Biomarkers in the blood and skeletal muscle for the improvement of viral myocarditis diagnostics

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The primary objectives of this project are the identification of biomarkers in the blood and skeletal muscle that can improve the diagnosis of viral myocarditis and the expansion and improvement of the viral diagnostics in these patients. However,...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Myocardial disorders
Study type	Observational invasive

Summary

ID

NL-OMON47465

Source
ToetsingOnline

Brief title
Diagnostic biomarkers in viral myocarditis

Condition

- Myocardial disorders
- Viral infectious disorders

Synonym
viral infection of the heart, viral myocarditis

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Industrie,Sanquin Bloedbank

Intervention

Keyword: Biomarkers, Diagnosis, Viral myocarditis

Outcome measures

Primary outcome

De primary study parameters are the differences in biomarker profile (in heart, blood and skeletal muscle) between viral myocarditis (and the potential subgroups within this group) and acute myocardial infarction patients, as well as the determination of virus type and titer in relation to the pathophysiology of these (sub)groups.

Secondary outcome

N.A.

Study description

Background summary

Myocarditis (inflammation of the heart) is an inflammatory disease of the heart that can lead to cardiomyocyte (heart muscle cell) death, the formation of connective tissue and eventually to severe heart function loss, i.e. heart failure. The most common cause of infectious myocarditis is a viral infection. At present approximately 20 different viruses have been described that can cause viral myocarditis. The pathophysiology of viral myocarditis is characterized by either direct virus-related cardiac damage (the virus infects cardiomyocytes and kills them) or cardiac damage because the reaction of the immune system against the virus also attacks the heart (auto-immune damage). The clinical presentation of viral myocarditis patients is very diverse and varies from mild shortness of breath and mild flu-like symptoms to chest pain, specific aberrations on the ECG, acute heart failure and sometimes sudden death.
This large variety in clinical presentation makes diagnosing viral myocarditis difficult. There are currently no specific serological markers available for viral myocarditis. In addition to the anamnesis, the ECG and/or echocardiography can be used to rule out other causes of heart failure such as, myocardial infarction, heart valve failure or congenital heart failure.

However, viral myocarditis often mimics myocardial infarction and patients can present with additional infarct-like symptoms such as ST-segment elevation on ECG, wall motion abnormalities, and elevated circulating cardiac troponin levels. In patients with infarct-like complaints coronary angiography (CAG) is most often used to distinguish between viral myocarditis and myocardial infarction, whereby epicardial coronary artery occlusion confirms myocardial infarction. However, in approximately 4-9% of patients with infarct-like complaints no coronary artery occlusion is found with CAG. In the majority of these patients myocardial infarction is still the cause of the complaints. This is called myocardial infarction with non-occluded coronary arteries (MINOCA). It is estimated that in about one-third of these patients, acute myocarditis is the underlying cause. Therefore there is a clinical need to distinguish between acute (viral) myocarditis and myocardial infarction.
However, to confirm the diagnosis viral myocarditis, histological examination of heart biopsies (endomyocardial biopsies; EMB) is necessary at present. Even then the usefulness of the EMB is limited. Viral myocarditis namely induces a very fragmented inflammation in the heart. The chance therefore, that the anomaly is not visible in the EMB is substantial. Therefore it is necessary to take multiple EMB (to a maximum of 5). Even then there is a chance of false-negative EMB. The collection of EMB is no sinecure for the patient. Such an invasive method is always accompanied by a chance of complications. In addition, since the sampling area for EMB in the heart is small, taking EMB at multiple time-points is generally not done. This makes monitoring disease progression or therapy effects difficult. Therefore, for a better clinical management of viral myocarditis, extension of the diagnostic repertoire is essential: 1) for a more accurate and less demanding diagnosis, 2) to guide application of therapy and to monitor its effects.
We have recently found increased infiltration of lymphocytes in quadriceps skeletal muscle, obtained at autopsy, in patients with viral myocarditis and in a mouse model of viral myocarditis. This suggests that skeletal muscle may be a *peripheral mirror* that reflects inflammation in the heart in viral myocarditis. Also, a lot of viruses that infect the heart can also infect skeletal muscle cells, which suggest that analysis of skeletal muscle may also reveal viral infection in the heart.
Taken together, these results suggest that skeletal muscle reflects the pathology of the heart in viral myocarditis and that skeletal muscle biopsies are a selective diagnostic tool for viral myocarditis.
In addition, at present the viral diagnostics in patients with viral myocarditis is limited. Whereas over 20 different viruses have been known to cause myocarditis, currently viral myocarditis patients in general are tested for only a few virus types. Presently, knowledge regarding the putative influence(s) of virus type on the pathophysiology of viral myocarditis is lacking. For this, improvement of the viral diagnostics in viral myocarditis is a clinical demand.

Study objective

The primary objectives of this project are the identification of biomarkers in the blood and skeletal muscle that can improve the diagnosis of viral myocarditis and the expansion and improvement of the viral diagnostics in these patients. However, the analysis of the skeletal muscle biopsy of the first 20 patients revealed that the expected increase in intramuscular inflammation was not observed. Therefore, we will as of 27-2-2019 stop with obtaining skeletal muscle biopsy from the patients until further notice.

Study design

The study design is as follows:
Patient selection: Patients at the Cardiology department at the VUmc that present with suspected viral myocarditis (show flu-like symptoms combined with acute loss of heart function) and comply to the ESC/ACC position statement for EMB will be asked to participate in this study (viral myocarditis group).
Because we require distinguishing biomarkers, we want to obtain blood from patients that developed cardiac inflammation through another cause also, i.e. patients with acute myocardial infarction (AMI). In AMI cardiac damage and cardiac inflammation are also induced, although not as a result of viral infection but as a result of impaired perfusion of the heart. Therefore, patients that present at the Cardiology department with AMI will be asked to participate in this study also (AMI group). These are patients with CAG-proven epicardial coronary occlusion reflecting AMI.
Because viral myocarditis can mimic AMI, we will also include patients who present with infarct-like complaints, but show non-occluded epicardial coronary arteries in CAG. Based on subsequent MRI analyses, these patients will later be subdivided into the AMI group (in case of MINOCA) or the viral myocarditis group.

Study-related proceedings: From all patients that are enrolled in this study three extra tubes of blood will be drawn. This will be done within 0-2 days after admission to the hospital. We plan to let this coincide (as much as possible) with a time point when blood is drawn for diagnostic purposes. From patients who are scheduled for CAG we aim to take the blood shortly after the CAG procedure. Participants in the viral myocarditis group are also asked to collect a faeces sample.
After approximately 6 month follow-up, from participants in the viral myocarditis group again three extra tubes of blood will be drawn.

One blood sample will be collected in a coagulation tube to obtain serum. Two blood samples will be collected in EDTA coated tubes to isolate plasma and peripheral blood mononuclear cells (PBMCs). Serum and plasma will be aliquoted and stored at -80*C. Also the PBMCs will be stored in liquid nitrogen.
Following consent from the patient, one third of the isolated PBMCs will be used for direct monocyte isolation to study their characteristics post AMI.
Faeces samples will be collected in stool containers and stored at -20*C. One

skeletal muscle biopsy will be frozen immediately (-80*C) for viral PCR and one will be fixed immediately in formalin for (immuno)histochemical biomarker research. All samples will receive an experimental code before storage. Left over material from EMB that were taken from these patients on medical indication for diagnostic purposes will be used for diagnostic biomarker validation and viral diagnosis. In theory this will create two groups within the viral myocarditis group: 1) patients with viral myocarditis confirmed by analysis of EMB, 2) patients with symptoms of viral myocarditis but with negative EMB (these patients may have viral myocarditis but a false-negative biopsy analysis or despite the symptoms they may not have viral myocarditis.

Promising biomarkers, identified in different mouse models of myocarditis that we are now studying will be analyzed in patients with (suspected or confirmed) viral myocarditis. In addition our findings from the quadriceps muscle and heart tissue obtained at autopsy of viral myocarditis patients will be analyzed in the living patient. In mice we induce different manifestations of viral myocarditis i.e. acute and chronic (auto-immune) myocarditis. We will use Coxsackievirus B3 and Parvo B19 virus; two viruses that most frequently appear to be responsible for inducing viral myocarditis in humans. In these models we will analyze the blood and quadriceps skeletal muscle for diagnostic biomarkers that are able to discern viral myocarditis in different stages of the disease. Biomarkers in the blood/skeletal muscle will be compared with heart function measurements, histological anomalies in the heart, viral titers and the incidence and severity of auto-immunity. Promising biomarkers, identified in the animal models will be analyzed in the blood, quadriceps skeletal muscle biopsies and EMB of patients in the viral myocarditis group. Hereby, biomarkers in the blood/skeletal muscle will be compared with heart function measurements, ECG, (immuno)histological analysis of EBM and to data obtained from routine diagnostic blood measurements (hemoglobin, blood cell counts, electrolytes, blood gasses, cardiac troponins, CK-MB, CRP). Furthermore, these biomarkers will be compared among the two (possible) different groups within the viral myocarditis group and the AMI group.

As for the viral diagnostics we will determine virus type and titer in the blood, quadriceps skeletal muscle biopsies, faeces and the EBM. In the heart and skeletal muscle biopsies we will analyze for the presence and titer of a wide range of cardiotropic viruses using PCR. Also here, the viral data obtained will be compared to heart function measurements, ECG, (immuno)histological analysis of EBM and to data obtained from routine diagnostic blood measurements. Furthermore, this data regarding virus type/titer will be compared among the different patient groups and to the different analyzed biomarkers.

Promising biomarkers, identified in the viral myocarditis patients will then be tested in the blood of patients with acute myocardial infarction also. In this way we hope to identify biomarkers that we can use to diagnose viral myocarditis with high incidence and to improve the viral diagnostics in these

patients.

Study burden and risks

Burden and risk for patients are minimal: only taking blood.
With taking blood, local phlebitis and thrombophlebitis are possible adverse events, but they are very rare. With taking skeletal muscle biopsies, local muscle pain, haematoma and a small chance of bleeding, infection and a local temporary numb feeling are possible side-effects. Patients that develop any of these side-effects will be given adequate treatment.

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 the viral myocarditis group patients will be included when they are mentally competent and when they present with suspected viral myocarditis (show flu-like symptoms combined with acute loss of heart function) and comply to the ESC/ACC position statement for endomyocardial biopsy. In the AMI group (controls) patients will be included when they are mentally competent and present with an acute myocardial infarction. Because viral myocarditis can mimic AMI, we will also include patients who present with infarct-like complaints, but show non-occluded epicardial coronary arteries with coronary angiography. Based on subsequent MRI analyses, these patients will later be subdivided into the AMI group (in case of myocardial infarction with non-occluded coronary arteries (MINOCA)) or the viral myocarditis group.

Exclusion criteria

In the viral myocarditis group the main exclusion criteria are: acute myocardial infarction, prednisolon use or fear of MRI. In the AMI group the main exclusion criteria are to suffer from a viral infection (including HIV). In both groups prednisolon use and mental incompetence is an exclusion cirteria.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-12-2013
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO Date:	07-06-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-08-2020
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
CCMO	NL39662.029.13