A double-blind, randomised, placebo-controlled trial of prolonged antibiotic treatment after intravenous ceftriaxone in patients with (possible) persistent Lyme disease.

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Prolonged antibiotic treatment of patients diagnosed with presumed PLD (as endorsed by the international ILADS guidelines) leads to better patient outcome than short-term treatment as endorsed by the Dutch CBO guidelines.

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

Summary

ID

NL-OMON20560

Source
NTR

Brief title
PLEASE

Health condition

Borrelia, Lyme

Sponsors and support

Primary sponsor: University Medical Center St Radboud
Source(s) of monetary or material Support: ZonMw: The Netherlands Organisation for Health Research and Development

Intervention

Outcome measures

Primary outcome

Because different operationalizations of the term ‘Global score 36-item Short-form General Health Survey (SF 36)’ exist, the primary outcome measure is specified here as the ‘physical component summary score’ (PCS) of the RAND-36 Health Status Inventory (RAND SF-36, Hays 1998), which is similar to the Medical Outcomes Study (MOS) 36-item Short-Form General Health Survey (SF-36). The PCS is also known as the physical health composite score (PHC). This specification has been communicated to the local Ethics Committee on March 1, 2011, and was approved on April 6, 2011.

Secondary outcome

1. Subscales 36-item Short-form General Health Survey (SF 36). Time Frame: Weeks 0, 14, 26 and 40;
2. Actometer recording during 14 days (objective physical activity). Time Frame: Weeks 0, 14 and 40;
3. Measurements of neuropsychological impairment. Time Frame: Weeks 0, 14, 26 and 40;
4. Economic evaluation: Questionaire EQ-5D, health consumption and productivity of labour. Time Frame: Weeks 0, 14, 26 and 40;
5. Fatigue subscale of Checklist Individual Strength (CIS). Time Frame: Weeks 0, 14, 26, and 40. After the last comprehensive outcome assessment at week 40, patients are surveyed by post-study questionnaires at week 52, regarding Subscales of 36-item Short-form General Health Survey, Economic evaluation and Fatigue subscale of Checklist Individual Strength. (Protocol version 3.8; dated July 17, 2009; final Ethics Committee approval April 29, 2010).

Study description

Background summary

This study is a double blind, randomised, placebo-controlled trial of prolonged antibiotic treatment after intravenous ceftriaxone. All patients will initially receive open-label i.v. ceftriaxone in a home-care setting for two weeks, which is the standard of care for presumed or proven neuroborreliosis according to both guidelines. Then patients will be randomised to one of 3 treatment arms. Subsequently, blinded oral follow-on treatment will be given in 3 randomisation arms:
1. Oral doxycycline for 12 weeks;
2. Oral clarithromycin plus hydroxychloroquine for 12 weeks, or;
3. Oral placebo for 12 weeks.

The primary goal of the study is to establish whether prolonged antibiotic treatment of patients diagnosed with presumed PLD (as endorsed by the international ILADS guidelines) leads to better patient outcome than short-term treatment as endorsed by the Dutch CBO guidelines. Secondary objectives will be studied in an explorative way. The secondary goals include the effect of randomised treatment modalities on pain, functional impairment, psychological functioning, social behaviour, cognitive functioning, and safety. Moreover, cost-effectiveness will be determined by assessment of costs from societal perspective and quality-adjusted life years.

Screening will be done according standard clinical and laboratory protocols. After obtaining informed consent, baseline assessments include clinical, laboratory, microbiological and (neuro)psychological evaluation and objective assessment of physical activity, using an accelerometer.
Study visits will be performed at baseline, week 2, 8 and 14 for safety evaluation. Efficacy evaluation will be performed at week 14 (end of treatment period, EOT), and at week 26 (12 weeks after EOT) and week 40 (end of study, EOS, 26 weeks after EOT), consisting of clinical and psychological assessment and accelerometer registration.

Study objective

Prolonged antibiotic treatment of patients diagnosed with presumed PLD (as endorsed by the international ILADS guidelines) leads to better patient outcome than short-term treatment as endorsed by the Dutch CBO guidelines.

Study design

Weeks 0, 14, 26 and 40.

Intervention

Arm 1: After open-label i.v. ceftriaxone 2000 mg qd via a peripheral i.v. catheter: oral Doxycycline 100 mg combined with a placebo b.i.d. for 12 weeks.

Arm 2: After open-label i.v. ceftriaxone 2000 mg qd via a peripheral i.v. catheter: clarithromycin 500 mg combined with hydroxychloroquine 200 mg b.i.d. for 12 weeks.

Arm 3: After open-label i.v. ceftriaxone 2000 mg qd via a peripheral i.v. catheter: 12 weeks' course of double placebo b.i.d.

Contacts

Public
Postbus 9101, Postnummer 463
A. Berende

UMC St Radboud, Algemene Interne Geneeskunde
Nijmegen 6500 HB
The Netherlands
+31 (0)24 3618819
Scientific
Postbus 9101, Postnummer 463
A. Berende
UMC St Radboud, Algemene Interne Geneeskunde
Nijmegen 6500 HB
The Netherlands
+31 (0)24 3618819

Eligibility criteria

Inclusion criteria

1. Males or non-pregnant, non-lactating females who are 18 years or older;
2. Women of child-bearing potential must agree to use contraception methods other than oral contraceptives during the study therapy period, since failure of oral contraceptives due to long-term antibiotic use has been described and doxycycline might be teratogenic;
3. Patients with presumed or proven PLD. In this study, clinical suspicion of PLD is defined as complaints of musculoskeletal pain, arthritis or arthralgia, neuralgia or sensory disturbances (such as paraesthesias or dysesthesias), neuropsychological or cognitive disorders, and persistent fatigue, that are:
temporally related to an episode of erythema migrans or otherwise proven symptomatic Lyme disease (defined as within 4 months after erythema migrans as assessed by a physician, or positive biopsy, PCR, culture, intrathecal B. burgdorferi antibodies), OR accompanied by a positive B. burgdorferi IgG or IgM immunoblot (as defined by strict criteria in line with the European Union Concerted Action on Lyme Borreliosis (EUCALB)), regardless of prior ELISA IgG/IgM screening results;
4. Subjects must sign a written informed consent form.

Exclusion criteria

1. Subjects with a known history of allergy or intolerance to tetracyclines, macrolides, hydroxychloroquine or ceftriaxone;
2. Subjects who have had more than 5 days of antimicrobial therapy with activity against B. burgdorferi within the previous 4 weeks;
3. Subjects with a presumed diagnosis of neuroborreliosis (CSF pleiocytosis or intrathecal antibody production) for which intravenous antimicrobial therapy is required;
4. Subjects with a known diagnosis of HIV-seropositivity or other immune disorders. (No HIV serologic testing is required for the study);

5. Subjects with positive syphilis serology or signs of other spirochetal diseases;
6. Subjects with moderate or severe liver disease defined as alkaline phosphatase, ALAT, or ASAT greater than 3 times upper limit of normal;
7. Subjects who are receiving and cannot discontinue cisapride, astemizole, terfenadine, barbiturates, phenytoin, or carbamazepine (The concentrations of these drugs may increase during clarithromycin therapy and/or lead to reduced availability of doxycycline);
8. Subjects who are currently enrolled on other investigational drug trials or receiving investigational agents;
9. Subjects who have been previously randomized into this study;
10. Severe physical or psychiatric co-morbidity that interferes with participation in the study protocol, including previous medical diagnosis of rheumatic conditions, chronic fatigue syndrome or chronic pain conditions as well as insufficient command of the Dutch language;
11. Co-morbidity that could (partially) account for the symptoms of the subject (e.g. vitamin B12 deficiency, anemia, hypothyroidism).

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-09-2010
Enrollment:	270
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	02-08-2010
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	NL2362
NTR-old	NTR2469
CCMO	NL27344.091.09

Study results

Summary results
N/A