Outcome of Second Immunomodulatory Treatment in Guillain-Barré Syndrome Patients with Poor Response to Initial Treatment in Neurological Institute of Thailand: A Single-Center Retrospective Observational Study

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ABSTRACT

Background : Guillain-Barré syndrome (GBS) is an immune-mediated polyneuropathy. The majority of patients have a good response to standard treatments which are intravenous immunoglobulin (IVIG) and plasma exchange (PE). However, some patients have poor responses, which do not improve and may deteriorate. Therefore, the second immunomodulatory treatment is considered for these patients.

Objectives : This research aimed to study the outcome of a second immunomodulatory treatment in GBS patients with poor response to initial treatment at the Neurological Institute of Thailand.

Materials and Methods : An observational retrospective review was performed, including patients with GBS between January 2017 and June 2023. Demographic data, clinical features, CSF profiles, electrodiagnostic classifications, MRC sum scores, and GBS disability scores at admission, 4 weeks, 8 weeks, 12 weeks, and 24 weeks were analyzed.

Results : A total of 64 patients with GBS were included. 17 patients (26.6%) had a poor response to the initial treatment. 7 patients (41.2%) received the second treatment. There were 6 patients (85.7%) who had PE followed by IVIG and 1 patient (14.3%) had a second dose of IVIG. The results showed no significant difference in the MRC sum score and GBS disability score during follow-up between the two groups. The patients in the second treatment group had higher serious complications including 1 patient (14.3%) had a catheter-related bloodstream infection and 1 patient (14.3%) had a thromboembolic event.

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Conclusion : The second immunomodulatory treatment in GBS patients with poor response to the initial treatment is not associated with an improvement in MRC sum scores and GBS disability scores, intubation periods, length of hospital stay, and mortality. There are increased risks of treatment-related complications, including catheter-related bloodstream infections, and thromboembolic events.

Keywords : Guillain-Barré syndrome; Second immunomodulatory treatment; Intravenous immunoglobulin; Plasma exchange

Introduction

Guillain-Barré syndrome (GBS) is an immune-mediated peripheral neuropathy and is the most common cause of acute flaccid paralysis with an annual worldwide incidence of approximately 1-2 per 100,000 person-year. GBS incidence increases around 20% in every 10 years of age, which is more frequently in male than female patients.[1-3]

GBS typically presents with acute progressive bilateral limb weakness, distal paresthesias or sensory loss, absence of reflex, and cranial nerve involvement. GBS is usually a monophasic disease reaching its nadir within two to four weeks after the onset. The clinical course of the disease ranges from mild or no disability to severe with bedridden, autonomic disturbance, and respiratory failure requiring a mechanical ventilator in 25% of them. The mortality rate is about 4-10% within 1 year of symptom onset, most commonly due to cardiovascular and respiratory complications.[1-3]

Intravenous immunoglobulin (IVIG) and plasma exchange (PE) are the standard immunomodulatory treatments of GBS, proven equal benefit for the patients.[4,5] Practically, IVIG is easier to administer and more available, so it is usually the first choice of treatment. The majority of patients about 80% have a good response to the standard immunomodulatory treatment. They can regain the ability to walk independently at 6 months after disease onset and 60% of GBS patients completely recover motor function at 1 year. The relapse episode is rare, affecting 2-5% of patients.[1-5]

However, 40-50% of GBS patients do not respond to the initial immunomodulatory treatment either IVIG or PE, which does not improve on GBS disability score at 4 weeks and may even further deteriorate.[6-9] Therefore, the second immunomodulatory treatments including repeating the same previous treatment or changing to another therapy are considered for these patients, although there is no consensus evidence about the best treatment for the patients who have a poor response or deteriorate after the primary treatment course.[10]

In current evidence, only a few studies have evaluated the outcome of the second course of treatment in GBS patients.[10-14] A double-blind, randomized, placebo-controlled trial evaluating the second IVIG in GBS patients in the Netherlands with poor prognosis (SID-GBS) was recently published in 2018 and showed no significant benefit from the second IVIG. Furthermore, it had a higher risk of thrombosis and infectious complications.[14] On the other hand, PE after IVIG remains unclear because PE would probably wash out the IVIG previously administered.[10] Only one small retrospective study in the U.S. reported that IVIG followed by PE was not better than IVIG as well as the patients who received both treatments had a worse GBS disability grade at discharge and longer length of hospital stay.[13]

There are many questions about whether subtypes of GBS patients in Western are different from Asia including Thailand. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common subtype in the United States and Europe presenting in about 60-90% of GBS patients while axonal forms, acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN), are more prevalent in China and South-east Asia.[1,2,15] Generally, axonal subtypes are different from AIDP. They tend to have a poor prognosis compared with AIDP. The therapeutic response to IVIG is good in the case of AIDP, but is unsatisfactory in the patients with the axonal forms.[16-18] Moreover, there are few case reports shown that some patients with axonal subtypes were likely to improve with PE after failing IVIG treatment.[17-19]

Therefore, this research aimed (1) to determine the clinical predictors are associated with poor response in GBS patients, (2) to study the outcome of a second immunomodulatory treatment in GBS patients with poor response to initial treatment in the Neurological Institute of Thailand.

Materials and Methods

Study design

An observational retrospective study was conducted at the Neurological Institute of Thailand, including all patients diagnosed with GBS between January 2017 and June 2023. The study was reviewed and approved by Institutional Review Board (IRB).

Study population

The study population included patients aged 18 years or more diagnosed with GBS according to Brighton criteria 2011.[1,20] The inclusion criteria are (1) progressive bilateral flaccid weakness of limbs, (2) Absent or decreased tendon reflexed in affected limbs, (3) time between onset to nadir within 4 weeks, (4) evidence of albuminocytologic dissociation defined as the combination of cerebrospinal fluid (CSF) protein level more than 45 mg/dl and cell count less than 50 cells/ul, (4) the reported electrodiagnostic features are compatible with the subtypes of GBS. We accepted in case protein levels are normal or electrodiagnostic studies are normal, especially within the first week of symptom onset.[1,20] In addition, the electrodiagnostic criteria are based on Uncini's criteria 2017, classified as AIDP, AMAN, AMSAN, inexcitable, equivocal, and normal.[21] The exclusion criteria are (1) the patients were finally diagnosed with another diagnosis; (2) medical data were incompletely recorded.

Data collection

The data recorded including age, gender, comorbidity, antecedent events within the 4 weeks preceding the onset of symptoms, date of onset, clinical manifestations, Medical Research Council (MRC) sum score, GBS disability score, CSF profiles, electrodiagnostic studies, an option of immunomodulatory treatment, treatment response, complications, and length of hospital stay.

The MRC sum score was used to assess muscle strength ranging from 0 (complete paralysis) to 60 (normal). The GBS disability score is a widely accepted scale for accessing the functional status of patients with GBS (0: normal; 1: minor symptoms but able to run; 2: able to walk 10 meters or more without assistance but unable to run; 3: able to walk 10 meters across an open space with help; 4: bedridden or chairbound; 5: requiring assisted ventilation for at least part of the day; 6: death)

Furthermore, immunomodulatory treatments are defined as the treatments that modulate the immune system including IVIG, and PE. The second immunomodulatory treatment is the second course of treatment in GBS patients who poorly respond to initial treatment such as a second dose of IVIG, PE followed by IVIG. In addition, the definition of poor response is an improvement in GBS disability score less than one grade at 4 weeks after the initial course of treatment.

Outcome

The clinical outcomes were presented by an improvement in GBS disability score, MRC sum score at 8 weeks, at 12 weeks, and 24 weeks after the start of treatment, duration of hospital stay, intubation period, and mortality.

Statistical analysis

Continuous variables were presented as the median and interquartile range, while categorical variables were described as percentages. The differences between groups were analyzed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. All probability values were two-sided and the level of significance was set at p-value < 0.05. Statistical analyses were performed using SPSS for Windows version 16.0 (SPSS Inc., Chicago, Illinois, USA)

Results

Demographics and clinical features

A total of 64 patients with GBS were included in the present study. The demographics and clinical features of the GBS patients are shown in Table 1. Male patients were slightly predominant (53.1%). The male-to-female ratio was 1.2:1. Median age at onset was 53.5 years (range from 42-64 years). Underlying diseases were hypertension (45.3%), diabetic mellitus (21.9%), coronary artery disease (7.8%), and HIV (6.3%). The most common antecedent events were URI (15.6%), diarrhea (7.8%), vaccination (7.8%), and fever of unknown origin (6.3%). The mean duration before the first evaluation was 7 days (range from 5 to 14 days).

Table 1 Demographic data and clinical manifestations of patients with GBS (n=64).

Variable	Total (n=64)	Good response (n=47)	Poor response (n=17)	p-valve
Demographic data				
Sex, male: female	1.2: 1	1: 1.1	2.4: 1	0.092
Age (years); median (IQR)	53.5 (42.0-64.0)	55.0 (38.0-64.0)	53.0 (46.5-65.0)	0.503
Comorbidity; n (%)				
Diabetic mellitus	14 (21.9)	11 (23.4)	3 (17.6)	0.742
Hypertension	29 (45.3)	20 (42.6)	9 (52.9)	0.461
HIV	4 (6.3)	3 (6.4)	1 (5.9)	1.000
Coronary artery disease	5 (7.8)	1 (2.1)	4 (23.5)	0.015*
Antecedent event; n (%)				
Diarrhea	5 (7.8)	4 (8.5)	1 (5.9)	1.000
URI	10 (15.6)	10 (21.3)	0	0.051
Vaccination	5 (7.8)	4 (8.5)	1 (5.9)	1.000
Fever unknown origin	4 (6.3)	3 (6.4)	1 (5.9)	1.000

Variable	Total (n=64)	Good response (n=47)	Poor response (n=17)	p-valve
Clinical manifestations				
Duration from symptom onset to admission (days); median (IQR)	7.0 (5.0-14.0)	7.0 (5.0-14.0)	8.0 (4.0-14.0)	0.830
Clinical features at admission; n (%)				
Weakness	64 (100)	47 (100.0)	17 (100.0)	NA
Sensory disturbance	50 (78.1)	38 (80.9)	12 (70.6)	0.495
Facial weakness	29 (45.3)	19 (40.4)	10 (58.8)	0.192
Ophthalmoplegia	16 (25.0)	11 (23.4)	5 (29.4)	0.745
Oropharyngeal weakness	31 (48.4)	18 (38.3)	13 (76.5)	0.007*
Hyporeflexia or areflexia	62 (96.9)	46 (97.9)	16 (94.1)	0.464
Radicular pain	6 (9.4)	4 (8.5)	2 (11.8)	0.652
Respiratory failure	25 (39.1)	12 (25.5)	13 (76.5)	<0.001*
Autonomic dysfunction	14 (21.9)	9 (19.1)	5 (29.4)	0.380
Alteration of mental status	3 (4.7)	1 (2.1)	2 (11.8)	0.170
MRC score at admission; median(IQR)	36.0 (30.0-48.0)	38.0 (30.0-48.0)	12.0 (5.0-19.0)	<0.001*
GBS score at admission; median (IQR)	4.0 (3.0-5.0)	4.0 (3.0-5.0)	5.0 (5.0-5.0)	<0.001*

The majority of GBS patients presented with sensorimotor polyneuropathy. Almost all patients had a symmetrical, proximal, and distal weakness with hyporeflexia or areflexia. Other clinical features were oropharyngeal weakness (48.4%), facial weakness (45.3%), respiratory failure (39.1%), ophthalmoplegia (25.0%), autonomic dysfunction (21.9%), radicular pain (9.4%) and altered mental status (4.7%)

For further analysis, the author classified the patients into 2 groups which are a good response group and a poor response group. There were 47 patients (73.4%) who had a good response to the initial treatment and 17 patients (26.6%) had a poor response to the initial treatment. There were no significant differences in gender, age, and antecedent events among the study group. However, GBS patients in the poor response group had higher comorbidity with coronary artery disease (23.5 vs. 2.1, p=0.015), higher oropharyngeal weakness (76.5% vs. 38.3%, p=0.007), and higher respiratory failure (76.5% vs. 25.5%, p<0.001) at admission. Furthermore, a low MRC sum score, especially less than 30 (100.0 vs. 27.7, p<0.001), low motor power grading, and high GBS disability score at the time of admission more than 4 (82.4 vs. 25.5, p<0.001) were associated with poor response to treatment.

Laboratory and electrophysiological findings

The CSF examination and electrodiagnostic studies were examined in all patients. The results are presented in Table 2. 81.3% of patients had albuminocytological dissociation with a median protein value of 113.5 mg/dl (range 53.0-146.5 mg/dl). There were no significant differences in the CSF profile between these study groups.

Table 2 CSF and electrodiagnostic features of patients with GBS (n=64).

Variable	Total (n=64)	Good response (n=47)	Poor response (n=17)	p-valve
CSF characteristics				
Albuminocytologic dissociation; n (%)	52 (81.3)	36 (76.6)	16. (94.1)	0.157
CSF protein (mg/dl); median (IQR)	113.5 (53.0-146.5)	112.0 (52.0-147.0)	115.0 (43.5-131.5)	0.676
Duration from symptom onset to LP (days); median (IQR)	7.0 (5.0-14.0)	7.0 (5.0-14.0)	8.0 (4.5-14.5)	0.825
Electrodiagnostic features				
Electrodiagnostic classification; n (%)				
AIDP	38 (59.4)	31 (66)	7 (41.2)	0.062
AMAN	8 (12.5)	6 (12.8)	2 (11.8)	0.062
AMSAN	8 (12.5)	6 (12.8)	2 (11.8)	0.062
Inexcitable	6 (9.4)	1 (2.1)	5 (29.4)	0.062
Normal	4 (6.3)	3 (6.4)	1 (5.9)	0.062
Conduction block; n (%)	10 (15.6)	8 (17.0)	2 (11.8)	1.000
Duration from symptom onset to study (days); median (IQR)	10.0 (5.2-15.8)	9.0 (5.0-14.0)	14.0 (10.0-20.5)	0.015*

For electrodiagnostic studies, the most frequent electrodiagnostic classifications were AIDP (59.4%), followed by AMAN (12.5%) and AMSAN (12.5%). Some patients were inexcitable (9.4%) and normal (6.3%). The electrodiagnostic study was performed at a median of 10 days (range from 5 to 15 days). There were no significant differences in the electrodiagnostic features between these study groups.

Treatment and outcomes

For initial treatment, 63 patients (98.4.%) were treated with 0.4 mg/kg/day intravenous immunoglobulin (IVIG) for 5 days and 1 patient (2.1%) received 5 cycles of plasma exchange (PE). Of all patients, 47 patients (73.4%) had a good response and 17 patients (26.6%) had a poor response to the initial treatment. For patients with a good response, the median times after treatment to the first clinical response were 8 days (ranging from 5-24 days). At 4, 8, 12, and 24 weeks after treatment, median MRC scores were 48.0 (range from 29.5-54.0), 56.0 (range from 44.5-60.0), 58.0 (range from 46.0-60.0), and 60.0 (range from 49.0-60.0) respectively, and GBS disabling scores were 3 (range from 2-4), 2 (range from 0-3), 1.0 (range from 0.0-2.5) and 0 (range from 0-2) respectively. Almost all patients (95.7%) were able to walk independently at 24 weeks after the treatment. The treatment outcome is shown in Table 3, Figure 1A, and Figure 1B.

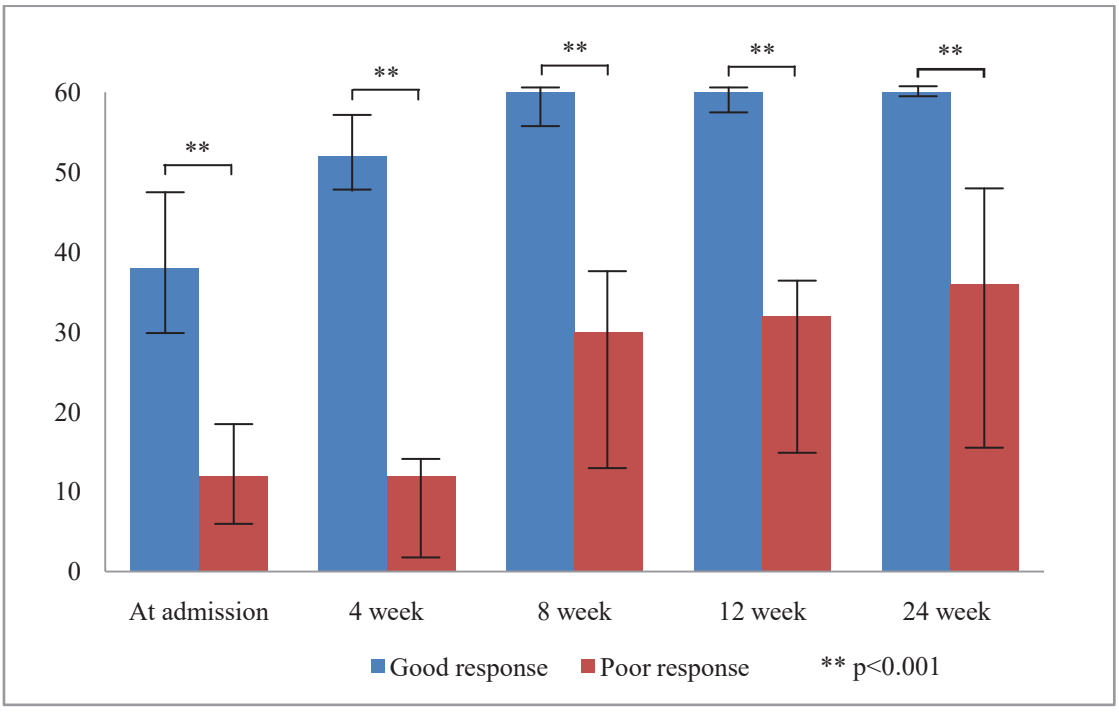


Figure 1A MRC sum score between good response group and poor response group.

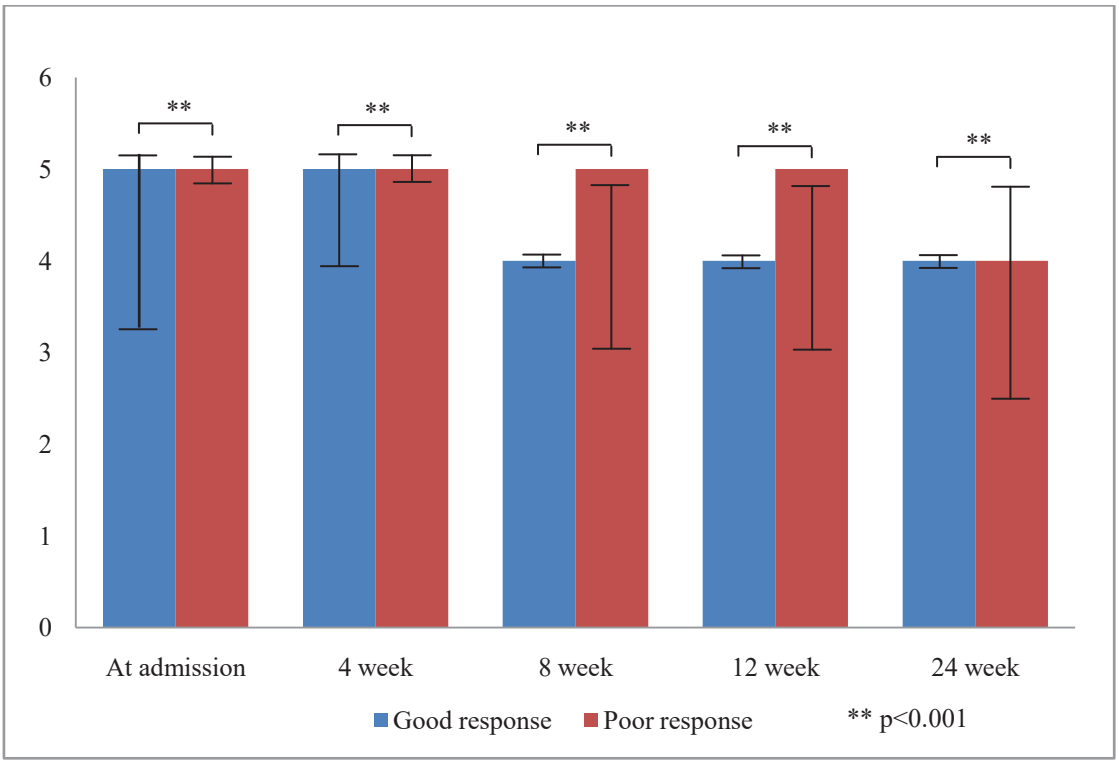


Figure 1B GBS disability score between good response group and poor response group.

Table 3 Treatment and outcome of patients with GBS (n=64).

Variable	Total (n=64)	Good response (n=47)	Poor response (n=17)	p-valve
Outcomes				
MRC score at 4 week; median (IQR)	48.0 (29.5-54.0)	52.0 (48.0-56.0)	12.0 (0.0-25.0)	<0.001*
MRC score at 8 week; median (IQR)	56.0 (44.5-60.0)	60.0 (54.0-60.0)	30.0 (12.0-38.0)	<0.001*
MRC score at 12 week; median (IQR)	58.0 (46.0-60.0)	60.0 (58.0-60.0)	32.0 (14.0-36.0)	<0.001*
MRC score at 24 week; median (IQR)	60.0 (49.0-60.0)	60.0 (60.0-60.0)	36.0 (15.0-48.0)	<0.001*
GBS score at 4 week; median (IQR)	3.0 (2.0-4.0)	2.0 (2.0-3.0)	5.0 (5.0-5.0)	<0.001*
GBS score at 8 week; median (IQR)	2.0 (0.0-3.0)	0.0 (0.0-2.0)	4.0 (3.0-5.0)	<0.001*
GBS score at 12 week; median (IQR)	1.0 (0.0-2.5)	0.0 (0.0-1.0)	4.0 (3.0-5.0)	<0.001*
GBS score at 24 week; median (IQR)	0.0 (0.0-2.0)	0.0 (0.0-0.0)	4.0 (2.5-5.0)	<0.001*
Duration from symptom onset to treatment (days); median (IQR)	9.5 (6.0-14.0)	8.0 (5.0-14.0)	14.0 (8.0-20.2)	0.120
Complications; n (%)				
Thromboembolism	1 (1.6)	0	1 (5.9)	0.266
Infection	20 (31.3)	7 (14.9)	13 (76.5)	<0.001*
Cardiovascular complication	4 (6.3)	2 (4.3)	2 (11.8)	0.285
Intubation (days); median (IQR)	12.0 (0.0-17.8)	4.0 (0.0-7.0)	38.0 (11.0-56.0)	<0.001*
Length of stay (days); median (IQR)	22.5 (8.5-43.0)	13.0 (7.0-25.0)	50.0 (38.5-64.5)	<0.001*
Death; n (%)	3 (4.7)	0	3 (17.6)	<0.001*

However, 17 patients (26.6%) had a poor response to the initial treatment. Median durations from symptom onset to treatment in this group were slightly longer, but non-significant difference (14 vs. 8, p=0.120). 10 patients (58.9%) received only a single course of IVIG and 7 patients (41.1%) received the second treatment. There were 6 patients (85.7%) who had PE after IVIG and 1 patient (14.3%) had a second dose of IVIG. Duration from the initial treatment to the second treatment was 21.5 days (range from 17.0 to 25.5 days). Patients with poor response had lower median MRC scores and higher GBS disabling scores during follow-up than other groups significantly. At 4 weeks, the median MRC score and GBS disabling score were 12.0 (0.0-25.0) and 5.0 (5.0-5.0) respectively. More than 76.5% of the patients required mechanical ventilation. At 8 weeks, the median MRC score and GBS disabling score were 30.0 (12.0-38.0) and 4.0 (3.0-5.0) respectively. About two-thirds of the patients (70.6%) were still bedbound. At 24 weeks, the median MRC score and GBS disabling score were 36.0 (15.0-48.0) and 4.0 (2.5-5.0) respectively. Only a few patients (23.5%) were able to walk independently. Moreover, there were significantly longer intubation periods (38.0 vs. 4.0, p<0.001), prolonged length of hospital stay (50.0 vs. 13.0, p<0.001), higher infectious complications (76.5% vs. 14.9%, p<0.001), and higher mortality (0 vs. 17.3%, p<0.001)

Comparison between single course and second course of immunomodulatory treatment in GBS patients with poor response to initial treatment

Of 17 patients with poor response to the initial treat-

ment, there were 10 patients (58.8%) received a single treatment of IVIG and 7 patients (41.2%) received a second treatment. 6 patients (85.7%) received PE followed by IVIG and 1 patient (14.3%) received a second dose of IVIG. The Majority of patients were male (85.7%) and had a median age of 54.5 years (range from 45.0-63.2 years). Underlying diseases were hypertension (42.9%), diabetic mellitus (14.3%), and coronary artery disease (14.3%). Median times from symptom onset to admission were 7.0 days (range from 2.5 to 18.5 days). The median MRC sum score and GBS disability score at admission were 12.0 (9.0-19.0) and 5.0 (4.75-5.0) respectively. All of them were albuminocytologic dissociation and median CSF protein levels were 122.5 mg/dl (93.5-191.7 mg/dl). Electrodiagnostic findings were AIDP (28.6%), AMAN (14.3%), and inexcitable (57.1%). Median times from the initial treatment to the second treatment were 21.5 days (range from 17.0 to 25.5 days). There were no significant differences in baseline characteristics including gender, age, comorbidities, clinical manifestations, MRC sum score and GBS disability score at admission, CSF profiles, and electrodiagnostic features among these patient groups. These results are demonstrated in Table 4, Figure 2A, and Figure 2B.

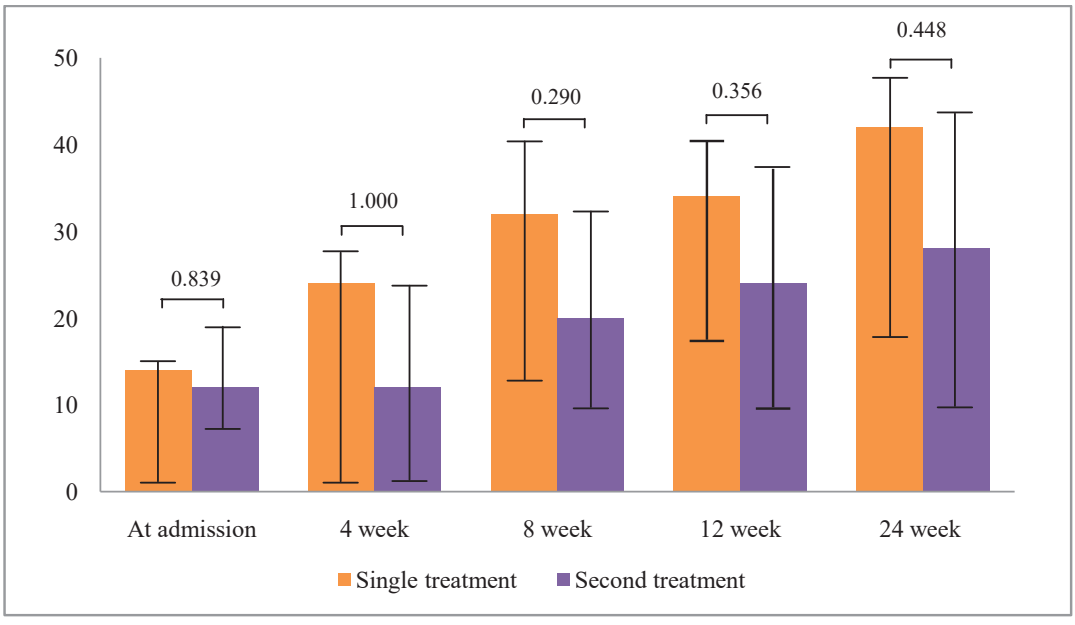


Figure 2A MRC sum score between GBS patients with poor response in single treatment group and second treatment group.

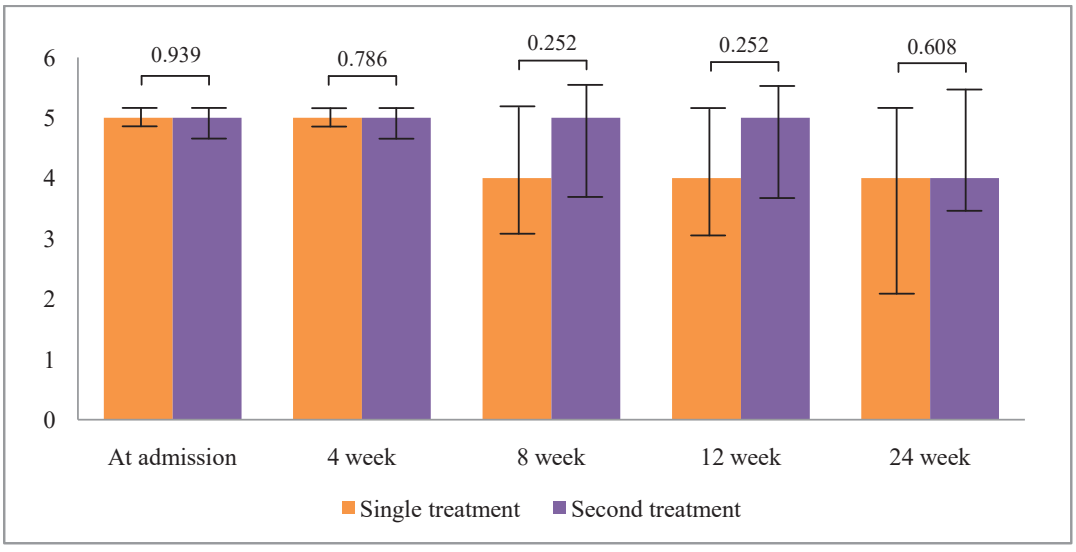


Figure 2B GBS disability score between GBS patients with poor response in single treatment group and second treatment group.

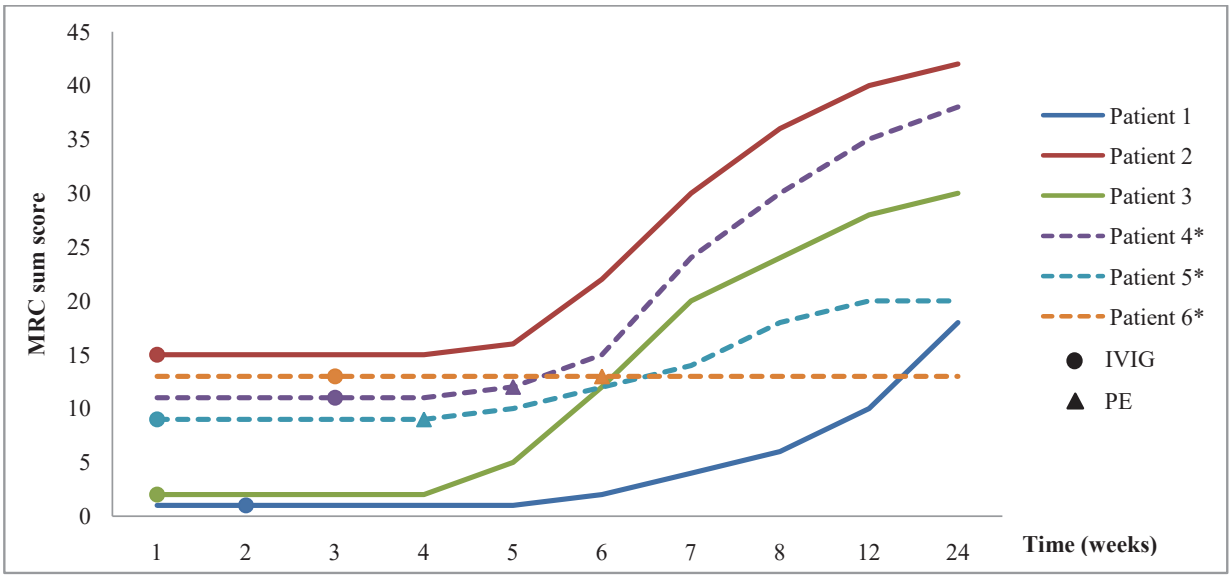
Table 4 Demographic data, clinical manifestations, CSF and electrodiagnostic features of GBS patient with poor response (n=17)

Variable	Single course (n=10)	Second course (n=7)	p-valve
Demographic data			
Male; n (%)	6 (54.5)	6 (100)	0.102
Age (years); median (IQR)	53.0 (47.0-71.0)	54.5 (45.0-63.2)	0.615
Comorbidity; n (%)			
Diabetic mellitus	2 (18.2)	1 (16.7)	1.000
Hypertension	7 (63.6)	2 (33.3)	0.335
HIV	1 (9.1)	0	1.000
Coronary artery disease	3 (27.3)	1 (16.7)	1.000
Clinical manifestations			
Duration from symptom onset to admission (days); median (IQR)	10.0 (5.0-14.0)	7.0 (2.5-18.5)	0.686
Clinical features at admission; n (%)			
Weakness	6 (100)	6 (100)	NA
Sensory disturbance	7 (63.6)	5 (83.3)	0.600
Facial weakness	6 (54.5)	4 (66.7)	1.000
Ophthalmoplegia	3 (27.3)	2 (33.3)	1.000
Oropharyngeal weakness	7 (63.6)	6 (100)	0.237
Absence or decrease of tendon reflex	10 (90.9)	6 (100)	1.000
Radicular pain	1 (9.1)	1 (16.7)	1.000
Respiratory failure	8 (72.7)	5 (83.3)	1.000
Autonomic dysfunction	3 (27.3)	2 (33.3)	1.000
Alteration of mental status	1 (9.1)	1 (16.7)	1.000

Variable	Single course (n=10)	Second course (n=7)	p-valve
MRC sum score at hospital admission; median (IQR)	14.0 (0.0-20.0)	12.0 (9.0-19.0)	0.839
GBS disability score at admission; median (IQR)	5.0 (5.0-5.0)	5.0 (4.75-5.0)	0.939
CSF characteristics			
Albuminocytologic dissociation; n (%)	10 (90.9)	6 (100)	1.000
CSF protein levels (mg/dl); median (IQR)	100.0 (27.0-128.0)	122.5 (93.5-191.7)	0.191
Duration from symptom onset to study (days); median (IQR)	7.0 (4.0-15.0)	9.0 (6.0-14.5)	0.724
Electrodiagnostic features			
Electrodiagnostic classification; n (%)			
AIDP	1 (9.1)	2 (33.3)	0.762
AMAN	5 (45.5)	1 (16.7)	0.762
AMSAN	1 (9.1)	0	0.762
Inexcitable	2 (18.2)	3 (50.0)	0.762
Normal	1 (9.1)	0	0.762
Conduction block; n (%)	1 (9.1)	1 (16.7)	1.000
Duration from symptom onset to study (days); median (IQR)	14.0 (7.0-19.0)	24.5 (10.75-36.0)	0.087

From the definition of poor response, it was defined as no improvement in GBS disability score at 4 weeks after the initial treatment. Most patients (64.7%) among both groups showed an improvement in the MRC sum score, although the GBS disability score did not change. There were 6 patients (35.3%) who had no change in GBS disability score and MRC sum score. 3 patients received a single treatment and 3 patients received a second treatment. Of these 6 patients, there were no significant difference in the MRC sum score and GBS disability score in patients who received single treatment or second treatment. The results are presented in Table 5, and Figure 3.

Furthermore, the patients who received the second treatment had higher treatment-related complications including 1 patient (14.3%) had a catheter-related bloodstream infection and 1 patient (14.3%) had a thromboembolic event. The results showed no significant differences in intubation periods (35.0 vs. 38.0, p=1.000), length of hospital stay (45.0 vs. 52.0, p=1.000), and mortality (28.6% vs. 18.2%, p=0.537).



Patient 1-3 represent single course of treatment, Patient 4*-6* represent second course of treatment Dots (●) represent IVIG, Triangles (▲) represent PE

Figure 3 Outcome of treatment in patients who did not change in MRC sum score at 4 week comparing between single treatment and second treatment

Table 5 Outcome of the second course immunomodulatory treatment in GBS patients with poor response to standard treatment compared to a single course of treatment (n=17).

Variable	Single course (n=10)	Second course (n=7)	p-valve
Outcomes			
MRC score at admission; median (IQR)	14.0 (0.0-20.0)	12.0 (9.0-19.0)	0.839
MRC sum score at 4 week; median (IQR)	24.0 (0.0-26.0)	12.0 (0.0-23.5)	1.000
MRC sum score at 8 week; median (IQR)	32.0 (12.0-40.0)	20.0 (9.0-33.5)	0.290
MRC sum score at 12 week; median (IQR)	34.0 (12.0-46.0)	24.0 (9.0-35.5)	0.356
MRC sum score at 24 week; median (IQR)	42.0 (18.0-48.0)	28.0 (9.0-41.5)	0.448
GBS score at admission; median (IQR)	5.0 (5.0-5.0)	5.0 (4.75-5.0)	0.939
GBS disability score at 4 week; median (IQR)	5.0 (5.0-5.0)	5.0 (4.75-5.0)	0.786
GBS disability score at 8 week; median (IQR)	4.0 (3.0-5.0)	5.0 (3.75-5.25)	0.252
GBS disability score at 12 week; median (IQR)	4.0 (3.0-5.0)	5.0 (3.75-5.25)	0.252
GBS disability score at 24 week; median (IQR)	4.0 (2.0-5.0)	4.0 (3.5-5.25)	0.608
Complications; n (%)			
Thromboembolism	0	1 (14.3)	1.000
Infection	6 (60.0)	7 (100.0)	0.237
Hospital acquired pneumonia	6 (100.0)	7 (100.0)	
Catheter-related bloodstream infection	0	1 (14.3)	
Cardiovascular complication	1 (10.0)	1 (14.3)	1.000
Intubation periods (days); median (IQR)	38.0 (5.0-60.0)	35.0 (12.7-52.0)	1.000
Length of stay (days); median (IQR)	52.0 (30.0-65.0)	45.0 (39.2-64.5)	1.000
Death; n (%)	1 (10.0%)	2 (28.6%)	0.537

Discussion

This study demonstrated overall demographic data, clinical manifestations, CSF profiles, electrodiagnostic characteristics, treatment outcomes, complications, and mortality were not different from previously published studies.[22-25] The majority of patients (73.4%) with GBS were a good response to treatment. The median time that showed the first clinical response was 8 days. Almost all patients (95.7%) were able to walk independently at 24 weeks. Unfortunately, 26.6% to 50% of GBS patients showed no improvements in GBS disability scores at 4 weeks after the treatment which reflects poor response to the initial treatment.[6-9] Only 23.5% of this group was able to walk independently at 24 weeks, and 4.6% died. In the present study, factors associated with poor response were underlying disease with coronary artery disease, oropharyngeal weakness, respiratory failure at admission, low MRC sum scores less than 30, and high GBS disability score at the time of admission more than 4. By comparison, low MRC sum scores of less than 40 at admission, high GBS disability score, presentation with bulbar weakness, respiratory failure requiring a mechanical ventilator, and severe motor weakness with inability to stand or lift elbow were significant predictors of poor outcomes in several studies.[26-30] Although many factors related to poor outcomes including high age more than 50 years, preceding diarrhea, and the short time from symptom onset to admission less than 7 days, it did not reach statistical significance in this study. Duration from symptom onset to treatment administration was also not significantly different. Moreover, electrodiagnostic predictors were not clear.

This study also demonstrated the outcome of the second course of treatment in the poor response group compared to a single treatment. There were 6 patients (85.7%) who had PE followed by IVIG and 1 patient (14.3%) had a second dose of IVIG. The median time from the initial treatment to the second treatment was 21.5 days. Most patients (64.7%) in both groups showed an improvement in MRC sum score during follow-up, even though the GBS disability scores did not change. Only 6 patients (35.3%) were not changed in the GBS disability scores and MRC sum scores. Of these groups, the results presented that there were no statistically significant differences in MRC sum scores, GBS disability scores during follow-up, intubation periods, duration of hospital stay, and mortality among these two groups. However, the patients with the second treatment had higher treatment-related complications, especially catheter-related bloodstream infections, and thromboembolic events.

These results were corresponding with the current studies. A double-blind, randomized, placebo-controlled trial evaluating the second IVIG in GBS patients in the Netherlands with poor prognosis (SID-GBS) was published in 2018 and showed no significant benefit from the second IVIG and it had a higher risk of thrombosis and infectious complications.[14] According to data from Oczko-Walker Malgorzata MD, this retrospective trial studied PE after initial IVIG in GBS. The results showed the patients who received both treatments had a worse GBS disability score at discharge with an increase in cost and hospitalization.[31]

The reason may explain about second immunomodulatory treatments do not show the obvious benefit because of severe axonal degeneration. The underlying pathogenesis of GBS is caused by

autoantibodies attack on myelin components, resulting in demyelination and secondary axonal injury or they can directly attack on axon, resulting in primary axonal injury. The recovery depends on the remyelination process and the degree of axonal degeneration.[2]

For this reason, there are severe axonal injury contribute to severe clinical features, poor response to treatment, and unpleasant clinical outcomes. Although the second immunomodulatory treatments are given, including neutralization of the autoantibodies by IVIG or removal by PE, they cannot restore the destroyed axon. Moreover, a second dose of IVIG may increase plasma viscosity and lead to an increased risk of serious adverse side effects, especially thromboembolic events.[14] Lastly, some expert opinions suggest that PE may be washed out of IVIG, as a result of preventing the therapeutic effect of IVIG.[32]

Limitation

There are several limitations in this study. Mainly, this is a retrospective study so it has many limitations when interpreting data on the chart reviews including missing data, lack of standard assessment, differences in timing of follow-up, and lack of long-term outcome data resulting from inconsistent follow-up of patients after discharge and some patients were referred back to their primary care physician. Secondly, there are no clear criteria to select patients who should receive the second immunomodulatory treatment after no clinical response to the initial treatment. Instead, the decision made by the attending physician depends on the patient's clinical situation. Finally, because of the limited sample size and single-center study, it cannot compare the effect of IVIG and PE on different subgroups, and it cannot accurately reflect the disease course in larger population samples. There is a need to multi-center study.

Conclusion

The second immunomodulatory treatment in GBS patients with poor response to the initial treatment is no significant differences in MRC scores, GBS disability scores during follow-up, intubation periods, length of hospital stay, and mortality compared to a single course of treatment. There are increased risks of serious treatment-related complications, including catheter-related bloodstream infections, and thromboembolic events.

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