Prevention of the return of nephrotic syndrome in children by adding levamisole to standard prednisone treatment.

Het voorkomen van terugval van het nefrotisch syndroom bij kinderen door het toevoegen van levamisol aan de standaardbehandelng met prednison.

No registrations found.

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

Summary

ID

NL-OMON27331

Source
NTR

Brief title
LEARNS

Health condition

Idiopathic nephrotic syndrome / Idiopathisch nefrotisch syndroom
Relapse / Recidief
Childeren / Kinderen
Levamisole / Kinderen

Sponsors and support

Primary sponsor: Academic Medical Center (AMC)
Postbus 22600
1100 DD Amsterdam
The Netherlands
+31 (0)20 566 9111
Source(s) of monetary or material Support: Dutch Kidney Foundation

Intervention

Outcome measures

Primary outcome

The occurrence of relapse within 12 months after first presentation. Relapse is defined as the recurrence of proteinuria (3+ urine dipstick or >200 mg/mmol creatinine) on three consecutive days.

Secondary outcome

- Time to first relapse.

- Relapse rate (number of relapses per person per year) over 2-year period after first presentation.

Cumulative steroid dose over 2-year period.

- Occurrence of adverse events and treatment discontinuation.

- Proportion of frequent relapsing or steroid dependent nephrotic syndrome over 2-year period.

- Toxicity of corticosteroids: difference in BMI, blood pressure, height, weight, and serum glucose between groups; Proportion of patients with overweight (BMI >25 kg/m2), hypertension (p>90), and hyperglycaemia.

- Toxicity of levamisole: Proportion of patients with elevated (>3 times upper limit of normal) of liver enzymes (ALAT, ASAT, gamma-GT, bilirubin), neutropenia (<1500/mm3), and/or positive ANCA.

- Days of school missing, outpatient visits, and hospitalisation days (macro-economic analysis).

- Number of treatment interruptions.

Study description

Background summary

Idiopathic nephrotic syndrome (INS) is a relatively rare disease, predominantly in children and adolescents, with an estimated incidence around 1.5 cases per 100,000 children/year in the Netherlands (approximately 60 newly diagnosed cases a year). After initial treatment with corticosteroids, the vast majority achieves remission. Unfortunately, relapse rates are high (80%), resulting in repeated and high doses of corticosteroids that have major physical and psychological side effects. Therefore, INS with its high risk of relapses might significantly impair the health-related quality of life (HRQoL) of affected children and may lead to substantial parental stress.

Previous randomized controlled studies (RCTs) showed promising results when levamisole, an antihelminthic drug, was added as adjuvant therapy to corticosteroids in children with frequently relapsing INS (FRNS) in reducing the occurrence of relapses. Therefore, we hypothesize that adding levamisole to corticosteroids as initial therapy in children with a first episode of INS will prevent relapses. This is substantiated by the fact that 1) levamisole is a immunomodulator that has the ability to skew Th2 immune response toward the Th1 response and 2) INS is characterized by a skewing of the immune response into Th2. As such levamisole may prevent relapses of INS by restoring that balance between Th1 and Th2.

In comparison to other steroid sparing drugs, levamisole does not induce immunosuppression. It knows only little adverse effects of which neutropenia (<1500/mm3) is the most common and most serious and for which regular testing is required.

In addition, the underlying causes of INS and the prognostic factors to estimate the risk of relapse in INS patients are poorly understood. Also, little is known about the mechanism of action, the pharmacokinetics (PK), and pharmacodynamics (PD) of levamisole in children. Therefore, the RCT will be extended with 1) HRQoL questionnaires, 2) PK/PD analyses of prednisolone and levamisole (as well as the feasibility of measurement of levamisole concentration in saliva), 3) biobanking for future research, 4) study on the pathogenesis of INS, and 5) the mechanism of action of levamisole.

Our primary objective is to investigate the effect of additional levamisole in comparison with placebo from 4 weeks to 6 months after the start of the first episode of steroid sensitive INS in children (age 2 – 16 years) on the occurrence of relapses within 12 months. We

hypothesize that adding levamisole to standard therapy with corticosteroids prevents relapses. To test our hypothesis, we will conduct an international (the Netherlands and Belgium), multicentre, double blind, randomized, placebo-controlled clinical trial. If remission is achieved, patients will be randomized in a 1:1 ratio to either levamisole (study group) or placebo (control group). Study medication will be used on alternate days for 24 weeks.

Study objective

Adjuvant therapy of levamisole to prednisolone prevents relapses in children with a first episode of idiopathic nephrotic syndrome.

Study design

Primary endpoint: 12 months after first presentation of INS.

Secondary endpoints: 24 months after first presentation of INS. Secondary endpoints are analysed as time to first occurrence and number of occurrences during 24 months.

Intervention

- Prednisolone schedule according to French protocol: tapering schedule of 18 weeks (in comparison to 12 weeks of prednisolone according to Dutch protocol 'Werkboek Kindernefrologie').

- Additional 6-month (24 weeks) treatment of either 2.5 mg/kg levamisole or placebo on alternate days.

Contacts

Public
Acedemic Medical Center (AMC)

F. Veltkamp
Postbuss 22600

Amsterdam 1100 DD
The Netherlands
Scientific
Acedemic Medical Center (AMC)

F. Veltkamp
Postbuss 22600

Amsterdam 1100 DD

The Netherlands

Eligibility criteria

Inclusion criteria

Inclusion criteria for Immunomics/Biobank:

- Age 2 to 16 years.

- First episode of idiopathic nephrotic syndrome, confirmed by:
hypoalbuminaemia <25 g/L; Proteinuria >200 mg/mmol creatinine; Complement C3 within normal range.

- Written informed consent.

Inclusion criteria for RCT:

- Steroid sensitive nephrotic syndrome (remission achieved after 4 weeks of oral treatment with prednisolone).

- Weight >9 kg

- Ability to swallow (placebo) 5 mg tablet of study medication in children <6 years of age.

- Negative pregnancy test in girls who are of childbearing potential.

- Absence of contraindication for levamisole: neutropenia <1500/mm3.

- Ability to comply to study protocol.

Exclusion criteria

Exclusion criteria for Immunomics/Biobank:

- Age <2 years or >16 years.

- Previous episodes of INS.

Exclusion criteria for RCT:

- Steroid resistant nephrotic syndrome (persistent proteinuria after 4 weeks of oral treatment with prednisolone).

- Previous or current malginancy, diabetes mellitus type 1, current liver disease, and/or convulsions.

- Hypersensitivity to levamisole or one of its substances (lactose).

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):	01-03-2018
Enrollment:	92
Type:	Anticipated

Ethics review

Positive opinion

Date:	06-02-2018
Application type:	First submission

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
NTR-new	NL6826
NTR-old	NTR7013
Other	Dutch Kidney Foundation : CP16.03

Study results