COBRA treat-to-target trial

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Observational non invasive

Summary

ID

NL-OMON44989

Source
ToetsingOnline

Brief title
COBRA treat-to-target trial

Condition

- Autoimmune disorders
- Joint disorders

Synonym
RA, rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: COBRA treatment, Early RA, Prognostic factors, Treat-to-target

Outcome measures

Primary outcome

The primary outcome is the difference in disease activity in the two randomisation arms of both groups, measured by the percentage of patients that reach an EULAR good response or a DAS44-score <1.6 at 26 weeks. EULAR good response is reached when the DAS44-score is *2.4 and has improved >1.2 points compared to baseline.

Secondary outcome

The secondary outcomes are functional ability, remission, radiological progression, and patient reported outcomes. In a subgroup of patients in the high risk group (n=40), PET/CT-scans will be made at baseline and after two weeks.

Clinical lab, bone mineral density, body composition, social demographic parameters, and lifestyle factors are tertiary parameters.

Study description

Background summary

Recent international guidelines advise to start with methotrexate (MTX) as early as possible after the diagnosis of rheumatoid arthritis (RA), either alone or in combination with glucocorticoids or other disease-modifying antirheumatic drugs (DMARDs). In case of failure (incomplete response, non-response, or adverse events) on these conventional DMARDs, a biological DMARD is started. However, a persistent ~50% of patients with an unfavourable prognosis do not respond optimally to intensive tailored treatment during the first three months of treatment initiation. Of patients with a milder prognosis, minimal data is available.

Study objective

The objective of this study is twofold. First, we want to investigate the effectiveness of a COBRA-plus therapy after incomplete response on COBRA-light therapy after 13 weeks to improve the percentage of RA-patients with a high disease activity and/or unfavourable prognostic factors that reach a good response to treatment. Second, we want to investigate the effectiveness of adding prednisone to MTX monotherapy in RA-patients with initial low disease activity failing MTX monotherapy after 13 weeks. By using treat-to-target strategies, this study aims a high percentage of all early RA patients with a good response to treatment at 26 weeks.

A secondary objective of this study is to study the psychometric properties of patient reported outcomes in low disease activity and remission and investigate the validity of the outcomes that have been shown to be important to patients in defining remission. Another secondary objective is to study the predictive value of both baseline and change (2 weeks) in synovial macrophage infiltration in joints as seen on Positron Emission Tomography/Computer Tomography (PET/CT) for clinical response to 13 weeks of COBRA-light therapy.

Study design

This is a multicenter study containing a randomisation step after incomplete response at 13 weeks and with two strategy arms: one arm of patients with unfavourable prognostic factors, the so-called *high risk group* (group 1), and in the other study arm patients without unfavourable prognostic factors, the *low risk group* (group 2). Patients are treated according to a treat-to-target protocol, using mono- and combination therapy commonly used in clinical practice. In case of suboptimal response after 13 weeks, patients are randomised to continue initial therapy or intensified therapy. Treatment is protocolised for 26 weeks and patients are followed for 52 weeks.After 26 weeks, the treating rheumatologist is at liberty to make an own treatment decision.

At baseline, and after 4, 13, 17, 26, 39, and 52 weeks, patients will visit their treating rheumatologist where usual measurements will take place (i.e. number of tender and swollen joints, lab tests, x-rays of hand and feet, patient reported outcomes in the form of questionnaires on perceived pain, global wellbeing, and physical functioning). In addition, research questionnaires will be collected on additional patient reported outcomes including fatigue, sleep, stiffness, and employment. In case of a moderate or non response according to European response criteria (EULAR criteria) after 13 weeks, treatment is randomised to continue initial therapy or to intensification of the therapy.

At baseline, the high risk group starts with COBRA-light therapy (a combination

of MTX 25 mg per week and initially 30 mg prednisolone per day tapered to 7.5 mg prednisone per day in eight weeks). If EULAR response after 13 weeks is good, COBRA-light therapy will be continued. If EULAR response is moderate or none, patients will be randomised to continue COBRA-light therapy or to intensification to COBRA-plus therapy (a combination of MTX 25 mg per week, initially 60 mg prednisolone per day tapered to 7.5 mg prednisone per day in seven weeks, sulfasalazine 2000 mg per day, and hydroxychloroquine 400 mg per day).

The low risk group starts with MTX monotherapy (started with 10 mg MTX per week increased to 25 mg per week in eight weeks). After 13 weeks, EULAR response will be determined. If EULAR response is good, initial medication will be continued. If EULAR response is moderate or none, patients will be randomised to continue MTX mono-therapy or to intensification to COBRA-light therapy.

Study burden and risks

The patients participating in this cohort will receive optimalised clinical care according to a treat-to-target strategy: in case of suboptimal response to treatment, patients are randomised to continue initial therapy or intensified therapy. There are no additional risks associated with participation in this study, since all drugs are registered drugs that are already used for several years in usual clinical practice of patient with RA (also in the combinations defined in this study). Furthermore, rheumatologists are all very experienced in the use of MTX, sulfasalazine, hydroxychloroquine, and glucocorticoids (prednisolone).

Furthermore, patients have to make seven visits to the treating rheumatologist during the first year of the study, which is one visit more than normal for treating early RA patients. In addition, the patients will visit a research nurse seven times a year, to monitor disease activity in a standardized way. These visits are also routine in most Dutch rheumatological clinics in the early phase of treatment.

Blood samples will be performed at each visit according to usual care to measure the level of disease activity and because of safety reasons in patients treated with MTX and prednisolone. However, per visit, up to a maximum of 52 ml extra will be collected as stored samples for additional scientific measurements.

Standard questionnaires will be completed at each visit. In addition, research questionnaires will be completed, which will take approximately 30 minutes extra per visit (week 0, 13, 26, and 52). X-rays and DXA-scans will be made at baseline and after 26 and 52 weeks, and PET/CT-scans will be made in a part of the patients in group 1 (*high risk group*) at baseline and after 2 weeks. For x-rays this is one time extra compared to usual clinical practice (week 13), DXA-scans and PET/CT-scans are not regularly performed in usual clinical

practice and are all part of research. The x-rays, DXA-scans, and PET/CT-scans result in extra radiation exposure. Urine samples will be collected at baseline and after 4, 13, 26, and 52 weeks.

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) RA according to the 2010 classification criteria of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR)
2) Age of 18 years and older
3) Early RA: disease activity of less than 2 years
4) Active RA, the patient must meet at least one of the following unfavourable prognostic markers: DAS44 score >3.7 OR presence of at least two of the four following features (CRP*35 mg/l OR ESR*50 mm/h; IgM-RF positive; aCCP positive; at least 1 erosion)

Patients meeting the first three criteria, but not the criteria for active RA, can participate in the group of patients with a high probability of a mild disease course (low risk group). Patients can also participate in the low risk group, if they score four or five points on the classification criteria (undifferentiated arthritis) ánd a strong suspicion of the treating rheumatologists that the patient will develop RA. Patients meeting all four inclusion criteria, including the active RA criterion, can participate in the group of patients with a potentially severe course of the disease (high risk group).

Exclusion criteria

- Prior treatment DMARDs (except hydroxychloroquine)
- Corticosteroid treatment with a supraphysiological dose (>7.5 mg/day) in the four weeks prior to screening
- Insulin-dependent Diabetes mellitus
- Uncontrollable non-insuline dependent diabetes mellitus
- Heart failure NYHA class 3-4
- Uncontrollable hypertension
- ALAT/ASAT >3 times normal values
- Reduced renal function
- Contra-indications for methotrexate, sulphasalazine or prednisolone
- Indications of probable tuberculosis
- Increased risk of harm due to contraindications to the study drugs
- Language problems

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-12-2013
Enrollment:	190
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ledertrexate®
Generic name:	Methotrexate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Plaquenil®
Generic name:	Hydroxychloroquine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prednisolone
Generic name:	Prednisolone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sulfasalazine
Generic name:	Sulfasalazine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	18-10-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-11-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2014

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 19866
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2013-003658-26-NL
CCMO	NL45991.029.13
OMON	NL-OMON19866