REduceren van STEroiden bij kinderen met een Recidief Nefrotisch syndroom – de RESTERN studie

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The main hypothesis is that relapses of the nephrotic syndrome in children can be treated adequately by a reduced duration of alternate day prednisone (2 weeks instead of the currently used 4-6 weeks) after a similar induction of remission.

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

Summary

ID

NL-OMON20897

Source
NTR

Brief title
RESTERN

Health condition

Nephrotic syndrome Nefrotisch syndroom

Sponsors and support

Primary sponsor: Dr. Michiel F Schreuder, MD PhD
Pediatric Nephrologist
Radboudumc Amalia Children's Hospital
Department of Pediatric Nephrology, 804
P.O.Box 9101, 6500 HB Nijmegen
The Netherlands
Source(s) of monetary or material Support: Dutch Kidney Foundation

Intervention

Outcome measures

Primary outcome

Time to first relapse after study randomization (censored at 12 and 24 months)

Secondary outcome

• Number of relapses after study randomization at 12 or 24 months
• Development of frequent relapsing nephrotic syndrome according to KDIGO criteria (four or more relapses in any 12-month period)
• Development of steroid dependent nephrotic syndrome according to KDIGO criteria (two consecutive relapses during corticosteroid therapy, or within 14 days of ceasing therapy)
• Cumulative dosage of prednisone during study period (at 12 and 24 months)

Study description

Background summary

Most children with steroid sensitive nephrotic syndrome experience several relapses, which are treated with steroids. For most children, long-term prognosis is for complete resolution of their disease over time and maintenance of normal kidney function. It is therefore vital to focus on minimizing adverse events of the disease and its therapy. Unfortunately, no randomized controlled trials are available to determine the optimal steroid treatment of an infrequent relapse of the nephrotic syndrome.
Recent studies show that treatment schedules of the first episode can safely be reduced (Hahn et al., 2015; Hoyer, 2015), which may reduce steroid toxicity. The hypothesis of the REducing STEroids in Relapsing Nephrotic syndrome (RESTERN) study is that a 2-4-week reduction of alternate day steroids after inducing remission is effective and safe, reduces steroid exposure by 35% on average, and is therefore preferable.
Using a nation-wide placebo-controlled randomized controlled trial, this hypothesis will be tested. A similar daily dose of prednisone is used until the induction of remission. Randomization in blocks (immunosuppressive maintenance therapy vs. no maintenance therapy) will be performed for either 4-6 weeks of alternate day prednisone (standard therapy) or 2 weeks alternate day prednisone followed by 2-4 weeks of alternate day placebo. For a non-inferiority trial with 80% power, 72 patients per group are needed, for which an estimated inclusion rate of 53% is needed.
The RESTERN project aims to improve clinical care for children with nephrotic syndrome by showing that at least equal clinical benefits can be obtained by reduced corticosteroid exposure, which minimizes toxicity.

Study objective

The main hypothesis is that relapses of the nephrotic syndrome in children can be treated adequately by a reduced duration of alternate day prednisone (2 weeks instead of the currently used 4-6 weeks) after a similar induction of remission.

Study design

12 months
24 months

Intervention

Treatment schedule
• Prednisone 60mg/m2 (max 60mg) daily in 1 dose until complete remission for 3 days (according to the KDIGO guideline)
• Randomization:
o Standard treatment: 4-6 weeks prednisone 40mg/m2 (max 40mg) every other day, then stop (no tapering)
o Study treatment: 2 weeks prednisone 40mg/m2 (max 40mg) every other day, then 2-4 weeks placebo every other day, then stop (no tapering)

Treatment of subsequent relapses according to Dutch standards (prednisone 60mg/m2 (max 60mg) daily in 1 dose until complete remission for 3 days, continued with prednisone 40mg/m2 (max 40mg) every other day during 6 weeks)

Contacts

Public
Radboudumc Amalia Children's Hospital - Department of Pediatric Nephrology, 804

Michiel F Schreuder
P.O.Box 9101

Nijmegen 6500 HB
The Netherlands
T +31 (0)24 361 44 30
Scientific
Radboudumc Amalia Children's Hospital - Department of Pediatric Nephrology, 804

Michiel F Schreuder
P.O.Box 9101

Nijmegen 6500 HB

The Netherlands
T +31 (0)24 361 44 30

Eligibility criteria

Inclusion criteria

• Age over 1 and less than 18 years
• Steroid sensitive nephrotic syndrome. This will include the following groups:
o Subjects without maintenance immunosuppressive therapy;
o Subjects with maintenance immunosuppressive therapy:
• Long-term immunosuppressive therapies, including levamisole, ciclosporine, tacrolimus, MMF, mycophenolate sodium, prednisolone;
• Subjects with prednisolone maintenance therapy may be included when administered every other day at a maximum of 4mg/m2 (10% of the study dose) • Subjects experience a relapse nephrotic syndrome, defined as Albustix positive proteinuria (3+ or greater) for three consecutive days or the presence of generalised oedema plus 3+ proteinuria;
• Informed consent;
• The last prednisolone use (at a dose over 10 mg/m2 on alternate days) for the treatment of a previous episode was at least 4 weeks ago.

Exclusion criteria

• Steroid resistant nephrotic syndrome;
• Documented or suspected significant non-compliance.
• Daily prednisolone maintenance therapy at any dose
• Alternate day prednisolone maintenance therapy at a dose over 4 mg/m2
• Pregnancy
• Stimulant drug use
• Comorbidity;
o Kidney transplant recipient
o Any disease that requires the variation in oral prednisolone to be at the discretion of the treating physician(s);
• Concomitant use of drugs that induce CYP 3A4: carbamazepine, phenobarbital, phenytoin and/or rifampicin;
• Concomitant use of drugs that inhibit CYP 3A4: ketaconazole, itraconazole, ritonavir, indinavir, macrolide antibiotics (erythromycin), diltiazem, verapamil.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-12-2016
Enrollment:	144
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	16-01-2016
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 47536
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL5549
NTR-old	NTR5670
Other	Dutch Kidney Foundation : 15OKG16
CCMO	NL58185.091.16
OMON	NL-OMON47536

Study results

Summary results
Schijvens AM, Dorresteijn EM, Roeleveld N, Ter Heine R, van Wijk JAE, Bouts AHM, Keijzer-Veen MG, van de Kar N, van den Heuvel L, Schreuder MF. REducing STEroids in Relapsing Nephrotic syndrome: the RESTERN study- protocol of a national, double-blind, randomised, placebo-controlled, non-inferiority intervention study. BMJ Open. 2017