Evaluation of GeranylGeranylAcetone in heart failure with preserved ejection fraction

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Primary objectivesTo study whether Geranyl-Geranyl Acetone (GGA) reduces left ventricular (LV) diastolic dysfunction in patients with HFpEF compared to placebo (and to assess/confirm its effectiveness and safety in patients with HFpEF)Secondary…

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

Summary

ID

NL-OMON53498

Source
ToetsingOnline

Brief title
GLADIATOR-HFpEF

Condition

- Myocardial disorders
- Renal disorders (excl nephropathies)

Synonym
Diastolic heart failure, heart failure with a preserved ejection fraction

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Beurs van de Nederlands Hartstichting

Intervention

Keyword: Diastolic function, geranylgeranylacetone, Heat shock proteins, HFpEF

Outcome measures

Primary outcome

7.9.1 Main study parameter/endpoint

Co-primary objectives:

1. Does GGA-treatment improve LV diastolic function in HFpEF, measured by echocardiography derived filling pressures (E/e*)?

2. Does GGA-treatment improve endothelial function, measured by EndoPAT®-derived reactive hyperemia index (RHI)?

Secondary outcome

Secondary objective(s):

Additional echocardiographic measures:

• Change in echocardiographically determined left atrial (LA) indexed volumes: (LAVImax, LAVImin, LAVIpre-A) and function (LA global strain and LA emptying fractions (reservoir, conduit and booster pump).

• Change in echocardiographically determined LV global longitudinal strain.

• Change in echocardiographically determined LV myocardial relaxation (e*).

• Change in echocardiographically determined LV distensibility, measured by E/e* and LV end-diastolic volume.

• Change in echocardiographically determined right ventricular systolic function (TAPSE, RV S*).Change in echocardiographically determined pulmonary artery pressure.

Patient reported outcomes and exercise capacity:

• Change in NYHA class between baseline and 13 weeks.

• Change in the total symptom score of the KCCQ quality of life assessment between baseline and 13 weeks.

• Change in 6-minute walking distance between baseline and 13 weeks.

Endothelial function assessment

• Change in flow-mediated vasodilatation in the finger, determined by applanation tonometry (EndoPAT®)

• Change in endothelium-dependent and -independent vasodilation in skin, determined by iontophoresis of acetylcholine (miochol) and sodium nitroprusside and measured using laser-Doppler (20)

• Microvascular and inflammatory biomarkers: Nitrosated hemoglobin (Hb(NO)4), nitrate/nitrite, H2S, CRP, endothelin-1

Kidney endpoints:

• Change in iohexol-measured GFR at baseline and 13 weeks of treatment

• Change in para-aminohippuric acid-measured effective renal plasma flow (ERPF)

• Change in intrakidney hemodynamic function including renal vascular resistance (RVR), glomerular pressure (Pglo), afferent vascular resistance (Ra) and efferent vascular resistance (Re).

• Changes in urinary albumin-creatinine ratio (UACR)

• Change in serum and urinary neutrophil gelatinase associated lipocalin (NGAL)

• Change in serum and urinary kidney injury molecule (KIM)-1

Study description

Background summary

Heart failure with a preserved ejection fraction (HFpEF), characterized by stiffening of the left ventricle and impaired filling, comprises the majority of heart failure cases and accounts for ±2% of the total EU healthcare budget (±30 billion Euro*s per year). In contrast to heart failure with a reduced ejection fraction (HFrEF), treatment options are limited. Sacubitril/valsartan has shown some benefit in subgroups of HFpEF patients,1 and empagliflozin has been shown in 2021 to reduce hospitalization rates in HFpEF.2 As no other treatment options exist, there is a major unmet clinical and societal need for safe, effective, and affordable treatments for HFpEF.
Early in the pathogenesis of HFpEF, compromised endothelial synthesis of nitric oxide (NO) and decreased levels of small heat shock proteins (HSPs), such as HSP27 and αB-Crystallin, cause stiffening of the cardiomyocytes.3-5 αB-Crystallin and HSP27 determine the conformation of the cytoskeletal protein titin and control muscle stiffness, and deficiency of αB-Crystallin greatly increases muscle stiffness.6 It has been proposed that αB-Crystallin and HSP27 determine the conformation of the flexible N2b part of titin, which is phosphorylated by cGMP-activated protein kinase (PKG). PKG activity in cardiomyocytes is controlled by the microvascular endothelium through NO and soluble guanylate cyclase (sGC).7 Microvascular dysfunction in the myocardium, particularly decreased synthesis of NO by capillary endothelium, is a second determinant of cardiomyocyte stiffness.
The prenylating agent geranylgeranylacetone (GGA), chemical name teprenone and currently sold outside of the EU by Eisai Co. Ltd. as part of the anti-ulcer agent Selbelle (before december 2020: Selbex), has been shown to enhance cardiomyocyte HSP expression as well as microvascular NO activity, both in animal models and in human studies. In RECONNECT, we demonstrated that 4 weeks of oral GGA administration decreases cardiomyocyte stiffness in hearts of ZSF1 rats by increasing the expression of HSP27 and αB-Crystallin (Waddingham, Handoko, Eringa, Paulus et al., manuscript in revision). The enhancing effect of oral GGA treatment on myofilament HSP27 abundance was replicated in patients undergoing bypass surgery.8 Furthermore, GGA was shown to enhance endothelial NO activity through HSP90 expression in healthy humans.9 In the context of kidney disease, GGA was shown to induce renal HSP70, ameliorate tubular damage and prevent deterioration of kidney function in acute and chronic models of kidney damage.10-12 These beneficial effects of GGA have been attributed to improvement of endothelial function, leading to favorable changes in kidney blood flow. While GGA has beneficial effects in man on key elements of the pathogenesis of HFpEF, i.e. increasing HSP activity and improving endothelial

function, while being well tolerated in patients, and exerts beneficial effects on myocardial stiffening in a model of HFpEF, proof of efficacy of GGA on signs and symptoms of HFpEF in man is lacking.9

Since 1984, GGA has been used as an over-the-counter anti-ulcer drug in Asian countries, with minor side effects at doses up to 1200 mg/day.13 In fact, this marketed effect of GGA is mediated by NO, and this GGA-induced increase in NO activity can now be tested for its therapeutic potential in HFpEF.14 In 2021, the sole manufacturer of pure GGA for human use is the Amsterdam UMC. In addition, the Stichting VUMC is holder of the patent for GGA as a treatment for diastolic dysfunction. We aim to use this opportunity, our combined expertise and the proven effects of GGA in man, for a phase 2 trial on the efficacy of GGA in HFpEF.
In the CVON-RECONNECT project on HFpEF funded by the Netherlands heart foundation, we provided proof of concept that cardiac capillary endothelium controls cardiomyocyte function through transfer of NO and that this specific endothelial function is impaired in human chronic kidney disease.4,15 Previous studies have shown that in HFpEF microvascular NO synthesis is reduced and that microvascular dysfunction predicts severity.5,16 Taken together, HSP expression and microvascular NO synthesis control cardiomyocyte stiffness in health and in human HFpEF and chronic kidney disease.
In the proposed phase 2 trial, we expect to obtain proof of concept for a beneficial effect of GGA on HFpEF. In HFpEF patients we will evaluate effects of GGA on signs and symptoms of HFpEF including echographic parameters of diastolic function, exercise tolerance, microvascular endothelial function and kidney function.

Study objective

Primary objectives
To study whether Geranyl-Geranyl Acetone (GGA) reduces left ventricular (LV) diastolic dysfunction in patients with HFpEF compared to placebo (and to assess/confirm its effectiveness and safety in patients with HFpEF)

Secondary objectives
• To assess whether GGA improves endothelial function in patients with HFpEF compared to placebo.
• To assess whether GGA improves renal (hemodynamic) function in patients with HFpEF compared to placebo
• To assess whether GGA improves self-reported quality of life and exercise tolerance in patients with HFpEF compared to placebo

Exploratory objectives
• To assess whether GGA changes biomarker profiles in patients with HFpEF compared to placebo

Study design

The design of the study will be a crossover multi-centre, double-blind, randomized control trial. The reversibility of the effect of GGA on HSP expression in human subjects enables a crossover study and the washout period for our groups is comparable to similar studies in patients with HFpEF.9,17,18
A schematic overview of the study is provided below (Figure 1).
After eligibility is checked and informed consent is obtained, baseline measurements are performed (Table 1). We will take a patient history, general measurements like weight, body mass index (BMI) and vital signs and perform a physical examination on baseline. Furthermore, we will ask patients to fill in questionnaires regarding their quality of life (QoL).
EndoPAT-measurements, kidney function measurements and laboratory values will be obtained after both treatment arms. The measurement after the placebo arms will provide us with baseline information regarding EndoPAT and kidney function.

Intervention

The participants in the study will be treated with the prenylating agent GGA 300mg/day.

Study burden and risks

In the GLADIATOR-HFpEF trial we study GGA (*Teprenone*, *Selbex*) which is an over-the-counter anti-ulcer drug authorized in Japan. GGA has not been proven to have functionality in patients with HFpEF, but GGA has been shown to enhance the expression of HSP*s in the human heart and endothelial cells, which determine cardiomyocyte stiffness and the synthesis of nitric oxide (NO).28
Literature and data from a phase I trial from the RECONNECT-consortium shows that 4 weeks of GGA treatment reverses cardiomyocyte stiffening and halts the diastolic dysfunction in ZSF-1 rats, which is a model for patients with HFpEF, (Waddingham, Eringa et al., manuscript under review), rats and patients undergoing coronary artery bypass graft (CABG).8,29
Side-effects of GGA have been thoroughly documented and have a low incidence (<0.5%). The dosage in which we aim to use GGA (300mg/day) is four-fold lower compared to the dosage that has been safely given to patients with gastritis and gastric ulcers.23
As vascular endothelium is present in all organs and tissues and HSPs are a ubiquitous mechanism for cellular protection from stressors, the mechanism induced by GGA is not selective to one tissue or organ. Despite this, only minor adverse side effects of GGA have been reported (see above). In contrast and consistent with pleiotropic effects of GGA-induced HSP expression, beneficial and protective effects of GGA have been reported in the brain, the lungs, and kidneys.
The most common side effects for GGA are elevated plasma concentrations

of liver enzymes (0.2%). Other side-effects have a lower incidence (<0.1%) and can be found in the supplementary *Selbex Bijsluiter*. To cover possible side-effects, we will perform safety lab tests for elevated liver enzymes after each treatment period of 13 weeks. Furthermore, we will take a patient history while patients are on-treatment at every follow-up visit to check for other side-effects.
The study population has been selected according to the power-calculation described in 4.4. The reversibility of the effect of GGA on HSP expression in human subjects enables a crossover study, which reduces the amount of people subjected to treatment. Patients will be their own controls. We will only include patients with diagnosed HFpEF who are in a stable condition and exclude women who are pregnant or have a wish for pregnancy. Patients will stay on their own heart failure medication as there are no reports of interacting medication with GGA. In case of hypersensitivity to GGA or any SAE that can be directly attributed to the use of GGA we will stop medication immediately and unblind the subject and inform the treating physician and PI/sponsor.
Since this study has a relatively low treatment time (2x13 weeks), a low number of included patients (40) and a low risk of side-effects and SAE*s as described above we will not institute a DSMB. We will have a monitoring and quality assurance plan to ensure the safety of the participants and the quality of the data.
We admit that the study protocol may be intense due to multiple tests that are performed, considering that these patients are physically compromised. However, we would like to stress out that each test is easy to perform and very low risk. All tests will be planned at one single day, to minimize the burden for the study participant. Participants will be compensated for costs of parking and a lunch is provided for them and their caregiver if relevant. Also, the total number of physical visits is 4-5 and the complete protocol will be finished within half a year. On the other hand, treatment options in HFpEF are very limited, and GGA treatment may be beneficial to the study participant at relative low risk, which cannot be prescribed otherwise. All considering, we believe that disadvantages and benefits of the study are in balance.

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

To be eligible to participate in this study, a subject must meet all of the following criteria:
1. Age>= 50 years
2. Patients with a diagnosis of symptomatic chronic heart failure (New York Heart Association class II or III) AND preserved systolic LV function (LV ejection fraction or LVEF >= 50%) documented within the last 6 months AND evidence of diastolic LV dysfunction with at least 1 out of the following 4 criteria:
- HFA-PEFF score >=5
- H2FPEF score >=6
- HFpEF according to the 2021 ESC HF Guidelines (NT-proBNP>125 pg/ml AND either LV mass indexed or LVMI >95 g/m2 for women and >115 g/m2 for men OR left atrial volume indexed or LAVI >34 ml/m2 OR mean e; septal/lateral < 9 cm/s) OR E/e* >13) OR TR velocity at rest > 2.8 m/s.
- Pulmonary capillary wedge pressure (PCWP) >15 mmHg and/or >25 mmHg during exercise

Exclusion criteria

1. Current acute decompensated heart failure, requiring hospitalization or augmented therapy with intravenous diuretics, vasodilators, and/or inotropic drugs
2. Acute coronary syndrome, transient ischemic attack/cerebrovascular accident,

major surgery within the previous 3 months
3. Hemoglobin <9 g/dl at screening
4. LVEF <40% measured at any time point in the history of the patient
5. History of mitral valve repair or replacement
6. Presence of significant valvular disease defined as mitral valve regurgitation defined as grade >= 3+ MR; tricuspid valve regurgitation defined as grade >= 2+ TR; aortic valve disease defined as >= 2+ AR or > moderate AS
7. Acute myocarditis within 3 months prior to randomization
8. Infiltrative cardiomyopathy
9. Genetic cardiomyopathy
10. Severe pulmonary disease requiring home oxygen or chronic oral steroid therapy
11. Precapillary pulmonary hypertension
12. BMI >40 kg/m2
13. Estimated glomerular filtration rate (GFR) <20 ml/min or >90 ml/min
14. History of solid organ transplantation including kidney transplantation
15. Atrial fibrillation or atrial flutter with resting ventricular rate >110 bpm
16. Not able to undergo the complete study protocol
17. Doubt about compliance
18. Pre-menopausal women who are nursing, pregnant, or of child-bearing potential and not practicing an acceptable method of birth control
19. Chronic absorption problems
20. Proven allergy for lactose products or cow-milk.
21. Proven allergy for Iodide-containing contrast, Iohexol or PAH.
22. Any documented or suspected malignancy or history of malignancy within 1 year prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of the cervix
23. Currently enrolled in another investigational device or drug trial
24. Estimated life expectancy <1 year

Study design

Design

Study phase:	2
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):	02-03-2023
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GeranylGeranylAcetone
Generic name:	Teprenone

Ethics review

Approved WMO Date:	17-02-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2023
Application type:	First submission
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	EUCTR2022-000655-36-NL
ClinicalTrials.gov	NCT05672134
CCMO	NL80684.018.23