The chemopreventive effect of Lithium on adenoma development in patients with familial adenomatous polyposis (FAP); a pilot study

Published: 05-04-2022
Last updated: 06-04-2024

The aim of this study is to investigate the effect of low-dose Lithium on stem cell dynamics, the number and size of polyps and, to assess safety outcomes of this drug in FAP patients.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON51473

Source
ToetsingOnline

Brief title
Lithium in FAP

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
familial adenomatous polyposis, familial intestinal polyps

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC

Source(s) of monetary or material Support: KWF beurs

Intervention

Keyword: Familial adenomatous polyposis, Lithium

Outcome measures

Primary outcome

- Clone sizes will be quantified as proportions of the crypt circumference positive for NOTUM (in parts of eight, 1:8 to 8:8). When a whole crypt is positive for NOTUM (8:8), this crypt is fixed (crypt fixation).

Secondary outcome

- Difference in number and size of polyps between baseline and end of study
- Patient reported side effects of Lithium using a Lithium side effect questionnaire (see appendix 2 of the protocol)
- Safety outcomes by analysing reported adverse events, physical examination and laboratory findings.

Study description

Background summary

Familial adenomatous polyposis (FAP) syndrome is characterized by the development of numerous colorectal polyps. If left untreated, these patients have a chance of nearly 100% of developing colorectal cancer (CRC) at a young age. Therefore, guidelines recommend a prophylactic colectomy during early adulthood. Even after colectomy, most patients will develop adenomas in the retained rectum or ileoanal pouch requiring further endoscopic surveillance. In a recent study in mouse models, a chemopreventive effect of Lithium was observed on the spread of Apc mutated cells within the crypts of normal intestinal mucosa, suggesting polyp formation can be prevented. Lithium is used to treat patients with bipolar disorders but has never been investigated in patients with FAP aiming to reduce polyp burden. We hypothesize that Lithium could reduce the spread of APC mutated cells within the crypt of normal

intestinal mucosa potentially reducing polyp burden in patients with FAP.

Study objective

The aim of this study is to investigate the effect of low-dose Lithium on stem cell dynamics, the number and size of polyps and, to assess safety outcomes of this drug in FAP patients.

Study design

A prospective phase II, single arm pilot trial that will take place at the Amsterdam Universitair Medisch Centrum (AMC), with a duration of 18 months. The drug will be administered between month 6 and 12.

Intervention

All patients will be treated with Lithium with an oral dose of 300mg a day for six months, achieving a therapeutic serum level between 0.2-0.4 mmol/L.

Study burden and risks

A physical examination and an endoscopy with biopsies will be performed at baseline and every six months (four in total). Laboratory testing will be done at baseline and every two months during Lithium treatment. Patients will be interviewed by phone and Lithium side effect questionnaires will be obtained at baseline and during Lithium treatment. Lithium serum levels will be measured at day 12 and 22 after start of the study drug (at month 6). When the therapeutic range has been achieved, serum level testing will be done every month. Most relevant side-effects that could potential occur include polyuria, hyperparathyroidism and hypothyroidism. Most side effects are dose-dependent and will be regularly monitored. Patients with FAP could potentially benefit from a chemopreventive therapy such as Lithium to postpone or even avoid invasive types of surgery.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Male or female between the age of 18 and 35 years;
- Confirmed APC germline mutation;
- Positive family history of a classical FAP phenotype (>100 colorectal adenomas);
- Intact colon, with a minimum of 50 polyps;
- Participant is willing and able to give informed consent for participation

Exclusion criteria

- Participation in any other clinical intervention study; observational trials accepted;
- Lithium use prior to participation of the study;
- Pregnancy, breast-feeding or no use of anticonception;
- No normal intestinal mucosa left for normal tissue biopsy;
- Indication for colectomy within 2 years;
- Known renal impairment, defined as GFR < 60 ml/min;
- Known severe cardiac disorder;
- Known severe brain injury;
- Hypothyroidism;
- Hyponatremia, defined as Na < 130mmol/L;
- Positive family history of Brugada syndrome
- Co-medication known for interacting with Lithium (as defined in the protocol).
- Regular NSAID use (defined as more than twice a week for 4 consecutive weeks) within 3 months prior to baseline;

- Use of immunosuppressive or anti-inflammatory drugs within 3 months prior to baseline;
- Use of any other FAP directed drug therapy within 3 months prior to baseline (use of any alternative supplements e.g. turmeric or fish-oil must be noted in questionnaire).

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-06-2022
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LithiumCarbonate
Generic name:	Lithiumcarbonate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	05-04-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	19-04-2022
Application type:	First submission
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
EudraCT	EUCTR2022-000240-30-NL
CCMO	NL80308.018.22