Second IVIg Course in Guillain-Barré Syndrome patients with poor prognosis (SID-GBS trial): protocol for a double-blind randomized, placebo-controlled clinical trial.

Christa Walgaard[1], Bart C. Jacobs[1,2], Hester F. Lingsma[3], Ewout W. Steyerberg[3,4], David R. Cornblath[5], Pieter A. van Doorn[1], and the Dutch GBS study group.

Department of Neurology[1], Immunology[2], and Public Health[3], Erasmus MC University Medical Center Rotterdam, The Netherlands. Department of Biomedical Data Sciences[4], LUMC, Leiden, The Netherlands. Department of Neurology[5], Johns Hopkins University, Baltimore, MD, USA.

Corresponding author:

Prof. Pieter A. van Doorn, Department of Neurology, Erasmus MC University Medical center. P.O. Box 2040, 3000 CA Rotterdam, The Netherlands, Tel: +(31)10-703-3780, Fax. +(31)10-704-4727, E-mail: p.a.vandoorn@erasmusmc.nl

Abstract

Rationale: One course of intravenous immunoglobulins (IVIg) of 2 g/kg is standard treatment in Guillain-Barré syndrome (GBS) patients unable to walk independently. Despite treatment some patients recover poorly, in part related to rapid consumption of IVIg, indicating that they may benefit from a second course of IVIg.

Objective: To determine whether a second course of IVIg, administered one week after start of the first course in patients with GBS and predicted poor outcome improves functional outcome on the GBS disability scale after 4 weeks. Secondary outcome measures include adverse events, MRC sumscore and GBS disability score after 8, 12 and 26 weeks, length of hospital and ICU admission, mortality and changes in serum IgG levels.

Study design:

GBS patients of 12 years and older with a poor prognosis, based on the modified Erasmus GBS Outcome Score (mEGOS) at one week after start of the first IVIg course are eligible for randomization in this double-blind, placebo-controlled (IVIg or albumin) clinical trial.

Conclusion: This study will determine if a second course of IVIg administered in the acute phase of the disease is safe, feasible and effective in patients with GBS and a poor prognosis.

Trial registration: This Dutch trial is registered prospectively as NTR 2224 in the Netherlands National Trial Register (NTR) which is the Primary Registry in the WHO Registry Network for the Netherlands.

Keywords: Guillain-Barré syndrome, protocol, trial, IVIg, treatment

Introduction

Guillain-Barré syndrome (GBS) is an immune-mediated polyradiculoneuropathy, and the most frequent cause of acute neuromuscular weakness affecting 0.81 to 1.89 persons per 100,000 per year worldwide (*Sejvar, et al., 2011; Willison, et al., 2016*). GBS is characterized by rapidly progressive flaccid paresis with a highly variable clinical course and outcome. Patients may develop mild limb paresis only, whereas others develop oculomotor, facial, and bulbar weakness, respiratory failure and tetraparalysis and remain bedbound for months (*Willison, et al., 2016*). Intravenous immunoglobulin (IVIg) and plasma exchange (PE) are proven effective treatments for GBS (*Chevret, et al., 2017; Hughes, et al., 2014*). Currently, IVIg in a dosage of 2 g/kg in 2-5 days, has become first choice treatment for patients with GBS who are unable to walk unaided or worse and who are still within the first 2 weeks from onset of weakness (*Willison, et al., 2016*). The outcome of GBS after 6 or 12 months however has not, or only marginally been improved since the introduction of PE and IVIg (*Hughes and Cornblath, 2005; Hughes, et al., 2007; van den Berg, et al., 2014; van Koningsveld, et al., 2004*). Despite these therapies, 25% progress during treatment, 20% require mechanical ventilation, 20% remain unable to walk after 6 months, and 3%-10% die of GBS. Patients with severe GBS and a poor prognosis may potentially benefit from additional or more aggressive therapy.

There are several arguments suggesting that GBS patients with a poor prognosis after the first course of IVIg may benefit from a second course:

1. About 10% have a 'treatment-related clinical fluctuation' that usually respond to a second course of IVIg (*Ruts, et al., 2010*).
2. A second course of IVIg is suggested to be effective in two small uncontrolled series of severe unresponsive GBS patients (*Farcas, et al., 1997; Godoy and Rabinstein, 2015*)

3. A smaller increase in serum IgG level after IVIg treatment is related with poor recovery after 6 months (*Kuitwaard, et al., 2009*).

We hypothesized that GBS patients with a poor prognosis after a first course of IVIg may benefit from a second course of IVIg when administered within the first weeks after onset of disease, when nerve damage is most likely still reversible.

Methods

Patients

The annual incidence of GBS in the Netherlands is 1.2 per 100.000 persons (*Van Koningsveld, et al., 2000*), so it is estimated that around 200 persons will develop GBS yearly. Neurologists in all hospitals in the Netherlands (91 hospitals in 2008) were contacted and asked to participate in this trial. All GBS patients of twelve years or older, within 2 weeks from onset of weakness and in need of IVIg treatment, according to the treating neurologist, in a standard dosage of 2 g/kg in 2-5 consecutive days are potentially eligible for this study after obtaining informed consent. The inclusion and exclusion criteria are shown in table 1(*Asbury and Cornblath, 1990*).

Modified EGOS (Erasmus GBS Outcome Score)

In the study we used the modified EGOS to select patients with poor prognosis (Table 2 and fig. 1) (*Walgaard, et al., 2011*). mEGOS was used at one week after start of the first IVIg course. The model uses age, preceding diarrhea and the MRC sumscore (a score often used in GBS research) as predictors for outcome. The model predicts outcome at 4 weeks and 6 months. The mEGOS has very good predictive power (Area Under the Receiver Operating Characteristic (ROC) Curve (AUC) = 0.87) for prediction of outcome after 4 weeks, indicating very good discriminative ability. The mEGOS was recently validated in a Japanese cohort and performed equally good in this cohort, underlining the validity of the model (*Yamagishi, et al., 2017*). In the SID-GBS trial an mEGOS score of at least 6 was used as a cutoff for poor prognosis. Of the patients with an mEGOS of ≥6 in the Erasmus GBS databank cohort (n=394), 85% were unable to walk unaided after 4 weeks and 35% were unable to walk unaided after 6 months.

Study design

A double-blind randomized placebo-controlled trial design was used in selected patients with a poor prognosis (mEGOS 6-12). In patients with a good prognosis (mEGOS 0-5) the study has an observational design. The prognosis (mEGOS) must preferentially be assessed 7 days after start of the first IVIg course, with a range to 8 or 9 days. Trial medication needs then to be started within 24 hours when indicated according to the mEGOS score (Fig 2). The IVIg treated GBS patients with a good prognosis (mEGOS 0-5) at day 7 are not randomized. These patients were also followed prospectively. This allows us to compare outcomes between patients with a good prognosis and those with a poor prognosis randomized to the treatment or control arm, and to further improve mEGOS with contemporary data.

Treatment

Patients with the poorest prognosis based upon the mEGOS (score 6-12) after the first (standard) IVIg course are randomized to get a second course of IVIg (Nanogam®) in a dosage of 0,4 g/kg (=8 ml/kg) for 5 days or placebo (Albumin 4%, GPO®) in a dosage of 8 ml/kg for 5 days. Patients with a good prognosis at day 7, with a range to 8 or 9 days, receive no additional treatment in the context of the trial (Fig 1). The local principal investigators use a web-based randomization procedure (Clinical Trial Center Maastricht; CTCM). The randomization is performed with randomization blocks (6 patients per block) into two groups. Randomization is stratified according to medical center. Randomization is double-blind. The pharmacist in each center has a randomization list and allocations are send to the pharmacies after randomization. This study is executed exclusively in the Netherlands, mainly because Sanquin blood supply, one of the subsidizing institutions of this study, supplies their IVIg (Nanogam®) only in the Netherlands. The Netherlands seems suited to perform such a trial

because of the short distances; according to treatment allocation Sanquin sends IVIg or albumin to the local pharmacy, who prepares the trial medication in a blinded fashion using a standardized protocol. This process should take place on the same day.

Study endpoints

The primary endpoint for evaluating the efficacy of treatments in GBS in most trials was based on the GBS disability at 4 weeks after start of treatment (*Hughes, et al., 1978; van der Meche and Schmitz, 1992; van Koningsveld, et al., 2004; Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group, 1997*). Therefore, we will also use the GBS disability scale at four weeks as primary outcome in this trial. The primary analysis will be proportional odds model comparing the GBS disability score at 4 weeks between the treatment groups, with adjustment for the mEGOS at randomization.

Secondary study endpoints are functional outcome and muscle strength after 8, 12 and 26 weeks, the percentage of patients needing artificial ventilation, number of days on respirator, number of days in an intensive care unit, mortality, number of days to hospital discharge, percentage of patients with secondary deterioration due to treatment-related fluctuations (TRF), adverse events and serum IgG levels at different time points.

Furthermore, all adverse events (AE's) reported spontaneously by the patient or observed by the investigators will be recorded, and all serious adverse events (SAE's) will be reported to the accredited METC that approved the protocol. Both AE's and SAE's will be compared between the randomized groups (placebo versus second IVIg course) using descriptive statistics.

Study procedures

When patients are included in the study they will undergo the following extra procedures;

- Throat swaps

To identify evidence of *Mycoplasma pneumoniae*, because a relation is described between *M. pneumoniae* infection and GBS (*Meyer Sauteur, et al., 2016*).

- Blood collection

Blood collection will take place before start of standard IVIg treatment (visit 1), after standard IVIg treatment (visit 2), after two weeks (visit 3), after 4 weeks (visit 4) and after 3 months (visit 6).

- CSF collection

At admission virtually all patients undergo a lumbar puncture as part of the standard medical workup; extra CSF will be collected for the SID-GBS study.

- Nerve conduction studies were not mandatory for this study but are performed when needed in the standard work-up according to local standard protocols. The participating neurologists were asked to perform an EMG according to an electrophysiology guideline, which was developed in a way that a minimum set of nerves is tested to enable classification of electrophysiological data according to Hadden and colleagues (*Hadden, et al., 1998*).

Hemolysis

In 2015 an amendment to the protocol was made due to a publication in which hemolytic anemia is described in three out of five GBS patients who received two courses of IVIg within a short sequence (*Nguyen, et al., 2014*). It was suggested that this may be caused by the presence of anti-A and anti-B blood type IgG antibodies present in IVIg derived from 0-type blood donors. Since this amendment, extra laboratory measurements on blood samples (in randomized patients only) were asked to conduct to trace possible hemolysis; Hb, Ht,

haptoglobine, LDH, Reticulocytes, Bilirubin, direct Coombs test. Blood group will also be determined. Retrospectively we collected information about already included and randomized patients and no evidence for hemolytic anemia was found so far in our cohort.

Study Monitoring

Sanquin Plasma Products has developed monitoring and auditing procedures. Monitors or delegates of Sanquin Plasma Products monitor the site, in order to comply with Good Clinical Practice (GCP) guidelines. All records from randomized patients are monitored. The expected average monitoring frequency is 6 months, or more frequent, if necessary, by personal visit. The pharmacy will be visited once a year or more frequent, if necessary. The hospital laboratory will be visited when required. Checking of the CRFs for completeness and clarity, and cross-checking with source documents in the presence of the investigator - giving due consideration to data protection and medical confidentiality - will be required.

Statistical analysis

All patients who were randomized and trial medication was actually started will be included in an intention-to-treat analysis. Additionally there will be a separate analysis on all the randomized patients, irrespective of trial medication was started. Outcomes will be compared between patients who received a second IVIg course and patients who received placebo. The primary analysis will be a proportional odds regression model with the full GBS as outcome. Scores on this ordinal scale will be compared between groups, with adjustment for the mEGOS after first IVIg. The treatment effect will be expressed as an adjusted proportional odds ratio with 95% confidence interval.

Proportional Odds model

The primary endpoint is the full GBS disability score at 4 weeks as an ordinal outcome, instead of a dichotomization of the GBS (e.g. GBS as ≤2 vs >2). Analysis will be with a proportional odds regression model (*Scott, et al., 1997*). The proportional odds model provides a more sensitive analysis than would be possible by arbitrarily dichotomizing the outcome variable and does so without imposing unverifiable assumptions regarding the structure of the data (*Scott, et al., 1997*). The disadvantage is that we have to make the assumption of proportional odds, i.e. that the treatment effect (as an odds ratio) is similar across all possible cut-offs for the GBS disability score. This assumption will be assessed by a test for heterogeneity of effect across cut-offs.

Covariate adjustment

We will use covariate adjustment, which is an established approach to deal with variation between patients in baseline risk and to increase statistical power in clinical phase III trials (*Roozenbeek, et al., 2009*). Using covariate adjustment we can also compare outcomes from the patients who receive a second IVIg course with the other included patients with good and poor prognosis. Unadjusted analysis can be expressed by the following formula, in which α indicates the intercept and β represents the regression coefficient for the treatment:

$$Log\ odds\ (GBS\ disability\ scale) = \alpha + \beta * treatment$$

The covariate-adjusted model uses mEGOS after first IVIg treatment as well as the treatment variable:

$$Log\ odds\ (GBS\ disability\ scale) = \alpha + \beta * treatment + \beta 1 * mEGOS$$

The increase in statistical power of covariate adjustment depends on the predictive strength of the baseline characteristics; this is difficult to quantify a priori, but the modified EGOS has a very good predictive power (AUC=0.87).

Sample size calculation

For the power calculation, we start from a crude comparison of the proportion of patients being able to walk unaided between the two treatment groups. If we assume a 20% difference in the proportion of patients being able to walk unaided between the patients with and without treatment we would need to randomize 145 patients with a poor prognosis (α=0.05 and power=0.80). We expected that covariate adjustment and the use of the ordinal outcome result in a reduction in required sample size of 40 to 50% (*Murray, 2006*). This leads to a required sample size of 60% of 145 patients, which is a total of 88 patients with a poor prognosis who will be randomized to receive a second course of IVIg (n=44) or placebo (n=44). Given the observed percentage of patients with poor prognosis in a historical cohort derived from previous trials, we initially expected that 50% of the included patients would have a poor prognosis and could be randomized in the SID-GBS trial. However, due to the inclusion of GBS patients with a broader range of severity, and the current day to day clinical practice to start IVIg also in some patients still being still able to walk without assistance, the percentage of all GBS patients treated with IVIg and having a poor prognosis at day 7 is lower (about 30%). This led to a longer period of inclusion.

Conclusion

In the SID-GBS trial the effects and safety of a second IVIg course, administered in the acute phase of the disease in a selected patient group with a poor predicted outcome based on the mEGOS prognostic model will be studied. If a second IVIg course is beneficial, this will result in an improvement of the outcome of this disease for the first time since the introduction of plasma exchange as the first treatment in 1985 (*French Cooperative Group on Plasma Exchange in Guillain-Barre syndrome 1987; The Guillain-Barre syndrome Study Group (1985*), and the introduction of a standard course of IVIg for treatment of GBS (*van der Meche and Schmitz, 1992*).

The first patient was included and randomized in the SID-GBS trial in February 2010, in June 2018 inclusion was stopped after 99 randomizations. It is expected that the first results of the SID-GBS RCT will be available early 2019.

Acknowledgements

The SID-GBS trial is an investigator initiated, independent academic trial. The study is run by a large group of local principal investigators (Dutch GBS Study Group), and a steering committee from the Erasmus medical center, both are involved in the inclusion, randomization and follow-up of the patients. Together they form the SID-GBS study group (Appendix). Decisions regarding continuation, amendments to the protocol, and publication of the results will be taken by the steering committee. The results of this study will be published in the name of the SID-GBS study group. The study is funded by the Prinses Beatrix Spierfonds (WAR07-28) and Sanquin plasma products.

Appendix – SID-GBS study group

Steering committee: P.A. van Doorn (chair)[1], B.C. Jacobs[1,2], C. Walgaard[1], M.C.Y. de Wit[1], E.W. Steyerberg[3,4], D.R. Cornblath[5].

Coordinating center at Erasmus MC, Rotterdam, the Netherlands: B. van den Berg[1,6], A.Y. Doets[1], S.E. Leonhard[1], J.C. Verboon[1], C. Walgaard[1], M. van Woerkom[1].

Affiliations

Department of [1]Neurology, [2]Immunology and [3]Public Health, Erasmus MC, Wytemaweg 80, 3015 CN, Rotterdam, The Netherlands. Department of [4]Biomedical Data Sciences, LUMC, Leiden, The Netherlands. Department of [5]Neurology, Johns Hopkins University, Baltimore, MD, USA. Department of [6]Neurology, Elisabeth-TweeSteden hospital, Tilburg, The Netherlands.

Principal investigators (neurologists):

U.A. Badrising, Van Weel-Bethesda hospital, Dirksland; H.M.E. Bienfait, Kennemer hospital, Haarlem; R.J. Blom, Diakonessenhuis, Utrecht; C.J.M. van Boheemen, St. Anna hospital, Geldrop; A.J. Breukelman, ZorgSaam hospital, Terneuzen; I.M. Bronner, Flevo hospital, Almere; H.J.G. Dieks, Rupke-Zweers hospital, Hardenberg; G.W. van Dijk, Canisius Wilhelmina hospital, Nijmegen; B.G.M. van Engelen, University MC St. Radboud, Nijmegen; C.G. Faber, Maastricht University MC, Maastricht; B. Feenstra, Lievensberg hospital, Bergen op Zoom; C. Fokke, Gelre hospital, Apeldoorn; M.P.J. Garssen, Jeroen Bosch hospital, ’s-Hertogenbosch; C.J. Gijsbers, Vlietland hospital, Schiedam; H. J. Gilhuis, Reinier de Graaf hospital, Delft; M.M. van der Graaff, BovenIJ hospital, Amsterdam; R.J. Groen, Haaglanden MC, Antoniushove, Leidschendam; T.A. Hoogendoorn, Rivierenland hospital, Tiel; A. Hovestad, Meander MC, Amersfoort; P.J.H.W. Jansen, Antonius hospital, Sneek; K. Jellema, Haaglanden MC, Westeinde, Den Haag; E. Keuter, Diaconessenhuis, Meppel; R.P. Kleyweg, Albert Schweitzer hospital, Dordrecht; R. van Koningsveld, Elkerliek

hospital, Helmond; A.J. van der Kooi, AMC, Amsterdam; E.L. van der Kooi, Leeuwarden Medical Center, Leeuwarden; J. Krudde, Leeuwarden Medical Center, Leeuwarden; J.B.M. Kuks, University Medical Center Groningen, Groningen; K. Kuitwaard, Albert Schweitzer hospital, Dordrecht; W.H.J.P. Linssen, Sint Lucas Andreas hospital, Amsterdam en Zaans medical Center, Zaandam, J. Lion, Bernhoven hospital, Uden; H. Lovenich, St. Jans hospital, Weert; S.M. Manschot, Haaglanden MC, Bronovo, Den Haag; S.J. Mellema, Isala klinieken, Zwolle; I.S.J. Merkies, Spaarne hospital, Hoofddorp; M.F.G. van der Meulen, St. Antonius hospital, Nieuwegein; W.D.M. van der Meulen, Rode Kruis hospital, Beverwijk; D.S.M. Molenaar, Amstelland hospital, Amstelveen; D.G. Oenema, Wilhelmina hospital, Assen; B.W. van Oosten, VU Medical Center, Amsterdam; J.C.H. van Oostrom, Rijnstate hospital, Arnhem; N.P. van Orshoven, Orbis Medical Center, Sittard; R.J.O.van der Ploeg, Martini hospital, Groningen; W.L. van der Pol, University Medical Center Utrecht, Utrecht; S. Polman, Isala hospitals, Zwolle; T.C. van der Ree, Westfries hospital, Hoorn; M.C. de Rijk, Catharina hospital, Eindhoven; A. Ruitenberg, Admiraal de Ruyter hospital, Goes; L. Ruts, Haven hospital, Rotterdam; J.P.A. Samijn, Maasstad hospital, Rotterdam; A.J.G.M. Schyns-Soeterboek, Laurentius hospital, Roermond; M. Stevens, Tergooi hospitals, Blaricum; F.H. Vermeij, Sint Fransicus hospital, Rotterdam; J.J.G.M. Verschuuren, Leids University Medical Center, Leiden; L.H. Visser, St. Elisabeth hospital, Tilburg; P.W. Wirtz, Haga hospital, Den Haag; M. Wohlgemuth, TweeSteden hospital, Tilburg; C.P. Zwetsloot, Waterland hospital, Purmerend.

Methodologist and trial statisticians: H.F. Lingsma, Erasmus MC, Rotterdam; E.W. Steyerberg, Erasmus MC Rotterdam/ LUMC Leiden.

Data monitoring and safety committee: D.W.J. Dippel, Erasmus MC, Rotterdam; R.Q. Hintzen, Erasmus MC, Rotterdam.

Tables

Table 1: Inclusion and exclusion criteria.

Inclusion criteria

A. To be <u>included</u> in this GBS study

- Patients are diagnosed with GBS (*Asbury and Cornblath, 1990*).
- There is an indication to start IVIg (irrespective of co-treatment with methylprednisolon (MP)) therapy:

1. Patient is unable to walk unaided for >10 meter (grade 3- 5 of the GBS disability scale) or
2. There is otherwise an indication to start IVIg (with or without MP) treatment according to the treating neurologist.

- Onset of weakness due to GBS is less than 2 weeks ago.
- Signed informed consent.

B. To be <u>randomized</u> in the second IVIg course phase (RCT), patients must fulfill the following criteria:

- First IVIg (with or without MP) treatment with (in principal) Nanogam® started within 2 weeks from onset of weakness.
- IVIg treatment has been 2g/kg administered in 2-5 days.
- Poor prognosis based upon the modified EGOS (mEGOS 6-12) at day 7 (range to 8-9 days) after start of first IVIg treatment.

Exclusion criteria

A. To enter this GBS study

- Age less than 12 years.
- Patient known to have a severe allergic reaction to properly matched blood products or plasma products.
- Pregnancy or breastfeeding.
- Patient known to have a selective IgA deficiency.
- Patient shows clear clinical evidence of a polyneuropathy caused by e.g. diabetes mellitus (except mild sensory), alcoholism, severe vitamin deficiency, porphyria.
- Patient received immunosuppressive treatment (e.g. azathioprine, cyclosporine, mycofenolaatmofetil, tacrolimus, sirolimus or > 20 mg prednisolon daily) during the last month.
- Patient known to have a severe concurrent disease, like malignancy, severe cardiovascular disease, AIDS, severe COPD.
- Inability to attend follow-up during 6 months.

B. Relative contra-indications for second IVIg course[§]:

- Patients known to have severe kidney dysfunction (GFR below 40 ml/min).
- Pre-existing risk factors of thrombo-embolic complications or severe ischemic heart disease.

§ These patient groups run a greater risk (although they are still rare) to develop serious complications like acute tubular necrosis and thrombo-embolic events. To prevent this the patient should be pre-treated with fluids and infusion rate of the trial medication must be adjusted.

Table 2

Modified Erasmus GBS Outcome Score (mEGOS).

Factor	**Category**	**Score**
Age (years)	≤ 40	0
	41 – 60	1
	> 60	2
Diarrhea	No	0
	Yes	1
MRC sumscore[§]	51 – 60	0
(1 week after inclusion)	41 – 50	3
	31 – 40	6
	0 – 30	9
mEGOS		0 – 12

[§]Bilateral m.deltoideus, m.biceps, wrist extensors, m.iliopsoas, m.quadriceps, m.tibialis anterior (range 0-60).

Figure legends

Figure 1

Predicted probability being able to walk at 4 weeks and 6 months according to mEGOS.

Patients with mEGOS 6-12 will be selected for randomization.

Figure 2

Trial flowchart.

References

1. Asbury AK, Cornblath DR (1990). Assessment of current diagnostic criteria for Guillain-Barre syndrome. Ann Neurol 27 Suppl:S21-24.
2. Chevret S, Hughes RA, Annane D (2017). Plasma exchange for Guillain-Barre syndrome. Cochrane Database Syst Rev 2:CD001798.
3. Farcas P, Avnun L, Frisher S, Herishanu YO, Wirguin I (1997). Efficacy of repeated intravenous immunoglobulin in severe unresponsive Guillain-Barre syndrome. Lancet 350:1747.
4. French Cooperative Group on Plasma Exchange in Guillain-Barre syndrome (1987). Efficiency of plasma exchange in Guillain-Barre syndrome: role of replacement fluids. Ann Neurol 22:753-761.
5. Godoy DA, Rabinstein A (2015). Is a second cycle of immunoglobulin justified in axonal forms of Guillain-Barre syndrome. Arq Neuropsiquiatr 73:848-851.
6. Hadden RD, Cornblath DR, Hughes RA, Zielasek J, Hartung HP, Toyka KV, Swan AV (1998). Electrophysiological classification of Guillain-Barre syndrome: clinical associations and outcome. Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. Ann Neurol 44:780-788.
7. Hughes RA, Cornblath DR (2005). Guillain-Barre syndrome. Lancet 366:1653-1666.
8. Hughes RA, Newsom-Davis JM, Perkin GD, Pierce JM (1978). Controlled trial prednisolone in acute polyneuropathy. Lancet 2:750-753.
9. Hughes RA, Swan AV, Raphael JC, Annane D, van Koningsveld R, van Doorn PA (2007). Immunotherapy for Guillain-Barre syndrome: a systematic review. Brain 130:2245-2257.
10. Hughes RA, Swan AV, van Doorn PA (2014). Intravenous immunoglobulin for Guillain-Barre syndrome. Cochrane Database Syst Rev:CD002063.
11. Kuitwaard K, de Gelder J, Tio-Gillen AP, Hop WC, van Gelder T, van Toorenenbergen AW, van Doorn PA, Jacobs BC (2009). Pharmacokinetics of intravenous immunoglobulin and outcome in Guillain-Barre syndrome. Ann Neurol 66:597-603.
12. Meyer Sauteur PM, Huizinga R, Tio-Gillen AP, Roodbol J, Hoogenboezem T, Jacobs E, van Rijn M, van der Eijk AA, Vink C, de Wit MC, van Rossum AM, Jacobs BC (2016). Mycoplasma pneumoniae triggering the Guillain-Barre syndrome: A case-control study. Ann Neurol 80:566-580.
13. Murray GDBI, Lu J et al. (2006). Approaches to outcome analysis in traumatic brain injury trials. J Neurotrauma 23:740-801.
14. Nguyen TP, Biliciler S, Wahed A, Sheikh K (2014). Occurrence of hemolytic anemia in patients with GBS treated with high-dose IVIg. Neurol Neuroimmunol Neuroinflamm 1:e50.
15. Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group (1997). Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barre syndrome. Lancet 349:225-230.
16. Roozenbeek B, Maas AI, Lingsma HF, Butcher I, Lu J, Marmarou A, McHugh GS, Weir J, Murray GD, Steyerberg EW, Group IS (2009). Baseline characteristics and statistical power in randomized controlled trials: selection, prognostic targeting, or covariate adjustment? Crit Care Med 37:2683-2690.
17. Ruts L, Drenthen J, Jongen JL, Hop WC, Visser GH, Jacobs BC, van Doorn PA, Dutch GBSSG (2010). Pain in Guillain-Barre syndrome: a long-term follow-up study. Neurology 75:1439-1447.
18. Scott SC, Goldberg MS, Mayo NE (1997). Statistical assessment of ordinal outcomes in comparative studies. J Clin Epidemiol 50:45-55.
19. Sejvar JJ, Baughman AL, Wise M, Morgan OW (2011). Population incidence of Guillain-Barre syndrome: a systematic review and meta-analysis. Neuroepidemiology 36:123-133.
20. The Guillain-Barre syndrom Study Group (1985). Plasmapheresis and acute Guillain-Barre syndrome. Neurology 35:1096-1104.
21. van den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, van Doorn PA (2014). Guillain-Barre syndrome: pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol 10:469-482.

22. van der Meche FG, Schmitz PI (1992). A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barre syndrome. Dutch Guillain-Barre Study Group. N Engl J Med 326:1123-1129.
23. van Koningsveld R, Schmitz PI, Meche FG, Visser LH, Meulstee J, van Doorn PA (2004). Effect of methylprednisolone when added to standard treatment with intravenous immunoglobulin for Guillain-Barre syndrome: randomised trial. Lancet 363:192-196.
24. Van Koningsveld R, Van Doorn PA, Schmitz PI, Ang CW, Van der Meche FG (2000). Mild forms of Guillain-Barre syndrome in an epidemiologic survey in The Netherlands. Neurology 54:620-625.
25. Walgaard C, Lingsma HF, Ruts L, van Doorn PA, Steyerberg EW, Jacobs BC (2011). Early recognition of poor prognosis in Guillain-Barre syndrome. Neurology 76:968-975.
26. Willison HJ, Jacobs BC, van Doorn PA (2016). Guillain-Barre syndrome. Lancet 388:717-727.
27. Yamagishi Y, Suzuki H, Sonoo M, Kuwabara S, Yokota T, Nomura K, Chiba A, Kaji R, Kanda T, Kaida K, Ikeda SI, Mutoh T, Yamasaki R, Takashima H, Matsui M, Nishiyama K, Sobue G, Kusunoki S (2017). Markers for Guillain-Barré syndrome with poor prognosis: a multi-center study. J Peripher Nerv Syst 22:433-439.