A RANDOMIZED TRIAL COMPARING INTRAVENOUS IMMUNE GLOBULIN AND PLASMA EXCHANGE IN GUILLAIN–BARRÉ SYNDROME

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Abstract *Background.* The subacute demyelinating polyneuropathy known as Guillain–Barré syndrome improves more rapidly with plasma exchange than with supportive care alone. We conducted a multicenter trial to determine whether intravenous immune globulin is as effective as the more complicated treatment with plasma exchange.

Methods. To enter the study, patients had to have had Guillain–Barré syndrome for less than two weeks and had to be unable to walk independently. They were randomly assigned to receive either five plasma exchanges (each of 200 to 250 ml per kilogram of body weight) or five doses of a preparation of intravenous immune globulin (0.4 g per kilogram per day). The predefined outcome measure was improvement at four weeks by at least one grade on a seven-point scale of motor function.

Results. After 150 patients had been treated, strength had improved by one grade or more in 34 percent of those treated with plasma exchange, as compared with 53 percent of those treated with immune globulin (difference, 19 percent; 95 percent confidence interval, 3 percent to 34 percent; $P = 0.024$). The median time to improvement by one grade was 41 days with plasma exchange and 27 days with immune globulin therapy ($P = 0.05$). The immune globulin group had significantly fewer complications and less need for artificial ventilation.

Conclusions. In the acute Guillain–Barré syndrome, treatment with intravenous immune globulin is at least as effective as plasma exchange and may be superior. (N Engl J Med 1992;326:1123-9.)

THE Guillain–Barré syndrome, a subacute inflammatory demyelinating polyneuropathy, leads to severe quadriparesis and requires artificial ventilation in about 20 percent of patients. Although functional recovery is the rule, 15 percent of patients have residual deficits.[1] For these reasons, more specific therapy has been sought in addition to supportive care. Because humoral factors may be involved in the pathogenesis of the disease,[2] plasma exchange has recently been evaluated in a number of clinical trials.[3-6] With plasma exchange, patients improve faster and have significantly shorter periods of artificial ventilation than with supportive care alone. At present there is consensus that plasma exchange is indicated in patients who have major deficits and who are still in the first weeks of their disease.[7]

Encouraged by the results of treatment with high-dose intravenous immune globulin in patients with chronic inflammatory demyelinating polyneuropathy,[8,9] we undertook a pilot study of this treatment in Guillain–Barré syndrome.[10] The results suggested that immune globulin might also be effective in this syndrome. Beneficial effects of therapy with immune globulin have been suggested in several other autoimmune-mediated diseases.[11-14] The biologic effects of high-dose immune globulin in these conditions have not been fully elucidated, but it is clear that the drug may influence the immune system in many ways.[13-19] It is not possible to predict the mechanism that might be beneficial in Guillain–Barré syndrome, since the pathogenesis of the syndrome is unknown. Therefore, as in the case of plasma exchange, the effect of immune globulin has to be judged on the basis of clinical evaluation alone.

If immune globulin and plasma exchange are equally effective, immune globulin has important practical advantages, since it is available in all hospitals and can be administered without delay. Furthermore, treatment with immune globulin is well tolerated and is considered safe, especially with respect to viral transmission.[20-22] On the other hand, plasma exchange is technically difficult to perform in children, and it may be contraindicated at any age because of cardiovascular instability; the largest trial of plasma exchange had a 10 percent dropout rate.[5] Therefore, it seemed appropriate to conduct a clinical trial with the aim of determining whether immune globulin therapy and plasma exchange have equal efficacy (within predefined limits) in the treatment of Guillain–Barré syndrome.

METHODS

This study was approved by the medical ethics committees at each participating center. The patients gave written informed consent unless paresis precluded their doing so, in which case oral consent was obtained.

Eligibility and Randomization

Patients were eligible if they fulfilled the criteria for acute Guillain–Barré syndrome,[23] were not able to walk 10 m independently, and could enter the study within two weeks of onset of the neuropathy. The criteria for exclusion were age of less than four years, a previous episode of Guillain–Barré syndrome, a previous severe allergic reaction to properly matched blood products, known selective IgA deficiency, pregnancy, treatment with immunosuppressive agents, severe concurrent medical disease, or unavailability for follow-up during the next six months. Patients with known selective IgA deficiency were excluded because some immune globulin products contain substantial amounts of IgA. We used a 24-hour telephone service for the randomization of patients. Randomization was stratified only according to center; within each center we used a

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*See the Appendix for a list of the participants in the Dutch Guillain–Barré Study Group.

fixed block size of six patients (three assigned to plasma exchange and three to immune globulin), and the block size was not known by the center investigators.

Treatment

Plasma exchange was started as soon as possible after randomization, but under optimal conditions according to the guidelines of the consensus conference.[6] The intention of this treatment was to exchange 200 to 250 ml of plasma per kilogram of body weight in five sessions within 7 to 14 days. The replacement fluids did not contain IgG, and 5 percent albumin was used most often. Two continuous techniques were used: ultrafiltration (in 42 patients) and centrifugation (in 31 patients).

Treatment with immune globulin was started as soon as possible after randomization. During the five subsequent days, 0.4 g of immune globulin (Gammagard, Baxter Healthcare, Hyland Division, Glendale, Calif.) was given per kilogram per day.

Recently, it has become apparent that in 10 to 20 percent of patients the primary response to treatment may be followed by a secondary deterioration that also responds to treatment.[10,24,25] Therefore, the option of repeating the same treatment was included in the protocol if, after a partial recovery or stabilization lasting more than one week, there was secondary deterioration.

Assessment of Motor Function

To enhance comparability, the degree of motor function was expressed on a seven-point functional scale used in previous trials, on which 0 denotes healthy; 1, having minor symptoms and signs but fully capable of manual work; 2, able to walk $\geq$10 m without assistance; 3, able to walk $\geq$10 m with a walker or support; 4, bedridden or chairbound (unable to walk 10 m with a walker or support); 5, requiring assisted ventilation for at least part of the day; and 6, dead.[4,5] With this scale, however, treatment-related fluctuations in the clinical course are not easily detected. For that reason, we introduced a second, more detailed score in which the Medical Research Council scores for six bilateral muscle groups were included, yielding a summary score that ranged from 60 (normal) to 0 (quadriplegic).[26] A formal study of these two scoring methods showed very good agreement between observers.[26]

Follow-up Schedule

The functional score and the Medical Research Council summary score were measured at study entry and 16 times during six months of follow-up: 3 times a week during weeks 1 and 2, once a week through week 6, and in weeks 8, 10, 14, 18, 22, and 26. Electromyography was performed at the time of randomization and one and four weeks later. This report includes only data on the amplitude of the compound muscle action potential of the abductor pollicis brevis muscle, with distal stimulation of the median nerve obtained at entry, since this has proved to be a prognostic factor in other studies.[27,28] Additional studies included routine testing of blood, urine, and cerebrospinal fluid; determinations of porphobilinogen and δ-aminolevulinic acid in urine to exclude porphyria; and serologic studies for infections known to precede the Guillain–Barré syndrome.

Pretreatment serum samples were tested at the coordinating center for the presence of antibodies to a mixture of antigens derived from *Campylobacter jejuni* and *C. coli* by counterimmunoelectrophoresis.[29] An enzyme-linked immunosorbent assay was used to detect antibodies against the peripheral-nerve ganglioside GM-1.[30] The results of these studies are described here only in relation to the discussion of potential prognostic factors.

Control of Bias

It was not feasible for the center investigators to remain unaware of the assignment to plasma-exchange treatment in the patients with Guillain–Barré syndrome. Therefore, we introduced a method of detecting bias in the assessment of motor function. During follow-up, one of the study coordinators who was unaware of the treatment assignments evaluated every patient once; the resulting blinded scores were compared with those of the individual investigators.

Outcome Measures

The main outcome measure for the study was improvement by one or more grades on the functional scale four weeks after randomization, as compared with the score at the time of randomization.

The secondary outcome measures were the time required to improve by at least one functional grade and the time required for the patient to regain the capacity for independent locomotion.

Number of Patients

An important methodologic issue in this study was its conservative character (i.e., the goal of detecting equal efficacy between treatments). The calculation of sample size in such a study has been described by Makuch and Simon.[31] The alpha error was set at 0.05, and the beta error at 0.20. On the assumption that immune globulin can be administered without delay and that the treatment has few contraindications as compared with plasma exchange, it was estimated that 55 percent of the patients in the plasma-exchange group and 65 percent of those in the immune globulin group would reach the main outcome. Finally, the lower bound of delta for the one-sided 95 percent confidence limit for the difference in proportional improvement was set at 0.07, which was considered a reasonable limit for "equal" efficacy. With these indexes it was calculated that 100 patients were needed in each treatment group.

Stopping Rule for a Conservative Trial

An interim analysis was initially planned after the accrual of 100 patients. However, there was no stopping rule applicable to a conservative trial in the statistical literature. Therefore, a stopping rule based on a test of significance was applied in the protocol: the trial should be terminated if one of the two treatments proved superior after the accrual of 100 patients ($P<0.030$, after correction for two analyses). At the interim analysis it was decided that not only the calculation of the number of patients, but also the stopping rule, should be based on the confidence interval. The lower bound of the one-sided 99 percent confidence limit for the difference in the proportion of patients reaching the main outcome should not exceed 7 percent to the disadvantage of the immune globulin group.[31] We used a 99 percent interval instead of 95 percent confidence limits to ensure that the overall confidence of this interval would not be less than 95 percent. This new rule had to be applied after the accrual of 150 patients instead of after 100 patients.

Statistical Analysis

Percentages in independent groups were compared by the chi-square test (without correction for continuity). Mean values in independent groups were compared by the Mann–Whitney U test. The time to reach an end point (for example, time to an improvement in the functional score by at least one grade) was analyzed by the method of Kaplan and Meier and the log-rank test. All confidence intervals were as described above — i.e., no adjustment was made for an interim analysis. For multivariate analyses of the dichotomous end point, we used logistic regression. All analyses were performed on an intention-to-treat basis with the personal-computer program STATA (version 2.05).

Results

Interim Analysis after the Accrual of 100 Patients

With respect to the main outcome measure, interim analysis after the accrual of 100 patients revealed that 30 percent of the patients in the plasma-exchange

group had improvement by one or more functional grades four weeks after randomization, as compared with 51 percent in the immune globulin group. The difference was 21 percent (99 percent confidence interval, −4 percent to 46 percent; P = 0.033). The level of significance was just above the value set in the original stopping rule (P = 0.030), and the study was continued until the next interim analysis, after the accrual of 150 patients, at which time the new rule based on the 99 percent confidence interval was applied to ensure at least 95 percent actual confidence.

Randomization and Follow-up

Of a total of 193 patients evaluated with respect to eligibility, 150 patients entered the study from June 1986 through December 1989. The reasons for ineligibility were as follows: predominantly bulbar symptoms (in 11 patients), concurrent medical disease interfering with follow-up or contraindicating plasma exchange (in 8), severity of disease (in 6), duration of disease (in 5), age under four years (in 3), immunosuppressive therapy (in 3), other polyneuropathies (in 3), lack of informed consent (in 2), inability to attend follow-up for a period of six months (in 1), and a previous episode of Guillain–Barré syndrome (in 1).

Three of the 150 randomized patients proved to be ineligible soon after randomization and were withdrawn from the study: 1 patient had unstable angina pectoris (a contraindication to plasma exchange), 1 appeared to have transverse myelitis, initially with depressed reflexes, and 1 had Miller Fisher's syndrome.

The distribution of factors shown in previous studies to have possible prognostic importance is shown in Table 1. These factors are analyzed further below. One patient in the plasma-exchange group was lost to follow-up after 10 weeks. With regard to the analysis of secondary outcome measures, he was considered to have remained at a functional score of 4.

Efficacy of the Treatment Protocol

The median delay before the start of treatment was one day in the plasma-exchange group and no days in the immune globulin group (Table 2).

In 12 patients one or more sessions of plasma exchange had to be discontinued, primarily because of hypotension and problems with venous flow. In one patient immune globulin was discontinued because of transient elevation of liver enzymes in serum. In three patients there were protocol violations with respect to therapy: one patient randomly assigned to plasma exchange had a contraindication before the first session and was treated with immune globulin. In a second patient assigned to plasma exchange a contraindication developed after he had received a total of 6 liters of fluid; he was also treated with immune globulin. The third patient needed a second course of treatment but declined plasma exchange, and he received immune globulin. All three patients were analyzed in the plasma-exchange group according to the intention-to-treat rule. Fourteen patients had treatment-related clinical fluctuations — six in the plasma-exchange group and eight in the immune globulin group. Ten of them received additional treatment as described in the Methods section, four of them in the plasma-exchange group and six in the immune globulin group. These patients are the subject of a separate report.[32]

Table 1. Distribution of Factors Shown to Have Prognostic Importance in Previous Studies, According to Treatment Group.

Variable	Plasma Exchange	Immune Globulin	All Patients	P Value
No. of patients	73	74	147	
Age (mean ±SD)	48.8±19.2	46.2±19.3	47.5±19.2	0.39
	no. (%) of patients			
Functional score at randomization				
3	16 (22)	13 (18)	29 (20)	
4	44 (60)	49 (66)	93 (63)	
5	13 (18)	12 (16)	25 (17)	0.74
Mechanical ventilation on day of randomization	15 (21)	13 (18)	28 (19)	0.65
Duration of disease ≤7 days before randomization	51 (70)	56 (76)	107 (73)	0.22
Amplitude of compound muscle action potential ≤3 mV*	26 (41)	17 (27)	43 (34)	0.09

* Tested in 126 patients.

Bias Control

The functional score determined by the center investigator was compared with that of the visiting, blinded coordinator for each patient (except one patient who died on the second day after enrollment). In the case of 121 patients there was agreement between the scores. As compared with the coordinators, the center investigators scored the condition of nine patients as worse and that of five as better in the plasma-exchange group, and they scored the condition of five patients as worse and that of six as better in the immune globulin group. It may therefore be concluded that no substantial bias occurred in this study.

Deaths

Three patients died during follow-up: two in the plasma-exchange group and one in the immune globulin group. Two deaths were the result of cardiovas-

Table 2. Efficacy of the Treatment Protocols.

Variable	Plasma Exchange	Immune Globulin
Days before start of treatment — median (range)	1 (0–4)	0 (0–3)
Days required to complete treatment (median)	9½	5
Median amount of therapy received	12.5 liters	140 g
No. of patients who had ≥1 session of treatment discontinued	12	1

cular complications, and in one patient in the plasma-exchange group, untreatable bronchospasm developed during artificial ventilation.

Primary Outcome

In the plasma-exchange group, 34 percent of the patients improved by one or more functional grades after four weeks, as compared with 53 percent in the immune globulin group, for a difference of 19 percent (99 percent confidence interval, −2 percent to 39 percent; 95 percent confidence interval, 3 percent to 34 percent; P = 0.024).

According to the test for homogeneity of DerSimonian and Laird,[33] the difference in the results of treatment was not inhomogeneously distributed among the cooperating centers (P = 0.33). After adjustment for differences between hospitals, the overall difference in favor of immune globulin with this approach was 20 percent (95 percent confidence interval, 6 percent to 34 percent).

Secondary Outcome Measures

At each time of data collection after randomization, the proportion of patients who did not improve on the functional scale was shown in a Kaplan–Meier curve (Fig. 1). The median times until there was improvement by one functional grade were 27 days for immune globulin and 41 days for plasma exchange (P = 0.05). The median times to the recovery of independent locomotion (a functional score of 2; Fig. 2) were 55 and 69 days for immune globulin and plasma exchange, respectively (P = 0.07).

Other Outcome Measures

A more general impression of the changes in functional score is given in Figure 3, in which the mean change in the score is shown over the duration of the follow-up period. The differences were most obvious earlier in the follow-up, when artificial ventilation was often required and when most of the complications occurred. Pneumonia, atelectasis, thrombosis, and hemodynamic difficulties all occurred more often in the plasma-exchange group. In all, 68 complications occurred in the plasma-exchange group, and 39 in the immune globulin group. Significantly more patients in the plasma-exchange group had multiple complications (16 patients, as compared with 5 in the immune globulin group; P<0.01).

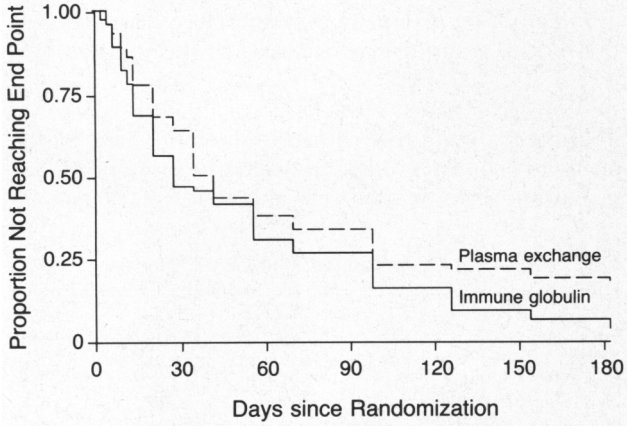

Figure 1. Kaplan–Meier Curves Indicating the Proportion of Patients Who Did Not Have Improvement by One or More Functional Grades during 182 Days of Follow-up, According to Treatment Group (P = 0.05).

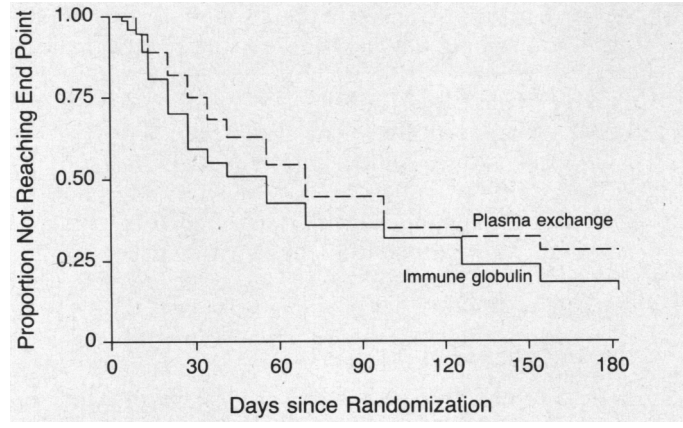

Figure 2. Kaplan–Meier Curves Indicating the Proportion of Patients Who Did Not Recover Independent Locomotion (Functional Grade 2) during 182 Days of Follow-up, According to Treatment Group (P = 0.07).

Fewer patients in the immune globulin group required artificial ventilation. The maximal difference occurred in the second week, when 27 percent of the immune globulin group and 42 percent of the plasma-exchange group received artificial ventilation (P<0.05). The mean duration of intubation was 15.2 days in the immune globulin group and 22.6 days in the plasma-exchange group. When calculated only for patients who received mechanical ventilation, these values were 43.3 and 50 days, respectively.

Prognostic Factors

The prognostic factors identified in previous studies and shown in Table 1 were subjected to multivariate analysis with regard to the main outcome measure. In the initial univariate analyses, only age was a significant factor (P = 0.001), and distal amplitude of the compound muscle action potential ≤3 mV approached significance (P = 0.053). In the multivariate logistic-regression analysis, only age remained statistically significant. However, it modified the positive effect of immune globulin very little (P = 0.038).

In the plasma-exchange group, the effect of centrifugation and ultrafiltration was evaluated, and no difference was found between these methods (P = 0.47). We also explored the possible prognostic value of serologically proved campylobacter infection, which was found in 36 percent of the 129 patients tested, and the presence of GM-1 antibodies, which were found in 30 percent. Both were predictors of

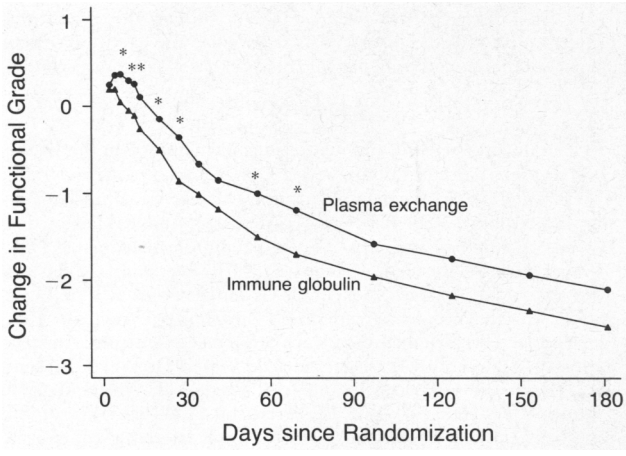

Figure 3. Mean Change in Functional Grade as Compared with the Grade at Entry during 182 Days of Follow-up, According to Treatment Group.
Asterisks indicate statistically significant differences between the plasma-exchange group and the immune globulin group ($P \leq 0.05$).

poorer outcomes in the univariate analysis, and they remained so in the multivariate analysis. In different multivariate models they never changed the direction of the treatment effect, although the level of significance varied.

Safety of Immune Globulin

In the course of the study, 380 infusions of immune globulin were given to 76 patients in the acute phase of the disease, 74 of whom were randomly assigned to this treatment and 2 of whom received the treatment as a result of a protocol violation. Five incidents temporally related to the infusions were reported: a decline in blood pressure not necessitating any treatment (two patients) and dyspnea treated with a diuretic agent, an increase in temperature treated with clemastine, and transient macroscopical hematuria (one patient each). In no instance was the course of treatment interrupted. Hematuria has not been reported as a complication of therapy with immune globulin, and its occurrence was considered coincidental.

Patients with Guillain–Barré syndrome often have elevated serum levels of liver enzymes before treatment.[34] At study entry the alanine aminotransferase concentration was more than 1.5 times the upper limit of normal in 30 percent of the patients in the plasma-exchange group and 21 percent of the patients in the immune globulin group. At 2 weeks these figures were 42 percent and 63 percent, respectively; at 4 weeks, 25 percent and 37 percent; at 14 weeks, 2 percent and 5 percent; and at 26 weeks, 6 percent and 4 percent. The increased frequency of an elevated alanine aminotransferase level during the two weeks after study entry was significant in the immune globulin group ($P \leq 0.001$) but not in the plasma-exchange group ($P = 0.2$). The alanine aminotransferase level rose significantly in both groups by two weeks after entry ($P < 0.01$), but more so in the immune globulin group (median alanine aminotransferase level in the plasma-exchange group, 1.02 times the upper limit of normal; immune globulin group, 2.03 times the upper limit of normal; $P = 0.02$). At 14 weeks the median level was identical in both groups (0.5 times the upper limit), and no patient was given a diagnosis of a chronic disorder of the liver.

Discussion

In this trial we evaluated whether treatment with immune globulin is as effective as plasma exchange in improving the clinical course of patients with Guillain–Barré syndrome. The interim analysis of 150 randomized patients revealed not only that immune globulin was as effective as plasma exchange but that significantly more patients in the immune globulin group reached the main outcome measure of an improvement by one or more grades on the functional scale at four weeks. There was a difference of 19 percent in favor of immune globulin therapy (95 percent confidence interval, 3 percent to 34 percent; $P = 0.024$). Secondary outcome measures were consistent with our main finding. The lower incidence of a requirement for mechanical ventilation and of complications was in accordance with the decreased severity of the clinical course in the immune globulin group. The beneficial effect of immune globulin is supported by an additional observation. From studies of treatment with plasma exchange, it is known that there may be treatment-related fluctuations in disease severity in about 10 percent of patients. This has been taken as additional evidence of the biologic efficacy of plasma exchange.[24,25] In this study, six patients in the plasma-exchange group and eight in the immune globulin group had such fluctuations. In both groups the patients responded to repeated treatment.[32]

Earlier studies have shown that plasma exchange decreased the need for hospital care and that the cost savings were greater than the costs of therapy.[35] In this trial the median time until the recovery of independent locomotion, a reasonable time for hospital discharge, was 14 days less in the immune globulin group than in the plasma-exchange group. In addition, the mean period of intubation was seven days less in the immune globulin group, reflecting a similar decrease in days spent in the intensive care unit. These savings have to be recognized when the difference in cost between immune globulin therapy and plasma exchange is assessed. Although this difference is minor in the Netherlands, it varies widely among countries and even among institutions.

Attention was given to the comparability of the two treatment groups. On the basis of factors identified in earlier studies, only age was confirmed as an independent prognostic factor in our multivariate analyses. We also identified some factors that are possibly related to the pathogenesis of Guillain–Barré

syndrome but that need confirmation in other studies: positive serologic tests for *C. jejuni* and *C. coli* and GM-1 antibodies. When these factors were incorporated in multivariate models that included the treatment effect, the difference always favored the immune globulin group, although the level of significance varied.

Since for ethical reasons plasma exchange cannot be given in a blinded fashion, bias could have occurred. The scoring of each patient once during follow-up by a study coordinator unaware of the treatment assignment and the comparison of this score with that made by the nonblinded center investigator should have revealed any systematic differences. No such differences were found, reinforcing the validity of the findings.

With respect to the efficacy of the treatment strategies, it is important to note that immune globulin therapy is safe and easy to use. Plasma exchange presented practical problems similar to those identified in previous trials, but in general it was employed according to schedule. In 16 percent of patients one or more sessions had to be discontinued for clinical reasons, as compared with 10 percent in the North American trial[5] and 18 percent in the French trial.[3]

The effect in the plasma-exchange group alone may be compared with that in the plasma-exchange groups in other large studies. In the North American trial, 52 percent of patients improved by one functional grade at four weeks, as compared with 34 percent in the present study. Probably the best explanation for this difference is that patients entered our study earlier in the course of their disease (mean, 5.6 days, as compared with 11.1 in the North American study). Patients in an early stage of disease may deteriorate further and need more time to improve by one functional grade than patients who are at the worst stages of their disease at study entry. This hypothesis is further supported when our results are compared with those of the French trial, in which all the patients were enrolled within 17 days of the onset of disease (mean, 6.3). Although no comparison can be made with respect to functional improvement at four weeks, the median time to the recovery of independent locomotion was documented in all three studies: 54 days in the North American trial, 70 days in the French trial, and 69 days in the present study (the latter two based on intention-to-treat analysis, in contrast to the explanatory analysis used in the North American trial). There was no difference between the plasma-exchange groups in the Dutch and the French trials with regard to this outcome variable; these trials were more alike with respect to the duration of the disease before treatment.

We conclude that immune globulin is a practical, safe, and effective treatment for Guillain–Barré syndrome.

We are indebted to Prof. Dr. A. Staal for support throughout the project, and to all the neurologists, residents, and laboratory personnel not mentioned by name who made extra efforts for this study.

Appendix

The following persons and institutions participated in the Dutch Guillain–Barré Study Group.

Coordinating center (University Hospital Dijkzigt, Erasmus University, Rotterdam): R.P. Kleyweg, J. Meulstee, and R.M. van den Hoven. *Monitoring Committee*: F.G.A. van der Meché, P.I.M. Schmitz, H.F.M. Busch, R.P. Kleyweg, M.L. Lee, and J. Meulstee. *Other centers:* Academisch Ziekenhuis Groningen — A.E.J. de Jager and T.W. van Weerden; Academisch Ziekenhuis Utrecht — P.L. Oey and J.P. Ter Bruggen; Academisch Medisch Centrum, Amsterdam — J. Stam and B.W. Ongerboer de Visser; De Wever Ziekenhuis, Heerlen — C.L. Franke and J.W. Vredeveld; Westeinde Ziekenhuis, Den Haag — W.F.M. Arts and A.W. de Weerd; St. Josephziekenhuis, Eindhoven — B.J. van Kasteren; Academisch Ziekenhuis bij de Vrije Universiteit, Amsterdam — J.J. Heimans, C. Polman, and R.P.M. Strijers; Verenigde Ziekenhuizen Ziekenzorg, Enschede — E.M. de Vries-Leenders and E.N.H. Jansen; Canisius-Wilhelmina Ziekenhuis, Nijmegen — C.W.G.M. Frenken and W.I.M. Verhagen; St. Clara Ziekenhuis, Rotterdam — H.J. v.d. Brand and H.A.W. Sinnige; Medisch Centrum Alkmaar — J.A. van Leusden; St. Elisabeth Ziekenhuis, Tilburg — A.A.W. Op de Coul and R.L.A.A. Schellens; St. Ziekenhuis Westelijke Mijnstreek, Sittard — J.J. Korten; Ziekenhuis Leijenburg, Den Haag — L.G.F. Sinnige, D.L.J. Tavy, and A.K. Wattendorf; Academisch Ziekenhuis Maastricht — C.J. Höweler and F. Spaans. *Serologic studies*: GM-1 — P.G. Oomes and H. Hooijkaas, Academisch Ziekenhuis Rotterdam; *C. jejuni* and *C. coli* — J.R.J. Bänffer, Gemeentelijke Gezondheid–Geneeskundige Dienst, Rotterdam.

References

1. Arnason BGW. Acute inflammatory demyelinating polyradiculoneuropathies. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. Peripheral neuropathy. 2nd ed. Philadelphia: W.B. Saunders, 1984:2050-100.
2. Toyka KV, Heininger K. Humoral factors in peripheral nerve disease. Muscle Nerve 1987;10:222-32.
3. French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Efficiency of plasma exchange in Guillain-Barré syndrome: role of replacement fluids. Ann Neurol 1987;22:753-61.
4. Greenwood RJ, Newson-Davis J, Hughes RAC, et al. Controlled trial of plasma exchange in acute inflammatory polyradiculoneuropathy. Lancet 1984;1:877-9.
5. Guillain-Barré syndrome study group. Plasmapheresis and acute Guillain-Barré syndrome. Neurology 1985;35:1096-104.
6. Osterman PO, Fagius J, Lundemo G, et al. Beneficial effects of plasma exchange in acute inflammatory polyradiculoneuropathy. Lancet 1984;2:1296-8.
7. The utility of therapeutic plasmapheresis for neurological disorders. JAMA 1986;256:1333-7.
8. Vermeulen M, van der Meché FGA, Speelman JD, Weber A, Busch HFM. Plasma and gamma-globulin infusion in chronic inflammatory polyneuropathy. J Neurol Sci 1985;70:317-26.
9. van der Meché FGA, Vermeulen M, Busch HFM. Chronic inflammatory demyelinating polyneuropathy: conduction failure before and during immunoglobulin or plasma therapy. Brain 1989;112:1563-71.
10. Kleyweg RP, van der Meché FGA, Meulstee J. Treatment of Guillain–Barré syndrome with high-dose gammaglobulin. Neurology 1988;38:1639-41.
11. Imbach P, Barandum S, d'Apuzzo V, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. Lancet 1981;1:1128-31.
12. Arsura EL, Bick A, Brunner NG, Namba T, Grob D. High-dose intravenous immunoglobulin in the management of myasthenia gravis. Arch Intern Med 1986;146:1365-8.
13. Cook L, Howard JF Jr, Folds JD. Immediate effects of intravenous IgG administration on peripheral blood B and T cells and polymorphonuclear cells in patients with myasthenia gravis. J Clin Immunol 1988;8:23-31.
14. Sultan Y, Kazatchkine MD, Maisonneuve P, Nydegger UE. Anti-idiotypic suppression of autoantibodies to factor VIII (antihaemophilic factor) by high-dose intravenous gammaglobulin. Lancet 1984;2:765-8.

15. Van Doorn PA, Brand A, Vermeulen M. Anti-neuroblastoma cell line antibodies in inflammatory demyelinating polyneuropathy: inhibition in vitro and in vivo by IV immunoglobulin. Neurology 1988;38:1592-5.
16. Bordet JC, Follea G, Carosella E, Dechavanne M. Intravenous high-dose IgG therapy induced alterations of spleen lymphocyte IgM secretion and T cell subsets in patients with idiopathic thrombocytopenic purpura. Thromb Res 1987;47:165-74.
17. Burleson DG, Mason AD Jr, McManus AT, Pruitt BA Jr. Lymphocyte phenotype and function changes in burn patients after intravenous IgG therapy. Arch Surg 1988;123:1379-82.
18. Uhr JW, Möller G. Regulatory effect of antibody on the immune response. Adv Immunol 1968;8:81-127.
19. Salama A, Mueller-Eckhardt C, Kiefel V. Effect of intravenous immunoglobulin in immune thrombocytopenia. Lancet 1983;2:193-5.
20. Lee ML, Kingdon HS, Hooper J, Courter SG, Holst SL, Piszkiewicz D. Safety of an intravenous immunoglobulin preparation: lack of seroconversion for human immunodeficiency virus antibodies. Clin Ther 1987;9:300-3.
21. Lee ML, Courter SG, Tait D, Kingdon HS. Long-term evaluation of intravenous immune globulin preparation with regard to non-A, non-B hepatitis safety. In: Zuckerman AJ, ed. Viral hepatitis and liver disease: proceedings of the International Symposium on Viral Hepatitis and Liver Disease, London, May 26–28, 1987. New York: Alan R. Liss, 1988:596-9.
22. Schwartz RS. Overview of the biochemistry and safety of a new native intravenous gamma globulin, IGIV, pH 4.25. Am J Med 1987;83:Suppl 4A:46-51.
23. Asbury AK. Diagnostic considerations in Guillain-Barré syndrome. Ann Neurol 1981;9:Suppl:1-5.
24. Osterman PO, Fagius J, Säfwenberg J, Danielsson BG, Wikström B. Early relapses after plasma exchange in acute inflammatory polyradiculoneuropathy. Lancet 1986;2:1161.
25. Ropper AH, Albert JW, Addison R. Limited relapse in Guillain–Barré syndrome after plasma exchange. Arch Neurol 1988;45:314-5.
26. Kleyweg RP, van der Meché FGA, Schmitz PIM. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain–Barré syndrome. Muscle Nerve 1991;14:1103-9.
27. McKhann GM, Griffin JW, Cornblath DR, Mellits ED, Fisher RS, Quaskey SA. Plasmapheresis and Guillain–Barré syndrome: analysis of prognostic factors and the effect of plasmapheresis. Ann Neurol 1988;23:347-53.
28. Winer JB, Hughes RAC, Osmond C. A prospective study of acute idiopathic neuropathy. I. Clinical features and their prognostic value. J Neurol Neurosurg Psychiatry 1988;51:605-12.
29. Bänffer JRJ, Duifhuis JCC, Mulder PGH. Counterimmunoelectrophoresis compared with complement fixation and passive haemagglutination tests in the evaluation of the immune response in Campylobacter infections. Antonie Van Leeuwenhoek 1987;53:183-90.
30. Oomes PG, van der Meché FGA, Toyka KV, Kleyweg RP. Antibodies to ganglioside GM1 in Guillain–Barré syndrome. Oxford, England: Peripheral Neuropathy Association of America (PNAA), 1990.
31. Makuch R, Simon R. Sample size requirements for evaluating a conservative therapy. Cancer Treat Rep 1978;62:1037-40.
32. Kleyweg RP, van der Meché FGA. Treatment related fluctuations in Guillain–Barré syndrome after high-dose immunoglobulins or plasma-exchange. J Neurol Neurosurg Psychiatry 1991;54:957-60.
33. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clin Trials 1986;7:177-88.
34. Oomes PG, van der Meché FGA, Kleyweg RP. Liver function disturbances in Guillain–Barré syndrome. J Neurol 1990;237:Suppl 1:S10. abstract.
35. Audet AM, Eckman M. Plasmapheresis in the treatment of Guillain–Barré syndrome: a cost-effectiveness analysis. Med Decis Making 1989; 9:324.