Oxylipins and lipoxygenases in cholestatic itch

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Are the elevated levels of oxylipins seen in itching cholestatic patients responsible for typical itch by activating TRPA1?

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatic and hepatobiliary disorders
Study type	Observational invasive

Summary

ID

NL-OMON50822

Source
ToetsingOnline

Brief title
OaLiCI

Condition

- Hepatic and hepatobiliary disorders

Synonym
cholestatic itch, cholestatic pruritus

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Stichting Dioraphte

Intervention

Keyword: Cholestasis, Itch, Lipoxygenases, Oxylipins

Outcome measures

Primary outcome

To assess oxylipin levels in itching cholestatic patients and compare the levels of these compounds with non-itching cholestatic patients and healthy controls.

Secondary outcome

Secondly, to investigate the association of itch and elevated levels of oxylipins (OXLAMs, OXAAMs) in serum and skin in different subgroups.
Thirdly, to asses if lipoxygenases are expressed in elevated levels, and thereby are the main source of oxylipins in patients with cholestatic itch.
Fourthly, to evaluate the effect of known therapies for cholestatic itch on lipoxygenase expression and oxylipin levels.
Fifthly, to determine the tissue of origin of these oxylipins (skin and/or leukocytes)
Lastly, we want to identify the lipoxygenase(s) responsible for the production of pruritogenic oxylipins found in itching cholestatic patients.

Study description

Background summary

Chronic cholestasis often leads to chronic itch which can become unbearable for the patient. The cause of this itch is unknown. Endoscopic or surgical interventions are only helpful when obstructions of large extrahepatic bile ducts play a role in itch development. Drug therapy has limited effects[1]. We have recently discovered that certain oxylipins (which, amongst others comprise of *oxidated linoleic acid metabolites* (OXLAMs) and oxidated arachidonic acid metabolites, OXAAMs)) accumulate in the blood of these patients and are likely to be factors which play a role in this form of itch, as they activate TRPA1, a

pruriceptor which is increasingly recognized as a chemical sensor on pain and itch neurons[2]. To further the hypothesis that oxylipins have a causal relationship with cholestatic itch, we want to perform a screening on serum and skin tissue for oxylipins using the HPLC-MS, to assess if they are present in elevated levels. Also q-PCRs will be performed to evaluate the expression of various genes, including those encoding lipoxygenases, in leucocytes and skin tissue, as this group of enzymes is responsible for OXLAM and OXAAM production. Leucocytes are needed as we hypothesize that leucocytes are induced to express lipoxygenases in cholestasis. Skin sampling procedures will be performed by tape stripping of the stratum corneum. The use of murine models in this study is inadequate since cholestatic mice do not experience itch.

Study objective

Are the elevated levels of oxylipins seen in itching cholestatic patients responsible for typical itch by activating TRPA1?

Study design

Observational study

Study burden and risks

The punch biopsy procedure is the standard procedure regarding biopsies in dermatologic care, and is known for its low invasiveness, to cause very few complications (expert opinion, no exact complication rate known).
Skin sampling in the form of tape stripping is generally non-invasive and painless, but local erythema and irritation can occur.

The use of Ultracain forte (articaïn(hydrochloride) 40 mg/ml, adrenalin (hydrochloride) 10 microg/ml (1:100.000) is common practice amongst dentists and dermatologists and is regarded as safe, when used secure and when made sure not injected intravenously.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 69-71
Amsterdam 1105 BK
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 69-71
Amsterdam 1105 BK
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject should:

1. Be able to provide informed consent
2. Meet the criteria of one of the following subgroups:

a) Patients of >=18 years of age who are diagnosed with non-hereditary hepatobiliary diseases leading to cholestasis e.g.:
Primary sclerosing cholangitis (PSC)
• Based on: elevated serum alkaline phosphatase and *GT and characteristic lesions on ERCP and/or magnetic resonance cholangiopancreaticography (MRCP)
Primary biliary cholangitis (PBC)
• Based on >=2 of 3 criteria: history of elevated alkaline phosphatase for at least 6 months, liver biopsy consistent with PBC, positive anti-mitochondrial antibody titer (or when low in titer anti-GP210 and/or anti-SP100 and/or anti-PDC-E2 antibodies)
Malignant cholestatic diseases (e.g. cholangiocarcinoma)
• Based on the criteria of the subdiagnosis.
b) Patients prone to hereditary cholestatic diseases (patients of < 18 years of age are exempted from punch biopsies):
Progressive familial intrahepatic cholestasis (PFIC)
• Based on: confirmed mutations in the ATP8B1, ABCB11 or ABCB4 genes.
Alagille syndrome

• Based on: confirmed mutations in the JAG1 or NOTCH2 genes.
c) Patients of >=18 years of age who are prone to intrahepatic cholestasis of pregnancy (ICP).
• Based on: pruritus in pregnancy, elevated serum ALT activities and fasting bile acid levels, and exclusion of other causes of liver dysfunction or itching. Serum liver tests and fasted bile acids should normalize after pregnancy.

Exclusion criteria

Subjects who could be considered as a vulnerable population will be excluded from participation in this study:

1. Clinically unstable subjects (as assessed by their treating physician)
2. Subjects with a confirmed infection
3. Subjects with a dermatologic disease other than the skin phenotype associated with cholestasis
4. Subjects admitted to the ICU
5. Subjects experiencing itch as a result of cholestasis for less than three months
6. Subject who are prone to another hepatic disease

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-03-2021
Enrollment:	220
Type:	Actual

Ethics review

Approved WMO Date:	26-02-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
CCMO	NL75400.018.20