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Title:

Six versus two weeks treatment with doxycycline in Lyme Neuroborreliosis: a multicenter, non-inferiority, penta-blinded and randomized controlled trial.

Anne Marit Solheim[1,2], Unn Ljøstad [1,2], Åse Mygland [1,2]

1. Department of Neurology, Sørlandet hospital, Kristiansand, Norway

2. Department of Clinical Medicine, University of Bergen, Bergen, Norway

UL and ÅM have contributed equally to the manuscript and should be listed as last author.

Correspondance to:

Anne Marit Solheim, anne.marit.solheim@sshf.no. Telephone 0047-38073910, Department of Neurology, Sørlandet hospital HF, Postbox 416, 4604 Kristiansand S, Norway.

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Abstract

Introduction

Current treatment guidelines for European Lyme neuroborreliosis (LNB) recommend cephalosporins, penicillin or doxycycline for 14 to 28 days but evidence for optimal treatment length is poor. Treatment lengths in clinical practice tend to exceed the recommendations. Most patients experience a rapid improvement of symptoms and neurological findings within days of treatment, but some report long-term complaints. The underlying mechanisms of remaining complaints are debated, and theories as ongoing chronic infection with *Borrelia burgdorferi*, dysregulated immune responses, genetic predisposition, co-infection with multiple tick-borne pathogens, structural changes in CNS, and personal traits have been suggested.

The main purpose of our trial is to address the hypothesis of persistent infection as cause of remaining symptoms, by comparing efficacy of treatment with two and six weeks courses of doxycycline in LNB

Methods and analysis

The trial has a multi-center, non-inferiority, penta-blinded design. One hundred and twenty patients diagnosed with LNB according to EFNS guidelines will be randomized to six or two weeks treatment with oral doxycycline. The patients will be followed for 12 months. The primary endpoint is improvement on a composite clinical score (CCS) from baseline to 6 months after inclusion. Secondary endpoints are improvements in the CCS 12 months after inclusion, fatigue scored on FSS, subjective symptoms on the PHQ-15 scale, health related quality of life scored on RAND 36- Item Short Form Health Survey, and safety as measured by side effects of the two treatment arms. Blood and CSF are collected from inclusion and through-out the follow-up and a biobank will be established. The study started including patients in November 2015 and will continue throughout December 2019.

Strengths and limitations of this study

Strengths:

- Penta-blinded design
- Inclusion criteria for LNB according to EFNS guidelines
- Well-defined endpoints
- Long follow-up

Weaknesses

- The composite clinical score is not validated

Ethics and dissemination

The study is approved by the Norwegian regional committees for medical and health research ethics (REC) and the Norwegian Medicines Agency (SLV).

Funding

This work is supported by the Norwegian Multiregional Health Authorities through the BorrSci project (Lyme borreliosis; a scientific approach to reduce diagnostic and therapeutic uncertainties, project 2015113), letter dated April 17th 2015 with case reference 14/01152-4.

Trial registration number

EudraCT number 2015-001481-5. The trial is registered on Clinicaltrials.org.

Introduction

European Lyme neuroborreliosis (LNB) is caused by the tick-borne spirochete *Borrelia burgdorferi (Bb).* LNB can manifest weeks or months after a tick bite that only half of the patients remember. The most common clinical manifestations are subacute painful radiculitis and cranial neuropathy (most often the facial nerve). More rare manifestations are myelitis, encephalitis, and peripheral neuropathies.

Patients diagnosed with LNB should be treated with antibiotics as early as possible to relieve symptoms and prevent sequelae (1-3). Most patients experience a rapid improvement within days of treatment, but some report long-term complaints (4). The most common long-term complaints are fatigue, pain, concentration and memory problems. Some patients may also have neurological sequela such as sensory disturbances, unsteadiness/vertigo, facial paresis and other paresis (5). The underlying mechanisms of remaining complaints are debated. Theories suggested are ongoing chronic *Bb* infection, dysregulated immune responses, genetic predisposition, co-infection with multiple tick-borne pathogens, structural changes in CNS, and personal traits.

Standard treatment for LNB is intravenous ceftriaxone or penicillin, or oral doxycycline for two to four weeks (6). Previous studies have shown that two weeks of oral doxycycline and intravenous ceftriaxone are equally effective for LNB with painful radiculitis or cranial neuritis and probably also for LNB with symptoms from the central nervous system (myelitis and encephalitis) (7-9). Arguments for choosing oral doxycycline are that it is inexpensive and convenient and effective against co-infections with other tick-borne agents (10, 11).

We lack evidence about the optimal duration of antibiotic treatment. Most guidelines recommend treatment for 14 to 28 days. (6, 12, 13) In Norway, the site for the current study, the guidelines recommend 14 days of treatment. A recent Cochrane review of six randomized treatment studies of adult patients with acute LNB reported improvement in the majority of patients after the initial course of antibiotics and no consistent evidence of treatment failure or need of retreatment (14). In another systematic review, the authors conclude that there is insufficient evidence to determine if extended antibiotic treatment is beneficial to outcome (15). Despite this, and perhaps because of

uncertainties surrounding LNB, there are varying treatment regimes in clinical practice, generally with more extensive treatment strategies than recommended in current guidelines. A recent study of the treatment practice of 253 Norwegian LNB patients showed that adherence to guidelines was poor and that two-thirds of the patients received more than two weeks of antibiotic treatment (16). In a time with increasing knowledge and awareness of microbial resistance and other complications of long-term antibiotic treatment these findings seem like a paradox. The present study therefore seeks to increase the evidence of the current treatment advice by evaluating if treatment with 14 days of doxycycline is as effective as a longer course of treatment or if a longer course may improve the course and long-term prognosis of LNB. By doing this the hypothesis of persistent infection will also be addressed.

Method

Study design and interventions

The study is a randomized, penta-blinded, placebo-controlled, multicenter trial with a non-inferiority design. We plan to recruit 120 patients diagnosed with definite or probable LNB according to EFNS guidelines (6) at six different hospitals in the southern part of Norway as shown in figure 1. The study is coordinated from Sørlandet hospital in Kristiansand, Agder County by neurologists connected to the large BorrSci study (Lyme borreliosis; a scientific approach to reduce diagnostic and therapeutic uncertainties). The inclusion and exclusion criteria are shown in Table 1. Inclusion started in 2015 and will continue through December 2019 or until the necessary sample size is obtained. Eligibility before inclusion is assessed by, or discussed with, a physician connected to the study and accustomed to evaluating patients with neurological symptoms. The patients are randomized into two treatment arms: A) doxycycline 200 mg daily for 2 weeks, followed by four weeks of placebo; B) doxycycline 200 mg daily for six weeks (Figure 2).

Table 1: Inclusion and exclusion criteria

INCLUSION CRITERIA
1 Neurological symptoms suggestive of LNB without other obvious reasons, and one or both of
A) CSF pleocytosis (leucocytes ≥5/mm3)
B) Intrathecal *Bb* antibodyproduction
2 Signed informed consent
EXCLUSION CRITERIA
1 Age less than 18 years
2 Treatment with cephalosporin, penicillin, or tetracycline macrolide during the last 14 days before start of doxycycline treatment
3 Pregnancy, breast-feeding and/or women of childbearing potential not using adequate contraception.
4 Adverse reaction to tetracyclines
5 Serious liver or kidney disease that contraindicates use of doxycyline
6 Lactose intolerance
7 Need to use medications contraindicated according to SmPC of the IMP (Antacid drugs, Didanosin, Probenecide, Phenobarbital, Phenytoin, Carbamazepine, Rifamphicin)

Allocation and blinding

Computerized allocation is performed at Department of clinical research support, Oslo University Hospital, by an internet-based solution. Maximum objective performance and reporting of the study is achieved by applying a "penta-blinded" approach. The first and second blinding is the traditional double blind design with blinding of participants and investigators. Thirdly, the staff evaluating endpoints and adverse effects is blinded to all other study information. Further, the content of all tables and figures will be fixed before any study data are available. Lastly, the statistical procedures will be performed with the two treatment arms marked as group A and B. Revealing the study arms for the investigators will not take place until all patients have completed the six-month visit, and for the patients after the 12 month visit.

Monitoring and data collection

The study is monitored independently according to Good Clinical Practice (GCP) by the Department of clinical research. The coordinating investigators at Sørlandet hospital and investigators at cooperating centers are certified according to GCP. The investigators will enter the data required by protocol into an electronic Case Report Form (Viedoc), also designed by the Department of clinical research. The same protocol for data management and monitoring is applied to all collected data.

Outcome measures

A composite clinical score (CCS) based on subjective symptoms and objective neurological findings from the peripheral and central nervous system (Table 2) is registered at baseline, 10 weeks, 6 months, and 12 months. Each of the 62 items of the CCS is scored 0=none, 1=mild (without influence on daily life), or 2=severe (with influence on daily life). Maximum total score is 64 .The primary endpoint of the study is the difference in CCS sum score at baseline and six months after inclusion. Secondary endpoints are the difference in CCS at baseline and 12 months after inclusion, fatigue scored according to the questionnaire FSS (Fatigue Severity Scale) at six and 12 months, subjective somatic symptoms scores according to the questionnaire PHQ-15 (Patient Health Questionnaire) at six and 12 months and health related quality of life according to RAND 36 item short form health survey at six months, and side effects of the treatment.

FSS measures level of agreement (1-7) with nine statements with the final score representing the mean value of nine items. Scores >5 are regarded as severe fatigue. The FSS has been translated into Norwegian, validated in the general Norwegian population, and normative Norwegian data are available (17).

PHQ-15 charts prevalence and intensity of 13 somatic symptoms; fatigue/lack of energy, and difficulty sleeping during the last 4 weeks. Sum score ranges from 0-28 for men and from 0-30 for women (only women are asked about menstrual symptoms). The following cut-off values for sum score have been stated for load of somatic symptom, 0-4 points: normal, 5-9 points: mild, 10-14 points: moderate, 15-30 points: severe. The PHQ-15 has been validated in several studies and languages, and normative Swedish data are available (18).

RAND 36 item short form health survey consists of 36 questions about different aspects of health-related quality of life. The answer to each question is transformed into a score ranging from 0 to 100, where a higher score indicates better health. The questionnaire is validated in Norwegian, and Norwegian normative data are available (19).

Systemic and CSF inflammation will be assessed with lumbar punctures and blood samples at six and 12 months after treatment. There will be established a biobank from this material. Figure 3 depicts a flow chart of the study procedures.

Table 2: Composite clinical score

Subjective symptoms related by the patient to the current LNB
Malaise
Fatigue
Headache
Neck and/or back pain
Abdominal and/or breast pain
Arm pain
Leg pain
Generalized pain located to joints and/or muscles
Memory and/or concentration problems
Other

Peripheral findings related to the current LNB
Facial palsy
Paresis of the eye muscles
Reduced hearing
Other cranial neuropathies
Cervical radicular sensory findings*
Cervical radicular paresis**
Thoracic radicular sensory findings*
Lumbar radicular sensory findings*
Lumbar radicular paresis**
Non-radicular sensory findings***
Non-radicular paresis****
Other
Central findings related to the current LNB
Central findings in one extremity#
Central findings in a hemi pattern
Central findings in both legs
Central findings in all extremities
Gait ataxia
Dysphasia/aphasia
Nystagmus
Involuntary movement including tremor
Cognitive impairment
Other

*Abnormal sensory pattern in a radicular pattern. **Paresis in a radicular pattern. ***Sensory findings matching with a peripheral nerve or plexus. ****Paresis matching a peripheral nerve or plexus #Central weakness and/or spasticity, impairment in pace or fine motor skills.

Safety

The patients are followed closely during and after treatment to monitor safety. They are contacted by phone one week after start of treatment and questioned about symptom severity and possible side effects. Blood sampling in regard to side effects takes place at two and four weeks after start of treatment. The patients are also asked to fill out a patient diary on symptoms and possible side effects once a week for 10 weeks. .

In cases of disease progression the patients will be evaluated by a physician and adequate intervention initiated. Disease progression is, in this trial, defined as worsening of the patient's condition attributed to LNB, despite treatment for 14 days with doxycycline, or serious progression of neurological signs from CNS during treatment.

Sample size

We used data from our previous treatment trial on 102 LNB patients treated with either oral doxycyline or IV cephtriaxone for two weeks and scored with an almost similar clinical scale as the CCS in the power analyses (7).

From a clinical point of view, a mean group difference of Δ=0.5 in disfavor of two weeks treatment compared to six weeks treatment was regarded as an appropriate non-inferiority margin. This non-inferiority margin corresponds to a Cohen's d effect size of $\Delta / \sigma = 0.5/1.0 = 0.5$, which is a small and clinical acceptable effect size. With a one-sided test and significance level of 0.05, 50 patients in each treatment group was found to be needed to claim non-inferiority with a non-inferiority margin on mean group difference of 0.5 and a SD of 1.0 with 80% power. To compensate for up to 20% dropouts and non-evaluable patients 120 (i.e. 60 in each group) patients will be enrolled.

Statistical analysis

The main statistical analysis is planned when all patients have completed the six months visit. Results will be reported as mean scores with standard deviation or proportions as appropriate.

To compare the primary outcome in the two groups we will use a general linear model with treatment group as factor, and adjustment for clinical presentation and baseline score. The analysis will be conducted according to the intention to treat principle.

For other analysis, comparison between groups will be done with e.g. independent samples t-test, nonparametric Mann-Whitney-U test or Pearson's chi-square test for crosstabs as appropriate.

P-values <0.05 will be considered statistically significant.

Ethics and dissemination

The Norwegian regional committees for medical and health research ethics (REC) and the Norwegian Medicines Agency (SLV) have approved the study. EudraCT number 2015-001481-5. The trial is registered on Clinicaltrials.org.

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

Each patient in the trial is submitted to extensive follow-up as previously described in terms of disease, effect of treatment and side effects to outweigh potential harms. The benefits are considered to outweigh the cons of this trial in the long term, with a potentially more evidence-based treatment of LNB and less extensive use of antibiotics.

Patient and Public involvement

Representatives from the Norwegian patient organization for Lyme borreliosis (Norsk Lyme Borreliose Forening, NLBF) were invited and participated in the early stages of planning of the BorrSci project's design and gave feedback on the drafts of the application for funding. They were also invited to continue work with the project. Inclusion to the study, implications of the intervention and

time required to participate is discussed with each individual patient. Local newspapers and other media have been involved in making the project known to the public in different parts of Norway.

Authors' contributions

AMS contributed in drafting this manuscript, has participated in revisions of the original protocol, includes patients to the study and coordinates the study at Sørlandet hospital and at the other centers of recruitment. UL and ÅM drafted the original protocol, worked on applications for funding, contributed in drafting this manuscript and include patients to the study.

Statement of competing interests

The authors have no competing interests to declare.

Figure 1: Map of Norway with the active centers of recruitment per August 2018 marked in red.
Figure 2: Inclusion procedures
Figure 3: Flow chart of the study procedures

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1488x891mm (96 x 96 DPI)

Figure 2: Inclusion procedures

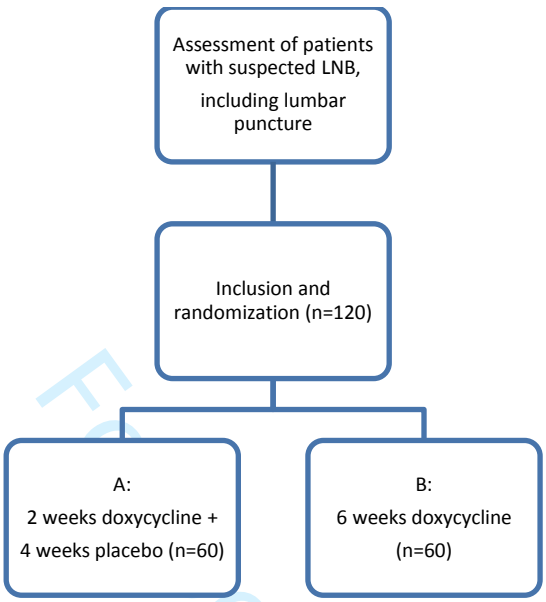
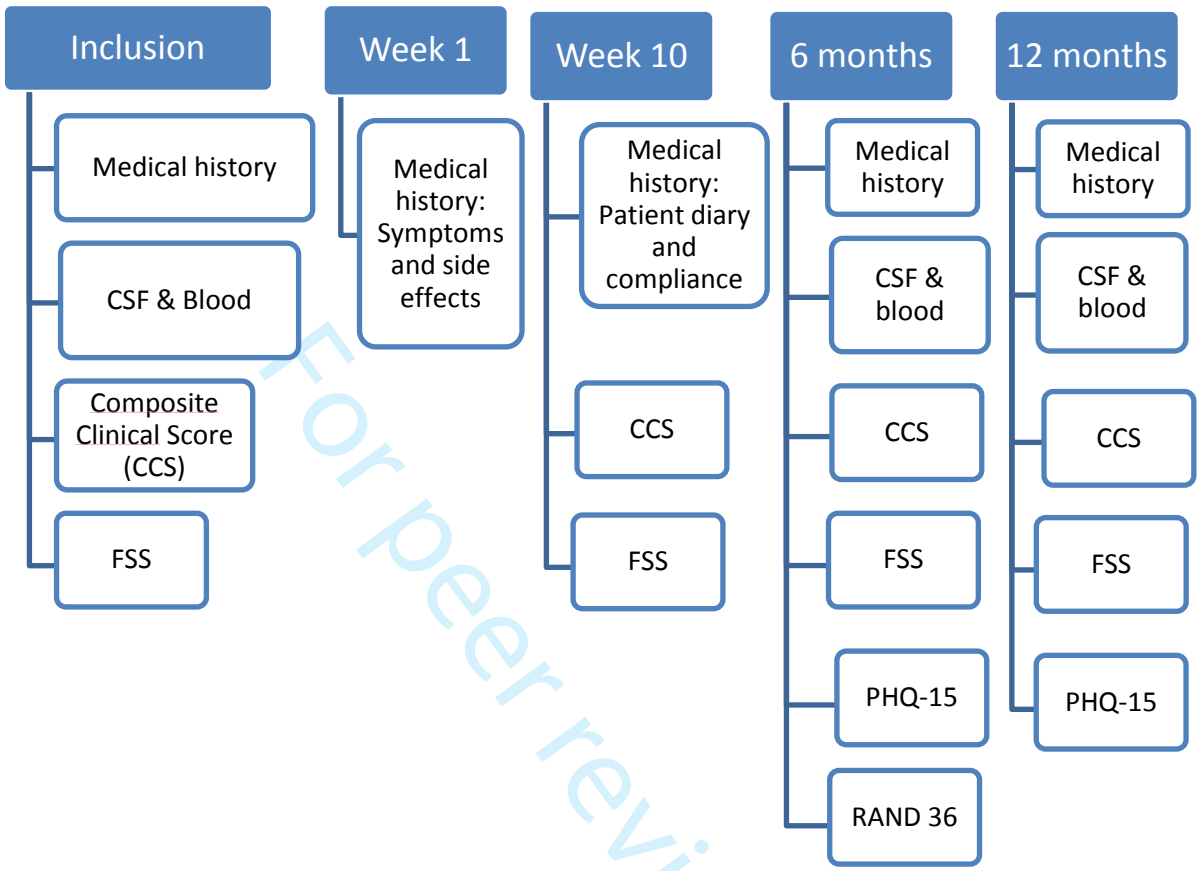


Figure 3: Flow chart of the study procedures



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The main purpose of our trial is to address the hypothesis of improved outcome after long-term antibiotic treatment of LNB, by comparing efficacy of treatment with two and six weeks courses of doxycycline

Methods and analysis

The trial has a multi-center, non-inferiority, double-blinded design. One hundred and twenty patients diagnosed with LNB according to EFNS guidelines will be randomized to six or two weeks treatment with oral doxycycline. The patients will be followed for 12 months. The primary endpoint is improvement on a composite clinical score (CCS) from baseline to 6 months after inclusion. Secondary endpoints are improvements in the CCS 12 months after inclusion, fatigue scored on FSS, subjective symptoms on the PHQ-15 scale, health related quality of life scored on RAND 36- Item Short Form Health Survey, and safety as measured by side effects of the two treatment arms. Blood and CSF are collected from inclusion and through-out the follow-up and a biobank will be established. The study started including patients in November 2015 and will continue throughout December 2019.

Ethics and dissemination

The study is approved by the Norwegian regional committees for medical and health research ethics (REC) and the Norwegian Medicines Agency (SLV).

Strengths and limitations of this study

The strengths of the trial are

- The double-blinded design
- Inclusion criteria for LNB according to the EFNS guidelines
- Well-defined endpoints
- Long period of follow-up of the included patients with registered symptoms, signs and potential side effects.

A weakness of the study is

- The primary scoring tool, the composite clinical score, is not validated.

Funding

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Method

Study design and interventions

The study is a randomized, double-blinded, placebo-controlled, multicenter trial with a non-inferiority design. We plan to recruit 120 patients diagnosed with definite or probable LNB according to EFNS guidelines (6) at six different hospitals in the southern part of Norway as shown in figure 1. The study is coordinated from Sørlandet hospital in Kristiansand, Agder County by neurologists connected to the large BorrSci study (Lyme borreliosis; a scientific approach to reduce diagnostic and therapeutic uncertainties). The inclusion and exclusion criteria are shown in Table 1. Inclusion started in 2015 and will continue through December 2019 or until the necessary sample size is obtained. Eligibility before inclusion is assessed by, or discussed with, a physician connected to the study and accustomed to evaluating patients with neurological symptoms. The patients are randomized into two treatment arms: A) doxycycline 200 mg daily for 2 weeks, followed by four weeks of placebo; B) doxycycline 200 mg daily for six weeks (Figure 2).

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2 Signed informed consent
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1 Age less than 18 years
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Computerized allocation (stratified according to hospital) is performed at Department of clinical research support, Oslo University Hospital, by an internet-based solution . Maximum objective performance and reporting of the study is achieved by applying a "penta-blinded" approach. The first and second blinding is the traditional double blind design with blinding of participants and investigators. Thirdly, the staff evaluating endpoints and adverse effects is blinded to all other study information. Further, the content of all tables and figures will be fixed before any study data are available. Lastly, the statistical procedures will be performed with the two treatment arms marked as group A and B. Revealing the study arms for the investigators will not take place until all patients have completed the six-month visit, and for the patients after the 12 month visit.

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The patient reported outcome measures (PROM) were included as secondary endpoints to evaluate the potential impact of residual symptoms on patients' daily life.

Systemic and CSF inflammation will be assessed with lumbar punctures and blood samples at six and 12 months after treatment. There will be established a biobank from this material. Figure 3 depicts a flow chart of the study procedures.

Table 2: Composite clinical score

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Leg pain
Generalized pain located to joints and/or muscles

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Paresis of the eye muscles
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Other cranial neuropathies
Cervical radicular sensory findings*
Cervical radicular paresis**
Thoracic radicular sensory findings*
Lumbar radicular sensory findings*
Lumbar radicular paresis**
Non-radicular sensory findings***
Non-radicular paresis****
Other
Central findings related to the current LNB
Central findings in one extremity#
Central findings in a hemi pattern
Central findings in both legs
Central findings in all extremities
Gait ataxia
Dysphasia/aphasia
Nystagmus
Involuntary movement including tremor
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Other

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The patients are followed closely during and after treatment to monitor safety. They are contacted by phone one week after start of treatment and questioned about symptom severity and possible side effects. Blood sampling with a status of hematology, liver and kidney function to monitor potential side effects takes place at two and four weeks after start of treatment. The patients are also asked to fill out a patient diary on symptoms and possible side effects once a week for 10 weeks.
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condition attributed to LNB, despite treatment for 14 days with doxycycline, or serious progression of neurological signs from CNS during treatment.

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P-values <0.05 will be considered statistically significant.

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Authors' contributions

AMS contributed in drafting this manuscript, has participated in revisions of the original protocol, includes patients to the study and coordinates the study at Sørlandet hospital and at the other centers of recruitment. UL and ÅM drafted the original protocol, worked on applications for funding, contributed in drafting this manuscript and include patients to the study.

Statement of competing interests

The authors have no competing interests to declare.

Figure 1: Map of Norway with the active centers of recruitment per August 2018 marked in red.
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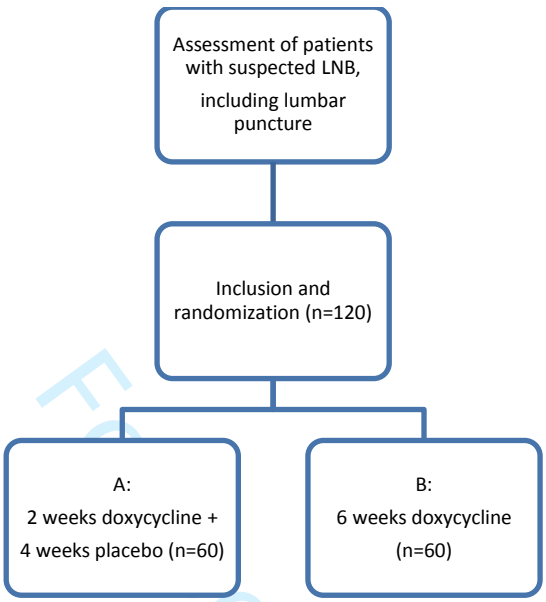

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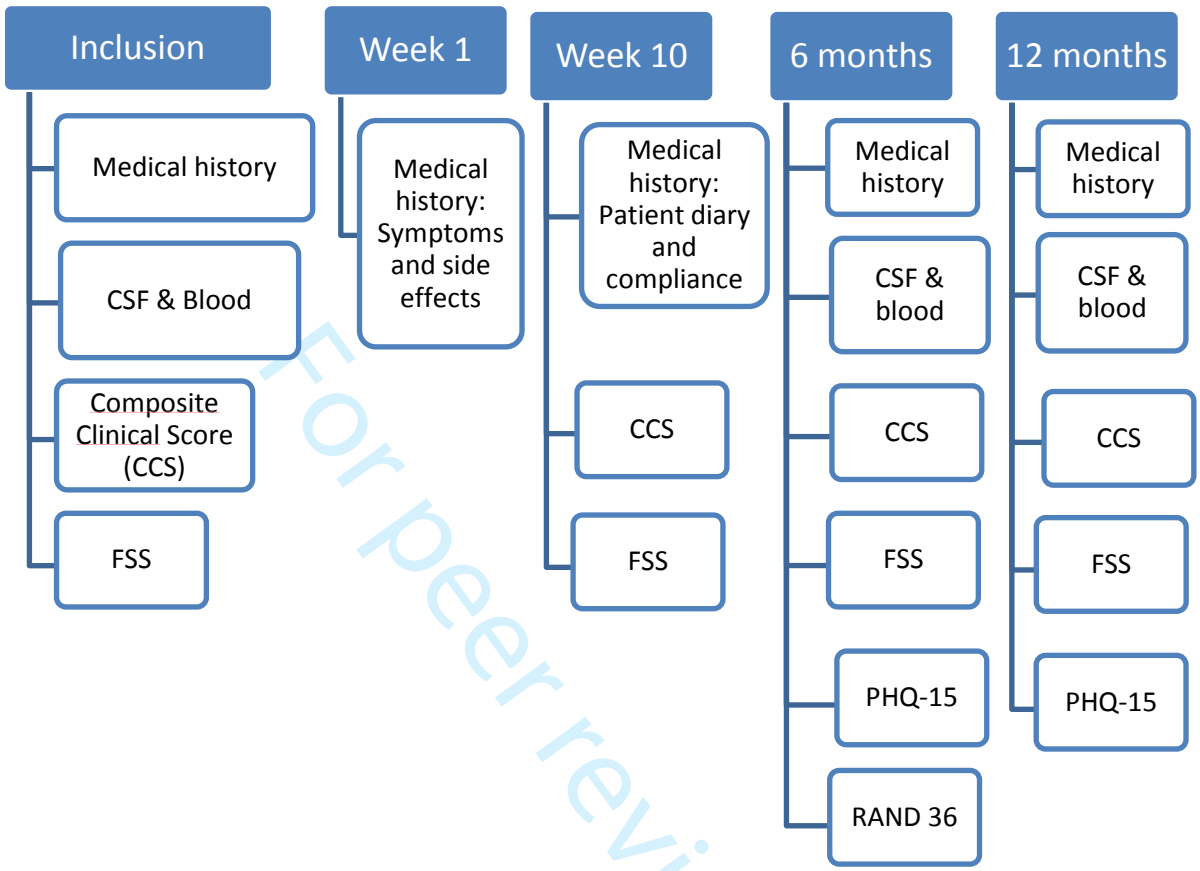

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Anne Marit Solheim[1,2], Unn Ljøstad [1,2], Åse Mygland [1,2]

1. Department of Neurology, Sørlandet hospital, Kristiansand, Norway

2. Department of Clinical Medicine, University of Bergen, Bergen, Norway

UL and ÅM have contributed equally to the manuscript and should be listed as last author.

Correspondance to:

Anne Marit Solheim, anne.marit.solheim@sshf.no. Telephone 0047-38073910, Department of Neurology, Sørlandet hospital HF, Postbox 416, 4604 Kristiansand S, Norway.

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Abstract

Introduction

Current treatment guidelines for European Lyme neuroborreliosis (LNB) recommend cephalosporins, penicillin or doxycycline for 14 to 28 days but evidence for optimal treatment length is poor. Treatment lengths in clinical practice tend to exceed the recommendations. Most patients experience a rapid improvement of symptoms and neurological findings within days of treatment, but some report long-term complaints. The underlying mechanisms of remaining complaints are debated, and theories as ongoing chronic infection with *Borrelia burgdorferi*, dysregulated immune responses, genetic predisposition, co-infection with multiple tick-borne pathogens, structural changes in CNS, and personal traits have been suggested.

The main purpose of our trial is to address the hypothesis of improved outcome after long-term antibiotic treatment of LNB, by comparing efficacy of treatment with two and six weeks courses of doxycycline

Methods and analysis

The trial has a multi-center, non-inferiority, double-blinded design. One hundred and twenty patients diagnosed with LNB according to EFNS guidelines will be randomized to six or two weeks treatment with oral doxycycline. The patients will be followed for 12 months. The primary endpoint is improvement on a composite clinical score (CCS) from baseline to 6 months after inclusion. Secondary endpoints are improvements in the CCS 12 months after inclusion, fatigue scored on FSS, subjective symptoms on the PHQ-15 scale, health related quality of life scored on RAND 36- Item Short Form Health Survey, and safety as measured by side effects of the two treatment arms. Blood and CSF are collected from inclusion and through-out the follow-up and a biobank will be established. The study started including patients in November 2015 and will continue throughout December 2019.

Ethics and dissemination

The study is approved by the Norwegian regional committees for medical and health research ethics (REC) and the Norwegian Medicines Agency (SLV). Data from the study will be published in peer-reviewed medical journals.

Strengths and limitations of this study

- The trial has a double-blinded design
- The inclusion criteria for LNB are according to the EFNS guidelines
- The endpoints of the trial are well-defined.

- The follow-up period of the included patients is long with registered symptoms, signs and potential side effects.

- A weakness of the study is that the primary scoring tool, the composite clinical score, is not validated.

Funding

This work is supported by the Norwegian Multiregional Health Authorities through the BorrSci project (Lyme borreliosis; a scientific approach to reduce diagnostic and therapeutic uncertainties, project 2015113), letter dated April 17th 2015 with case reference 14/01152-4.

Trial registration number

EudraCT number 2015-001481-25. The trial is registered on Clinicaltrials.org.

Introduction

European Lyme neuroborreliosis (LNB) is caused by the tick-borne spirochete *Borrelia burgdorferi (Bb).* LNB can manifest weeks or months after a tick bite that only half of the patients remember. The most common clinical manifestations are subacute painful radiculitis and cranial neuropathy (most often the facial nerve). More rare manifestations are myelitis, encephalitis, and peripheral neuropathies.

Patients diagnosed with LNB should be treated with antibiotics as early as possible to relieve symptoms and prevent sequelae (1-3). Most patients experience a rapid improvement within days of treatment, but some report long-term complaints (4). The most common long-term complaints are fatigue, pain, concentration and memory problems. Some patients may also have neurological sequela such as sensory disturbances, unsteadiness/vertigo, facial paresis and other paresis (5). The underlying mechanisms of remaining complaints are debated. Theories suggested are ongoing chronic *Bb* infection, dysregulated immune responses, genetic predisposition, co-infection with multiple tick-borne pathogens, structural changes in CNS, and personal traits.

Standard treatment for LNB is intravenous ceftriaxone or penicillin, or oral doxycycline for two to four weeks (6). Previous studies have shown that two weeks of oral doxycycline and intravenous ceftriaxone are equally effective for LNB with painful radiculitis or cranial neuritis and probably also for LNB with symptoms from the central nervous system (myelitis and encephalitis) (7-9). Arguments for choosing oral doxycycline are that it is inexpensive and convenient, is found to penetrate the blood-brain-barrier and give adequate concentrations in the CSF and is effective against co-infections with other tick-borne agents (10, 11).

We lack evidence about the optimal duration of antibiotic treatment. Most guidelines recommend treatment for 14 to 28 days. (6, 12, 13) In Norway, the site for the current study, the guidelines recommend 14 days of treatment. A recent Cochrane review of six randomized treatment studies of

adult patients with acute LNB reported improvement in the majority of patients after the initial course of antibiotics and no consistent evidence of treatment failure or need of retreatment (14). In another systematic review, the authors conclude that there is insufficient evidence to determine if extended antibiotic treatment is beneficial to outcome (15). Despite this, and perhaps because of uncertainties surrounding LNB, there are varying treatment regimes in clinical practice, generally with more extensive treatment strategies than recommended in current guidelines. A recent study of the treatment practice of 253 Norwegian LNB patients showed that adherence to guidelines was poor and that two-thirds of the patients received more than two weeks of antibiotic treatment (16). In a time with increasing knowledge and awareness of microbial resistance and other complications of long-term antibiotic treatment these findings seem like a paradox. The present study therefore seeks to increase the evidence of the current treatment advice by evaluating if treatment with doxycycline in 14 days is inferior or not to treatment for six weeks with respect to long-term prognosis of LNB.

Method

Study design and interventions

The study is a randomized, double-blinded, placebo-controlled, multicenter trial with a non-inferiority design. We plan to recruit 120 patients diagnosed with definite or probable LNB according to EFNS guidelines (6) at six different hospitals in the southern part of Norway as shown in figure 1. The study is coordinated from Sørlandet hospital in Kristiansand, Agder County by neurologists connected to the large BorrSci study (Lyme borreliosis; a scientific approach to reduce diagnostic and therapeutic uncertainties). The inclusion and exclusion criteria are shown in Table 1. Inclusion started in 2015 and will continue through December 2019 or until the necessary sample size is obtained. Eligibility before inclusion is assessed by, or discussed with, a physician connected to the study and accustomed to evaluating patients with neurological symptoms. The patients are randomized into two treatment arms: A) doxycycline 200 mg daily for 2 weeks, followed by four weeks of placebo; B) doxycycline 200 mg daily for six weeks (Figure 2).

INCLUSION CRITERIA
1 Neurological symptoms suggestive of LNB without other obvious reasons, and one or both of
A) CSF pleocytosis (leucocytes ≥5/mm3)
B) Intrathecal *Bb* antibodyproduction
2 Signed informed consent
EXCLUSION CRITERIA
1 Age less than 18 years
2 Treatment with cephalosporin, penicillin, or tetracycline macrolide during the last 14 days before start of doxycycline treatment
3 Pregnancy, breast-feeding and/or women of childbearing potential not using adequate contraception.
4 Adverse reaction to tetracyclines
5 Serious liver or kidney disease that contraindicates use of doxycyline
6 Lactose intolerance
7 Need to use medications contraindicated according to SmPC of the IMP (Antacid drugs, Didanosin, Probenecide, Phenobarbital, Phenytoin, Carbamazepine, Rifamphicin)

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Figure 3: Flow chart of the study procedures

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Figure 1: Map of Norway with the active centers of recruitment per August 2018 marked in red.

1488x891mm (96 x 96 DPI)

Figure 2: Inclusion procedures

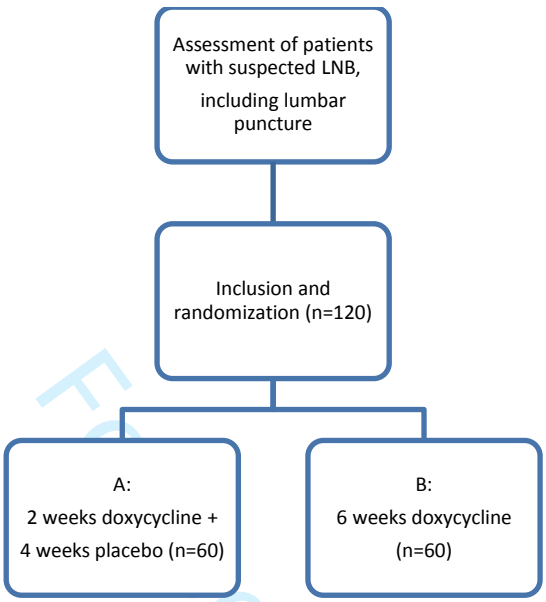

Figure 3: Flow chart of the study procedures