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Interleukin-1 Blockade in Recently Decompensated Systolic Heart Failure: Study Design of the Recently Decompensated Heart Failure Anakinra Response Trial (RED-HART)

Benjamin W. Van Tassell[1#*], Juan Valle Raleigh[1#], Claudia Oddi[1], Salvatore Carbone[1], Justin Canada[1], Nayef A. Abouzaki[1], Giuseppe Biondi-Zoccai[2], Ross Arena[3] and Antonio Abbate[1]

[1]VCU Pauley Heart Center and Department of Pharmacotherapy and Outcome Studies, Virginia Commonwealth University, Richmond, VA, US

[2]Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University, Latina, Italy

[3]Department of Physical Therapy, University of Illinois, Chicago, IL, US

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***Corresponding author:** Antonio Abbate, Roberts Professor of Cardiology, Virginia Commonwealth University, Pauley Heart Center, 1200 E. Broad street, Box 980204, Richmond, VA, 23298, USA, E-mail: aabbate@vcu.edu*

Abstract

Heart Failure (HF) is a clinical syndrome characterized by dyspnea, fatigue, and poor exercise capacity due to impaired cardiac function. The incidence of HF is increasing and represents the leading cause of hospitalization in the United States among patients > 65 years of age. Neurohormonal blockade has proven to reduce morbidity and mortality; however the persistent toll of HF demonstrates the urgent need to continue to develop novel drugs that target other pathophysiological paradigms. The presence of inflammation in cardiovascular disease has been well-established and interleukin-1 (IL-1), the prototypical proinflammatory agent, has been shown in preclinical animal models to induce cardiac dysfunction. The current study will investigate the role of IL-1 as an inflammatory mediator of HF progression and investigate whether IL-1 blockade with anakinra, recombinant human IL-1 receptor antagonist, improves aerobic exercise performance in patients with recently decompensated systolic HF. This study will be composed of 3 treatment arms (20 patients each): 1) anakinra 100mg daily for 12 weeks; 2) anakinra 100mg daily for 2 weeks followed by placebo for 10 weeks; or 3) placebo for 12 weeks. All patients will be followed for at least 24 weeks. The co-primary endpoints will be placebo-corrected interval changes in peak oxygen consumption (VO2) and ventilatory efficiency (VE/VCO2 slope) measured by Cardiopulmonary Exercise Testing (CPX) after 2 weeks of anakinra treatment. Secondary endpoints will include interval changes in 1) CPX variables at 4, 12 and 24 weeks; 2) echocardiographic measures of cardiac dimension/function; 3) quality of life assessments; 4) inflammatory biomarkers; and 5) clinical outcome including days alive outside of the hospital and survival free of re-hospitalization for HF. The RED-HART study will be the first study to address the potential benefits of IL-1 blockade on aerobic exercise performance in patients with recently decompensated HF.

Keywords: Heart failure; Inflammation; Interleukin 1; Anakinra

Background

Heart failure (HF) is a complex clinical syndrome characterized by fatigue, dyspnea, and exercise intolerance due to impaired cardiac function and associated pathophysiologic consequences [1]. HF represents a common final pathway of both ischemic and non-ischemic cardiomyopathy, with an annual incidence of more than six hundred thousand cases, prevalence of more than 6 million patients, and an estimated annual cost of more than $30 billion in the United States (US) alone [2]. Although pharmacological treatment has improved survival and life expectancy over the past decades [1], HF remains the leading cause of hospitalization among patients over 65 years of age and readmission after discharge represents a poor prognostic factor for quality of life in this population [3-5]. Thus, there is an urgent need to develop novel therapeutic approaches to ameliorate cardiac dysfunction, alleviate symptoms, and improve long-term outcomes among HF patients.

The neurohormonal paradigm in HF stipulates that a chronic state of low cardiac output leads to increased activation of the sympathetic and renin-angiotensin-aldosterone systems, which promote peripheral vasoconstriction, fluid retention, adverse cardiac remodeling, and adverse clinical outcomes [1]. This paradigm has been validated by the numerous clinical trials showing improved outcomes with neurohormonal blockers [1]. Despite these improvements, however, HF survival rates at 5 years are no better than many forms of cancer [2]. Moreover, numerous clinical trials investigating the acute management of patients with decompensated HF have failed to reduce the rates of hospital readmissions and other clinical outcomes after discharge [6-12], with resultant rates of hospital readmission ranging from 20 to 50% at 3 months [4,13]. These data highlight the need to improve treatment approaches after discharge and suggest that the current standard for pharmacological treatment fails to interrupt one or more key mechanisms of disease

progression.

The evidence of heightened systemic inflammation in heart disease is overwhelming [14,15]. However, there are currently no anti-inflammatory strategies approved for the treatment of HF. Inflammation is broadly defined as a coordinated cellular-humoral response to cell or tissue injury [16,17]. Inflammatory signaling begins locally at the site of injury and rapidly progresses to a systemic response by the means of chemical mediators (i.e. cytokines, chemokines) [16,17]. Interleukin-1 (IL-1) is a prototypical pro-inflammatory cytokine that amplifies the inflammatory response by inducing synthesis and expression of several hundred secondary mediators. Notably, IL-1 also induces its own production through a process described as "autoinflammation" [14-16].

IL-1 has been widely studied in preclinical models of cardiovascular disease and has been shown to promote adverse cardiac remodeling after myocardial injury [14-16,18]. Administration of exogenous IL-1 (in one of its 2 isoforms, IL-1α or IL-1β) also induces reversible contractile dysfunction both *in vitro* and *in vivo* [18]. The injection of plasma from patients with acutely decompensated HF in healthy mice also induced cardiac systolic dysfunction that could be fully prevented by treatment with an IL-1 blocker [19].

A recently completed proof-of-concept study tested the feasibility of IL-1 blockade with anakinra (Kineret™, Swedish Orphan Biovitrum, Stockholm, Sweden) for 14 days in patients with stable systolic HF and elevated CRP [19], finding a significant reduction in CRP (from 5.7 to 0.9 mg/L, *p=0.016*) associated with a significant improvement in the peak oxygen consumption (VO_2) (+2.8 ml•kg^{-1}•min^{-1}, p= *0.016* vs. baseline), exercise time (+2.9 min, *p=0.016* vs. baseline), and the minute ventilation/carbon dioxide production (VE/VCO_2) slope (-3.2, *p= 0.031* vs. baseline).

Study Hypothesis

We hypothesize that in patients with recently decompensated systolic HF and evidence of systemic inflammation, IL-1 blockade with anakinra will translate into an improvement in aerobic exercise performance.

Methods

Study design

We designed a placebo-controlled, double-blinded, randomized clinical trial of anakinra or placebo in patients with recently decompensated systolic HF – the Recently Decompensated Heart failure Anakinra Response Trial (RED-HART).

After an initial screening and evaluation, the patients will undergo a Cardiopulmonary Exercise Test (CPX), a transthoracic echocardio-Doppler study, and inflammatory and HF-related biomarkers, at baseline, 2, 4, 12, and 24 weeks (Figure 1). The study is composed of 3 treatment arms exploring 2 different durations of anakinra treatment: 1) anakinra 100 mg daily for 12 weeks; 2) anakinra 100 mg daily for 2 weeks, followed by placebo (equal volume of 0.67 ml) daily for the remaining 12 weeks; and 3) placebo daily for 12 weeks. The anakinra dosing will follow the FDA-approved regimen for rheumatoid arthritis and is the same regimen utilized in the 2-week proof-of-concept study [19]. After baseline procedures, patients will be given a 2-week supply of anakinra or placebo and will receive instruction from the investigators regarding the storage, use, subcutaneous self-injection technique, and disposal. Assessment of compliance will be performed at each visit. At the 2-week visit, patients will be given the remaining 10-week supply of anakinra or placebo.

Setting

The study will be performed at 3 academic clinical centers: the Virginia Commonwealth University Pauley Heart Center (Richmond, VA, USA), the University of Virginia Hospital Medical Center (Charlottesville, VA, USA), and the Hunter Holmes McGuire VA Medical Center (Richmond, VA, USA).

Screening and Enrollment

Patients admitted to the hospital (or seen in clinic for follow-up post hospital discharge) will be initially screened for inclusion and exclusion criteria. Patients meeting entry criteria will be approached to obtain informed consent either during admission or within 2 weeks of discharge.

Inclusion Criteria (all 6 criteria need to be met): Established diagnosis of decompensated heart failure at admission defined as dyspnea or respiratory distress or tachypnea at rest or with minimum exertion; and evidence of elevated cardiac filling pressures or pulmonary congestion (at least one): pulmonary

Table 1: Sample size estimates for phase III clinical trial based upon potential outcomes of R34 pilot study.

Index	Time	Expected Event Placebo Rate	Potential Treatment Effect	Hazard Ratio	Potential Treatment Event Rate	Sample Size Estimate* (β=0.20)	Sample Size Estimate* (β=0.10)
Hospital Readmission (Heart Failure)	6 months	0.300	-10%	0.90	0.2574	1575	2108
			-15%	0.85	0.2431	667	893
			-20%	0.80	0.2288	357	478
			-25%	0.75	0.2145	217	291
Hospital Readmission (all-cause)	6 months	0.500	-10%	0.90	0.4500	764	1023
			-15%	0.85	0.4250	333	445
			-20%	0.80	0.4000	183	245
			-25%	0.75	0.3750	56	74

*Total sample size estimate for randomized 2-groups comparison (treatment versus placebo)

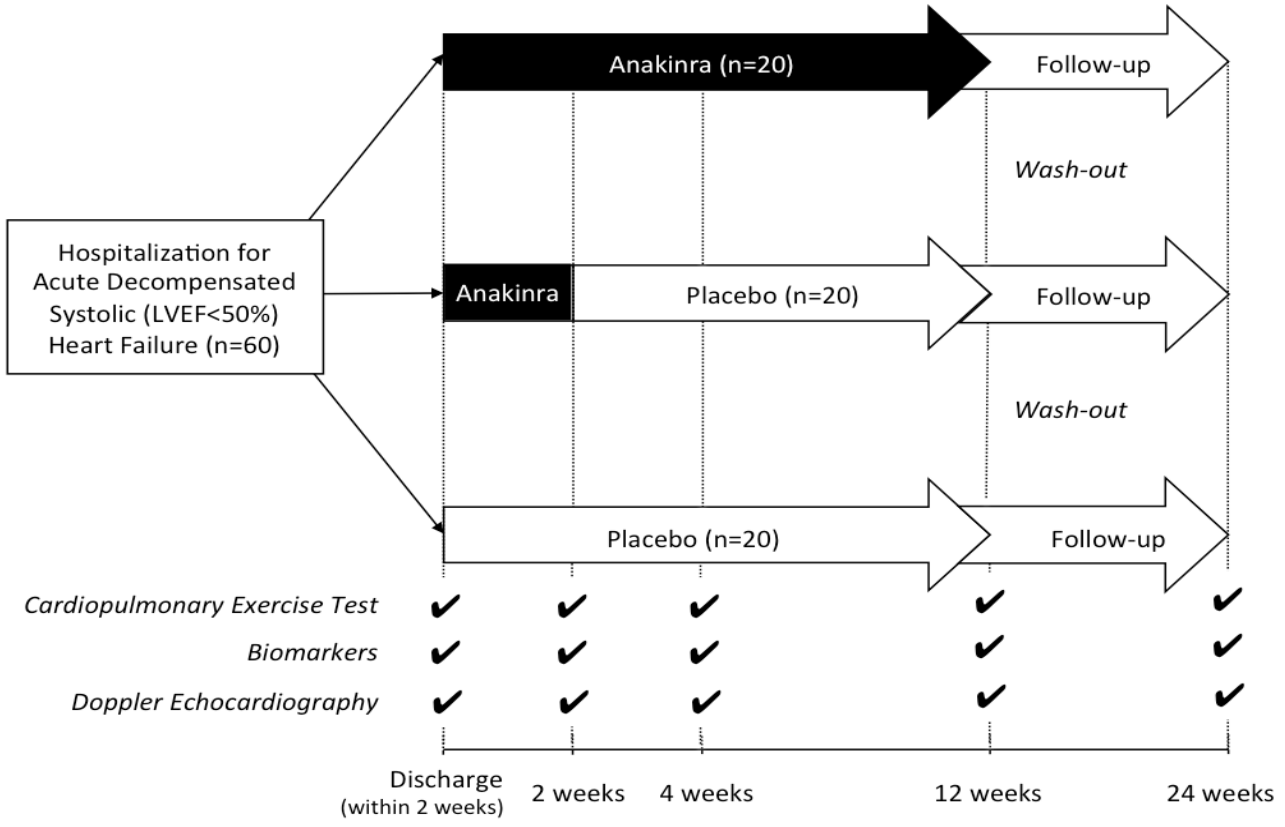

Figure 1: Schematic design of the study. LVEF: left ventricular ejection fraction.

congestion/edema at physical exam or chest X-ray, plasma BNP > 200 pg/ml, left ventricular end-diastolic pressure > 18 mmHg or of pulmonary artery occluding pressure > 16 mmHg [20].

Prior documentation of impaired left ventricular systolic function (ejection fraction <50%) at most recent assessment by any imaging modality (within 12 months).

The patient is now clinically stable and meets standard criteria for hospital discharge as documented by all 3 following conditions: absence of dyspnea or pulmonary congestion/ distress at rest; absence of pitting edema in the lower extremities or any region; and stable hemodynamic parameters.

The patient is 21 years or older and is willing and able to provide written informed consent.

The patient is willing and able to comply with the protocol (i.e. self-administration of the treatment and exercise test).

C-reactive protein plasma levels > 2 mg/L (measured by high-sensitivity assay).

Exclusion criteria: Acute decompensated heart failure is not the primary diagnosis but rather secondary to other conditions such as acute coronary syndromes, hypertensive urgency/ emergency, tachy- or brady-arrhythmias.

Concomitant clinically significant comorbidities that would interfere with the execution or interpretation of the study including but not limited to acute coronary syndromes, uncontrolled hypertension or orthostatic hypotension, tachy- or brady-arrythmias, acute or chronic pulmonary disease or neuromuscular disorders affecting respiration. This includes a submaximal test as shown by a Respiratory Exchange Ratio (RER) <1.0.

Recent (<3 months) or planned (in the following 3 months) Cardiac Resynchronization Therapy (CRT), coronary artery revascularization procedures (percutaneous or surgical) or heart valve interventions (percutaneous or surgical).

Previous or planned implantation of a left ventricular assist device or heart-transplant.

Chronic use of intravenous inotropes.

Recent (<14 days) use of immunosuppressive or anti-inflammatory drugs (not including non-steroidal anti-inflammatory drugs, short term (<10 days) low dose prednisone [<0.5 mg/kg or equivalents]), or inhaled corticosteroids.

Chronic inflammatory disorder (including but not limited to rheumatoid arthritis, systemic lupus erythematosus).

Active infection (of any type), including chronic/recurrent infectious disease (HBV, HCV and HIV/AIDS).

Prior (within the past 10 years) or current malignancy.

Any comorbidity limiting survival or ability to complete the

study.

Stage IV or V kidney disease.

Neutropenia (<2.000/mm^3) or Thrombocytopenia (<50.000/mm^3).

Pregnancy.

Angina, arrhythmias or ST segment changes at Electrocardiograph (ECG) occurring during the baseline CPX testing and limiting maximum exertion.

Randomization and allocation concealment

An independent investigator (Giuseppe Biondi Zoccai, MD - "Sapienza" University of Rome, Italy) has created a randomization sheet that was then provided to the Investigational Pharmacy in Richmond, VA. Anakinra or placebo (vehicle) 0.67 ml syringes were provided by SOBI (Stockholm, Sweden). These syringes are identifiable by lot number but are otherwise indistinguishable. The lead pharmacist (Robin Sculthorpe, RPh, or staff members in the VCU Investigational Pharmacy) will label the syringes with the name of the patient and provide basic storage instructions. To further ensure concealment of group allocation, the investigators will be kept blinded to all CRP levels other than the screening level to determine study eligibility. Access to a randomization log will be restricted and allowed only in case of emergency, or as requested by the Data Safety and Monitoring Board, or at the end of the study following the completion of all data collection.

Safety assessment

Anakinra is generally well tolerated by patients following acute and chronic administration. Common adverse events include headache, nausea, diarrhea, and injection site reactions [15]. When combined with immunosuppressive agents in patients with rheumatoid arthritis, a 2- to 3-fold in serious infections has been observed, but there does not appear to be any observable impact on infection-related mortality [15].

For the current trial, Serious Adverse Events (SAE) are defined as any adverse event occurring between baseline assessments and the final study visit that results in any of the following outcomes: 1) Death; 2) Life threatening event (immediate risk of death); 3) Event requiring inpatient hospitalization or prolongation of existing hospitalization; 4) Event resulting in a persistent or significant disability or incapacity; and 5) Medical events that may not result in death, be life threatening, or require hospitalization, but are considered to jeopardize the subject's wellbeing and require medical assistance to prevent one of the outcomes listed in this definition.

Abnormal laboratory results obtained through routine clinical care that are observed after randomization through study completion will be recorded as an AE, unless they are present or detected at the start of the study and do not worsen, or they are considered to represent fluctuations of the baseline values expected for the disease state.

Data and safety monitoring board

The Data and Safety Monitoring Board is formed according to Food and Drug Administration recommendations [21]. The DSMB is chaired by Dominick Angiolillo, MD, PhD (Associate Professor of Medicine, Division of Cardiology, Interventional Cardiology, University of Florida, Jacksonville, FL, USA) and comprised of 4 additional voting members, including a heart failure specialist (Richard Cooke, MD - Chief of the Heart Failure Section, VCU), an interventional cardiologist (Ion Jovin, MD – Chief of Cardiac Catheterization Laboratory, McGuire Veterans Administration hospital, Richmond, VA), an infectious disease specialist (Gonzalo Bearman, MD, MPH – Chairman of the Infectious Disease division at VCU), and a general internal medicine specialist (Jeffrey Kushinka, MD – Associate Chair for Clinical Affairs in the General Internal Medicine Division at VCU). Coordination of DSMB meetings and distribution of DSMB decisions will be conducted by Christine DeWilde, RN (DSMB coordinator). The DSMB will meet every 6 months or sooner in case of unanticipated SAEs. The DSMB also has the power to temporarily or permanently stop the study, or interrupt the treatment of one or more patients.

Cardiopulmonary Exercise Testing (CPX)

A supervised maximal aerobic exercise test will be administered using a metabolic cart that is adapted to a treadmill using a conservative ramping treadmill protocol. The test will utilize a ramped exercise protocol designed specifically for HF patients [19]. Prior to each test, oxygen (O_2) and carbon dioxide (CO_2) sensors will be calibrated as well as the flow sensor using standard procedures. Subjects will then be briefed regarding the protocol and will be requested to exercise to fatigue. A 12-lead electrocardiogram will be conducted at baseline, throughout exercise, and during recovery. Blood pressure will be measured every 2 minutes using an automated exercise-compatible device [*Tango, SunTech Medical*]. During exercise, a mouthpiece-mounted sensor will be used to continuously measure expired gases and O_2 uptake; the highest 10-second average value of O_2 uptake during the final 30 seconds of exercise defines peak O_2 consumption (VO_2 in $mLO_2 \bullet kg^{-1} \bullet min^{-1}$). The ventilatory equivalents method will be used to determine VO_2 at ventilatory threshold. Ten second averaged VE and VCO_2 data, from the initiation of exercise to peak, will be input into the spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA) to calculate the VE/VCO_2 slope via least squares linear regression. The peak RER (VCO_2/VO_2) will be used to determine subject effort. A peak RER ≥ 1.10 is accepted as a maximal effort and a peak value ≥ 1.00 is considered a minimal acceptable threshold [22-24]. American Heart Association guidelines for exercise testing contraindications and termination criteria will be followed [24]. Patients with results suggestive of ischemic heart disease (angina, ischemic ECG changes, and abnormal blood pressure) will be excluded. The data from each CPX will be transferred (free of patient identifiers) for analysis to the Core Lab at the University of Illinois, Chicago, IL.

Endothelial function

At VCU only, a small cuff will be placed on the subject's finger to measure blood flow [ccNexfin, Edwards Scientific] for a minimum of 3 minutes. A standard blood pressure cuff will then

be placed on the arm and inflated for 2-3 minutes. The finger cuff will measure changes in blood flow before and after cuff deflation to provide an estimate of flow mediated dilatation, a surrogate marker of endothelial function.

Doppler echocardiogram

All subjects will undergo a transthoracic Doppler echocardiogram prior to initiation of treatment and at each additional visit. Left ventricular diastolic and systolic volumes, transmitral flow Doppler spectra, mitral and tricuspid valve annulus tissue Doppler spectra, and tricuspid annulus plane systolic excursion will be measured according to recommendations of the American Society of Echocardiography [25-27]. All images and loops will be acquired in an electronic format and transferred to the VCU Pauley Heart Center for blinded centralized measurements at the end of the study.

Laboratory analysis and biomarkers

Blood samples will be used for a complete blood count with differential, comprehensive metabolic profile, and plasma levels of biomarkers (e.g. high sensitivity C-Reactive Protein (CRP), Brain Natriuretic Peptide (BNP), inflammatory cytokines).

Study end-points

The co-primary endpoints will be placebo-corrected changes in peak VO_2 or the VE/VCO_2 slope after 2 weeks of treatment. This will compare patients treated with anakinra (pooled anakinra group, N = 40) vs. placebo (n = 20), and provide a randomized, double-blinded assessment of the effects of 2 weeks of IL-1 blockade on aerobic exercise performance.

Secondary exploratory endpoints will include the following: 1) Additional CPX parameters such as changes in peak VO_2 or the VE/VCO_2 slope at 4, 12 and 24 weeks; 2) Echocardiography: Structural and functional parameters (left and right ventricular dimensions, mass, systolic and diastolic function) to provide mechanistic insight regarding whether hypothesized changes in aerobic exercise performance relates with cardiac dimension and function; 3) Quality of life assessment: the Minnesota Living with Heart Failure (MLWHF) and the Duke Activity Status Index (DASI); 4) Biomarkers; and 5) Clinical outcomes: Incidence of death (cardiac and non-cardiac), hospitalizations for HF or other causes, and use of concomitant HF medications.

Clinical Events

A dedicated committee chaired by Michael Kontos, MD (Director of the Cardiac Intensive Care Unit, VCU Pauley Heart Center) and composed of another cardiologist, Gautham Kalahasty, MD (specialist in Electrophysiology, VCU) and a general internal medicine specialist, Elizabeth Miller, MD (VCU) will adjudicate all events. The adjudicated events are:

1) Death;

2) Cardiac death in which a direct causes attributable to cardiac disease is present;

3) Sudden cardiac death in which cardiac death occurred out of the hospital (and suddenly) or in the hospital due to ventricular arrhythmias unrelated to other concomitant cardiac conditions;

4) Non-cardiac death in which the event of death is considered not to be a direct consequence of cardiac disease;

5) Hospitalization for any cause;

6) Hospitalization for heart failure (in which the primary diagnosis for hospitalization is decompensated heart failure established as the finding at admission of both of the following conditions listed:

a. dyspnea or respiratory distress or tachypnea at rest or with minimal exertion;

b. evidence of elevated cardiac filling pressure or pulmonary congestion (at least one of the conditions must be met: pulmonary congestion/edema at physical exam OR chest X-Ray; plasma BNP levels ≥ 200 pg/ml; or invasive measurement of left ventricular end-diastolic pressure > 18 mmHg or of pulmonary artery occluding pressure (wedge) > 16 mmHg) [20];

7) Acute myocardial infarction, as defined by the WHO consensus statement [28];

8) Unstable angina, or need for coronary revascularization;

9) Cardiac tachy- or brady-arrhythmias leading to a new hospitalization or to prolongation of hospital stay;

10) Acute renal failure (defined as in increase in plasma creatinine levels of 50% or 0.5 mg/L);

11) Acute respiratory failure (not due to heart failure);

12) Sepsis or other serious infection requiring antibiotic therapy; or

13) Acute stroke

The analysis will consider time to first event and time to each event. It will also consider event rates at 1, 3 and 6 months and at longest available endpoint, in order to perform homogeneous comparisons with other study outcomes [9,12]. The number of days free of hospitalization during the first 1, 3 and 6 months will also be measured and compared between groups.

Statistical Analysis

Demographics and baseline characteristics

Descriptive summaries of continuous measurements will be provided as median and interquartile ranges due to potential deviation from Gaussian distribution. Descriptive summaries of categorical measurements will consist of frequencies, proportions and 95% confidence intervals, when applicable. All analyses will be conducted after database locking. The Statistical Package for Social Studies (SPSS) software 22.0 (IBM, New York, NY, US) will be used.

Analysis of the co-primary endpoints

The difference in interval changes in peak VO_2 or VE/VCO_2 slope at 2 weeks between the pooled anakinra vs. placebo groups

will be compared using random-effect analysis of variance for repeated measures to analyze the effects of time_X_group allocation. Unadjusted p-values will be reported throughout, with statistical significance at the 2-tailed 0.025 level due to the use of co-primary endpoints. Cases with missing data will be omitted from the primary endpoint analysis.

Analysis of secondary endpoints

To evaluate differences in the secondary endpoints at 2 weeks (CPX, echocardiogram, biomarkers, quality of life, or event rates), key data will be compared using the pooled anakinra versus placebo group using the random-effect analysis of variance for repeated measures as indicated above for paired analyses, or Kaplan-Meyer curves with Logrank testing for event rates.

For endpoints at 4, 12 and 24 weeks, the random-effect analysis of variance for repeated measures will be used comparing the placebo versus the pooled anakinra group, the anakinra 2-week group, or the anakinra 12-week group. An additional analysis will be performed as an *on-treatment* analysis at 4 and 12 weeks in which patients treated with placebo or with anakinra for the first 2 weeks only will be pooled in one group (*off-treatment* group) and compared with the anakinra 12-week group. Similarly, Kaplan-Meyer curves will be created for each of the groups including the pooled anakinra group, the anakinra 2-week treatment, the anakinra 12-week treatment, the placebo group, as well as the *off-treatment* group and compared using the Logrank test for event rates at 2, 4, and 12 weeks. An exploratory analysis will be performed also at 24 weeks (i.e., washout period).

Sample Size Considerations

The sample size for this pilot study was calculated according to the primary endpoint difference in interval change in peak VO_2 at 2 weeks between anakinra (both groups) and placebo. Given an expected average peak VO_2 of 15 ± 3.5 $mL \bullet kg^{-1} \bullet min^{-1}$ for HF patients, 40 subjects randomized to anakinra and 20 to placebo (2:1 randomization) would provide > 99% power to detect a difference of 3.5 $mL \bullet kg^{-1} \bullet min^{-1}$ in the peak VO_2 primary endpoint, as seen in the previous proof-of-concept clinical study [19]. An estimate of 20% loss to follow-up or withdrawal would retain > 95% power. The design would also provide > 99%, 99%, and 86% power to detect smaller effects of 3.0, 2.5, and 2.0 $mL \bullet kg^{-1} \bullet min^{-1}$ in peak VO_2, respectively.

Discussion

There is an urgent need to develop novel therapeutic strategies to improve cardiac function, alleviate symptoms, and reduce hospitalizations in HF patients. This pilot study is structured to provide the sufficient information needed to design a subsequent multicenter, randomized, double-blinded, phase III clinical trial of the safety and efficacy of IL-1 blockade in patients with systolic HF. For example, the degree of peak VO_2 improvement with anakinra in the current study may be used to estimate the potential value of anakinra as an add-on treatment for HF in a subsequent phase III clinical trial. Considering the hypothesized link between inflammation and HF, and the scientific data linking IL-1 with impaired cardiac function and contractile reserve, we expect to see improved aerobic exercise performance with anakinra. Given that the primary endpoints selected for this trial (peak VO_2 and V_E/V_{CO2} slope) represent both prognostic risk factors and functional assessments of exercise capacity, a significant improvement in either of the co-primary endpoints would be sufficient to justify the conduct of a future phase III clinical study.

The use of the exploratory end-points will also potentially guide future studies. The proof-of-concept study of anakinra in stable HF suggested that 2 weeks of anakinra are sufficient to suppress CRP levels by > 75% [19]. It remains unknown whether a longer treatment is needed for recently decompensated HF or whether a longer suppression of the inflammation is needed to see the full benefit of IL-1 blockade. The use of serial CPX tests over time and the comparison of a shorter (2 weeks) vs. longer (12 weeks) anakinra treatment will potentially show whether a longer treatment course is necessary. Moreover, given that "IL-1 induces IL-1" through a positive feedback loop that characterizes autoinflammatory diseases; interruption of this feedback may result in sustained anti-inflammatory effects beyond the actual pharmacological half-life of the drug. In a study of patients with diabetes, treatment with anakinra for 13 weeks showed an improvement in pancreatic β-cell function that was maintained at 52 weeks (39 weeks after discontinuation of treatment) [29]. Canakinumab, a monoclonal antibody blocking IL-1β, also lowers CRP levels for longer than the reported 24-day half-life [30]. The design of the RED-HART with prolonged wash-out periods after a short (2 weeks) or longer (12 weeks) treatment will provide data in regards to the duration of the effects after termination of therapy.

The use of serial Doppler echocardiography studies over time will allow determination of whether changes in aerobic exercise performance correlate with changes in cardiac systolic and/or diastolic function. Biomarkers will be used to correlate with changes in clinical status, CPX, and Doppler echocardiography parameters.

The RED-HART trial, as any phase II study has several limitations, primarily the small number of participants. The study is powered to detect differences at 2 weeks in the pooled anakinra versus placebo group, whereas it is not powered to answer additional questions regarding optimal duration of the treatment or duration of the effect. These additional analyses must therefore be considered *hypothesis-generating*. The study is not powered to detect differences in readmission rates, yet we believe it may provide a signal to estimate effect size and thus appropriately power future studies (Table 1). Additionally, the choice of selecting patients with CRP levels > 2 mg/L was based on a validated cutoff to identify a patient population with a demonstrable inflammatory burden [31-33] and to identify patients at higher risk of cardiovascular complications, but we cannot exclude the possibility that those patients with low CRP would have a similar response to anakinra treatment. Moreover, HF patients represent a notoriously heterogeneous patient population and practice patterns may vary substantially (even within a single institution) in terms of criteria for hospital

discharge from the index hospitalization. Therefore, all patients will be evaluated for euvolemia, clinical symptoms, and functional status at their initial study visit prior to randomization. All other treatments (including HF medications) will continue to be monitored and titrated as needed in accordance with standard of care.

We believe that this is the first clinical study to evaluate IL-1 blockade in the context of recently decompensated systolic HF. If a significant improvement in peak VO_2 occurs can be established, we anticipate numerous opportunities to identify collaborators and medical centers for future studies across a wide range of patient demographics. IL-1 blockade is also substantially different from other "anti-inflammatory" treatments that have been evaluated in patients with HF—most notably the TNFα antagonists (i.e. etanercept and infliximab). While TNFα and IL-1 are both pro-inflammatory cytokines, they activate distinct signaling pathways that are largely not convergent [15]. For example, TNFα antagonists are associated with immunosuppression and opportunistic infections, whereas IL-1 blockers are not. Moreover, 2-week administration of anakinra in the proof-of-concept study produced marked reductions in CRP without any appreciable effect on TNFα concentration [19].

In conclusion, the RED-HART study will determine whether IL-1 blockade with anakinra in patients with recently decompensate systolic HF will improve aerobic exercise performance and ventilator efficiency, important surrogates for clinical stability and HF morbidity and mortality.

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