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SHORT COMMUNICATION

Interleukin-1 blockade in heart failure: an on-treatment and off-treatment cardiorespiratory fitness analysis

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Abstract

Aims Interleukin-1 (IL-1) blockade may improve exercise capacity in patients with heart failure (HF) patients. The extent of the improvement and its persistence beyond discontinuation of IL-1 blockade is unknown.

Methods and results The primary objective was to determine changes in cardiorespiratory fitness and cardiac function on-treatment with IL-1 blocker, anakinra, and off-treatment, after treatment cessation. We performed cardiopulmonary exercise testing, Doppler echocardiography, and biomarkers in 73 patients with HF, 37 (51%) females, 52 (71%) Black–African–American, before and after treatment with anakinra 100 mg daily. In a subset of 46 patients, testing was also repeated after treatment cessation. Quality of life was assessed in each patient using standardized questionnaires. Data are presented as median and interquartile range. Treatment with anakinra for 4 [2–12] weeks was associated with a significant improvement in high-sensitivity C-reactive protein (from 6.2 [3.3–15.4] to 1.4 [0.8–3.4] mg/L, $P < 0.001$), peak oxygen consumption (VO_{2peak}, from 13.9 [11.6–16.6] to 15.2 [12.9–17.4] mL/kg/min, $P < 0.001$). Ventilatory efficiency, exercise time, Doppler-derived signs and biomarkers of elevated intracardiac pressures, and quality-of-life measures also improved with anakinra. In the 46 patients in whom off-treatment data were available 12 [4–12] weeks later, many of the favourable changes seen with anakinra were largely reversed (from 1.5 [1.0–3.4] to 5.9 [1.8–13.1], $P = 0.001$ for C-reactive protein, and from 16.2 [14.0–18.4] to 14.9 [11.5–17.8] mL/kg/min, $P = 0.017$, for VO_{2peak}).

Conclusions These data validate IL-1 as an active and dynamic modulator of cardiac function and cardiorespiratory fitness in HF.

Keywords Cardiorespiratory fitness; C-reactive protein; Heart failure; IL-1 blockade

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Background

Preclinical studies have shown that interleukin-1 (IL-1) induces a transient cardiac dysfunction in isolated cardiomyocytes and animals.[1] Pilot clinical trials of IL-1 blockade in patients with heart failure (HF) show inhibition of systemic inflammation and improvement in cardiac function and cardiorespiratory fitness (CRF).[2–5]

Aims

The aim of the present work was to appraise the role of IL-1 in HF by assessing whether dynamic changes in peak oxygen consumption (VO_{2peak}) occur with IL-1 blockade while on-treatment with anakinra that are reversed upon discontinuation of treatment (off-treatment).

Methods

We analysed data from patients with HF who were treated with anakinra, recombinant IL-1 receptor antagonist, 100 mg daily, and underwent cardiopulmonary exercise testing (CPX) at baseline and during treatment with anakinra in the setting of a clinical trial, and after treatment suspension, when available. The analysis included the pooled active anakinra treatment arms in four previously published randomized-controlled trials of anakinra in HF.[2–5] Study design, inclusion/exclusion criteria, population characteristics, and main results of the trials have been published elsewhere.[2,4,5] CPX was administered using a conservative ramping treadmill protocol, as previously described.[2,4,5] All patients underwent transthoracic echocardiography and biomarkers determination during the same outpatient visit.

Individual patient data were pooled in a single prespecified data set and analysed. As different trials had different treatment and follow-up duration after treatment discontinuation, we considered for each patient the longest follow-up treatment and follow-up available after discontinuation. Categorical variables were compared using χ^2 test, or Fisher's exact test when appropriate. The within-group paired differences were compared using Wilcoxon signed-rank test. Correlation between continuous variables was assessed using Spearman's rank correlation coefficient. A two-sided *P*-value $\leq$0.05 was considered statistically significant.

Results

Seventy-three patients with CPX and C-reactive protein (CRP) values, measured with high-sensitivity assay, (2–5) were available before and during anakinra treatment, and 46 (63%) had repeat CPX and CRP values after cessation of treatment. The

Table 1 Clinical characteristics and cardiorespiratory fitness in the on-treatment and off-treatment cohorts

	On-treatment cohort (*N* = 73)			Off-treatment cohort (*N* = 46)		
Clinical variables						
Age (years)	55 [51–62]			54 [51–59]		
Sex: F (%)/M (%)	37 (51) /36 (49)			21 (46) /25 (54)		
Race: Black (%)/White (%)	52 (71) /21 (29)			33 (72) /13 (28)		
BMI (kg/m^2)	38 [32–44]			38 [34–44]		
CAD	18 (25%)			10 (22%)		
DM	44 (60%)			25 (54%)		
HTN	66 (90%)			40 (87%)		
HLP	50 (69%)			31 (67%)		
ACE-I/ARB	58 (80%)			37 (80%)		
Beta-blocker	66 (90%)			42 (91%)		
MRA	33 (45%)			22 (48%)		
CPX variables	Baseline	On-treatment	*P*	On-treatment	Off-treatment	*P*
Peak RER	1.11 [1.04–1.18]	1.13 [1.04–1.20]	0.181	1.16 [1.06–1.20]	1.10 [1.06–1.18]	0.149
Peak VO_2 (mL/kg/min)	13.9 [11.6–16.6]	15.2 [12.9–17.4]	**<0.001**	16.2 [14.0–18.4]	14.9 [11.5–17.8]	**0.017**
OUES	1.90 [1.50–2.21]	2.00 [1.68–2.45]	**0.007**	2.08 [1.71–2.39]	1.84 [1.56–2.32]	**0.011**
VE/VCO_2 slope	31 [27–35]	30 [25–33]	**0.001**	31 [26–33]	32 [28–34]	**0.028**
Exercise time (s)	460 [291–545]	490 [370–600]	**<0.001**	530 [415–668]	568 [383–663]	0.508
Echo-Doppler variables	Baseline	On-treatment	*P*	On-treatment	Off-treatment	*P*
LVEF (%)	45 [33–60]	45 [36–58]	0.757	44 [35–57]	50 [39–59]	0.327
E/e'	14.3 [9.7–20.0]	11.8 [8.6–14.9]	**0.002**	11.4 [8.7–14.6]	12.3 [8.6–17.6]	**0.017**
Biomarkers	Baseline	On-treatment	*P*	On-treatment	Off-treatment	*P*
CRP (mg/L)	6.2 [3.3–15.4]	1.4 [0.8–3.4]	**<0.001**	1.5 [1.0–3.8]	5.9 [1.8–13.1]	**0.001**
NT-proBNP (pg/mL)	549 [168–1604]	342 [87–1032]	**0.002**	342 [87–966]	242 [77–1003]	0.164
WBC ($\times 10^3$ cells/μL)	6.7 [5.6–8.4]	5.8 [4.6–6.9]	**<0.001**	5.7 [4.7–6.9]	6.7 [5.4–8.1]	**<0.001**
Neutrophils ($\times 10^3$ cells/μL)	4.3 [3.2–5.7]	2.9 [2.0–4.0]	**<0.001**	2.9 [2.0–3.9]	4.2 [2.9–5.3]	**<0.001**
Quality of life measures	Baseline	On-treatment	*P*	On-treatment	Off-treatment	*P*
DASI	24 [16–37]	32 [21–40]	**<0.001**	32 [20–37]	29 [19–50]	0.60
MLHFQ	51 [34–67]	40 [14–61]	**0.002**	40 [15–60]	22 [10–54]	0.087

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockade; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; DASI, Duke activity status index; DM, diabetes mellitus; E/e', early mitral inflow velocity/early diastolic mitral annual velocity; HLP, hyperlipidaemia; HTN, hypertension; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota living with heart failure questionnaire; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OUES, oxygen uptake efficiency slope; RER, respiratory exchange ratio; VE/VCO_2, minute ventilation/carbon dioxide production; VO_{2peak}, peak oxygen consumption; WBC, white blood cells.

duration of treatment was 4 [2–12] weeks. The time from discontinuation of anakinra to the latest off-treatment CPX was 12 [4–12] weeks. *Table 1* summarizes baseline demographic, clinical characteristics, and changes in CPX, biomarkers, and echocardiography.

VO_{2peak} improved significantly on-treatment with anakinra from 13.9 [11.6–16.6] to 15.2 [12.9–17.4] mL/kg/min ($P < 0.001$). After treatment cessation, VO_{2peak} significantly decreased from 16.2 [14.0–18.4] to 14.9 [11.5–17.8] mL/kg/min with suspension ($P = 0.017$). Similarly, exercise time, the oxygen uptake efficiency slope, and ventilation/carbon dioxide production slope, significantly improved upon anakinra introduction and worsened after suspension (*Table 1*).

Anakinra reduced CRP (from 6.2 [3.3–15.4] mg/L to 1.4 [0.8–3.4] mg/L, $P < 0.001$). After anakinra suspension, CRP significantly increased (from 1.5 [1.0–3.8] mg/L on treatment to 5.9 [1.8–13.1] mg/L after treatment suspension ($P = 0.001$). Of note, the changes in CRP were significantly negatively correlated to the changes in VO_{2peak} (Spearman's rho = −0.289, $P = 0.001$). Anakinra treatment was also associated with a significant decrease in white blood cell, neutrophil, and basophil counts, with these changes reverted in the off-treatment analysis (*Table 1*). N-terminal pro-B-type natriuretic peptide levels significantly decreased on-treatment with anakinra (549 [168–1604] pg/mL to 342 [87–1032] pg/mL, $P = 0.002$, with no significant changes in off-treatment analysis, *Table 1*).

No differences in LVEF were detected on- or off-treatment with anakinra. The early mitral inflow velocity/early diastolic mitral annual velocity (E/e') decreased on-treatment (14.3 [9.7–20.0] vs. 11.8 [8.6–14.9], $P = 0.002$) and increased in the off-treatment analyses (11.4 [8.7–14.6] vs. 12.3 [8.6–17.6], $P = 0.017$; *Table 1*).

The Duke Activity Status Index score, a subjective measure of exercise capacity, significantly increased while on-treatment with anakinra, reflecting better perceived functional capacity, and the Minnesota Living with Heart Failure Questionnaire was significantly reduced, reflecting reduced HF burden while on-treatment with anakinra (*Table 1*); no significant changes in Duke Activity Status Index or Minnesota Living with Heart Failure Questionnaire off-treatment were, however, noted.

Three of four studies included placebo, albeit in a minority of patients. We identified 31 placebo patients with CPX and CRP values available before and during treatment, and of these 14 with repeat CPX and CRP values after cessation of treatment. No significant changes were seen in VO_{2peak} (13.8 [11.4–16.1] vs. 14.3 [11.7–17.7] mL/kg/min, $P = 0.233$) or CRP (5.05 [2.5–12.6] vs. 4.8 [2.6–15.3] mg/L, $P = 0.399$) values in patients receiving placebo, and no changes with discontinuation of placebo treatment in those who had available data (VO_{2peak}: 15.3 [13.1–20.1] to 14.1 [12.6–17.1] mL/kg/min, $P = 0.600$; CRP: 5.0 [3.1–14.7] to 6.0 [1.5–11.6] mg/L, $P = 0.103$).

Conclusions

In summary, the pooled analysis of patients with HF treated with anakinra showed that (i) IL-1 blockade is associated with dynamic changes in CRF; (ii) changes in VO_{2peak} with anakinra are significantly associated with changes in systemic inflammation; (iii) changes in CRF are related to dynamic changes in Doppler-derived estimates of left ventricular end-diastolic pressure (E/e', and N-terminal pro-B-type levels). These data support the hypothesis that IL-1 is an active and dynamic regulator of cardiac function and CRF in HF. Whether a longer duration of anakinra treatment would provide sustained clinical benefit is unknown.

Conflict of interest

Drs. Abbate and Van Tassell have received grant support from and have served as consultants to Swedish Orphan Biovitrum (SOBI, Stockholm, Sweden) in the past. Dr. Giuseppe Biondi-Zoccai has consulted for Amarin, Balmed, Cardionovum, Crannmedical, Endocore Lab, Eukon, Innovheart, Guidotti, Meditrial, Microport, Opsens Medical, Replycare, Teleflex, Terumo, and Translumina. None of the other authors report any conflict of interest regarding the content of this article.

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