Concentration-guided dose reduction versus standard dosing in tocilizumab-treated rheumatoid arthritis patients: a randomised, international, multicenter, non-inferiority trial (TODORA)

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This study has been transitioned to CTIS with ID 2025-520513-30-00 check the CTIS register for the current data. We aim to optimize the treatment of rheumatoid arthritis patients using concentration measurements. By doing this we hope to reduce the...

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

Summary

ID

NL-OMON52409

Source
ToetsingOnline

Brief title
Use of tocilizumab drug levels to optimize treatment of RA (TODORA)

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: rheumatoid arthritis, rheumatology, therapeutic drug monitoring, tocilizumab

Outcome measures

Primary outcome

The primary objective of the study is to investigate the difference in mean time weighted Disease Activity Score in 28 joints (DAS28-ESR) after 28 weeks in patients with RA with serum trough concentrations higher than 15 mg/L who are randomly assigned to continuation of the standard dose or to increase dosing interval to every two weeks.

Secondary outcome

The secondary objectives of the study are to investigate the difference in mean time weighted DAS28-ESR after 52 weeks, and the difference in Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), and HAQ score after 28 and 52 weeks, between the two treatment groups; to study the direct medical costs of using TDM to identify overexposure; to study the difference in number of flares between the two treatment arms at 28 and 52 weeks; to study the number and severity of adverse events in both treatment arms; to determine the difference in drug levels between the two treatment arms after 52 weeks; to study the relationship between dose, drug concentration, and clinical disease activity; to invent a pharmacokinetic model and develop an algorithm and a dashboard system to assure the implementation of TDM in clinical practice; and

to study the perspective of patients towards concentration-guided dosing.

Study description

Background summary

All patients diagnosed with RA and treated with tocilizumab sc receive the same dose, so treatment with expensive biologicals is currently based on a *one size fits all* approach. Our unpublished data showed that this standard dosing regimen results in a wide range of serum concentrations (from 0-35 mg/L). In the search to optimize the dose for individual patients, it was demonstrated that serum levels of tocilizumab of 1 mg/L are adequate to block the IL-6 receptor systemically, as indicated by a reduction in CRP level to normal in patients with these low trough concentrations. Given the median tocilizumab concentration of 24 mg/L after 28 weeks of treatment, a substantial proportion of patients is likely to be overexposed to tocilizumab. This overtreatment is a waste of health care resources and might be associated with an increased risk of adverse events, mainly infections. We believe that we can reduce the overexposure effectively by making use of the drug concentrations found in the blood of individual patients.

Study objective

This study has been transitioned to CTIS with ID 2025-520513-30-00 check the CTIS register for the current data.

We aim to optimize the treatment of rheumatoid arthritis patients using concentration measurements. By doing this we hope to reduce the overexposure to the drug, save costs and reduce the number of adverse events, especially infections. The goal of this multicenter trial is also to gain more knowledge on Therapeutic Drug Monitoring (TDM) in general and create more awareness among both patients and rheumatologists. This will hopefully result in a succesful implementation of TDM in clinical practice once it has proven to be effective.

Study design

This study is a 52 weeks non-inferiority, multicenter, international, randomized controlled study in rheumatoid arthritis patients treated with subcutaneous tocilizumab 162 mg weekly for at least the last 6 months. Several centers will approach eligible patients and invite them to participate in the study. After informed consent is obtained during the baseline visit, blood will be drawn to measure drug trough concentrations. Patients with a tocilizumab concentration above 15 mg/L will be randomly assigned to dose reduction by increasing their dosing-interval from once every week to once every two weeks,

or to continuation of their tocilizumab dose (standard dose). Patients with concentrations below 15 mg/L during the first study visit will not be randomized and all continue standard treatment.

Patients will be followed for a period of 52 weeks. Data regarding disease status and functioning will be collected during the baseline visit, and 12, 28, 40 and 52 weeks thereafter. Due to the limited amount of resources of this study, participating centers may choose to cancel visit 40, resulting in a total of four visits instead of five. Also, patients with a concentration of < 15 mg/L during the baseline visit will be asked to complete only one follow-up visit at 52 weeks instead of four follow-up visits. visits instead of five.

After patients have agreed to participate in the study, they will be asked whether or not they would like to participate in the part of the study were the finger prick developed by Sanquin (Amsterdam) will be validated to measure drug levels of tocilizumab. This will comprise performing three finger pricks additional to the blood that is drawn already during the study. These finger pricks will be performed during the visit at week 12 with the help of a nurse, and at home during the two weeks after this visit. Data from the finger prick will also be used to collect additional information about the drug levels of tocilizumab, which will be used in the pharmacokinetic analyses.

Intervention

All patients with a tocilizumab concentration above 15 mg/L will be randomised, and those patients that are allocated in the intervention group will reduce the dose by prolonging the dose-interval from 162 mg weekly to 162 mg every two weeks. This dose reduction will start after the baseline visit and will be maintained until 52 weeks of follow-up. After the end of the study, the treating rheumatologist will discuss with the patient whether it is desirable to maintain on this alternative dosing regimen. Patients allocated to the control group will not taper their tocilizumab treatment, as this is not current practice and limited data on tocilizumab tapering is available.

Study burden and risks

We hypothesize that patients with high tocilizumab concentrations can prolong their dose interval while maintaining stable disease activity. However, an increase in disease activity cannot be excluded. If this happens, patients that started tapering will return to the standard dose. Previous studies showed that disease activity can be controlled adequately after this dose adjustment. By participating in the study, patients might also experience burden from the additional blood that will be obtained. The amount of blood drawn from the patients will therefore be as little as possible.

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 according to the ACR 1897 or 2010 criteria;
- Current use of subcutaneous tocilizumab 162 mg weekly, for at least the last 6 months;
- The treating rheumatologist is convinced of the benefit of tocilizumab continuation;
- No changes in the treatment with glucocorticoids and DMARDs such as methotrexate in the past 3 months;
- Written informed consent.

Exclusion criteria

A scheduled surgery in the next 12 months or other pre-planned reasons for treatment discontinuation.

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):	16-04-2020
Enrollment:	88
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	RoActemra (sc)
Generic name:	Tocilizumab (sc)
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	15-05-2019
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-08-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2021
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-01-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-02-2023
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
EU-CTR	CTIS2025-520513-30-00
EudraCT	EUCTR2018-004605-57-NL
ClinicalTrials.gov	NCT03895879
CCMO	NL68462.029.19