

SHORT REPORT

Intravenous immune globulins in patients with Guillain-Barré syndrome and contraindications to plasma exchange: 3 days versus 6 days

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Abstract

Plasma exchange is contraindicated in 10 to 20% of patients with Guillain-Barré syndrome (GBS). The optimal schedule for intravenous immune globulin (IVIg) therapy has not yet been established in these patients.

The objective was to compare the efficacy and safety of two IVIg treatment durations in patients with GBS with contraindications for plasma exchange.

In this randomised, double blind, multicentre phase II trial conducted in seven French centres, patients with GBS with severe haemostasis, unstable haemodynamics, or uncontrolled sepsis were randomly assigned to 0.4 g/kg/day IVIg for 3 or 6 days. The primary outcome measure was the time needed to regain the ability to walk with assistance.

Thirty nine patients were included from March 1994 to May 1997, 21 in the 3 day group and 18 in the 6 day group. Time to walking with assistance was non-significantly shorter in the 6 day group (84 (23-121) v 131 days (51-210), p=0.08); the difference was significant in ventilated patients (86 days (13-151) in the 6 day group v 152 days (54-332) in the 3 day group; p=0.04). The prevalence and severity of IVIg related adverse effects were comparable between the two groups.

In conclusion, in patients with GBS and contraindications for plasma exchange, especially those who need ventilatory assistance, IVIg (0.4 g/kg/day) may be more beneficial when given for 6 days rather than 3 days.

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Several randomised clinical trials have demonstrated the efficacy of plasma exchange¹ and intravenous immune globulins (IVIg) in Guillain-Barré syndrome (GBS).¹⁻³ However, about 4% to 10% of patients have contraindications for plasma exchange at the diagnosis of GBS, and events requiring discontinuation of

plasma exchange occur in 4% to 15% of patients with GBS receiving this treatment.¹⁻⁴⁻⁵ Administration of IVIg therapy at a dose of 0.4 g/kg/day for 5 days is often recommended for all patients with GBS. Higher cumulative doses of IVIg may be more effective but also more likely to induce adverse effects. We conducted a pilot trial to compare the efficacy and safety of two cumulative doses of IVIg in patients with GBS with contraindications for plasma exchange

Methods

The study protocol was approved by the Saint-Germain-en-Laye ethics committee. Written informed consent was obtained from all patients before randomisation.

ELIGIBILITY

Patients with GBS were recruited at seven French centres, without selection on disease severity. Inclusion criteria were fulfilment of accepted clinical and CSF diagnostic criteria for GBS,⁶ age older than 16 years, disease duration shorter than 30 days, and presence of a contraindication for plasma exchange (severe haemostasis abnormalities, unstable haemodynamics, or uncontrolled sepsis).

Exclusion criteria were pregnancy, severe underlying disease (cancer, blood dyscrasia, insulin dependent diabetes mellitus, severe liver or kidney disease, or human immunodeficiency virus infection), atypical GBS, spontaneous motor improvement before randomisation, residual motor dysfunction due to an earlier disease, and contraindications for IVIg (known allergic reaction to blood products and selective IgA deficiency).

RANDOMISATION

Randomisation was performed in a centralised manner using a permuted block algorithm with stratification by study centre. Randomisation codes were given to the investigators by telephone. The IVIg supplier (LFB) prepared the IVIg and the placebo in opaque coded bottles, then sent these to the pharmacies of the study hospitals. The bottles were stored in the hospital pharmacies and dispensed by the hospital pharmacists. The patients, investigators,

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and caregivers were blinded to treatment assignment until completion of the final analyses. IVIg (Laboratoire Français des Biotechnologies, LFB) therapy was given at a dose of 0.4 g/kg body weight/day as a 12 hour infusion for 3 or 6 consecutive days. Double blinding was ensured by giving intravenous infusions of a placebo (3.8% albumin) from the 4th to the 6th day to the patients assigned to 3 days of IVIg therapy.

FOLLOW UP

Patients were examined at randomisation, then every 2 days for 12 days, every 3 days until day 30, on day 45, on day 60, and monthly thereafter until discharge. Each examination included a complete neurological assessment with evaluations of cranial nerve function, trunk and respiratory muscle involvement, sensory loss, reflexes, and the Guillain-Barré syndrome disability grade (DG) scale as recently modified.³ Other treatments and complications such as pneumonia, bacteraemia, autonomic dysfunction (greater than 20 beats/minute drop in heart rate and/or a greater than 40 mm Hg increase or decrease in systolic blood pressure) were recorded. Relapse was defined as deterioration in at least two functional score items at two consecutive examinations, as described elsewhere.² A final neurological examination was scheduled at 12 months.

Bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyl transferase (γ -GT), and alkaline phosphatase (AP) were assayed in the plasma using routine laboratory methods at randomisation and on day 15. Liver dysfunction was defined as a ratio between measured values and the upper limit of the normal range greater than 1.5 for ALT and γ -GT.⁷

OUTCOME MEASURES

The primary outcome measure was the time needed to regain the ability to walk 5 m with

assistance (DG 3).³ Secondary outcome measures were a one grade or greater improvement in the DG after 4 weeks,³ duration of mechanical ventilation, 1 year mortality, full muscle strength recovery after 1 year,² and evidence of intolerance to IVIg.

SAMPLE SIZE COMPUTATION

Assuming that the median time to walking with assistance would be 50 days in the 3 day group, with the α risk set at 5% and the β risk at 10%, the number of patients needed to demonstrate a 40% reduction in time to walking with assistance in the 6 day group compared with the 3 day group was 52 per group.

The study was discontinued in May 1997 when the French Health Services prohibited the use of albumin as a placebo. Consequently, the projected sample size was not achieved.

STATISTICAL ANALYSIS

Statistical analyses were performed on an intention to treat basis. Wilcoxon's rank sum test and Fisher's exact test were used for uncensored data. The Kaplan-Meier estimate and the log rank test were used for censored data. Patients who died were censored at the time of death in all calculations of failure times. Two sided tests were performed for comparisons of the two treatments. *p* Values ≤ 0.05 were considered statistically significant. All statistical tests were performed using the SAS (SAS Institute, Cary, North Carolina) software package.

Results

Thirty nine patients were included from 26 March 1994 to 23 May 1997, 21 in the 3 day group and 18 in the 6 day group (fig 1 and table 1). During the same period, 108 patients with GBS with no contraindications for plasma exchange were enrolled in a prospective randomised trial comparing two IVIg regimens with plasma exchange.

The most common contraindication for plasma exchange was uncontrolled sepsis (62% in the 3 day group and 44% in the 6 day group; $p=1.00$ by Fisher's exact test).

In the overall population, median age was 64 years (25th-75th percentiles, 50-73). The proportion of patients with ventilatory failure at randomisation was 51%, and the 1 year mortality rate was 15%. Baseline characteristics were similar in the two groups except that the proportion of ventilated patients was slightly higher in the 3 day group (table 1). Liver dysfunction was found in 14 (38%) patients at randomisation (30% in the 3 day group and 47% in the 6 day group) and in 21 (68%) patients on day 15 (75% and 60%). Between day 0 and day 15, liver function tests worsened in 11 patients (seven in the 3 day group and four in the 6 day group) and improved in four. After 1 year, all the study patients had normal liver function tests.

The time needed to regain the ability to walk with assistance was shorter in the 6 day group than in the 3 day group, although the difference was not significant overall ($p=0.08$, table 1 and fig 2). The difference was significant in the

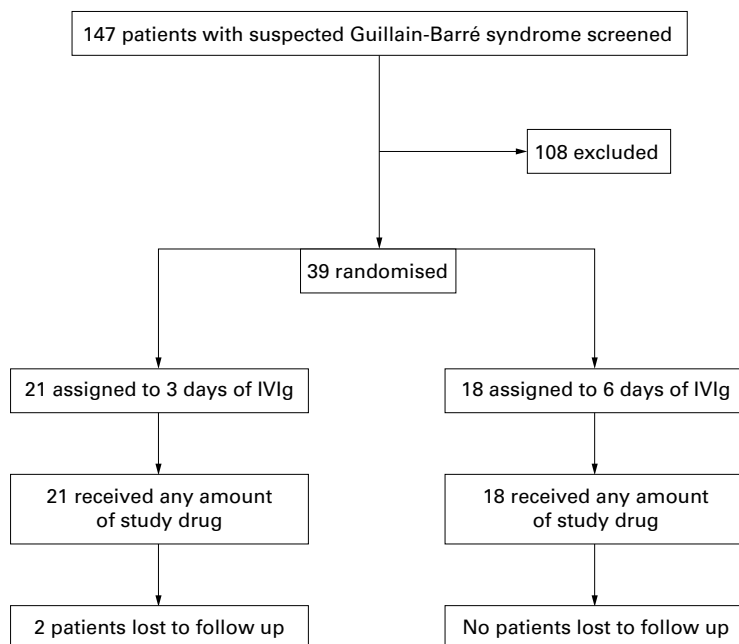


Figure 1 Flow chart.

subset of patients who required mechanical ventilation ($p=0.04$, table 1 and fig 2). A trend towards a higher proportion of patients with one grade or more of DG improvement at 4 weeks was found in the 6 day group (44% *v* 22%, $p=0.27$). The proportion of patients with recovery of full muscular strength at 1 year was also slightly higher in the 6 day group (69% *v* 40%, $p=0.08$). The incidence and intensity of IVIg related adverse effects were closely similar in the two groups. The most common adverse event was fever defined as an at least 1 degree increase in body temperature during the IVIg infusion (48% in the 3 day group *v* 33% in the 6 day group; $p=0.37$). Hypotension, defined as a drop in systolic blood pressure of at least 40 mm Hg occurred in four patients (5% in the 3 day group *v* 17% in the 6 day group). One patient in each group complained of nausea. IVIg therapy was discontinued prematurely in three patients, all of whom were in the 3 day group. In one of these patients, the study treatment was erroneously discontinued on day 5 instead of day 6 (the patient received IVIg for 3 days followed by the placebo for two days). In another patient, who had a history of ischaemic heart disease, severe bronchospasm and hypercapnia developed after infusion of 12.5 g IVIg and resolved after discontinuation of IVIg. In the last patient, an episode of severe hypotension occurred on day 5, during the placebo infusion. One relapse occurred in the 3 day group, after 3 weeks. There were no relapses in the 6 day group. The mortality rate was slightly higher in the 3 day group than in the 6 day group, but this difference was not significant (table 1).

Discussion

All the randomised clinical trials in patients with GBS published to date compared plasma exchange with IVIg at a dosage of 0.4 g/kg/day for 5 days. It follows that the effects of lower or higher dosages remain unknown. We addressed this issue in patients with contraindications for plasma exchange, a subgroup in which the efficacy of IVIg has not been established.

Our patients with GBS with contraindications to plasma exchange were older and had a higher ventilatory failure rate, more severe

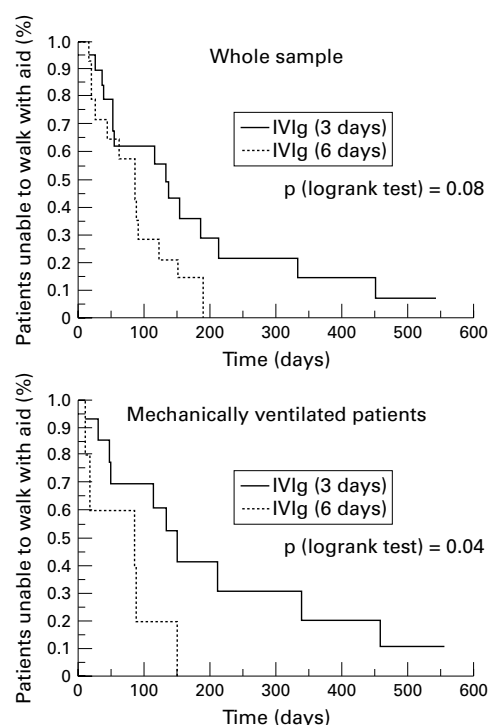


Figure 2 Time needed to regain the ability to walk with assistance in the overall study population (top panel) and in the subset treated with mechanical ventilation at randomisation (bottom panel).

functional disability, and a higher mortality rate than patients with GBS without contraindications for plasma exchange who were included in previous randomised trials.¹⁻³

The results of our phase II randomised clinical trial suggest that IVIg therapy at a dosage of 0.4 g/kg/day may be more beneficial in patients with GBS and contraindications for plasma exchange when given for 6 days rather than 3. A non-significant trend towards greater improvement in the 6 day group was seen in the overall population. The difference was significant in the subset of patients who required mechanical ventilation. In addition, adverse effects were neither more common nor more severe when IVIg therapy was given for 6 days. The main adverse effects (fever, hypotension, and nausea) occurred at rates similar to those

Table 1 Comparison of the two randomised groups.

	IVIg 3 days (n=21)	IVIg 6 days (n=18)	p Value*
At randomisation:			
Men	10 (48)	12 (67)	0.23
Age (y)	66 (51-72)	63.5 (50-73)	0.77
Previous enteritis	3 (14)	2 (11)	1.00
Mechanical ventilation	14 (67)	6 (33)	0.004
Time from disease onset (days)	7 (4-9)	8 (3-11)	0.80
Outcome measures:			
Improvement by 1 disability grade after 4 weeks	4/18 (22)	7/16 (44)	0.27
Mean improvement (SD)	0.3 (1.1)	0.8 (1.3)	0.22
Time to walking with assistance (days):			
In the overall study group	131 (51-210)	84 (23-121)	0.08
In ventilated patients	164 (54-332)	86 (13-151)	0.04
Time to walking without aid (days)	152 (110-193)	97 (51-202)	0.39
Number of ventilated patients after randomisation	3 (14)	4 (22)	0.68
Duration of mechanical ventilation	33 (19-84)	28 (16-131)	0.63
Full muscle strength recovery after 1 year†	6/15 (40)	11/16 (69)	0.08
One year mortality	4 (19)	2 (11)	0.67

Numbers are given with percentage in parentheses. Times are given as median with 25th-75th percentile in parentheses.

*Percentages were compared using the exact Fisher's test and median values using Wilcoxon's rank sum test.

†Missing for two patients in the IVIg 3 days group.

seen in a previous study of the early complications of IVIg therapy.⁸

In the present study, the proportion of patients with liver dysfunction (38%) before IVIg infusion was very similar to that in 100 consecutive patients with GBS studied by Oomes *et al* (35%),⁷ whereas the proportion of patients with liver dysfunction 2 weeks after admission was higher (68% *v* 54%). Oomes *et al* concluded from their findings that IVIg therapy was associated with transient liver dysfunction.⁷ Our results suggest that the increased rate of liver dysfunction seen after IVIg therapy was not related to the cumulative IVIg dose. Thus, the mechanisms of liver dysfunction disturbances in patients with GBS remain unclear.

Although the statistical power of our study was not sufficient to allow definitive conclusions, the results strongly suggest that 6 days of IVIg therapy may be better than 3 days in patients with GBS with contraindications for plasma exchange, especially in those who need mechanical ventilation.

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Appendix

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