The effect of neoadjuvant treatment of colorectal cancer with simvastatin on the expression and activation of elements of the Bone Morphogenetic Protein pathway.

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Does oral simvastatin at standard doses alter BMP pathway signalling in colorectal cancer specimens in humans?

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON31290

Source
ToetsingOnline

Brief title
Simvastatin in colon cancer.

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
colon cancer, colorectal adenocarcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: KWF

Intervention

Keyword: Bone Morphogenetic Protein, Colorectal cancer, Simvastatin

Outcome measures

Primary outcome

A tissue microarray (TMA) will be used to semi-quantify the protein expression levels in the resection specimens of treated and nontreated patients. The TMA will be analysed by immunohistochemistry for levels of BMP2 and 4, pSMAD1, SMAD4 and ID-2. We will also analyse markers of apoptosis (cleaved caspase 3) proliferation (Ki-67) and angiogenesis (VEGF and CD31). Staining will be scored in a semiquantitative fashion by 3 independent investigators with no patient information.

Tumour samples taken before initiation of Simvastatin treatment will be compared to tumour samples taken after therapy. We will use immunohistochemistry for elements of the BMP pathway as well as Elisa (BMP2) and qRT-PCR using the frozen tissue where RNA and protein will be isolated from samples that consist of more that 70% tumour cells as analysed by frozen section.

Secondary outcome

Not applicable

Study description

Background summary

In 2005 a large epidemiological study found that the use of statins was associated with a 50% reduced risk of the development of CRC. This has excited widespread interest in statins as chemopreventative agents in CRC and has lead several authors to suggest large prospective trials of statins.

Statins are powerful modulators of the BMP pathway. A screen of 30,000 molecules identified Lovostatin as the most potent upregulator of BMP2 production in bone cells. We have shown that BMP2 has proapoptotic effects in CRC cells and we hypothesised that the actions of the statins in CRC are due to actions on the BMP pathway. Our preliminary experiments confirm that statins induce apoptosis in CRC cells by inducing the BMP pathway. We are able to block the effects of statins with the specific BMP antagonist Noggin.

Study objective

Does oral simvastatin at standard doses alter BMP pathway signalling in colorectal cancer specimens in humans?

Study design

30 patients with colorectal cancer will be randomised to either receive 40mg simvastatin per day from their inclusion in the trial up to their operation date, or to receive no simvastatin.

6 extra biopsies from the tumour will be taken at the time of the initial colonoscopy and tumour material not needed for pathological diagosis will be taken from the resection specimen by the pathologist at the time of operation.

Tumour samples will be analysed for expression of BMPs and activity of the BMP pathway using RT-PCR, western blotting and immunohisochemistry.

Intervention

40mg simvastatin per day from the point of inclusion in the trial until the operation.

Study burden and risks

The risks are limited to the risk of the extra 6 biopsies of the tumour (no risk) and the risks of taking Simvastatin 40mg per day until the operation (

0,01 - 0,1% risk of side-effects according to the pharmacotherapeutic kompas)

Contacts

Public
Leids Universitair Medisch Centrum

Postbus 9600
2300 RC Leiden
NL
Scientific
Leids Universitair Medisch Centrum

Postbus 9600
2300 RC Leiden
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

>18 years
histologically confirmed colorectal cancer
Eligible for surgical resection

Exclusion criteria

Current use of cholesterol lowering drugs or NSAIDs.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-11-2008
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Simvastatin (generic form)
Generic name:	Simvastatin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	05-07-2007
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2007-001179-13-NL
CCMO	NL16891.058.07