Dose response of IVIg in CIDP.

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON24231

Source
NTR

Brief title
DRIP

Health condition

Chronic inflammatory demyelinating polyradiculoneuopathy is an autoimmune peripheral nerve disorder leading to muscle weakness and sensory dysfunction.
keywords: CIDP, IV immunoglobulin

Sponsors and support

Primary sponsor: Erasmus MC
's Gravendijkwal 230
Rotterdam
3000 CA
Netherlands
Source(s) of monetary or material Support: This study is supported by an unconditional grant from Baxter Healthcare B.V, The Netherlands.

Intervention

Outcome measures

Primary outcome

Hand grip strength (Vigorimeter) will be used as the primary outcome measure. A difference in the (mean of the 4) Vigorimeter changes from baseline between the two groups of > 8 kPa (mean of both hands) is considered clinically relevant. A difference of > 8 kPa in Vigorimeter change from baseline in favour of the group treated with half the dosage and interval as compared with the other treatment group will be considered a clinical relevant improvement.

Secondary outcome

The Rasch-built overall disability scale (R-ODS) measuring activity status, Rasch fatigue severity scale (R-FSS) measuring fatigue, and quality of life (SF-36) will be used as secondary outcome measures. The secondary objective will be to record the occurrence of side-effects.

Study description

Background summary

Rationale:

High peak levels of serum IgG may not be needed for maintenance treatment of CIDP with intravenous immunoglobulin (IVIg). More frequent dosing of IVIg leads to more stable IgG levels and higher trough levels which appear to correspond with clinical efficacy. Furthermore more frequent dosing leads to lower peak levels which when high are responsible for the systemic side-effects.

Objectives:

The main objective is to investigate whether high frequency low dosage IVIg treatment is more effective than low frequency high dosage as maintenance treatment for CIDP. The secondary objective is to investigate whether high frequency low dosage of IVIg results in less adverse events compared to low frequency high dosage.

Study design:

Double-blind randomised controlled cross-over intervention study.

Study population:

Chronic inflammatory demyelinating polyneuropathy (CIDP) patients who are IVIg dependent receiving a stable maintenance dose and interval of IVIg (Kiovig).

Intervention:

One group will be treated with half their normal dosage of IVIg (with placebo added to maintain the total volume) at half their interval (double their frequency). The other group will be treated with their normal dosage and interval of IVIg followed by a placebo (albumin) infusion. After a wash-out phase, patients will cross-over to the other treatment group.

Main study parameters/endpoints:

Hand grip strength (Vigorimeter) will be used as the primary outcome measure. A difference of > 8 kPa in the mean of the 4 Vigorimeter changes from baseline in favour of the group treated with half the dosage and interval as compared with the other group will be considered a clinical relevant improvement. Changes in the R-ODS, R-FSS, and SF-36 and the occurrence of side-effects will be used as secondary outcome measures.

Study objective

The main objective is to investigate whether high frequency low dosage IVIg treatment is more effective than low frequency high dosage as maintenance treatment for CIDP. The secondary objective is to investigate whether high frequency low dosage of IVIg results in less adverse events compared to low frequency high dosage.

Study design

The study period will be approximately 14-26 weeks, depending on infusion frequency prior to randomisation and includes two “wash-out” infusions. Prior to every infusion, muscle grip strength (Vigorimeter) will be measured (mean of three measurements of both hands) by the nurse. The R-ODS, R-FSS and SF-36 questionnaires will be completed by the patient just before every IVIg infusion.

AEs will be reported by the nurse during every infusion. Just after every infusion a side-effect questionnaire will be completed by the patient.

Intervention

Intervention group/arm:

4 infusions of IVIg of half the normal dosage (with placebo added to maintain the total volume) and half the interval (double the frequency).

Control group/arm:

2 infusion of IVIg according to the normal; dose and interval as well as two sham (placebo) infusions.

The total amount of IVIg given during the whole double-blind phase will remain the same in both groups. As this is a crossover study all patients will receive both treatment schedules once.

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Eligibility criteria

Inclusion criteria

1. Diagnosis of CIDP or acute-onset CIDP made by a consultant neurologist, fulfilling the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) clinical

diagnostic criteria;

2. Age 18 years or older;

3. Significant improvement following the first use of IVIg, defined as a decrease of ≥ 1 grade on the modified Rankin disability scale;

4. To indicate that the patient is still IVIg dependent and has active CIDP, he/she must have shown an objective deterioration (decrease in muscle strength measured with the vigorimeter and/or MRC sum score) following reduction of IVIg dose at some time during the 9 months before randomization or an objective improvement following an increase in IVIg during the 9 months before randomization;

5. Ongoing intermittent treatment with 10% liquid IVIg (Kiovig) for at least 2 infusions. The dose must have been not changed within the 8 weeks prior to the study;

6. EMG findings compatible with CIDP showing peripheral nerve demyelination at least once during their illness;

7. Signed informed consent by the patient.

Exclusion criteria

1. Known IgA deficiency or known allergic reaction to IVIg.

2. Hand grip strength measured by the Martin Vigorimeter equal or more than the median value (kPa) for an age and sex matched healthy control;

3. Maintenance dose less than 15 gram of IVIg every infusion or an infusion interval less than 14 days;

4. Known hereditary neuropathy or severe concomitant diseases such as HIV infection, Lyme disease, chronic active hepatitis, congestive heart failure, systemic lupus erythematosus, drug or toxin induced neuropathy, vasculitis, and malignancies;

5. Multifocal motor neuropathy (MMN), fulfilling the European Federation of Neurological Societies /Peripheral Nerve Society criteria;

6. IgM paraprotein with anti-myelin-associated glycoprotein (MAG) antibodies;

7. Atypical CIDP with pure sensory or persistent unifocal impairment or significant central nervous system involvement;

8. Participation in a controlled trial of an investigational medicinal product within the past 12 weeks;

9. Severe known abnormalities in liver, kidney function or serum glucose level;

10. Treatment with more than 20 milligrams of prednisone a day;

11. Treatment with other immunosuppressives (e.g. methotrexate, azathioprine, prednisone) if the dosage has been changed within 8 weeks prior to start of the study.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-11-2014
Enrollment:	17
Type:	Actual

IPD sharing statement

Plan to share IPD: Yes

Plan description
STATISTICAL ANALYSIS PLAN

Dose response trial of IV immunoglobulin in

chronic inflammatory demyelinating polyradiculoneuropathy

DRIP study
NTR number: 3705

Erasmus MC, Rotterdam, The Netherlands

Version 2
February 14th 2019
Protocol version 1.04

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Introduction

The purpose of the dose response double-blind randomised placebo-controlled trial (DRIP trial) of intravenous immunoglobulin (IVIg) in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is to assess whether high frequency low dosage IVIg treatment is more effective and results in less side effects than low frequency high dosage maintenance treatment for CIDP. The protocol was published earlier. 1
Here we will summarize the statistical analysis of the data. We will describe how missing data will be handled and how (subgroup) analyses will be performed. We do not imply that all analysis will be described in the main paper, because of space restrictions.

Status of the trial

The first patient was included in the DRIP trial in April 2015. In the following years a total of 25 patients were included in 3 centres in the Netherlands. From these 25 patients, 22 patients completed both treatments of this double-blind crossover trial. Three patients did not receive the second treatment because of clinical worsening due to either a treatment failure or a normal fluctuation of their CIDP. The last follow-up took place in July 2018.

Research questions

Primary research question

The primary objective of this study is to assess whether more frequent low dosage IVIg treatment is more effective than less frequent high dosage IVIg treatment as maintenance treatment for CIDP.

Secondary research questions

The secondary objectives are to assess whether more frequent low dosage of IVIg results in less adverse events compared to less frequent high IVIg dosage and to prove that more frequent low dosage of IVIg results in higher IgG trough levels than less frequent high dosage.

Trial design

This is a multi-centre randomised placebo controlled double-blind cross-over intervention trial. In this trial every patient will be treated at baseline (one infusion) according to their own individual established IVIg dosage and interval prior to start of the trial. During the double-blind phase (4 infusions) one group (intervention group) will be treated with half of their normal dosage of IVIg (with placebo added to maintain the total volume) at half of the interval. The other group (contrast treatment) will be treated with their normal dosage and interval of IVIg, followed by a placebo infusion between their regular infusions, so that they receive an infusion of either IVIg or placebo at half of the interval. After a wash-out phase (2 infusions) patients will cross-over to the other treatment group. The total amount of IVIg given during the whole double-blind phase will remain the same in both treatment groups.

Inclusion and exclusion criteria
For a complete list of in- and exclusion criteria we refer to paragraph 4.2 and 4.3 of the protocol version 1.4 on page 16-17, as well as to the publication of the protocol. 1 In short, patients with CIDP of 18 years and older, who are IVIg dependent and who received a stable maintenance dose and interval of IVIg are in principle eligible for inclusion in the trial. To indicate that each single patient is still IVIg dependent and has active CIDP, patients must have shown either an objective deterioration (decrease in muscle strength as measured by the Vigorimeter or the MRC sumscore) following a reduction of IVIg dose or lengthening of the IVIg interval, or an objective improvement following an increase in IVIg dose or shortening of the IVIg interval at some time during the 9 months before randomisation. To be able to measure an improvement in the primary outcome measurement, patients are only eligible when their hand grip strength as measured on the Martin Vigorimeter is less than the median value for an age and sex matched healthy control. 2

Primary and secondary outcomes
The primary outcome is the score on the Martin Vigorimeter (hand grip strength).3, 4 Prior to every infusion, hand grip strength will be measured (mean of the three measurements of both hands will be used) by the nurse administrating the IVIg. To avoid any difference between Vigorimeters, the same Vigorimeter will be used throughout the whole study. The mean of the two Vigorimeter measurements before the first infusion of each double-blind phase will be taken as baseline measurement. In order to assess the effect of the second treatment period, each patient will also be examined (Vigorimeter) at the first infusion after finishing the second part of the study. A difference of > 8 kPa in the mean of the four Vigorimeter changes from baseline in favor of the group treated with half the dosage and interval as compared with the other treatment group will be considered a relevant clinical improvement. The value of 8 kPa is based on the minimum clinically important difference cut-off value of 8 kPa for grip strength (Vigorimeter) using the ½ SD technique. 5
Secondary outcomes concern clinical parameters (regarding disability, fatigue and quality of life), laboratory parameters and safety parameters. Blood samples will be drawn before and after every infusion and questionnaires will be completed after every infusion (except for the Sf-36 which will be taken less often).
Clinical parameters:
- Changes in the score on the Rasch-built Overall Disability Scale (R-ODS). 6, 7
- Changes in the score on the modified Rasch-built Fatigue Severity Scale (R-FSS).8, 9
- Changes in the score on the Short Form (36) Health Survey, Dutch language acute version 2 (SF-36). 10

Laboratory parameters:
- Changes in the serum IgG level as determined by turbidimetry.

The percentage of patients with at least one serious adverse event (SAE) will be compared. Furthermore, the most common reported side effects will be described and the number of patients reporting these will be compared between both groups.

Randomisation and blinding
A computer-generated list of random assignments was prepared by the study statistician. A block randomisation was made for each centre. The pharmacist holds treatment codes for all participants in the trial. Allocation concealment was ensured via sequentially numbered, opaque, sealed envelopes. A trial pharmacist prepared and blinded the trial medication during both blind phases of the trial. Albumin 0.5% was chosen as the placebo because of its identical appearance to IVIg during visual inspection in EVA bags and has been used in other IVIg trials.11 Blinded study medication was always divided over two EVA bags during the whole study so that IVIg as well as placebo did not have to be diluted and in order to maintain the blind. When half the dosage of IVIg was given, placebo was added to maintain the blind by using the same volume in total. Allocation will be revealed after all patients have completed the trial and data entry has been declared complete.

Statistical analysis
Primary effect analysis
The main analysis of this trial consists of a comparison of the change from baseline in Vigorimeter measurements between the two treatments. A cross-over design was chosen because of its statistical efficiency where each patient acts as his/her own control, enabling a more precise estimate of the treatment effect. The analysis is based on the intention-to-treat principle. Patients who did not complete both treatments in this cross-over trial are described in detail, but will be excluded from the analysis. The mean Vigorimeter change from baseline, as well as the changes in secondary outcomes such as in serum IgG level, will be compared between both treatments using mixed models adjusting for possible carry-over effect. The percentage of patients with at least one SAE (for which a doctor was consulted) will be compared using McNemar’s test. The most common reported side-effects will be described using descriptive statistics and the number of patients reporting these in both groups will be compared using chi-square test of Fisher’s exact test.
Missing data
Missing data (if any) for secondary outcome variables will be analysed for randomness and imputed with standard methods. Missing items responses on the SF-36 are handled according to the user’s manual for the SF-36 version 2 Health survey. 12

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11. Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol 2008; 7(2): 136-44.
12. Ware JE Jr KM, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. User's manual for the SF-36v2 Health Survey. . Quality Metric Inc Lincoln 2007; 6(5): 53-64.

Ethics review

Positive opinion

Date:	14-11-2012
Application type:	First submission

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
NTR-new	NL3555
NTR-old	NTR3705
Other	METC Erasmus MC : MEC-2014-407
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A