The effect of colchicine in patients with atherosclerosis of the heart vessels on white blood cells stimulated with crystals

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Colchicine admission attenuates inflammatory response of monocytes and neutrophils stimulated with MSU crystals, isolated from patients with chronic coronary artery disease after colchicine 0.5mg daily during one month, compared to placebo

Ethical review	Approved WMO
Status	Other
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON25814

Source
NTR

Brief title
CrystaLo

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Myocardial infarction, atherosclerosis, coronary artery disease

Health condition
History of myocardial infarction

Research involving
Human

Sponsors and support

Primary sponsor: None
Source(s) of monetary or material Support: None

Intervention

Explanation

Outcome measures

Primary outcome
The change in inflammatory cytokine release of monocytes and neutrophils, after stimulation with MSU crystals, isolated before versus after treatment with low dose colchicine of 0.5mg daily during one month, and compared to a cross over control period with placebo

Secondary outcome
Secondary objective: Correlation between change in serum hsCRP and change in cytokine release of

monocytes and neutrophils after stimulation with MSU crystals after one month of colchicine treatment 0.5mg once daily

Tertiary objective: Changes in RNA expression in CD14+ monocytes, isolated from patients with

chronic coronary artery disease before versus after colchicine 0.5mg daily during one month,

compared to placebo.

Study description

Background summary

Rationale: The progression of atherosclerosis consists of a cholesterol crystal-induced chronic inflammatory, with novel microscopic techniques revealing cholesterol crystals in early stages of atherosclerotic lesions. These cholesterol crystals destabilise lysosomes after phagocytosis by macrophages, which initiates inflammation via the nucleotide-binding, leucine-rich repeat, and pyrin-domain-containing 3 (NLRP3) inflammasome. Colchicine is an ancient drug which blocks assembly and polymerization of microtubules. This results in inhibition of NLRP3 inflammasome activation, possibly by its effect on mitochondria transport, which blocks NLRP3 inflammasome assembly. However, since colchicine affects many additional cellular processes, establishing which affected process is most relevant in

atherosclerosis remains challenging. In vitro a number of studies have established the inhibitory effect of colchicine on the NLRP3 inflammasome pathways, measuring pro inflammatory cytokine secretion, e.g. interleukin (IL)-1β, of monocytes stimulated with monosodium urate crystals (MSU). In vivo studies in patients with cardiovascular disease provide varying results, but seem to suggest colchicine inhibits inflammatory cytokine release during acute myocardial infarction, and reduces circulating neutrophilic cytokines in patients with chronic coronary artery disease. Studies on the effect of colchicine in patients with chronic coronary disease are even scarcer, but report a significant reduction of the downstream C-reactive protein, while reducing cardiovascular events and reduce low attenuation plaque volume on coronary computed tomography angiography. In this study we hypothesis that this reduction is caused by an inhibited response of monocytes and neutrophils on crystals present in atherosclerotic lesions, by colchicine-induced inhibition of NLRP3 inflammasome activation. Objective: To assess changes in inflammatory cytokine release of monocytes and neutrophils stimulated with MSU crystals, isolated from patients with chronic coronary artery disease before vs after treatment with colchicine Study design: This is a mono-centre intervention study with a crossover design, adding colchicine to usual medical therapy for one month with a control group receiving placebo Study population: Patients with a history of acute coronary syndrome Intervention: Low dose colchicine 0.5mg once daily during one month Main study parameters/endpoints: The change in inflammatory cytokine release of monocytes and neutrophils, stimulated with MSU crystals, isolated before versus after treatment with colchicine 0.5mg during one month. Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Awaiting the outcome studies for colchicine in chronic coronary artery disease patients, individual patients will not gain direct ‘health’ benefit from this study. The results are expected to provide insight into the anti-inflammatory properties of colchicine on monocytes and neutrophils. The burden and risk of participating in this study are estimated to be intermediate. The study requires a maximum of 4 study visits. Maximal blood withdrawal will be 167ml (7ml the first visit, 4 x 10ml vacutainer tubes of EDTA each subsequent visit).

Study objective

Colchicine admission attenuates inflammatory response of monocytes and neutrophils stimulated with MSU crystals, isolated from patients with chronic coronary artery disease after colchicine 0.5mg daily during one month, compared to placebo

Study design

Visits with blood withdrawal: V1: Informed consent, blood withdrawal in order to assess renal function and CRP V2: Baseline measurements, randomization; start colchicine 0.5mg once daily or placebo V3: 1 month after V1, start washout period V4: 2 week after V2; Crossover: Start placebo or colchicine 0.5mg once daily V5: 1 month after V3, end of study

Intervention

Colchicine

Contacts

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Eligibility criteria

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

Inclusion criteria

• Have suffered from type 1 myocardial infarction • Have been clinically stable for at least three months • Provided written informed consent

Exclusion criteria

• Age below 18 years or above 80 years • Use of CYP3A4 or P-glycoprotein inhibitors such as macrolids (claritromycin and erytromycin), ciclosporin, ketoconazol, itraconazol, voriconazol, HIV protease inhibitors, calciumchannel antagonists such as verapamil and diltiazem • Women who are pregnant, breast feeding or may be considering pregnancy during the study period or six month after the end of study participation • Male patients who may be considering conceiving during the study period or before six months after the end of study participation • Have renal impairment as evidenced by a serum creatinine >150 µmol/l or eGFR <50mL/min/1.73m2) • Have an elevated inflammatory profile as evidenced by a hsCRP >10mg/l in order to exclude patients with intercurrent (subclinical) infections • Have a moderate to severe hepatic disease • Suffer from pre-existing chronic gastro-intestinal complaints which might obscure signs of colchicine toxicity • Malignant disease in past five years or any medical condition that could interfere with the conduct of the study in the opinion of the investigator. • Chronic or recent (<1 month) infections and/or clinical signs of acute infection • Suffering from auto-immune / inflammatory diseases • Chronic use of

immunosuppressants or anti-inflammatory drugs, including colchicine • A history of haematological malignant disease • Recent hospital admission or surgery with general anaesthesia (<3 months) • Previous vaccination within 1 month prior to study entry • Inability or unwillingness to comply with the protocol requirements, or deemed by investigator to be unfit for the study. • Are currently enrolled in a competing trial

Study design

Design

Study phase:	N/A
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Other
Start date (anticipated):	20-01-2021
Enrollment:	20
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Approved WMO

Date:	09-09-2020
Application type:	First submission
Review commission:	METC Oost-Nederland
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Study registrations

Followed up by the following (possibly more current) registration

ID: 49134
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL8582
CCMO	NL73042.091.20
EudraCT	2020-000656-35
OMON	NL-OMON49134

Study results

Summary results
We plan to publish the results of this study in peer-reviewed scientific journals.