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ARTICLE

Is a second cycle of immunoglobulin justified in axonal forms of Guillain-Barré syndrome?

É justificável utilizar um segundo ciclo de imunoglobulina para as formas axonais da síndrome de Guillain-Barré?

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ABSTRACT

Objective: In certain situations, severe forms of Guillain-Barré syndrome (GBS) show no response or continue to deteriorate after intravenous immunoglobulin (IVIg) infusion. It is unclear what the best treatment option would be in these circumstances. **Method:** This is a case report on patients with severe axonal GBS in whom a second cycle of IVIg was used. **Results:** Three patients on mechanical ventilation who presented axonal variants of GBS, with autonomic dysfunction, bulbar impairment and Erasmus score > 6, showed no improvement after IVIg infusion of 400 mg/kg/d for 5 days. After 6 weeks, we started a second cycle of IVIg using the same doses and regimen as in the previous one. On average, 5 days after the second infusion, all the patients were weaned off mechanical ventilation and showed resolution of their blood pressure and heart rate fluctuations. **Conclusions:** A second cycle of IVIg may be an option for treating severe forms of GBS.

Keywords: Guillain-Barré syndrome, acute inflammatory demyelinating polyradiculoneuropathy, flaccid acute paralysis, immunotherapy, immunoglobulin.

RESUMO

Objetivo: Em determinadas situações, as formas graves da síndrome de Guillain-Barré (GBS) não mostram resposta ou continuam a deteriorar após a infusão endovenosa de imunoglobulina (IVIg). Não está claro qual seria a melhor opção de tratamento nestas circunstâncias. **Método:** Este é o relato de caso de pacientes com grave comprometimento axonal em GBS, nos quais um segundo ciclo de IVIg foi utilizado. **Resultados:** Três pacientes em ventilação mecânica que apresentavam variantes de GBS com disfunção autonômica, comprometimento bulbar e valores de Erasmus > 6, não mostraram melhora após infusão de IVIg 400 mg/kg/d por 5 dias. Após 6 semanas, foi iniciado um segundo ciclo de IVIg utilizando as mesmas doses e esquema feitos previamente. Em média, após 5 dias da segunda infusão, todos os pacientes haviam sido retirados da ventilação mecânica e mostravam resolução de suas flutuações de pressão arterial e frequência cardíaca. **Conclusões:** O segundo ciclo de IVIg pode ser uma alternativa para tratamento de formas graves de GBS.

Palavras chave: síndome de Guillain-Barré, poliradiculoneuropatia inflamatória aguda, paralisia flácida aguda, imunoterapia, imunoglobulina.

Guillain Barre syndrome (GBS) is one of the most frequent causes of admission to intensive care unit for muscle weakness and acute flaccid paralysis[1,2,3]. It is an acute autoimmune inflammatory polyradiculoneuropathy that can present with various degrees of severity and has a monophasic course[1,2,3,4,5]. Immunotherapy with either plasma exchange (PE) or immunoglobulin (IVIg) is one of the keystones of the treatment[1,2,3,4,5]. About 25% of the patients develop neuromuscular respiratory failure that requires mechanical ventilation, severe bulbar muscle weakness and hemodynamic instability due to dysautonomy[1,2,3,4,5,6]. In this group, the mortality rates are more elevated, averaging 20%[1,2,3,4,5,6].

Although this approach has not been formally evaluated, certain subsets of patients with GBS might benefit from more intensive immunotherapy, such as those who do not respond to the usual treatment course[7], relapse after a short period of improvement[8,9,10], do not have adequate increase in immunoglobulin G (IgG) levels after IVIg treatment[11,12] or have poor initial prognosis[6,12]. We report 3 cases of severe GBS in which a second course of IVIg was utilized.

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METHOD

We report 3 cases of severe GBS who did not show any response to treatment with IVIg, remaining in the same clinical condition after the nadir of the disease. The diagnosis of GBS was performed following adapted criteria of Asbury[13] and the level of diagnostic certainty was confirmed with Brighton criteria[14]. In all patients electromyography (EMG) of both arms and legs was performed within 48 hours of admission to neurointensive care unit.

The severity of the syndrome was classified based on the Erasmus score[15], need of mechanical ventilation and artificial nutrition thought nasogastric or nasoyeyunal tube because of bulbar involvement and the presence of dysautonomia[1,2,3,4,5,6,16]. Autonomic failure was considered present when the individual have had marked fluctuations in blood pressure and or heart rate, arrhythmias, profuse sweating or paralytic ileus[1,2,3,4,5,6,16].

IVIg was started as soon as the diagnosis was established at 0.4g/kg/day during 5 consecutive days (Sandoglobulin, CSI, Behring, Switzerland).

RESULTS

Catamarca is a state of 400.000 people, located in the northwestern region of Argentina. During one year period (February 1, 2013-2014) we receive to our neurocritical care unit of 10-beds (the only unit of its kind in the state), 9 patients with Guillain Barre syndrome, corresponding to annual incidence of 2.25/100.000 inhabitants.

6 patients presented with classic clinical picture of acute inflammatory demyelinating polyradiculoneuropathy, characterized by progressive, ascendant and relatively symmetrical weakness in both legs and arms with areflexia/hyporeflexia and without sensory signs or symptoms, disautonomy, bulbar or respiratory compromise. Cranial nerves were not compromised. The average time of progression of symptoms was 5.5 days. At admission, 4 patients showed in cerebrospinal fluid (CSF) samples, high concentration of proteins with normal cells count; whereas in 2 CSF was normal. EMG findings included normal compound of muscle action potentials (CMAP), slowed motor conduction velocities, partial motor conduction blocks and prolonged distal motor and F-wave latencies. All patients were treated with intravenous immunoglobulin at standard dose (400 mg/kg/d x 5 d), and began to recover after the average nadir of weakness of 4 weeks.

There were 3 severe cases; all were axonal forms, two motor (AMAN) and another sensory-motor (AMSAN) by EMG findings. Onset of symptoms of weakness of the limbs and paraesthesia was between 3 and 6 days prior to admission. Two patients had preceding gastroenteritis and one had influenza syndrome. Severe quadriparesia with areflexia, bulbar symptoms and need of mechanical ventilation occurred within the first 3 days of admission in 2 cases. The other patient showed progressive deterioration and required mechanical ventilation 9 days after admission. The median Erasmus score 2 weeks after admission was 6.2.

The average time between ICU admission and start of IVIg infusion was 50 hours (range 24-78 hours). Table shows general characteristics of the patients.

After 4 weeks these patients had not shown any improvement, remained mechanically ventilated and had persistent symptoms of severe bulbar weakness and autonomic dysfunction. A second cycle was administered approximately 6 weeks after admission (range: 5-7.3 weeks). Between 3 and 5 days post-infusion, all patients could be weaned from mechanical ventilation. Additionally, all became hemodynamically more stable, with disappearance of fluctuations in heart rate, blood pressure and profuse sweating episodes. (Figure). Cardiac rhythm disorders (supraventricular tachycardia in 2 individuals and 5 episodes of ventricular arrhythmias in two patients) were normalized. All these situations clearly indicate resolution of autonomic dysfunction. Two patients regained safe swallowing and another required a feeding tube for 3 more weeks. At 6 months, none of the 3 were able to walk without assistance and one remained tracheostomized for management of secretions.

DISCUSSION

GBS has varied clinical forms, degrees of severity, and functional prognosis[1,2,3,4,5,6]. The functional prognosis and the need for mechanical ventilation can be estimated upon admission with the application of different scores, though none of these scores was designed to predict refractoriness to treatment[17,18,19,20]. A quarter of the patients have severe forms, characterized by axonal compromise on EMG, bulbar and respiratory failure requiring artificial life support, and hemodynamic instability with risk of sudden death related to autonomic dysfunction[1,2,3,4,5,6,16].

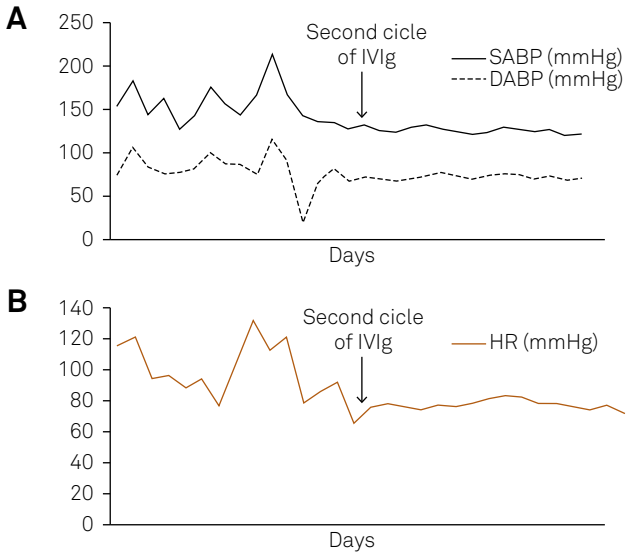
Immunotherapy with PE[21,22,23,24] or IVIg[25,26,27,28] is the mainstay of GBS treatment and is most beneficial when started within the first two weeks of the onset of symptoms[21,22,23,24,25,26,27,28]. PE and IVIg have similar effectiveness; trials have shown no differences between them in regards to degree of disability at 4 weeks, days of mechanical ventilation, mortality or residual disability[25,28]. Administering IVIg after PE did not confer additional benefit in one trial[23]. Since the publication of the trials proving its effectiveness, IVIg, has become the preferred treatment for GBS in many centers throughout the world, mainly because of the ease of administration, availability, and avoidance of invasive catheters, blood manipulation, fluid replacement therapy and complex equipment demanded by PE.

Yet, despite treatment with IVIg, some patients fail to improve or continue worsening beyond 4 weeks of evolution

Table. General characteristics of the population analyzed.

Variables	Patient 1	Patient 2	Patient 3
Age (years)	52	51	54
Sex (M/F)	M	F	M
Comorbidities	Hypertension	Hypertension. Diabetes type II	None
Time symptoms onset-ICU admission (hs)	72	144	26
Previous Diarrhea	Yes	No	Yes
Previous Respiratory infection	No	Yes	No
Time ICU admission-Mechanical ventilation (hs)	36	54	216
Time ICU admission-IVIg infusion	48	78	24
Bulbar compromise	Yes	Yes	Yes
Autonomic dysfunction	Yes	Yes	Yes
Erasmus score	6.5	5.5	6.5
CSF cells/mm^3	4	2	3
CSF proteins (mg/dl)	34	99	117
EMG findings	AMAN	AMAN	AMSAN
Tracheostomy	Yes	Yes	Yes
Time admission-2d cycle of IVIg (weeks)	5.5	5	7.3
Days of mechanical ventilation previous to 2nd cycle of IVIg	40	35	52
Time in mechanical ventilation after 2nd cycle of IVIg (days)	5	3	7
Time 2nd cycle IVIg-cessation of autonomic failure (days)	4	5	4
Days in ICU	55	48	71
Complications	Acute gastrointestinal bleeding Pneumonia Ventricular arrhythmia	Ventricular arrhythmia Acute kidney injury	Pneumonia

AMAN: Acute motor axonal neuropathy. The compound motor of action potentials (CMAP) are absent or markedly reduced with sensory response within normal limits. AMSAN: Acute motor and sensitive neuropathy. CMAP absent or reduced + severe compromise of sensory potentials (reduced or absent).



SABP: systolic arterial blood pressure (mmHg); DABP: diastolic arterial blood pressure (mmHg); HR: heart rate (bpm).

Figure. Autonomic dysfunction. Register of blood pressure (a) and heart rate (b); before and after a second cycle of IVIg.

(nadir period). Although the reason for this refractoriness is not known, it is thought that it may be due to greater axonal damage secondary to more prolonged and severe autoimmune attack[2,6,8,11]. A small study suggests that a second course of IVIg may be effective in these situations; however those cases had not exceeded the time-limit of the syndrome nadir like the cases studied in this paper[7]. Also, about 10% of patients who were infused with IVIg, show relapse after improvement[8,9,10,12]. There are evidence that this therapeutic related forms (TRF) benefits from a second cycle of IVIg[8,9,10,11,12].

The regimen of IVIg administration in GBS (2 g/kg, divided as 400 mg/kg daily for 5 days) was determined arbitrarily, mainly by extrapolation from studies on hematologic autoimmune disorders [11, 29]. Alternative doses and regimens of IVIg administration have not been tested in GBS patients. The pharmacokinetic properties of IVIg are highly variable[11]. A recent study showed that lower increase in levels of immunoglobulin G (IgG) after 2 weeks of infusion of IVIg are associated with poor outcomes in GBS, suggesting that this population could benefit from a new cycle of IVIg[11].

In our patients, we deemed a second cycle of IVIg was justified based on: a) severity of the clinical picture (marked weakness with bulbar and respiratory compromise requiring artificial support plus autonomic dysfunction), b) poor prognosis (axonal forms with Erasmus score > 6), c) no response to usual treatment course after 6 weeks. None of the patients was able to walk without assistance at 6 months; however, all survived, were weaned from mechanical ventilation and were no longer dysautonomic within the week after the second cycle of IVIg.

Accelerating the liberation from mechanical ventilation can reduce the risk of superimposed infections, facilitate mobilization, decrease costs related to more prolonged stay

in the intensive care unit, and allow faster transfer to the rehabilitation unit.

Obviously our small observational report has limitations. The main one is the small number of patients. Also, it is impossible to be certain that the improvement observed after the second course of IVIg was directly caused by the intervention rather than to spontaneous resolution of the syndrome; however, the lack of any improvement up to that point and the chronological relationship between the booster cycle of IVIg and the clinical improvement in all 3 cases supports the argument of therapeutic benefit. Finally, we did not measure serial IgG concentrations and therefore cannot determine if such measurements were lower at 2 weeks than in our other cases with good response to the usual single course of IVIg.

There is an ongoing international trial (I-SID-GBS)[29,30] designed to study the effect of a second dose of IVIg in patients with poor prognosis. Until the results of this trial become available, we think it is reasonable to consider a second course of IVIg in patients who fail to improve or continue to decline after the usual regimen.

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