

ORIGINAL RESEARCH

Second IVIg course in Guillain-Barré syndrome with poor prognosis: the non-randomised ISID study

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ABSTRACT

Objective To compare disease course in patients with Guillain-Barré syndrome (GBS) with a poor prognosis who were treated with one or with two intravenous immunoglobulin (IVIg) courses.

Methods From the International GBS Outcome Study, we selected patients whose modified Erasmus GBS Outcome Score at week 1 predicted a poor prognosis. We compared those treated with one IVIg course to those treated with two IVIg courses. The primary endpoint, the GBS disability scale at 4 weeks, was assessed with multivariable ordinal regression.

Results Of 237 eligible patients, 199 patients received a single IVIg course. Twenty patients received an 'early' second IVIg course (1–2 weeks after start of the first IVIg course) and 18 patients a 'late' second IVIg course (2–4 weeks after start of IVIg). At baseline and 1 week, those receiving two IVIg courses were more disabled than those receiving one course. Compared with the one course group, the adjusted OR for a better GBS disability score at 4 weeks was 0.70 (95%CI 0.16 to 3.04) for the early group and 0.66 (95%CI 0.18 to 2.50) for the late group. The secondary endpoints were not in favour of a second IVIg course.

Conclusions This observational study did not show better outcomes after a second IVIg course in GBS with poor prognosis. The study was limited by small numbers and baseline imbalances. Lack of improvement was likely an incentive to start a second IVIg course. A prospective randomised trial is needed to evaluate whether a second IVIg course improves outcome in GBS.

more quickly than those with a small increment.⁸ There are however reasons not to treat all GBS patients with a second IVIg course. First, approximately 80% of GBS patients treated with one IVIg course recover relatively well.⁵ Second, serious side effects may occur, including anaphylaxis, acute kidney injury, thromboembolic events or haemolytic anaemia.^{9–10} Third, IVIg is an expensive and relatively scarce blood product.

Therefore, careful selection of patients who might benefit from a second course of IVIg is important. The modified Erasmus GBS Outcome Score (mEGOS) identifies patients who are more likely to have a poor prognosis, defined as being unable to walk independently.¹¹ These patients in particular might benefit from a second course of IVIg if administered within the first weeks after onset of disease, when nerve damage is most likely reversible. We used the database of the prospective, observational International Guillain-Barré Syndrome Outcome Study (IGOS) to compare disease course in patients treated with one IVIg course versus two IVIg courses and we aimed to assess whether a second IVIg course in patients with GBS and a predicted poor prognosis improved functional outcome.¹²

METHODS

Study design

IGOS is an ongoing, prospective, observational cohort study which includes patients with GBS within the first 2 weeks of onset. The IGOS study protocol has been published previously.¹²

Study population and treatment

For this International Second IVIg dose (ISID) study, we identified those treated with a standard course of 2 g/kg IVIg over 2–5 consecutive days. As mEGOS has not been validated in young children, patients aged under 6 were excluded.¹¹ We excluded patients who had died or were lost to follow-up in the first 7 days from study entry, or who received a second IVIg course because of a reported treatment related fluctuation (TRF) observed by the local physician.¹³ We also excluded patients who participated in a randomised controlled study (Second Immunoglobulin Dose in GBS patients (SID-GBS)

INTRODUCTION

A standard course of intravenous immunoglobulin (IVIg, 2 g/kg in 2–5 days) shortens time to recovery in Guillain-Barré syndrome (GBS) when administered within the first 2 weeks.^{1–4} However, approximately 20% of patients are unable to walk independently at 6 months.⁵ Evidence-based treatment options to improve outcome are currently lacking.⁶ One small, uncontrolled series of 'treatment unresponsive' patients suggested that a second IVIg course was more effective than one course.⁷ In addition, patients with a large increment in serum IgG level after IVIg treatment recovered



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trial^{14 15} or Inhibition of Complement Activation in GBS (ICA-GBS) trial).¹⁶

Multiple imputation was used for patients with missing age (n=9/1300) or medical research council (MRC) sum score at week 1 (n=120/1300).¹⁷ Based on a standard set of five imputation samples, medians were calculated for age and MRC sum score. In this way, mEGOS could be calculated for all patients, using age, preceding diarrhoea and MRC sum score at week 1. We further identified patients with mEGOS 6–12 at 1 week who considered to have a poor prognosis (35% probability or higher of not being able to walk independently at 6 months).¹¹

IVIg groups

From the group of patients with poor prognosis treated with at least one IVIg course, we selected those treated with a second course of IVIg. Because of the observational nature of IGOS, the decision to administer two IVIg courses was made by the local treating investigators. As a result, the second IVIg course was not given at a standardised time point. In the analysis, we separated patients treated with a second IVIg course early (started within 2 weeks after start of the first IVIg course) from those treated late (started after 2 weeks but within 3–4 weeks after start of the first IVIg course and completed before the assessment of week 4). Patients who received one standard course of IVIg before the 4 week assessment were considered controls. Other additional treatments such as corticosteroids and plasma exchange (PE) were ignored.

Assessments

Demographic and clinical data including GBS disability score,^{18 19} MRC sum score,²⁰ sensory deficits, facial weakness, previous diarrhoea and clinical variants were collected at entry, and subsequently at week 1, 2 and 26 (GBS disability score, MRC sum score).¹² According to the IGOS protocol,¹² study entry should coincide with the first day of treatment, even if informed consent was obtained after start of treatment. Due to ethical regulations in some countries, study entry was set by the date of informed consent. Results of the first nerve conduction study were classified according to the criteria of Hadden and colleagues into demyelinating, axonal, inexcitable, equivocal or normal.²¹ Treatment information was collected regarding dates of start and end of treatment, treatment type (IVIg, PE, other), treatment regimen and side effects after IVIg.

Deterioration at the time of starting the second IVIg course was determined by worsening at least one MRC sum score point on the visits prior to and after the moment of starting the second IVIg course.

Study endpoints

The primary endpoint was improved functional outcome on the GBS disability scale after 4 weeks. Secondary endpoints were GBS disability score at 26 weeks, improvement of ≥ 1 score on the GBS disability scale at 4 and 26 weeks, median change in the MRC sum score at 4 and 26 weeks, being able to walk independently at 26 weeks, requiring ventilation at any time during follow-up, time admitted to the intensive care unit (ICU), time on a ventilator, GBS related mortality at 6 months, TRF, and complications (not further specified).

Statistical analysis

Statistical analyses were performed using SPSS software V.21.0 and V.24.0. Data were expressed as medians with IQR or as proportions. Mann-Whitney U tests were used to compare

continuous variables across two groups, and one-way ANOVA or Kruskal-Wallis tests (if variances differed significantly) were used to compare continuous variables across three groups. χ^2 or Fisher's exact tests were performed to compare proportions. Reported p-values were calculated between the three groups unless stated otherwise. A two-sided p-value < 0.05 was considered to be significant. Treatment effect on the GBS disability scale at 4 and 26 weeks was evaluated for the early and late second IVIg groups using multivariable ordinal regression analysis, adjusting for prognostic factors and disease severity (age, GBS disability score at entry and week 1, MRC sum score at entry and week 1, occurrence of diarrhoea, electrophysiological axonal or inexcitable pattern) and country of residence. The reported OR express the odds of having a better outcome (ie, a lower GBS disability score).

Sub-analysis: propensity score matching

We recognised that the non-randomised study design could have caused confounding by indication due to observed and unobserved confounders. To correct for the effect of confounders, we developed a multivariable regression model and performed a propensity score matched analysis. With this method, propensity scores for receiving treatment were calculated for each individual, given an individual's covariates.²² We calculated the propensity scores for each individual in the multivariable logistic regression model with independent variables: age, gender, time to enter the study, time to start first IVIg course, GBS disability score at entry and week 1, MRC sum score at week 1, GBS variant at entry, preceding diarrhoea and country of residence. Variables with missing values would result in a lower number of matched controls and were therefore not added in the model (eg, electrophysiological classification, deterioration or improvement at starting the second course). In our model, the calculated propensity scores expressed the probability of receiving a second IVIg course. The propensity score was subsequently used to match controls to patients in both the early and late second IVIg group (nearest neighbour matching 1:1 with a calliper of 0.1). After propensity score matching, we performed a new unadjusted ordinal regression analysis.

RESULTS

Patients

In January 2017, 1300 patients with a follow-up period of 6 months had been enrolled in IGOS. Seventy-one patients (5%) were excluded because of alternative diagnosis, 6 (0.5%) because of protocol violation, 34 (3%) because of young age and 29 (2%) because of insufficient data.

Of the remaining 1165 patients, 831 (71%) were initially treated with IVIg. Seventeen patients were lost to follow-up at the first week and seven died before 7 days after study entry, so that prognosis could be predicted in 807 patients based on the mEGOS. Poor prognosis (mEGOS 6–12) was predicted in 260 patients (32%), of whom 23 were excluded because they participated in a randomised controlled trial (RCT, SID-GBS trial 11; ICA-GBS trial 1) or because they received the second IVIg course because of a TRF (11). Ultimately, 237 patients with a poor prognosis fulfilled the entry criteria for this study (figure 1).

Control group

The primary endpoint of this study concerned improvement at 4 weeks. Therefore, the control group included the 199 patients treated with one IVIg course within the first 4 weeks from study entry irrespective of other treatments before or after 4 weeks. Of

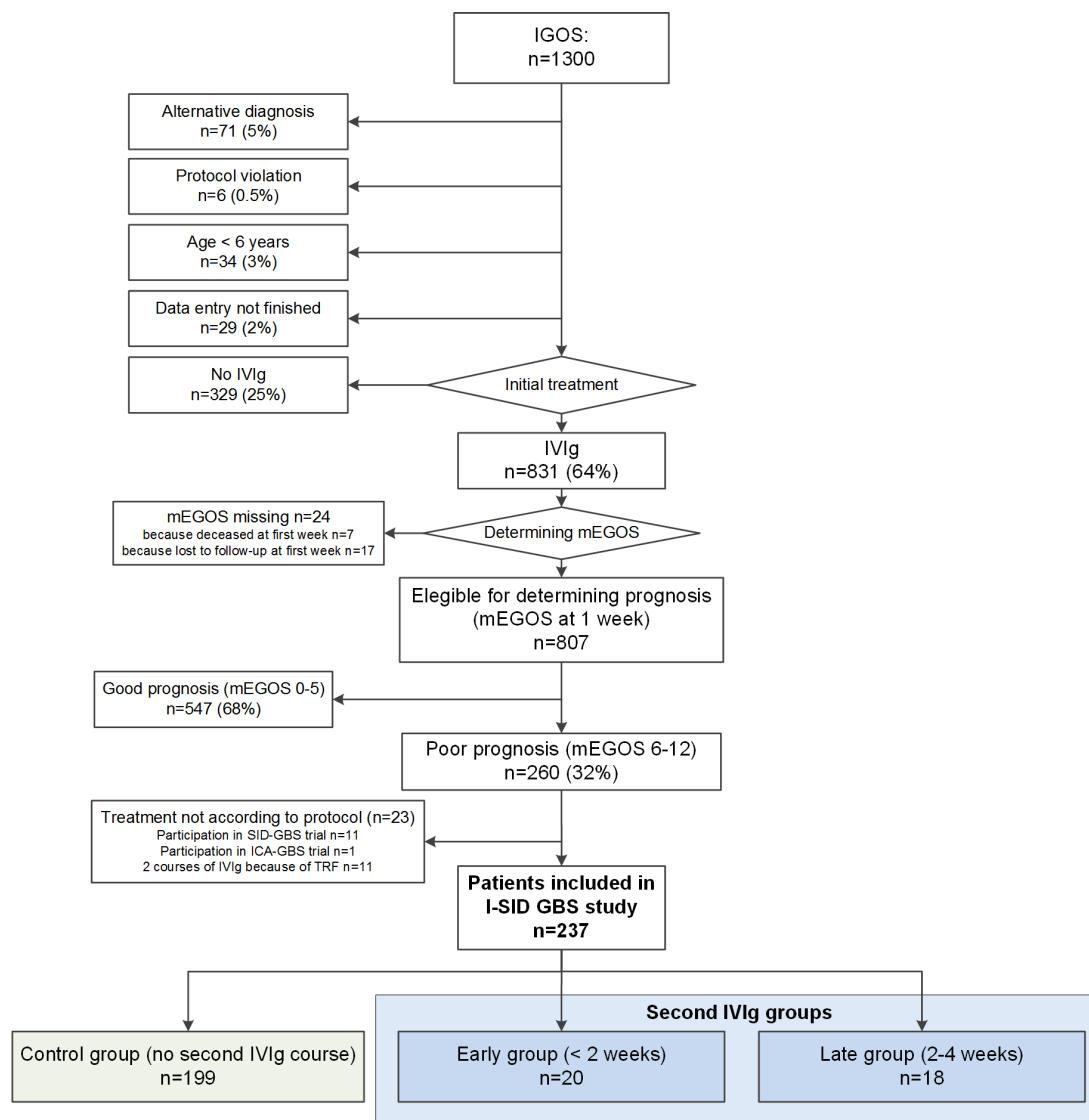


Figure 1 Patient selection for the I-SID study. GBS, Guillain-Barré Syndrome; ICA-GBS, Inhibition of Complement Activation in GBS; IGOS, International GBS Outcome Study; I-SID GBS, International Second Immunoglobulin Dose in GBS patients; IVIg, Intravenous immunoglobulin; mEGOS, modified Erasmus GBS Outcome Score; TRF, treatment related fluctuation.

the 199 patients, 160 (80%) received standard treatment only (1 IVIg course within 4 weeks of study entry), 31 patients were additionally treated with PE before or after 4 weeks, and six patients were treated with additional IVIg after 4 weeks. One additional patient received IVIg within 4 weeks, followed by IVIg after 4 weeks and was thereafter treated because of vasculitis. Another patient received IVIg and 7 PE sessions within 4 weeks and was after his GBS diagnosed with granulomatous polyangiitis.

Early second IVIg group

Twenty patients were treated with a second IVIg course that started within 14 days after start of the first IVIg course and were included in the 'early second IVIg group'. Sixteen (80%) were treated with only one additional IVIg course and four were treated with various combinations of IVIg and PE.

Late second IVIg group

Eighteen patients were treated with a second IVIg course two to 4 weeks after start of the first IVIg course and were included in the 'late second IVIg group'. Fourteen (78%) were treated with

only one additional IVIg course while four patients were treated with various combinations of IVIg and PE.

Data completeness

At week 4, the primary endpoint was available in 167/199 (84%) patients in the control group (eight patients lost to follow-up and 24 missed the visit). In both the early and the late second IVIg group one patient was lost to follow-up and one patient had a missed visit. Therefore, the primary endpoint was available in 90% (18/20 and 16/18) in the two IVIg groups.

Patient characteristics

At baseline, there were no significant differences between the three treatment groups regarding age, gender, MRC sum score at entry, sensory deficits, preceding diarrhoea or GBS variant (table 1). There were significant differences in the proportion of patients already ventilated at study entry in the early second IVIg group (n=9, 45%) and in the late second IVIg group (n=6, 33%) compared with the control group (n=36, 18%) (3-way p value, p=0.01).

Table 1 Demographic and clinical characteristics at entry and during disease course

	Control group (1x IVIg) n=199	Early second IVIg group (2x IVIg) n=20	Late second IVIg group (2x IVIg) n=18	P value among three groups*
Demographics				
Males, n (%)	109 (55)	12 (60)	12 (67)	0.58
Age, years, median (IQR)	59 (43–70)	65 (54–70)	59 (53–71)	0.54
Clinical features at entry				
Time from onset to study entry, days, median (IQR)	5 (3–8)	4 (2–8)	5 (2–8)	0.68
Time from onset to first IVIg course, days, median (IQR)	3 (2–6)	2 (1–3)	2 (1–5)	0.11
Antecedent diarrhoea, n (%)	73 (37)	4 (20)	5 (28)	0.27
Facial weakness, n (%)	71 (36)	8 (40)	9 (50)	0.47
MRC sum score, median (IQR)	32 (18–42)	27 (5–42)	30 (3–46)	0.56
Sensory deficits, n (%)	113 (57)	13 (65)	7 (39)	0.47
GBS variant, n (%)				
No	141 (71)	15 (75)	12 (67)	0.85
Pure motor	46 (23)	3 (15)	6 (33)	0.41
Miller Fisher (overlap)	10 (5)	2 (10)	0 (0)	0.37
Other	2 (1)	0 (0)	0 (0)	†
Clinical features after 1 week follow-up				
MRC sum score, median (IQR)	25 (8–35)	10 (0–26)	6 (1–32)	0.004‡§
mEGOS, median (IQR)	10 (8–11)	11 (9–11)	10 (8–11)	0.10
Clinical features at nadir				
MRC sum score, median (IQR)	21 (4–33)	4 (0–20)	2 (0–16)	<0.001‡§
GBS disability score, n, (%)				
Unable to run (2)	1 (1)	0 (0)	0 (0)	0.03‡
Unable to walk independently (3)	7 (4)	0 (0)	0 (0)	
Bedridden or chairbound (4)	107 (54)	4 (20)	6 (33)	
Ventilated (5)	84 (42)	16 (80)	12 (67)	
Electrophysiological classification, n (%)				
Demyelinating	87/154 (57)	9/12 (75)	9/17 (53)	†
Axonal	18/154 (12)	1/12 (8)	5/17 (29)	
Inexcitable	8/154 (5)	0 (0)	1/17 (6)	
Equivocal	40/154 (26)	2/12 (17)	2/17 (12)	
Normal	1/154 (1)	0 (0)	0 (0)	
Time until NCS, days, median (IQR)	6 (4–10)	2 (2–10)	7 (4–9)	0.52

*There were no significant differences between the early and late second IVIg group.

†Not calculated because of small patient numbers.

‡P-value < 0.05 for control group versus early second IVIg group.

§P-value < 0.05 for control group versus late second IVIg group.

GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin; mEGOS, modified Erasmus GBS Outcome Score; MRC, medical research council; NCS, nerve conduction study.

One week after study entry, patients in the early and late second IVIg group had significantly lower MRC sum scores (10, IQR 0–26, and 6, IQR 1–32) than controls (25, IQR 8–35) ($p=0.004$) and were thus more severely affected. This was also reflected by higher GBS disability scores (figure 2).

Patients in the control group were often already improving at least one point on the MRC sum score between the first to the second study week ($n=102$, 63%). However, patients in the second IVIg groups were often still deteriorating at least one point in MRC sum score at the time of starting their second IVIg course ($n=13$, 81% in the early group and $n=8$, 47% in the late group).

Primary endpoint

Treatment with a second IVIg course made no significant difference to the GBS disability score 4 weeks after study entry. The adjusted OR for a lower GBS disability score was 0.70 (95% CI 0.16 to 3.04) for the early second IVIg group, and 0.66 (95% CI 0.18 to 2.50) for the late group (figure 2, table 2).

Secondary endpoints

There was also no significant difference in the GBS disability score at 26 weeks. The adjusted OR for a lower GBS disability score was 0.89 for the early group (95% CI 0.22 to 3.53) and 0.40 (95% CI 0.10 to 1.62) for the late group (figure 2, table 2).

Fifty-one (31%) patients in the control group improved at least one point on the GBS disability scale 4 weeks after study entry, compared with only 3 (17%, $p=0.22$) of the early group and none ($p=0.01$) of the late group (table 3). At 26 weeks, 127 of 145 (88%) patients in the control group improved at least one point on the GBS disability scale compared with 12/16 (75%, $p=0.16$) in the early and only 4/11 (36%, $p<0.001$) in the late IVIg group (table 3).

In the control group, patients improved by a median of 4 points on the MRC sum score (IQR –8 to 12) from entry to 4 weeks. The MRC sum score decreased by two points (IQR –23 to 10) in the early group ($p=0.14$) and by four points (IQR –36 to 2) in the late group ($p<0.001$). After 26 weeks, the patients in the early second IVIg group improved more on the MRC sum

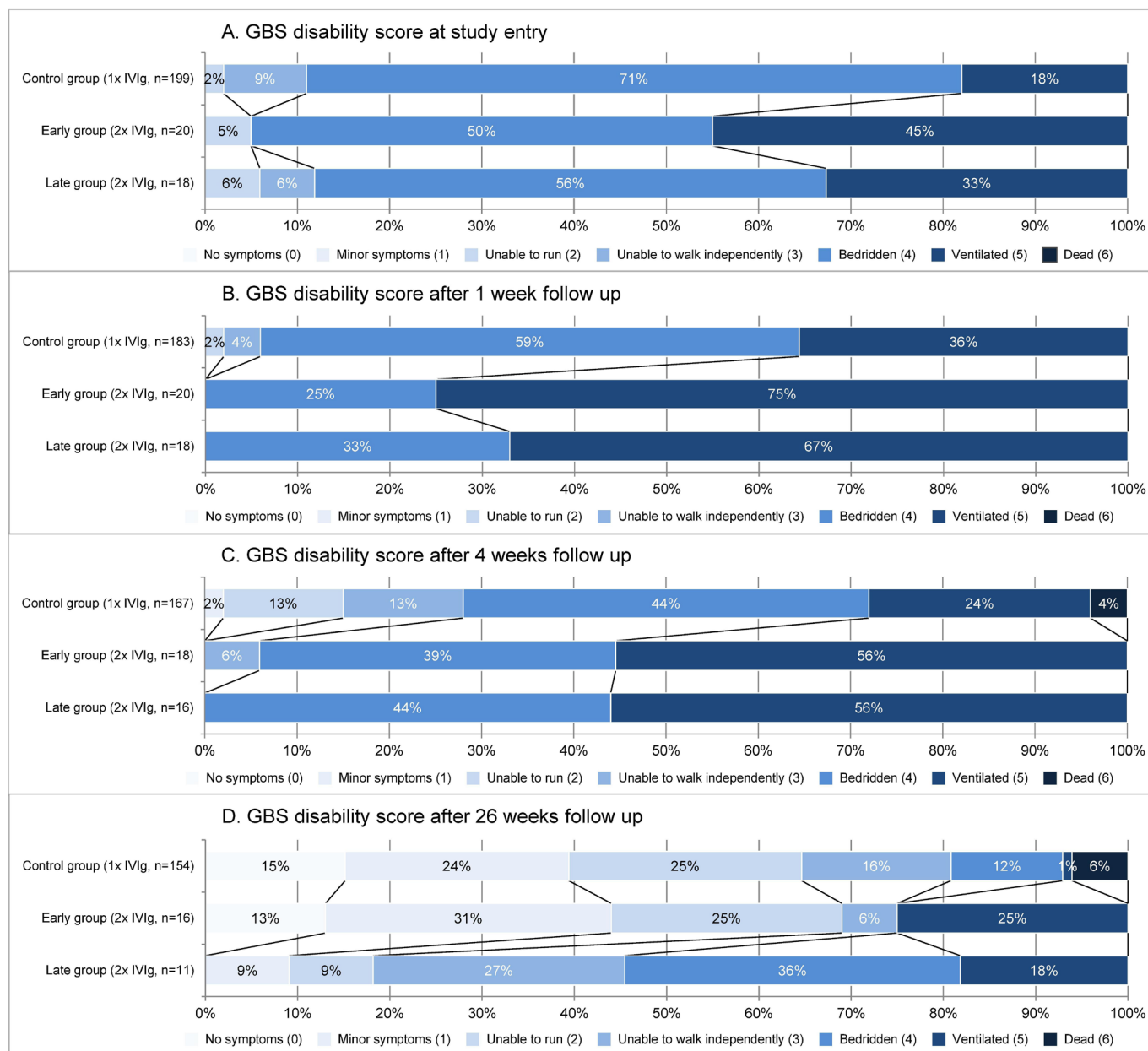


Figure 2 GBS disability score at study entry (A), 1 (B), 4 (C) and 26 weeks (D). GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin.

Table 2 ORs for a lower GBS disability score at 4 and 26 weeks

	N	Unadjusted OR (95% CI)	P value	N	Adjusted OR* (95% CI)	P value
Week 4:						
Treatment						
Control	167	Ref.		125	Ref.	
Early second IVIg	18	0.31 (0.12 to 0.78)	0.01	10	0.70 (0.16 to 3.04)	0.63
Late second IVIg	16	0.28 (0.11 to 0.76)	0.01	14	0.66 (0.18 to 2.50)	0.54
Week 26:						
Treatment						
Control	154	Ref.		105	Ref.	
Early second IVIg	16	0.98 (0.39 to 2.44)	0.97	8	0.89 (0.22 to 3.53)	0.87
Late second IVIg	11	0.23 (0.08 to 0.70)	0.01	8	0.40 (0.10 to 1.62)	0.40

*Adjusted for age, preceding diarrhoea, GBS disability score at entry and week 1, MRC sum score at entry and week 1, axonal or inexcitable NCS, country of residence. GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin; MRC, medical research council; NCS, nerve conduction study.

Table 3 Endpoints at 4 and 26 weeks

	Control group (1x IVIg) n=199	Early second IVIg group (2x IVIg) n=20	Late second IVIg group (2x IVIg) n=18	P value
Secondary endpoints				
Improving ≥ 1 score on GBS disability score, n (%) at:				
4 weeks	51/167 (31)	3/18 (17)	0 (0)	0.002*†
26 weeks	127/145 (88)	12/16 (75)	4/11 (36)	0.001*†
Able to walk independently, n (%) at:				
26 weeks	99/154 (64)	11/16 (69)	2/11 (18)	0.01*†‡
Change in MRC sum score (median, IQR) at:				
4 weeks	4 (–8 to 12)	–2 (–23 to 10)	–4 (–36 to 2)	<0.001
26 weeks	18 (12–32)	27 (3–48)	11 (–4 to 21)	0.06
Requiring ventilation, n (%)	88 (44)	16 (80)	12 (67)	0.003§
GBS related mortality at 6 months, n (%)	9/154 (6)	0 (0)	0 (0)	0.44
TRF¶, n (%)	4 (2)	2 (10)	1 (6)	0.11
Complications after first IVIg course, n (%)				
Headache	3 (2)	0 (0)	1 (6)	
Shivering	1 (1)	0 (0)	0 (0)	
Nausea/vomiting	1 (1)	0 (0)	0 (0)	
Hallucinations/psychosis	0 (0)	1 (5)	0 (0)	
Hypo/hypertension	1 (1)	0 (0)	0 (0)	
Complications after second IVIg course, n (%)				
Headache	0 (0)	0 (0)	1 (6)	

*P value derived from unadjusted binary logistic regression analysis.

†P value < 0.05 for control group versus late second IVIg group.

‡P value < 0.05 for early versus late second IVIg group.

§P value < 0.05 for control group versus early second IVIg group.

¶The second IVIg course in the early and late groups was not given because of the TRF.

GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin; MRC, medical research council; TRF, treatment related fluctuation.

score (median change 27, IQR 3–48) than the control group (18, IQR 12–32, $p=0.43$) and the late group (11, IQR –4 to 21, $p=0.05$).

Treatment related fluctuations were reported, but not treated with a second IVIg course, in 4 of the control patients, 2 of the early group patients and in 1 patient of the late group.

ICU admission was longest in patients after late treatment (64 days, IQR 33–144), whereas the controls (30 days, IQR 13–55) and patients in the early group (31 days, IQR 18–82) had similar ICU admission stays. Patients in the late group required longer ventilatory support (76 days, IQR 33–239) than the controls (27 days, IQR 15–61) and early group (55 days, IQR 26–220).

Serious complications of the second IVIg courses were not reported. Six control patients experienced headache, shivering, nausea or vomiting and/or blood pressure changes after their first IVIg course. In the early group, one patient had hallucinations/psychosis and in the late group, one patient experienced headache after the first IVIg course. Headache was reported in one patient after the second full IVIg course.

Nine patients in the control group died within 6 months (6%) while in the second IVIg groups, no patients died. Causes of death were: cardiac arrest as a consequence of multi-organ system failure ($n=2$), respiratory failure ($n=2$, of whom one chose to have ventilator support withdrawn after 2 weeks), pneumonia and sepsis ($n=2$) and other ($n=3$).

Sub-analysis: ordinal regression analysis after propensity score matching

Patients from the early and late second IVIg group were matched separately to controls by propensity scores. The unadjusted OR for a lower GBS disability score was calculated for the early and late group separately. The highest OR for a lower GBS disability

score was found at 26 weeks for the early group (1.26, 95% CI 0.35 to 4.60) but this was not statistically significant. The other ORs were also not in favour of a second IVIg course (table 4).

DISCUSSION

This is the first prospective study evaluating outcome after a second course of IVIg in patients with GBS. We did not observe a benefit from a second course of IVIg in GBS patients with a poor prognosis as defined by the mEGOS prognostic model. Severe complications such as haemolytic anaemia or thromboembolism were not reported after the second course of IVIg.

Table 4 ORs for a lower GBS disability score at 4 and 26 weeks after propensity score matching.

	N	Unadjusted OR (95% CI)	P value
Week 4:			
Treatment			
Control	18	Ref.	
Early second IVIg	18	0.74 (0.21 to 2.64)	0.64
Week 26:			
Treatment			
Control	16	Ref.	
Early second IVIg	16	1.26 (0.35 to 4.60)	0.73
Control	12	Ref.	
Late second IVIg	11	0.42 (0.09 to 1.90)	0.26

IVIg, intravenous immunoglobulin.

After 1 week, patients in the second IVIg groups were significantly more disabled (lower MRC sum scores and higher GBS disability scores) than the IVIg controls. These patients also were deteriorating more often at the start of their second IVIg course compared with the one IVIg course group (deteriorating at least one point on the MRC sum score: 13/16, 81% in the early group, 8/17, 47% in the late group). Conversely, patients treated with one IVIg course were often already improving when a second course was administered in the second IVIg groups (ie, 102/163, 63% improving from the first to the second IGOS study week, and 112/151, 74% improving from the second to the fourth IGOS study week). Continued deterioration was therefore the most likely reason for the treating physicians to start a second IVIg course, whereas improvement probably prevented starting a second course. The unbalanced disease severity likely caused confounding by indication because a poor neurological condition may have influenced the investigators' decision to initiate a second IVIg treatment but likely also resulted in a worse outcome. Despite correcting for disease severity in a multivariable ordinal regression model, the data did not show a beneficial effect from a second course of IVIg.

Duration of ICU stay and ventilation were secondary endpoints. These situations however also may have prompted the decision to administer a second course of IVIg; a higher proportion of patients who received a second IVIg course had longer ICU admission and required assisted ventilation. The median time on a ventilator was longer than the time admitted to the ICU in all groups because in some countries patients were discharged to rehabilitation centres with mechanical ventilation facilities.

In addition to observed confounding factors, unbalanced unobserved confounders likely played a role too. This is demonstrated by the difference between unadjusted and adjusted ORs. One of the unobserved confounders could be IgG or albumin levels.^{8,23} In this study we did not have data on IgG and serum albumin concentrations. Other unobserved confounders could have been insurance status, availability of IVIg, and other unknown patient, physician or hospital related factors. In our attempt to mitigate the effect of confounders, we conducted a secondary analysis in which we matched patients on propensity scores, defined as the probability of receiving an early or late second IVIg course. Even with this analysis, the data did not show positive ORs for a better outcome.

In order to prevent further nerve damage, treatment might be most effective in the early stage of GBS. In our study, only eight patients received a second IVIg course within 9 days after start of the first IVIg course, while the other patients received the second IVIg course later, possibly because they were in a poor neurological condition. Furthermore, 20% of the patients in all three IVIg groups were also treated with PE, or with more than two IVIg courses or combinations of PE and IVIg. Approximating the preferred analysis of a randomised controlled trial, we conducted an 'intention-to-treat' analysis. Therefore, we did not exclude patients treated with IVIg combined with other treatments and also not the two patients in the control group who later on were diagnosed with vasculitis and granulomatous polyangiitis. A large RCT showed that IVIg administered immediately after PE was not better than IVIg or PE alone.¹ No randomised trials have been performed to evaluate the effect of PE after IVIg. However, since PE removes IVIg, this sequence of treatment should logically be avoided, or used only at least 2 weeks after IVIg. By that stage however any treatment is likely to have only marginal effects as nerve damage has already occurred.⁶

We selected patients with a poor prognosis because we expected that these patients might benefit most from a second IVIg course. These patients have previously been identified to have a probability of 35% or greater of not being able to walk independently.¹¹ This does not mean that all patients with a high mEGOS score have poor outcome. The predictive value of the mEGOS has been validated recently in another cohort of 177 patients where a significant correlation was found between higher mEGOS and poor outcomes.²⁴

Next to the major limitation of the observational nature of this study, other limitations can be pointed out. First, the 4 week endpoint was chosen as the primary outcome because it corresponds to the primary endpoint in previous randomised controlled trials. However, it may be that this time point was not best suited for this observational study, especially in the late group, since the GBS disability score was usually recorded less than 1 week after the completion of the second IVIg course. Second, in ordinal regression analysis the treatment effect ideally should be the same across all cut-off values of the outcome scale (the proportional odds assumption), but in this study the treatment effect was not similar across the GBS disability scale (figure 2). However, it has been argued in the statistical literature that the proportional odds model is still valid when the proportional odds assumption is not met.²⁵ Lastly, despite starting with a large group of GBS patients and using multiple imputation to increase the number of eligible subjects, we ultimately had small numbers in the second IVIg groups (n=20 in the early group and n=18 in the late group).

In conclusion, the observational design of this large prospective multicentre international study introduced bias by observed and unobserved confounding factors. This study however reflects current daily practice in GBS patients with a poor prognosis, and showed no positive effect of a second IVIg course on functional outcome. The second IVIg course was often started late, and this was likely because of severe neurological impairment after a standard IVIg course. A positive effect of a second IVIg course cannot be ruled out but needs to be investigated further as is being done in the SID-GBS RCT.^{14,15}

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