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Clinical short communication

Outcomes in Guillain-Barré Syndrome following a second therapeutic cycle – A single-centre retrospective observational study

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ABSTRACT

Introduction: The treatment of Guillain-Barré Syndrome (GBS) with intravenous immunoglobulin (IVIg) or plasma exchange (PE) reduces time to clinical recovery. Although sometimes used in clinical practice, the benefit of a second treatment cycle is of unproven benefit.
Aims: Our aim was to compare GBS prognosis in patients treated with one or two cycles of IVIg or PE.
Methods: We selected patients with electrophysiological studies compatible with acute inflammatory demyelinating polyneuropathy or acute motor-sensory axonal neuropathy, from January 2018 to December 2020 in our hospital. Our primary outcome was any improvement in the Guillain-Barré Syndrome Disability Score (GBS-DS) at a mean of twelve weeks. We compared patients treated with one or two treatment cycles with a binary regression.
Results: We included twenty-six patients, 65.4% with the classical presentation and 30.8% were treated with two cycles. Patients treated with two cycles presented a higher basal GBS-DS (median 4; IQR 1–5) compared with the group of patients treated with one cycle (median 3; IQR 1–5), $p = 0.01$. The remaining basal characteristics were similar between groups. The two-cycle treatment regimen did not associate with an improvement in GBS-DS (OR 0.28, 95% CI 0.03–2.35, $p = 0.24$). Likewise there was no benefit in the need for intensive care unit (OR 2.0, 95% CI 0.37–10.92, $p = 0.42$) or mechanical invasive ventilation (OR 10.2, 95% CI 0.86–120.96, $p = 0.66$).
Discussion: Our analysis reinforces the recent literature data regarding the absence of benefit of two treatment cycles in patients with GBS.

1. Introduction

Guillain-Barré Syndrome (GBS) comprises a heterogeneous group of immune-mediated peripheral nerve disorders with a median incidence of 1.1 cases per 100,000 person-years [1]. GBS usually presents with a monophasic course reaching its nadir at two weeks (maximum at four weeks) with a rapid disease progression with 20% developing respiratory failure and the need for mechanical ventilation [2]. For the identification of patients with a higher chance of poor outcome, prognostic scales were created and validated such as the Modified Erasmus GBS Outcome Score (mEGOS) based on the age of onset, preceding diarrhea and Medical Research Council sum score (MRC-SS) at admission. This scale also predicts long-term GBS disability scores (GBS-DS) [3].

The treatment of Guillain-Barré Syndrome with intravenous immunoglobulin (IVIg) or plasma exchange (PE) has been shown to diminish time to clinical recovery, in patients unable to walk independently for ten meters [2], when started within two weeks after the initial symptoms [4]. There are no differences in terms of long-term functional outcome between the use of IVIg or PE [5].

Although sometimes used in clinical practice, the benefit of a second treatment cycle is of unproven value. In the current treatment practice, patients with poor recovery after the first treatment cycle are frequently treated despite the absence of evidence supporting this management [6]. Recently, the results of the SID-GBS trial were published reporting the absence of benefit of a second cycle of IVIg in patients with a poor prognosis (mEGOS of six or more), with a higher risk of thrombotic and infectious complications [7]. The efficacy of a second cycle with PE remains to be fully elucidated, bearing in mind the possibility of attempting different therapeutic targets, despite of precociously washing out the IVIg [6,8]; as well as the possible initial treatment with PE followed by IVIg. Therefore, there is still a need of further studies to evaluate the efficacy of adopting different treatment modalities. In this

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study, our aim was to compare GBS prognosis in patients treated with one or two cycles of IVIg or PE.

2. Methods

An observational retrospective study was conducted, including all patients submitted to electrophysiological studies between January 2018 and December 2020. We included all patients with an electrophysiological study compatible with acute inflammatory demyelinating polyneuropathy (AIDP), acute motor and sensory axonal neuropathy (AMSAN) or acute motor axonal neuropathy (AMAN). Baseline variables (at the time of diagnosis) were collected from patient's records, including age, gender, antiganglioside antibodies, Guillain-Barré Syndrome Disability Score (GBS-DS), Modified Erasmus GBS Outcome Score (mEGOS) and initial Medical Research Council sum score (MRC-SS). We also characterized the different clinical phenotypes of the included patients.

A final GBS-DS was also obtained from medical records and an improvement in the GDS-DS was the primary outcome. Secondary outcomes also analyzed were the need for admission in an intensive care unit (ICU) or the need for invasive mechanical ventilation (IMV). Quantitative variables were summarized by mean value and standard deviation or median and interquartile range.

Comparisons between patients that received one treatment cycle of either IVIg or PE and patients that received two treatment cycles were conducted, to evaluate the different prognosis in the different treatment groups. Comparisons between groups were performed through chi-square, t-student or Mann-Whitney test, using SPSS version 25. We compared the outcomes between patients treated with one or two treatment cycles through a logistic binary regression and presented the results as Odds Ratio (OR). The *p*-value was considered significant if inferior to 0.05.

The study was approved by the local Ethics Committee and informed consent was obtained from all participants (or next of kin).

3. Results

During the study period, twenty-six patients had an electrophysiological study compatible with AIDP, AMSAN or AMAN and the twenty-six patients were included in our final analysis.

The majority were men ($n = 17$, 65.4%) with a mean age of 56.8 years (standard deviation (SD) 18.4). The most frequent phenotype was the classical variant of GBS with acute flaccid tetraparesis with areflexia ($n = 17$, 65.4%). There was also the Miller-Fisher Syndrome variant in seven patients (26.9%) and bilateral facial palsy in two patients (7.7%). Regarding the electrophysiological subtypes, most were AIDP ($n = 24$, 92.3%) with two patients with an axonal subtype (7.7%).

Most patients received one treatment cycle with IVIg ($n = 18$, 69.0%). No patients were treated with a single cycle of PE. A minority of patients were submitted to a second treatment cycle of either IVIg or PE ($n = 8$, 30.8%): seven with a classic phenotype (two with electrophysiology studies compatible with AMAN/AMSAN and five with AIDP) and one with a severe form of Miller Fisher syndrome (AIDP in the electrophysiological study). These patients were all treated initially with IVIg and the second treatment cycle was 50% with IVIg ($n = 4$) and 50% with PE (n = 4).

Patients treated with two cycles of either IVIg or PE presented a higher basal GBS-DS (median 4; IQR 1–5) compared to the remaining (median 3; IQR 1–5), $p = 0.01$. The remaining basal characteristics were similar between groups, including median age, gender, Modified Erasmus GBS Outcome Score (EGOS) and initial Medical Research Council sum score (MRC-SS) – presented in Table 1. The group characteristics between the group treated with a second cycle of IVIg and the group treated with a second cycle of PE also did not differ: age ($p = 0.69$), gender ($p = 1.0$), baseline mEGOS ($p = 0.20$), baseline GBS-DS ($p = 0.49$), baseline MRC-SS (p = 0.69) and presence of antiganglioside antibodies ($p = 1.00$). The patients treated with PE after IVIg did not show any clinical deterioration, considering the possibility of PE diminishing IVIg effect.

Table 1
Baseline characteristics of the two groups.

	One cycle (n = 18)	Two cycles (n = 8)	
Age (years), median (IQR)	52 (21–75)	71.5 (35–88)	p = 0.20
Female gender, n (%)	4 (22.2)	5 (62.5)	p = 0.08
MRC sum score, mean (SD)	52.1 (7.7)	37.6 (14.1)	p = 0.20
mEGOS, median (IQR)	2 (0–6)	5 (1–9)	p = 0.09
GBS-DS, median (IQR)	3 (1–5)	4 (1–5)	p = 0.01
Presence of antiganglioside antibodies, n (%)	10 (55.6)	4 (50)	p = 1.00

IQR – interquartile range; SD – standard deviation; Guillain-Barré Syndrome Disability Score (GBS-DS), Modified Erasmus GBS Outcome Score (EGOS) and initial Medical Research Council (MRC).

The logistic regression adjusted to the initial GBS-DS did not show an improvement in the score with two treatment cycles (OR 0.28, 95% CI 0.03–2.35, $p = 0.24$). Likewise there was no benefit in the need for intensive care unit (OR 2.0, 95% CI 0.37–10.92, $p = 0.42$) or mechanical invasive ventilation (OR 10.2, 95% CI 0.86–120.96, $p = 0.66$).

The patients in our sample did not experience treatment-related fluctuations. There were no serious adverse events related to two treatment cycles in the patients studied and the patients included were not submitted to more than two treatment cycles.

Despite the low number of patients included in each group, we performed a subanalysis and compared patients treated with a second cycle of IVIg or PE. In the second cycle of IVIg group adjusted to initial GBS-DS there was no improvement in GBS-DS (OR 0.21, 95% CI 0.19–2.22, $p = 0.19$) and no difference in the need for intensive care unit (OR 0.67, 95% CI 0.57–7.85, $p = 0.75$) or mechanical invasive ventilation (OR 5.67, 95% CI 0.27–117.45, $p = 0.26$). In the PE second cycle group adjusted to initial GBS-DS there was no significant improvement in GBS-DS (OR 10.60, 95% CI 0.97–1115.90, $p = 0.53$) and no difference in the need for intensive care unit (OR 6.0, 95% CI 0.51–70.67, $p = 0.15$) or mechanical invasive ventilation (OR 17.0, 95% CI 1.02–283.01, $p = 0.05$).

4. Discussion

Our analysis reinforces the recent literature data regarding the absence of clinical benefit of two treatment cycles in patients with GBS with poor outcome, with no effect in the prevention of respiratory failure. Our analysis included patients treated with a second cycle of IVIg or PE in the same distribution and with no differences between the two group baseline characteristics. The use of PE as the second treatment has been seldom assessed; probably explained by the higher accessibility to IVIg and its easier administration. This may imply that its use in patients with no clinical recovery after initial treatment is also ineffective, as previously shown in few studies [9,10].

The main limitation of our study was the small sample size and the inclusion of patients with different baseline characteristics in each treatment group. Higher age and worse basal clinical score probably mediate a worse final prognosis, and can obscure the benefit of receiving a second cycle of treatment. However, the binary regression adjusted to baseline characteristics still didn't show a benefit in administering a second treatment course. Additionally, despite being the scoring system in use to assess the functional status of GBS patients, using improvement in GBS-DS as our outcome might be limited due to its main emphasis in walking ability and lack of assessment of other clinical factors that might

be of importance, particularly in GBS variants. Moreover, although our results did not show a statistically significant improvement with a second cycle with either IVIg or PE, it is not possible to draw conclusions from the low number of patients included in each group of treatment. Also, the small sample size prevents us from analyzing the benefit accordingly with different clinical and neurophysiological variants. Further studies are needed to evaluate the impact of a second course of treatment according to those parameters.

Available data suggests that a second treatment cycle is not useful for the treatment of patients with a poor initial response to treatment. A second additionally IVIg cycle has been demonstrated to be harmful with no additional therapeutic effect [7]. However, there are patients that have a poor clinical outcome and do not respond to initial treatment, giving the physicians the need to offer additional treatment, despite absence of clinical evidence. On the other hand, the use of initial PE followed by IVIg has not been studied in GBS patients with poor outcome and might be an alternative treatment plan in predefined patients.

Our findings support the need to propose new randomized controlled trials including PE in order to define an optimized therapeutic plan in patients with poor outcome.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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