Treatment related fluctuations in Guillain-Barré syndrome after high-dose immunoglobulins or plasma-exchange

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Abstract

Since the introduction of plasma exchange as a treatment for Guillain-Barré syndrome (GBS) patients, treatment related fluctuations have been found to occur in about 10% of the patients. These fluctuations are considered additional evidence of the beneficial effect of plasma exchange. In this report the occurrence of such treatment related fluctuations is described in the 147 patients who took part in the Dutch Guillain-Barré trial comparing high dose intravenous immunoglobulin with plasma exchange. Six of 72 patients in the plasma exchange group and eight of 74 in the immunoglobulin group showed such fluctuation. These results support the biological effect of immunoglobulin. More general use of immunoglobulin should await the full analysis of the Dutch GBS trial which is in progress.

In Guillain-Barré syndrome (GBS), relapses occur in about 1-6% of the patients, after a symptom free interval of months or years.[1-6] Many of these relapsing patients were suffering from a chronic inflammatory demyelinating polyneuropathy (CIDP). In a retrospective study of the natural history of the GBS in 68 consecutive patients we observed no relapses during a follow up period ranging from two to 14 years.[7]

Several trials have recently established the beneficial effect of plasma exchange (PE).[8 9] Since the wider application of this treatment, early relapses have been shown to occur in patients with an initially good response.[10 11] Osterman described six patients (out of a series of 37 of whom 23 responded to PE) who deteriorated again two to four weeks after completing PE.[10] In Ropper's series, 10 out of 94 patients with GBS relapsed five to 42 days after PE.[11] When a second series of plasma exchanges was subsequently performed, they again observed a favourable response. Occasionally, a third treatment was necessary. During follow up (eight months to five years), however, none of these patients developed a CIDP. The fluctuating course of these patients is considered to be induced by the temporary effect of PE on the actual disease process, which, in these cases, is longer than a few weeks. To avoid confusion with the sometimes relapsing course of CIDP it is preferable to use a more specific description, such as "treatment related fluctuations" rather than "relapses". The occurrence of such treatment related fluctuations after PE is considered to be an additional strong argument in favour of the biological effect of PE.[10 11] In a recent pilot study on the effect of high dose immunoglobulins administered intravenously (IgIV), one patient showed such a course.[12] Since then, 147 GBS patients have been treated in the Dutch Guillain-Barré trial comparing high dose IgIV with PE. We analysed the treatment related fluctuations in both groups on the basis of the hypothesis that if IgIV has similar biological efficacy as PE, such fluctuations should occur with equal frequency in both groups.

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Patients and methods

All 147 patients of the Dutch GBS trial were screened for relapses after an initial response related to PE or IgIV. PE was performed by cell separator or by membrane ultrafiltration; 200-250 ml/kg body weight was exchanged in 10-14 days. Immunoglobulin (Gammagard^{R}, Baxter) was administered intravenously in a dose of 0·4 g/kg per day for five consecutive days.

All patients were examined three times a week, then after two weeks with a gradually decreasing frequency up to 26 weeks. During each visit a functional score (F score), also used in other GBS studies was assessed.[8 13] F = 0: healthy; F = 1: minor symptoms and signs, fully capable of manual work; F = 2: able to walk >10 m without any assistance; F = 3: able to walk >10 m with a walker or support; F = 4: bed or chair-bound (unable to walk >10 m with a walker or support) and F = 5: assisted ventilation required for at least part of the day. Furthermore, we assessed the MRC-sumscore, obtained by adding the MRC scores of six muscle groups on each side (abduction of the arm, flexion of the forearm, extension of the wrist, flexion of the leg, extension of the knee and dorsal flexion of the foot). The MRC score is assessed according to the guidelines of the Medical Research Council.[14] The MRC-sumscore, ranging from 0 (total paralysis) to 60 (normal strength), gives an overall impression of muscle strength and gives valuable information about the strength, especially in bed-bound and artificially ventilated patients.[13]

All patients were still deteriorating at the time of admission and unable to walk independently. They were treated with either PE or IgIV as soon as possible.

A treatment related fluctuation has been

defined as: 1) Improvement in functional score of at least one grade or improvement in MRC-sumscore of more than five points within four weeks, followed by a decrease in the MRC-sumscore of more than five points or a worsening in functional score of at least one grade or: 2) Stabilisation of the clinical course for more than one week followed by a further worsening with more than five points on the MRC-sumscore or at least one grade of the functional score. In the last situation, an arrest of progression for more than one week is considered to be caused by treatment and not to be in accordance with the natural course. Improvement, stabilisation and deterioration had to be documented in at least two subsequent examinations, with an interval of three to seven days, by the same investigator.

Results (table)

From the 147 patients we studied, 14 patients (six of 72 in the PE group and eight of 74 in the IgIV group) showed a secondary deterioration after an initial response to treatment. Of these 14 patients four were, for no special reason, not retreated; six received a second treatment course and four required several treatment courses. Figure 1 gives an example of a patient with a single fluctuation and fig 2 of a patient needing a number of treatments.

In the group of 10 patients, who received no or only one extra treatment, five patients were in the PE group and five received IgIV. Duration of the neurological signs before treatment had been between three and eight days. Seven patients showed improvement after treatment, starting 1–13 days (median four days) after the onset of therapy and ranging between six and 34 points MRC-sumscore. Three patients showed stabilisation of the clinical course after initiation of treatment.

Relapses occurred 10–60 days (median 21 days) after the start of therapy. The decline, however, was usually not as severe as before the initial response. In two patients, 2 and 6, there was considerable delay between treatment and secondary deterioration.

Follow up, however, showed that these patients cannot be considered to have a CIDP.

In four of the six patients the second treatment course was followed by improvement after five to 10 days (median 8·5 days) without any further deterioration. In two patients (2 and 5) deterioration, leading to a second treatment, was arrested. Subsequently they recovered more slowly.

Four patients who did not receive a second treatment, improved again, shortly after their relapse. After six months, two patients (1 and 8) were still chairbound, although they were recovering slowly; all others made an excellent recovery. No further relapses occurred during the follow up period which spanned 12–50 months.

Four patients (11–14), one in the PE group and three in the IgIV group, required several treatment courses (fig 2). The fluctuations in the MRC-sumscore were often accompanied by changes in functional score. Duration of signs before treatment in this group had been four to 14 days. Patient 11 improved considerably in the functional and MRC-sumscore during treatment with IgIV. Two weeks later, however, secondary deterioration occurred. He was retreated with IgIV but no improvement occurred. At the same time he had developed a severe alveolitis requiring intubation with sedation for 10 days, so strength could not be properly assessed. Also a third treatment with IgIV, two weeks later, did not lead to recovery. After six months he was still chairbound. Patient 12 received a total of three PE treatment courses. Each time, PE was followed by a rapid increase in strength (reflected in increase in the MRC-sumscore and improvement in the F score) with deterioration a few weeks later. Finally, after a third relapse she refused any further PE. Instead she received IgIV, after which she again showed improvement. She has had no further relapses to date (32 months since her last treatment). Patient 13 needed five treatment courses with IgIV. After each treatment there weas a definite improvement after which she deteriorated again (fig 2). Finally, after the fifth treatment, she achieved almost complete recovery without further relapse for 24 months after the last treatment. The fourth patient in this group, patient 14, has been dependent on treatment for 12 months. During the follow up period in the clinical trial, he received six courses of treatment with IgIV, each time with temporary success. This patient is now considered to have CIDP, not GBS.

Table *Patients with treatment related fluctuations who received either one or no retreatment*

Patient	Age	Treatment IgIV/PE	Disease duration in days before treatment	Admission F	Admission MRC	Nadir F	Nadir MRC	Response 1* t_1	Response 1* F	Response 1* MRC	Relapse** t_2	Relapse** F	Relapse** MRC	Response 2*** t_3	Response 2*** response	Six months after admission F	Six months after admission MRC
1	57	PE	8	4	28	4	26	7	4	34	24	4	26	10	improvement	4	37
2	29	PE	3	4	46	4	38	13	2	56	60	4	41	0	stabilisation	2	53
3	24	IgIV	3	3	48	3	48	0	3	48	21	5	45	10	improvement	1	56
4	66	IgIV	6	3	48	4	48	4	4	54	21	4	48	7	improvement	1	58
5	14	IgIV	4	4	43	4	43	0	4	43	10	4	30	0	stabilisation	1	58
6	20	PE	5	4	46	5	26	4	2	58	40	2	48	5	improvement	1	60
7	74	IgIV	3	4	30	5	0	4	5	34	21	4	22	no 2nd treatment		0	60
8	56	IgIV	3	5	32	5	32	0	5	32	21	5	24	no 2nd treatment		4	42
9	42	PE	3	3	46	3	46	2	2	58	11	3	53	no 2nd treatment		0	60
10	68	PE	7	4	30	5	41	1	4	56	28	5	46	no 2nd treatment		1	58

F = Functional score
MRC = MRC – sumscore
(*) response 1 = best score after treatment; t_1 = time from start of treatment until the onset of the response in days.
(**) relapse = lowest score before secondary improvement or stabilisation; t_2 = time until onset of relapse in days after the start of the first treatment.
(***) response 2 = improvement or stabilisation within 2 weeks after the start of the second treatment; t_3 = time after the start of the second treatment in days.

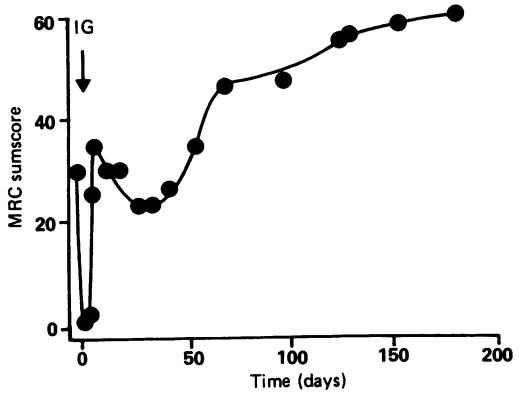

Figure 1 Clinical course, measured by the MRC-sumscore, of patient 8. IG = high dose immunoglobulins intravenously.

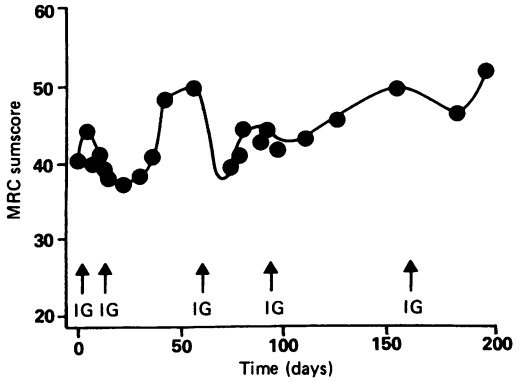

Figure 2 Clinical course, measured by the MRC-sumscore of patient 13 needing more than one retreatment. IG = high dose immunoglobulins intravenously.

Discussion

In 147 Guillain Barré patients, treatment related fluctuations occurred in 10% (95% confidence limits: 6–17%); six of 73 patients in the PE group and eight of 74 patients in the IgIV group. Only one patient in the IgIV group appeared to have CIDP. These fluctuations occur early in the course of the disease and have been related to therapy. They should therefore not be considered a naturally occurring relapse as these occur after months or years.[1–6]

Our results agree with the results of both Osterman[10] and Ropper[11] who reported secondary deteriorations after PE. The fluctuations in GBS patients treated with PE, are considered to strongly support the biological effectiveness of the treatment and provide further confirmation of the outcome of several trials showing a beneficial effect of PE.[8,9] We have now shown that this phenomenon occurs alike in patients randomly treated with either PE or IgIV. This new observation of similar therapy related fluctuations in both treatments indirectly supports our earlier suggestion that the beneficial therapeutic effect of IgIV might be similar to that of PE.[12]

In the case of a relapse after a response to treatment it is conceivable that the pathogenetic process, which is suppressed by PE or IgIV, is still active or reactivated after therapy. One reason why this occurs in only a minority of patients, might be that these patients are treated earlier in the course of the disease so that the active disease phase is not yet over at the end of treatment. In one study, the group of relapsing patients was treated slightly earlier in the disease course.[11] In another study only some patients who were exchanged rapidly within five days using a continuous flow technique relapsed, whereas no patients relapsed who were exchanged over a period of 7–13 days using an intermittent flow technique.[10] In our patients with a treatment induced fluctuation, the duration of disease before the start of treatment was very short (three to 14 days; median 4·5 days), although not shorter than for the whole group.

In some patients, the active phase of the disease seemed to be much longer than generally assumed as shown from the clinical course in the patients who required several treatments. One might argue that this long active phase of the disease is induced by treatment, for instance by interfering with regulatory feed back mechanisms. This, however, is unlikely as it occurs too infrequently to be a generally occurring mechanism. A long duration of the active disease process might have been common in pretreatment days, but at that time it would not have been easily detected; either a long active phase or axonal degeneration might have been responsible for a long plateau phase.

Two of the patients (12 and 13), who had several treatment related fluctuating courses, ultimately made a good recovery without relapses during the follow up perod of 32 and 24 months, respectively. In one patient (14), demonstrating a relapsing and remitting course, the initial diagnosis had to be changed from GBS to CIDP, the onset of which may sometimes be subacute.[15] This patient now successfully receives chronic therapy, with smaller doses of IgIV at regular intervals, as has been reported previously.[16–18]

Not all patients with secondary deterioration need additional treatment. We saw four patients who improved spontaneously following their relapse, confirming the observations of Ropper.[11] There was no difference between these and the other patients; they showed a comparable clinical course with those patients who received a second course of treatment. At present, however, it is not possible to tell in advance how long deterioration will proceed and therefore it is difficult to withhold a second treatment if a patient has responded well and is again showing deterioration.

In conclusion, the earlier report,[12] suggesting a beneficial response to IgIV in GBS, is supported by this study on treatment related fluctuating course in some GBS patients following IgIV. This is an important, independent, observation to confirm the biological efficacy of IgIV. This study further supports the preliminary positive results of the Dutch Guillain-Barré trial. Initial analysis of the main outcome criterion has shown that IgIV compares favourably with PE.[19] At present a full analysis of this trial is in progress. This analysis should be awaited before deciding to apply IgIV routinely in GBS patients.

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