PCSK9 and ENaC in nephrotic syndrome in man

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Nephropathies
Study type	Interventional

Summary

ID

NL-OMON51030

Source
ToetsingOnline

Brief title
PCKS9 and ENaC in nephrotic syndrome

Condition

- Nephropathies

Synonym
nephrotic syndrome, protein losing illness

Research involving
Human

Sponsors and support

Primary sponsor: Rijnstate Ziekenhuis
Source(s) of monetary or material Support: aanvraag gedaan bij vriendenfonds rijnstate

Intervention

Keyword: ENaC, hypercholesterolemia, nephrotic syndrome, PCSL9

Outcome measures

Primary outcome

The main study parameter is serum LDL cholesterol

Secondary outcome

ENaC activity assessed by urine Na/K ratio

Study description

Background summary

Marked hypercholesterolemia is common in patients with nephrotic syndrome (NS), but the exact underlying pathophysiology is
unknown. A common accepted theory is that proteinuria causes a low serum oncotic pressure which leads to reactive hepatic
protein synthesis including lipoproteins. More recent studies showed that proprotein convertase subtilisin/kexin type 9 (PCSK9) in
plasma is elevated in patients with NS, and that PCSK9 decreased low-density lipoprotein (LDL) receptor mediated LDL cholesterol
clearance from the circulation, possibly being the most important mechanism causing hypercholesterolemia. Generally thought to be
mainly liver-derived, a recent study in mice with NS demonstrated that PCSK9 is principally upregulated in the cortical collecting
duct, and suggested that this kidney-derived PCSK9 is responsible for the hypercholesterolemia. This study also showed that
PCSK9 is a chaperone of the epithelial sodium channel (ENaC), and that blocking ENaC causes further upregulation of PCSK9. If
these mechanisms occur in men as well, PCSK9 inhibitors form a rational therapy for nephrotic syndrome induced
hypercholesterolemia.

Study objective

The aim of this pilot study is to further unravel the pathophysiologic mechanism of NS-induced hypercholesterolemia which will
further guide the treatment of patients with NS.
Given the recent insights on PCSK9-ENaC inhibition, our hypothesis is that

PCSK9-inhibition will lower plasma cholesterol in NS, whereas ENaC-inhibition will increase it.

Study design

An intervention study in which 10 patients with NS and hypercholesterolemia will receive one 150 mg gift of the PCSK9-inhibitor alirocumab. Five of these 10 patients will receive 20 mg of the ENaC-blocker amiloride on the five days before alirocumab injection.

Intervention

Five patients will receive 20 mg amiloride orally on two consecutive days and receive 150 mg alirocumab as a subcutaneous injection on the third day, and five patients will only receive 150 mg evolocumab as a subcutaneous injection.

Study burden and risks

In the amiloride/alirocumab group, four blood samples and three urine samples will be taken. In the alirocumab only group, three blood samples and three urine samples will be taken. The risks of the study are minor. Amiloride, regularly prescribed for patients in NS, is on the market for over 50 years and is on the WHO List of Essential Medicines. There is a small risk of inducing hyperkalemia or hypotension. However, laboratory values and blood pressure will be closely monitored and patients with pre-existing hyperkalemia or hypotension will be excluded from participation in the study. Alirocumab is approved for use in patients with hypercholesterolemia. Nasopharyngeal complaints and injection site reactions have been reported in some cases. No known interactions have been described between amiloride and alirocumab.

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

- Presence of heavy proteinuria (>3.5g/24h)
- Presence of hypoalbuminemia (<30g/L)
- Presence of peripheral edema, based on clinical assessment of the treating physician
- Presence of hypercholesterolemia (LDL cholesterol >3.0 mmol/L)
- Age >=18 years

Exclusion criteria

- Use of immunosuppressive drugs
- Estimated glomerular filtration rate (eGFR) of <15, as calculated by the chronic
kidney disease epidemiology collaboration (CKD-epi) formula
- Serum potassium of >5.0 mmol/L
- Blood pressure of <120/80 mmHg
- Unable to give informed consent
- Pregnancy

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	alirocumab
Generic name:	praluent
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	amiloride
Generic name:	amiloride
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	22-03-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	29-06-2021
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	EUCTR2021-001364-18-NL
CCMO	NL77139.091.21