The inflammatory response of monocytes and neutrophils to Crystals after Low dose colchicine in patients with coronary artery disease

Published: 25-05-2020
Last updated: 15-05-2024

To assess changes in inflammatory cytokine release 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 no colchicine...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON49134

Source
ToetsingOnline

Brief title
CrystaLo

Condition

- Coronary artery disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
calcifications of the coronary arteries, Coronary artery disease

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: colchicine, coronary artery disease, monocytes, neutrophils

Outcome measures

Primary outcome

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 compared to placebo

Secondary outcome

- To assess whether hsCRP change in serum correlates with change in cytokine release by 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

- To assess changes of RNA expression in CD14+ monocytes, isolated from patients with chronic coronary artery disease after colchicine 0.5mg daily during one month, compared to placebo

Study description

Background summary

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)-1*, 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.

Study objective

To assess changes in inflammatory cytokine release 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 no colchicine treatment

Study design

This is a mono-centre intervention study with a randomized double-blind placebo-controlled crossover design, adding colchicine to usual medical therapy for one month with a control group receiving placebo

Intervention

Colchicine 0.5mg once daily during one month.

Study burden and risks

The burden and risk of participating in this study are estimated to be low. The study requires
a maximum of 5 study visits. Maximal blood withdrawal including clinical

laboratory assessment will be 167ml in total, spread over 2,5-3 months.
Colchicine is a registered drug for another indication, gout, and has been described for decades in the same dosages as in this study to prevent gout. In addition, to further avoid colchicine toxicity we exclude patients with impaired kidney functions or use of CYP3A4 or P-glycoprotein inhibitors. As such, we assess no risk apart from the usual mild gastro-intestinal side-effects.
No structured risk analysis including mechanism of action, pharmacokinetic considerations and management of effect is described in this protocol as colchicine is a registered product.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
* Have suffered from type 1 myocardial infarction
* Have been clinically stable for at least three months
* Provided written informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
* 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 *mol/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:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

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

Medical products/devices used

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

Ethics review

Approved WMO Date:	25-05-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-09-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	25-04-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-05-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 25814
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-000656-35-NL
CCMO	NL73042.091.20
Other	NL8582
OMON	NL-OMON25814