A randomised, controlled, observer-blinded phase III clinical trial to compare the effect of intravenous ferric carboxymaltose to placebo on exercise capacity and cardiac function in patients with chronic heart failure and iron deficiency - EFfect of Ferric Carboxymaltose on exercIse CApacity and Cardiac function in patients with iron deficiencY and chronic Heart Failure

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Ethical review	Approved WMO
Status	Pending
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON32525

Source
ToetsingOnline

Brief title
EFFICACY-HF

Condition

- Heart failures

Synonym
Heart failure, iron deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Vifor Pharma - Vifor International AG
Source(s) of monetary or material Support: Firma Vifor Pharma- Vifor International AG

Intervention

Keyword: Heart failure, Iron deficiency

Outcome measures

Primary outcome

1. Evolution from baseline of the distance covered in the six-minute walk tests

performed at 4, 12 and 24 weeks after the start of study treatment.

2. Evolution from baseline in New York Heart Association (NYHA) functional

class assessed at weeks 4, 12 and 24 weeks after the start of study treatment

Secondary outcome

1. Evolution from baseline of cardiac function parameters as assessed by 2D

Echo/Doppler cardiography at 4, 12 and 24 weeks.

2. Self-reported patient global assessment of treatment at 4, 12 and 24 weeks.

3. Quality of life as assessed by the European Quality of Life * 5 Dimensions

and Kansas City Cardiomyopathy Questionnaire questionnaires at 4, 12 and 24

weeks

Study description

Background summary

HF (heart failure) results in poor life expectancy, impaired quality of life, repeated hospitalisations and is a considerable economic burden, accounting for 1*2% of health care expenditure in European countries. Estimates of the prevalence of anaemia and/or iron deficiency in patients with chronic CHF vary from 4% to 61% (median 18%). In CHF patients, even mild anaemia is associated with worsening symptoms, increa¬sed NYHA class and impaired functional capacity, quality of life and survival. Recent data show that CHF patients with persistent anaemia have a 2.43-fold higher long-term mortality rate than those whose anaemia resolved after 6 months of follow-up. Anaemia in patients with CHF is often related to iron deficiency and has been shown to be remediable with elemental iron, with or without EPO (erythropoietin). Nonetheless, the pathophysiologic mechanism involved is not completely under¬stood. Possible causes that have been suggested are: chronic inflammation associ-ated with CHF, iron deficiency caused by prophylactic intake of aspirin or other anti-thrombotic agents, down-regulation of EPO by ACE (angiotensin converting enzyme) inhibitors, presence of chronic renal failure, bone marrow depression related to the presence of cytokines such as tumour necrosis factor, and interference with iron release and utilisation.Sandek et al. have described significant morphological and functional alterations of the intestine in CHF patients. It has been hypothesised that, because of the inflammatory changes caused by CHF, the absorption of iron from the intestine is impaired. The adverse effects of anaemia and iron deficiency on cardiac function are multiple. In anaemic CHF patients, hemodynamic mechanisms that increase cardiac output and compensate for hypoxia are activated. These compensatory mechanisms (i.e. activa¬tion of the renin angiotensin aldosterone system and tachycardia) are well establish¬ed risk factors in CHF for induction of progressive LV (left-ventricular) hypertrophy and dilation. In comparison to non-anaemic CHF patients, this results in, amongst others, increased mortality, a reduction in LVEF (LV ejection fraction), impaired cardiac function, exercise capacity and quality of life, a progressive reduction in renal function, an increase in of the need for hospitalisations and the need for high-dose diuretic use and signs of malnutrition. Current guidelines for the diagnosis and treatment of chronic CHF* do not contain any specific recommendations for the evaluation or treatment of anaemia and/or iron deficiency in patients with CHF. Corroboration earlier observations,* Toblli et al. showed that 6 months i.v. iron treatment of CHF patients who at baseline were in NYHA class III or IV, and who had a baseline LVEF <35%, improved quality of life, 6-minute walk test distance and LVEF, and reduced the number of hospitalisations compared to controls. NTproBNP (amino-terminal fragment of the *-type natriuretic peptide molecule) and CRP (C-reactive protein) levels also decreased. A similar study showed a significant improvement of peak VO2 (oxygen consumption). Mancini et al.*

compared EPO plus oral ferrous gluconate and folate to placebo EPO only, and observed significant improvements of Hb, peak VO2 and exercise capacity. A recently reported randomised double-blind trial compared oral iron plus EPO versus oral iron alone, and showed that, compared to oral iron alone, oral iron plus EPO increased Hb from a mean of 10.4 to 12.4 g/dl. To date, effects of iron therapy on LV function have been studied only in small clinical trials. It is therefore opportune to investigate the effect of iron therapy on remodelling to corroborate earlier findings and to relate remodelling to changes in symptoms and exercise capacity.

Study objective

Secondary objectives are to evaluate the effect of intravenous FCM compared to pla¬cebo on:
1. Evolution from baseline of cardiac function parameters as assessed by 2D Echo/Doppler cardiography 4, 12 and 24 weeks after start of study treatment.
2. Self-reported patient global assessment (PGA) of treatment at 4, 12 and 24 weeks after start of study treatment.
3. Health related quality of life (HRQoL) as assessed by the EQ-5D (European quality of life * 5 dimensions) and KCCQ (Kansas City Cardiomyopathy Questionnaire) self-administered questionnaires 4, 12 and 24 weeks after start of study treatment.
Objectives for safety are to evaluate the effect of intravenous FCM compared to pla¬cebo on:
1. Evolution of estimated glomerular filtration rate, vital signs, electrocardiographic findings and laboratory test results (haematology, clinical chemistry, iron status, urinalysis, neurohormone and inflammatory markers).
2. Number and duration of hospitalisations (total and for cardiovascular conditions).
3. Total and cardiovascular mortality.
4. (Serious) adverse events

Evaluation of health economics
At the 4, 12 and 24 week planned out-patient visits (POVs), the patient*s health care resource utilisation since the previous visit when the patient was seen or contacted will be recorded to allow for the calculation of direct, indirect and total costs for at least one country from two perspectives (payer*s and societal perspective). FCM and placebo treatment arms will be compared to assess the cost-effectiveness of FCM using relevant parameters

Study design

EFFICACY-HF is a randomised, controlled, observer-blinded multi-centre clinical trial with two parallel groups of equal size.

Intervention

Active: FCM (ferric carboxymaltose) solution containing 50 mg iron/mL given as an i.v. bolus of 2 or 4 mL.
Placebo: 0.9% weight/volume NaCl (normal saline).

Study burden and risks

The parenteral iron preparation (Ferinject®) that will be used in this trial has been approved for the treatment of anaemia in most European countries. The approval was without any stipulation with regard to the extent of any elevation of haemoglobin. The only known potential risks of participation in this trial are the occurrence of elevated iron status parameters (including haemoglobin) or hypersensitivity reactions in patients assigned FCM (ferric carboxymaltose), and severe anaemia in patients assigned placebo. The IgE mediated anaphylactic reactions that have been associated with i.v. iron dextran preparations cannot occur in patients treated with FCM. Non-IgE mediated anaphylactoid reactions have thus far not been reported. Drug related hypersensitivity reactions to FCM (rash, urticaria, hyperthermia) are infrequent (less than 1% of patients) and transitory without sequel.*

To limit the occurrence of elevated iron status parameters (including haemoglobin) and of severe anaemia in this trial, the following precautions are taken:
(a) The total iron repletion dose to be administered to each patient will be calculated using the widely-accepted and validated Ganzoni formula.*
(b) In patients assigned FCM, i.v. iron (200mg or 100 mg) will be administered as FCM once weekly during the correction phase until the total iron repletion dose has been administered. Blood tests to determine the patient*s iron status will be performed every second week in conjunction with weekly administrations of study treatment.
(c) In patients assigned FCM, 200 mg i.v. iron will be administered as FCM once monthly during the maintenance phase. Blood tests to determine the patient*s iron status will be performed monthly in conjunction with monthly administra-tions of study treatment.
(d) If laboratory test results suggest elevated iron status parameters in a patient assigned FCM, study treatment will be continued with pla-cebo.
(e) If severe anaemia develops, study treatment will be discontinued

Although there are currently no guidelines for the treatment of anaemia in patients with chronic CHF,* data from small studies have shown that patients with chronic CHF and anaemia receiving i.v. iron therapy may benefit from an improved quality of life and cardiac function. In patients with chronic CHF and iron deficiency, treatment with oral iron alone was not shown to be effective. Oral iron has gastro-intestinal side effects and limited absorption, in

particular when the iron transport inhibitor hepcidin is upregulated. Erythropoeisis stimulating proteins are at present still under clinical investigation in patients with anaemia and CHF. Their safety has been a matter of concern.*

The current assessment of the risk/benefit ratio of the treatment modality concerned suggests that participation can be considered in the patient*s interest. Importantly in this regard, this trial does not require any unusual investigational procedures that could present a risk independent of study treatment

Contacts

Public
Vifor Pharma - Vifor International AG

Rechenstrasse 37
9001 St Gallen
Zwitserland
Scientific
Vifor Pharma - Vifor International AG

Rechenstrasse 37
9001 St Gallen
Zwitserland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Heart failure patients with EF 40% or lower, NYHA class II or III; Patients have been treated (unplanned hospitalisation or acute care admission) for congestive heart failure within last 24 months; Patients are treated for at least 4 weeks with standard heart failure medication, and 2 weeks without change in medication; Hemoglobin between 5,9 mmol/L and 8,4 mmol/L. Ferritin < 100 microgram/L, or ferritin < 300 microgram/L and transferrin saturation < 20%.

Exclusion criteria

Anemia by other causes than iron deficiency, Unstable angina pectoris.
Walking distance limited by intermittent claudication.
Significant valvular disease or outflow tract obstruction.
Immunosuppressive therapy or renal dialysis.
Recent (within 12 weeks) myocardial infarction, percutaneous coronary intervention or CABG.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2008
Enrollment:	60
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ferinject
Generic name:	Ferric Carboxymaltose
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-09-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2009
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	EUCTR2008-001503-26-NL
CCMO	NL24876.018.08