ARTIGO DE REVISÃO/REVIEW ARTICLE

Immunotherapy in Pediatric Guillain-Barré Syndrome: Intravenous Immunoglobulin, Plasmapheresis, Both or Something Else?

Imunoterapia na Síndrome de Guillain-Barré Pediátrica: Imunoglobulina Endovenosa, Plasmaferese, Ambas ou Algo Mais?

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Abstract

Guillain-Barré syndrome (GBS) is an autoimmune disease of the peripheral nervous system that is clinically characterized by rapidly progressing and symmetric muscle weakness, loss (or decrease) of deep tendon reflexes and respiratory distress, leading in some cases to the need for artificial ventilation. This is a clinical diagnosis that can be supported by the integration of several results, coming from cerebrospinal fluid examination, neuroimaging, nerve conduction studies and serum analysis. Plasma exchange and intravenous immunoglobulin (IgIV) are both treatments that have proven to be effective in improving motor recovery and reducing the need for mechanic ventilation. While their efficacy is comparable, IgIV is the first line treatment and plasma exchange is not used as the primary approach due to the need for specialized personnel and specific equipment. However, some long-term results with intravenous monotherapy are not always the most favorable and, therefore, studies combining the two interventions have begun to be developed. One of them, defining the zipper method, proved that intercalating both techniques may improve the outcome when compared to each therapy on its own. Nevertheless, approaches with monoclonal antibodies, such as eculizumab, seem interesting, but only in adults, so far. In this article, we aim to review existing evidence on the immune therapeutic approach to GBS in children.

Resumo

A síndrome de Guillain-Barré (SGB) é uma doença autoimune do sistema nervoso periférico que se caracteriza clinicamente por fraqueza muscular simétrica e de rápida progressão, perda (ou atenuação) dos reflexos miotáticos e dificuldade respiratória, levando em alguns casos à necessidade de ventilação artificial. Este é um diagnóstico clínico, que pode ser sustentado pela integração de diversos resultados, provenientes da análise do líquido cérebro-espinhal, da neuroimagem, dos estudos de condução nervosa e serológicos. A plasmaferese e a imunoglobulina intravenosa (IgIV) são tratamentos que se mostraram eficazes em acelerar a recuperação motora e reduzir a necessidade de ventilação mecânica. Embora a sua eficácia seja comparável, a IgIV é o tratamento de primeira linha e a plasmaferese não é usada numa primeira abordagem devido à necessidade de pessoal especializado e equipamento específico. No entanto, alguns resultados a longo prazo com a monoterapia intravenosa nem sempre são os mais favoráveis e, portanto, estudos combinando as duas intervenções começaram

a ser desenvolvidos. Um deles, definindo o método "zipper", comprovou que a alternância das duas técnicas pode melhorar o resultado, quando comparada a cada intervenção isoladamente. Ainda assim, abordagens com anticorpos monoclonais, como o eculizumab, parecem interessantes, mas apenas em adultos, até ao momento. Neste artigo, o nosso objetivo é rever a evidência existente sobre a abordagem terapêutica imunológica da SGB em crianças.

Introduction

Guillain-Barré syndrome (GBS) is an acute demyelinating polyneuropathy characterized by rapidly progressing areflexia and symmetric weakness in previously healthy individuals, affecting between 0.3 to 2 children out of 100 000 per year.[1] Its incidence varies in different populations, reflecting genetic susceptibility and environmental exposure. This autoimmune disease is the most common form of acute flaccid paralysis in children and is normally triggered by a respiratory or gastrointestinal infection (50%-70% of cases).[2]

GBS results from the activation of B-cells and T-cells by pathogenic agents, which lead to the production of autoantibodies and cytokines, and to macrophages and T-cell activation, enhancing phagocytic activity and the release of several toxic substances that cause nerve tissue damage. The mechanism most associated with this immune response is molecular mimicry. The microorganism *Campylobacter jejuni* is the most common pathogen responsible for this reaction, once it has several peripheral molecules that share some of the biochemical properties of human gangliosides.[3,4]

Regarding clinical characteristics, it is important to evaluate the weakness in arms and/or legs and the absence or decrease of deep tendon reflexes that have progressed for a period not exceeding 6 weeks. These symptoms may be associated with autonomic abnormalities, pain, respiratory and sensory complaints.[5,6] Symptoms start approximately 2 to 4 weeks after the infection. Muscle weakness starts in the distal extremities and has a proximal progression, which can cause a possible failure of respiratory muscles, leading to the need for mechanic ventilation, reaching its peak 2 weeks after the onset of symptoms.[2,3,7]

In neuroimaging, gadolinium enhancement of the *cauda equina* and nerve roots can be very suggestive of the diagnosis, particularly in children. Considering the cerebrospinal fluid, there is a frequent dissociation between protein levels and cell count: protein levels increase, while cell count remains normal (mononuclear cell count <50 cells/mm^3). Electromyography is a relevant test used not only to diagnose this disease, but mainly for establishing an early prognosis, since it has in consideration neurophysiological aspects related with the degree of nerve fiber damage.[2,4-8]

This disease has a mortality rate of 3%-7%, including in children, and it is usually associated with pulmonary complications (acute respiratory distress, aspiration pneumonia and atelectasis, in addition to respiratory arrest) or autonomic failure. However, with prompt treatment, most patients will be able to recover their functional capacity.[2,4,5,9] The therapeutic approach to this condition consists of general medical care that includes respiratory vigilance, treatment of dysautonomic manifestations, pain management and immunological intervention, where options such as intravenous immunoglobulins (IgIV) and plasma exchange (PLEX) may be considered.[2-4]

The objective of this paper is to review what has been written precisely about the immunological intervention in GBS, in children.

Methods

Online research was conducted using PubMed as the preferred database and using as MeSH terms: Child, Guillain-Barré Syndrome, Immunotherapy, Plasma Exchange, Plasmapheresis, Intravenous Immunoglobulin, and Immunomodulation. After this research, 682 articles were found, until January 2020. After excluding articles based on the language (English was the only language admitted for this study), we defined the type of article as another exclusion criteria. The following types were considered: case report, clinical study, clinical trial, controlled clinical trial, meta-analysis, randomized controlled trial, review, systematic review and observational study. After these filters, 387 articles remained. An analysis of the abstract was then conducted, and repetitive information was deleted. After that, 49 articles remained and were used in this review. Besides PubMed, the Cochrane Library was

also used. Due to the rarity of this medical condition and to the little research done in children, there was no temporal cut-off, in terms of online research.

Results

The treatment of pediatric GBS is based on general medical care and on the usage of immune-directed interventions. This approach consists of PLEX and IgIV, separately or combined. Based on the report of the quality standards subcommittee of the American Academy of Neurology in 2004, both immunological treatments are used in severe pediatric GBS, as opposed to steroids, that are not recommended.[3,10]

Plasma Exchange (PLEX)

PLEX consists of extracting plasma from the blood of the patient by utilizing centrifugal separators. This technique allows the removal of neurotoxic antibodies, inflammatory mediators, complement factors and immune complexes that might be responsible for the disease.[2,4,6] In total, the exchanges should mount to approximately 250 mL/kg.[2,3,6,11] It has proved effective since the 1980s in adults, and its results have been, in part, extrapolated to children. One of the earlier studies regarding the efficacy of PLEX in pediatric GBS submitted 8 children to different procedures, 7 of whom received treatment within the first 7 days of illness. The mean total volume of plasma removed was 217 mL/kg (range: 74-415 mL/kg), and, one week after the last treatment, patients showed a significant clinical improvement, presenting a decrease in the number of days of mechanical ventilation, time until motor recovery and overall cost. One child did not improve as quickly, which was attributed to a Campylobacter jejuni infection during the sessions. This study concluded that PLEX could be a successful treatment in children with this clinical condition, even though a standardized protocol still needed to be studied and implemented.[12]

A French Cooperative Group studied the use of PLEX on GBS and the correlation between the severity of the disease and the number of exchanges needed to treat the patients. To participate in this study, the patient had to be at least 16 years old. The subjects were divided into 3 groups depending on the severity of the disease: mild, moderate and severe (although the majority of patients recruited were adults and late adolescents, the main conclusions can be extrapolated from this protocol for pediatric populations). In severe cases, patients were given either 4 or 6 exchanges. In terms of recovery and ability to walk, there were no differences between 4 and 6 exchanges, although 4 slightly shortened the motor recovery, when compared to 6. Patients which were submitted to 6 exchanges suffered more systolic pressure instability than those that were given 4. This finding attests to the current treatment of a maximum of 5 exchanges implemented in actual protocols.[3,6,11]

A study where 40 pediatric patients were submitted to a total of 122 PLEX procedures over a one-and-a-half-year span showed a significant improvement from complete paralysis to the possibility of movement. This study showed that PLEX reduced hospital stay, mortality and morbidity, proving that it can be used as a first line approach or as an adjuvant.[13]

There are 6 controlled trials containing 649 patients (mostly adults), which compared PLEX with supportive treatment. After 4 weeks, patients treated with PLEX fared better, in terms of recovering of mobility, walking without aid and necessity of mechanic ventilation. One of those trials showed that there was a real cut-off of 7 days that affected how well the patients responded and recovered. Other studies contradict it, by saying that even after 7 days of onset of the disease, patients' response was the same.[14,15]

There is still a lack of controlled randomized trials in children to effectively measure the benefits and risks of this technique in this population, comparing with adults. There are a number of studies revealing the short-term effect of PLEX, but there are no reports of its efficacy after 1 year.[16,17]

Intravenous Immunoglobulin (IgIV)

IgIV acts by inhibiting antibody production, by targeting B and T cells, leading to a faster catabolism of the referred antibodies, preventing the phagocytic activity of macrophages, and limiting cytokines and other adhesion molecules responsible for the inflammatory process, diminishing nerve damage.[1,6,11,19,29,30] It has also been suggested to improve peripheral remyelination in GBS. This proposition arises from the study of a monoclonal antibody (IgMk), which has been proved to promote myelination and, at the same time, to suppress inflammatory responses.[9]

IgIV is easy to administrate and has less hemodynamic impact than PLEX, having its maximum efficacy when given within 2 weeks of the onset of the disease.[2,18] A study

published in 2009 discovered a correlation between serum IgG levels and the time to recovery of patients. More specifically, if IgG levels after the first dose of IgIV were elevated, patient recovery would be slower, leading to a poorer outcome. A second dose could improve the outcome and this biomarker may prove to be useful, in practical terms, for monitoring the response to therapy (this still needs further investigation).[19]

A review compared the efficacy of IgIV and the timing of its administration. Thirty-four patients of mean age of 5.1 years were selected to enter the study. Of these, 11 only received supportive treatment, 3 received PLEX and 10 IgIV. These were divided into subgroups with two different time cut-offs. Initially, the study compared the efficacy of the treatment if given before or after 7 days of symptoms onset. Seven children were given the therapy within 7 days of the beginning of symptoms, while 3 were given after 7 days. Patients with early treatment improved faster in every category of outcomes defined, when compared with patients submitted to the late treatment regimen.[20] The 7 children needed on average 7.7 days to improve one grade in the Motor Disability Grading Scale, which ranges from 0 (healthy) to 6 (dead),[20] as opposed to 9.0 days of children with late treatment. Furthermore, with early treatment children left the hospital on average after 17.4 days, as opposed to the 47.5 days needed by the other patients. Another time cut-off was tested, being early treatment defined as within 10 days of symptom onset. This treatment group was formed by 8 children and the late (after 10 days) by 2. The 8 children needed an average of 7.1 days to improve one grade in the same motor disability scale, as opposed to 11.5 days by the other 2 children.[20] Furthermore, the mean length of hospital stay in these two groups was not different from what had already been considered (17.4 versus 47.5 days). In both definitions (and despite being studies with a retrospective design and with a small number of participants), the early treatment has suggested to improve the motor recovery, while shortening the hospital stay. However, it is not clear if the optimal time of action is before 7 or 10 days.[20]

Another study compared the efficacy of IgIV and of supportive treatment. This retrospective and non-randomized study selected 55 children, where 25 received the immunotherapy and 30 only a supportive intervention, due to logistical unavailability of IgIV. The 25 patients received 0.4 g/kg/day for 5 days and the average time elapsed from the onset of symptoms to the onset of treatment administration was 9.1 ± 5.8 days (range: 3-31). In contrast with other studies, there were no significant differences between the time of recovery of the two groups. Furthermore, the treatment group had a higher rate of mortality and of mechanic ventilation dependence.[21] Nevertheless, it should be noted that the study was not randomized, the start of treatment could have been quite late for an important proportion of patients and only the most disabled were selected for immunotherapy. Therefore, they were already biased in the sense of having the worst functional prognosis.[21]

Comparison between PLEX and IgIV

The most relevant studies that allow evaluating both treatments in children are summarized in **Table 1**. A retrospective study including 35 children that were diagnosed with GBS over a 20-year span used both PLEX and IgIV as a therapeutic option. Of all the children that were treated with PLEX as a first line, 88% showed improvement. This therapy had a greater success rate than IgIV, with whom 70% improved. This study´s result contradicts others, where IgIV is considered a better option or, at the very least, of equal efficacy than PLEX.[22]

Other retrospective study was conducted with 62 children, to determine which of the two immune-targeted therapies could be the most favorable. Thirty children received a dose of 0.4 g/kg of IgIV for 5 days and 32 were submitted to 200-250 mL/kg of PLEX for 7-10 days. After the procedures, patients treated with PLEX had a lesser need for ventilation and their hospital stay was inferior to the patients treated with IgIV. Complete recovery was achieved in patients treated with PLEX after 6 months and fewer side effects were reported, when compared with IgIV-treated patients.[23] Even so, the adverse effects reported for IgIV were mild, corresponding to infusion rate reactions, headache, myalgia, flushing and paresthesia.[23]

A study conducted over a period of 3 years submitted a group of 44 children with severe GBS, in need of mechanic ventilation, to either PLEX (21 children) or IgIV (20 children) (1 PLEX a day for 5 days and 0.4 g/kg of IgIV for 5 days). In terms of recovery of the motor function, there were no significant differences between the 2 groups. However, patients submitted to PLEX revealed a shorter hospital stay and less need for mechanic ventilation. Both therapies did not provoke relevant side effects, highlighting their safety.[24,25]

A different study, published in 2001, compared the ac-

Table 1. Studies evaluating IgIV and PE exclusively in pediatric populations*.

Author	Number of patients (n)	Type of treatment	Median age (y)	Invasive ventilated patients (n)	Mortality (n)	Main outcomes
Kalita *et al* (2019)[45]	138	63 IgIV 75 controls	12	9 IgIV 8 controls	3	IgIV: 16.5 days of hospitalization Controls: 23.8 days of hospitalization
Kesici *et al* (2019)[29]	9	All in alternate program of PE and IgIV (zipper method)	10.9	9	0	18 days of hospitalization All patients able to walk independently
Saad *et al* (2016)[23]	62	30 IgIV 32 PE	8	20 IgIV 4 PE	6 IgIV 6 PE	IgIV: 15.7 days of hospitalization PE: 4 days of hospitalization
Gajjar *et al* (2016)[13]	40	40 PE	9	ND	1	27 patients improved from grades 0 and 1 in muscle strength to grade 3 (MRCS)
El-Bayoumi *et al* (2011)[25]	41	20 IgIV 21 PE	8	IgIV: 13.0 ± 2.1 days PE: 11.0 ± 1.5 days	ND	IgIV: 13 ± 2.1 days of hospitalization PE: 11± 1.5 days of hospitalization
Hicks *et al* (2010)[22]	35	23 IgIV 15 PE (7 IgIV+ PE)	13.1	ND	0	Success rate: PE 88%; IgIV 70%
Ma *et al* (2010)[20]	36	2 PE 2 corticosteroid 21 controls	5.1	3	1	Early IgIV (<10 days of symptoms): 17.4 days of hospitalization (*vs* 47.5)
Kalra *et al* (2009)[9]	52	43 IgIV 9 controls	5	10	6	7 with full recovery in one year
Kuitwaard *et al* (2009)[19]	174	174 IgIV	12.4	ND	ND	Patients with lower Ig levels at 2 weeks have a more severe disease
Ortiz-Corredor *et al* (2007)[49]	54	34 IgIV 20 controls	6.5 ± 4.2	96	1	48.8% quadriplegic at day 10
Tasdemir *et al* (2006)[21]	55	25 IgIV 25 controls	6.4 ± 4.2	9 IgIV 2 controls	9	4 deaths in the IgIV group IgIV: 20.7 days of hospitalization Controls: 17.6 days of hospitalization
Ko-rinthen-berg *et al* (2005)[43]	95	Group 1 (early IgIV treatment over 2 days): 21 Group 2 (late IgIV treatment over 2 or 4 days): 53	6.2	Group 1: 1 Group 2: 13	ND	Relapses more frequent with 2 days of treatment
Shahar *et al* (2003)[40]	23	15 IgIV 8 controls	ND	ND	ND	1 relapse in the IgIV group after 5 months
Singhi *et al* (1999)[40]	33	22 IgIV 11 controls	5.11	6 in IgIV group 9 in controls	ND	IgIV: 1 with minor neurologic deficits Controls: 3 with minor neurologic deficits
Abd-Allah *et al* (1997)[37]	7	4 IgIV 3 controls	5.8	1	ND	1 relapse after 2 weeks in IgIV group
Zafeiriou *et al* (1997)[33]	9	9 IgIV	7	0	0	Mean duration of symptoms 5.7 days
Gurses *et al* (1995)[39]	18	9 IgIV 9 controls	10.4	2 in each group	1	IgIV: 3 days of ventilation; 4.5 days of hospitalization Controls: 16.5 days of ventilation; 23.8 days of hospitalization
Al-Qudah (1994)[35]	4	4 IgIV	14.1	ND	0	1 patient relapsed and presented with severe neurological deficit at 6 months
Jansen *et al* (1993)[12]	19	8 PE 11 controls	8.9	7 PE 4 controls	0	PE: 16.7 days of hospitalization Controls: 47.5 days of hospitalization
Shahar *et al* (1990)[34]	3	3 IgIV	12.3	ND	ND	No neurologic sequelae at 6 months
Epstein *et al* (1990)[30]	23	9 PE 14 controls	8.8	1 in each group	0	PE: 5.9 days of disease Controls: 9.8 days of disease
Yoshioka *et al* (1985)[31]	4	All PE	10.3	1	0	3 with minor neurological deficits

* Studies that also included adults, in addition to children, are not mentioned in this table. Studies are organized in order of publication, from the most recent to the oldest.

IgIV: intravenous immunoglobulins; n: number; MRCS: Medical Research Council Scale; ND: not described; PE: plasma exchange; y: years.

tion of PLEX and IgIV in children. Even though the specific outcome measures for this study were not available, children that received IgIV had a faster recovery of bulbar and respiratory functions than those submitted to PLEX, 17 and 30 days respectively.[24,26]

Few studies have been published in which there was a poor response to an initial treatment with PLEX or IgIV. A retrospective study identified 116 children diagnosed with GBS, in which patients received standard PLEX or IgIV, but 20 children did not recover their motor capacity and required another set of treatment. Of these, 7 received IgIV 0.4 g/kg/day for 5 days and 13 received 5 exchanges of plasma over 1-2 weeks. Nineteen children served as the control group. These children were evaluated in terms of their Hughes score and length of hospital stay. The treatment group improved in the Hughes scale after 1 month of follow-up, when compared with the control group, but not after 3 and 6 months. Furthermore, the treatment group left the hospital, on average, after 55 days when compared with 11 days in the control group. Nearly 41% of children in the treatment group had a Hughes score of 4 or 5 after the rescue treatment. So, a second line of treatment is still not well established, if the first course of treatment proves to be unsuccessful.[27]

Combination of PLEX and IgIV

There are few studies testing the combination of PLEX and IgIV treatment. Of those, a randomized trial submitted 128 patients over 16 years old to a regimen of 5 exchanges of 50 mL/kg followed by 5 days of 0.4 g/kg of IgIV after the last exchange. This had the intent of understanding if the two techniques combined prove to be better than each one alone. Primary outcome was to see if this combination was better in reducing the disability after 4 weeks of treatment. After the trial and subsequent follow-up period, this combination gave only a small advantage when comparing with the therapies alone. There were 3 secondary measures studied, time to independent walking, time to discontinuation of mechanic ventilation and rate of recovery. Considering these 3, only time to independent walking did not reveal an advantage of the combined treatment. This trial showed that combining both therapies does not seem to confer a significant advantage.[28]

In 2019, a new technique was presented in the treatment of severe GBS, the "zipper method".[29] Over the course of 7 days, 9 children were submitted to an alternate program of PLEX and IgIV. They received an exchange of 1.5 their plasma volume on the first day. After this exchange was finished, they would receive right away 0.4 g/kg of IgIV. The second exchange had to be given 24 hours after the end of the immunoglobulin and not immediately. This process was conducted 5 times, and, in this study, children left mechanic ventilation after 7 days of treatment.[29] This was not a controlled trial, and a comparison was made with a study published 22 years earlier,[28] in addition to the fact that all cases treated with the zipper method were acute motor axonal neuropathies.[29] Even so, if IgIV was used alone, the mean time required for ventilation withdrawal was 26 days. In terms of PLEX, the time ascended to 29 days and with both combined (not using the zipper method) to about 18 days.[29] Regarding the duration of hospital stay, if IgIV was used alone, this period was on average 53 days. With PLEX it ascended to 63 days and in combination to about 51 days. With the zipper method, the hospital discharge was obtained after 18 days, on average.[29] In terms of ability to walk without help, the PLEX group took 49 days to do so, the IgIV group took 51 days and the combination of both, without using the zipper method, took 40 days.[29] With the zipper method, patients were able to walk unaided after 24 days on average. Furthermore, all patients submitted to this novel treatment approach were able to walk independently.[29] On the contrary, after 48 weeks, 16.7% of patients only given PLEX were not able to walk unaided. In the group that received IgIV, 16.5% were also not able to walk without help after that period. When combining both (not using the zipper method), 13.7% of patients were not able to walk unaided after 48 weeks of follow-up.[3] In this study there was no mortality observed and even though it had a small sample size, the fact that there were no deaths is an encouraging sight for this therapeutic approach. The only potential negative effect associated with this technique is the cost. However, it can be stated that by increasing the time of recovery and decreasing the need for mechanic ventilation, it may limit the cost of hospitalization and be more cost-effective that each one of the techniques alone.[29]

Discussion

GBS requires an assertive treatment approach, as it is a life-threatening condition. PLEX emerged in the 1980s and has proven to be an effective treatment in severe cases of childhood GBS, by accelerating motor recovery, reducing hospital stay and the need for mechanic ventila-

tion.[11-14,30,31] The ideal dosage for this therapy is stated in several articles as 5 exchanges of a total of 250 mL/kg for 7-14 days.[1,4,19,10,32] The number of exchanges is a critical point, because more exchanges than necessary may lead to hemodynamic instability.[2,3,32] Regarding treatment initiation, the timing is still not clearly defined, because some studies state that it should be given within 7 days of the onset, but other report says that 7 days is not a strict timepoint.[14,15] This technique has proved to be effective, however it is not the first line of treatment, due to the necessity of trained personnel and specific equipment. Furthermore, it is not safe for children under 10 kg of weight, due to their low blood volume, leading to hemodynamic instability.[16,17] Currently, this intervention is used in severe cases, but more research is needed to shed a better light on the safety of this intervention.[2,4,18]

IgIV is the first-line treatment, because of its efficacy, accessibility and safety. Even though an early study showed the effectiveness of a single dose of 1 g/kg of immunoglobulin,[33] several studies state that the dosage determined to be the most effective is 2 g/kg, for 2-5 days. This can be administered as a single dose of 2 g/kg or 0.4 g/kg for 5 consecutive days. Consequently, the dosage is set, independently of the duration of the treatment. This intervention proved to improve motor recovery, to shorten hospital stay and the need for mechanic ventilation, but a higher rate of early relapses was observed in the 2-day treatment group.[24,32,34-42] It has proven to cause less side effects than PLEX. For maximum effectiveness, it should be given within 2 weeks of the onset of symptoms.[2,34,43] Several studies prove that this therapy is a good treatment option in pediatric GBS, being safe and accessible. One small and non-randomized study[21] contradicted these findings, but results should be interpreted with caution. This treatment must be carefully monitored, to prevent iatrogenic lung injury and several minor complications, mainly due to hemorheological effects of immunoglobulins.[44,45]

Regarding the comparative effectiveness of the two approaches, it appears that both are effective in speeding patients' motor recovery. However, it is not clear which is more effective, because different studies present different conclusions. Equally, there is not a unanimous conclusion regarding the need for mechanic ventilation. Most articles state that PLEX reduces the need for artificial ventilation,[22,23] which is contradicted in the van der Meché *et al* 1992 article.[46] Even so, care must be taken in interpreting this contradiction, as surely since 1992 many technical aspects have improved the use of plasmapheresis and its impact on ventilation techniques. One thing in that all articles agree is that IgIV is a very safe treatment option, as well as accessible. PLEX is not as safe as immunoglobulins, especially in children under 10 kg, making exchanges a very difficult process.[2,4,43,46] One point that needs to be clarified is when the first line of treatment is not successful what should be the correct approach, even because there is a study stating that the patients submitted to a second course of therapy had a lengthier hospital stay and slower motor recovery (nevertheless, there could be some improvement at the end of the first month of treatment, although at 3 and 6 months the differences were not significant, with a large amount of loss to follow-up).[27]

There are not many studies, particularly in children, where both PLEX and IgIV are used simultaneously. In one of the few early articles[47] there were no significant differences between using each technique alone or in combination. However, in fulminant GBS, the combination of both immunological therapies and supportive treatment are essential.[47-49] In 2019, an innovative approach was published, using both therapies intercalated.[29] In this study, patients had better results in every parameter, when comparing with each therapy alone. Even so, the study is of small dimensions and the fact is that its conclusions are not easily transferred to clinical practice. The zipper method,[29] as is became known, it is not the most immediate way to approach GBS at any age, let alone children. And the natural evolution of therapeutic intervention in this area must also be considered. Some monoclonal antibodies have already been used in adults diagnosed with GBS. Eculizumab (anti-C5), rituximab (anti-CD20) and alemtuzumab (anti-CD52)[50] seem to embody a much more rational intervention strategy, focused on very specific protein targets. The deepening of knowledge related to the pathophysiology of the disease favors the use of monoclonal antibodies, but it should also be noted that only eculizumab has ongoing clinical trials for this indication.[50] The experience with rituximab and alemtuzumab is only anecdotal[50] and none of the cases described in the literature concern children. As such, nothing can be said about the use of these drugs in children diagnosed with GBS, but this will be a perspective of future interest. If this could be more interesting than the zipper method itself, the future will also tell.

Conclusion

PLEX and IgIV infusion are two interesting, effective and generically safe approaches in pediatric GBS. There are no data suggesting a clear superiority of one of them in children, so their use in clinical practice is essentially related to the greater or lesser experience of clinical teams in the field. It has recently been pointed out that both techniques may be used interchangeably in the same patient, but the results of this type of intervention lack practical validation. It is likely that the future of GBS treatment will involve the use of monoclonal antibodies, but there is still no study of any drug of this type in children. ■

Contributorship Statement / Declaração de Contribuição

GF: Study design and execution, manuscript elaboration and final approval.

JA: Study design and execution, manuscript elaboration and final approval.

CG: Manuscript review and final approval.

FP: Study design and execution, manuscript review and final approval.

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