Research into the effects of lower doses rituximab in patients with rheumatoid arthritis

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23732

Source
Nationaal Trial Register

Brief title
REDO

Health condition

Rheumatoid Arthritis

Sponsors and support

Primary sponsor: The Sint Maartenskliniek
Source(s) of monetary or material Support: Funding is obtained from two Dutch health care insurers: CZ and Menzis

Intervention

Outcome measures

Primary outcome

• DAS28-CRP at 3 and 6 months

The primary endpoints will be tested using 95% confidence intervals based on linear regression with the change in DAS28-CRP as outcome, dose group as determinant, and baseline values of DAS28-CRP as covariate (ANCOVA). A non-inferiority margin of 0.6 will be used.

Multiplicity over the primary endpoints will be protected by a fixed testing procedure as follows. First the non-inferiority of the 500mg vs 1000mg at 3 months will be tested at $p<0.05$ (two-sided). If this is statistically significant, then 500mg vs 1000mg will be tested at $p<0.05$ (two-sided) at 6 months. If that is successful, then 200mg vs 1000mg will be tested at $p<0.05$ (two-sided) at 3 months and if that is statistically significant, the last test will be 200mg vs 1000mg at $p<0.05$ (two-sided) at 6 months.

Secondary outcome

• Other measures for disease activity (VAS-pain, VAS-global care provider, OMERACT flare questionnaire)

• Function (HAQ-DI)

• Quality of life (EQ5D-5L)

• Adverse events

• Medication use

• Costs

Study description

Background summary

Background:

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 x 500 mg, 1 x 1000 mg (low-dose) or 2 x 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 1000 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 infusion 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 randomized 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.

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.

Study population:

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 x 1000 mg, 2 x 1000 mg or 2 x 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 (below 1 x 1000 mg)

- Current corticosteroid dosing above 10 mg per day prednisolone equivalent

Intervention:

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. Patients allocated to the ultra-low dose groups, will receive a single 500 mg or 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.

Primary outcome:

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

Secondary outcomes:

- 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 and pharmacodynamics

- Costs

Study design

• Baseline

• 3 months

• 6 months

Intervention

For retreatment with RTX, RA patients already using RTX will be randomized into three groups: usual care (1 x 1000mg) or one of the two intervention groups (1 x 500mg and 1 x 200mg). Patients will be allocated to one of the three groups using a concealed randomization procedure and receive a single dose of RTX. Participants will be allocated at a ratio of 1:2:2 (usual care (1 × 1000mg) versus 1 × 500mg versus 1 × 200mg) to allow for the use of more predictive factors for response to lower doses of RTX.

Contacts

Public
Sint Maartenskliniek, Research department, Hengstdal 3

Lise Verhoef
Ubbergen 6574 NA
The Netherlands
Tel: 0031 24 3272726
Scientific
Sint Maartenskliniek, Research department, Hengstdal 3

Lise Verhoef
Ubbergen 6574 NA
The Netherlands
Tel: 0031 24 3272726

Eligibility criteria

Inclusion criteria

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Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-12-2016
Enrollment:	140
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	15-11-2016
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 47117
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL5936
NTR-old	NTR6117
CCMO	NL57520.091.16
OMON	NL-OMON47117

Study results

Summary results
https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(19)30066-9/fulltext