Mesalamine for Colorectal Cancer Prevention Program in Lynch syndrome

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Primairy Objective* To test whether 5-ASA reduces the occurrence of colonic benign or malignant neoplasia compared to placebo in Lynch syndrome (LS) patients as detected by any colonoscopy until the end of study.Secondary Objectives* To test wheter...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON44695

Source
ToetsingOnline

Brief title
MesaCAPP studie

Condition

- Congenital and hereditary disorders NEC
- Gastrointestinal conditions NEC

Synonym
hereditary colon cancer, Lynch syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Medical University of Vienna
Source(s) of monetary or material Support: KWF

Intervention

Keyword: colorectal cancer, Lynch syndrome, mesalamine, phase 2

Outcome measures

Primary outcome

The occurrence of neoplasms will be described by absolute frequencies and percentages together with 95 % confidence intervals. A logistic regression is used to assess differences between active treatment and placebo for the occurrence of neoplasms, adjusted for country and history of cancer before randomization. Treatment effects are assessed by odds-ratios and corresponding 95 % confidence intervals.

Secondary outcome

The number of neoplasms per patient will be tested between groups by an analysis of variance, adjusting for country and history of cancer before randomization. In case of non-normally distributed residuals a suitable transformation to achieve normal distribution or a Poisson regression model is considered , whatever achieves a better model fit. The tumor progress in the 4 ordered stages will be tested between groups by a chi-square trend test stratified for country and and history of cancer before randomization. Additionally ordinal logistic regression will be applied in analyogy to the analysis of the primary endpoint. The same methods are used to assess differences between low and high dose 5-ASA on the occurrence of neoplasms, the number of neoplasms and tumor progression. Additionally interactions of CRC history, gender and patients age (<45 years and *45 years) with treatment are analysed by including interactions of

these variables with treatment to the corresponding regressions models

adjusted also for country.

Study description

Background summary

Colorectaal cancer (CRC) has become the second leading cause of cancer death for both females and males. Individuals with Lynch syndrome (LS) live under constant threat of cancer development throughout adulthood. LS individuals here are defined as carriers of a deleterious mismatch repair (MMR) gene mutation in MLH1, MSH2, MSH6, or PMS2, have a 50%-80% lifetime risk for the development of CRC (colorectal cancer). The prevalence of LS in colorectal and endometrial cancer patients is about 1-4% [1, 2]. On extrapolation to the entire population, the incidence of LS is estimated between 1:2000 and 1:660. There are even higher estimates that the population incidence of LS is approximately 1 in 370 [3]. Thus, over a quarter- to one million individuals may be affected within the European Union [1]. Chemoprevention is a big hope for LS family members.

Cancer prevention in LS has been studied in the past. The CaPP2 trial has tested the effect of 600mg aspirin in a large multinational cohort and showed no benefit for its primary outcome [20]. A secondary post-hoc analysis demonstrated a statistical significant effect as a delayed response [21] leaving the problem unanswered [22]. Since 600mg of aspirin are difficult to tolerate for longer periods and the chemopreventive effect may be just as high with a lower dosage, the authors of CaPP2 have initiated a follow-up trial to compare lower doses of aspirin with 600mg (CaPP3; communication John Burn).

Cancer development in LS occurs through a mutational mechanism called microsatellite instability (MSI). One way to interfere with cancer development in LS is to improve replication fidelity and thereby reduce the speed of MSI. In vitro, mesalamine (5-ASA), a well-tolerated drug that had been used for over 30 years in ulcerative colitis, reduces MSI via improvement of replication fidelity [5]. 5-ASA activates a replication checkpoint thereby allowing more time for cells to pass through S-phase leading to less replications errors [6]. This effect of 5-ASA is specific for the position of the amino group [7], as 3 ASA or 4-ASA had no such effect, and applicable for various repetitive sequences such as mono- (including TGFBR2 and ACVR2), di- and tetranucleotide repeats [8]. In Msh2 loxP/loxP Villin-Cre mice [9], which best resemble LS of the intestine, 5-ASA reduces tumor incidence, multiplicity and reduces the number of mutations in five selected microsatellite repeats in the normal mucosa [10]. Such a chemopreventive

effect was not observed upon aspirin [11], which has no effect on MSI either [5]. 5-ASA has minimal toxicity as it is delivered to the colon through slow release formulations and immediately inactivated (N-acetylated) within the colonic mucosa. The drug is not systemically active. Thereby it would fulfill all requirements for a designer drug for CRC prevention in LS. In addition epidemiological data support its chemopreventive properties in humans as it reduces the risk of CRC in patients with ulcerative colitis [12]. However, so far it is unclear whether such effect is mediated through its anti-inflammatory or various anti-neoplastic properties [13]

Study objective

Primairy Objective
* To test whether 5-ASA reduces the occurrence of colonic benign or malignant neoplasia compared to placebo in Lynch syndrome (LS) patients as detected by any colonoscopy until the end of study.

Secondary Objectives
* To test wheter 5-ASA reduces the number of neoplasms (tumor multiplicity) and tumor progression to placebo in LS patients at the end of the study. Advanced adenomas are defined by a diameter above 1 cm villous or tubulu villous histology or high grade dysplasia.
* To investigate if differences between 5-ASA effects and placebo effects on the occurrence of colonic neoplasia, tumor multiplicity or tumor progression depend on the history of
colorectal cancer, sex and patients age (LS patients below 45 years of age or 45 years of age and older).
* To investigate differences between low and high dose 5-ASA with respect to the occurrence of colonic neoplasia, to tumor multiplicity and tumor progression.

Study design

Multicenter, multinational, randomized, 3-arm, double-blind, phase II clinical study with 2400mg 5-ASA, 1200mg 5-ASA or placebo in LS patients for 2 years.

Intervention

screening visit: laboratory examinations (hematology, serum chemistry, creatinine, amylase and lipase), pregnancy test, colonoscopy, (colonoscopy is standard test) serum and stool. Total amount of blood collection is 16 ml.

randomization visit/control visits: creatinine, amylase and lipase. Total amount of blood collection is 6 ml.

1 year control visits: creatinine, amylase and lipase, colonoscopy, (colonoscopy only if patient is used to have a yearly colonoscopy). Total amount of blood collection is 6 ml.

end of study visit: laboratory examinations (hematology, serum chemistry, creatinine, amylase and lipase), pregnancy test, colonoscopy, (colonoscopy is standard test) serum and stool. Total amount of blood collection is 16 ml.

Study burden and risks

Load
There are no expected impacts or restrictions on the lifestyle of the patient. The patient should take 2 tablets once daily in the morning and write them down in his patient diary. Every 5-7 weeks between two visits, the patient receives a call from his study doctor or study staff. The patient should visit the hospital every three months. It is important that the patient goes to the scheduled visits and that the planned study procedures and tests are performed. It is also important that the patient takes the study medication as prescribed and the patient writes down the study medication intake in his patients diary. The patient should return all unused study medication and all containers (even empty containers) at the first next visit in the hospital. It is also important that the patient informs the study team about any other medications that he has used before and during the study. Because some drugs are not permitted during the study, the patient should first discuss the planned treatment with his study doctor before starting to use the drug.

Risk
Mesalamine is a very well-tolerated. As every medication, the treatment with Mesalamine can induce possible side effects or other disorders. Known side effects include soft stool, outright diarrhea, abdominal discomfort, nausea, flatulence, and less common headache and rash or other hypersensitivity reactions. Blood sampling can cause pain, bruising and light headedness.

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

* Proven tumor-free (including patients in which the polyps are removed endoscopically) carriers of a germline pathologic mutation on one of the MMR genes including MLH1, MSH2 (including EpCAM) en MSH6.
* Male or female subjects with the age > 30 years
* Signed written informed consent prior to inclusion in the study

Exclusion criteria

* Presence of colonic endoscopically non-removable benign neoplasia (patient can be included
if the adenoma is removed)
* Carriers of germline mutations in PMS2.
* Patients with history of stage 3 and 4 CRC are excluded
* Presence of metastatic disease
* Regular use of aspirin: daily use of *100mg in more than 3 continuous months within the last
year
* Regular use of NSAIDs or COX-2 inhibitors: daily use in more than 3 continuous months within the last year
* Hypersensitivity to 5-ASA
* Patients after total or subtotal colectomy
* Colorectal surgery within the previous 6 months
* Unwillingness to participate or who is considered incompetent to give an informed consent

* Pregnant or breastfeeding women
* Participation in another clinical study investigating another IMP within 1 month prior to screening
* Renal insufficiency (GFR <30ml/min/1.73m²)
* Severe liver disease or liver failure (elevation of liver enzymes above 3xULN)
* Current or history of serious psychiatric disorder or alcohol/drug abuse that in the opinion of the investigator may impact the assessment of safety, efficacy or protocol adherence.
* Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that
may increase the risk associated with study participation or ability to comply with study procedures, investigational product administration and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	170
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	31-05-2017
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-11-2017
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-03-2018
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2013-003413-18-NL
CCMO	NL51172.058.17