TApering strategies in Rheumatoid Arthritis remission induced by anti-TNF&classic DMARDs. Should we taper the classic DMARD or anti-TNF first?

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

Summary

ID

NL-OMON41388

Source
ToetsingOnline

Brief title
TARA

Condition

- Joint disorders

Synonym
rheumatism, rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: (Cost-)effectiveness, Remission, Rheumatoid Arthritis, Tapering

Outcome measures

Primary outcome

Primary outcome clinical effectiveness: Disease flare defined as DAS44>2.4 or swollen joint count>1 during the first year of the study.

Primary outcome cost-effectiveness: Incremental Cost Effectiveness Ratio (ICER) of tapering DMARDs versus tapering anti-TNF in terms of cost per QALY gained and in terms of cost per tapered patient.

Secondary outcome

Secondary outcomes will include the number of disease flares during the second year of the study, radiographic progression at 1 and 2 years, presence of ultrasonographic synovitis and erosions over the first 12 months, the HAQ, the SF36, sick leave, productivity loss at work and cost-effectiveness modelled over the long term. Informed patient preferences about tapering strategies in anti-TNF&MTX users will be obtained in a subgroup of (potential) study candidates using discrete choice experiments.

Outcomes blood research:

- serum concentrations of adalimumab/etanercept, methotrexate (methotrexate polyglutamate in erythrocytes) and anti-drug antibodies.

- the ratio between Th-17-lymfocytes and other T-lymfocytes at baseline, flare (DAS44>2.4 or SJC>1) and 3 months after the occurence of a flare.

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and 3 months after the occurence of a flare.

Study description

Background summary

Economic evaluation of tapering medication in Rheumatoid Arthritis (RA) is important because of the increasing use of expensive biologicals in the treatment of RA. Previous uncontrolled cohort studies showed that it is possible to taper anti-TNF or MTX while maintaining remission of disease in approximately 40% of the rheumatoid arthritis (RA) patients that use the combination of MTX&anti-TNF. This is not yet common practice which may relate to the fact that it is unclear which step down (tapering) regime would be optimal. There are no head-to-head studies available comparing the tapering of DMARDs, suchs as MTX, with tapering of anti-TNF in DMARDs&anti-TNF using patients in clinical remission.

Study objective

Our main aim is to evaluate the effectiveness and cost-effectiveness of two tapering strategies:(i)DMARD tapering and (ii)anti-TNF tapering in RA patients with DMARD&anti-TNF(etanercept, adalimumab, certolizumab or golimumab) induced remission.

Study design

A multicenter randomised single-blind controlled trial with a parallel cost-effectiveness study will be set up to compare the outcomes of the 2 tapering strategies over a 2-yr period

Intervention

The aim of treatment is to maintain low disease activity as expressed by the Disease Activity Score (DAS)<=2.4 while tapering the medication. Treatment strategies will be tightly controlled, with patients being examined every three months. The tapering strategy will be predefined for the first 12 months, after which the rheumatologists are free to prescribe they see fit continuing tight-controlled care aiming for remission. The appended flow diagram shows the two tapering strategies over time.

1)Tapering DMARD
The DMARD will be tapered in 2 steps. First the baseline DMARD dosage will be

cut in half, followed in the second step by a quarter of the initial nbDMARD dosage. Thereafter, DMARD will be stopped. During the first year of the study, anti-TNF will be continued at the initial dosage. In case the classic DMARD was successfully discontinued in the first year of the study, the anti-TNF will be tapered during the second year of the study.

2)Tapering anti-TNF
Anti-TNF will be tapered in 2 steps. First the time between 2 gifts is extended. Enbrel will be given each fortnight, Humira and Cimzia once every 4 weeks and Simponi once every two months. This is followed by half of the initial dosage, that is 25 mg of Enbrel, 20 mg of Humira, 100 mg of Cimzia or 25 mg of Simponi..Thereafter, anti-TNF will be stopped. During the first year of the study, the nbDMARDs will be continued at their initial dosages. In case the anti-TNF was successfully discontinued in the first year of the study, the classic DMARD will be tapered during the second year of the study.

Discontinuation of tapering
Tapering will be terminated at the time the DAS >2.4 or swollen joint count > 1. If the DAS increases above 2.4 the treatment will be intensified to the last effective dosage when the patient was still in remission. E.g. if the patient flares on MTX 12 1/2 mg per week and the previous step was MTX 25 mg per week, the MTX dosage will be increased to the 25 mg MTX while anti-TNF is continued. No further attempts will be taken to taper medication in the first year of the study.

Study burden and risks

Participating in the TARA trial yields no extra risk for the patient. Patients taper down their medication under the supervision of their rheumatologist. In case disease activity increases the last effective dosage will be restarted.

In principle, the risk for having a disease flare for patients tapering down medication in our study is no greater than that for patients tapering down medication on a regular basis.

Benefits:
Participating in the study yields no direct benefit for the patient.

Burden:
De patient*s burden consists of:
- Three monthly visits to the research nurse (30-45 minutes/visit, visits will be combined with the regular check-up visits at the rheumatologist).
- Three monthly completing of questionnaires (20-30 minutes).
- If available at the patient*s hospital: 5 ultrasonographic evaluations of the joints (ca. 30 minutes/evaluation, will be combined with the regular check-ups at the rheumatologist).

- Drawing of blood every 3 months (20 ml every visit; at baseline, in case of a flare and 3 months after a flare max 104 ml every visit)

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

RA patients, aged >17 years, treated with DMARDs&etanercept,adalimumab,certolizumab or golimumab, DAS <= 2.4 and swollen joint count <=1 for two consecutive time points (3 months)

Exclusion criteria

Not being able to understand, speak and write in Dutch.
Being diagnosed with a psychiatric or personality disorder.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-06-2011
Enrollment:	355
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cimzia
Generic name:	certolizumab pegol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Enbrel
Generic name:	etanercept
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Humira
Generic name:	adalimumab
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	methotrexate
Generic name:	methotrexate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Simponi
Generic name:	golimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-05-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-05-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-09-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-11-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	20-12-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-04-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-04-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-10-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-08-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-09-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-10-2014
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-12-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2010-024504-10-NL
CCMO	NL35282.078.11