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Intravenous immunoglobulin and intravenous methylprednisolone as optimal first line treatment in chronic inflammatory demyelinating polyneuropathy (CIDP)

Submission date
26/01/2018

Recruitment status
No longer recruiting

Registration date
12/02/2018

Overall study status
Completed

Last Edited
03/01/2024

Condition category
Nervous System Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare neurological disorder which causes chronic inflammation (swelling) of nerves causing weakness and sensory problems in legs and arms. Induction treatment (the first phase of treatment) CIDP currently consists of either intravenous immunoglobulin (IVIg) (treatment made from donated blood that contains health anitbodies) infusions or high dose corticosteroids (anti-inflammatory medication), including daily oral prednisolone, pulsed dexamethasone or pulsed intravenous methylprednisolone (IVMP) (types of steroids). Both IVIg and IVMP are recommended as first line treatment, but choice of induction treatment is usually based on patients' and physicians' preferences as both treatment options have their own specific advantages. Patients treated with IVIg usually respond fast, but this treatment rarely leads to long term remissions (meaning the symptoms are gone). Corticosteroids may lead to long term remissions. Both fast clinical response and long term remissions can be considered equally important. The aim of this study is to determine whether the addition of methylprednisolone to IVIg as induction treatment leads to a better outcome.

Who can participate?
Adults aged 18 and older who have probably or definite CIDP.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group receive intravenous immunoglobulin (IVIg) + intravenous methylprednisolone. Those in the second group receive intravenous immunoglobulin (IVIg) + placebo (saline infusion). Participants receive seven infusions every three weeks over the course of 18 weeks. During the 18 week intervention period participants are prescribed osteoporosis prophylactics (vitamin D daily and alendronic acid weekly). In the Netherlands the first treatment is given in the hospital and the remaining six infusions are given at home. Outpatient clinic visits are planned every six weeks during the

intervention period and a consultation by phone is planned three weeks after start of intervention period. Three follow-up visits are planned in week 24, 52 and 104. Unscheduled visits can be planned at any time during study.

What are the possible benefits and risks of participating?
Participants can benefit from the combination therapy: a fast improvement of symptoms (attributed to the IVIg) and long term remission (attributed to the methylprednisolone), without the need for further treatments. Risks include medication induced side effects. These side effects include (and not limited to) gastro-intestinal complaints, headaches, muscle aches, oedema, mood/behavior disorders (methylprednisolone); musculoskeletal complaints (muscle, joint and/or bone aches) and gastro-intestinal complaints (alendronic acid); skin rash, hypertension, headaches and gasto-intestinal complaints (IVIg, standard care).

Where is the study run from?
This study is being run by the Academic Medical Center (AMC) (The Netherlands). A total of 14 hospitals (8 in The Netherlands and 6 in the United Kingdom) are participating in this trial.

When is the study starting and how long is it expected to run for?
January 2018 to March 2025

Who is funding the study?
The Academic Medical Center (AMC) (The Netherlands)

Who is the main contact?
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Contact information

Type(s)
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Additional identifiers

EudraCT/CTIS number
2017-002511-34

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
Protocol version 1.0 (26NOV2017); ABR: NL 62561.018.17

Study information

Scientific Title
Intravenous immunoglobulin and intravenous methylprednisolone as optimal induction treatment in CIDP

Acronym
OPTIC

Study objectives
Primary objective of this randomized controlled trial is to assess whether combining IVIg and methylprednisolone leads to more frequent long-term remission in CIDP compared to treatment with IVIg alone.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 16/01/2018, METC (Medical Ethics Committee) Amsterdam UMC (Meibergdreef 9, Amsterdam, 1105AZ, Netherlands; +3120; metc@amsterdamumc.nl), ref: METC project 2017_316

Study design

Multicentre randomized double-blind placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Interventions
All participants are treated with intravenous IVIg, which is considered standard care. In addition, participants are randomized to receive either 7 infusions methylprednisolone (IVMP) 1000 mg in sodium chloride 0,9%, or placebo (100 ml sodium chloride 0,9%). Participants are treated every 3 weeks during an 18-week intervention period. In addition, all patients receive osteoporosis prophylactics (calcium/vitamin D 500 mg/800IE daily and alendronic acid 80 mg weekly) during the 18 week intervention period.

In the Netherlands the first treatment is given in the hospital and the remaining six infusions are given at home. Outpatient clinic visits are planned every 6 weeks during the intervention period and a consultation by phone is planned 3 weeks after start of intervention period. Three follow-up visits are planned in week 24, 52 and 104. Unscheduled visits can be planned at any time during study. A total of 14 hospitals (8 in The Netherlands and 6 in the United Kingdom) are participating in this trial. The Academic Medical Center (AMC) in Amsterdam (The Netherlands) is the study sponsor.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
IVIg (standard care) Methylprednisolone (intervention) Sodium chloride 0.9% (placebo) Calcium /vitamin D (osteoporosis prophylactic) Alendronic acid (osteoporosis prophylactic)

Primary outcome measure
The number of patients in remission is a value determined 1 year after start of the intervention period by accounting for the patients who fit the criteria for remission. Remission is defined as: sustained improvement without the need for further treatment. Improvement is defined as

improvement by at least the minimal clinical important difference (MCID) on the inflammatory Rasch Disability Scale (I-RODS) and/or improvement (ie, decrease) of one point or more on the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale at 18 weeks compared to baseline. Sustained is defined as no deterioration between week 18 and week 52, i. e. difference on the I-RODS of less than the individual MCID difference and/or no increase on the adjusted INCAT disability scale.

Secondary outcome measures
Secondary parameters are assessed at 18 and 52 weeks, or earlier if a preliminary endpoint is reached:
1. The number of patients with improvement on disability equal or more than the MCID: disability is measured using the iRODS and the INCAT disability scale, the number of patients are calculated by counting the patients who fit the definition of improvement
2. Time to improvement (≥ MCID) on disability: time to improvement is calculated and given in days and/or weeks
3. Mean change in disability: disability is measured using the iRODS and INCAT disability scale
4. Mean change in grip strength: grip strength (in kPa) is measured using a handheld (Martin) Vigorimeter
5. Mean change in muscle strength: The Medical Research Council (MRC) sum score of 12 predefined muscle groups (including shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and foot dorsiflexion) is used to measure muscle strength
6. Mean change in sensory impairment: measured using the Inflammatory Neuropathy Cause and Treatment sensory sumscore (INCAT-SS)
7. Mean change in fatigue: measured using the Fatigue Severity Scale (FSS)
8. Mean change in pain: measured using the pain intensity numeric rating scale (PI-NRS)
9. Mean change in health related quality of life (HRQL): measured using the EuroQol
10. Number of (serious) adverse events (including corticosteroid associated adverse events): number of (serious) adverse events (including corticosteroid associated adverse events) are measured using a structured questionnaire with short term corticosteroid and IVIg related AE's at the 18 week visit. AEs are scored as mild, moderate or severe by the investigator. Long-term corticosteroid related AEs will be filled in by the investigator at 52 weeks (secondary outcome) and 104 weeks (safety follow-up). Adverse events questionnaires will be filled in only after completion of all other outcome assessments.
11. Care use and overall healthcare-related costs: measured using the working documents and the Medical Consumption Questionnaire (iMCQ) complemented with extra questions relevant for the study population and the Productivity Cost Questionnaire (iPCQ)

Overall study start date
01/01/2018

Completion date
15/03/2025

Eligibility

Key inclusion criteria
1. Probable or definite CIDP according to the EFNS/PNS criteria 2010 (all CIDP phenotypes)
2. Age ≥ 18 years
3.1. Treatment naïve patients; or

3.2. Previously treated patients who have a relapse after a remission of at least 1 year; or
3.3. Patients treated with subjective or objective improvement after a single loading dose of IVIg in the last 3 months, and subsequent deterioration as judged by his or her treating physician.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
96

Key exclusion criteria
Current exclusion criteria as of 22/11/2022:

1. Presence of IgM paraproteinemia and/or anti-MAG antibodies or known CIDP-specific antibodies associated with poor treatment response to IVIg
2. Use of drugs known to cause a demyelinating neuropathy
3. Use of any immunosuppressive or immunomodulatory drugs in the previous 6 months (except for a single loading dose of IVIg within 3 months or low dose prednisolone (20 mg or less) for a short period not exceeding two weeks)
4. Known serious adverse events (SAEs) with previous IVIg or corticosteroid treatment. Hypersensitivity to methylprednisolone or any component of the formulation. Hypersensitivity to the human immunoglobulins or to any of the excipients. Selective IgA deficiency patients who developed antibodies to IgA
5. Systemic fungal infections, unless specific anti-infective therapy is employed
6. Known hyperprolinaemia type I or II or known fructose intolerance
7. One or more of the risk factors associated with increased risk of AEs of IVIg or IVMP or conditions that could lead to unblinding of treatment (i.e. diabetes; IgA deficiency; gastric ulcers; psychosis; severe hypertension (180/110 mmHg or more on repeated measurements); hypocalcaemia (lower than 2.20 mmol/L, corrected for albumin); moderate or severe heart failure; severe cardiovascular disease (i.e. more than one myocardial infarction and or ischemic stroke); renal failure (glomerular filtration rate < 30 ml/min)
8. History of osteoporosis or osteoporotic fractures
9. Known active malignancy, currently treated with chemotherapy or immunomodulatory drugs, or with a life expectancy of less than one year
10. Bodyweight more than 120 kg
11. Pregnancy or nursing mother; intention to become pregnant during the course of the study; female patients of childbearing potential either not using or not willing to use a medically reliable method of contraception for the entire duration of the study. A woman is considered of childbearing potential from menarche and until becoming post-menopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Acceptable methods of contraception are: combined (oestrogen

and progestogen-containing) hormonal contraception associated with inhibition of ovulation (whether oral, intravaginal or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (whether oral, injectable or implantable), progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, male or female condom with or without spermicide, cap or diaphragm, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
12. Known cataract requiring surgery (previously: Known cataract or cataract obvious on fundoscopy)
13. Current psychosis or past history of psychosis
14. Poor dental status
15. Known pulmonary embolism or other deep venous thrombosis in patient's medical history, without current anticoagulant therapy
16. Adults lacking capacity to give informed consent (IC)
17. Lack of written IC

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Previous exclusion criteria as of 30/05/2018, to reflect changes approved by the ethics committee 25/05/2018:

1. Presence of IgM paraproteinemia and/or anti-MAG antibodies or CIDP-specific antibodies associated with poor treatment response to IVIg
2. Use of drugs associated with a demyelinating neuropathy
3. Use of any immunosuppressive or immunomodulatory drugs in the previous 6 months (except for a single loading dose of IVIg within 3 months or low dose prednisolone (20 mg or less) during a short period (maximum duration of two weeks).
4. Known serious adverse events with previous IVIg or corticosteroid treatment
5. One or more of the risk factors associated with increased risk of adverse events of IVIg or IVMP or conditions that could lead to unblinding of treatment (i.e. diabetes; IgA deficiency; gastric ulcers; psychosis; severe hypertension (180/110 mmHg or more on repeated measurements); hypocalcaemia (lower than 2.20 mmol/L, corrected for albumin); moderate or severe heart failure; severe cardiovascular disease (i.e. more than one myocardial infarction and or ischemic stroke); renal failure (glomerular filtration rate < 30 ml/min)
6. History of osteoporosis or osteoporotic fractures
7. Known malignancy with a survival expectancy of less than 1 year
8. Bodyweight more than 120 kg
9. Pregnancy or nursing mother; intention to become pregnant during the course of the study; female patients of childbearing potential either not using or not willing to use a medically reliable method of contraception for the entire duration of the study
10. Cataract
11. Psychosis
12. Poor dental status
13. Known pulmonary embolism or other deep venous thrombosis in patient's medical history, without current anticoagulant therapy
14. Legally incompetent adults
15. Lack of written informed consent

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Previous exclusion criteria:

1. Presence of IgM paraproteinemia and/or anti-MAG antibodies or CIDP-specific antibodies associated with poor treatment response to IVIg
2. Use of drugs associated with a demyelinating neuropathy
3. Use of any immunosuppressive or immunomodulatory drugs in previous 6 months (except for a single loading dose of IVIg within 3 months or low dose prednisolone (20 mg or less) during a short period (maximum duration of two weeks).
4. Known serious adverse events with previous IVIg or corticosteroid treatment
5. One or more of the risk factors associated with increased risk of adverse events of IVIg or IVMP or conditions that could lead to unblinding of treatment (i.e. diabetes; IgA deficiency; gastric ulcers; psychosis; severe hypertension (180/110 mmHg or more on repeated measurements); hypocalcaemia (lower than 2.20 mmol/L, corrected for albumin); moderate or severe heart failure; severe cardiovascular disease (i.e. more than one myocardial infarction and or ischemic stroke); renal failure (glomerular filtration rate < 30 ml/min)
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10. Cataract
11. Psychosis
12. Poor dental status
13. Legally incompetent adults
14. Lack of written informed consent

Date of first enrolment
19/02/2018

Date of final enrolment
01/12/2024

Locations

Countries of recruitment
England

Netherlands

Scotland

United Kingdom

Study participating centre
Academic Medical Center (AMC)
Meibergdreef 9
Amsterdam
Netherlands
1105 AZ

Study participating centre
Erasmus Medical Center
Rotterdam
Netherlands
3015 CE

Study participating centre
University Medical Center Utrecht
Utrecht
Netherlands
3584 CX

Study participating centre
Maastricht University Medical Center
Maastricht
Netherlands
6229 HX

Study participating centre
Radboud University Medical Center
Nijmegen
Netherlands
6525 GA

Study participating centre
University College London Hospital
London
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London NW1 2BU

Study participating centre
King's College Hospital
London
United Kingdom
SE5 9RS

Study participating centre

University Hospitals of Birmingham
Birmingham
United Kingdom
B15 2TH

Study participating centre
Queen Elizabeth University Hospital
Glasgow
United Kingdom
G51 4TF

Study participating centre
Royal Victoria Infirmary
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
The Walton Centre
Liverpool
United Kingdom
L9 7LJ

Sponsor information

Organisation
Academic Medical Center (AMC)

Sponsor details
Meibergdreef 9
Amsterdam
Netherlands
1105 AZ

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/03t4gr691

Funder(s)

Funder type
Charity

Funder Name
ZonMw

Alternative Name(s)
Netherlands Organisation for Health Research and Development

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Netherlands

Funder Name
Prinses Beatrix Spierfonds

Funder Name
Sanquin Plasma Products B.V.

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal, with the intent to publish the results in one year following overall trial end date.

Added 28/02/2020:
Protocol, including statistical analysis plan, will be published in a peer-reviewed journal in 2020 (prior to inclusion of last patient).

Intention to publish date
01/06/2024

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date. When this information becomes available we will disclose it.

Added 28/02/2020:
The manuscript reporting on the results of this clinical trial will include an Individual Participant Data (IPD) sharing statement, which is in line with the 2017 ICMJE statement.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	19/02/2021	22/02/2021	Yes	No