

Exploring durable remission with rituximab in ANCA associated vasculitis

No registrations found.

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

Summary

ID

NL-OMON21172

Source

NTR

Brief title

The ENDURRANCE-1 Study

Health condition

ANCA-associated vasculitis

Sponsors and support

Primary sponsor: LUMC

Source(s) of monetary or material Support: LUMC

Intervention

Outcome measures

Primary outcome

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.

Secondary outcome

Secondary objectives are:

- time to a ANCA negative test
- Percentage of patients that have ANCA return during follow-up
- number of Rituximab infusions as maintenance therapy
- duration of B-cell depletion
- composition of the memory B-cell and plasma cell compartment before and after treatment
- to investigate whether MRA is associated with disease flares
- to investigate whether MRA is associated with (a shorter) time to a disease flares
- to investigate whether the presence or absence of MRA after RTX can guide a personalized treatment
- to assess the safety parameters of each treatment arm including adverse events according to WHO toxicity criteria, time to immune reconstitution and recording of infectious events

Study description

Background summary

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 cyclophosphamide infusions.

Study objective

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.

Study design

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

Intervention

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 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 prednisolone 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.

Contacts

Public

LUMC

Laura van Dam

+31715262011

Scientific

LUMC

Laura van Dam

+31715262011

Eligibility criteria

Inclusion criteria

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

Exclusion criteria

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 or 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

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL	
Recruitment status:	Recruiting
Start date (anticipated):	11-04-2019
Enrollment:	47
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Ethics review

Positive opinion	
Date:	11-04-2019
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

NTR-new

Other

ID

NL7658

METC LUMC : P18.216

Study results