Intravenous immunoglobulin therapy for small fiber neuropathy: a randomized, double-blind, placebo-controlled study on efficacy and safety.

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Primary objective: To evaluate the efficacy of IVIg treatment (4 courses of treatment, 3 weeks apart) compared to placebo on pain alleviation. Secondary objectives: 1. Pain intensity, pain qualities, and other SFN related complaints, daily and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Peripheral neuropathies
Study type	Interventional

Summary

ID

NL-OMON47574

Source
ToetsingOnline

Brief title
IVIg in SFN

Condition

- Peripheral neuropathies

Synonym
small fiber neuropathy

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht

Source(s) of monetary or material Support: Grifols

Intervention

Keyword: Intravenous immunoglobulin, Small fiber neuropathy, Treatment

Outcome measures

Primary outcome

The primary endpoint is the comparison of the percentage of responder subjects between the two treatment groups from the first randomization during 12 weeks treatment. A responder is defined as * 2 points PI-NRS improvement on the mean weekly peak pain relative to baseline.

Secondary outcome

* The daily pain intensity (defined as the mean pain experienced during the day: from waking up to 6 pm), the nocturnal pain intensity (6 pm until waking up), and the average of these two will also be assessed using the PI-NRS, twice a week (Monday/Friday).

* Change of painful symptoms will be compared to baseline using the patients* global impression of change (PGIC) on a 7-point Likert scale. Subsequent scores of the PGIC are 1) *worse than ever*; 2) *much worse*; 3) *little worse*; 4) *no change*; 5)*little improved*; 6) *much improved*; 7)*completely resolved*. *Completely resolved* and *much improved* are considered as a relevant improvement. Clinically relevant pain reduction on PGIC for pain will be defined as score 6 (*much improved*) or 7 (*completely resolved*).

* The Rasch-transformed 13 items SFN symptoms inventory questionnaire (RT-SFN-SIQ) highlights sensory symptoms, pain and autonomic complaints.16 Differences between the two arms will be examined using its score obtained

after interval transformation using the Rasch method.

* The amount of pain medication used during the trial will be registered in the pain diary and will be used to compare the impact of the treatment versus placebo arms.

* Pain relief will also be captured twice a week (Monday/ Friday) using a 5-point Likert-scale: 0: no relief, 1: slight, 2: moderate, 3: good, and 4: complete relief. This is according to the IMMPACT recommendations.

* The neuropathic pain scale (NPS) will also be recorded to determine the various pain qualities.

* Daily Sleep Interference Scale (DSIS) will also be completed by subject twice a week on waking (11-point numerical scale ranging from 0 (pain does not interfere with sleep) to 10 (pain completely interferes with sleep)).

* Rasch-built Overall disability Outcome Scale specifically designed for SFN (SFN-RODS): the SFN-RODS is the only clinimetrically evaluated scale at the activity and participation level for assessing outcome in this disorder. Its incorporation will be providing data on its possible responsiveness.

* The Short Form 36 Health Survey (SF-36) is a generic quality of life measure.

* Adverse events.

Study description

Background summary

Small fiber neuropathy (SFN) is the most common cause of neuropathic pain in peripheral neuropathies, with a prevalence of at least 53/100.000. Patients with SFN may have excruciating pain and current anti-neuropathic and other pain drugs do not relief pain substantially. Several studies suggested an

immunological basis in SFN and case studies have reported efficacy of treatment with intravenous immunoglobulin (IVIg) in patients with SFN. It is therefore conceivable that immunological mechanisms play a role in idiopathic SFN (I-SFN). However, to date no randomized controlled study with IVIg in patients with SFN has been performed. The aim of the current study is to investigate the efficacy and safety of IVIg in patients with I-SFN in a randomized, double-blind, placebo-controlled study.

Study objective

Primary objective: To evaluate the efficacy of IVIg treatment (4 courses of treatment, 3 weeks apart) compared to placebo on pain alleviation.
Secondary objectives: 1. Pain intensity, pain qualities, and other SFN related complaints, daily and social functioning, as well as quality of life will be assessed, as secondary objectives; 2. Safety: Adverse events, vital signs and laboratory values outside the normal range.

Study design

Randomized, double-blind, placebo-controlled, prospective pilot study.

Intervention

The test product is intravenous human immunoglobulin. The period will start with a loading dose of 2 g/kg body weight over 2-4 consecutive days. All other infusions are given as maintenance doses of 1 g/kg body weight at intervals of 3 weeks. Placebo is 0.9% saline. According to the double-blind character of the study, the volume and mode of placebo infusion will be identical to that of IVIg. The trial will be registered at ClinicalTrials.gov and at EudraCT.

Study burden and risks

Risks of the study are related to known side effects of IVIg. IVIg may have a beneficial effect on pain, which can be excruciating in patients with SFN.
Study duration will be 12 weeks.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria:
* 18 years or older.
* Skin-biopsy proven idiopathic SFN or idiopathic painful neuropathy with predominantly SFN pattern
* Pain intensity rated * 5 on the PI-NRS (maximum pain) or on the neuropathic pain scale question number 1 for at least 12 weeks before the study as declared by each patient to the best of their knowledge; if available, medical records of each patient will be consulted on the reported pain intensity.
* Each subject will receive an information leaflet and an informed consent form. Subjects must give informed consent by signing and dating prior to study entry.
* Eligible patients must be willing to complete all study-related activities and examination required by the protocol.

Exclusion criteria

Patients will be excluded if they:
* Are unable or unwilling to provide written informed consent.
* Have predominant clinical picture of large nerve fiber involvement (i.e., weakness, loss of vibration sense, hypo-/areflexia).
* Had treatment with IVIg or any other immunomodulatory/immunosuppressive agents (e.g.,

steroids) within the last 12 weeks prior to the date of informed consent.
* Have an underlying cause of SFN (diabetes, SCN9A/10A/11A mutations, hypothyroidism, renal failure, vitamin B12 deficiency, monoclonal gammopathy, alcohol abuse (more than 5 IU/day), malignancies, drugs that cause neuropathy (e.g. chemotherapy, amiodarone, propafenone)).
* Have a history of anaphylaxis or severe systemic response to immunoglobulin or with a blood product.
* Have cardiac insufficiency (NYHA III/IV), cardiomyopathy, significant cardiac dysrhythmia requiring treatment, unstable or advanced ischemic heart disease, or history of congestive heart failure, severe hypertension (diastolic blood pressure >120 mmHg or systolic >170 mmHg).
* Are females who are pregnant, breast-feeding, or if of childbearing potential, or unwilling to practice adequate contraception throughout the study.
* Have known hyperviscosity.
* Have a history of renal insufficiency or high serum creatinine levels .
* Have known selective IgA deficiency.
* Have conditions whose symptoms and effects could alter protein catabolism and/or IgG utilization (e.g. protein-losing enteropathies, nephrotic syndrome).
* Have a known hypercoagulable state.
* Are mentally challenged adult subjects unable to give independent informed consent.
* The use of pain (analgesic/anti-neuropathic) medication is allowed, but only if dosages are remained unchanged for at least 30 days prior to randomization. A change in dosage of these drugs will not be allowed throughout the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-07-2016

Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gamunex 10%
Generic name:	human immunoglobulin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-11-2015
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-12-2015
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-08-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-10-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2015-002624-31-NL
CCMO	NL53861.068.15

Study results

Date completed:	31-10-2019
Actual enrolment:	60