Vasospastic angina treatment by Endothelin Receptor Antagonism; a proof of concept study

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To determine whether VSA treatment with the novel ERA macitentan reduces the frequency and severity of anginal complaints among patients with clinically defined VSA. To determine side effects related to treatment with macitentan in patients with VSA...

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

Summary

ID

NL-OMON55720

Source
ToetsingOnline

Brief title
VERA

Condition

- Coronary artery disorders

Synonym
vasospastic angina pectoris, vessel spasm of the coronary artery

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Actelion Pharmaceuticals,de studiemedicatie (macitentan en een placebo) worden kosteloos verstrekt door Actelion

Pharmaceuticals B.V.

Intervention

Keyword: angina pectoris, endothelin receptor antagnist, vasospasm

Outcome measures

Primary outcome

The burden of anginal complaints, calculated as:

1. the duration (in minutes) * severity (on a VAS scale 1-10) during the study period up to 2 weeks after discontinuation of the study medication;

2. the frequency of angina attacks * severity (on a VAS scale 1-10) during the study period up to 2 weeks after discontinuation of the study medication.

Secondary outcome

Efficacy endpoint:

* Incidence and severity of angina complaints as obtained by the Seattle Angina Questionnaire during the study period up to 2 weeks after discontinuation of the study medication.

Safety endpoints:

* Detrimental changes in physical, laboratory or ECG parameters during the study period up to 2 weeks after discontinuation of the study medication.

* The occurrence of adverse events (i.e. hospitalization for anginal symptoms and/or myocardial infarction) during the study period up to 2 weeks after discontinuation of the study medication.

All possible side effects will be recorded during the study period up to 2

weeks after discontinuation of the study medication.

Study description

Background summary

A considerable proportion of patients with typical anginal complaints have no or only mildly obstructive coronary artery disease as diagnosed by coronary angiography (CAG). This disease is called non-obstructive artery disease (NOCAD). While women have a larger burden of many cardiovascular risk factors than men and have a similar or even higher prevalence of angina, fewer cases of obstructive coronary artery disease (OCAD) are observed in women. Women with NOCAD are at increased risk for cardiovascular events compared to women with comparable CAG outcome, but without symptoms and have a worse prognosis compared to men with NOCAD. These findings underscore clinically relevant sex differences in the pathophysiology of CAD. The pathophysiology of NOCAD remains unresolved, but includes vasospasm of the epicardial coronary arteries and impaired function of the microcirculation (microvascular dysfunction (MVD)). Prinzmetal et al. were the first to describe this variant form of angina pectoris which occurred at rest, was associated with ST-segment elevation on the surface ECG and was relieved by administration of nitroglycerin. Their hypothesis that coronary spasm was the cause of this syndrome was later confirmed using coronary angiography. Another cause of myocardial ischemia in patients without fixed obstructive coronary artery disease, is microvascular dysfunction. Coronary spasm and microvascular dysfunction comprise a spectrum of macrovascular and microvascular coronary disease characterized by endothelial dysfunction and abnormal vasodilatory reserve. This form of coronary artery disease is particularly prevalent among middle-aged women, and pharmacological treatment options are a large unmet clinical need in this patient population.
Endothelin (ET)-1 is a potent vasoconstrictor peptide produced by vascular endothelium which plays an important role in cardiovascular regulation. It is becoming increasingly clear that an imbalance between ET-1 and nitric oxide, the most prominent vasodilator, is a characteristic of endothelial dysfunction and is important in the progression of vascular disease. The production of ET-1 is stimulated in a variety of different cell types under the influence of cardiovascular risk factors and during the development of cardiovascular disease. ET-1 is present in human coronary atherosclerotic plaque. Among patients with coronary artery disease, circulating ET-1 levels were associated with the extent and severity of coronary stenoses. Based on these observations and the biological effects of ET-1, including vasoconstriction, pro-inflammatory actions, mitogenic and proliferative effects, stimulation of free radical formation and platelet activation, ET-1 has been implicated as an important factor in the development and progression of vascular dysfunction and

cardiovascular disease. ET-1 levels have been shown to be elevated among patients with vasospastic angina. In addition, ET-1 levels are associated with impaired coronary vasodilatory response. Among patients with coronary artery disease, intracoronary administration of the endothelin receptor antagonist (ERA) bosentan was shown to induce coronary vasodilatation. In addition, two case reports (including one from VU medical center) have documented the beneficial effects of bosentan in the treatment vasospastic angina.
Bosentan is an ERA with affinity for both the ETA- and ETB-receptor. Treating coronary vasospasm or microvascular dysfunction is conceptually even more interesting with selective ETA-receptor blockers that leave the ETB-receptor and its downstream denominator nitric oxide relatively unopposed. In vitro, the novel ERA macitentan is 100x more selective for ETA-receptor than ETB-receptor. We hypothesize that treatment with macitentan reduces the frequency and severity of anginal complaints among patients with clinically defined vasospastic angina.

Study objective

To determine whether VSA treatment with the novel ERA macitentan reduces the frequency and severity of anginal complaints among patients with clinically defined VSA. To determine side effects related to treatment with macitentan in patients with VSA.

Study design

Pilot proof-of-concept, multicenter, randomized, cross-over trial. The trial is double-blind placebo-controlled.

Intervention

The trial is cross-over placebo controlled. Patients will recieve placebo for 4 weeks and macitentan for 4 weeks while on background (standard) medication. The order of placebo or macitentan is left to randomisation.

Study burden and risks

Details of medical history, risk factors, Seattle Angina Questionnaire, WHO functional status will be recorded at baseline and follow-up. The number of office visits will be 6 times: at baseline (Visit1), at 4 weeks (Visit 2), at 8 weeks (Visit 3), at 10 weeks (visit 4), at 14 weeks (Visit 5), end at 16 weeks (Visit 6). Visits 1, 2, 4, 6 will take each about 30-45 minutes: medical history, risk factors, Seattle Angina Questionnaire, WHO functional status (15-30 minutes), electrocardiogram (5 minutes), laboratory analysis (10 minutes, 9ml). All investigations are part of regular medical care according to international guidelines and the current standardized protocol being used in the Academic Medical Center. Most commonly reported adverse reactions of

macitentan are nasopharyngitis, pharyngitis, influenza, nasal congestion, bronchitis, decrease in leucocytes and thrombocytes, headache, edema, fluid retention, urinary tract infection. The majority of these reactions are of mild to moderate intensity and are manageable with symptom relieve treatment. Less frequent side effects are liver function abnormalities, however, the study medication is given for 4 weeks only. The use of other (non)-cardiac medication by the study population during this study is allowed, and is recorded.

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 inclusion criteria:
* Male and female patients * 18 and <75 years old;

* Patients with a high frequency (>3 times per week) and duration of anginal complaints, presumed to be caused by VSA;
* Absence of significant obstructive coronary artery disease (defined as stenosis > 50% in an epicardial coronary artery) documented by invasive coronary angiography;
* Supporting evidence of myocardial ischemia or spasm, defined as either:
(a) documented dynamic ECG abnormalities during an episode of angina, or
(b) documented troponin rise during an episode of angina, or
(c) documented coronary spasm during invasive coronary angiography with or without acetylcholine provocation testing;
* Anginal complaints for at least 3 months despite optimal anti-anginal treatment, which is at the discretion of the treating cardiologist.
* Signed informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
* Patients who are pregnant or nursing and those who plan pregnancy in the period up to 1 months after the study;
* Women of childbearing potential not using contraception;
* Patients with a limited life expectancy less than one year;
* Patients unable to provide written informed consent, or are otherwise not suitable for inclusion according to the investigator.Contraindication for macitentan
* Patients with active liver disease or severe liver dysfunction with ASAT and/or ALAT >3x upper limit of normal (ULM);
* Patients with known renal impairment (GFR<60 ml/min);
* Patients with anemia;
* Use of potent CYP3A4 inducers (rifampicin, St. John's wort, carbamazepine, phenytoin) due to reduced efficacy of macitentan.
* Use of potent CYP3A4 inhibitors (itraconazole, ketoconazole, voriconazole, clarithromycin, ritonavir, saquinavir).
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Study design

Design

Study phase:	4
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):	14-11-2019
Enrollment:	30
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	22-01-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-07-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-11-2020
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	EUCTR2018-002623-42-NL
CCMO	NL66623.018.18