RhEumatoid arthritis REtreatment with ultra-low dose Rituximab: Disease Outcome after Dose Optimization

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To assess the difference in efficacy between two ultra-low doses (1 x 500 mg and 1 x 200 mg) and standard low dose (1 x 1000 mg) of RTX retreatment on the change in DAS28-CRP, compared to a pre-specified non-inferiority margin of 0.6, at 3 and 6...

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

Summary

ID

NL-OMON47117

Source
ToetsingOnline

Brief title
REDO

Condition

- Autoimmune disorders
- Joint disorders

Synonym
chronic inflammation of the joints, Rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Sint Maartenskliniek
Source(s) of monetary or material Support: Het onderzoek wordt gefinancieerd door de

Sint Maartenskliniek zelf. Externe funding is verkregen van twee zorgverzekeraars: CZ en Menzis.

Intervention

Keyword: dose reduction, low dose, rheumatoid arthritis, rituximab

Outcome measures

Primary outcome

Disease activity measured with the DAS28-CRP at baseline, 3 and 6 months.

Secondary outcome

- Baseline characteristics: demographics, disease characteristics, treatment characteristics, joint damage, patient and rheumatologist expectations of lower dose.

- Functioning: measured with HAQ-DI at baseline, 3 and 6 months

- Quality of life: measured with EuroQolEQ5D-5L at baseline, 3 and 6 months

- Adverse events: occurrence of adverse events during study period.

- Medication use: use of DMARDs, corticosteroids, NSAIDs during study period

- Pharmacokinetics: serum RTX, serum anti-RTX at four time points: before infusion, after infusion, after 3 and after 6 months.

- Pharmacodynamics: To be able to study the pharmacodynamics of RTX in patients and possible predictors of response, we will analyze at baseline, 3 months and 6 months: CD19+ B-cell count (baseline only), serum free light chains, S100A8/9.

- Costs

- Process evaluation: study integrity

Study description

Background summary

Rituximab (RTX) is a biological that is registered for use in patients with Rheumatoid Arthritis (RA). Nowadays, the RTX doses used in clinical practice are either 2 × 500 mg, 1 × 1000 mg (low-dose) or 2 × 1000 mg (high-dose) at least every 6 months.
Evidence from several case reports and an observational open label study suggests the possibility that lower doses of RTX (1 x 100 mg and 1 x 500 mg) might be sufficient for effective treatment of RA patients. Furthermore, a lower dose of RTX may be needed for retreatment compared to initial treatment. Also, similar anti B-cell monoclonal antibodies (ocrelizumab and ofatumumab) are successfully used in a lower doses than RTX for RA.
Several disadvantages of RTX could be ameliorated by the use of lower doses of RTX. These include the dose-dependent risk of infection, long infustion time, infusion related adverse events and high costs. However, the use of very low doses of RTX for retreatment of RA has never been studied in a randomised controlled trial, partly because this is not the priority of the pharmaceutical company that, after all, registered RTX in higher dosages for treatment of Lymphoma.

Study objective

To assess the difference in efficacy between two ultra-low doses (1 x 500 mg and 1 x 200 mg) and standard low dose (1 x 1000 mg) of RTX retreatment on the change in DAS28-CRP, compared to a pre-specified non-inferiority margin of 0.6, at 3 and 6 months in patients with RA.

Study design

We will perform a pragmatic multicenter randomized controlled non-inferiority trial. Patients will be randomized into three groups: conventional low dose (1 x 1000 mg RTX) or one of the two intervention groups (1 x 500 mg or 1 x 200 mg RTX) in a ratio of 1:2:2. Patients, care providers and researchers will be blinded for allocation. Follow up duration is 6 months for all patients.
Patients will be approached by their treating rheumatologist for participation in this trial. Three visits will be planned during the 6-month study period: baseline, 3 and 6 months follow up.

Intervention

Conventional low dose: 1 × 1000 mg
Patients allocated to the conventional low dose group will receive a single 1000 mg RTX infusion according to the standard protocol for infusion of

rituximab

Ultra-low dose: 1 × 500 mg
Patients allocated in this group will receive a single 500 mg RTX infusion. This dose will be diluted to the same volume as the usual care infusion to ensure the blinding of the study.

Ultra-low dose: 1 × 200 mg
Patients allocated in this group will receive a single 200 mg RTX infusion. This dose will be diluted to the same volume as the usual care infusion to ensure the blinding of the study.

Study burden and risks

Normally, patients visit the treating rheumatologist for a regular control of their rheumatoid arthritis once every three or six months. A blood sample is taken during a regular visit.
In this study the participants will be scheduled to a visit once every three months. At the baseline visit, patients are asked for baseline characteristics and radiographs will be made of hands and feet if no radiographs had been made in the past three months. Patients are asked to complete a short questionnaire after the RTX infusion on the occurrence of infusion-related adverse events. During this first visit, two blood samples will be collected, one before and one after infusion of the study medication. During the other visits one blood sample will be collected. In a subgroup of patients (convenient sample who are willing), an extra blood sample will be taken 1 month after infusion. During all visits several short questionnaires will be completed: the OMERACT flare questionnaire, HAQ-DI, EUROQOL-5D-5L and a questionnaire on health related absenteeism. The extra time required for this study will amount to approximately 1 hour for the first visit and 15 minutes for the other visits. This results in a total of 1,5 hours of extra time required for a patient to take part in the study (excluding travel time).
Risks of participation in this study includes the chance of a temporary increase in disease activity in the patients receiving a lower dose than they used to. However, if this happens, the increase in disease activity will be short-lived as the rheumatologist will act on this. On the other hand, patients receiving a lower dose of RTX will have a reduced chance on RTX related side effects.

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.
- RTX retreatment: at least once RTX in the last 18 months for RA in a dose of 1 × 1000 mg, 2 × 1000 mg or 2 × 500 mg and no other biologicals received after last RTX dose. Patients treated with innovator RTX (MabThera) as well as registered biosimilars will be included.
- At least 6 months of stable, low disease activity after the last RTX infusion (operationalized by either DAS28-CRP<2.9 (DAS28-BSE <3.2) or judgement of low disease activity by a rheumatologist) AND a current DAS28-CRP *3.5 (DAS28-BSE*3.8).
- Patient informed consent, *18 years old and mentally competent
- Ability to measure the outcome of the study in this patient (e.g. life expectancy * 6 months, no planned relocation out of reach of study centre)
- Ability to read and communicate well in Dutch

Exclusion criteria

- Patients with known (non-)response to ultra-low dose RTX (below 1 × 1000 mg)

- Current corticosteroid dosing above 10 mg per day prednisolone equivalent

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-12-2016
Enrollment:	140
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MabThera
Generic name:	Rituximab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	23-08-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	08-11-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-01-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-01-2018
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: 23732
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2016-002908-15-NL
CCMO	NL57520.091.16

Register	ID
OMON	NL-OMON23732