previous treatments*	*Anti-GM1 antibodies*
1	39/M	MMN	UL/D/A	L Radial/L Ulnar R Radial	9	IVIg[1]/Cyclophos (2x)[2a]/Predn[3] Cyclophos[2b]+Predn[3]/ IVIg[1]+Mpredn[4]	+ (1 : 12800)
2	60/F	MMN	UL/D/A	R Median/L Ulnar	8	IVIg (3x)[1]	–
3	53/F	MMN	UL/D/A	L Ulnar	7	IVIg (2x)[1]/IVIg[1]+Mpredn[4]	+ (1 : 200)
4	54/M	CIDP	LL/D>P/S	L+R Posterior tibial and peroneal	9	IVIg (2x)[1]/IVIg[1]+Mpredn[4]/ Predn[3]/PE[5] Cyclophos[2a]+Predn[3]/Cyclophos[2c]	+ (1 : 12800)

MMN=multifocal motor neuropathy; CIDP=chronic inflammatory demyelinating polyneuropathy; UL=upper limb; LL=lower limb; D=distal; P=proximal; A=asymmetric; S=symmetric; L=left; R=right; IVIg=intravenous immunoglobulins; Cyclophos=cyclophosphamide; MPredn=methylprednisolone; PE=plasma exchange; [1]=0.4 g/kg body weight/day for 5 days; [2a]=0.5 g/day intravenously for 14 days; [2b]=0.15 g/day orally for half a year; [2c]=monthly 0.5 g/day orally for 4 days for 6 months; [3]=60–80 mg/day orally for 6 weeks, thereafter tapering to zero in 6 months; [4]=0.5g /day for 5 days; [5]=2 exchange sessions (each 2.5 litres plasma)/week for 5 consecutive weeks.

Two patients with multifocal motor neuropathy and the patient with chronic inflammatory demyelinating polyneuropathy had IgM anti-GM1 antibodies. Anti-MAG (myelin associated glycoprotein) antibodies were absent in the patient with chronic inflammatory demyelinating polyneuropathy. The duration of the symptoms ranged from 7 to 9 years before the start of INF-β1a treatment. All patients developed marked amyotrophy and their ambulation also decreased gradually during the disease period. At entry to this study, one patient was almost always wheelchair dependent and two patients needed a walking stick and ankle orthesis at both sites to cover short distances and a wheelchair for longer distances. Patient 3 did not experience much problem when walking very short distances, but she noticed that her legs gave way after walking for 5–10 minutes. Her walking endurance was also deteriorating and she could walk outdoors for only 15 minutes. The patients received different types of therapy during the course of their illness, but despite these treatments none showed clinical improvement. The study was approved by the medical ethics committee of our hospital and took place between February 1996 and September 1997. All patients gave informed consent. No immunosuppressive drugs were given within the 3 months before the study.

IFN-β1a (Rebif®; Serono Benelux) was self administered at a dosage of 6 million IU three times a week for 6 months and then, if clinical improvement was found (defined as at least one point improvement on the modified Rankin scale) the treatment was continued for an additional period of 6 months. To minimise the chance of adverse events a lower dose of 1.2 MIU Rebif was administered during the first week and 3.0 MIU during the second week. Thereafter the full dosage was given. Acetaminophen (500–1000 mg/day) was administered prophylactically during the first 6 weeks of treatment to ameliorate known constitutional symptoms of IFN-β1a.

CLINICAL ASSESSMENT

Primary outcome was assessed at the disability level using the nine hole peg test, the 10 metres walking test, and the modified Rankin scale.[9–11] All patients received training in fulfilling the nine hole peg test before the start of the study to exclude any training effect. Secondary outcome was measured at the impairment level using the MRC sumscore, which was slightly modified.[12] The following muscle pairs were examined: upper arm abductors, elbow flexors, wrist extensors, interosseus muscles, hip flexors, knee extensors, foot plantar flexors, and foot dorsal flexors (score range 0–80). All tests were assessed under predefined standard conditions. The scales were applied at entry and once a week in weeks 2, 4, 6, 8, 10, 12, 16, 21, and 26 in all patients, 3 months after stopping IFN-β1a in two patients and in weeks 32,42, and 52 in the other two patients. Two investigators (ISJM/PAvD) did the follow up assessments, each examining two patients. All measurements were compared with the baseline findings for each patient. Adverse events were recorded.

ADDITIONAL INVESTIGATIONS

Routine physical examination and laboratory studies, including enzyme linked immunosorbent assay (ELISA) tests for antibodies against the ganglioside GM1[13] were performed within 2 weeks before the start of the study and subsequently five times during the treatment period. Electromyography was performed under standard conditions using supramaximal stimulation by the same examiner (JM) within 2 weeks before day 1, and consecutively 3–5 times during therapy time. Nerve conduction velocities and compound muscle action potentials (CMAPs) were examined in eight motor nerves (four of the upper and four of the lower limbs). The examination always included the affected nerve(s) resulting in impairment.

STATISTICAL ANALYSIS

Conventional linear and linear spline (piecewise method) regression analyses[14] were used to evaluate the obtained serial data for the nine hole peg test and the 10 metres walking test. The knots of the linear spline functions were taken at week 12 of treatment, based on the clinical picture found. All analyses were performed using Stata 5.0 for Windows 95 (Stata Statistical Software: Release 5.0. 702 University Drive East, College station, TX: Stata Corporation 1997). A p value$\leq$0.05 was considered to be significant.

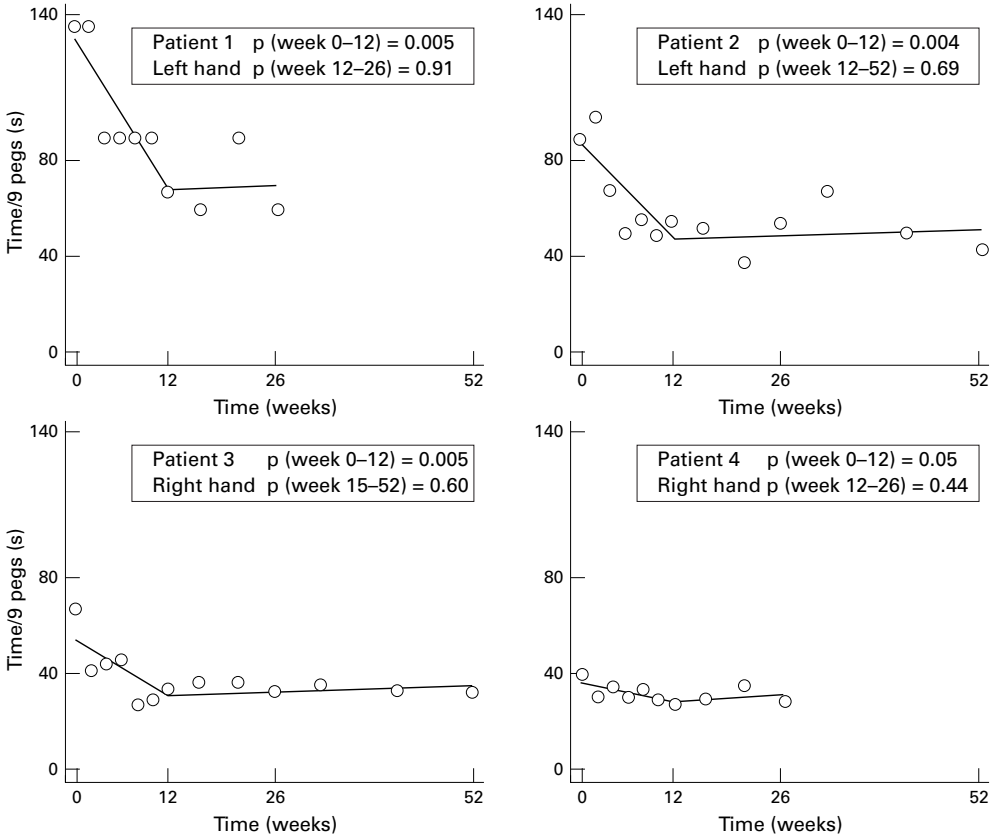

Figure 1 Nine hole peg test; the most affected hand of each patient. The analysis was performed using linear spline regression methods with the knots of the linear spline functions taken at 12 weeks.

Results

After 2–4 weeks of treatment the patients reported some improvement in walking and their daily manual skills. A maximum improvement was reached around 3 months of therapy, followed by stabilisation or only minimal clinical improvement. None of the patients experienced deterioration during treatment.

Manual skills such as washing and brushing hair, dressing the upper part of the body, doing up and undoing buttons and zips, and opening a jar or a bottle were more easily accomplished. The time needed to fulfil the nine hole peg test by the most affected hand of each patient was significantly reduced in all patients during the first 12 weeks of treatment (fig 1). Improvement was also seen in the less affected hands in the first 12 weeks, but this was significant only in patient 3 (p=0.003).

Improvement in ambulation consisted of an easier walking pattern in all patients. All patients claimed to need less assistance from another person and used their aid(s) less then they were used to. An ability to walk for a longer time was also experienced by two patients. The time required to walk 10 metres was significantly reduced in three patients in the first 3 months (fig 2). Although improvement in ambulation in patient 3 was not significant, her endurance improved considerably within the first 3 months of treatment as she could walk for more than 2 hours in the woods. The Rankin score also changed notably in this patient, from 3 to 1 around 3 months of therapy. Although the other three patients showed improvement at the level of impairment and disability, the Rankin score only improved in patient 2 (from 4 to 3). The Rankin score of the other two patients remained 3. Based on these results we decided to discontinue IFN-β1a in patients 1 and 4 with unchanged Rankin score after 6 months. Patient 4 remained stable at all levels of measuring outcome during the next 3 months. Patient 1 experienced slight deterioration in strength, dexterity, and mobility, but his Rankin score remained unchanged. The IFN-β1a treatment was continued for another 6 months in two patients (1and 4).

Conventional linear regression analysis showed significant improvement in muscle strength in all patients during the course of treatment ($p \leq 0.001$ for patients 1–3; p=0.04 for patient 4). The MRC sumscore increased from 40 to 53, 53 to 60, 69 to 73, and 49 to 57 respectively in patients 1 to 4.

All patients had motor conduction blocks (MCBs), outside the usual nerve compression sites in various nerves, ranging from 35%-94%. Only the patient with chronic inflammatory demyelinating polyneuropathy had a marked partial decrease in motor conduction block, in the right ulnar (82%→37%), left ulnar (70%→24%), and left median nerves (94%→53%). Motor nerve conduction velocities did not improve. Anti-GM1 antibody titres did not change. The recorded side effects of IFN-β1a were flu-like symptoms, fever, sweating, and erythema at the injection sites. These disappeared gradually within 2 months. The

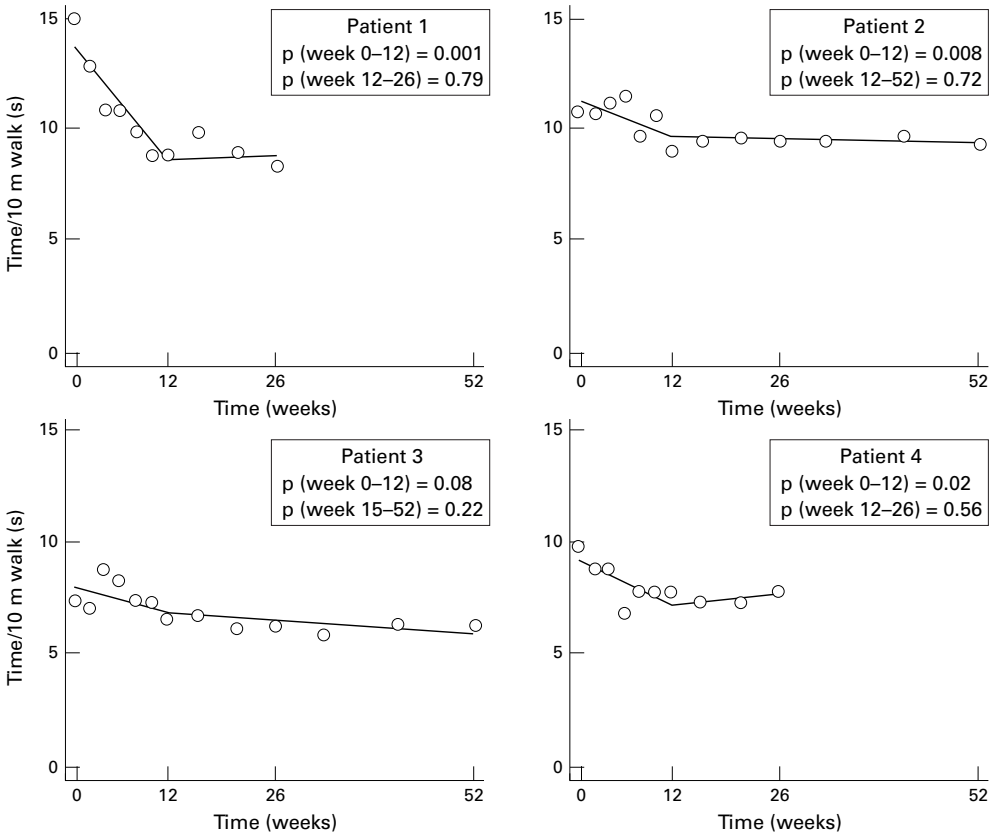

Figure 2 10 metre walking test; analysis performed using linear spline regression methods with the knots of the linear spline functions taken at 12 weeks.

drug was well tolerated. Physical examination and routine blood and urine analysis remained normal.

Discussion

In this open prospective study, treatment with IFN-β1a induced clinical improvement in the first 3 months of therapy in all 4 patients with severe chronic motor neuropathies not improving after conventional therapies. All patients remained stable during the follow up treatment period. However, improvement on the modified Rankin scale was only found in two patients. A possible explanation for this is that the grading definitions of the modified Rankin scale are very broad classifications of disability and therefore not sensitive enough to detect the improvement found on the other scales used. A similar finding was noted in a recent publication studying the effect of IVIg in chronic inflammatory demyelinating polyneuropathy.[15] Patient 3 seemed to be less profoundly affected than the other patients. She especially had less severe amyotrophy, which probably explains her better score on the modified Rankin scale. The response to treatment, therefore, seems to be correlated with the degree of being affected and the severity of amyotrophy.

Improvement after IFN-β1a was also recently found by Choudhary *et al* in a patient with an 8 year history of a relapsing and remitting sensory-motor chronic inflammatory demyelinating polyneuropathy not responding to various conventional treatments.[16] This patient received 3 MIU IFN-β1a, three times a week. Improvement began 2 weeks after administration and as in our patients a maximum was reached after 12 weeks. Other reports have also shown a possible therapeutic effect of this group of regulatory cytokines in chronic immune mediated neuropathies.[17–19] The present study provides some support for the effectiveness of IFN-β1a in patients with chronic immune mediated neuropathies, particularly in patients with multifocal motor neuropathy.

A poor correlation between clinical improvement and neurophysiological data, as seen in this study, has also been reported by others.[5 6 20] One of the possible explanations for this discrepancy is fluctuation in temporal dispersion, which may result in alterations of the form of the CMAPs.[20] Another possible cause is that restored conduction blocks located at the most proximal nerve segments may not be detected by neurophysiological studies.

The pathophysiological mechanism of action of IFN-β in chronic immune mediated neuropathies in not known. Presently, the knowledge regarding its immunoloigcal effects is mainly derived from studies on multiple sclerosis.[21 22] The IFN-β may counteract the effects of IFN-γ such as down regulation of major histocompatibility (MHC) class II antigen expression on neuroendothelial cells.[21 22] This may be of importance as upregulation of MHC class II molecules on endoneurial cells has been shown in chronic inflammatory demyelinating polyneuropathy.[23] Other immunomodulating effects of IFN-β that may be sig-

nificant in multifocal motor neuropathy and chronic inflammatory demyelinating polyneuropathy include enhancement of T suppressor cell function, reduction of T cell activation and the production of IFN-γ, down regulation of the production of certain cytokines such as tumour necrosis factor α and induction of the production and secretion of interleukin-4 and interleukin-10.[21 22 24]

No severe adverse events were recorded and none of the patients deteriorated during the administration of IFN-β1a. This suggests that IFN-β1a can be prescribed safely in patients with a chronic motor neuropathy. It is suggested that if patients respond to treatment with IFN-β1a, improvement generally starts after 2 to 4 weeks. If there is no improvement after about 3 months, therapy should be discontinued.

In conclusion, our findings indicate that severely affected patients with chronic immune mediated motor neuropathies not responding to conventional treatments may show improvement when treated with IFN-β1a. A controlled trial is required to confirm these findings.

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