Galectin-3 and the Mineralocorticoid Receptor Antagonist Canrenone in Mild Heart Failure

Francesco Clemenza, MD; Serge Masson, PhD; Pier Giulio Conaldi, MD; Daniele Di Carlo, MD; Alessandro Bocanelli, MD; Gian Francesco Mureddu, MD; Lucio Gonzini; Donata Lucci; Aldo P. Maggioni, MD; Andrea Di Lenarda, MD; Enrico B. Nicolì; Massimo Vanasia, MD; Roberto Latini, MD
on behalf of the AREA IN-CHF Investigators

Background: Galectin-3 (Gal-3) is involved in collagen deposition and inflammation and is a prognostic biomarker in heart failure (HF).

Methods and Results: Gal-3 and other markers of fibrosis or cardiac stress were measured serially in 413 patients with mild HF randomized to the mineralocorticoid receptor antagonist canrenone or placebo to evaluate treatment effect and association with clinical outcome. Gal-3 increased slightly over 6 months in both arms of the study and was associated with clinical endpoints.

Conclusions: Although Gal-3 showed prognostic value, the effect of canrenone on clinical outcomes was unaffected by baseline concentrations of biomarkers of fibrosis or cardiac stress.

Key Words: B-type natriuretic peptide; Clinical trials; Galectin-3; Heart failure; Mineralocorticoid receptor antagonist

Galectin-3 (Gal-3), a protein of the β-galactoside-binding lectin family, is involved in collagen deposition and inflammation, and has been shown to be a prognostic biomarker in heart failure (HF). Because the role of circulating Gal-3 levels in the individualizing of therapy and management of HF remains to be elucidated, we investigated the effect of the mineralocorticoid receptor antagonist (MRA) canrenone on Gal-3 levels and their interaction on clinical outcomes in patients with mild, chronic HF with reduced ejection fraction (EF) enrolled in a clinical trial.

Methods

AREA IN-CHF was a multicenter, randomized, double-blind, placebo-controlled trial comparing canrenone with placebo in 467 patients with mild, chronic HF over 12 months of follow-up. The investigation conformed with the principles of the Declaration of Helsinki, the protocol was approved by the ethics committees of all participating centers and informed consent was obtained from all enrolled subjects. The prespecified primary endpoint was a change in echocardiographic left ventricular (LV) end-diastolic volume over 12 months. Secondary endpoints included total deaths, hospitalization for cardiac causes, and the combination of cardiac death and hospitalization for cardiac causes. Blood samples were collected at randomization and after 6 months and sent to a central laboratory for measurement of B-type natriuretic peptide (BNP), procollagen type III aminoterminal peptide (PIIINP), and aldosterone (at baseline). Gal-3 at baseline (n=413) and 6 months (n=339) was measured with a chemiluminescent microparticle immunoassay (Abbott Diagnostics).

The effects of time (baseline and 6 months) and study treatment on biomarker concentrations were assessed with a 2-way ANOVA analysis. Logistic regression analyses were done to test the biomarker’s associations with clinical events at 12-month follow-up, considering Gal-3 as continuous, with the only exception of the non-linear relation with hospitalization for cardiac causes. The multivariable models were adjusted for treatment arm, age, hospitalization for HF in the previous year, diabetes, chronic obstructive pulmonary disease (COPD), creatinine, prescription of diuretics and of angiotensin-converting enzyme inhibitor (ACEi)/angiotensin-receptor blocker (ARB), with a backward selection forcing the single marker in the model.

Received June 19, 2017; revised manuscript received July 14, 2017; accepted August 7, 2017; released online August 31, 2017

Time for primary review: 24 days
Heart Failure Unit (F.C.), Department of Laboratory Medicine and Advanced Biotechnologies (P.G.C., D.D.C.), ISMETT, Palermo; Department of Cardiovascular Research, IRCCS-Istituto di Ricerche Farmacologiche “Mario Negri”, Milan (S.M., E.B.N., R.L.); Cardiology Department, Quisisana Hospital, Rome (A.B.); Cardiology Unit, San Giovanni-Addolorata Hospital, Rome (G.F.M.); ANMCO Research Center, Florence (L.G., D.L., A.P.M.); Cardiovascular Center, ASUI, Trieste (A.D.L.); and Therabel GiEne Pharma, Milan (M.V.), Italy

Mailing address: Francesco Clemenza, MD, Heart Failure Unit, ISMETT, via Tricomi 5, 90100 Palermo, Italy. E-mail: fclemenza@ismett.edu

ISSN-1346-9843 All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp
Finally, an interaction between Gal-3, BNP, PIIINP, aldosterone, and study treatment on clinical outcomes was assessed by Breslow-Day test for the homogeneity of the odds ratios (ORs). A 2-sided P<0.05 was considered statistically significant.

### Results

Patients with baseline Gal-3 concentration above the median (10.8 ng/mL) were older, more frequently diabetic, with a prior hospitalization for HF, with peripheral artery
Galectin-3 and Canrenone in Mild HF

The effect of canrenone on clinical outcomes at 12-month follow-up was unaffected by baseline concentrations of the 4 biomarkers. Nonetheless, its clinical benefit (lower incidence of cardiac death/hospitalization for cardiac causes) tended to be higher in patients with Gal-3 levels over the median concentration, although the interaction was not statistically significant (Figure). This is in agreement with other studies on MRAs. In contrast, in Val-HeFT valsartan significantly reduced hospitalizations for HF in patients with lower than the median levels of Gal-3 at entry, while in CORONA rosuvastatin reduced the primary endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke in patients with Gal-3 <19.0 ng/mL.

Low Gal-3 may reflect reversible as opposed to irreversible myocardial fibrosis, as suggested by the findings from the PARAMOUNT trial in HF with preserved EF where LCZ696 reduced left atrial volume more effectively in patients with sST2 and Gal-3 levels below their respective medians. However, there are no clinical trials prospectively selecting patients with HF based on Gal-3 concentrations.

Conclusions

Gal-3 in mild HF was associated with the severity of HF and clinical outcomes. However, BNP but not Gal-3 levels over 6 months were affected by canrenone. The effect of canrenone on clinical outcomes was unaffected by baseline concentrations of biomarkers of fibrosis or cardiac stress. However, a non-statistically significant trend for a larger beneficial effect of canrenone was apparent in patients with above median concentrations of Gal-3, BNP, and aldosterone.

Acknowledgments

We thank Giuseppe Fraterrigo and Rossana Spatola for their skillful assistance with performing Gal-3 assays.
Conflicts of Interest

The funding source (Therabel GiEnne Pharma SpA) had no role in
the trial design, conduct, data collection, analyses and data interpre-
tation.

M.V. is employed by Therabel GiEnne Pharma SpA. L.G., D.L.,
and A.P.M. are employed at Heart Care Foundation, ANMCO
Research Center, an independent research institution that received
unrestricted funding from Therabel GiEnne Pharma SpA to conduct
the study. The echocardiography (G.F.M.) and the biomarker core
laboratories (S.M., E.B.N., and R.L.) received a research grant from
Therabel GiEnne Pharma SpA. F.C., A.B., P.G.C., D.D.C., and
A.D.L. have no conflicts of interest to declare.

References

1. Yang RY, Rabinovich GA, Liu FT. Galectins: Structure,
10: e17.
2. Chen A, Hou W, Zhang Y, Chen Y, He B. Prognostic value of
serum galectin-3 in patients with heart failure: A meta-analysis.
Int J Cardiol 2015; 182: 168 – 170.
3. Koukou F, Desmoulin F, Galinier M, Barutaut M, Caubère C,
Evaristi MF, et al. The prognostic value of plasma galectin-3 in
chronic heart failure patients is maintained when treated with
mineralocorticoid receptor antagonists. PLoS One 2015; 10:
e0119160.
4. Edelmann F, Holzendorf V, Wächter R, Nolte K, Schmidt AG,
Kraigher-Krainer E, et al. Galectin-3 in patients with heart failure
with preserved ejection fraction: Results from the Aldo-DHF
5. Boccanelli A, Mureddu GF, Cacciatore G, Clemenza F, Di
in patients with mild chronic heart failure (AREA IN-CHF
7. Gandhi PU, Motiwala SR, Belcher AM, Gaggin HK, Weiner
RB, Baggish AL, et al. Galectin-3 and mineralocorticoid receptor
antagonist use in patients with chronic heart failure due to left
ventricular systolic dysfunction. Am Heart J 2015; 169:
404 – 411.e3.
8. Anand IS, Rector TS, Kuskowski M, Adourian A, Muntendam
P, Cohn JN. Baseline and serial measurements of galectin-3 in
patients with heart failure: Relationship to prognosis and effect
of treatment with valsartan in the Val-HeFT. Eur J Heart Fail
9. Gullestad L, Ueland T, Kjekshus J, Nymo SH, Hulthe J,
Muntendam P, et al. Galectin-3 predicts response to statin therapy
in the Controlled Rosuvastatin Multinational Trial in Heart
10. Zile MR, Jhund PS, Baicu CF, Claggett BL, Pieske B, Voors AA,
et al; Prospective Comparison of ARNI With ARB on Management
of Heart Failure With Preserved Ejection Fraction (PARAMOUNT)
Investigators. Plasma biomarkers reflecting profibrotic processes in
heart failure with a preserved ejection fraction: Data from the Prospective Comparison of ARNI With
ARB on Management of Heart Failure With Preserved Ejection