SHORT REPORT

ABSTRACT: To clarify the question of whether Guillain–Barré syndrome (GBS) patients treated with intravenous immune globulin (IVIG) relapse at a higher frequency than those treated with plasma exchange (PE), 54 patients with GBS were studied retrospectively. A higher frequency of relapses was noted in the PE-treated patients than in those receiving IVIG. The presence of an associated medical condition correlated with an increased risk of relapses, while earlier onset of treatment resulted in a decrease of relapses of GBS. This study found no support for prior suggestions of increased relapses in patients with GBS treated with IVIG as opposed to those treated with PE.

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RELAPSES IN THE GUILLAIN–BARRÉ SYNDROME AFTER TREATMENT WITH INTRAVENOUS IMMUNE GLOBULIN OR PLASMA EXCHANGE

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Relapses in the Guillain–Barré syndrome (GBS) have been described in 1–10% of untreated patients, occurring 4 months to 8 years after the original presentation.[7,9,11,12,16] From the time that plasma exchange (PE) was found to be effective in treating GBS,[4] occasional relapses have been described weeks after initiation of therapy. After the publication of the results of the Dutch Guillain–Barré Study Group intravenous immune globulin (IVIG) Trial,[14] treatment of GBS with IVIG has become common practice at many centers, with similar therapeutic outcomes to PE.[5] Some have suggested a higher than predicted incidence of relapses in patients treated with IVIG. In a report[2] of 15 patients with GBS treated with IVIG, 7 deteriorated within 5 days of treatment. Another study[6] reported 7 patients treated with IVIG, of whom 5 relapsed within 16 days from initiation of therapy. To determine whether GBS patients treated with IVIG relapse at a higher frequency than those treated with PE, we have undertaken a retrospective study at the University of Miami/Jackson Memorial Medical Center, comparing patients treated with IVIG with those treated with PE.

Key words: Guillain–Barré syndrome; intravenous immune globulin; plasma exchange; relapses
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METHODS

Medical charts of patients seen from April 1988 through June 1995 with a discharge diagnosis of GBS, inflammatory polyneuropathy, or polyradiculoneuropathy were reviewed. To be included, the patient had to fulfill the strict criteria for GBS as described by Asbury et al.[1] for the presenting illness, and had to be treated with either IVIG or PE or both. A functional grade (described in Winer et al.[16]) was assigned for each hospital day and each follow-up encounter. Telephone contact was attempted to assess the present functional grade. A relapse was defined as a worsening by at least one functional grade after initial improvement from the paralytic episode.

RESULTS

Of 145 charts reviewed, 91 were excluded for incomplete documentation (10), not receiving IVIG or PE (7), nadir of illness more than 4 weeks after the onset of symptoms (26), or having another diagnosis (48). A total of 54 patients with GBS were available

for analysis. The age, gender, and ethnicity of each subgroup is described in Table 1. Patients treated with PE alone had six (26.1%) relapses; time to relapse from the initial illness was 60.5 ± 48.6 days. In comparison, only one relapse was noted in patients treated with IVIG alone (5.9%), which occurred 264 days after the onset of the initial illness. Fourteen patients were treated with both PE and IVIG (PE → IVIG and IVIG → PE); three relapses were recorded in 2 patients (1 patient relapsed twice); mean time to relapse was 383 days (120 days to 29 months).

When the patients treated with PE alone and patients treated with PE followed by IVIG were analyzed together (group A), eight relapses occurred in 29 patients (27.6%) (1 patient relapsed twice) at an average time of 78 days after the original episode. In those patients who received either IVIG alone or IVIG followed by PE (group B), two relapses were noted in 25 patients (8%). These occurred at 264 and 885 days. The difference in the number of relapses between both groups reflected a trend for less relapses in group B ($P = 0.1$). The mean maximum functional grade was not significantly different between both groups ($P = 0.47$). No correlation was found between the degree of severity and relapse rate (Table 1).

Of the 9 patients who relapsed in both treatment groups, 6 (66%) had an associated medical condition [HIV positive (2) with CD4 counts of 124 and 258, respectively; Waldenstrom's macroglobulinemia (1); pregnancy (1); systemic lupus erythematosus (1 patient who relapsed twice); and squamous cell carcinoma of the skin (1)], contrasted with only 3 of the 45 patients (6.6%) who did not relapse [systemic lupus erythematosus, HIV positive (CD4 365), and acute liver rejection after transplantation], representing a strong correlation ($P < 0.0001$) between GBS relapses and the presence of an associated medical condition.

The time from presentation to onset of treatment, the duration of treatment, and the number of exchanges and dose of IVIG are described in Table 1. There was a significant relationship ($P = 0.03$) between the risk of relapse and the interval between

Table 1. Description of study population.

	A	PE	PE → IVIG	B	IVIG	IVIG → PE
Number	29	23	6	25	17	8
Relapses	8 (27.6%)	6 (26.1%)	2 (33.3%)*	2 (8%)	1 (5.9%)	1 (12.5%)
Average time to relapse in days (range)	78.4 (25–155)	60.5 (25–155)	132	537	264	885
Follow-up in days (range)	554.6	582.7 (16 days to 87 months)	728.3 (34 days to 52 months)	263	204.2 (9 days to 30 months)	378.6 (14 days to 33 months)
Age (years)	43.1	44.4	38.0	35.1	29.1	48.0
Sex						
Male	15	13	2	11	5	6
Female	14	10	4	14	12	2
Race						
White	26	20	6	16	11	5
Black	3	3	0	9	6	3
Antecedent illness						
None	11	9	2	11	10	1
Respiratory	11	10†	1	8	4	4
Diarrhea	6	4†	2	4	3	1
Other	1	1	0	2	0	2
Associated condition	4	3	1	5	2	3
Mean maximum functional grade	4.1 ± 0.6			4.0 ± 0.8		
Of patients who relapsed	3.9 ± 0.4			4.5 ± 0.7		
Time to treatment (days)	11.7 ± 13.4	12.2 ± 14.5	9.8 ± 8.5	11.3 ± 7.5	13.9 ± 7.1	5.8 ± 5.1
No exchanges (±SD)	7.2 ± 1.6	7.3 ± 1.5	6.7 ± 2.0			
Days IVIG (±SD)				5 (range 2–6)	4.7 ± 0.9	4.6 ± 1.5
Liters of exchange	18.7 ± 6.8	18.6 ± 6.9	19.0 ± 6.9			
IVIG g/kg/day				0.5 ± 0.2	0.5 ± 0.2	0.6 ± 0.2

PE, plasma exchange; IVIG, intravenous immune globulin; A, patients treated with PE and PE followed by IVIG (PE → IVIG); B, patients treated with IVIG and PE followed by PE (IVIG → PE).
**One patient relapsed twice.*
†One patient had both respiratory and diarrheal antecedent illness.

onset of symptoms and initiation of treatment, with increased risk of relapse with longer intervals. In all 54 patients, the average time from onset of symptoms to initiation of treatment was 11.5 days. In a statistical model where all patients were treated at 11.5 days from presentation, the probability of recurrence was significantly higher if there was an associated medical illness, regardless of treatment modality (84% for group A and 37.4% for group B), compared with those patients without an associated medical condition (8.6% for group A and 1.1% for group B).

DISCUSSION

The PE-treated group had higher frequency of relapses (8 of 29 patients) than the IVIG-treated group (2 of 25 patients), which indicated a trend favoring IVIG ($P = 0.1$); these relapses occurred earlier in the first group. Although the length of follow-up was longer in the PE group, all relapses in this group occurred within 155 days from presentation of the initial GBS, which was a shorter length of time than the mean follow-up time for the IVIG-treated group (263 days). The PE-treated group tended to be older, with a higher proportion of males and whites than the IVIG-treated group. Those patients that relapsed had a higher frequency of associated medical conditions.

After correcting for all variables (analysis of variance), a number of correlations arose. Patients treated with IVIG alone or followed by PE had a lower probability of recurrence than those treated with PE, alone or with subsequent IVIG ($P = 0.1$). The risk of relapse was lower in patients treated earlier in their disease regardless of the mode of treatment ($P = 0.03$). Patients with an associated medical condition had a much higher probability of relapsing ($P < 0.0001$).

Early relapses (or treatment-related fluctuations) as described by Kleyweg and van der Meche[8] were not noted in the IVIG- or PE-treated patients, and the frequency of late relapses in our series was similar to the natural history of untreated GBS[7,9,11,16] and other studies of IVIG therapy in GBS.[3,8]

In our series, the later onset of treatment was associated with a higher probability of relapse. Other studies[15] have reported treatment-related fluctuations to occur in those patients treated earlier in the course of the illness. These have been interpreted as being due to the pathogenic process still being active after the beneficial effects of treatment had waned.[14] A large randomized trial[10] found significantly more improvement with later onset of therapy, suggesting that patients treated later were nearing spontaneous recovery. It is theoretically possible that later onset of therapy allows the formation of B cell clonal lines that may reactivate after new stimulation and produce a relapse.[13] No early treatment-related fluctuations were noted in our series of patients; the earliest relapse occurred 25 days after the onset of the illness. This study found no support for prior suggestions of increased relapses in patients with GBS treated with IVIG as opposed to those treated with PE.

A recent study by Visser et al. (*J Neurol Neurosurg Psychiatry* 1998;64:242–244) evaluated 172 patients with GBS after initial therapeutically induced stabilization or improvement. Treatment-related fluctuations were noted in 16 patients (9%). These occurred in 7% of patients treated with PE, in 12% of those who received IVIG, and in 8% of patients treated with both IVIG and methylprednisolone. The differences between each treatment group were not statistically significant.

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