Randomized placebo-controlled trial to investigate clinical efficacy, anti-inflammatory properties and safety of prednisolone in hand osteoarthritis: a proof-of-concept study

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Primary Objective: The main objective of this study is to identify a new treatment to alleviate pain and diminish inflammation in patients with hand osteoarthritis with symptoms and signs of inflammation.Secondary Objectives: The secondary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Joint disorders
Study type	Interventional

Summary

ID

NL-OMON44904

Source
ToetsingOnline

Brief title
HOPE

Condition

- Joint disorders

Synonym
osteoarthritis

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Stichting Nationaal Reumafonds

Intervention

Keyword: clinical trial, corticosteroids, hand, osteoarthritis

Outcome measures

Primary outcome

The primary endpoint is the change in digital joint pain after 6 weeks,

assessed by a 100 mm VAS.

Secondary outcome

The secondary endpoints are:

• Change in joint pain after 6 weeks assessed by AUSCAN pain subscale;

• Change in thumb base pain after 6 weeks assessed by a 100 mm VAS;

• Change in physical function after 6 weeks assessed by AUSCAN physical

function subscale;

• Change in physical function after 6 weeks assessed by FIHOA;

• Change in physical function after 6 weeks assessed by HAQ;

• Change in patient global assessment after 6 weeks assessed by a 100 mm VAS;

• Change in physician global assessment after 6 weeks assessed by a 100 mm VAS;

• Change in number of hand joints with pain upon palpation (physical exam)

after 6 weeks;

• Change in inflammatory ultrasonography signs after 6 weeks;

• Change in MRI inflammatory signs after 6 weeks;

• Change in quality of life assessed by SF-36 after 6 weeks;

• Change in grip strength after 6 weeks;

• Fulfilment of OARSI responder criteria after 6 weeks;

• Change in pain, physical function, patient and physician global assessment and quality of life after 8 weeks;

• Change in pain, physical function, patient and physician global assessment, number of painful joints upon palpation, inflammatory signs at US and MRI, quality of life, grip strength, and fulfilment of OARSI responder criteria after 14 weeks.

As exploratory parameters we will collect the following questionnaires: fatigue on a 100 mm VAS (baseline, 6 and 14 weeks), Michigan Hand Outcomes Questionnaire (MHOQ) (baseline, 6 and 14 weeks), the Illness Perception Questionnaire (IPQ) (baseline and 14 weeks), the Coping with Rheumatic Stressors questionnaire (CORS) (baseline and 14 weeks), the Hospital Anxiety Depression Scale (HADS) (baseline) and anchor questions regarding pain, physical function, fatigue and quality of life (after 6 weeks). We will assess hand function using the Moberg Pick Up Test at baseline, 6 and 14 weeks. We will assess hand mobility using different measures, e.g. the Modified Kapandji Index, HAMIS and fingertip-to-palm-distance at baseline, 6 and 14 weeks.

Study description

Background summary

Hand osteoarthritis is a prevalent joint disorder affecting finger and thumb base joints. Hand osteoarthritis leads to pain, which is especially experienced

during flares, periods of pain often accompanied by redness and soft tissue swelling. It also results in restriction in daily activity and decreased quality of life. Despite this, hand osteoarthritis has been a *forgotten disease* for many years. No treatments are available to modify the disease course; the usual aim is to alleviate symptoms. However there is limited efficacy, which may be due to a lack of understanding of pathogenetic mechanisms, a limited number of high quality studies and low effect sizes of existing treatments. Therefore there is a great unmet need for effective treatment in patients with hand osteoarthritis.

Osteoarthritis results from an imbalance between degradation and repair processes, in which all compartments of the joint are involved. Insights have emerged that synovial inflammation negatively affects the balance between degradation and repair and plays a crucial role in the osteoarthritic process. Inflammation is prevalent in osteoarthritic joints. We and others have shown in ultrasonography (US) and MRI studies that synovitis and effusion are frequently seen. The presence of inflammation seems to be dependent on disease stage and is especially prevalent during severe stages. Inflammation is associated with pain. We and others have shown that pain in an osteoarthritic joint -in hand, but also in knee and hip osteoarthritis- is associated with synovitis. The causality of this association is supported by clinical trials in knee or hip osteoarthritis, showing that strong anti-inflammatory medication, such as intra-articular corticosteroids, alleviate pain. Furthermore, inflammation leads to structural damage and impairment at the long term, since synovitis and effusion are associated with cartilage damage.

The efficacy of anti-inflammatory medication in hand osteoarthritis is scarcely investigated and has led to equivocal results. Two randomized controlled trials investigating intra-articular corticosteroids for thumb base osteoarthritis did not show efficacy over placebo. Of two randomized controlled trials with systemic corticosteroids in hand osteoarthritis one did and the other did not show efficacy of prednisolone over placebo. In a randomized controlled trial comparing two adalimumab injections with placebo no effect on pain after 6 weeks was seen. The controversial results from these trials could be due to the differences in hand osteoarthritis phenotypes and disease stages studied, outcome measures used to evaluate efficacy, use of concomitant medication, and whether inflammation, such as synovitis or effusion, was present.

Therefore, a study with a strong anti-inflammatory drug in a homogeneous patient population, during a flare of the disease with evidence of synovitis, and evaluated by outcome measurements sensitive to change is warranted, not only to find new treatment modalities for hand osteoarthritis, but also to better understand the underlying pathogenetic mechanisms.

Study objective

Primary Objective: The main objective of this study is to identify a new

treatment to alleviate pain and diminish inflammation in patients with hand osteoarthritis with symptoms and signs of inflammation.

Secondary Objectives: The secondary objectives of this study are to increase our knowledge on synovial inflammation in hand osteoarthritis, e.g. it*s role in pain experience, it*s course over three months and it*s responsiveness to prednisolone. Moreover, we want to gain insight in the differences in sensitivity-to-change of several instruments to assess pain, physical function, and synovitis in patients with hand osteoarthritis.

Study design

Our research proposal comprises a randomized double-blind placebo-controlled trial of 14 weeks duration to investigate oral prednisolone in hand osteoarthritis. This clinical trial is set up as proof-of-concept study aiming not only to investigate the clinical efficacy and safety of prednisolone in hand osteoarthritis, but also its anti-inflammatory effects as mechanism of action. Patients will be randomly assigned to either of 2 treatment groups of 45 patients each: receiving treatment with prednisolone 10 mg daily or placebo during 6 weeks. After 6 weeks the medication will be tapered (one week of 5 mg prednisolone daily or placebo and thereafter one week 2.5 mg prednisolone daily or placebo). Between week 8 and the end of the study, patients will be followed to assess lasting efficacy, safety and anti-inflammatory effects.
A flare study design will be employed. After entering the study patients will discontinue their NSAIDs. After a washout period of at least 48 hours, those with a flare (defined as worsening by > 20mm on a 100 mm visual analogue scale (VAS) pain scale) will be randomized. Study visits will be performed at baseline, 2, 4, 6, 8 and 14 weeks.

Intervention

Patients in the intervention group will receive 2 ml prednisolone oral solution once daily (10 mg) during 6 weeks. The control group will receive 2 ml placebo oral solution once daily during 6 weeks. After 6 weeks the medication will be tapered (one week of 1 ml prednisolone oral solution once daily (5 mg) or 1 ml placebo oral solution once daily and thereafter one week 0.5 ml prednisolone oral solution once daily (2.5 mg) or 0.5 ml placebo oral solution once daily).

Study burden and risks

The outcome of this study could be a new evidence based treatment option to alleviate pain and inflammation for patients with osteoarthritis of the hand. Even if this study will be negative, patients will benefit, since nowadays in clinical practice patients are regularly treated with prednisolone. However, prednisolone is not without adverse effects and should not be administered when no effect can be expected. Also society will benefit, since osteoarthritis is a

frequent health problem which occurs, contrary to general beliefs, already in relatively early years of life. In the Netherlands it was estimated that 1.5 million people suffer from osteoarthritis; 348.000 persons suffer from hand osteoarthritis. The direct health costs are estimated at minimal 1% of the gross national product. In addition extra indirect costs for society are expected since the working capacity of osteoarthritis patients is diminished.

At the screening visit patient characteristics will be assessed using standardized questionnaires. The following questionnaires will be collected at each study visit (baseline, 2, 4, 6, 8 and 14 weeks): digital pain and thumb base pain on 100 mm VAS scales, the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) pain, disability, and stiffness subscales, the functional index for hand osteoarthritis (FIHOA) and health assessment questionnaire (HAQ), patient and physician global assessment on a 100 mm VAS scale, Short Form-36, and consumption of rescue paracetamol. The Michigan Hand Outcomes Questionnaire (MHOQ) and fatigue on a 100 mm VAS scale will be collected at baseline, 6 and 14 weeks. The Illness Perception Questionnaire (IPQ) and the Coping with Rheumatic Stressors questionnaire (CORS) will both be collected at baseline and 14 weeks. The Hospital Anxiety Depression Scale (HADS) will only be collected at baseline. Anchor questions regarding pain, physical function, fatigue and quality of life will be collected once after 6 weeks. At each study visit a physical examination will be performed and grip strength will be assessed by a hydraulic hand dynamometer. Hand radiographs will be made at screening (or existing hand radiographs will be used in case these are not longer than 6 months old). At baseline and after 6 and 14 weeks ultrasonography will be obtained of the hand joints. At baseline and after 6 weeks MR images of both hands will be obtained. All patients will be monitored for clinical and laboratory evidence of adverse events on a routine basis throughout the study.

Prednisolone is a drug that is used very frequently in general clinical practice for many indications. The mechanisms of action as well as the potential adverse events are very well-known. A side effect of prednisolone is that it can increase blood glucose levels, especially in patients diagnosed with diabetes mellitus. Therefore, patients* blood glucose levels will be monitored during the six week treatment course. Patients will also be informed that if they are known to have diabetes mellitus, they should be aware that their blood glucose levels may be altered during the course of the treatment. The effect of prednisolone on blood glucose will go away a day or two after the patient has stopped taking it. A potential issue of concern when prescribing prednisolone for longer periods of time could be the development of adrenal insufficiency. Although it seems unlikely that adrenal insufficiency will develop after 6 weeks of 10 mg prednisolone daily, we changed the protocol following the advice of the endocrinologists from the LUMC, adding a tapering scheme of prednisolone after 6 weeks of treatment to avoid any risk (after 6 weeks of 10 mg prednisolone or placebo treatment 1 week of 5 mg prednisolone daily or placebo and 1 week of 2.5 mg prednisolone or placebo). Another risk of chronic prednisolone use could be the development of osteoporosis. The risk of

developing osteoporosis after 6 weeks of 10 mg prednisolone use is also very low. However, to minimize the risks, calcium and vitamin D status will be accessed before start of the study and in case of insufficiency these will be supplied before start of the trial. Since prednisolone 10 mg daily is only supplied for 6 weeks, no bisphosphonate prescription is needed. Patients who have one or more of the following risk factors for developing gastric or duodenal ulcers will be prescribed a proton pump inhibitor at the start of the study: age >=60 years, previous gastric or duodenal ulcer, concomitant use of anticoagulants or salicylates or selective serotonin reuptake inhibitors, heart failure or diabetes mellitus.

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

Patients of either sex with *inflammatory* interphalangeal osteoarthritis, defined as at least 4 osteoarthritic interphalangeal joints (IPJs) with nodes, at least 1 IPJ with soft tissue swelling or erythema and at least 1 IPJ with positive power Doppler signal at US, will be recruited. All patients have to fulfill the American College of Rheumatology (ACR) criteria for hand osteoarthritis. A minimal amount of osteoarthritic digital pain (pain at rest >30 mm on VAS) that fluctuates upon drug administration (worsening by >20 mm on the VAS after NSAID wash out) is required. Patients have to use NSAIDs for digital joint pain. In case of digital pain and thumb base pain, digital pain has to be the most intense.

Exclusion criteria

Exclusion criteria comprise chronic inflammatory rheumatic disease (such as rheumatoid arthritis or gout), fibromyalgia, use of immunomodulating drugs (such as antimalarials and systemic or local corticosteroids) within 90 days, hyaluronic acid injections in the thumb base within 90 days, pregnancy or breast-feeding during the trial, positive rheumatoid factor or anti-CCP antibodies, psoriasis, blood dyscrasias and coagulation disorders, malignancy (except successfully treated squamous or basal cell skin carcinoma), uncontrolled diabetes mellitus or hypertension, unstable ischemic heart disease, heart failure (New York Heart Association III/ IV), severe pulmonary disease, recent stroke, bone marrow hypoplasia, elevated liver enzyme levels (aspartate transaminase (AST) and/or alanine transaminase (ALT) >=2 times normal value), creatinine clearance <=60 ml/min, latex sensitivity, drug or alcohol abuse in the last year, severe and opportunistic infections, chronic infections.

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):	14-12-2015
Enrollment:	90
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Placebo
Generic name:	Placebo
Product type:	Medicine
Brand name:	Prednisolone
Generic name:	Prednisolone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	15-04-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	18-11-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	17-12-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	24-02-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	06-03-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	16-06-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	19-02-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	07-03-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	EUCTR2015-000687-33-NL
CCMO	NL52477.058.15

Study results

Date completed:	04-10-2018
Results posted:	21-11-2019
Actual enrolment:	92

First publication
21-11-2019