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Usefulness of Canakinumab to Improve Exercise Capacity in Patients With Long-Term Systolic Heart Failure and Elevated C-Reactive Protein

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Abstract

Interleukin-1 β (IL-1 β) is a cytokine involved in atherothrombosis and is known to depress cardiac function. We hypothesized that blocking IL-1 β in patients with symptomatic systolic heart failure (HF) would improve their cardiorespiratory fitness. The purpose of the study was to measure changes in peak oxygen consumption (VO₂) in 30 patients with prior myocardial infarction, high-sensitivity C-reactive protein \geq 2 mg/l and HF with left ventricular ejection fraction (LVEF) < 50% enrolled in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) in an independent single center substudy. We measured peak VO₂ before and after 3 and 12 months of treatment with Canakinumab every 3 months (50, 150, or 300 mg subcutaneously) or placebo, and measured LVEF before and after 12 months. In December 2013, the CANTOS study announced early termination of enrollment, halting enrollment for this substudy after only 15 patients, of which 3 were assigned to placebo and 12 to Canakinumab (50 mg [1; 7%], 150 mg [5; 33%], 300 mg [6; 40%]). Patients treated with Canakinumab had a significant improvement in peak VO₂, from 19.2 to 22.8 ml/kg/min at 3 months ($p = 0.023$ within-group changes, $p = 0.026$ for time_x_group interaction versus placebo [primary end point]), and an improvement in LVEF 38% (33–43) to 44% (38–52) at 12 months ($p = 0.012$ for within-group changes). No significant changes were seen in the placebo group. In conclusion, the findings of this small prespecified secondary analysis of the CANTOS trial support the positive results of the overall study, and

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confirm IL-1 as a potential therapeutic target in HF. <https://clinicaltrials.gov/ct2/show/NCT01900600>

Keywords

Inflammation; Translational Studies; Heart Failure

Interleukin-1 β (IL-1 β) is the prototypical inflammatory cytokine that is known to modulate cardiac contractility, behaving as a “*soluble myocardial depressant factor*”.¹ In early phase studies of stable systolic heart failure² and recently decompensated heart failure (HF), IL-1 receptor blockade with anakinra improved peak aerobic capacity.³ The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) clinical trial⁴ tested Canakinumab, a humanized IL-1 β blocking antibody, to prevent recurrent atherothrombotic events in patients with previous myocardial infarction (MI) and elevated C-reactive protein (high sensitivity C-reactive protein [hs] CRP) ≥ 2 mg/l. The current study was designed as an independent investigator-initiated single-center substudy to determine whether Canakinumab improves peak oxygen consumption (VO₂) in systolic HF (left ventricular ejection fraction [LVEF] < 50%).

Methods

The study design of the CANTOS trial⁴ and the main results⁵ have been published elsewhere. Briefly, 10,061 patients with prior MI and hsCRP level ≥ 2 mg/l were randomized to three different doses of Canakinumab or placebo. Exclusion criteria have been described.⁴ Randomization was not stratified by site. The Western Institutional Review Board approved both the main CANTOS trial and substudy, which required patients to be also symptomatic with NYHA class II III, Stage C HF and LVEF < 50%.⁶ All participants gave written informed consent. The substudy was registered as a separate study on clinicaltrials.gov (NCT01900600).

All patients underwent a maximal cardiopulmonary exercise test using a metabolic cart interfaced with a treadmill at baseline (during the screening visit or initial visit but before treatment) and 3 months to measure interval changes in peak VO₂ with Canakinumab versus placebo (*primary end point*), and again at 12 months.³ For the test to be considered suitable for analysis, all the following conditions were needed to be met: (1) patient was limited by shortness of breath or fatigue; (2) no evidence of ischemia, arrhythmias, or uncontrolled hypertension limiting exercise; and (3) a respiratory exchange ratio > 1.0 at peak exercise.³ Interval changes in LVEF, another surrogate for systolic HF,⁷ were measured with transthoracic echocardiography at baseline, 3-months, and 12-months.³ Simpson method was used to measure LVEF in 4- and 2-chamber apical views. All images and loops were recorded and analyzed off-line at the end of the study by two experienced investigators unaware of treatment allocation: the values obtained by the two readers were averaged if the differences were <5% or reviewed jointly and remeasured for values differing $\geq 5\%$.

We hypothesized that IL-1 β blockade with Canakinumab on top of standard of care treatment would improve cardiorespiratory fitness, measured by peak VO₂, in patients with

systolic HF due to ischemic cardiomyopathy. Given an expected average peak VO_2 of 13 ± 3 ml/kg/min for patients with symptomatic systolic HF, we planned to enroll 30 subjects (assuming 2:1 randomization) to provide a >90% power to detect a difference of 3.5 ml/kg/min (standard deviation of 2 ml/kg/min) between the interval change in peak VO_2 between Canakinumab (all three doses combined) and placebo at 3 months, and >80% power to detect a similar difference between each individual Canakinumab dose and placebo at 3 months. We considered that an improvement in peak VO_2 of 3.5 ml/kg/min, equaling 1-metabolic equivalent, would be both clinically significant since it has been associated with a reduction in mortality,⁸ and achievable as already seen in the first proof-of-concept study of IL-1 blockade with anakinra in stable systolic HF patients completed in 2011.² Data was collected at the Virginia Commonwealth University and sent to a core analysis laboratory at the University of Illinois at Chicago to an investigator blinded to treatment allocation (R.A.) for analysis and database creation. Here the data are presented as median and interquartile range. Changes within the group were assessed with the Wilcoxon or the Friedman tests. We used the repeated measures analysis of variance (ANOVA)(time_x_group interaction) to compare paired changes in peak VO_2 comparing Canakinumab and placebo at 3 months. No missing data imputation was used for instances in which subjects did not complete a follow-up test. In consideration that only 3 patients were in the placebo group, the data regarding placebo is presented as individual data point with the absolute range, rather than median and interquartile range, as a distribution in quartiles would have been misrepresentative. We therefore present individual data points. All analyses regarding the placebo-treated subjects are presented, but the limited statistical power needs to be acknowledged, and results need to be considered subject to error. The effects of Canakinumab on the outcomes of interest are presented as within-group analysis, but also as between-group analysis as prespecified, albeit significantly under-powered due to small size of the placebo group.

Results

Patients were enrolled in the substudy between April 2013 and February 2014 and randomly assigned to Canakinumab or matching placebo administered subcutaneously every 3 months. In December 2013, the main CANTOS study announced early termination of enrollment at the request of the sponsor, since power recalculations predicted that a sample size of 10,000 (instead of 17,200) would be sufficient to test the hypothesis.⁹ Overall 10,061 patients were enrolled in the CANTOS study, and enrollment for this substudy was unexpectedly stopped after 15 patients were enrolled at Virginia Commonwealth University (VCU): 12 patients were assigned to Canakinumab (50 mg [1; 7%], 150 mg [5; 33%] or 300 mg [6; 40%]) and 3 patients (20%) to placebo (Table 1).

Of the 15 subjects, 13 (87%) were male, 8 (53%) were Caucasian, 6 (40%) were African-American, and 1 was (7%) Hispanic. Time from acute MI was 34 (12 114) months. All patients were on a stable (>3 months) regimen of maximally-tolerated guideline-directed medications for HF. Seven (47%) patients had New York Heart Association class II and 8 (53%) class III symptoms. No significant changes in hsCRP were seen in the placebo group [5.3, 5.4, and 8.2 mg/l at baseline, 2.7, 6.0, and 6.2 mg/dl at 3 months, and 5.6, 6.6, and 11.6 mg/dl at 12 months, $p = 0.10$ for within group changes]. Treatment with Canakinumab significantly reduced hsCRP levels from 5.3 mg/l (3.0 11.2) to 2.0 (0.9 5.2) at 3 months ($p =$

0.028), and to 1.0 (0.7 2.6) at 12 months ($p = 0.002$ for within-group changes, $p = 0.042$ for between-group difference).

Treatment with Canakinumab significantly increased peak VO_2 from 19.2 to 22.8 ml/kg/min at 3 months ($p = 0.023$ within-group changes, $p = 0.026$ between group changes [*primary end point*] with a median interval change of +1.6 [-0.4/+3.4] ml/kg/min) (Figure 1, Table 1). Of the 3 doses, only Canakinumab 150 mg was independently associated with a significant increase in peak VO_2 at 3 months (from 18.4 [13.6 21.6] to 22.5 [16.8 24.4], with a median increase of +3.5 [+1.8/+4.5] ml/kg/min, uncorrected $p = 0.043$) (Figure 1). No significant effect of placebo was detected on peak VO_2 at 3 months (Table 1, Figure 2). Only 9 of the 12 Canakinumab-treated patients and 1 placebo-treated patient had repeat peak VO_2 assessed at 12 months; peak VO_2 showed a trend toward improvement with Canakinumab in a within-group analysis [from 18.4 (14.0 23.4) to 19.8 (15.0 24.8), $p = 0.066$](a time_x_group interaction analysis could not be performed as only 1 placebo-treated patient had peak VO_2 measured at 12 months)(Figures 1 and 2).

Paired echocardiograms were available in all 15 substudy patients. Canakinumab-treated patients experienced an improvement in LVEF from 38% (33 43) to 44% (38 52) at 12 months ($p = 0.012$ for within-group changes, with median change of +7% [+2/+12]) which, however, did not reach statistical significance for time_x_group interaction versus placebo ($p = 0.30$) (Table 1, Figures 1 and 2). Of the 3 doses, only Canakinumab 150 mg was associated with a significant increase in LVEF at 12 months (from 38% [31 46] to 46% [42 57], with a median increase of +12% [+3/+17], uncorrected $p = 0.043$). There were no significant changes in peak VO_2 or LVEF in the placebo group ($n = 3$) at any time point (Figure 2).

In addition to the above variables, changes in other cardiopulmonary exercise test and Doppler echocardiographic are provided in the Table 1. There were 2 HF admissions within the first 12 months: one in the placebo (1, 33%) and 1 in the low dose (50 mg) Canakinumab group (1, 8%). One patient in the placebo group (33%) was hospitalized for critical limb ischemia, and 4 (25%) Canakinumab-treated patients were hospitalized for noncardiac reasons. Reasons for hospitalization among Canakinumab-treated patients included pneumonia/sepsis ($n = 1$), pulmonary embolism ($n = 1$), and noncardiac chest pain ($n = 2$). None of the patients discontinued treatment.

Discussion

The findings of improved peak VO_2 and LVEF in patients with systolic HF treated with Canakinumab supports the hypothesis that IL-1b can modulate cardiac function by acting as a soluble cardiodepressant factor¹ and exercise capacity,¹⁰ and is consistent with the effects of anakinra, a recombinant IL-1 receptor antagonist, in patients with stable or with recently decompensated systolic HF.^{2,3} Peak VO_2 and LVEF are two strong and independent predictors of outcomes in patients with systolic heart failure.^{7,11} Peak VO_2 is a highly reliable and reproducible measure of cardiorespiratory fitness that integrates cardiac function as well as oxygen exchange, transport, and delivery. When the patient provides a maximal effort and is limited by cardiac output (as evidenced by gas exchange), peak VO_2 provides a

reliable and valid measure of cardiac function.¹² LVEF is also a measure of cardiac function and predicts outcome, but is sensitive to changes in pre- and afterload and therefore may reflect a direct or indirect improvement in cardiac function. Nevertheless, the improvement in both peak VO₂ and LVEF with Canakinumab is encouraging and in-line with the proposed mechanism by which IL-1 β impairs cardiac function by depressing contractility.¹

The limitations of this small substudy include the small sample size representing a very small part of the patients in the CANTOS trial with HF at a single site, even smaller than the planned 30 patients. Moreover, this substudy represents the results of a randomization not stratified by site, thus providing an imbalance in groups with only included 3 placebo-treated patients and only 1 patient treated with low dose Canakinumab. Many of the patients also had peak VO₂ levels which were higher than expected, a feature which may have limited the ability to detect further improvement and responsiveness to IL-1 blockade, as previously described.¹³ Despite the smaller-than-planned sample size and the imbalance between the doses, Canakinumab led to a significant increase in peak VO₂ at 3 months, which was the predefined end point. The overall change was less than predicted, but increases in peak VO₂ >1 ml/kg/min have been associated with improved prognosis.¹⁴ The Canakinumab 150 mg dose was associated with a significant median increase in peak VO₂ of 3.5 ml/kg/min, as predicted in the sample size analysis, although this was without adjusting for multiple group comparisons. Of note, Canakinumab 150 mg was also the only dose meeting the predefined significance criteria in terms of reduction of primary clinical outcome in the CANTOS trial.⁵ The current findings support the expanded therapeutic potential of Canakinumab (specifically) and IL-1 blockers (in general), as a potential means to improve exercise capacity in patients with systolic HF; however, due to the above limitations should be considered exploratory. Additional analysis on hard outcomes of the entire cohort of CANTOS patients with systolic heart failure may further explore whether functional improvement with IL-1 blockade may translate into improved clinical outcomes as suggested by the pilot phase II clinical trials.^{3,15}

Acknowledgments

Disclosure

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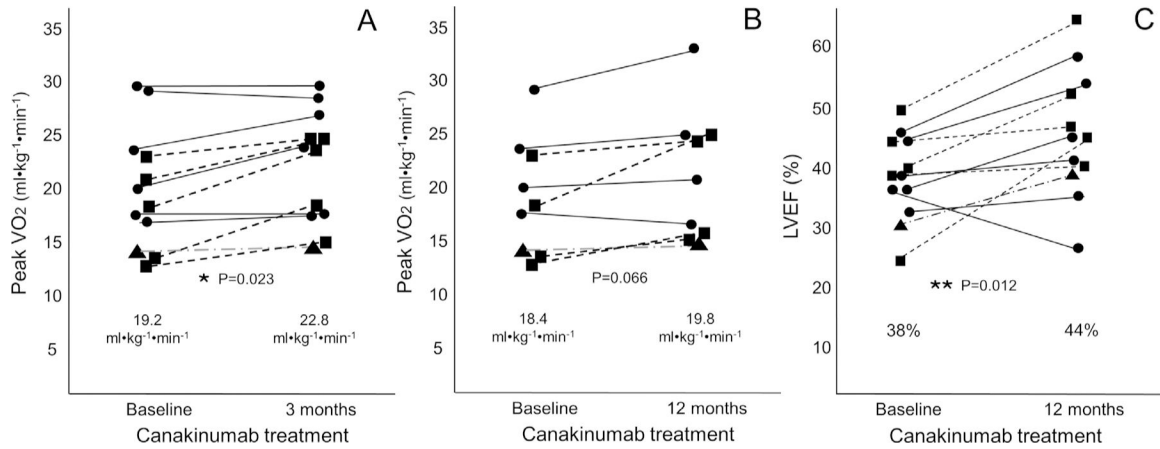


Figure 1. Interval changes in peak oxygen consumption with Canakinumab.

Individual patient values are shown according to Canakinumab dose (triangle = 50 mg [n = 1]; squares = 150 mg [n = 5]; circles = 300 mg [n = 6]). Panel A shows changes in peak oxygen consumption (VO₂) at 3 months, *p = 0.023 for within group changes versus baseline, and p = 0.026 versus placebo at time_x_group interaction at 3 months. Of the 3 doses, only Canakinumab 150 mg (squares) was associated with a significant increase in peak VO₂ at 3 months (from 18.4 [13.6—21.6] to 22.5 [16.8—24.4], p = 0.043 with a median increase of +3.5 [+1.8/+4.5] ml/kg/min). Panel B shows changes in VO₂ at 12 months. Panel C shows changes in left ventricular ejection fraction (LVEF) at 12 months. **p = 0.012 for within group changes versus baseline, and p = 0.30 versus placebo at time_x_group interaction. Of the 3 doses, only Canakinumab 150 mg was associated with a significant increase in LVEF at 12 months (from 38% [31—46] to 46% [42—57], p = 0.043 with a median increase of +12% [+3/+17]).

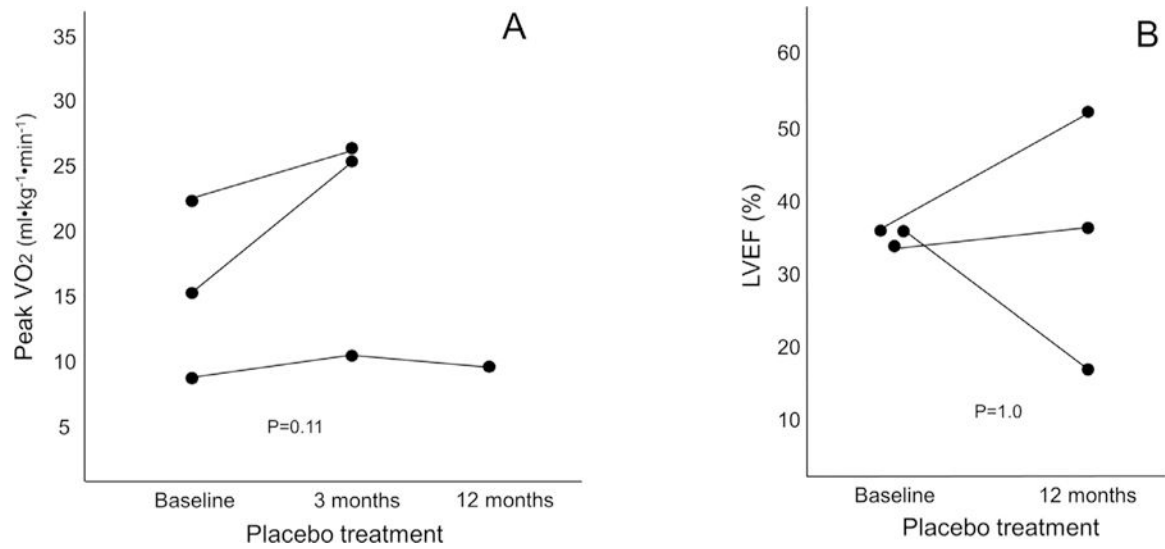


Figure 2.

Interval changes in peak oxygen consumption in patients treated with placebo are shown (circles). Panel A shows changes in peak oxygen consumption (VO₂) at 3 months and 12 months (Of the 3 patients, only 1 patient had peak VO₂ measured at 12 months). Panel B shows changes in left ventricular ejection fraction in the 3 patients at echocardiography at 12 months.

Table 1

Additional cardiopulmonary exercise test and Doppler echocardiography parameters.

Subject (#)	Age (yrs)	Gender	Ethnicity	Baseline										3 months										12 months									
				Exercise time	Peak VO ₂ (ml/kg/min)	VE/VCO ₂ Slope	OUES	RER	LVEDV (mL)	LVEF (%)	Exercise time (sec)	Peak VO ₂ (ml/kg/min)	VE/VCO ₂	OUES	RER	Exercise time	Peak VO ₂ (ml/kg/min)	VE/VCO ₂	OUES	RER	Exercise time	Peak VO ₂ (ml/kg/min)	VE/VCO ₂	OUES	RER	LVEDV (mL)	LVEF (%)						
Cinacumab 50 mg	1	M	C	6.4	14.3	38.0	2.25	1.01	168	30	8.1	14.4	30.3	2.52	1.07	8.2	14.7	37.5	2.29	1.23	205	38	8.2	14.7	37.5	2.29	1.23	205	38				
	2	M	C	9.3	22.4	25.6	2.85	1.11	155	39	11.0	24.4	25.9	3.84	1.18	10.5	23.4	25.3	2.87	1.09	147	51	10.5	23.4	25.3	2.87	1.09	147	51				
	3	F	C	6.0	13.3	30.8	1.81	1.05	71	43	6.4	15.0	32.3	2.68	1.10	6.5	16.3	30.6	2.18	0.98	71	46	6.5	16.3	30.6	2.18	0.98	71	46				
Cinacumab 150 mg	4	M	AA	7.5	20.9	33.5	1.93	1.13	170	38	8.1	24.4	32.7	2.20	1.10	8.3	16.9	36.8	1.94	1.02	132	39	8.3	16.9	36.8	1.94	1.02	132	39				
	5	M	C	7.2	13.8	54.8	1.15	1.13	180	24	9.0	18.7	48.5	1.19	1.05	8.0	14.5	55.0	1.37	1.22	170	44	8.0	14.5	55.0	1.37	1.22	170	44				
	6	M	C	11.0	18.4	29.3	2.09	1.14	103	50	12.3	22.5	29.4	2.01	1.06	12.5	24.8	31.8	2.22	1.12	92	63	12.5	24.8	31.8	2.22	1.12	92	63				
Cinacumab 300 mg	7	M	H	15.2	29.2	21.6	3.80	1.11	154	36	14.5	27.8	25.0	3.00	1.15	16.2	34.1	26.9	3.70	0.92	200	44	16.2	34.1	26.9	3.70	0.92	200	44				
	8	M	AA	9.1	20.0	29.1	2.11	1.02	152	38	10.4	23.0	28.6	2.57	1.11	9.4	19.8	31.4	2.17	1.02	134	40	9.4	19.8	31.4	2.17	1.02	134	40				
	9	M	AA	12.0	29.8	26.1	3.33	1.26	211	32	14.0	29.3	33.9	2.70	1.23	n/a	n/a	n/a	n/a	n/a	n/a	210	35	n/a	n/a	n/a	n/a	n/a	210	35			
Placebo	10	M	C	6.5	17.5	31.0	2.54	1.11	169	36	7.5	16.9	29.1	3.16	1.00	5.1	15.6	33.7	3.13	0.91	198	28	5.1	15.6	33.7	3.13	0.91	198	28				
	11	M	AA	6.2	16.1	27.4	2.36	1.10	93	43	8.0	16.8	29.7	2.33	1.13	7.3	13.8	34.0	2.00	1.00	117	52	7.3	13.8	34.0	2.00	1.00	117	52				
	12	M	C	10.4	24.4	28.9	2.71	1.20	100	45	11.1	26.0	31.3	2.50	1.17	11.3	24.8	31.6	2.45	1.21	100	56	11.3	24.8	31.6	2.45	1.21	100	56				
Placebo	1	M	C	8.4	15.7	23.1	3.02	1.09	196	36	8.4	25.6	25.9	4.42	1.15	n/a	n/a	n/a	n/a	n/a	n/a	218	16	n/a	n/a	n/a	n/a	n/a	218	16			
	2	F	AA	3.3	9.0	43.4	1.61	1.15	146	34	3.1	11.8	42.1	1.26	1.16	3.3	9.6	36.3	1.28	1.23	131	37	3.3	9.6	36.3	1.28	1.23	131	37				
	3	M	AA	10.5	22.6	25.2	2.92	1.05	100	36	11.5	26.3	25.6	3.38	1.13	n/a	n/a	n/a	n/a	n/a	n/a	76	54	n/a	n/a	n/a	n/a	n/a	76	54			

Abbreviations: AA = African-American; BNP = Brain natriuretic peptide (pg/ml); C = Caucasian; E/E' = ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity; F = female; hs-CRP = high sensitivity C-reactive protein (mg/L); LVEDV = left ventricular end-diastolic volume (mL); LVEF = left ventricular ejection fraction (%); M = male; n/a = not available; OUES = oxygen-uptake efficiency slope; Peak VO₂ = maximal oxygen consumption during cardiopulmonary exercise testing (ml.kg.min⁻¹); VE/VCO₂ = minute ventilation to carbon dioxide production ratio; Y = yes.