Exploring durable remission with rituximab in ANCA associated vasculitis

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

Samenvatting

ID

NL-OMON21172

Bron
NTR

Verkorte titel
The ENDURRANCE-1 Study

Aandoening

ANCA-associated vasculitis

Ondersteuning

Primaire sponsor: LUMC
Overige ondersteuning: LUMC

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

In this randomized study the primary objective is to prove the superiority of combination treatment RTX with cyclophosphamide to achieve a state of durable immunological remission

in AAV patients as compared to RTX alone. The primary objective is to assess the number of patients that reach a ANCA negative test within 24 weeks of therapy.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale: Most recent insights in the treatment for patients with ANCA-associated vasculitis (AAV) have demonstrated that ‘tailored’ maintenance treatment with rituximab (RTX) is effective to achieve durable remission of disease. As such, RTX re-treatment can be tailored on the basis of relevant immunological parameters that reflect minimal residual autoimmunity (MRA) in AAV patients. Now, the present study intends to evaluate whether combining rituximab with cyclophosphamide is superior to current standard of care with rituximab only to induce a favorable immunological state of MRA in AAV patients that can beneficially influence, i.e. reduce, the necessity of tailored re-treatment with rituximab
Objectives: The primary objective is to prove the superiority of combination treatment RTX with cyclophosphamide to achieve a state of MRA as defined as number of patients that reach ANCA seroconversion to negative within 24 weeks. The secondary objectives are alternative measurements for MRA such as time to ANCA return, duration of B-cell depletion and the composition of the memory B-cell and plasma cell populations.
Study design: Open label, two-center, randomized controlled trial
Study population: Adult AAV patients with a clinical diagnosis of granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) who have ‘generalised disease’ and a positive ANCA-test for anti-PR3 or anti-MPO.
Intervention: In addition to standard of care corticosteroid therapy, AAV patients will be randomized to receive either standard induction therapy with 2 infusions of RTX 1000 mg or induction therapy combining 2 infusions of RTX 1000 mg RTX with 6 infusions of low dose intravenous cyclophosphamide 500mg. Thereafter, as part of standard of care patients will receive tailored RTX re-treatment as maintenance therapy.
Main study parameters: AAV patients will be evaluated for MRA by prospectively and consecutively studying ANCA levels, B-cell depletion by standard flowcytometry and subsets of the B-cell and plasma cell compartment with high-sensitivity flowcytometry at predefined timepoints. Additionally, the study will perform safety and toxicity monitoring according to WHO toxicity criteria and evaluate the clinical response, the number of RTX re-treatments and the number of moderate and severe flares during study follow-up.
Study duration: 2 years
Nature and extent of the burden and risks associated with participation and potential benefits:
A potential, but thus far uncertain, benefit lies in the rationale that combination treatment could result in a better more prolonged clinical improvement of the patient’s AAV disease based upon previous uncontrolled studies and our own single center experience. Also, patients participating in the study will be able to taper their concomitant immunosuppression to zero while intensively monitored for receiving tailored rituximab infusions as maintenance treatment. Lastly, long-term immunosuppressive treatment is associated with (cumulative)

toxicity and long- term increased risk for infections or malignancies which is reduced in patients treated with rituximab. The risks related to study participation lies predominantly in the side effect profile of the described treatments and a minor risk with the intravenous access needle necessary for rituximab and cylcophosphamide infusions.

Doel van het onderzoek

Based on most recent insights in AAV treatment, the present study intends to evaluate whether combining rituximab with cyclophosphamide is superior to current standard of care with rituximab only to induce a favorable immunological state of MRA in AAV patients. The latter is defined as seroconversion of ANCA to negative, prolonged B-cell depletion or both. Additionally, the study will apply standardized highly sensitive flow cytometry (HSFC) to perform in-depth B-cell immunomonitoring in AAV patients which can help identify novel and more precise biomarkers of 'minimal residual autoimmunity', e.g. the residual presence of autoreactive memory B-cells. These biomarkers can potentially help to guide RTX (re-)treatment of future AAV patients.

Onderzoeksopzet

Follow-up evaluations will be performed every two months up to 104 weeks after treatment start or until study withdrawal.

Onderzoeksproduct en/of interventie

The study is designed as an open-label, 1:1 randomized, prospective study between RTX with cyclophosphamide and RTX alone. The duration of the study is 104 weeks during which AAV patients will be evaluated for MRA by studying ANCA levels, the B-cell and plasma cell compartment with HSFC analysis at predefined timepoints.

5.1.1. Rituximab
Patients will be intravenously treated with Rituximab 1000mg (or biosimilar) in the first week and receive a 2nd dosage of 1000mg 14 days later. Before every infusion of Rituximab patients will receive intravenous methylprednisolon 100mg together with oral acetaminophen 1000 mg and and intravenous Tavegil 2 mg. At any time during the study, a rituximab biosimilar (e.g. truxima or rixathon) is allowed as a substitute for the bio-originator rituximab.

5.1.2. Cyclophosphamide
Patients will be intravenously treated with a total of 6 infusions of cyclophosphamide 500mg every 2 weeks. Before every infusion of cyclophosphamide patients will receive intravenous granisetron to prevent nausea.

5.1.3. Standard of care (SoC)
5.1.3.1. Pulse steroids
Patients are given 1-3 pulses of 500mg methylprednisolon i.v. up to a maximum cumulative dose of 3000mg, taking into account any doses of intravenous methylprednisolone administered within 12 weeks prior to screening.

5.1.3.2. Oral steroids
After intravenous pulse methylprednisolone, oral prenisolone will be given at a dose of 1mg/kg daily and tapered according to the recommendations in section 5.3.3.1.

5.1.3.3. Re-treatment with rituximab
Patients will receive a tailored regimen for intravenous rituximab 500mg retreatment when one of the following criteria is met after induction treatment (i.e. 12 weeks and onwards) and clinical remission is achieved:
- CD19+ counts > 5x106 cells/L
- ANCA reappearance (e.g. conversion from negative to positive)
- ANCA-ELISA units doubled from previous nadir
At any time during the study, a rituximab biosimilar (e.g. truxima or rixathon) is allowed as a substitute for the bio-originator rituximab.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

4.1. Inclusion criteria
Subjects enrolled in the study must meet the following inclusion criteria:
1) Clinical diagnosis of granulomatosis with polyangiitis (GPA) or microscopic Polyangiitis (MPA), consistent with Chapel-Hill Consensus Conference definitions26
2) Aged at least 18 years, with newly-diagnosed or relapsed AAV with ‘generalised disease’, defined as involvement of at least one major organ (e.g. kidney, lung, heart, peripheral or

central nervous system), requiring induction treatment with cyclophosphamide or rituximab
3) Positive test for anti-PR3 or anti-MPO (current or historic)
4) Willing and able to give written Informed Consent and to comply with the requirements of the study protocol

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

4.2. Exclusion criteria
Subjects will be excluded from participation if they meet any of the following exclusion criteria:
1) Pregnant or breast-feeding
2) Active pregnancy, as proven by a positive urine beta-HCG test or a positive serum beta-HCG
3) Significant hypogammaglobulinemia (IgG < 4.0 g/L) or an IgA deficiency (IgA < 0.1 g/L)
5) Active infection at time of screening, as follows:
- Hospitalization for treatment of infection within previous 60 days of day 0 of the study
- Use of parenteral (intravenous of intramuscular) antibiotics (including anti-bacterials, anti-virals, anti-fungals or anti-parasitic agents) within previous 60 days of day 0 of the study
- Serological evidence of viral hepatitis defined as: patients positive for HbsAg test or HBcAb or a positive hepatitis C antibody not treated with antiviral medication
- Have a historically positive HIV test or test positive at screening for HIV
6) Have a history of a primary immunodeficiency
7) Have a significant infection history that in the opinion of the investigator would make the candidate unsuitable for the study
8) Have a neutrophil count of < 1.5x10E9/L
9) Evidence of hepatic disease: AST, ALT, alkaline phosphatase, or bilirubin > 3 times the upper limit of normal before start of dosing
11) Have any other clinically significant abnormal laboratory value in the opinion of the investigator
12) Required dialysis or plasma exchange within 12 weeks prior to screening
13) Received intravenous glucocorticoids, >3000mg methylprednisolone equivalent, within 4 weeks prior to screening
14) Immunization with a live vaccine 1 month before screening
15) History or presence of any medical condition or disease which, in the opinion of the Investigator, may place the patient at unacceptable risk for study participation.
16) Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	Geneesmiddel

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	11-04-2019
Aantal proefpersonen:	47
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Ethische beoordeling

Positief advies

Datum:	11-04-2019
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	NL7658
Ander register	METC LUMC : P18.216

Resultaten