Efficacy of rituximab in comparison to continued corticosteroid treatment in idiopathic nephrotic syndrome unresponsive to 8 weeks of high dose prednisone.

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To evalute the efficacy of rituximab in comparison to continued corticosteroid treatment in ipatients with diopathic nephrotic syndrome unresponsive to 8 weeks of high dose prednisolone.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Nephropathies
Study type	Interventional

Summary

ID

NL-OMON44222

Source
ToetsingOnline

Brief title
Rituximab in SRNS

Condition

- Nephropathies

Synonym
focal segmental glomerulosclerosis, idiopathic nephrotic syndrome, minimal change disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Idiopathic Nephrotic syndrome, Randomized clinical trial, Rituximab, Steroid-resistant

Outcome measures

Primary outcome

Primary endpoint: The proportion of patients reaching complete remission (CR)

at 8 weeks

Secondary outcome

1. Proportion of patients with a partial remission at 8 weeks

2. Proportion of patients with a late remission (partial and complete) between

2 and 12 months

3. Time to remission (partial and complete) over 12 months

4. Proportion of patients with a relapse and time to remission over 12 months

5. Proportion of patients treated with additional immunosuppressive therapy

other than assigned treatment with rituximab or prednisolone at 2 and

12 months

6. Difference in quality of life measured by RAND-36 and TNO-AZL Questionnaire

for Adult's Health-Related Quality of Life for people of 16 years

and older (TAAQOL) measured at 0, 2 and 12 months

7. Side effects: Proportion of patients with >= 1 adverse event; Proportion of

patients with >= 1 serious adverse event; Proportion of patients with >= 1

adverse event grade 3 or 4; Proportion of patients with >= 1 infection which

required treatment; Proportion of patients with diabetes defined as

new onset diabetes, initiation of treatment with oral antidiabetic

medication or insuline, addition of another class of oral antidiabetics more

Adverse events will be graded according to the Common Terminology Criteria

for Adverse Events (NCI-CTCAE v4.03)

8. Cost-effectiveness analysis and cost-utility analysis according to the

guidelines provided by Zorginstituut Nederland 2015 with use of the

EuroQol-5D-5L measure of health-related quality of life

9. Difference in creatinine clearance and estimated glomerular filtration rate

10. Proportion of patients with an increase of baseline serum creatinine >= 50%

Study description

Background summary

Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are important causes of idiopathic nephrotic syndrome. As advised by national and international guidelines, initial treatment consists of high dose prednisolone until a complete remission is achieved with a maximum of 16 weeks. However, serious concerns exist about the side effects of this treatment. Specifically treatment > 8 weeks is associated with serious side effects such as weight gain, diabetes mellitus, striae, cataract, skin and muscle atrophy, and psychological disturbances. Unfortunately the likelihood of attaining a remission decreases if prolonged treatment is needed. Retrospective studies suggested that Rituximab may be more effective in patients unresponsive to 8 weeks of high dose prednisolone. Treatment with rituximab was associated with a higher proportion of patients attaining remission of proteinuria and with fewer side effects. A formal, prospective and randomized trial is needed to determine the efficacy of rituximab regarding remission of proteinuria, time to remissions, side effects, quality of life, kidney function and costs.

Study objective

To evalute the efficacy of rituximab in comparison to continued corticosteroid treatment in ipatients with diopathic nephrotic syndrome unresponsive to 8

weeks of high dose prednisolone.

Study design

This will be an open-label, randomized controlled trial which compares continued treatment with high dose prednisolone (standard therapy) to treatment with rituximab in patients with an idiopathic nephrotic syndrome. All patients will be treated with high dose prednisolone (1 mg/kg/day) for 8 weeks according to current national and international guideline. Patients can be included in the trial in case of persistent persistent proteinuria >= 2 g/ 24 hours or a protein-to-creatinine ratio >= 2 g/10mmol (2 g/g) after 8 weeks of treatment with high dose prednisolone
Patients either receive 2 doses of Rituximab 375 mg/m2 iv at time 0 and 14 days with termination of prednisolone or standard therapy which consist of 8 additional weeks of high dose prednisolone treatment. In the Rituximab group, B-cells will be monitored weekly, and if no complete depletion is achieved, additional dose(s) of Rituximab will be given at a weekly interval (maximum of 2 additional doses) until complete B cell depletion. Second line treatment is started in both arms in the case of intractable edema. Expected duration of follow-up is 12 months, consisting of 9 visits.

Intervention

Trial intervention (study treatment in drug clinical trial):

The arms of treatment will be the following:

First arm: Rituximab 375 mg/m2 at t=0 en t= 2 weeks
B-cells will be monitored, and if no complete depletion is achieved, additional dose(s) of Rituximab will be given at a weekly interval until complete B cell depletion (maximum of 2 additional doses)

Second arm: Standard treatment with prednisolone 1 mg/kg/day (max 80 mg/day) for 8 weeks

Study burden and risks

For patients in the control arm of the study (continued treatment with high dose prednisolone) the risks associated with participation are not different from those associated with standard of care treatment, and mainly consist of the risk of side effects to therapy. There are no direct benefits for these patients by participating in the study, since they receive the normal standard of care treatment. For patients treated with rituximab the risks associated with participation, are also associated with the risk of side effects. In

general side effects of prolonged treatment with high dose prednisolone are considered more severe.
The number of visits to the hospital is similar to the number of visits needed for the standard of care treatment. The extra burden associated with participation consist of visits to the RadboudUMC instead of a local hospital and more blood samples are collected during the visits.
An extra burden for patients in the Rituximab arm are 2 hospital admissions for IV administration of rituximab. On the other hand these patients benefit from cessation of prednisolone therapy. Another benefit of participating in his study for patients treated with rituximab may be a higher remission rate and that they theoretically may experience less (severe) side effects than patients treated with the standard of care protocol.
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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

Age >= 18 years

Persistent proteinuria >= 2 g/ 24 hours or a protein-to-creatinine ratio >= 2 g/10mmol (2 g/g) after 8 weeks of treatment with high dose prednisone 1 mg/kg/day (max 80 mg/day)

Idiopathic nephrotic syndrome caused by biopsy proven minimal change disease or focal segmental glomerulosclerosis

Exclusion criteria

• Severe nephrotic syndrome with hypotension
• Previous treatment with immunosuppressive medication other than prednisone
• Treatment with prednisone > 10 weeks in last six months
• Secondary form of FSGS or minimal change disease
• Patients who test positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody
(anti-HBc).
• Patients infected with HIV or suffering from other active infections
• Patients inoculated with a live vaccine within 4 weeks prior to inclusion
• Pregnancy, breast feeding, women with inadequate contraception
• Malignancy
• Kidney transplantation
• Previous treatment with monoclonal antibodies

Study design

Design

Study phase:	3
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):	22-08-2018
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mabthera, Rixathion, Truxima
Generic name:	Rituximab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Prednisone
Generic name:	Prednisolone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-10-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-12-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EudraCT	EUCTR2017-003366-27-NL
CCMO	NL63099.091.17
Other	volgt