Use of Tocilizumab Drug Levels to Optimize Treatment in RA

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20556

Source
Nationaal Trial Register

Brief title
TODORA

Health condition

Rheumatoid Arthritis

Sponsors and support

Primary sponsor: Reade Rheumatology Research Institute
Source(s) of monetary or material Support: ZonMw: The Netherlands Organisation for Health Research and Development

Intervention

Outcome measures

Primary outcome

The main objective is to investigate the difference in mean time weighted Disease Activity Score in 28 joints, including erythrocyte sedimentation rate (DAS28-ESR) after 28 weeks in RA patients with serum 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 are to investigate the difference in mean time weighted DAS28-ESR after 52 weeks between patients undergoing concentration-guided dose reduction or standard dosing; to investigate the difference in Clinical Disease Activity Index (CDAI), Simple Disease Activity Index (SDAI), and Health Assessment Questionnaire (HAQ) after both 28 and 52 weeks between the two treatment groups; to study the direct medical costs of applying therapeutic drug monitoring (TDM); to study the difference in number of flares at 28 and 52 weeks between the two treatment arms; to investigate the difference in number and severity of adverse events at 28 and 52 weeks in both treatment arms; to study the difference in drug level in the intervention group between week 0 and 52; and to study the perspective of patients towards concentration-guided dosing.

Study description

Background summary

Tocilizumab is a humanized monoclonal antibody targeting the IL-6 receptor (IL-6R). It has proven to be effective in reducing inflammation and symptoms in rheumatoid arthritis (RA). The registered standard dose of tocilizumab subcutaneously (sc) is 162 mg weekly for every patient. 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. Because of the large inter-individual variability in the pharmacokinetics of tocilizumab this standard dose results in a wide range of serum concentrations. In the search to optimize the dose for individual patients it was demonstrated that serum levels of 1 mg/L of tocilizumab are adequate to block the IL-6 receptor systemically, as indicated by a reduction in CRP levels in patients with these low trough concentrations. Therefore, 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 overexposure can be reduced effectively by making use of the drug concentrations found in the serum of individual patients. Our hypothesis is therefore that reducing the dose in the setting of therapeutic drug monitoring (TDM) does not affect clinical disease activity and safety, while it will reduce costs.

Based on previous studies we believe that a concentration around 5 mg/L is sufficient to reach the maximal treatment effect. Therefore tapering strategy was developed aiming for serum concentrations just above 5 mg/L. Monte Carlo modelling was performed to determine the cut-off concentration for interval prolongation to be used in this study. Simulations were performed and it was found that patients with trough concentrations above 15 mg/L can safely prolong their dosing interval, as this will result in levels around 5 mg/L in the majority of patients.

This study is a 52 weeks randomised, multicenter, non-inferiority trial in rheumatoid arthritis patients treated with subcutaneous tocilizumab 162 mg weekly for at least the previous 6 months. 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). After randomization, patients are 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. Blood will also be drawn from the patients during these visits. All patients with concentrations below 15 mg/L during the first study visit will not be randomized and all continue standard treatment. Only one follow-up visit, after 52 weeks, will be performed in this group of patients.

Patients can also choose to participate in a sub-study where the finger prick developed by Sanquin (Amsterdam) will be validated to measure tocilizumab drug levels. This part of the study will comprise performing three finger pricks. 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.

Study objective

Reducing the dose in the setting of therapeutic drug monitoring (TDM) does not affect clinical disease activity and safety, while it will reduce costs.

Study design

0, 12, 28, 40, 52

Intervention

Patients with tocilizumab trough concentrations 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 the standard dose. All patients with concentrations below 15 mg/L during the first study visit will not be randomized and all continue standard treatment.

Contacts

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Eligibility criteria

Inclusion criteria

- Rheumatoid arthritis according to the American College of Rheumatology (ACR) 1987 or 2010 criteria;
- Current use of subcutaneous tocilizumab 162 mg weekly, for at leas the previous 6 months;
- The treating rheumatologist is convinced of the benefit of tocilizumab continuation;
- Written informed consent.

Exclusion criteria

- A scheduled surgery in the next 52 weeks or other pre-planned reasons for treatment discontinuation;
- Changes in the treatment with glucocorticoids or DMARDs such as methotrexate in the past three months.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-08-2019

Enrollment:	98
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Yes

Plan description
To avoid duplication of research, the data gathered in this study will be shared once all desirable data analysis have been performed and the results are published.

Ethics review

Positive opinion

Date:	17-07-2019
Application type:	First submission

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
NTR-new	NL7878
Other	METC VUmc : 2019.097 - NL68462.029.19 (METC VUmc), NCT03895879 (www.clinicaltrials.gov), 2018-004605-57 (EudraCT Number)

Study results