Second IVIg Dose in GBS patients with poor prognosis (SID-GBS trial)

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

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON47229

Source
ToetsingOnline

Brief title
SID-GBS trial

Condition

- Autoimmune disorders
- Peripheral neuropathies

Synonym
acute inflammatory demyelinating polyneuropathy (AIDP), Guillain-Barre syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Prinses Beatrix Fonds. ,Sanquin

Intervention

Keyword: Guillain-Barre syndrome, immunoglobulin, prognosis

Outcome measures

Primary outcome

GBS disability score at 4 weeks after start of first IVIg course. The full range of scores will be considered as an ordinal outcome scale. In analyzing we will use a proportional odds model. (Extent of) improvement on this ordinal scale will be compared between groups.

Secondary outcome

- Percentage of patients that improve:

at least 1, 2, 3 or 4 points on the GBS disability score at 4, 8, 12 and 26 weeks,

at least 4, 8 or 12 points on MRC sum score (ranging from 0-60) at 4, 8, 12 and 26 weeks,

at least 2, 4 or 6 points on ONLS score (ranging from 0-12) at 4, 8, 12 and 26 weeks.

- Percentage of patients needing artificial ventilation.

- Time (number of days) on respirator.

- Time (number of days) on intensive care unit.

- Percentage of patients that die because of GBS.

- Time (number of days) to hospital discharge.

- Percentage of patients with secondary deterioration due to treatment-related fluctuations (TRF).

- Development of complications possibly related to a second IVIg course.

- Serum IgG levels at 5 different time points.

Study description

Background summary

Guillain-Barré syndrome (GBS) is an immune mediated peripheral polyradiculoneuropathy characterized by rapid onset flaccid paresis and sensory disturbances with a very heterogenic distribution in clinical characteristics and in prognosis. Some patients develop mild limb paresis, whereas others develop oculomotor, facial, bulbar, respiratory muscle and limb paralysis and remain bed bound for several months. GBS is the most frequent cause of acute neuromuscular weakness in the Western world. It affects 1.2 persons per 100,000 per year. Intravenous immunoglobulin (IVIg) and plasma exchange (PE) are shown to be effective in patients with GBS. These studies primarily assessed the proportion of patients that improved 4 weeks after onset of this treatment. Nowadays, IVIg (2 g/kg in 5 days) has become standard treatment for patients with GBS who are unable to walk unaided and still within the first 2 weeks from onset of weakness. The outcome of GBS after 6 or 12 months however has not, or only marginally been improved. Approximately 20% are still disabled after 6 months, mechanical ventilation is needed in 20-30% and 3%-10% of the patients die. Patients with severe GBS and poor prognosis may need additional or more aggressive therapy to recover. A recent study showed that the prognosis of individual GBS patients can accurately be predicted based on three simple clinical factors that can easily be obtained early during the course of disease. The selection of patients for the RCT phase of this SID-GBS study is based on this prognostic model.
There are several arguments suggesting that a second IVIg course can be effective in patients with a poor prognosis;
1. It is known that about 10% of GBS patients only have short-lasting improvement after a single IVIg course (*treatment-related clinical fluctuation*), a second dose of IVIg is then followed by functional improvement, suggesting that one IVIg course in these patients is insufficient
2. A second course of IVIg is suggested to be effective in a small uncontrolled series of severe unresponsive GBS patients
3. Additionally, recent data from our group show that patients with a relatively minor increase in serum IgG level after IVIg treatment recover significantly slower and fewer patients were able to walk unaided after 6 months.
Based on these findings, it is likely that at least a proportion of GBS patients may benefit from repeated courses of IVIg, especially the subgroup of patients with poor prognosis.

Study objective

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

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.
* All GBS patients in need of IVIg treatment, according to the treating neurologist, in a standard dosage of 2 g/kg in 5 consecutive days are potentially eligible for this study after obtaining informed consent.
* When patients sign *Informed consent* they principally agree to be randomized to get a second IVIg dose or placebo when having a poor prognosis at day 7 and to be followed up for 6 months.
* Patients with the poorest prognosis based upon the modified EGOS (mEGOS 6-12) after the first IVIg course will be randomized to get a second course of IVIg (Nanogam) in a dosage of 8 ml/kg (=0,4 g/kg) for 5 days or placebo (GPO) in a dosage of 8 ml/kg for 5 days in a blinded fashion.
* mEGOS must preferentially be assessed 7 days after start of 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 (see figure 4).
* Patient follow-up will be 6 months.
* Total patient inclusion will end when 44 patients with a poor prognosis received a second IVIg dosage.
* After covariate adjustment, to deal with variation between patients in baseline risk and to increase statistical power, data of the placebo group and the intervention group will be compared

Intervention

Second IVIg treatment or placebo (GPO) in selected group of GBS patients

Study burden and risks

When patients are included in the study they will undergo the following extra procedures;
- Throat swaps
- 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). Mostly it will be possible to collect blood for the study simultaneously with vena punctures performed in the scope of the medical work-up.
- 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. In

this way there is no need for an extra spinal puncture. For the study a small sample (5 cc) of CSF is sufficient. If no lumbar puncture was performed for various reasons, no lumbar puncture will be performed in the scope of this study.
- EMG examination generally is comparable with the situation outside a study, but may be more extensive in some patients. This depends on the local procedures in the participating hospitals. An EMG guideline is developed in a way that a minimum set of nerves is tested to enable classification of electrophysiological data according to Hadden.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients are diagnosed with GBS.
There is an indication to start IVIg therapy:
1. Patient is unable to walk unaided for >10 meter (grade 3, 4 or 5 of the GBS disability scale) or 2. There is otherwise an indication to start IVIg treatment according to the treating neurologist.
Onset of weakness due to GBS is less than 2 weeks ago.
Signed informed consent.

Exclusion criteria

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 CARA.
Inability to attend follow-up during 6 months.
Relative contra-indications for second IVIg dose:
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.
Contra-indications for GPO:
proven hypersensitivity to albumin products
every situation in which hypervolaemia or haemodilution can form a special risk; examples of such conditions are: heart failure, severe hypertension, oesophageal varices, pulmonary oedema, haemorrhagic diathesis, severe anaemia, renal and postrenal anuria

Study design

Design

Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-02-2009
Enrollment:	260
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GPO
Generic name:	Gepasteuriseerde Plasma-eiwit Oplossing
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Nanogam
Generic name:	immunoglobulinen
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	21-09-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	28-01-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	22-06-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-05-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	15-06-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-005659-83-NL
CCMO	NL26512.078.09

Study results

Date completed:	05-12-2018
Actual enrolment:	339