Sirolimus for the treatment of severe intestinal polyposis in patients with familial adenomatous polyposis (FAP); a pilot study

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Benign neoplasms gastrointestinal
Study type	Interventional

Summary

ID

NL-OMON47156

Source
ToetsingOnline

Brief title
Sirolimus and FAP

Condition

- Benign neoplasms gastrointestinal

Synonym
Familial adenomatous polyposis, familial intestinal polyps

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Pfizer,Studiemedicatie wordt gratis geleverd

door Pfizer. De overige kosten zijn voor de investigator.

Intervention

Keyword: Familial adenomatous polyposis, Sirolimus

Outcome measures

Primary outcome

• Size of 5 marked polyps 5 patients with FAP and a large intestinal polyp

burden

• Safety outcomes reported by summary analysis of adverse events , clinical

laboratory abnormalities and regular physical examination

Secondary outcome

• Number of polyps

• Global polyp burden

• Histology (tubular, tubulovillous or villous histology and degree of

dysplasia)

• Patient reported quality of life using HRQoL questionnaires

• Rate of cell proliferation in healthy intestinal mucosa and adenomatous tissue

• Immunohistochemistry of mTOR targets (such as eEF2 kinase, phospho-S6) in

healthy intestinal mucosa and adenomatous tissue

Study description

Background summary

Due to the presence of numerous colorectal polyps, nearly all patients with familial adenomatous polyposis (FAP) develop colorectal cancer (CRC) at an average age of 39 years, if left untreated. Therefore, a prophylactic colectomy is recommended. After surgery, adenomas are likely to reappear in the pouch or

rectum. Recently, studies in APC-deficient mice have shown that the mTOR inhibitor sirolimus can cause intestinal tumour cells to undergo growth arrest and differentiation and could even lead to regression of polyps. In current practice, sirolimus is used as an immunomodulator for patients after renal transplantation. Sirolimus has never been investigated in patients with FAP. We hypothesize that sirolimus could lead to regression of intestinal polyps in patients with FAP.

Study objective

The aim of our study is to investigate the effect of sirolimus on the progression of intestinal adenomas in patients with FAP and to assess the safety of this treatment.

Study design

This is a prospective phase II pilot study that will take place at the Academic Medical Center (AMC). Five patients with FAP will be invited for study participation. The total study duration will be 6 months. At baseline and at 6 months follow-up all included patients will undergo a lower gastrointestinal (LGI) endoscopy. Safety outcomes will be assessed by laboratory tests, physical examinations and telephone check-ups. Sirolimus trough levels will be measured regularly and if needed dosing adjustments will be made.

Intervention

All patients will receive sirolimus for the duration of the study (6 months), with a trough level target range of 5-8 ng/ml.

Study burden and risks

At baseline and at three monthly visits a medical history will be taken and physical examinations will be performed, as well as laboratory tests and HRQoL questionnaires. Trough level testing of sirolimus will be measured at day 7 after start of the study drug and weekly until the therapeutic range has been achieved, after which the next trough level will be measured at 3 and 6 months follow-up. Finally, monthly telephone check-ups will be carried out. LGI endoscopies will be done at baseline and at 6 months. For this study, we include patients with severe intestinal polyposis as they are expected to have an indication for invasive surgery on a short-term and no other less invasive alternative therapy is available.
The use of sirolimus is associated with a risk of several side-effects. By frequent telephone contact, lab testing, physical examination and trough level testing, side-effects can be identified on a short term base and if indicated they can be treated or surveilled. The relatively short study duration and low

dosing of sirolimus minimize the chance of developing side-effects.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- >= 18 years
-A genetically confirmed APC mutation
-Classical FAP phenotype (100-1000 colorectal adenomatous polyps)
-Subtotal colectomy with ileorectal anastomosis (IRA) or ileo-anal pouch anastomosis
-Severe rectal or pouch polyposis, defined as having >25 polyps amenable to complete removal (InSiGHT 2011 Staging System score of 3)
-Fertile patients must use effective contraception during study treatment and until 12 weeks after treatment

Exclusion criteria

-Inability to give informed consent
-Participation in another interventional clinical trial
-Subjects who are pregnant or breast-feeding
-Prior pelvic irradiation
-Invasive malignancy in the past 5 years
-Subjects who are HIV positive
-Subjects with severe systemic infections, current or within 2 weeks prior to study start
-Subjects with known severe restrictive or obstructive pulmonary disorders
-History of pulmonary embolism or deep venous thrombosis
-Major surgery less than or equal to 2 weeks prior to enrollment or any planned surgery within treatment period
-Active post-operative complication, e.g. infection, delayed wound healing
-History of hypersensitivity to sirolimus or to its excipients or drugs of similar chemical classes
-Regular NSAID use
-Use of other FAP directed drug therapies
-Subjects requiring systemic anticoagulation
-Co-medication that could interact with sirolimus: Ciclosporine, IL-2-receptorantibodies, Calcineurine inhibitors, HMG-CoA-reductase inhibitors, fibrates, CYP3A4-inhibitors (such as ketoconazol, voriconazol, itraconazol, telitromycine, claritromycine, troleandomycine, verapamil, diltiazem, erytromycine, ritonavir, indinavir, boceprevir, telapravir, nicardipine, bromocriptine, cimetidine, danazol), CYP3A4-inductors (such as rifampicine, rifabutine, St. Janskruid, carbamazepine, fenobarbital, fenytoine), ACE-inhibitors, cisapride, metoclopramide), Pgp inhibitors
-Use of grapefruit juice
-Use of attenuated vaccins;-Significant abnormalities in hepatic function
-Significant hematologic abnormalities
-Increased fasting serum cholesterol or triglyceride (whether or not on lipid-lowering therapy)
-Increased glucose
-Electrolyte abnormalities
-Calculated glomerular filtration rate (GFR) less than 40 mL/min/1.73m2
using the simplified Modification of Diet in Renal Disease (MDRD) formula
-Spot urine protein to creatinine ratio (UPr/Cr) greater than or equal to 0.5

Study design

Design

Study phase: 2

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-10-2017
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Rapamune
Generic name:	Sirolimus
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-12-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-12-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2018
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
EudraCT	EUCTR2015-005527-12-NL
CCMO	NL55868.018.15