An international, randomised, open label trial comparing a rituxmab based regimen with a standard cyclophosphamide/azathioprine regimen in the treatment of active, 'generalised' ANCA associated vasculitis

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To assess the rates of preliminary response and sustained remission of AASV following rituximab (on the basis of former studies, 86% sustained remission expected with rituximab compared to 75% in control group).To assess safety of a rituximab...

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

Summary

ID

NL-OMON29858

Source
ToetsingOnline

Brief title
Rituxvas Clinical Trial

Condition

- Autoimmune disorders
- Renal disorders (excl nephropathies)

Synonym
Wegener granulomatosis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: MPA, Rituximab, Treatment, Wegener

Outcome measures

Primary outcome

Endpoints

Primary end points will be assessed upon trial completion at 2 years.

However interim analyses will be performed when

30 patients have completed 6 weeks, to assess efficacy (treatment response) and

safety (severe adverse events).

40 patients have completed 6 months to assess efficacy (remission rates) and

safety (severe adverse events).

i Primary

Sustained remission (BVAS = 0 at 6 months and sustained for 6 months).

Severe adverse events (CTCAE grade >= 3) at 2 years.

Secondary outcome

ii Secondary

Efficacy

Response rate at 6 weeks (BVAS < 50% baseline)

Remission at 6 months (BVAS=0 for 2 months by 6 months)

Time to remission (BVAS=0)

Relapses (all relapses and major/minor)

BVAS area under the curve

Change in GFR

Change in SF-36

Change in VDI

Safety

Severe adverse events (CTCAE grade >= 3) at 6 weeks and 6 months

All adverse events

Death

Prednisolone cumulative dose

Cyclophosphamide cumulative dose

iii Tertiary

Human anti-chimeric antibody testing

Correlation of B cells with disease activity

Change in ANCA and disease activity

Histopathology predictors of outcome

Study description

Background summary

The ANCA associated vasculitides (AASV), namely Wegener*s granulomatosis, microscopic polyangiitis, and renal limited vasculitis are autoimmune, multi-system,
progressive diseases which untreated can lead to rapidly progressive renal

failure and death.
Randomised, prospective, clinical trials have demonstrated the efficacy of immunosuppressive treatments for vasculitis and have defined treatment protocols at different disease points. The current *gold standard* treatment for active AASV with glomerulonephritis is cyclophosphamide with steroids. However the standard treatment is associated with significant morbidity and mortality, largely due to infections and malignancy with cumulative cyclophosphamide dosing. Other effective treatments for AASV are being sought, with safer side effect profiles. Rituximab is an anti CD20 chimeric monoclonal antibody, which is used for the treatment of non-Hodgkin*s lymphoma (NHL). It is well tolerated in humans with a good safety profile. Rituximab has been shown in small series to induce remission in AASV and is now being increasingly used for other (non-ANCA) autoimmune conditions such as lupus and rheumatoid arthritis.
RITUXVAS has been designed to test the hypothesis that Rituximab leads to a higher rate of sustained remission compared to standard therapies (cyclophosphamide /azathioprine) with a lower rate of adverse events and reduced cyclophosphamide exposure as treatments for active, *generalised* AASV.
We plan a randomised phase II/phase III trial to compare a rituximab based regimen to standard of care. For the initial phase II part, 44 patients will be randomised 3:1 to rituximab or control. Following this analysis, the trial may be extended to a phase III stage. The trial will be conducted by 14 centres from 8 countries.

Study objective

To assess the rates of preliminary response and sustained remission of AASV following rituximab (on the basis of former studies, 86% sustained remission expected with rituximab compared to 75% in control group).
To assess safety of a rituximab regimen in terms of severe adverse events (in patients receiving standard therapies, adverse advent rate is 45% at 2 years, at least 50% of which are infection relapted. In comparison rituximab use is only rarely associated with infections, therefore 22.5% adverse event rate expected with rituximab compared to 45% at 2 years in control group).

Study design

Trial Overview

Entry
(Eligibility criteria)

Randomisation

(experimental limb 33:control limb 11)

Rituximab 375mg/m2 IV x4 IV Cyclophosphamide Cyclophosphamide 15mg/kg IV x2 (minimum 3months, max
Methylprednisolone 1g IV 6 months).
Prednisolone PO Methylprednisolone 1gIV
Prednisolone PO

Remission/maintenance
Azathioprine 2mg/kg

2 years
Trial End

Analyses

6 weeks: Initial response evaluation

6 months: Efficacy and safety evaluation

24 months: Trial end and efficacy and safety evaluation

Intervention

1.3 Rituximab
Rituximab is an anti CD 20 chimeric mouse/human monoclonal antibody, with human IgG1 constant regions and murine light/heavy chain variable regions (7). CD 20 is a ligand which exists on developing B cells, excluding stem cells and plasma cells. The role of the CD 20 ligand in nature is not fully understood, although mediation of apoptosis has been suggested. The mechanisms by which rituximab causes B cell depletion may involve complement induced B cell lysis, Fc receptor mediated cytotoxic cell killing or the direct induction of B cell apoptosis by rituximab.
Rituximab therapy correlates positively with B cell depletion and rituximab levels. Different dosing regimens have been trialled. In patients with systemic lupus erythematosus (SLE), the efficacy of rituximab is dependant upon B cell depletion. 4 infusions of 375mg/m2 rituximab infusions (one per week for four weeks) were required for this to occur (13,14). In 3 published reports 375mg/m2 has resulted in B cell depletion and clinical response in patients with refractory vasculitis (10-13). On the basis of these results a dose of 4 x 375mg/m2 infusions will be used in RITUXVAS.
In RITUXVAS, 2 doses cyclophosphamide will still be administered with the 1st and 3rd rituximab infusions, for two reasons. Firstly, the necrotising

cresentic glomerulonephritis associated with AASV progresses rapidly and the therapeutic effect of rituximab is delayed. The use of cyclophosphamide/high dose steroid, which are standard components of induction therapy, will allow adequate immunosuppression in the early crucial treatment of AASV. Secondly, human anti-chimeric antibody (HACA) formation has been reported in NHL, SLE, and RA with varying frequencies, (4.3% of patients in RA (8)). The long term implications of these antibodies are not known. However, the possibility of anaphylactic reactions and rituximab resistance with further treatments exists. Co-administration of an immunosuppressant effective in the treatment of vasculitis is thus a logical approach to minimise HACA development.
Rituximab has now been used to treat 300,000 patients with NHL. Long-term safety regarding carcinogenicity and fertility has yet to be established. However, no major long-term adverse sequelae have been reported (1).
Up to 50% of patients receiving rituximab for an indication will develop infusion reactions with symptoms including; fevers, chills, rigors, flushing, throat irritation rash rhinitis fatigue headache, nausea, vomiting, urticaria, angioedema, bronchospasm, myalgia, arthralgia, hypotension, hypertension and exacerbation of angina or congestive cardiac failure. Later reactions include diarrhoea, leucopenia, neutropenia, thrombocytopenia, anaemia, and infections in 30%, which may or may not be drug related (investigators brochure).

Study burden and risks

ANCA geassocieerde vasculitides zijn ernstige aandoeningen. In verband met hoge mortaliteit indien onbehandeld wordt al jaren een standaardtherapie gegeven met cyclofosfamide en prednisolon. Deze standaardtherapie gaat gepaard met ernstige bijwerkingen op de korte termijn (infecties en hematologische afwijkingen) en op de langere termijn (infertiliteit en ontwikkeling van maligniteiten). Men is naarstig op zoek naar therapieën met mindere bijwerkingen. In de huidige studie wordt getest of rituximab cyclofosfamide sparend kan werken. Het nadeel van rituximab lijkt beperkt. In de uitgebreide ervaring bij andere aandoeningen zoals non-Hodgkin lymfoom en reumatoïde arthritis en uit de beperkte ervaring bij vasculitis blijkt dat rituximab over het algemeen zeer goed verdragen wordt. Behalve transfusie reacties is er theoretisch in ieder geval een risico op infecties. Daarnaast kunnen er antistoffen tegen rituximab gemaakt worden waardoor een enkele keer serumziekte kan optreden. Serumziekte is echter over het algemeen ook passager en kan goed behandeld worden met corticosteroïden.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Active ANCA-associated vasculitis

Exclusion criteria

Pregnancy and malignancy

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-12-2006
Enrollment:	2
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Mabthera
Generic name:	Rituxmab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	14-08-2006
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	27-11-2006
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
Other	05/Q1604/153
EudraCT	EUCTR2005-003610-15-NL
CCMO	NL12816.068.06