Adalimumab dose optimisation in rheumatoid arthritis using therapeutic drug monitoring (ADDORA): multi-centre open label randomised controlled trail

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The main objective is to evaluate whether adalimumab dose reduction using adalimumab serum measurements (TDM strategy) will minimize medical costs, compared to disease activity guided dose reduction in rheumatoid arthritis (RA) patients.

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

Summary

ID

NL-OMON47985

Source
ToetsingOnline

Brief title
ADDORA

Condition

- Autoimmune disorders

Synonym
rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Jan van Breemen Instituut

Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: Adalimumab, Rheumathoid arthritis, rheumatology, Tappering, Therapeutic drug monitoring

Outcome measures

Primary outcome

The main parameter used to investigate the primary objective is direct medical

costs associated with adalimumab dose reduction strategies (medication,

non-scheduled visits due flares, cost TDM testing) over 52 weeks.

Secondary outcome

Difference in mean time weighted DAS28-CRP between study groups at 16, 28, 52

and 80 weeks.

Direct medical costs (medication, visits, cost TDM testing) of both study

groups after 28, 40 and 80 weeks.

Indirect medical costs of both study group at 52 and 80 weeks of treatment.

Percentage of patients with DAS28-CRP<2.9 in both study groups at 52 and 80

weeks.

Number of flares and dose-interval shortenings in both study groups at 52 and

80 weeks.

Agreement between algorithm predicted and measured adalimumab concentrations at

week 28 and week 52 (only drug concentration guided group).

Study description

Background summary

Several prior studies have shown that dose reduction of Tumor Necrosis Factor (TNF)-inhibitors like adalimumab is possible in substantial number of rheumatic disease patients without an increase in disease activity. Biologic therapy is expensive, and is associated with patient burden as dose dependant risk for serious infections . A dose reduction will decrease the risk of side effects and result in substantial cost savings. Currently, most clinicians use Disease Activity Score in 28 joints (DAS28) and the Clinical Disease Activity Index (CDAI) to monitor dose tapering strategies. Although this approach is cost-effective, it might be improved by information on the extent of drug levels, as several studies have shown that adalimumab drug levels are associated with clinical outcome. Therefore, a study comparing dose reduction strategy using therapeutic drug monitoring (TDM) with dose reduction strategy using disease activity is timely

Study objective

The main objective is to evaluate whether adalimumab dose reduction using adalimumab serum measurements (TDM strategy) will minimize medical costs, compared to disease activity guided dose reduction in rheumatoid arthritis (RA) patients.

Study design

This study is a multi-centre, randomised, open-label trail which consists of three consecutive phases, with a total study duration of 80 weeks:

Phase 1 (week 0 to 16) an observational phase; patients will be treated, in accordance with current Dutch clinical guidelines, with adalimumab 40 mg every other week.

Phase 2 (week 16 to 52) randomized, cost-minimization, open trial; patients who achieved EULAR moderate or good response (15) during phase 1 are randomly assigned (1:1) to adalimumab dose reduction using drug concentration or disease activity scores
- Drug concentration-guided group: Dose-interval will be prolonged at week 16 according to the adalimumab serum concentration at week 16, irrespective of disease activity, targeting at 5 mg/L. A newly developed algorithm (see below) was used to determine the interval prolongation for each patient. At week 28, the dose-interval is prolonged further, targeting at 2 mg/L.
- Disease activity-guided group: Patients continue the standard dose up to week 28.Thereafter, the dose interval is prolonged in patients who achieve DAS28-CRP <=2.9 according to the DRESS-protocol (16).

Phase 3 (week 52-80) extension phase; patients who successfully prolonged the dose interval to 40 mg every 4 weeks in the disease activity-guided group will

discontinue adalimumab at week 52 and be followed up to week 80. Patients who successfully prolonged their dose-interval in the drug concentration guided group and achieve a serum concentration of 2.0 mg/L, will maintain their dose for another 28 weeks (up to week 80). Serum trough levels do not predict successful discontinuation of adalimumab, therefore, these patients will continue low dose adalimumab

Intervention

- Drug concentration guided group: Dose-interval will be prolonged using adalimumab serum concentration at week 16,
- Disease activity-guided group: dose interval is prolonged using disease activity scores.

Study burden and risks

The main risk associated with this study is an increase of disease activity with loss of response. Several studies have shown that tapering of bDMARDs is safe. Furthermore we have already demonstrated that adalimumab concentration of <5mg/L is sufficient to control disease activity. Stated the increased risk of overtreatment and higher medical costs, dose reduction appears to be reasonable in patient with rheumatoid arthritis. Since the main propose of this tapering study is to optimize treatment, to reduce risk of overtreatment and to reduce medical cost, we are convinced that the execution of the study exceeds the burden and risks of this 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 patient, according to ACR 1987 /2010 criteria;
Starting adalimumab as the first biological therapy
Written informed consent
Age 18 years or older.

Exclusion criteria

Scheduled surgery during the follow-up of the study or other pre-planned reasons for treatment discontinuation;
Life expectancy shorter than follow-up period of the study;
Other disease that might flare if adalimumab is tapered like psoriasis, inflammatory bowel disease.

Study design

Design

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

Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-07-2020
Enrollment:	267
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Humira
Generic name:	adalimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	04-10-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-10-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-01-2023

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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-001554-25-NL
CCMO	NL68946.029.19