International Second Immunoglobulin Dose in Guillain-Barre Syndrome patients with poor prognosis.

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Primary objectiveTo determine whether a second IVIg dose in GBS patients with a poor prognosis improves functional outcome after 4 weeks.Secondary objectives To investigate whether: - a second IVIg dose in GBS patients with a poor prognosis improves...

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

Summary

ID

NL-OMON35287

Source
ToetsingOnline

Brief title
I-SID GBS study

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: Talecris Plasma Resources

Intervention

Keyword: Guillain-Barre Syndrome, Immunoglobulins, Prognosis

Outcome measures

Primary outcome

Main study endpoint

GBS disability score at 4 weeks after start of first IVIg dose. 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

Secondary study endpoints

- 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 4 different time points.

Other study parameters

- To correct for known prognostic factors (age, preceding diarrhea, positive serology of different micro-organisms, antibodies against gangliosides) we will ask questions about antecedent events, as diarrhea and upper respiratory tract infection and perform laboratory measurements (serology against Campylobacter jejuni, cytomegalovirus (CMV), Epstein-Barr virus (EBV), Mycoplasma pneumonia and IgG, IgM and IgA antibodies against GM1, GD1a and GQ1b).

Study description

Background summary

Guillain-Barré syndrome (GBS) is the most frequent cause of acute neuromuscular weakness in the Western world that can occur at any age. GBS is a rapidly progressive *inflammatory* disorder of the peripheral nerves often leading to a severe paresis of arms and legs. Most GBS patients also have sensory disturbances (tingling or dull feeling) and pain. Some patients also have double vision or problems with swallowing. GBS may also involve the respiratory muscles, leading to insufficient respiration and admission on an intensive care unit. About 25% of patients need artificial respiration for a period ranging from weeks to several months. Progression of weakness in GBS is fast and reaches its maximum within 4 weeks (by definition), but the maximum is generally reached within 2 weeks. Thereafter the patients have a variable prognosis. GBS is mostly preceded by a common infection with Campylobacter or an upper respiratory tract infection. Auto-reactive antibodies play a role in the pathogenesis of the disorder. GBS is - at least partially - a treatable disorder. Intravenous immunoglobulin (IVIg) 2 g/kg administered in 5 days (one *dose*) was shown to be effective when applied within the first two weeks after onset of weakness, and nowadays is the treatment of choice. Although treatment with a standard single dosage of IVIg improves outcome, recovery from GBS often

is far from good. Patients with severe GBS and poor prognosis may need additional or a more aggressive therapy to recover. Careful selection of patients eligible for extra therapy is important, because extra treatment entail added complication risks and costs. Multiple clinical, electrophysiology, serological and laboratory factors have been identified as predictors for poor outcome. These include older age, rapid disease progression, preceding diarrhoea/Campylobacter jejuni serology, absence of antecedent upper respiratory tract infection, axonal EMG and anti-GM1 antibodies. 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 a second IVIg course in hospitals were this is common practice is based on this prognostic model.

The I-SID GBS study will be conducted in cooperation with the Inflammatory Neuropathy Consortium (INC). The INC is a worldwide network of neurologists interested to study patients with immune-mediated neuropathies, including GBS. The INC is a working group of the Peripheral Nerve Society (www.PNSociety.com). Members of the INC have been informed by email about this I-SID GBS study. A questionnaire was sent to invent the local IVIg treatment policy in GBS patients among neurologists in different places around the world. According to this questionnaire (response, n=27) 25-50% of the centers treat patients with a poor prognosis already with a second dose of IVIg. However, 96% of the neurologists considered it ethical to randomise GBS patients with a poor prognosis for a second IVIg dose, because the effect this additional IVIg treatment has not been investigated yet. The I-SID GBS study is a prospective international multicenter observational study in which (based on logistics and a limited budget) no randomisation will take place. This has been discussed extensively within the INC.Treatment policy is at full discretion of the individual center. The centers will be asked prior to start of the study whether they are used to treat patients with a poor prognosis (based upon the mEGOS prognostic model) with a second dose IVIg or not and are asked to do the same in this I-SID GBS study.

Study objective

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

Secondary objectives
To investigate whether:
- a second IVIg dose in GBS patients with a poor prognosis improves functional outcome or muscle strength after 8, 12 and 26 weeks.
- a second IVIg dose in GBS patients with a poor prognosis lowers the percentage of patients needing artificial ventilation, lower the time (number of days) on respirator or time on the intensive care.

- a second IVIg dose in GBS patients with a poor prognosis reduces the time to hospital discharge.
- a second IVIg dose in GBS patients with a poor prognosis reduce the chance of secondary deterioration due to treatment-related fluctuations.
- patients treated with a second IVIg dose develop more complications possibly related to the second IVIg treatment.
- a second IVIg dose in GBS patients with a poor prognosis lowers the percentage of patients that die because of GBS.
- serum IgG increase after the first IVIg dose is lower in patients with a poor prognosis.
- serum IgG increases further (and to what extent) after a second IVIg dose in relation to prognosis.

Study design

A prospective international multicenter observational study design will be used.
All GBS patients in need of IVIg treatment, according to the treating neurologist, in a standard dose of 2 g/kg in 2-5 consecutive days, are potentially eligible for this study after obtaining informed consent.
• When patients sign *Informed Consent* they principally agree to be followed up for this I-SID GBS study for a period of 6 months.
• Patients with the poorest prognosis based upon the mEGOS (score 6-12) after the first IVIg dose are treated with a second dose of IVIg in the same dosage as the initial IVIg treatment or receive no additional treatment, according to the local treatment policy.
• mEGOS must preferentially be assessed 7 days after start of first IVIg dose with a range to 8 or 9 days. A second IVIg dose (in patients with mEGOS 6-12) preferentially should be started within 24 hours after determining the mEGOS score at day 7 (max 8-9).
• Patient follow-up will be 6 months.
• Patient inclusion will end when 300 patient (whole range of severity) were included, this is likely to be feasible with approximately 3 years of accrual.

Study burden and risks

Patients will undergo extra blood sampling because of the study participation. Blood sampling will take place before start of standard IVIg treatment, after standard IVIg treatment, after two weeks, after 4 weeks and after 3 months. Mostly it will be possible to collect blood for the study simultaneously with vena punctures performed in the scope of the medical work-up.

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)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

• Patients are diagnosed with GBS according to NINDS diagnostic criteria.(3)
• Indication to start IVIg treatment:
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 6 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, mycofenolatemofetil, 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.
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.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-11-2011
Enrollment:	15
Type:	Anticipated

Ethics review

Approved WMO Date:	23-12-2011
Application type:	First submission
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
CCMO	NL38252.078.11