Second intravenous immunoglobulin dose in patients with Guillain-Barré syndrome with poor prognosis (SID-GBS): a double-blind, randomised, placebo-controlled trial

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Summary

Background Treatment with one standard dose (2 g/kg) of intravenous immunoglobulin is insufficient in a proportion of patients with severe Guillain-Barré syndrome. Worldwide, around 25% of patients severely affected with the syndrome are given a second intravenous immunoglobulin dose (SID), although it has not been proven effective. We aimed to investigate whether a SID is effective in patients with Guillain-Barré syndrome with a predicted poor outcome.

Methods In this randomised, double-blind, placebo-controlled trial (SID-GBS), we included patients (≥12 years) with Guillain-Barré syndrome admitted to one of 59 participating hospitals in the Netherlands. Patients were included on the first day of standard intravenous immunoglobulin treatment (2 g/kg over 5 days). Only patients with a poor prognosis (score of ≥6) according to the modified Erasmus Guillain-Barré syndrome Outcome Score were randomly assigned, via block randomisation stratified by centre, to SID (2 g/kg over 5 days) or to placebo, 7–9 days after inclusion. Patients, outcome adjudicators, monitors, and the steering committee were masked to treatment allocation. The primary outcome measure was the Guillain-Barré syndrome disability score 4 weeks after inclusion. All patients in whom allocated trial medication was started were included in the modified intention-to-treat analysis. This study is registered with the Netherlands Trial Register, NTR 2224/NL2107.

Findings Between Feb 16, 2010, and June 5, 2018, 327 of 339 patients assessed for eligibility were included. 112 had a poor prognosis. Of those, 93 patients with a poor prognosis were included in the modified intention-to-treat analysis: 49 (53%) received SID and 44 (47%) received placebo. The adjusted common odds ratio for improvement on the Guillain-Barré syndrome disability score at 4 weeks was 1·4 (95% CI 0·6–3·3; p=0·45). Patients given SID had more serious adverse events (35% *vs* 16% in the first 30 days), including thromboembolic events, than those in the placebo group. Four patients died in the intervention group (13–24 weeks after randomisation).

Interpretation Our study does not provide evidence that patients with Guillain-Barré syndrome with a poor prognosis benefit from a second intravenous immunoglobulin course; moreover, it entails a risk of serious adverse events. Therefore, a second intravenous immunoglobulin course should not be considered for treatment of Guillain-Barre syndrome because of a poor prognosis. The results indicate the need for treatment trials with other immune modulators in patients severely affected by Guillain-Barré syndrome.

Funding Prinses Beatrix Spierfonds and Sanquin Plasma Products.

Introduction

Guillain-Barré syndrome is an immune-mediated polyradiculoneuropathy, which affects 0·81–1·89 per 100 000 people annually worldwide.[1] Guillain-Barré syndrome is usually a monophasic disease with rapidly progressive limb weakness.[2] The clinical severity, course, and outcome are variable.[1] Intravenous immunoglobulin and plasma exchange are proven effective treatments.[3,4] Even with standard intravenous immunoglobulin treatment, about 20% of patients remain unable to walk after 6 months. In 20–30% of patients, mechanical ventilation is needed, 3–7% die, and many have persistent residual complaints such as fatigue and pain.[5] Patients with a poor prognosis early in their disease course might gain particular benefit from additional treatment. A second intravenous immunoglobulin dose (SID), administered early in the course of disease, before severe or irreversible nerve damage has occurred, might be

Lancet Neurol 2021; 20: 275–83

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*A complete list of investigators in the SID-GBS trial is provided in the appendix (p 2)

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Research in context

Evidence before this study

A PubMed search for articles in English, published from database inception up until May 22, 2020, for "[Guillain-Barré syndrome], and [second IVIg course]", "[Guillain-Barré syndrome], and [repeated intravenous immunoglobulin]", and "[Guillain-Barré syndrome], and [second cycle immunoglobulin]" identified four case reports, two case series, and one observational study in which additional intravenous immunoglobulin treatment was investigated in patients with Guillain-Barré syndrome with a severe disease course. The case reports and case series (n=11) suggested additional benefit from a second intravenous immunoglobulin course. The observational study based on patients with Guillain-Barré syndrome enrolled in the international Guillain-Barré syndrome outcome study selected patients with a poor predicted outcome according to the modified Erasmus GBS Outcome Scale prognostic model. No difference in outcome was found between patients given one intravenous immunoglobulin course (n=199) or two intravenous immunoglobulin courses (n=38). None of these studies reported complications possibly attributable to the additional intravenous immunoglobulin treatment. Not all patients in these studies received an early second intravenous immunoglobulin course and publication bias could have played an important role in the positive findings.

Added value of this study

The SID-GBS trial is the first randomised, placebo-controlled, double-blind trial investigating the added value of a second intravenous immunoglobulin course in patients with Guillain-Barré syndrome with a poor predicted outcome, to our knowledge. The study showed that a second intravenous immunoglobulin course in these patients does not have a clinically meaningful benefit for recovery. All secondary endpoints did not differ between treatment groups. This trial was the first controlled study to show a possible harmful effect of a second intravenous immunoglobulin course.

Implications of all the available evidence

A second intravenous immunoglobulin course in patients with Guillain-Barré syndrome with a poor prognosis is not recommended. The results are based on the absence of evidence for a better outcome and on the higher frequency of serious adverse events, including severe thromboembolic complications. Although the absence of evidence does not equate to evidence of ineffectiveness, it is very unlikely that a second intravenous immunoglobulin course will have a clinically relevant positive effect.

beneficial, although there is scant evidence to support this approach.[6,7]

In current practice, about a quarter of patients with Guillain-Barré syndrome given intravenous immunoglobulin who show no clinical improvement are re-treated with intravenous immunoglobulin.[7] This practice could be based on results from a small uncontrolled case series of patients with severe Guillain-Barré syndrome and a phase 2 trial suggesting that a higher dose of intravenous immunoglobulin was more beneficial than a lower dose.[8–10] Another argument that repeated intravenous immunoglobulin doses might be effective comes from the observation that about 10% of patients with Guillain-Barré syndrome have a so-called treatment-related fluctuation, which seems to respond to a SID.[11] Additionally, patients have a variable increase in serum IgG concentration after a standard dose of intravenous immunoglobulin, and a low IgG increase is associated with poor outcome, indicating that these patients might benefit from additional intravenous immunoglobulin treatment.[12] However, intravenous immunoglobulin is costly; moreover uncommon severe side-effects might be more frequent when administered repeatedly. We aimed to evaluate the effect of SID in patients with Guillain-Barré syndrome with poor prognosis.

Methods

Study design and participants

We did a double-blind, randomised, placebo-controlled phase 3 trial (SID-GBS) in patients with Guillain-Barre syndrome with a poor prognosis. The protocol of this trial has been published.[13] Patients were included from 59 hospitals in the Netherlands (a list of participating centres and number of inclusions per centre is available in the appendix (p 17). Patients aged 12 years or older, diagnosed with Guillain-Barré syndrome, and with an indication for intravenous immunoglobulin treatment according to the treating neurologist, were potentially eligible for inclusion in the trial.[2] Full eligibility criteria are available in the appendix (p 18).

Patients were randomly allocated (1:1) to receive SID or placebo for 5 days, which was administered at 7–9 days after the start of the first standard intravenous immunoglobulin treatment (2 g/kg administered over 5 consecutive days). Interim monitoring was done after 36 randomisations.

All patients (poor and good prognosis) were included on the first day of their standard intravenous immunoglobulin treatment. We used the modified Erasmus GBS Outcome Scale (mEGOS) 7–9 days after start of the standard intravenous immunoglobulin dose to select patients with a poor prognosis.[6] Only patients with a poor prognosis were randomly assigned to SID or placebo. The mEGOS prognostic model ranges from 0 (best prognosis) to 12 (worst prognosis) and uses age, preceding diarrhoea, and the Medical Research Council (MRC) sumscore[14] as clinical predictors of outcome (appendix pp 9, 19).[6] In this trial, an mEGOS of six or more was used as the cutoff for poor prognosis. Using this cutoff, we expected to

select about 50% of the included patients for random assignment.

The trial was approved by the ethics committee of all participating centres, and all patients provided written informed consent before random assignment.

Randomisation and masking

A web-based computerised random number generator from an external party (Clinical Trial Centre Maastricht) allocated treatment in a 1:1 ratio by block randomisation (six patients per block with the block size unknown to local sites), stratified according to participating centre. Placebo (albumin) was matched to the study drug by volume (8 mL/kg) and fluid aspect (due to proteins in intravenous immunoglobulin and albumin, both are slightly foaming liquids). As the colour of intravenous immunoglobulin can differ between batches, the bag (ethylene vinyl acetate) containing the trial medication was concealed using aluminum foil and opaque connecting lines were used to mask study staff. Patients, outcome adjudicators, monitors, and the steering committee were masked to treatment allocation.

Procedures

Patients with a poor prognosis were randomly assigned to receive either SID (Nanogam 50 mg/mL, Sanquin Plasma Products, Amsterdam, Netherlands) or placebo (albumin 4%, pasteurised plasma protein solution until June, 2012, and Albuman 40 g/L from June, 2012, onwards, Sanquin Plasma Products) in a dose of 8 mL/kg, both for 5 days. Patients with a good prognosis (mEGOS 0–5) were not randomly assigned, but had otherwise the same follow-up and outcome parameters assessment as the randomly assigned participants. All patients underwent clinical assessments at the start of standard intravenous immunoglobulin treatment; at week 1 (randomisation); weeks 2 and 4 (primary endpoint); and weeks 8, 12, and 26 after start of standard intravenous immunoglobulin treatment. Adverse events were assessed at every study visit. At study entry, blood was collected and serum was stored for detection of antiganglioside antibodies, antibodies to cytomegalovirus, Epstein-Barr virus, hepatitis E, and *Campylobacter jejuni* using routine diagnostic assays.[15–18] Also IgG and albumin concentrations were measured in serial serum samples (baseline, 1, 2, 4, and 13 weeks). Nerve conduction studies were reviewed in the coordinating centre by two masked trial electrophysiologists (JD and SA) and classified according to the Hadden criteria.[19] All patients were given standard supportive care as recommended by guidelines, including low molecular weight heparin.[20]

Outcomes

The primary outcome was Guillain-Barré syndrome disability scale[21] score at 4 weeks after the start of standard intravenous immunoglobulin treatment. This disability scale is the most frequently used clinical outcome measure in Guillain-Barré syndrome trials. It is a seven-point scale ranging from 0 (no symptoms) to 6 (death).[4] Prespecified secondary outcomes were assessed at weeks 4, 8, 12, and 26, and comprised the Guillain-Barré syndrome disability scale,[21] improvement of at least one grade on the Guillain-Barré syndrome disability scale,[21] the MRC sumscore,[14] the Overall Neuropathy Limitations Scale,[22] the percentage of patients needing artificial ventilation, duration of artificial ventilation, intensive care admission and hospital admission, mortality, percentage of treatment-related fluctuations, and serum IgG concentrations at subsequent timepoints. Adverse events and serious adverse events were collected by treating physicians, according to the International Conference on Harmonization Good Clinical Practice guidelines, and compared between the randomised groups using descriptive statistics.

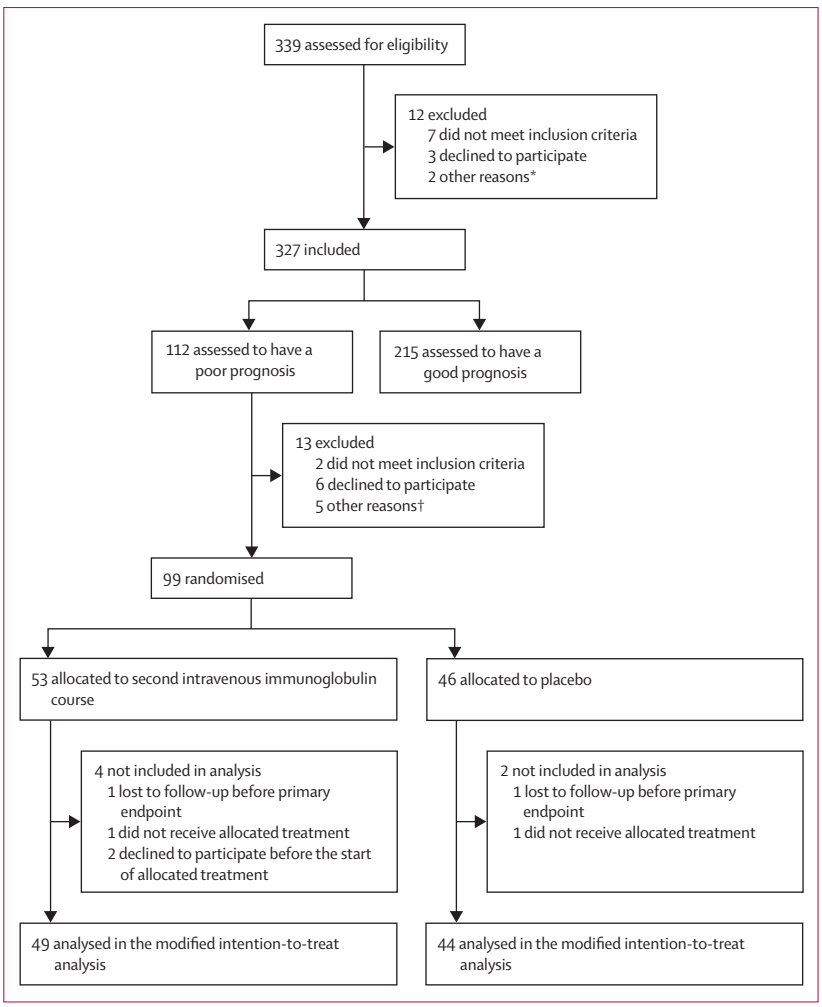

Figure 1: **Trial profile**

*Other refers to transfer to hospital abroad or pharmacy not prepared to deliver allocated treatment. †Other refers to receiving open second intravenous immunoglobulin dose before random assignment, erroneously marked as good prognosis (n=3), or case report files lost in participating hospital.

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See Online for appendix

	SID (n=49)	Placebo (n=44)
Age, years	66·0 (59·5–74·0)	59·0 (42·5–70·0)
Sex		
Women	18 (37%)	10 (23%)
Men	31 (63%)	34 (77%)
Preceding diarrhoea*	24 (49%)	14 (32%)
Disability score at randomisation		
3	1 (2%)	1 (2%)
4	28 (57%)	23 (52%)
5	20 (41%)	20 (45%)
MRC sumscore at randomisation, 0–60	23 (6–38)	26 (12–35)
Nerve conduction studies†		
Demyelinating	31 (63%)	29 (66%)
Axonal	2 (4%)	2 (5%)
Equivocal	7 (14%)	4 (9%)
Inexcitable	7 (14%)	4 (9%)
Not performed or unjudgable	2 (4%)	5 (11%)
Positive *Campylobacter jejuni* serology‡	16 (33%)	10/42 (24%)
Antiganglioside IgM or IgG antibodies		
GM1	15/48 (31%)	11/42 (26%)
GD1a	5/48 (10%)	4/42 (10%)
Mean serum delta IgG concentration, g/L§	16·1 (95% CI 13·6–18·5)	18·4 (95% CI 15·7–21·1)
Mean serum albumin concentration after intravenous immunoglobulin, g/dL¶	32·5 (95% CI 30·7–34·3)	35·1 (95% CI 33·5–36·7)

Data are median (IQR), n (%), or n/N (%), unless specified. SID=second intravenous immunoglobulin dose. MRC=Medical Research Council. *Diarrhoea in the 4 weeks preceding the onset of weakness. †According to the Hadden criteria.[19] ‡Data were missing for two patients in the placebo group. §Value 1 week after start of the first standard intravenous immunoglobulin dose: baseline (pre-treatment) or, when missing, 3 months after intravenous immunoglobulin treatment. ¶Data were missing for five patients in the intervention group and five patients in the control group.

Table 1: **Baseline characteristics**

Statistical analysis

We assumed that a 20% difference in the proportion of patients improving at least one grade on the Guillain-Barré syndrome disability scale between the patients with and without SID treatment 4 weeks after the start of standard intravenous immunoglobulin treatment would be clinically relevant. Without covariate adjustment and ordinal outcome analysis, we needed to randomly assign 145 patients with a poor prognosis (α=0·05, power 0·80) to detect this difference. We expected covariate adjustment and ordinal outcome analysis to result in a reduction in required sample size of 40–50%.[23] This expectation reduced the required sample size to between 73 and 88 patients.[13]

The primary analysis was modified intention to treat, in which all randomly assigned patients in whom allocated trial medication was started were included. The primary efficacy outcome was estimated with a proportional odds regression analysis.[24,25] For both primary and secondary endpoints, prespecified covariate adjustment was done to adjust for variation in baseline prognostic risk between patients. We adjusted for age, preceding diarrhoea, and MRC sumscore at randomisation.[13,26] This adjustment resulted in an adjusted common odds ratio for the effect of treatment with a 95% CI and corresponding p value. A two-tailed p value of less than 0·05 was considered statistically significant. Multiple imputation was applied to account for missing values in covariates and secondary endpoints; the primary endpoint was not imputed. There was no adjustment for multiple comparisons of secondary outcomes and these are presented as point estimates with unadjusted 95% CIs, from which no inferences can be made. Treatment-effect modification was explored in prespecified subgroups of patients as defined in the appendix (p 7). A trial data safety and monitoring board overlooked the trial and interim monitoring was done after 36 randomisations. This study is registered with the Netherlands Trial Register, NTR 2224/NL2107 and the statistical analysis plan was published here before unblinding the trial data. Analyses were done using R Studio version 3.6.1.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Feb 16, 2010, and June 5, 2018, 327 of 339 patients assessed for eligibility with Guillain-Barré syndrome were included (figure 1). 12 were excluded before mEGOS could be determined at days 7–9 (figure 1). 215 had a good prognosis (mEGOS <6), and 112 had a poor prognosis (mEGOS ≥6). 13 (12%) of the 112 patients with a poor prognosis were excluded before random assignment (mainly because of withdrawal of consent). Of the 99 randomly assigned patients, 53 (54%) were assigned to the SID group and 46 (46%) to the placebo group. Six patients were excluded after random assignment: two declined to participate before the start of allocated treatment, two patients did not receive the allocated treatment, and two patients were lost to follow-up shortly after randomisation when it became clear that they had an alternative diagnosis (one case of eosinophilic vasculitis in the placebo group and one case of myelopathy in the SID group). Of these patients, four had been assigned to SID and two had been assigned to placebo (figure 1). In the modified intention-to-treat analysis, 49 (53%) patients received SID and 44 (47%) received placebo.

Almost all patients who had been randomly assigned had severe weakness (as assessed with the MRC sumscore and Guillain-Barré syndrome disability score) and 85% were still deteriorating at 1 week according to the MRC sumscore, despite a standard intravenous immunoglobulin course (appendix pp 14–16).

Predictors of poor outcome were not evenly distributed between the two groups. Typically, patients in the SID group were older and had preceding diarrhoea more commonly than those in the placebo group (table 1, appendix p 12). Prespecified covariate adjustment was done for known prognostic factors.

Data for the primary outcome were complete (table 2). The adjusted common odds ratio for improvement on the Guillain-Barré syndrome disability score at 4 weeks was 1·4 (95% CI 0·6–3·3; p=0·45; figure 2, table 2). The unadjusted common odds ratio was 1·3 (95% CI 0·6–3·3). There was no evidence of a difference between treatment groups for any of the secondary outcomes. Guillain-Barré syndrome disability scores at weeks 8, 12, and 26 did not differ between groups (appendix p 16). Additionally, the probability of improving one grade or more on the Guillain-Barré syndrome disability scale at four different timepoints did not differ between groups. The MRC sumscore and Overall Neuropathy Limitations Scale were not different between groups at weeks 4, 8, 12, and 26 (appendix pp 14–15). Duration of hospital admission, intensive care unit admission, and mechanical ventilation were not different between groups (table 2, appendix p 11). Outcomes in the prespecified subgroups did not differ between treatment groups (figure 3). Patients with a good prognosis (n=208, seven excluded) had a median Guillain-Barré syndrome disability score of 2 (IQR 2–3) at 4 weeks, 1 (1–2) at 12 weeks, and 1 (0–2) at 26 weeks, indicating a generally good outcome in this group.

Four patients died during the trial, all of whom were assigned to SID. The deaths included a 59-year-old man who was previously healthy before developing Guillain-Barré syndrome, who died 16 weeks after random assignment due to asystole that was deemed possibly related to a serious adverse event (acute coronary syndrome), which occurred 4 days after administration of SID. An 82-year-old woman died 13 weeks after randomisation due to discontinuation of artificial ventilation at the request of the patient, after no signs of improvement, multiple complications, and severe pain. A 72-year-old woman died 21 weeks after randomisation from a cardiac cause in a nursing home. An 81-year-old woman died 24 weeks after randomisation, because of discontinuation of artificial ventilation at the request of the patient after no signs of improvement, and multiple complications. Serious adverse events, including thromboembolic events, occurred more often in the SID group than the placebo group (51% *vs* 23%, table 3, appendix p 12). Trial medication was not completed in two cases due to adverse events (ophthalmoplegia due to pituitary adenoma after placebo and severe skin rash after SID). From 2015 onward, randomly assigned patients (24 [26%] of 93) were tested for haemolytic anaemia after a protocol amendment based on a report about this possible adverse event in high-dose intravenous immunoglobulin treatment, but this adverse event was not seen in our trial.[27]

In the SID group, serum IgG was maintained at a high concentration longer than in the placebo group (median 34 g/L [IQR 30–43] *vs* 17 g/L [16–20] at 2 weeks after start of the standard intravenous immunoglobulin dose; appendix p 13). Median serum IgG at 4 weeks was still higher in the SID group than in the placebo group (median 19 g/L [IQR 16–22] *vs* 15 g/L [12–18]), but serum IgG concentrations were similar in both groups after 12 weeks.

We compared IgG concentrations in association with thromboembolic events, and found that patients with thromboembolic events did not have higher IgG concentrations after one standard course of intravenous immunoglobulin (mean IgG 26 g/L compared with 30 g/L in patients without thromboembolic events) or after SID (mean IgG 29 g/L compared with 37 g/L in patients without thromboembolic events).

	SID (n=49)	Placebo (n=44)	Adjusted common odds ratio (95% CI)
Primary outcome			
Disability score at 4 weeks	4 (4–5)	4 (4–5)	1·4 (0·6 to 3·3)
Secondary outcomes			
Disability score at 8 weeks	4 (3–4)	4 (2–4)	1·5 (0·7 to 3·3)
Disability score at 12 weeks	3 (2–3)	3 (2–3)	2·1 (0·9 to 4·6)
Disability score at 26 weeks	2 (1–4)	2 (1–3)	1·0 (0·5 to 2·2)
Disability score improvement (≥1 point)			
4 weeks	18 (37%)	12 (27%)	1·8 (0·6 to 5·3)
8 weeks	27 (55%)	26 (59%)	1·0 (0·4 to 2·5)
12 weeks	36 (73%)	34 (77%)	1·7 (0·5 to 5·4)
26 weeks	40 (82%)	41 (93%)	0·4 (0·1 to 2·6)
ONLS score			
4 weeks	10 (8–12)	10 (7–12)	1·2 (0·5 to 2·6)
8 weeks	8 (6–10)	9 (4–11)	0·9 (0·4 to 1·9)
12 weeks	6 (3–9)	7 (2–10)	1·8 (0·8 to 3·7)
26 weeks	3 (1–7)	3 (1–5)	0·9 (0·4 to 1·9)
Mechanical ventilation	30 (61%)	25 (57%)	1·3 (0·5 to 3·3)
Treatment related fluctuation	3 (6%)	5 (11%)	0·6 (0·1 to 2·7)
Mean MRC sumscore			
4 weeks	32 (26–37)	30 (25–36)	1·3 (–1·6 to 4·1)*
8 weeks	37 (32–43)	37 (32–42)	1·2 (–1·9 to 4·3)*
12 weeks	40 (35–46)	43 (38–48)	–0·1 (–3·2 to 3·0)*
26 weeks	46 (41–52)	51 (47–55)	–2·0 (-4·8 to 0·8)*
Duration of mechanical ventilation, days	26 (12–58)	43 (9–80)	NA
Duration of intensive care unit admission, days	23 (8–55)	25 (4–77)	NA
Duration of hospital admission, days	39 (21–67)	30 (21–73)	NA

Data are median (IQR), n (%), or mean (95% CI) unless specified. SID=second intravenous immunoglobulin dose. NA=not analysed as the assumptions of the linear regression model were not met due to non-normal distributions of the outcome. ONLS=Overall Neuropathy Limitations Scale. MRC=Medical Research Council. *β coefficient from linear regression presented here.

Table 2: **Primary and secondary endpoints**

Discussion

This randomised trial did not show a significant clinical benefit of SID in selected patients with Guillain-Barré syndrome who had a predicted poor outcome after a first course of intravenous immunoglobulin. These patients

Figure 2: **Guillain-Barré syndrome disability score at 4 weeks in the modified intention-to-treat population**

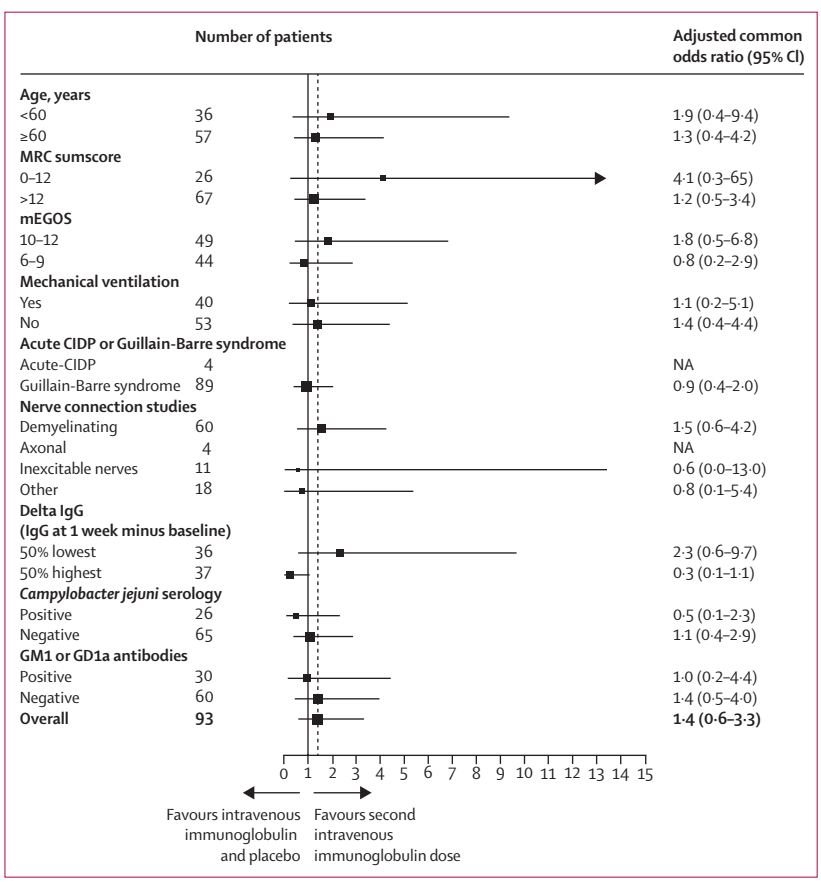

Figure 3: **Subgroup analyses**
Treatment effect in prespecified subgroup analyses. The outcome is improvement on the Guillain-Barré syndrome disability score at 4 weeks after inclusion (using proportional odds analysis, after covariate adjustment for mEGOS at 1 week). Each dot represents the adjusted common odds ratio, the size of the dot represents the number of patients in each subgroup, and the line represents the 95% CI. mEGOS=modified Erasmus GBS Outcome Scale. NA=not applicable. CIDP=chronic inflammatory demyelinating polyneuropathy. MRC=Medical Research Council.

almost all continued to deteriorate at 1 week after the first intravenous immunoglobulin course, and were in a poor neurological condition based on the MRC sumscore and Guillain-Barré syndrome disability score. Our results complement earlier studies, which found that additional immunotherapy (ie, either intravenous immunoglobulin after plasma exchange, six instead of four cycles of plasma exchange, or intravenous methylprednisolone with intravenous immunoglobulin) in the general Guillain-Barré syndrome population was not beneficial.[28–31] We believe our results can be generalised to the entire Guillain-Barré syndrome population even though we studied SID only in those with a poor prognosis.

One of the arguments that suggests a second series of intravenous immunoglobulin might be effective was the observation that a larger increase in serum IgG concentration after intravenous immunoglobulin treatment was related to a more substantial recovery.[12,13] Our trial showed that SID is able to increase the serum IgG concentration further and for a prolonged period of time than controls (appendix p 13), but this effect did not improve outcome. It might be that a relatively small rise in serum IgG after standard intravenous immunoglobulin treatment is an indicator for disease severity or more rapid intravenous immunoglobulin catabolism, rather than a target for therapy. It seems probable that intravenous immunoglobulin in Guillain-Barré syndrome is predominantly effective very early in the course of disease and that prolonging a high serum IgG concentration provides no additional benefit. This hypothesis could explain both the results of the previous study, in which a higher delta IgG was related to a better outcome than a lower delta IgG,[12] and the results of the current trial. Further research into the mechanisms of the treatment-modifying effect of IgG in Guillain-Barré syndrome is needed.

Another possible reason for not finding a positive effect of a SID could be that the included patients had too severe disease. Too much axonal damage might have already occured at the time of SID administration to find a difference between the groups. However, there was no suggestion of a positive effect of a SID in the subgroup of patients predicted to have a less severe outcome. Instead of repeating the standard dose, doubling the initial intravenous immunoglobulin dose could have resulted in better outcomes, but even more serious adverse events might have occurred as a consequence.

Patients who were given SID had more serious adverse events than those who were given a single intravenous immunoglobulin dose and placebo. Thromboembolic events were reported more often in patients who were given SID than in those who were given placebo. Thromboembolic events are a well known, rare, side-effect of

intravenous immunoglobulin, and their mechanism is thought to be due to a dose-dependent increase of plasma viscosity.[32] For this reason, known pre-existing vascular risk factors were a contraindication for randomisation in this trial (appendix p 18). However, other factors such as immobility, dehydration, leucocytosis, and coexisting inflammation can also cause a critical increase of plasma viscosity causing this serious adverse event. Patients with thromboembolic events did not have higher IgG concentrations after one standard course of intravenous immunoglobulin or after SID when compared with patients without these events, and therefore the administration of a second intravenous immunoglobulin course rather than the serum IgG concentration only might be related to these serious adverse events.

Our trial has several limitations. First, the sample size was relatively small, and the estimated odds ratio of 1·45 had wide CIs. However, we believe that our results are valid as the main trial result is the same using modified intention-to-treat or full intention-to-treat analyses; covariate adjustment as prespecified in the statistical analysis plan and protocol did not change the interpretation of the trial; there were no differences between treatment groups for any of the secondary endpoints; and we did not find differences in the subgroup analysis. Although a larger sample size would have increased the statistical power, the trial was powered to find a large treatment effect to improve treatment for this group of severely affected patients, considering that smaller effects would not be clinically meaningful.

Second, some of the baseline variables were unbalanced between groups even though the patients were randomly assigned, which could have affected the outcome. Both age and preceding diarrhoea are known prognostic factors, and correction for these factors (together with baseline MRC sumscore) using covariate adjustment was prespecified in the protocol. Covariate adjustment did not change the interpretation of the trial, as the unadjusted and adjusted common odds ratios were similar.[25,26]

Third, acute-onset chronic inflammatory demyelinating polyneuropathy (CIDP) was diagnosed in four patients during follow-up (two in each group), which is consistent with the frequency reported in the literature in general in trials for the syndrome.[11] Patients with acute-onset CIDP or with a treatment related fluctuation were given additional intravenous immunoglobulin in the trial (according to established guidelines).[11] These patients were retained in the main analysis; their exclusion did not affect the results of the trial in a prespecified subgroup analysis. The results of the trial should not change treatment practice of patients with acute-onset CIDP or with treatment related fluctuations.

Fourth, in two patients, the diagnosis was changed (eosinophilic vasculitis in the placebo group and myelopathy in the SID group) shortly after random assignment and initiation of trial medication. Once the alternative diagnosis was made, follow-up stopped, and primary endpoint analysis was not possible. A full intention-to-treat analysis (n=96, three missing endpoints) resulted in an adjusted common odds ratio of 1·3 (95% CI 0·6–3·1), which was not different from the modified intention-to-treat analysis.

	SID (n=49)	Placebo (n=44)
Serious adverse events*		
Any serious adverse event during study (excluding deaths)†	25 (51%)	10 (23%)
Any serious adverse event in the first 30 days (excluding deaths)	17 (35%)	7 (16%)
Coronary ischaemia	1 (2%)	1 (2%)
Asystole	2 (4%)	0
Transient ischaemic attack (multiple)	1 (2%)	0
Pulmonary embolism	2 (4%)	0
Radial artery thrombosis	1 (2%)	0
Renal insufficiency	1 (2%)	1 (2%)
Pneumonia	12 (24%)	7 (16%)
Other infection	2 (4%)	1 (2%)
Other serious complications‡	8 (16%)	3 (7%)
Other possible related complications§		
Haemolytic anaemia	0	0
Blood transfusion¶	3 (6%)	0

Data are n (%). SID=second intravenous immunoglobulin dose. *Only first events of a certain type are listed. Patients having multiple events of one type were counted once. †Odds ratio 3·54 (95% CI 1·44–8·72); p=0·0050. ‡See appendix (p 21). §Prospectively collected from 2015 onward (24 of 93 patients). ¶For various reasons other than haemolytic anaemia.

Table 3: **Safety measures and serious adverse events**

Lastly, our trial had an inclusion period of more than 8 years. This long inclusion period was largely due to the rarity of Guillain-Barré syndrome, and only patients with a poor prognosis were randomly assigned. However, immune treatment of Guillain-Barré syndrome in the Netherlands has not changed over the past 8 years, so we expect that the population recruited in this trial was given the same treatments, despite the long recruitment period.

In conclusion, we found no significant clinical benefit of a second intravenous immunoglobulin course administered shortly after the first standard intravenous immunoglobulin dose in patients with Guillain-Barré syndrome with poor prognosis. Additionally, the group given a second series of intravenous immunoglobulin had more serious adverse events than those given placebo. When looking for better treatments for Guillain-Barré syndrome, we should consider agents acting through a different mechanism than intravenous immunoglobulin, including complement inhibitors (NCT04035135) and IgG degrading enzymes (NCT03943589).

Contributors

CW was responsible for study conception, design, data acquisition, analysis, access and verification of the data, and interpretation and drafting of the manuscript. BCJ and PAvD were responsible for study conception, design, supervision, data acquisition, access and verification

of the data, and interpretation and drafting of the manuscript. HFL was responsible for study conception, design, access and verification of the data, analysis and interpretation, and drafting of the manuscript. EWS was responsible for study conception, design, and interpretation and drafting of the manuscript. RACH and DRC were responsible for study conception, design, supervision, and interpretation and drafting of the manuscript. All other authors were responsible for data acquisition and for revision of the manuscript. All authors vouch for the fidelity of trial conduct to the protocol, accuracy of outcome reporting, and of adverse events. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

BCJ reports grants from Baxalta, Grifols, CSL-Behring, Annexon, Prinses-Beatrix Spierfonds, Guillain-Barré syndrome/chronic inflammatory demyelinating polyneuropathy (GBS/CIDP) Foundation International, Hansa Biopharma, and EU's Horizon 2020, outside the submitted work. AYD declares that her host institution, the Erasmus MC, pays her salary with a fund from Annexon Biosciences (January, 2017), a pharmaceutical company that develops complement inhibitors for Guillain-Barré syndrome. Neither her PhD research nor her employment is contingent on this funding, and AYD has no control over the use of the funds. AYD has also received an honorarium for a lecture from CSL Behring (November, 2018). The money was paid directly to the Erasmus MC and AYD did not financially benefit from this honorarium. KK reports grants from Baxalta now part of Shire/Takeda, outside the submitted work. RH reports grants from Grifols, and GBS/CIDP Foundation International, outside the submitted work. AJvdK reports a grant from CSL Behring, outside the submitted work. FE reports grants from CSL Behring, Kedrion, Terumo BCT, and Takeda Pharmaceutical Company, outside the submitted work. Grants were paid to their institution and were used for investigator-initiated studies within INCbase, an international CIDP registry. He also received consultancy fees from UCB pharma, paid to his institution, outside the submitted work. CGF reports grants from EU's Horizon 2020 research and innovation programme, Marie Sklodowska-Curie grant for PAIN-Net, Molecule-to-man pain network (grant number 721841), Prinses Beatrix Spierfonds, Grifols, and Lamepro for a trial on intravenous immunoglobulin in small fibre neuropathy, was a member on steering committees and an advisory board for studies in small fibre neuropathy of Biogen/Convergence and Vertex, outside the submitted work. ISJM reports grants from Talecris Talents program, GBS/CIDP Foundation International and FP7 EU program, outside the submitted work; Furthermore, a research foundation at the University of Maastricht received honoraria on behalf of him for participation in steering committees of the Talecris Immune Globulin Intravenous For Chronic Inflammatory Demyelinating Polyneuropathy Study, Commonwealth Serum Laboratories, Behring, Octapharma, LFB, Novartis, Union Chimique Belge, outside the submitted work. UAB reports financial compensation for costs made to include patients in a trial from Novartis, outside the submitted work. RACH reports personal fees from LFB, Hansa Biopharma, and Sanofi, outside the submitted work and is a medical patron of GAIN. DRC reports consulting for Amgen, Annexon Biosciences, argenx SE, Biotest Pharmaceuticals, Cigna Health Management, CSL Behring, CytomX Therapeutics, Grifols, New Enterprise Associates, Octapharma, Pfizer, Pharnext, Polyneuron Pharmaceuticals, Seattle Genetics, Syntimmune, and UCB. DRC was on the Data Safety Monitoring Board for the following: Alnylam Pharmaceuticals, PledPharma, Momenta Pharma, Hansa Medical, and Mitsubishi Tanabe Pharma Corporation. DRC was involved with technology licensing for AstraZeneca Pharmaceuticals, LP Pharmaceuticals (Xiamen), Genentech, Levicept, Seattle Genetics, Merrimack Pharmaceuticals, and Disarm Therapeutics, outside the submitted work. PAvD reports grants from Sanquin Blood Supply and Prinses Beatrix Spierfonds, during the conduct of the study; and grants from Grifols, Takeda, Annexion, Argenx, Commonwealth Serum Laboratories, Octapharma, and Hansa, outside the submitted work. All grants were paid to the institution and used for investigator-initiated studies. All other authors declare no competing interests.

Data sharing

In compliance with the General Data Protection Regulation, source data are not available for other researchers as no patient approval has been obtained for sharing coded data. Information about analytic methods, syntax, and output files of statistical analyses will be made available by the corresponding author upon reasonable request.

Acknowledgments

We thank the following people for their help and advice during the conduct of the SID-GBS trial:
Data monitoring and safety committee: Chair: DWJ Dippel; Member: RQ Hintzen; Independent statistician: SE Hoeks, all from Erasmus MC University Medical Center, Rotterdam, Netherlands.
Trial coordinator: M van Woerkom, Erasmus MC University Medical Center, Rotterdam, Netherlands.
Laboratory investigations: AP Tio-Gillen, W van Rijs; Department of Immunology, Erasmus MC University Medical Center, Rotterdam, Netherlands. S Scherbeijn, AA van der Eijk, Department of Virology, Erasmus MC University Medical Center, Rotterdam, Netherlands; M de Waart, CRB Ramakers, Department of Clinical Chemistry, Erasmus MC University Medical Center, Rotterdam, Netherlands. M Maas, M Batstra, P Herbrink, Department of Microbiology, Reinier de Graaf Hospital, Delft, Netherlands.
Handling trial medication and drug accountability: M Zoetekouw–Bakker; The Medical Department, Sanquin Plasma Products, Amsterdam, Netherlands.

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