Randomised controlled study of dose reduction and withdrawal strategies of adalimumab and etanercept in rheumatoid arthritis: saving costs at what expense?

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This study has 4 primary objectives:1: To compare the cumulative incidence of patients fulfilling prespecified loss of response/flare criteria in the intervention group with the usual care group after 9 months and after 18 months of follow up.2:To...

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

Summary

ID

NL-OMON38325

Source
ToetsingOnline

Brief title
DRESS study: Dose REduction Strategies of Subcutaneous TNF inhibitors

Condition

- Joint disorders

Synonym
chronic arthritis, rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Sint Maartenskliniek
Source(s) of monetary or material Support: stichting Mycelium

Intervention

Keyword: anti-TNF, cost minimisation, down titration, PET scanning

Outcome measures

Primary outcome

- Cumulative incidence of patients fulfilling prespecified loss of response/flare criteria in the intervention and the usual care group after 9 months and after 18 months of follow up.

- Cost effectiveness (cost minimisation) ratio between intervention group and usual care group for the 9 month induction phase and for the 12 months maintenance phase.

- Predictive values/characteristics of a prediction model including (change in) serum drug levels and PET arthritis.

- Proportion of patients with a change in modified Sharp-van der Heijde Score> MCIC in the intervention and usual care group.

Secondary outcome

- Mean DAS28 in intervention and usual care group at 9 and 18 months follow up.

- Mean time averaged DAS28 in intervention and usual care group at 9 and 18

months follow up.

- Proportion of patients with a DAS28<3.2, DAS28<2.6 and fulfilling remission criteria according to ACR/EULAR criteria in the intervention and usual care group at 9 and 18 months follow up.

- Mean HAQ in intervention and usual care group at 9 and 18 months follow-up.

- Proportion of patients in the intervention group who, after reinstating adalimumab/etanercept because of a flare, didn*t achieve low disease activity again at 9 en 18 months follow up.

- (Dosage and) proportion of patients using NSAID, corticosteroid*s or DMARD*s in the intervention and usual care group at 9 and 18 months follow up .

- Proportion of patients developing adverse events with special attention for allergic (injection) reactions in the intervention and usual care group.

- Minimal inhibitory concentration of the anti TNF agent in serum in patients in the intervention arm fulfilling prespecified loss of response/flare criteria at any time.

Study description

Background summary

TNF blocking agents are effective in the treatment of Rheumatoid Arthritis (RA), with Adalimumab (humira ®) and etanercept (enbrel ®) being the two most frequently used agents in the Netherlands. These drugs are associated with side effects, including a dose dependent increase risk for infection. Also, these agents are much more expensive than traditional anti-rheumatic drugs (DMARD*s), thus increasing the costs of treatment. Therefore, it seems rational to give these drugs in the lowest effective dose or even stop the treatment when there are no longer necessary.
There are data that suggest that dose reduction and withdrawal of TNF blocking agents is feasible in a subgroup of patients without relevant increase in disease activity. Using this approach, the same clinical outcome could be reached with lower risk for side effects and less direct and total cost for society. However, a number of patients will not be able to reduce dose of medication. These patients will develop a temporary increase in disease activity which may give adverse effects for example loss of quality of life and radiologic damage. Therefore it is usefull to find predivitve factors for succesfull dose reduction.

Study objective

This study has 4 primary objectives:

1: To compare the cumulative incidence of patients fulfilling prespecified loss of response/flare criteria in the intervention group with the usual care group after 9 months and after 18 months of follow up.

2:To estimate cost effectiveness ratio of a protocollised dose reduction/withdrawal strategy of adalimumab or etanercept compared to usual care for the 9 months induction phase and for the 12 months maintenance phase.

3: To predict in the intervention group which baseline factors (including [change in] serum drug levels and antibody levels and [change in] PET arthritis) are associated with successful initial (9 months follow up) and maintained (18 months follow up) dose reduction.

4: To assess the safety of this strategy with respect to proportion of patients developing radiological damage (change in modified Sharp - van der Heijde18 Score > Minimal Clinical Important Change).

Study design

Pragmatic open randomized controlled cost effectiveness strategy trial, stratified for anti-TNF agent. This study has an induction phase from 0 to 9 months and a maintenance phase from 6 to 18 months.

The induction phase starts at baseline and continues to 9 months follow up. This phase will gave information about the period in which treating rheumatologist is advised to actively reduce dose of anti-TNF in 6 months. This part of the study ends 3 months after withdrawal of anti TNF in the patients who are able to withdraw. The maintenance phase starts at 6 months follow up, the time point where some patients can stop anti TNF, and continues to 18 months follow up. This phase will gave information about the period when patients are on a stable lower dose of or stopped the anti TNF. This distinction has been made, because it can be foreseen that the cost effectiveness is very different between these time periods. In the induction phase, medication costs are still high, patients are seen more often and quality of life might be compromised by temporary flares. In the maintenance phase, cost effectiveness may be substantially better for opposite reasons, and this can probably be extrapolated to subsequent years.

Intervention

In the intervention group usual care and tight control is provided and the treating rheumatologist is advised to try to increase interval of adalimumab or etanercept.
If a patient uses adalimumab the interval will be stepwise increased every three months from 14 to 21 to 28 days, after that the adalimumab will be stopped. If a patient uses etanercept, the dosage will be kept the same and the interval will be stepwise increased every three months from 7 to 10 to 14 days, after that the etanercept will be stopped. When a persistent flare occurs in disease activity, the treatment is intensified and interval shortened back to the last effective interval.

Study burden and risks

Planned visits every 3 months during the study are usual care and represent no additional burden. Patients are asked to complete additional questionnaires. Also a number of times during the study a serum sample will be taken and at 2 time points X-rays of hands and feet are made** wich is also consistent with standard treatment.
There is a risk a flare of the rheumatoid arthritis will occur. This can happen in the intervention group as well as in the usual care group. Patients are encouraged to call if they experience more symptoms in between planned visits. They can then come to the clinic.

A separate part of the study is the PET scan. This is done in the intervention group, 1 or 2 times during the study. PET scan is not a standard examination in the diagnosis of rheumatoid arthritis. The PET scan lasts 2 hours and there is a preparation to it. Patients who are pregnant or breastfeeding are excluded from this part of the study.
Patients receive seperate information and informed consent form for this part

of the study.

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

- Rheumatoid arthritis (either 2010 ACR RA and/or 1987 RA criteria and/or clinical diagnosis of the treating rheumatologist, fulfilled at any time point between start of the disease and inclusion)
- Using either adalimumab or etanercept (all dose/interval regimens, all background medication including DMARDs and corticosteroids up to 5 mg, higher doses of steroids should be reduced first)
- 6 months of stable low disease activity while using adalimumab or etanercept (operationalised by either a DAS28 < 3.2 or judgment of low disease activity by rheumatologist at at least two subsequent visits)

- 6 months stable treatment with adalimumab or etanercept (previous dose reduction/interval increase is allowed when more than three months ago) and stable DMARDs and corticosteroids for more than 4 weeks

Exclusion criteria

- Co morbidity that also requires treatment with anti-TNF and thus prevents dose reduction

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-12-2011
Enrollment:	180
Type:	Actual

Ethics review

Approved WMO Date:	17-11-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-05-2012

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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: 20595
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL37704.091.11
OMON	NL-OMON20595

Study results

Date completed:	21-05-2014
Actual enrolment:	180