Prevention of relapses with Levamisole as adjuvant therapy to corticosteroids in children with first episode of idiopathic nephrotic syndrome.

Published: 06-12-2017
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-517467-23-00 check the CTIS register for the current data. Primary objective: - To investigate the effect of additional levamisole in comparison with placebo from 4 weeks to 6 months after the...

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

Summary

ID

NL-OMON55651

Source
ToetsingOnline

Brief title
LEARNS

Condition

- Nephropathies

Synonym
idiopathic nephrotic syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: ACE Pharmaceuticals BV,Nederlandse Nierstichting

Intervention

Keyword: child, idiopathic nephrotic syndrome, levamisole, relapse

Outcome measures

Primary outcome

The primary endpoint is the occurrence of a first relapse within 12 months

after randomization. A relapse is defined as the recurrence of proteinuria (3+

urine dipstick or proteinuria> 200 mg/mmol creatinine) for 3 consecutive days.

Secondary outcome

Secondary endpoints:

- Time to first relapse;

- Relapse rate (number of relapses per person year) over 2-year period;

- Cumulative steroid dosage up to 2 years;

- Occurrence of adverse events and treatment discontinuation;

- Proportion of frequent relapsers or steroid dependency over 2-year period;

- Toxicity of levamisole:

- Proportion of patients with elevated ASAT-/ALAT-levels, neutropenia

(<1500/mm3) or positive ANCA.

- Toxicity of corticosteroids:

- Differences in BMI, blood pressure, height, weight, serum glucose between

groups.

- Proportion of patients with overweight (BMI >25 kg/m2, hypertension (p>90),

and (fasting) hyperglycemia.

- Days of school missing, outpatient visits and hospitalization 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 and 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 has 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 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 applicability 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.

Study objective

This study has been transitioned to CTIS with ID 2024-517467-23-00 check the CTIS register for the current data.

Primary objective:

- 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.

Secondary Objectives:
- To investigate HRQoL at different stages of treatment (before the start of prednisolone treatment, during steroid treatment, after cessation of steroid treatment but still on levamisole treatment, and without treatment) (longitudinal and cross-sectional).
- To identify medical and personal factors related to HRQoL, psychosocial adaptation and parental distress.
- To investigate the saliva/plasma concentration ratio of prednisolone and levamisole.
- To determine pharmacokinetics and -dynamics of levamisole and prednisolone in children with INS.
- To investigate the applicability of saliva for determination of the prednisolone and levamisole plasma concentrations in daily clinical use.
- To establish the functional immune disorders in INS using full-blood stimulation before and after start of treatment and upon relapse.
- To establish the phenotype changes of the immune system using 14-colour flow-cytometry for T-cell, B-cell, DCs and ILCs subsets before and after treatment and upon relapse.
- To establish the differences of genotype of the immune system in INS using the Immune Response Array Genotyping.
- To establish the stratification of patients at risk for recurrent disease and identify immunological pathways involved in INS.
- To provide insight in the mechanism of action of levamisole in the prevention of relapses using a) full blood stimulation; b) Seahorse technology to assess metabolism of inflammatory cells; c) inhibitors and activators of the nicotinic acetylcholine receptors.
- To investigate the consequences of the disease in terms of days of missing school, outpatient visits, hospital admission and therapy costs

Study design

International multi-centre randomized, double blind, placebo-controlled trial. Patients will be randomized in a 1:1 ratio in two groups, receiving either levamisole 2.5 mg/kg on alternate days (treatment group) or placebo (control group). The total duration of the study will be 4 years: 2 years of inclusion and 2 years of follow-up. For each individual patient, there is a screening period of 4 weeks, followed by a study treatment period of 6 months. The patient will be followed up until 2 years after the first presentation of INS.

Intervention

Treatment group receives levamisole 2.5 mg/kg on alternate days, maximum of 150 mg per day (tablets of 5, 10, 25, and 50 mg). Start of study medication is at 4 weeks after the start of steroid treatment, only when remission is achieved. Total duration of treatment period with study medication will be 6 months. The control group receives placebo, similar in appearance, taste and weight. Due to possible pooling of clinical data with a currently ongoing resembling trial in France, we will adapt the French prednisolone dosing schedule:
- 60 mg/mm2/day; 4 weeks, followed by
- 60 mg/mm2/alternate days; 8 weeks, followed by
- 45 mg/mm2/alternate days; 2 weeks, followed by
- 30 mg/mm2/alternate days; 2 weeks, followed by
- 15 mg/mm2/alternate days; 2 weeks.

Study burden and risks

Levamisole has few side effects of which neutropenia is the most common (0-14%) and most serious for which regular testing is indicated. All reported adverse effects in previous studies (including skin rash, and, although rarely reported, vascular necrosis, convulsions and liver toxicity) were reversible after cessation of the treatment. The number of visits will be around 10 in the first year of the study and are combined with standard care visits. Still, the number of visits might be more than is usual for a child with INS (however, differences exist between hospitals). Visits will be done in one of the participating centres, therefore, travel distance from home to a participating hospital might be longer. Blood and urine sampling for biobanking and immunomic analyses are combined with routine tests in order to avoid unnecessary punctures. Additional testing (two days in first year, each time 5 blood samples on different time points) for PK- and PD- analysis is additional to standard care. To minimize physical and emotional discomfort, an intravenous catheter is placed for obtaining all blood samples. If the patient wishes so, these tests can be done at home and will also include regular follow-up, thus these home visits will be instead of a visit to the hospital. In total, a maximum of 15 and 18 mL of additional blood samples will be collected from children <6 year and children of 6 years and older, respectively. The HRQoL questionnaires can be filled out at home via the KLIK-website. The average time needed is 15-30 minutes for the child and 30 minutes for the parent(s). Patients and parents, if applicable, are asked to keep a diary to keep track of relapses, treatment compliance and prednisolone use (in case of relapse). There will be a paper as well as a web-based version of the diary (available through KLIK-website).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Children (2-11 years)

Inclusion criteria

Children (age 2-16 years) with a first episode of idiopathic nephrotic syndrome

Exclusion criteria

Steroid-resistant nephrotic syndrome (no remission after 4 weeks of steroid treatment)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-04-2018
Enrollment:	87
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Elmisol
Generic name:	Levamisole

Ethics review

Approved WMO Date:	06-12-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2018
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2019
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-08-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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
EU-CTR	CTIS2024-517467-23-00
EudraCT	EUCTR2017-001025-41-NL
CCMO	NL61906.018.17
Other	NL6826 (NTR7013)