The ENDURRANCE-1 Study. ;Exploring durable remission with rituximab in ANCA associated vasculitis

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This study has been transitioned to CTIS with ID 2023-507868-39-00 check the CTIS register for the current data. In this randomized study the primary objective is to demonstrate a clinical significant reduction of RTX retreatments in AAV patients...

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

Summary

ID

NL-OMON54623

Source
ToetsingOnline

Brief title
The ENDURRANCE-1 study

Condition

- Autoimmune disorders
- Renal disorders (excl nephropathies)
- Vascular disorders NEC

Synonym
ANCA associated vasculitis

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Nierstichting;zonmw

Intervention

Keyword: ANCA vasculitis, Cyclophosphamide, Rituximab, seroconversion

Outcome measures

Primary outcome

In this randomized study the primary objective is to demonstrate a clinical significant reduction of RTX retreatments in AAV patients receiving combination RTX with cyclophosphamide remission-induction therapy as compared to RTX alone.

Secondary outcome

Secondary objectives are:

- 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

- to assess quality of life by assessing patient-reported outcome measurements

- to assess durable immunological responses of each treatment arm including time to an ANCA negative test, percentage of patients that reach seroconversion of ANCA to negative, time to ANCA return, percentage of patients that have ANCA return during follow-up, time to B-cell depletion and duration of B-cell depletion

- to assess clinical responses in each arm including BVAS scores, clinical biomarkers of disease activity and number of relapses.

Study description

Background summary

AAV is a systemic autoimmune disease characterized by capillaritis or small-vessel vasculitis and the most severe manifestations are kidney failure, lung hemorrhage or cerebritis. Current (inter-)national guidelines recommend, in addition to steroid therapy, to use either cyclophosphamide or rituximab as remission induction therapy and azathioprine or rituximab as maintenance therapy1,2. As such, the guidelines do not provide a clear answer as to which is the optimal treatment strategy for AAV patients. Also, because rituximab is a relatively expensive, biological treatment, the widespread use of this effective and safe drug is hampered in the Netherlands. Nevertheless, the pathophysiology of AAV is closely associated with levels of anti-neutrophil cytoplasmic autoantibodies (ANCA) against proteinase-3 (PR3) or myeloperoxidase (MPO)3. As such, B-cell depletion with Rituximab (RTX) is successfully applied as induction and maintenance treatment in ANCA-associated vasculitis (AAV) patients4-6. Moreover, there is accumulating data that long-term safety profile of rituximab might outperform cyclophosphamide7. However, because rituximab is a relatively expensive, biological treatment, the widespread use of this effective and safe drug is hampered in the Netherlands. This is mostly due to the fact that the optimal treatment strategy for using RTX in AAV patients is much debated and not yet well established8.

Remission induction therapy
Both RTX and high-dose cyclophosphamide combined with steroids are effective remission induction therapies in AAV patients1,2. A previous randomized controlled study on remission-induction therapy compared rituximab followed by placebo with high-dose oral cyclophosphamide followed by azathioprine maintenance treatment. Both treatment strategies were equivalent with respect to duration of complete remission, frequency of relapses and severity of relapses9. A few studies have investigated the clinical effects of combining RTX with low-dose cyclophosphamide as a remission induction treatment strategy. In an uncontrolled cohort the combination of RTX with six low-dose infusions of cyclophosphamide (CycLowVas study) achieved clinical remission and a favorable immunological state quickly (i.e. median of 20 weeks) with low relapse rates.10 Similar positive observations were seen in two other uncontrolled cohorts.11,12 From a safety perspective, rates of infection and hypogammaglobulinaemia were comparable with other studies including a recent analysis of AAV patients retreated with rituximab multiple times10,11. Also, no excess of malignancies was observed, in keeping with a recent retrospective analysis that suggested patients with AAV treated with rituximab have a comparable risk of malignancy with the general population7. Taken together, RTX combined with cyclophosphamide is a promising novel treatment strategy in AAV patients. 10,11.

Tailoring Rituximab as Maintenance therapy
When embarking upon RTX induction treatment for AAV, there is a strong immunological rationale for combining RTX with cyclophosphamide based on their

differential effect across the B-cell lineage. RTX depletes precursors of autoantibody-producing cells, but has little direct effect on ANCA-producing plasmablasts and plasma cells that do not express CD20.13 Previous studies have already demonstrated that induction treatment with RTX alone frequently (up to 75% of patients) necessitates re-treatment with RTX (as maintenance treatment) to control disease activity and prevent (early) severe disease flares14-17. As a direct consequence of the need for repetitive RTX treatment as maintenance therapy to prevent disease flares, a fixed (6 monthly) re-dosing regimen with RTX was demonstrated to be superior to the usual, standard of care maintenance treatment with azathioprine 18,19. However, a fixed re-dosing regimen with RTX can be appreciated as a relapse-preventive strategy at the cost of potential overtreatment. Therefore, very recently a *tailored* re-dosing regimen (based upon ANCA levels and B-cell repopulation) with RTX had equivalent efficacy as a relapse-prevention strategy while it avoided overtreatment and reduced overall treatment costs20.
Taken together all the recent evidence from high-quality trials on RTX treatment for AAV patients has demonstrated that *tailored* maintenance treatment with RTX is effective to achieve durable remission. Nevertheless, tailoring RTX re-treatment on the basis of immunological parameters directly implicates that the induction treatment can beneficially affect these immunological parameters in AAV patients. Consequently, if re-treatment rituximab infusions is guided by B-cell- and ANCA-levels it can be hypothesized that less *tailored* infusions are needed as a maintenance treatment compared to the current standard of care.

ENDURRANCE: Exploring durable remission with RTX in AAV
Based on these most recent insights in AAV treatment, the present study will be the first study to directly compare RTX with low-dose cyclophosphamide to current standard of care with RTX alone in AAV patients with respect to their potency to reduce the cumulative number of tailored rituximab retreatments needed to maintain clinical remission over two years.

Study objective

This study has been transitioned to CTIS with ID 2023-507868-39-00 check the CTIS register for the current data.

In this randomized study the primary objective is to demonstrate a clinical significant reduction of RTX retreatments in AAV patients receiving combination RTX with cyclophosphamide remission-induction therapy as compared to RTX alone.

Secondary objectives are:
- 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
- to assess quality of life by assessing patient-reported outcome measurements
- to assess durable immunological responses of each treatment arm including

time to an ANCA negative test, percentage of patients that reach seroconversion of ANCA to negative, time to ANCA return, percentage of patients that have ANCA return during follow-up, time to B-cell depletion and duration of B-cell depletion
- to assess clinical responses in each arm including BVAS scores, clinical biomarkers of disease activity and number of relapses.

Study design

The study is designed as an open-label, multicenter, 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 the number of RTX infusions needed to maintain clinical remission over 2 years, tailored by B-cell and ANCA status and clinical status.

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.

Study burden and risks

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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

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)
4) Active infection not compatible with start of remission-induction therapy in the opinion of the treating physician and/or investigator, e.g.:
- 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
5) Have a history of a primary immunodeficiency
6) Have a significant infection history that in the opinion of the investigator would make the candidate unsuitable for the study
7) Have a neutrophil count of < 1.5x10E9/L
8) Evidence of hepatic disease: AST, ALT, alkaline phosphatase, or bilirubin > 3 times the upper limit of normal before start of dosing
9) Have any other clinically significant abnormal laboratory value in the opinion of the investigator
10) Required dialysis or plasma exchange within 12 weeks prior to screening
11) Received intravenous glucocorticoids, >3000mg methylprednisolone equivalent, within 4 weeks prior to screening
12) Immunization with a live vaccine 1 month before screening
13) 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.
14) Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-05-2019
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Endoxan
Generic name:	Cyclophosphamide
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	08-11-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	07-03-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	24-06-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	11-11-2019

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	19-11-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	26-11-2020
Application type:	Amendment
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Approved WMO Date:	09-05-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	15-12-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	16-03-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	02-05-2022

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	21-06-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	21-07-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	03-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	11-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	07-02-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	20-02-2023

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	29-03-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	19-04-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	03-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	13-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	CTIS2023-507868-39-00
EudraCT	EUCTR2018-003588-69-NL
CCMO	NL67515.058.18