SEQUENTIAL THERAPY WITH TACROLIMUS AND RITUXIMAB IN PRIMARY MEMBRANOUS NEPHROPATHY

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PRINCIPAL OBJECTIVE To evaluate whether sequential therapy with tacrolimus for 9 months (6 months of full therapy and 3 months of tapering doses) followed by a dose of RTX leads to a greater increase in the proportion of primary MN patients with...

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

Summary

ID

NL-OMON44594

Source
ToetsingOnline

Brief title
STARMEN

Condition

- Nephropathies

Synonym
membranous glomerulonephritis, nephrotic syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Sociedad Española de Nefrologia (senefro), prof. Manuel Praga
Source(s) of monetary or material Support: Fundación Renal Iñigo Alvarez de Toledo (FRIAT);Madrid;Spanje

Intervention

Keyword: immunosuppressive treatment, membranous nephropathy, randomized clinical trial, rituximab

Outcome measures

Primary outcome

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

and partial remission (PR) at 24 months of study treatment.

Secondary outcome

Secondary endpoints:

a) The number of patients with an increase of serum creatinine >= 50% at the end

of follow-up (renal survival).

b) The proportion of patients with an nephrotic syndrome relapses in those

patients who previously presented a PR or CR.

c) The time to NS relapses in both arms after the treatment period.

d) The number of patients with limited response at 12, 18 and 24 months of

study treatment.

e) The percentage of patients with preserved renal function (eGFR>=45 ml/min)

after the treatment period.

f) Serum antibodies anti-PLA2R levels before, and after treatment study in both

arms (0,12, and 24 months).

g) Status of immune cells (CD4+, and CD8+ T cells and CD19+ B cells) before and

after the treatment study in both arms (0,12, and 24 months).

h) Proportion of patients with drug-related adverse events during the study

Study description

Background summary

Cyclical treatment with corticosteroids and alkylating agents remains the first therapeutic option in primary membranous nephropathy (MN), after showing in several randomized controlled trials (RCT) a higher number of remissions and improved long-term renal survival in comparison with supportive therapy. However, serious concerns exist about the short and long-term side effects of this treatment. Calcineurin inhibitors (CNI) have been recommended as an alternative to cyclical treatments. CNI also induce a high number of remissions, but relapses of nephrotic syndrome (NS) are common after CNI discontinuation. Rituximab (RTX) has shown to induce remissions in primary MN, although no prospective RCT have been performed. Recent observational studies have shown that RTX administered after tacrolimus tapering can decrease the incidence of NS relapse following tacrolimus withdrawal. This sequential therapy tacrolimus-RTX showed a good safety profile, with only minor side effects.
Since many nephrologists are still reluctant to use cyclical treatment with steroids and alkylating agents in patients with primary MN due to the severity of side effects, the use of CNI (particularly tacrolimus), RTX, and combined sequential tacrolimus-RTX is increasing. However, no comparative RCT between both therapies have been performed.
A formal, prospective and randomized trial in selected patients with primary MN is needed to determine the efficacy of both therapies regarding NS remissions, time to remissions, number and time of NS relapses, long-term renal survival and side effects. This trial would also provide very important information with better clinical evidence levels about the clinical use of tacrolimus followed by RTX in the treatment of primary MN.

Study objective

PRINCIPAL OBJECTIVE
To evaluate whether sequential therapy with tacrolimus for 9 months (6 months of full therapy and 3 months of tapering doses) followed by a dose of RTX leads to a greater increase in the proportion of primary MN patients with complete remission (CR) defined as a reduction of proteinuria since baseline level to a value equal or lower than 0.3 g/24 h proteinuria plus stable renal function (eGFR >= 45 ml/min/1.73m2) and the proportion of patients with partial remission (PR) defined as a reduction of proteinuria since baseline level to a value less than 3.5 g/24 h and 50% lower than baseline proteinuria plus stable renal function (eGFR >= 45 ml/min/1.73m2) when compared with patients receiving cyclical treatment with corticosteroids and cyclophosphamide for 6 months. This will be assessed after 24 months.

Study design

SUMMARY OF TRIAL DESIGN
1. Phase of the trial: and design: Phase III study, open label, randomized, and active controlled trial.
This study will have 3 stages: screening and recruitment of patients for 12 months, treatment period for six months in corticosteroids plus cyclophosphamide group and 9 months in Tacrolimus-RTX group, and finally post-treatment follow-up period until to complete 24 months of follow-up since initial treatment.
2. This will be an open-label, randomized and active controlled trial, with parallel treatment design (two arms of treatment).
3. Expected duration of patient participation: Two years.
4. Number of visits: 13 within 24.

This study will compare the standard therapy for primary MN patients with nephrotic range proteinuria (active control of steroids plus cyclophosphamide) with a novel sequential therapy of tacrolimus and RTX, an approach of potential high efficacy, low toxicity and more acceptable safety profile.

Intervention

TRIAL INTERVENTION (STUDY TREATMENT IN DRUG CLINICAL TRIALS)
The arms of treatment will be the following:

First Arm: Cyclical Corticosteroids plus Cyclophosphamide (6 months)
Month 1: 1g IV methylprednisolone daily for three doses (days 1, 2, and 3),
Oral prednisolone (0.5mg/kg/day) for 27 days (days 4 to 30).
Month 2: Oral Cyclophosphamide (2.0 mg/kg/day) for 30days
Months 3, 5: Repeat Month 1
Months 4, 6: Repeat Month 2

Second Arm: Sequential Tacrolimus-Rituximab
A) Oral Tacrolimus: Initial dose: 0.05 mg/Kg/day, adjusted to achieve blood trough levels of 5-7 ng/ml) for six

months. Starting at the end of month 6, tacrolimus dosage will be reduced by 25% per month,

resulting in a complete withdrawal at the end of month 9.
B) Rituximab: A dose 1 g IV will be given during month 6 (at day 180), before the onset of tacrolimus dose

reduction.

Study burden and risks

In general, the extent of burden associated with participation is in line with standard of care treatment, except for about 6 extra scheduled visits to the hospital.

For patients in the active control arm (corticosteroids and cyclophosphamide treamtent) the risks associated with participation are equal to those associated with standard of care treatment, and mainly consist of the risk of side effects to therpay. There are no direct benefits for these patients of participating in the study, as in fact the receive the normal standard of care therapy.

For patients in the arm of the study with sequential tacrolimus-rituximab, the risks associated with participation, are also associated with the risk of side effects of these particular drugs. In general side effects of corticosteroids/cyclophosphamide are considered more severe. In theory, patients in the second treatment arm have a risk of progression of their renal disease if the studymedication appears to be less effective than standard of care. To minimize this risk, subject withdrawal criteria include disease progression.
The extra burden for the patients in the second arm is a treatment duration of 9 months instead of 6 months. On the other hand, they benefit from less frequent IV medication (only once instead of 9 times).
Another benefit of participating in his study for patients in this second group may be that they theoretically may experience less, and less severe, adverse events and side effects than patients treated with the standard of care protocol.

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

1. Biopsy-proven primary MN. Patients with nephrotic syndrome relapse after remission (either spontaneous or induced by immunosuppression) can be included without a new renal biopsy, provided that they meet all the other inclusion/exclusion criteria.
2. Age older than 18 years.
3. Estimated GFR > 45 ml/min/1.73m2 in at least two measurements performed within the two weeks prior to randomization
4. Nephrotic-range proteinuria (>4 g/day and remaining >50% of the baseline value) accompanied by hypoalbuminemia (<3 g/dL) during at least a six-month period before screening. Proteinuria should be >4 g/day and serum albumin <3 g/dl in at least two measurements performed within the two weeks prior to randomization.Those patients showing severe or disabling symptons related to the nephrotic syndrome or severe hypoalbuminemia (<2 g/dL) can be included before the completion of this 6-month observation period, at the investigator*s discretion.
5. Treatment with an ACEI or ARB for at least 2 months before screening (unless intolerance to ACEI/ARB, contraindications to their use or a low blood pressure that could induce side effects at the investigator*s discretion) with a controlled blood pressure in at least last three months (target < 140/90 mmHg).
6. Negative urine pregnancy test for female potentially fertile.

Exclusion criteria

1. Diagnosis of secondary causes of membranous nephropathy: diagnosis of malignancy (cancer), systemic infections (which include viral, malaria, B and C hepatitis, leprosy and syphilis), systemic autoimmune diseases (e.g. Systemic Lupus Erythematosus; SLE), or any

other acute or chronic inflammatory disease.
2. HIV infection.
3.Moderate or severe liver disease (AST and ALT > 2.5x upper range limit and total bilirubin > 1.5 x upper range limit).
4. Patients are taking part in any other study with an investigational study and/or are receiving or have received treatment with another investigational drug or intervention (within the first month prior to the study).
5.Suspected or known hypersensitivity, allergy and/or immunogenic reaction history of either rituximab, cyclosporine, tacrolimus, corticosteroids, CYC or any of their ingredients (which include excipients) and of any other drug from the same pharmacotherapeutic group (i.e. calcineurin inhibitors, specific monoclonal antibodies or alkylating agents).
6.Previous treatment with corticosteroids or any other immunosuppressive drug in the two-year period before screening.
7. Patients who were non responders to previous immunosuppressors.
8.Women showing a positive pregnancy test or during lactation period or plans to become pregnant. Women not using contraceptive methods during the complete study.
9.Inability or unwillingness of individual to give written informed consent.
10.Any other medical unstable, uncontrolled, or severe condition or any other relevant laboratory test finding which, at the investigator*s own discretion, could possibly increase the associated risk of the patient*s participation in the study.
11. Current drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

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:	Recruitment stopped
Start date (anticipated):	23-04-2016

Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cytoxan
Generic name:	cyclophosphamide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	prednisone
Generic name:	prednisolone
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Prograf
Generic name:	tacrolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Rituxan
Generic name:	rituximab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Solu-Medrol
Generic name:	methylprednisolone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-06-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-03-2015
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-02-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-04-2016
Application type:	Amendment
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	EUCTR2013-000226-55-NL
ClinicalTrials.gov	NCT01955187
CCMO	NL48106.091.14

Study results

Date completed:	20-06-2019
Actual enrolment:	7