A placebo-controlled double blind randomized trial to investigate the efficacy and safety of the combination of Penicillin G / Hydrocortisone treatment in ALS patients (PHALS).

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The objective is to compare the efficacy and safety of intravenous high-dose penicillin G and hydrocortisone versus placebo in combination with riluzole in the treatment of patients suffering from Amyotrophic Lateral Sclerosis (ALS).

Ethical review	Approved WMO
Status	Completed
Health condition type	Neuromuscular disorders
Study type	Interventional

Summary

ID

NL-OMON44566

Source
ToetsingOnline

Brief title
PHALS

Condition

- Neuromuscular disorders

Synonym
Amyotrophic lateral sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: subsidie van ALS Stichting Nederland

Intervention

Keyword: ALS, Amyotrophic lateral sclerosis, Hydrocortisone, Penicillin G

Outcome measures

Primary outcome

Change from baseline to week 48 in Amyotrophic Lateral Sclerosis Functional

Rating Scale - Revised (ALSFRS-R).

Secondary outcome

Changes in both treatment arms:

- Survival

- Change in sVC (measure for lungcapacity)

- Change in muscle strength

- Change in plasma creatinin

- Mean time spent in each stage of the King*s staging system and ALS

Milano-Torino Staging system (ALS-MITOS).

- Time to gastrostomy defined as the time from randomization to the time of

the gastrostomy.

- Changes in score on the EQ-5D-5L.

- Change in the Center for Neurological Study - Bulbar Functional Scale

(CNS-BFS)

- Safety: Number of Serious Adverse Events (SAEs), changes on clinical

examination including vital signs and weight, laboratory exams (biochemistry

and hematology).

Study description

Background summary

In a recent case series improvement and/or stabilization of neurological deficits was reported in ALS patients in response to treatment with penicillin G and hydrocortisone. Although limited preclinical data on available penicillin G and hydrocortisone is available, there is a considerable body of evidence suggesting that beta-lactam antibiotics, the category to which penicillin belongs, might have neuroprotective effects in ALS by inducing EAAT2 expression leading to lower levels of glutamate and hereby ameliorating excitotoxicity.

Study objective

The objective is to compare the efficacy and safety of intravenous high-dose penicillin G and hydrocortisone versus placebo in combination with riluzole in the treatment of patients suffering from Amyotrophic Lateral Sclerosis (ALS).

Study design

A mono-center randomized, placebo-controlled, double blind Phase 2 trial of Penicillin G and Hydrocortisone in ALS

Intervention

A total of 16 patients will be randomized in 2 groups, where one group will receive intravenous penicillin G (1 - 20 million units in escalating dose) during 3 weeks and 100 mg hydrocortisone during the first 2 weeks in combination with riluzole at 3-month intervals over the course of 48 weeks and the other group will receive placebo (intravenous 0.9% saline solution identical to the actual medication) for 3 weeks in combination with riluzole at 3-month intervals over the course of 48 weeks.

Study burden and risks

Patients will undergo 4 courses of intravenous treatment at 3 month intervals lasting 3 weeks each, during which study medication will be administered daily over the course of 8 hours. For all 4 courses of treatment patients will be admitted to the neurology ward of the UMC Utrecht. At Day 1 and 21 of each

treatment cycle patients will undergo a neurological examination, muscle strength testing, respiratory assessment, laboratory investigations and fill in questionnaires. Each visit will take approximately two-three hours and beside a blood draw patients will not experience any discomfort. The main risks associated with penicillin are seen in patients with penicillin allergy or those with bacterial infections. Patients with either of these conditions will not be permitted to participate. Short courses of hydrocortisone are generally well-tolerated and if side effects do occur they subside after treatment is discontinued. In this study hydrocortisone will be given for 2 weeks during each treatment course. All side effects can be effectively managed by any physician in accordance with standard practices. Therefore the risks of the study medication appear to be acceptable. The limited clinical findings reported in the literature suggest that ALS patient may stabilize or even improve in response to this treatment, in what is now a relentlessly progressive and fatal neurodegenerative disease. Therefore potential benefits outweigh the potential risks for this study.

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

1. Patients must be over 18 years of age.
2. Patients diagnosed with laboratory supported, clinically probable or definite ALS according to the World Federation of Neurology Revised El Escorial criteria (Brooks, 1994).
3. Disease duration from symptoms onset no longer than 24 months at the screening visit.
4. Patient with a FVC (Forced Vital Capacity) equal to or more than 80% predicted normal value for gender, height, and age at the screening visit
5. Patients must have bulbar involvement (defined as clinically evident dysarthria or a >=1 point drop on questions 1-3 of the revised version of the ALS functional rating scale (ALS-FRS-R).
6. Patient treated with a stable dose of riluzole (100 mg/day) for at least 30 days prior to screening.

Exclusion criteria

1. Patients with concomitant frontotemporal dementia (FTD).
2. Patients who underwent gastrostomy.
3. Patients with syphilis or a medical history of syphilis.
4. Patients with known penicillin allergy or patients with a positive penicillin allergy skin test.
5. Patients with a contra-indication for using penicillin (use of methotrexate, renal insufficiency).
6. Patients with a medical history of epilepsy.
7. Patients with a contra-indication for using hydrocortisone (uncontrolled hypertension or diabetes mellitus, ulcus ventriculi or ulcus duodeni, patients with acute infections)
8. In the case of a female with childbearing potential, the patient must not be pregnant or breast-feeding. Women of childbearing potential should use adequate contraception.
9. Patients with a concomitant infection.
10.Patients currently treated with corticosteroids.

Study design

Design

Study phase:	2
Study type:	Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	21-11-2017
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Hydrocortisone - powder for solution
Generic name:	Hydrocotisone
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	natriumbenzylpenicillin - powder for solution
Generic name:	penicillin G
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	29-08-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	28-09-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-02-2018

Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2017-001983-39-NL
CCMO	NL61931.041.17

Study results

Date completed:	04-04-2019
Results posted:	15-07-2020

First publication
15-07-2020