Second IVIg Dose in Guillain-Barre syndrome patients with poor prognosis.

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To determine whether a second IVIg course in GBS patients with a poor prognosis improves functional outcome after 4 weeks. Secondary outcomes include functional outcome after 8, 12 and 26 weeks, mechanical ventilation, length of hospital and ICU...

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON22921

Bron
Nationaal Trial Register

Verkorte titel
SID-GBS trial

Aandoening

Guillain-Barre syndrome

Ondersteuning

Primaire sponsor: Erasmus MC Rotterdam
Overige ondersteuning: Prinses Beatrix Fonds
Sanquin plasmaproducts (productsponsoring)

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

To determine whether a second IVIg dosage in GBS patients with a poor prognosis improve

functional outcome after 4 weeks.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale:

Guillain-Barré syndrome (GBS) is the most frequent cause of acute neuromuscular weakness in the Western world. GBS patients have a variable prognosis, 20-30% needs mechanical ventilation, 20% is unable to walk after 6 months and 3% dies. Using a simple scoring system it is
possible to accurately predict which patient has a poor prognosis. GBS patients with a poor prognosis may benefit from a second course of IVIg.

Objective:

To determine whether a second IVIg course in GBS patients
with a poor prognosis improves functional outcome after 4 weeks.

Secondary outcomes include functional outcome after 8, 12 and 26 weeks, mechanical ventilation, length of hospital and ICU admission, occurrence of TRF’s, mortality and blood IgG levels.

Study design:

A double-blind randomized placebo-controlled trial
design will be used in selected patients with a poor prognosis. In patients with a good prognosis the study will have an observational design.

Study population:

GBS patients of 6 years and older, who have an
indication for IVIg treatment.

Intervention:

Patients with a poor prognosis according to the
prediction model (mEGOS) will be randomized to receive a second IVIg course or placebo.

Main study parameters/endpoints:

The main study endpoint is functional outcome on the GBS disability scale 4 weeks after start of the first IVIg course. Other endpoints include functional outcome after 26 weeks.

Nature and extent of the burden and risks associated with
participation, benefit and group relatedness:

The participant will be physically examined at 7 standardized time-points, mostly in combination
with the standard patient care. Extra blood and CSF (extra spinal tab is not requested) will be used for trial purposes. An EMG will be performed in the standard clinical work-up. A throat swab will be requested. Serious adverse effects of IVIg are rare (details in SPC). It is anticipated that also in children benefits will outweigh the risks of participating in this treatment trial. Standard treatment in children is
the same as in adults, long-term prognosis is better as in adults; however 25% is still not symptom free at a median of 228 days in a large observational study.

Doel van het onderzoek

To determine whether a second IVIg course in GBS patients with a poor prognosis improves functional outcome after 4 weeks. Secondary outcomes include functional outcome after 8, 12 and 26 weeks, mechanical ventilation, length of hospital and ICU admission, occurrence of TRF’s, mortality and blood IgG levels.

Onderzoeksopzet

Admission and 1, 2, 4, 8, 12 and 26 weeks after admission.

Onderzoeksproduct en/of interventie

Second IVIg dose or placebo in selected patientgroup with a poor prognosis.

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

To enter this GBS study:

1. Patients are diagnosed with GBS[30];

2. There is an indication to start IVIg (irrespective of co-treatment with methylprednisolon (MP)) therapy:

A. Patient is unable to walk unaided for >10 meter (grade 3, 4 or 5 of the GBS disability scale), or;

B. There is otherwise an indication to start IVIg (with or without MP) treatment according to the treating neurologist.

3. Onset of weakness due to GBS is less than 2 weeks ago;

4. Signed informed consent.

To be randomized in the second IVIg dose phase (RCT), patients must fulfill the following criteria:

1. First IVIg (with or without MP) treatment with Nanogam® started within 2 weeks from

onset of weakness;

2. IVIg treatment has been 2g/kg administered in 2-5 days;

3. Poor prognosis based upon the modified EGOS (mEGOS 6-12) at day 7 after start of first IVIg treatment.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Age less than 6 years;

2. Patient known to have a severe allergic reaction to properly matched blood products or plasma products;

3. Pregnancy or breastfeeding;

4. Patient known to have a selective IgA deficiency;

5. Patient shows clear clinical evidence of a polyneuropathy caused by e.g. diabetes mellitus (except mild sensory), alcoholism, severe vitamin deficiency, porphyria;

6. Patient received immunosuppressive treatment (e.g. azathioprine, cyclosporine, mycofenolaatmofetil, tacrolimus, sirolimus or > 20 mg prednisolon daily) during the last month;

7. Patient known to have a severe concurrent disease, like malignancy, severe cardiovascular disease, AIDS, severe CARA;

8. Inability to attend follow-up during 6 months.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	16-02-2010
Aantal proefpersonen:	176
Type:	Werkelijke startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Ja

Toelichting

STATISTICAL ANALYSIS PLAN
Second IVIg Course in Guillain-Barré Syndrome patients with poor prognosis (SID-GBS trial): a double-blind randomized, placebo-controlled clinical trial.
SID-GBS trial
NTR number: 2224

Erasmus MC
Rotterdam
The Netherlands

Version 1
February 18th 2019
Protocol version 12

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Introduction

The purpose of the randomized Second IVIg Course in Guillain-Barre syndrome patients with poor prognosis (SID-GBS) is to assess the safety and effect on functional outcome of a second IVIg course administered shortly after the first standard IVIg course in GBS patients with poor prognosis. The protocol was published earlier.1
Here we will summarize the statistical analysis of the data, including how missing data will be handled and which subgroup analyses will be performed. Although we list an extensive number of analyses, this does not imply that all these will be described in the main publication, because of space restrictions.
Where details differ between the protocol and the Statistical Analysis Plan (SAP), this SAP is leading.

Status of the trial

The first patient was included in the trial in February 2010. In the following years 339 patients (good and poor prognosis) were included in 53 centers in the Netherlands. In June 2018 the last patient was included and last follow-up visit took place in December 2018.

Research questions.

Primary research question

The primary objective of this study is to estimate the effect of a second IVIg course (administered 7 days after start of the first IVIg course) in GBS patients with a poor prognosis on functional outcome at 4 weeks after start of the first IVIg course.

Secondary research questions

The secondary objectives are to assess the safety of a second IVIg course with respect to the occurrence of renal dysfunction and thrombo-embolic complications, and the efficacy with regard to long-term muscle weakness, long-term functional outcome, duration of hospital and ICU admittance, duration of mechanical ventilation, and mortality.

Study Design

A double-blind, randomized placebo-controlled trial design was used in patients with poor prognosis, defined as a score of 6-12 on the mEGOS prediction model one week after start of the first IVIg course.2 Selected patients who met the inclusion and exclusion criteria and gave consent were randomly allocated (1:1) to receive 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 shortly after the first standard IVIg treatment for GBS.

Inclusion and exclusion criteria

For a complete list of inclusion and exclusion criteria we refer to paragraph 4.2 and 4.3 of the protocol version 12 on page 12-13. In short, patients of 12 years or older diagnosed with GBS

according to the treating neurologist, with onset of weakness less than 2 weeks ago are in principle eligible for inclusion in the trial.

Primary and secondary outcomes

The primary outcome is the score on the GBS disability scale3 at 4 weeks after start of the first IVIg course.

Secondary outcomes are:
• GBS disability score at 8, 12 and 26 weeks.
• MRC sum score (summation of MRC scores of 6 bilateral muscles groups; m. deltoid, m. biceps, wrist extensors, m. iliopsoas, m. quadriceps femoris, m. tibialis anterior, ranging from 0-60) at 4, 8, 12 and 26 weeks.4
• ONLS score at 4, 8, 12 and 26 weeks.5
• Improvement of 1 point or more compared to baseline/randomization on the GBS disability score at 4, 8, 12 and 26 weeks, for comparison with previous studies.
• Need for artificial ventilation.
• Days on respirator.
• Length of stay on intensive care unit
• Mortality
• Length of stay in hospital
• Secondary deterioration due to treatment-related fluctuations (TRF).
• Any complications possibly related to a second IVIg course.
• Serum IgG levels at 5 different time points.

Randomization and blinding

A web-based computerized random number generation procedure from an external party (Clinical Trial Center Maastricht; CTCM) was used and treatment allocation was in a 1:1 ratio with use of block randomization and was stratified according to participating center. The local pharmacy prepared and blinded the trial medication according to a standardized protocol. Placebo (albumin) was matched to the study drug by volume (8 ml/kg) and fluid aspect (due to proteins in IVIg and albumin, both are slightly foaming liquids). As the color of IVIg can differ between batches of IVIg, the bag (ethylene vinyl acetate; EVA bag) of the trial medication was blinded using aluminum foil and opaque connecting lines were used.

Statistical Principles

Primary effect analysis

The main analysis of this trial consists of a single comparison of the primary outcome between the treatment groups. The analysis is based on the intention-to-treat principle (all patients who were randomized and the allocated trial medication was actually started will be included in an intention-to-treat analysis). The primary effect parameter is estimated with a proportional odds regression model to take the whole range of the GBS disability scale into account, and is defined as a proportional odds ratio for the effect of treatment with a 95% confidence interval6, and the corresponding p-value. A p-value of <0.05 will be considered

statistically significant. Covariate adjustment 7will be used to adjust for variation in baseline prognostic variables between intervention and control group, with the following covariates:
• Age,
• Preceding diarrhea,
• MRC sum score4 at randomization.

The proportional odds (PO) model assumes that the odds ratios (the estimated effect of the treatment) is comparable for each cut-off of the outcome scale. However, it has been argued that if there is agreement that each score on the outcome scale is more favourable than a one point higher (in case of the GBS disability score) score, statistical testing of the PO assumption is redundant.8 In addition, even when the PO assumption is formally violated, the common odds ration from the proportional odds model provides an interpretable summary measure of the treatment effect over the full outcome scale and increases statistical power compared to dichotomization of the outcome scale.9

Primary effect analysis in subgroups
The primary effect parameter will be estimated in the following subgroups, using the same analysis as described above.
Heterogeneity of the treatment effect between subgroups will be tested with inclusion of an interaction term between treatment and the specific subgroup in the model.
• Age 60 or more versus less than 60 year.
• MRC sum score zero versus greater than zero at randomization.
• MRC sum score 0-12 versus greater than 12 at randomization.
• mEGOS <10 versus mEGOS 10-12 at randomization.
• Mechanical ventilation versus no mechanical ventilation.
• A-CIDP (final diagnosis) versus GBS (final diagnosis).
• A-CIDP (final diagnosis) and patients with IVIg treated TRF's versus GBS (final diagnosis) patients without IVIg treated TRF's.
• Demyelinating nerve conduction studies versus axonal nerve conduction studies according to the Hadden criteria.10
• Inexcitable nerve conduction studies versus all other Hadden classifications.
• 50% of the patients with the lowest delta IgG (IgG level before standard IVIg compared with IgG level at day 7-9; before start of SID) versus 50% highest delta IgG.11
• with positive campylobacter jejuni serology versus negative campylobacter jejuni serology.
• Patients with GM1 and/or GD1a antibodies versus patients without these antibodies.

Secondary effect analysis

Secondary outcomes will be will be analyzed in the same way as the primary outcome, i.e. in a regression model with covariate adjustment with the same covariates.

Ordinal secondary outcomes (GBS disability score at week 8, 12 and 26, ONLS at week 4, 8, 12 and 26) will be analyzed with proportional odds regression resulting in an adjusted odds ratio with 95% confidence interval and the corresponding p-value as effect parameter.
Binary secondary outcomes (improvement of at least 1point on the GBS disability score at week 4, 8, 12, or 26, mortality, mechanical ventilation, intensive care admission) will be analyzed with logistic regression resulting in an adjusted odds ratio with 95% confidence

interval and the corresponding p-value as effect parameter.

Continuous secondary outcomes (MRC sum score at 4, 8, 12 and 26 weeks, number of days on intensive care unit, number of days on respirator) will be analyzed with linear regression resulting in an adjusted beta with 95% confidence interval and the corresponding p-value as effect parameter. If the outcomes are not normally distributed, a suitable transformation will be used.

Secondary time-to-event outcomes (time to regain independent walking (GBS disability score 0-2), time to regain the ability to run (GBS disability score 0-1), time to hospital discharge) will be analyzed with logistic regression resulting in an adjusted odds ratio with 95% confidence interval and the corresponding p-value as effect parameter.

For analysis of (S)AE's and serum IgG levels descriptive statistics will be used.

Additional ad-hoc analyses may be conducted as deemed suitable.

Missing data and death

After complete recovery on the GBS disability score, MRC sum score and the ONLS further follow-up was not needed according to the protocol, because GBS is usually a monophasic disease. In that case, following endpoints were inserted according to last observation carried forward.

Patients who die within the study period will be assigned the worst score on all outcome measures from that time point and remain included in the analysis.
Multiple imputation will be used to account for missing values of baseline characteristics when they were used for covariate adjustment. Multiple imputation will also be used to account for missing values of secondary endpoints. Because serial measurements were performed this will result in very reliable imputations estimates. The imputation model will use age, sex, preceding infection, number of days between start of weakness and inclusion, presence of pain, and at serial time points (entry, 1, 2, 4, 8, 12, and 26 weeks) cranial nerve deficit, MRC scores of the individual muscles from the MRC sum score, GBS disability score and ONLS score. The primary endpoint will not be imputed.

References

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Ethische beoordeling

Positief advies

Datum:	24-02-2010
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL2107
NTR-old	NTR2224
Ander register	METC Erasmus MC : MEC-2009-368
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A