Induction of Cure in Early Arthritis. A single blind randomized clinical trial.

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Primary Objectives: * to establish - which is the best treatment, MTX or baricitinib, to ensure rapid symptom relief of recent onset UA, based on clinical and patient reported outcomes from baseline to 3 months. Secondary Objective: * to establish...

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

Summary

ID

NL-OMON54053

Source
ToetsingOnline

Brief title
I CEA

Condition

- Autoimmune disorders
- Joint disorders

Synonym
early inflammatory joint complaints, early unclassified arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Eli Lilly

Intervention

Keyword: baricitinib, early unclassified artritis, methotrexaat, randomized clinical trial (RCT)

Outcome measures

Primary outcome

Main study parameters/endpoints

- decrease in disease activity at 3 months

Secondary outcome

Secondary study parameters/endpoints:

-Disease Activity Score (DAS) based on a 44 swollen joint count including a 53 joint Ritchie Articular Index.

-Functional ability as measured by the Health Assessment Questionnaire (HAQ)

-Physical and emotional wellbeing as measured by the ShortForm-36 (SF-36)

-Functional ability in preferred activities as measured by the MACTAR

-Quality of life as measured by the EuroQol 5-dimensional questionnaire (EQ-5D)

-Toxicity as defined by number and severity of adverse events based on routine laboratory tests as required for study medications, open end questioning during study visits, and interim reports of adverse events

-Local joint pain as measured on a 100 mm Visual Analogue Scale (VAS), measuring from 0 (no pain) to 100 (maximum imaginable pain)

-General fatigue as measured on a 100 mm VAS (no to maximum)

-Morning stiffness as measured on a 100 mm VAS (no to maximum)

-General functional disability as measured on a 100 mm VAS (no to maximum)

- General satisfaction with medication use (convenience) on a 100 mm VAS (no to maximum)

- General dissatisfaction with medication use on a 100 mm VAS (no to maximum)

- The extent to which benefits of medication use are more important than downsides on a 100 mm VAS (no to maximum)

- Feelings of depression as measured with the Hospital Axiety and Depression Scale (HADS)

-Time to clinical remission from baseline and per drug (MTX or baricitinib) from start of treatment

-Time to clinical improvement (by patient diary and clinical assessments at weeks 2,4 and 8)

-Progression to classifiable RA (2010 criteria) over time from baseline

-Time to flare (from absence of any arthritis to at least one joint with active arthritis)

-(Progression of) radiologic damage as measured with the Sharp-vanderHeijde Score (screening, 6, and 12 months)

-Disease activity as assessed by the treating rheumatologist on a 100 mm VAS at 3 months and 12 months and over time

Study description

Background summary

Based on previous research, rheumatologists in daily clinical now will start treatment in patients with (suspected) rheumatoid arthritis as early as possible, aiming at achieving rapid remission, and often will then start tapering medication, potentially to nil. This approach has resulted in significant improvements in the disease outcomes of patients with early RA. As disease activity is rapidly and effectively suppressed, functional ability is improved to almost normal and radiologic damage progression is prevented. In a large proportion of RA patients it is now possible to taper, and sometimes

stop, medication.
In the Leiden EAC (early arthritis clinic) we have shown that there appears to be a window of opportunity, where initiation of effective treatment may prevent chronicity and induce sustained drug free remission. [2].

To date, rheumatologists are poised to recognize and treat UA patients as early as possible, starting with methotrexate (MTX), a conventional synthetic Disease Modifying Anti-Rheumatic Drug (csDMARD), in line with EULAR/ACR recommendation 1 on the treatment of early arthritis [3].
However, although the benefits of early treatment initiation for patients with RA are clear, for patients with UA this is less so. Some may need only temporary symptom relief with analgesics, non-steroid anti-inflammatory drugs (NSAIDs) and/or a single injection with corticosteroids, as in up to 30% of UA patients the symptoms go into spontaneous remission.[4]
Yet the majority of UA patients continue to have chronic arthritis, about half of those progressing to classifiable RA. There have been few studies that tested whether in UA early DMARD treatment results in induction of remission, or even earlier symptom relief. In cohort studies. Methotrexate, dose adjusted aiming at low disease activity (Disease Activity Score, DAS <=2.4) was tested against placebo in the PROMPT study in 110 patients with undifferentiated arthritis (UA), clinically (anti-citrullinated peptide antibodies, ACPA, were at that time not routinely available) suspected to have early RA. The results showed that in patients with ACPA, MTX prevented progression to RA, but when MTX was stopped after 12 months, most patients still progressed. In UA patients without ACPA, MTX did not outperform placebo. [5]
If early DMARD treatment is better than a wait and see policy, is MTX the best option for treatment of UA? Despite having the reputation of being the *corner stone* of RA treatment, MTX as initial monotherapy is only successful in inducing early remission in a minority of patients with classifiable RA. [6-8]
Especially when aiming at rapid efficacy, a downside of MTX is that it is slow-acting. International recommendations therefore advise to (temporary) co-treat early RA patients with corticosteroids. And despite being generally safe, MTX is associated with nausea, malaise and increased liver enzymes in many patients. [9-11]
A recently developed multi-target antirheumatic drug, JAK-inhibitor baricitinib, has been shown to be more and more rapidly effective than MTX in patients with early RA [12]. It may be also more effective than MTX in induction of rapid remission in patients with UA. If this would be so, it has to be answered whether patients can then immediately stop baricitinib, or whether it is better to continue for 6 more months to prevent relapses and insure cure.

Study objective

Primary Objectives:
* to establish
- which is the best treatment, MTX or baricitinib, to ensure rapid symptom

relief of recent onset UA, based on clinical and patient reported outcomes from baseline to 3 months.

Secondary Objective:
* to establish
- which is the best strategy to ensure early remission (within 3 months) of recent onset undifferentiated arthritis (UA): early treatment with MTX or baricitinib or delayed treatment in case spontaneous remission does not occur within 3 months.
- which is the best strategy to achieve cure (or sustained drug free remission) of recent onset UA: early treatment with MTX or baricitinib
-which is the best treatment to prevent (or delay) progression of early unclassified arthritis to rheumatoid arthritis
-which is the best treatment in terms of patients* (in)tolerance of medication and reported side effects (including depressive feelings) and drug toxicity over time
-which is the best treatment to ensure optimal functional ability over time
-which is the best treatment in terms of patients* satisfaction with treatment, to be assessed after 3 months on NSAIDs, MTX or baricitinib

- Exploratory goals:
* to identify potential patient and/or disease characteristics which are associated with clinical response and disease outcomes in the 3 treatment strategy arms.
* to identify potential factors in illness perception and/or patient coping strategies which are associated with functional outcomes and quality of life (HAQ and SF-36) irrespective of disease activity.

Study design

This will be a single blind (using independent disease activity assessors) randomized multicenter clinical trial.

Study group expertise
Our study group is uniquely prepared to conduct and complete the proposed study. In the Netherlands there is an established practice to refer patients with (suspected) arthritis as rapidly as possible to the rheumatologist. In our rheumatology outpatient clinics we have reserved *slots* for such patients to avoid referral delays. Since 1997 we systematically follow these patients up in the Leiden Early Arthritis Clinic (EAC). Since 1993 we collaborate with rheumatologists in hospitals in the Southwest of the Netherlands in the Foundation for Applied Rheumatology Research. Together, we have done several large multicenter studies in patients with early RA and/or UA to improve treatment strategies for these patients: the BeSt study, PROMPT study and IMPROVED study. Combined these studies have resulted in over 90 publications in major rheumatology journals. Following up on data from the Leiden *clinically suspect arthralgia* (CSA) cohort, we are currently doing an ongoing multicenter

randomized clinical trial to test methotrexate against placebo to see whether (and in which) patients with CSA development of clinical arthritis can be prevented. Thus we have shown to be in the forefront of developing treatment improvements for patients with arthritis and we have the infrastructure, knowledge and experience to conduct the currently proposed trial.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness
Patients will be asked to return for study visits every three months, to undergo physical examinations and laboratory tests (ca 6 ml per blood draw), fill in multiple questionnaires, have radiographs of hands and feet taken every 6 months, and follow the treatment protocol as determined by randomization. All treatments in this study are registered medications, routinely used for treatment of early unclassified arthritis, with the exception of baricitinib, which is currently approved and used for the treatment of rheumatoid arthritis, but is not used for early unclassified arthritis. This will be provided as study medication in the current trial.
Benefits of participation are related to the benefits of intensive monitoring and close access to care while in the study, and the potential access to treatment with baricitinib, which in trials in rheumatoid arthritis patients has proven to be more and more rapidly effective than methotrexate and safe.

Intervention

Intervention
After giving informed consent, patients will be randomized to three treatment arms:
-arm 1: treat symptomatically with NSAID or COXIB and a single dose of intramuscular or local intra-articular corticosteroids and wait for spontaneous remission.
-arm 2: methotrexate (or sulfasalazine as alternative) increased to max. tolerated dose in 4 weeks, and a single dose of intramuscular or local intra-articular corticosteroids. NSAID or COXIB allowed.
-arm 3: baricitinib and a single dose of intramuscular or local intra-articular corticosteroids. NSAID or COXIB allowed.

Total study duration per patient: 12 months

Study burden and risks

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Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Inclusion criteria
- >=18 and < 65 years of age and able to give written informed consent (in Dutch or English) and fill out questionnaires in Dutch (or English version, if

available)
- Clinical early unclassified arthritis of at least one joint, not fulfilling ACR/EULAR 2010 criteria for rheumatoid arthritis
- Symptom duration of arthritis <1 year
- Other diagnoses causing the arthritis rejected (including infection, (pseudo-)gout, psoriatic arthritis, non-rheumatoid auto-immune disease, paraneoplastic arthritis)
- DAS>1.6 and at least two swollen and painful joints
- No wish to become pregnant, breastfeed or father a child during the study
- No contraindications to treatment with NSAIDs, MTX (or sulfasalazine or leflunomide as alternative) and baricitinib as required in the study

Exclusion criteria

Exclusion criteria
- Alcohol or substance abuse, current smoking or a long history of smoking
- Immuno-compromised state either based on co-morbidity or co-medication
- Leucopenia <3*10^9/l, and/or neutropenia <1*10^9/l
- Hemoglobin <5 mmol/l
- Increased liver enzymes > 3x upper limit of normal
- Renal insufficiency with estimated creatinine clearance <60%
- Interstitial lung disease as seen on X-thorax
- Maintenance treatment with corticosteroids exceeding prednisone 10 mg daily or equivalent
- Active or ongoing chronic infection, (recurrent) serious infection(s) in past 4 months, latent TB who refuse anti-tuberculous treatment, hepatitis B with positive DNA viral load or hepatitis C with positive RNA viral load, patients with anti-HB2 and anti-HBc antibodies who refuse monitoring of hepatitis B DNA expression
-increased tendency to develop arterial or venous thrombosis or increased risk for major cardiovascular events as assessed by the treating rheumatologist. Risk of arterial thrombosis is based on calculation of the "cardiovascular SCORE", which includes cholesterol ratio, systolic blood pressure, age, gender, diabetes, history of cardiovascular disease and smoking status. Only patients in the "green" category of the NHG CVRM risk table will be included
- Increased risk of malignancy; this includes patients with a history of a malignancy (except basal cell carcinoma, and squamous cell carcinoma, and cervical carcinoma in situ and other malignancies that have been treated curatively >10 years ago, for instance types of thyroid cancer) and patients with syndrome which increase cancer risk (e.g. BRCA/HNPCC/LYNCH).

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	17-02-2021
Enrollment:	111
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	celecoxib, etoricoxib, parecoxib
Generic name:	Coxibs (cox 2 inhibitor)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Methotrexate
Generic name:	Methotrexate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	methylprednisolone
Generic name:	glucocorticoids
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Nonsteroidal anti-inflammatory drugs (NSAIDs)
Generic name:	Nonsteroidal anti-inflammatory drugs (NSAIDs)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Olumiant

Generic name:	Baricitinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-06-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	23-10-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	17-12-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	19-12-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	19-07-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO
Date: 29-07-2021

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 12-11-2021

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 30-11-2021

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 19-05-2022

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 12-07-2022

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 11-02-2023

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	21-03-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	17-06-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2019-004359-35-NL
CCMO	NL73202.058.20
Other	NL8195