

Articles

Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis

Franz Fazekas, Florian Deisenhammer, Siegrid Strasser-Fuchs, Gerhard Nahler, Bruno Mamoli, for the Austrian Immunoglobulin in Multiple Sclerosis Study Group*

Summary

Background Multiple sclerosis is an autoimmune disorder characterised by the repeated occurrence of demyelinating lesions within the central nervous system. Uncontrolled studies and experimental evidence suggest beneficial effects of repeated administration of intravenous immunoglobulin (IVIg) by immunomodulating mechanisms and induction or remyelination. We aimed to investigate the efficacy of IVIg in a randomised double-blind multicentre study.

Methods Patients with relapsing-remitting multiple sclerosis were randomly assigned a monthly dose of IVIg (0·15–0·2 g/kg bodyweight) or placebo. Duration of treatment was 2 years. The primary outcome measures were the effect of treatment on clinical disability—measured by the absolute change in Kurtzke's expanded disability status scale (EDSS) score—and the proportion of patients with improved, stable, or worse clinical disability ($\geq 1\cdot0$ grade on EDSS score).

Findings Of the 243 patients screened, 150 met our eligibility criteria and were randomly assigned to IVIg or placebo. Before the start of treatment two patients in the placebo group dropped out, so there were 75 patients in the IVIg group and 73 in the placebo group. Intention-to-treat analysis showed that IVIg treatment had a beneficial effect on the course of clinical disability. The EDSS score decreased in the IVIg-treated patients and increased in the placebo group ($-0\cdot23$ [95% CI $-0\cdot43$ to $-0\cdot03$] vs $0\cdot12$ [$-0\cdot13$ to $0\cdot37$], $p=0\cdot008$). In the IVIg group, the numbers of patients with improved, stable, or worse clinical disability were 23 (31%), 40 (53%), and 12 (16%) compared with ten (14%), 46 (63%), and 17 (23%) in the placebo group. Side-effects were reported in three (4%) IVIg-treated patients and in four (5%) placebo-group patients, but were not directly linked to study medication.

Interpretation Monthly IVIg is an effective and well-tolerated treatment for patients with relapsing-remitting multiple sclerosis.

See Commentary page 586

Lancet 1997; 349: 589–93

*Participants listed at end of paper

Department of Neurology, Karl-Franzens University, Anenbruggerplatz 22, A-8036 Graz, Austria (F Fazekas MD, S Strasser-Fuchs MD); Department of Neurology, Leopold-Franzens University, Innsbruck (F Deisenhammer MD); CIS Clinical Investigation Support GmbH & Co KG, Vienna (G Nahler MD); and Department of Neurology II, Hospital Rosenhügel, Vienna (B Mamoli MD)

Correspondence to: Dr Franz Fazekas

Introduction

Multiple sclerosis is the most common demyelinating disorder of the central nervous system, and is characterised by repeated episodes of neurological dysfunction with variable remission. Previous studies have suggested that autoimmune mechanisms have an important role in the pathogenesis of multiple sclerosis.^{1,2} Intravenous immunoglobulin (IVIg) has been successful in other autoimmune neurological disorders, such as acute and chronic inflammatory demyelinating radiculoneuropathies,^{3,4} myasthenia gravis,⁵ and dermatomyositis.⁶ Yan and colleagues⁷ recommended IVIg treatment for acute exacerbations of multiple sclerosis and three uncontrolled or open-label studies reported a beneficial effect of long-term IVIg treatment on the course of the disease.^{8–11} Several immunological mechanisms may be involved in multiple sclerosis.^{12,13} IVIg produced from pooled blood from healthy donors may contain anti-idiotypic antibodies, which have regulatory effects on antibody production and lymphocyte activity.¹⁴ IVIg may also reduce the autoaggressive effect of macrophages by blocking their Fc-receptors,¹⁵ or it may act as a receptor for activated complement components preventing their binding to the oligodendrocyte surface and myelin proteins.¹⁶ In addition, IVIg can down-regulate cytokine production and neutralise inflammatory cytokines.¹⁷ All these mechanisms are involved in the pathogenesis of multiple sclerosis lesions.

Experiments in mice have shown that IVIg may promote remyelination within demyelinative lesions induced by Theiler's virus.¹⁸ The clinical significance of this mechanism was supported by van Engelen and colleagues' study¹⁹ of five multiple sclerosis patients with optic neuritis: after a period of stable visual impairment for between 7 months and 4 years, IVIg treatment led to an increase in visual acuity and colour vision 1–2 months after the start of treatment which continued thereafter.¹⁹ This finding suggests that repeated IVIg therapy may not only delay or prevent the progression of multiple sclerosis but can even induce clinical improvement.²⁰

Our randomised, double-blind, placebo-controlled, multicentre study was designed to assess the effect of monthly IVIg treatment on the clinical course of relapsing-remitting multiple sclerosis.

Methods

Between December, 1992, and January, 1996, 243 patients from 13 neurological centres throughout Austria were considered for enrolment in our study.

Our definition of relapsing-remitting multiple sclerosis included individuals with complete and incomplete remissions.²¹ Inclusion criteria were a clinically definite diagnosis of relapsing-remitting multiple sclerosis,²² a baseline Kurtzke's expanded disability status scale (EDSS)²¹ score of between 1·0 (minor

neurological signs but no disability) and 6·0 (ambulatory with assistance), and a history of at least two clearly identified and documented relapses during the previous 2 years. In addition, eligible patients were men and women aged 15–64 years whose first manifestation of multiple sclerosis was at age 10–59 years (age range set below 60). Patients had to have stopped any immunosuppressive or immunomodulatory therapy at least 3 months before enrolment and were excluded if they had taken corticosteroids within 2 weeks of study entry. Other exclusion criteria were lack of reliable contraception, a primary or secondary progressive course of multiple sclerosis, or a benign course of the disease as indicated by a deterioration rate of less than 0·25. The deterioration rate was the actual EDSS score divided by the duration of the disease in years.²⁴ All eligible patients gave written informed consent to take part in the study. The protocol was approved by the appropriate ethics committee.

After being screened for eligibility, patients were randomly allocated intravenous IVIg or saline placebo. Patients received 0·15–0·20 g/kg bodyweight study medication every month (± 10 days) for 2 years. IVIg was supplied by Sero-Mérieux (Vienna, Austria).

We used a centralised, computer-generated randomisation schedule that involved stratification by centre, age, sex, and deterioration rate. Infusions of IVIg and placebo were identical in appearance and were stored in plastic bags for concealment during administration. The randomisation code was only broken for statistical analysis.

At each monthly visit a neurologist who was aware of treatment allocation (treating physician) administered the study medication and asked the patient about any side-effects. Patients were assessed on the first day of treatment, every 6 months, and at the end of the 2-year study by a different neurologist (assessing physician) who was unaware of treatment allocation. Clinical disability was measured with the EDSS and the functional systems scale.²¹

All patients were told to contact their centre as soon as there was any change in their condition. In such cases, the assessing physician examined the patient to confirm a possible relapse and to assess the severity of the disability. After a relapse had been confirmed, the treating physician administered pulses of 1 g methylprednisolone for 5–10 days, with subsequent tapering. During an acute relapse, study medication was stopped and then restarted 3 weeks (± 1 week) after the last steroid dose. Subsequent intervals between the administration of study medication were adjusted to catch up with any missed infusion. Thus, relapses did not affect the total number of infusions that were administered during the study.

The primary outcome measures were the between-group differences in the absolute change on the EDSS score and in the proportion of patients with improved, stable, or worse clinical disability, as defined by an increase or decrease of at least 1·0 grade on the EDSS score by the end of the study.

Secondary outcome measures were: the number of relapses, the annual relapse rate, the proportion of relapse-free patients, and the time to first relapse during the study period. We defined a relapse as the appearance or reappearance of one or more neurological abnormalities that persisted for at least 24 h and had been preceded by a stable or improving neurological state of at least 30 days.²⁶ A relapse was confirmed only if the patient's symptoms were accompanied by objective changes of at least one grade in the score for one of the eight functional groups on the EDSS.^{21,26}

Our calculation of the required sample size was initially based on the assumption that the clinical disability of 20% of IVIg-treated patients and 50% of placebo-treated patients would deteriorate during the 2-year study. However, after the publication of the IFNB Multiple Sclerosis Study²⁵ in 1993, we recalculated the absolute change in EDSS score that would be detectable with the same sample size. Thus, we estimated that 150 patients (75 in each group) were required to give a power of 90% and a significance level of 0·05 in detecting a mean difference of 0·81 (SD 1·37) in the change of the EDSS score between the groups (including 20% drop-outs).

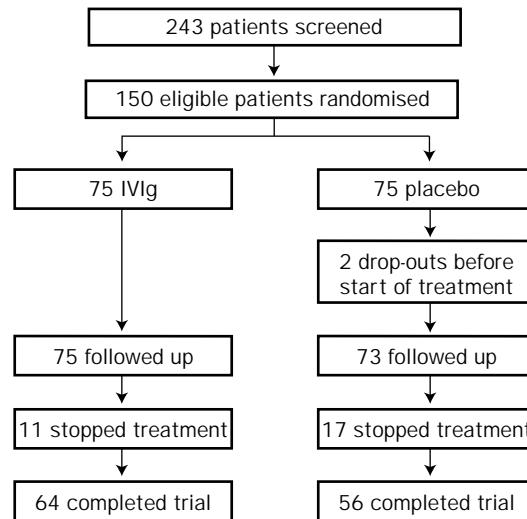


Figure 1: Trial profile

The primary analysis was by intention to treat, but we also did a subgroup analysis of the patients who completed 2 years of treatment. The baseline characteristics of the IVIg and placebo groups were compared by two-tailed *t* tests for continuous variables and χ^2 tests for discrete variables. For comparison of the EDSS score between groups, we used the Wilcoxon two-sample test, because the EDSS is ordinally scaled and the scores are not normally distributed. We calculated the absolute change in EDSS score by subtraction of the baseline from the final score. Between-group differences were also assessed by the Wilcoxon two-sample test.

Improvement or deterioration of clinical disability within groups was further analysed by fitting straight lines to the time course of the EDSS scores of each patient by ordinary least square. This analysis included all available EDSS scores during the study period, except the scores recorded at the start and end of a relapse. The slopes of these lines were tested against zero within each treatment group by the Wilcoxon one-sample signed-rank test. We chose this test because the data were not normally distributed. The difference between the slopes of the IVIg group and the placebo group was tested with the Wilcoxon two-sample test. This technique was deemed to be appropriate to accommodate missing data and drop-outs.²⁷

The proportional between-group difference in the change of clinical disability was tested by the χ^2 test on two-by-three contingency tables. This method was also used to analyse differences in the number of relapses and in the proportion of relapse-free patients. The relapse rate for each patient was calculated as the number of relapses divided by days of follow-up, and then standardised as the number of relapses per year (annual relapse rate). Differences between the groups were tested with the two-sample Wilcoxon test. To detect differences in the time to first relapse, we constructed survival curves for both groups, which we tested by the log-rank test. Multivariate analysis was not done because there were no baseline differences in potential confounding factors, such as age, sex, progression rate, previous medication, and centre between the groups. Statistical significance was defined as $p < 0·05$.

Characteristics	IVIg (n=75)	Placebo (n=73)
Age (years)	36·7 (34·3–39·1)	37·3 (35·0–39·6)
M/F	18/57	19/54
Duration of multiple sclerosis (years)	6·8 (5·7–7·9)	7·3 (6·0–8·6)
Prestudy annual relapse rate	1·3 (1·1–1·5)	1·4 (1·2–1·6)
EDSS score at baseline	3·3 (3·0–3·6)	3·3 (2·9–3·7)
Time from last prestudy relapse to start of study medication (days)	151 (117–185)	185 (143–227)

Data are mean (95% CI), except for the M/F ratio. EDSS=Kurtzke's expanded disability status scale.

Table 1: Characteristics of patients

Results

Of the 243 patients screened for eligibility, 93 did not meet the inclusion criteria: 17 had an EDSS score of less than 1·0 or more than 6·0; 16 had too low progression rates; seven had had fewer than two relapses within the previous 2 years; 12 did not have relapsing-remitting multiple sclerosis; 14 were taking immunomodulatory drugs, four were not available to take part in the study; 12 did not give their consent; and 11 were excluded for other reasons. Two patients withdrew their consent to take part in the study between randomisation and the start of treatment; both were in the placebo group and were not included in the statistical analysis. Thus, 148 patients took part in the study: 75 in the IVIg group and 73 in the placebo group. The trial profile shows the numbers of patients throughout the trial (figure 1).

The groups were well matched in terms of baseline characteristics (table 1). 64 patients in the IVIg group and 56 in the placebo group completed 2 years of treatment. The mean follow-up was 21·9 (SD 6·1) months in the IVIg group and 20·9 (6·9) months in the placebo group.

Clinical disability

All the analyses showed that IVIg treatment had a beneficial effect on the course of clinical disability. Overall, the clinical disability of IVIg-treated patients tended to improve. The final EDSS score of the IVIg group decreased from baseline, whereas that of the placebo group increased slightly (table 2). This between-group difference in the mean change of the EDSS score was significant ($p=0.008$).

73 (97%) IVIg-treated patients and 70 (96%) placebo-group patients had at least two routine EDSS assessments. Regression of the slopes of these patients' EDSS scores against months on study medication showed a slight but significant improvement in the clinical disability of the IVIg group (mean slope -0.01305 , $p=0.012$). No significant change in clinical disability was found in the placebo group (mean slope 0.0032 , $p=0.29$). The difference between these slopes was significant ($p=0.012$).

There was an improvement of 1·0 grade or more on the EDSS in 23 (31%) IVIg-treated patients, compared with ten (14%) placebo-group patients. By contrast, deterioration of clinical disability occurred in 12 (16%) IVIg-treated patients and in 17 (23%) placebo-group patients ($p=0.041$, figure 2). Overall, 24% of patients did better on IVIg than on placebo in terms of the positive effects of IVIg treatment on improvement (17%) plus prevention of deterioration (7%).

Among the patients who completed the trial (64 IVIg and 56 placebo), improvement of clinical disability was found in 21 (33%) IVIg-group patients versus eight (14%)

	IVIg	Placebo	<i>P</i>
Intention-to-treat analysis			
Total patients	75	73	
Baseline EDSS score	3.33 (3.01 to 3.65)	3.37 (2.96 to 3.76)	0.99
Final EDSS score	3.09 (2.72 to 3.46)	3.49 (3.06 to 3.92)	0.008
Change in EDSS score	-0.23 (-0.43 to -0.03)	0.12 (-0.13 to 0.37)	0.008
Subgroup analysis*			
Total patients	64	56	
Baseline EDSS score	3.38 (3.03 to 3.73)	3.45 (2.97 to 3.93)	0.99
Final EDSS score	3.14 (2.73 to 3.55)	3.57 (3.07 to 4.07)	0.022
Change in EDSS score	-0.23 (-0.46 to 0.00)	0.13 (-0.18 to 0.44)	0.02

Data are mean (95% CI). *Only those patients who completed the 2-year study.

Table 2: Clinical disability according to EDSS score

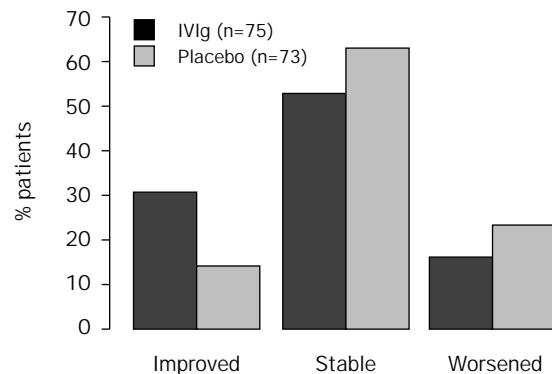


Figure 2: Proportion of patients with change in clinical disability (≥ 1.0 grade on EDSS score) by intention to treat

placebo-group patients. Deterioration of clinical disability by 1·0 grade or more on the EDSS score occurred in 11 (17%) IVIg-treated patients compared with 13 (23%) placebo-group patients ($p=0.06$).

Acute relapses

Table 3 shows the occurrence of acute relapses in both groups. The number of confirmed relapses in IVIg-treated patients was about half that in the placebo group. Similarly the proportion of relapse-free patients was significantly lower during the study than in the prestudy period; this decrease was significantly greater in IVIg-treated patients than in placebo-treated patients. In the IVIg group, the annual relapse-rate reduction was similar during year 1 and year 2 of the study. By contrast, in the placebo group, some reduction was noted only in year 2. The time from baseline to first relapse did not differ significantly between the groups. However, the interval between relapses during the study period was significantly longer among patients in the IVIg group than among those in the placebo group. The severity of relapses during the study, as measured by the change in EDSS score, did not differ significantly between the groups.

Withdrawals and adverse events

11 patients in the IVIg group and 17 in the placebo group withdrew from the study. The reasons for early discontinuation of study medication are shown in table 4. The rate of withdrawal because of lack of efficacy was four times higher in the placebo group than in the IVIg group.

	IVIg (n=75)	Placebo (n=73)	<i>P</i>
Number of relapses	62	116	
Relapse-free patients	40 (53%)	26 (36%)	0.03
Mean (95% CI) annual relapse rates			
Prestudy	1.30 (1.09–1.51)	1.41 (1.21–1.61)	0.4
Study period	0.52 (0.32–0.72)	1.26 (0.75–1.77)	0.0037
Year 1	0.49 (0.29–0.69)	1.30 (0.79–1.81)	0.011
Year 2*	0.42 (0.24–0.60)	0.83 (0.59–1.07)	0.006
Characteristics of relapses†			
Mean (range) days to first relapse	237 (4–659)	151 (2–719)	0.35
Mean (range) days between relapses	720 (83–744)	362 (28–738)	0.026
Mean (95% CI) change in EDSS score during relapse	1.00 (0.78–1.22)	1.26 (1.04–1.48)	0.22

*IVIg (n=65), placebo (n=63). †IVIg (n=35), placebo (n=47).

Table 3: Acute relapses

	IVIg (n=75)	Placebo (n=73)
Reason for withdrawal		
Deterioration/lack of efficacy	2	8
Psychological problems	1	3
Non-compliant/unknown	5	5
Adverse events	3	1
Total	11 (15%)	17 (23%)
Adverse events		
Cutaneous reaction	2	0
Depression	1	0
Eosinophilia	0	1
Hypogastric pain	0	1
Myocardial infarction	0	1
Pulmonary embolism	0	1
Ileus	0	1
Total number of patients	3 (4%)	4 (5%)

Table 4: Withdrawals and adverse events

Adverse events were reported by three IVIg-treated patients and four patients in the placebo group. Cutaneous reactions were reported by two IVIg-treated patients; symptoms consisted of a short-lived rash which developed a few days after the infusion but was not seen by the treating physician. One of these patients had a known allergy to a combination of trimethoprim and sulphamethoxazole (co-trimoxazole) and egg white. These side-effects occurred after the second and eleventh infusion. In addition, one patient in the IVIg group who was on anafranil developed eosinophilia and the depression recurred; he decided to discontinue the study medication after the sixth infusion. None of the adverse events reported by placebo-group patients caused early discontinuation of study medication.

Discussion

Our study is the first large-scale placebo-controlled trial of the efficacy of long-term IVIg treatment in relapsing-remitting multiple sclerosis. Our findings show that a monthly dose of IVIg (0.15–0.20 g/kg bodyweight) improved the course of clinical disability and reduced the frequency of relapses. At the end of 2 years, the magnitude of the absolute change in EDSS score and, thus, in clinical disability was small in both groups. However, the between-group difference in absolute change in EDSS score was highly significant ($p=0.008$), with a tendency for improvement of clinical disability in the IVIg group compared with further deterioration in the placebo group. 24% more patients in the IVIg group than in the placebo group did better by at least 1.0 EDSS grade. Moreover, IVIg treatment led to a significant reduction in the number of relapses. There was a higher proportion of relapse-free patients and a 59% lower annual relapse rate in the IVIg group than in the placebo group.

Our findings accord with previous uncontrolled or open-label studies of the efficacy of IVIg treatment in multiple sclerosis.^{8–11,28} Direct comparison of our findings with data reported for other immunomodulatory drugs would be inappropriate;^{25,29,30} however, it may be useful to consider the magnitude of the treatment effects of these other drugs. The percentage of patients with reduced clinical disability because of active treatment (defined as the proportion of active-treatment patients who improved or remained stable *vs* placebo-treated patients) was 18% in Johnson and colleagues' trial²⁴ of copolymer 1 and 19% in Jacobs and colleagues' study³⁰ of interferon β -1a. Unfortunately, no 2-year data have been reported by the IFNB Multiple Sclerosis Study Group.²⁵ In our study,

IVIg treatment resulted in 24% of patients with reduced clinical disability. Annual relapse-rate reduction by active treatment over placebo was 29% with copolymer 1,²⁹ 32% with interferon β -1a,³⁰ 34% with interferon β -1b,²⁵ and 59% in this study. In keeping with the previous studies, even placebo-treated patients showed a significant decrease in the annual relapse rate compared with the prestudy period. This reduction has been explained by a true placebo effect and regression towards the mean. Withdrawal of those patients with persistent disease activity because of treatment failure is another potential factor, and may explain the fall in the rate of relapses among placebo-treated patients during year 2 of our trial.

Current interval treatments of relapsing-remitting multiple sclerosis, such as interferon β , copolymer 1, and IVIg, may slow the progression of disability, but do not stop it. Thus, the need for long-term medication that satisfies issues of patient comfort and side-effects is of paramount importance. In this study, monthly infusions of IVIg were well tolerated—side-effects were reported in only three (4%) patients; moreover, none of these adverse events were unequivocally related to IVIg. However, our trial was not designed to monitor side-effects under masked conditions. The treating physician, who was aware of treatment allocation, asked the patient about any concomitant events to keep to a minimum the risk of unmasking during the assessments by the assessing physician. Masked conditions in our study were also maintained by the lack of local reactions after the administration of IVIg.

Our trial had some limitations. Our findings do not explain the precise mechanism by which monthly IVIg treatment altered the clinical course of relapsing-remitting multiple sclerosis. The trend for a decrease in the EDSS score during the study period and the improvement of clinical disability in 31% of IVIg-treated patients may suggest effects of remyelination. A reduction in relapses by almost half the number that occurred in placebo-treated patients should also contribute to the long-term efficacy of IVIg treatment. Parallel monitoring of disease activity and of changes in the total lesion load by magnetic resonance imaging would have been needed to address these issues.³¹ Although the clinical observation of improvement in the course of clinical disability after IVIg treatment remains the decisive outcome measure, the collection of data from magnetic resonance imaging in future trials should be attempted so that the capacity of IVIg for suppressing disease activity can be better assessed.³¹ This study included no dose-finding attempt. In the absence of other similar trials, the optimum regimen for IVIg treatment remains unknown. Our findings indicate that patients with multiple sclerosis benefit from lower doses of IVIg than those recommended for the long-term treatment of neuromuscular autoimmune disorders.^{32,33} Such low doses reduce the risk of severe side-effects,³⁴ but the benefit of a higher dose might be even greater.

In conclusion, we have shown that IVIg is a feasible option for the treatment of relapsing-remitting multiple sclerosis. Monthly administration of IVIg seems to be at least as effective as treatment with interferon- β or copolymer 1 in improving clinical disability and reducing the rate of relapses, and may also cause less inconvenience to the patient and fewer adverse events. Although our findings represent an important step towards ameliorating the course of relapsing-remitting multiple sclerosis, the optimum treatment strategy has yet to be identified.

Austrian Immunoglobulin in Multiple Sclerosis Study Group
Clinical centres and participants—Niederösterreichische
 Landesnervenklinik Gugging (A Seiser), Universitätsklinik für Neurologie, Graz (S Strasser-Fuchs, R Scheuchl, F Fazekas), Krankenhaus der Barmherzigen Brüder Eggenberg, Graz (J Kirisits), Universitätsklinik für Neurologie, Innsbruck (P Pohl, G Grubwieser, S Kiechl, F Deisenhammer), A Ö Krankenhaus Klagenfurt (J Zechner), A Ö Krankenhaus der Stadt Linz (D Bibl), Ö Krankenhaus der Barmherzigen Schwestern, Linz (I Huemer), Oberösterreichische Landesnervenklinik Wagner-Jauregg, Linz (H Markut, C Adelwöhrer), Landeskrankenhaus Bruck/Mur (S Varosanec), Landesnervenklinik Salzburg (E Hess-Eberle), Landeskrankenhaus Rankweil, Valduna (G Barolin, S Koppi, U Weiser), Ludwig Boltzmann Institut für Epilepsie und Neuromuskuläre Erkrankungen am Neurologischen Krankenhaus der Stadt Wien Rosenhügel, Wien (B Mamoli, I Fuchs, K Unger), A Ö Krankenhaus Wiener Neustadt (W Soukop).

Planning, Data Monitoring, and Statistical Centre—CIS Clinical Investigation Support GmbH & Co KG, Wien (G Nahler, H Petto).

Acknowledgments

We thank Christian Confavreux, Jean-François Dartigues, Otto R Hommes, and Michel D Kazatchkine for their advice about the design of this study, and David H Miller for his critical revision of the manuscript. This study was supported by Sero-Merieux, Vienna, Austria.

References

- 1 Reder AT, Arnason BGW. Immunology of multiple sclerosis. In: Vinken PJ, Bruyn GW, Klawans HL, Koetsier JC, eds. *Handbook of clinical neurology, volume 2: demyelinating diseases*. Amsterdam: Elsevier Science, 1985: 337–95.
- 2 Hafler DA, Weiner HL. MS: a CNS and systemic autoimmune disease. *Immunol Today* 1989; **10**: 104–07.
- 3 van Der Meeche FGA, Schmitz PIM, for the Dutch Guillain Barré Study Group. A randomised trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. *N Engl J Med* 1992; **326**: 1123–29.
- 4 Vermeulen M, Van Doorn PA, Brand A, Strengers PFW, Jennekens FGI, Busch HFM. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1993; **56**: 36–39.
- 5 Ippoliti G, Cosi V, Piccolo G, Lombardi M, Mantegaz R. High-dose intravenous gammaglobulin for myasthenia gravis. *Lancet* 1984; ii: 809.
- 6 Dalakas MC, Illia I, Dambrosia JM, et al. A controlled trial of high dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993; **329**: 1993–2000.
- 7 Yan J, Richert JR, Sirdofsky MD. High-dose intravenous immunoglobulin for multiple sclerosis. *Lancet* 1990; ii: 692.
- 8 Rothfelder U, Neu I, Pelka R. Therapy of multiple sclerosis with immunoglobulin G. *Munch Med Wochenschr* 1982; **124**: 74–78.
- 9 Schuller E, Govaerts A. First results of immunotherapy with immunoglobulin G in multiple sclerosis patients. *Eur Neurol* 1983; **22**: 205–12.
- 10 Soukop W, Tschabitscher H. Gamma globulin therapy in multiple sclerosis: theoretical considerations and initial clinical experiences with 7S immunoglobulins in MS therapy. *Wien Med Wochenschr* 1986; **136**: 477–80.
- 11 Achiron A, Pras E, Gilad R, et al. Open controlled therapeutic trial of intravenous immune globulin in relapsing-remitting multiple sclerosis. *Arch Neurol* 1992; **49**: 1233–36.
- 12 Weiner HL, Hafler DA. Immunotherapy of multiple sclerosis. *Ann Neurol* 1988; **23**: 211–22.
- 13 Soelberg Sorensen P. Treatment of multiple sclerosis with IVIg: potential effects and methodology of clinical trials. *J Neurol Neurosurg Psychiatry* 1994; **57**: S62–64.
- 14 Tenser RB, Hay KA, Aberg JA. Immunoglobulin G immunosuppression of multiple sclerosis: suppression of all three major lymphocyte subsets. *Arch Neurol* 1993; **50**: 417–20.
- 15 Jungi TW, Breie M, Kuhnert P, et al. Effect of IgG for intravenous use on Fc receptor mediated phagocytosis by human monocytes. *Clin Exp Immunol* 1990; **82**: 163–69.
- 16 Frank MM, Basta M, Fries LF. The effect of intravenous immune globulin on complement-dependent immune damage of cells and tissues. *Clin Immunol Immunopathol* 1992; **62**: S82–86.
- 17 Anderson UG, Bjork L, Skansen-Saphir U, Anderson JP. Down-regulation of cytokine production and interleukin-2 receptor expression by pooled human IgG. *Immunology* 1993; **79**: 211–16.
- 18 Rodriguez M, Lennon VA. Immunoglobulins promote remyelination in the central nervous system. *Ann Neurol* 1990; **27**: 12–17.
- 19 van Engelen BGM, Hommes OR, Pinckers A, Cruysberg JRM, Barkhof F, Rodriguez M. Improved vision after intravenous immunoglobulin in stable demyelinating optic neuritis. *Ann Neurol* 1992; **32**: 835–36.
- 20 Noseworthy JH, O'Brien PC, van Engelen BGM, Rodriguez M. Intravenous immunoglobulin therapy in multiple sclerosis: progress from remyelination in the Theiler's virus model to a randomised, double-blind, placebo-controlled clinical trial. *J Neurol Neurosurg Psychiatry* 1994; **57**: S11–14.
- 21 Hauser SL. Multiple sclerosis and other demyelinating diseases. In: Isselbacher KJ, Braunwald E, Wilson JD, et al, eds. *Harrison's principles of internal medicine, volume 2*. New York: McGraw-Hill, 1994: 2287–95.
- 22 Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983; **13**: 227–31.
- 23 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; **33**: 1444–52.
- 24 Miller DH, Barkhof F, Berry I, et al. Magnetic resonance imaging in monitoring the treatment of multiple sclerosis: concerted action guidelines. *J Neurol Neurosurg Psychiatry* 1991; **54**: 683–88.
- 25 The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis: clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993; **43**: 655–61.
- 26 Bornstein MB, Miller A, Slagle S, et al. A pilot trial of COP 1 in exacerbating-remitting multiple sclerosis. *N Engl J Med* 1987; **317**: 408–14.
- 27 Berry DA. Statistical methodology in the pharmaceutical sciences: statistics volume 104. New York: M Dekker, 1990.
- 28 Achiron A, Gilad R, Margalit R, et al. Intravenous gammaglobulin treatment in multiple sclerosis and experimental autoimmune encephalomyelitis: delineation of usage and mode of action. *J Neurol Neurosurg Psychiatry* 1994; **57**: S57–61.
- 29 Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. *Neurology* 1995; **45**: 1268–76.
- 30 Jacobs DL, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996; **39**: 285–94.
- 31 Miller DH, Albert PS, Barkhoff F, et al. Guidelines for the use of magnetic resonance techniques in monitoring the treatment of multiple sclerosis. *Ann Neurol* 1996; **39**: 6–16.
- 32 van Doorn PA. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy. *J Neurol Neurosurg Psychiatry* 1994; **57**: S38–42.
- 33 Cherin P, Herson S. Indications for intravenous gammaglobulin therapy in inflammatory myopathies. *J Neurol Neurosurg Psychiatry* 1994; **57**: S50–54.
- 34 Reinhart WH, Berchtold PE. Effect of high-dose intravenous immunoglobulin therapy on blood rheology. *Lancet* 1992; **339**: 662–64.