Use of Tocilizumab Drug Levels to Optimize Treatment in RA

Gepubliceerd: 17-07-2019 Laatst bijgewerkt: 13-12-2022

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

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON20556

Bron
Nationaal Trial Register

Verkorte titel
TODORA

Aandoening

Rheumatoid Arthritis

Ondersteuning

Primaire sponsor: Reade Rheumatology Research Institute
Overige ondersteuning: ZonMw: The Netherlands Organisation for Health Research and Development

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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.

Toelichting onderzoek

Achtergrond van het onderzoek

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.

Doel van het onderzoek

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

Onderzoeksopzet

0, 12, 28, 40, 52

Onderzoeksproduct en/of interventie

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.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- 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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- 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.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Enkelblind
Controle:	Actieve controle groep

Deelname

Nederland Status:	Werving gestart
(Verwachte) startdatum:	01-08-2019
Aantal proefpersonen:	98
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Ja

Toelichting
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.

Ethische beoordeling

Positief advies

Datum:	17-07-2019
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

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

Resultaten