Galectin-3 and Cardiac Function in Survivors of Acute Myocardial Infarction

Weir et al: Galectin-3 Post-Infarction Remodeling

Robin A.P. Weir¹, MD; Colin J. Petrie², MBChB; C. Aengus Murphy², MD; Suzanne Clements³, BSc; Tracey Steedman³, BSc; Ashley M. Miller⁴, PhD; Iain B. McInnes⁴, PhD; Iain B. Squire⁵, MD; Leong L. Ng⁵, MD; Henry J. Dargie³, MBChB; John J.V. McMurray³, MD

¹Cardiology Department, Hairmyres Hospital, Lanarkshire, Scotland, UK
²Cardiology Department, Monklands Hospital, Lanarkshire, Scotland, UK
³Cardiology Department, Western Infirmary, Glasgow, Scotland, UK
⁴Division of Immunology, Infection and Inflammation, Glasgow Biomedical Research Centre, University of Glasgow, Scotland, UK
⁵Department of Cardiovascular Sciences, Leicester Royal Infirmary, Leicester, UK and Leicester National Institute for Health Research Cardiovascular Biomedical Research Unit, UK

Correspondence to
Robin AP Weir
Cardiology Department
Hairmyres Hospital
Eaglesham Road
East Kilbride G75 8RG, Scotland, UK
Email: robinweir75@hotmail.com
Tel: +441355584086
Fax: +441412111791

DOI: 10.1161/CIRCHEARTFAILURE.112.000146

Journal Subject Codes: [4], [11], [30], [118]
Abstract

Background—Galectin-3 is a biomarker associated with inflammation and fibrosis which predicts adverse outcome and relates to biomarkers of extracellular matrix (ECM) turnover in patients with heart failure, particularly when left ventricular [LV] systolic function is preserved. Whether galectin-3 is related to LV remodeling after acute myocardial infarction (AMI) is unknown.

Methods and Results—Circulating galectin-3 and various ECM biomarkers were measured in 100 patients (age 58.9±12.0 years, 77% male) admitted with AMI and LV dysfunction, at baseline (mean 46h) and at 24 weeks, with cardiac magnetic resonance imaging at each time-point. LV remodeling was defined as change in LV end-systolic volume index. Relationships between galectin-3, biomarkers and LV remodeling were analyzed across the entire cohort, then according median baseline LV ejection fraction (LVEF). Galectin-3 levels were elevated in 22 patients (22%) at baseline and increased significantly over time from 14.7±5.5 to 16.3±6.6ng/mL (p=0.007). Baseline galectin-3 did not correlate with any LV parameter at baseline or change in any parameter over time. Galectin-3 was positively associated with remodeling in patients with supramedian baseline LVEF (ie. >49.2%; r = 0.40, p = 0.01) but not when LVEF was ≤49.2%. Galectin-3 correlated significantly with matrix metalloproteinase-3 and monocyte chemoattractant protein-1 at baseline, biomarkers that have been shown to relate to LV remodeling in this cohort.

Conclusions—Galectin-3 correlated significantly with certain biomarkers involved in ECM turnover although no definite relationship was identified with LV remodeling. Whether galectin-3 plays a pathological role in remodeling remains unclear but merits further study.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00132093.

Key Words: Galectin-3, acute myocardial infarction, remodelling, cardiac magnetic resonance
With the widespread introduction of optimal reperfusion therapy for the management of ST-elevation acute myocardial infarction (AMI), and significant advances in the treatment of non-ST-elevation acute coronary syndromes (ACS), greater numbers of patients survive an acute infarct but remain at risk of developing heart failure. Following acute myocardial injury, even if coronary blood flow is promptly restored, a series of mechanical and neurohormonal triggers may precipitate geometric changes that result in progressive left ventricular (LV) dilatation and dysfunction, leading ultimately to heart failure and premature death; this process is termed remodeling.\textsuperscript{1-4} Attenuation (or even reversal) of LV remodeling is already a major focus in the management of survivors of ACS.

Galectin-3 is a \(\beta\)-galactoside-binding lectin secreted by activated macrophages which has gained interest as at least a marker of, or possibly even a potential mediator in inflammation and fibrosis, processes that are central to the pathophysiology of LV remodeling.\textsuperscript{5,6} Upregulation of galectin-3 expression has been demonstrated in murine models of hypertensive heart disease, myocarditis and cardiomyopathy, and in the hypertrophied ventricular myocardium of humans with aortic stenosis and depressed LV systolic function.\textsuperscript{7-9} Serum galectin-3 is increased in patients with acutely decompensated heart failure (ADHF), while elevated serum galectin-3 levels in patients with chronic heart failure (CHF) are associated with higher New York Heart Association (NYHA) class and predict poorer outcome.\textsuperscript{10-12} Correlation between serum galectin-3 and echocardiographic measures of diastolic function and right ventricular (RV) performance have been demonstrated in dyspnoeic patients with and without ADHF, but detailed cardiac structural data in relation to galectin-3 levels are lacking.\textsuperscript{13} Moreover there are no human studies examining the role of galectin-3 in LV remodeling following AMI. We measured galectin-3 on plasma samples from a cohort of patients admitted with AMI and enrolled in a randomized trial assessing the
effects of aldosterone antagonism on LV remodeling, and present data on the relationships over time of plasma galectin-3 and cardiac structural and functional parameters, using cardiac magnetic resonance imaging (CMR).

Methods

Patients

The subjects of this study were participants in a randomized, double-blinded, placebo-controlled clinical trial investigating the effects of eplerenone on LV remodeling following AMI. Inclusion criteria were: age ≥18 years; able to provide written, informed consent; AMI 1-14 days prior to enrolment; screening transthoracic echocardiographic (TTE) LV ejection fraction (LVEF) <40% (Simpson’s biplane rule). The main exclusion criteria were: clinical or radiological heart failure (Killip score >1); diabetes mellitus; pregnancy; serum creatinine >220 μmol/L (~2.5 mg/dL); serum potassium >5.0 mmol/L; planned coronary artery bypass surgery; contraindication to CMR. The trial protocol complied with the declaration of Helsinki and was approved by the local ethics committee.

Methods

At baseline eligible patients had venous blood collected for measurement of blood chemistry and biomarker concentrations (including galectin-3), after which contrast-enhanced CMR (ceCMR) was performed. Patients were then randomized to double-blind eplerenone or placebo, with repeat ceCMR and measurement of plasma biomarkers at 24 weeks after which study drug was withdrawn and individual patient involvement in the trial ceased.
Measurement of Galectin-3

For galectin-3 measurement, we used an enzyme-linked immunosorbent assay (ELISA) developed by BG Medicine, Inc. Waltham, MA, USA, which quantitatively measures galectin-3 concentrations on plasma samples. At both time-points, blood was collected into chilled tubes containing potassium EDTA (1mg/mL blood) and aprotinin (50 KIU/mL blood), and centrifuged within one hour at 2000g for 15 minutes at ambient temperature. Plasma was extracted and stored at -70°C until batched blinded analysis after trial completion. Each aliquot was subjected to two freeze-thaw cycles. The coefficient of variation (CV) for the assay was <10%, and the limit of detection 1.13ng/mL.

Measurement of Other Biomarkers

Blood similarly collected into chilled tubes containing potassium EDTA and aprotinin, and centrifuged within one hour prior to plasma extraction and storage at -70°C, was used for quantification of matrix metalloproteinases (MMP-2, -3 and -9), tissue inhibitors of metalloproteinase (TIMP-1, -2 and -4) and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Each aliquot was subjected to one freeze-thaw cycle only. The MMPs and TIMPs were measured using commercially-available ELISA kits (R&D systems, Abindgon, Oxfordshire UK). The intra- and inter-assay CV was <10% for each assay. NT-proBNP was measured using a chemiluminescent assay kit (Roche Diagnostics) on an Elecsys 2010 autoanalyzer (CV <2%, limit of detection of 5pg/mL).

Blood simultaneously collected into plain tubes, allowed to clot, then centrifuged at 2000g for 15 minutes at ambient temperature prior to serum extraction and storage at -70°C was used to measure several biomarkers. Serum cytokines were analysed in a 20-plex human cytokine assay (Biosource, Invitrogen) for simultaneous quantification of interleukin-1 (IL-1)
receptor antagonist (IL-1Ra), IL-2 receptor (IL-2R), IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12(p40), IL-15, IL-21 and monocyte chemoattractant protein-1 (MCP-1). This assay was run according to the manufacturer’s procedure and read on the Bio-Plex suspension array system (CV <5%). Serum soluble ST2 (sST2) was quantified using a human IL-1 R4/ST2 ELISA (R&D Systems), with CV <5% and lower limit of detection 32 pg/mL. Apelin quantification was performed using the Apelin-12 microplate ELISA assay kit (Phoenix Pharmaceuticals) according to the manufacturer’s instructions (CV <5%).

ceCMR Protocol and Analysis

ceCMR was performed using a 1.5T Siemens Sonata with a phased-array chest coil, during breath-hold, and gated to the electrocardiogram. The sequences employed in cine image acquisition and in inversion-recovery imaging following administration of gadolinium diethylenetriaminepentaacetate (GE Healthcare), together with the techniques used in measuring LV volumes, LVEF and infarct volumes, have been described in detail previously.14

Statistics

ceCMR measurements were adjusted for total body surface area, creating the following indexed quantities: LV end-systolic volume index (LVESVI), LV end-diastolic volume index (LVEDVI), LV mass index (LVMI) and LV infarct volume index. Only patients with both a baseline and 24 week follow-up scan were analyzed; patients with an incomplete dataset were excluded. Left ventricular remodeling was defined as the change in LVESVI between baseline and 24 weeks as this is more strongly predictive of adverse cardiovascular outcome than change in LVEDVI (or even change in LVEF).4 All baseline biomarker measurements were taken prior to randomization, and serial biomarker data were analysed regardless of
parent study treatment allocation; galectin-3 data were then analysed by treatment group. Normally distributed, continuous data are expressed as mean values (±SD). Non-normally distributed continuous data are expressed as medians [interquartile range]. Differences between mean values were analysed using the Student’s t-test and those between median values by the Mann-Whitney U test. Paired comparisons in biomarker concentrations over time were performed using the Wilcoxon match-pairs signed-rank test. The biomarker data were non-normally distributed and thus were logarithmic-transformed prior to correlative analysis. Bonferroni post-hoc correction was applied to comparisons of mean concentrations of galectin-3 and the sampled biomarkers listed above; where quoted, the p values for such comparisons are (SPSS) Bonferroni-corrected. Spearman correlation coefficients were used to assess the relationships between biomarker values and ceCMR parameters of LV function.

Given that galectin-3 is a more powerful prognostic marker in CHF with preserved LVEF (HF-PEF) than in CHF with reduced LVEF (HF-REF)12, we categorised LVEF at baseline according to median LVEF, then analyzed the relationship between galectin-3 and remodeling in relation to median baseline LVEF. In order to test for interaction between baseline galectin-3, LVEF and remodeling in each of these two sub-groups (baseline LVEF ≤ median, baseline LVEF > median), linear regression analysis was performed with baseline LVEF, galectin-3 and an interaction quotient – defined as the product of baseline LVEF and galectin-3 – inserted as independent variables to assess the effects on change in LVESVI in each group. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA). A probability value of p<0.05 was considered significant.
Results

Baseline characteristics are shown in Table 1. The mean time from AMI to screening TTE was 34 hours, and to the first ceCMR scan was 97 hours; biomarker sampling was performed at a mean 46 hours after AMI and again at 24 weeks. Paired analysis of both ceCMR and biomarker results was performed in the 93 patients who completed the entire 24 weeks follow-up (3 died, 4 withdrew).

Galectin-3 Levels

For all study subjects (n = 100) at baseline, mean plasma galectin-3 concentration was 14.7 ± 5.4 (SD) ng/mL. Twenty-two patients (22%) had galectin-3 levels above the upper limit of normal cut-off value for galectin-3 of 17.7 ng/mL. Higher galectin-3 concentrations were associated with older age \( (r = 0.29, p = 0.004) \), higher serum creatinine \( (r = 0.39, p<0.001) \) and (weakly) with the use of an ACE inhibitor at baseline \( (r = 0.20, p = 0.049) \). Paired analysis of galectin-3 concentrations in the 93 patients who completed the study revealed a significant increase in plasma galectin-3 between baseline and 24 weeks, from 14.7 ± 5.5 to 16.3 ± 6.6 ng/mL \( (p = 0.007) \). Over the same time period, serum creatinine was unchanged \( (100.0 ± 21.3 \mu\text{mol/L at baseline, 98.8 ± 21.6 } \mu\text{mol/L at 24 weeks; } p = 0.46) \).

Galectin-3 and LV Function

Across the cohort, LVEF increased significantly between baseline and 24 weeks, from 48.9 (8.8) to 52.9 (11.9)\%, \( p<0.001 \). Baseline galectin-3 had no correlation with baseline CMR measurements: LVESVI \( (r = 0.02, p = 0.083) \), LV end-diastolic volume index (LVEDVI; \( r = 0.01, p = 0.95 \)), LVEF \( (r = -0.14, p = 0.16) \) or infarct volume index \( (r = 0.10, p = 0.34) \).

Similarly, there were no significant relationships between baseline galectin-3 and change from baseline to 24 weeks in any CMR measure (\( \Delta \text{LVESVI, } \Delta \text{LVEDVI, } \Delta \text{LVEF or } \Delta \text{infarct} \).
volume index). When analyzed in relation to 24-week values of these CMR parameters, baseline galectin-3 displayed inverse correlation with 24-week LVEF \( (r = -0.25, p = 0.023) \) but not with any other parameter. Change in galectin-3 from baseline to 24 weeks had no association with the change in any LV or infarct volume measurement over time (Figure).

Median LVEF was 49.2%. The relationships between galectin-3 and remodelling were analyzed according to whether baseline LVEF was >49.2% or ≤49.2%. In patients with supra-median LVEF at baseline, galectin-3 increased significantly from 13.9 ± 4.3 to 15.5 ± 5.3 ng/mL (\( p = 0.016 \)) while in those with baseline LVEF ≤49.2%, galectin-3 was 15.5 ± 6.4 ng/mL at baseline and 17.0 ± 7.7 ng/mL at 24 weeks (\( p = 0.11 \)). There were no significant associations between baseline galectin-3 and \( \Delta \)LVESVI (ie. remodeling: \( r = 0.11, p = 0.46 \)), \( \Delta \)LVEDVI (\( r = 0.02, p = 0.91 \)) or change in any other LV parameter over time in patients with LVEF ≤49.2%. In those with supramedian LVEF at baseline, however, galectin-3 correlated significantly with both \( \Delta \)LVESVI (\( r = 0.40, p = 0.01 \)) and \( \Delta \)LVEDVI (\( r = 0.42, p = 0.008 \)) but not with change in any other parameter. In patients with baseline LVEF ≤49.2%, interaction tests revealed no significant relationships between \( \Delta \)LVESVI and baseline galectin-3 (\( \beta \) coefficient -2.3, \( p = 0.10 \)), baseline LVEF (\( \beta \) -0.45, \( p = 0.27 \)) or the galectin-3/LVEF interaction coefficient (\( \beta 0.26, p = 0.09 \)). In the sub-group of patients with baseline LVEF >49.2%, however, galectin-3 remained a significant predictor of \( \Delta \)LVESVI (\( \beta 2.7, p = 0.04 \)); the relationship between \( \Delta \)LVESVI and the galectin-3/LVEF interaction coefficient was of borderline statistical significance (\( \beta -2.5, p = 0.05 \)). Baseline LVEF was not a significant predictor of \( \Delta \)LVESVI in this sub-group (\( \beta 0.75, p = 0.10 \)).
Galectin-3 and Natriuretic Peptides

NT-proBNP fell from 2587 (2732) pg/mL at baseline to 841 (1982) pg/mL at 24 weeks (p<0.001). Baseline galectin-3 correlated with baseline NT-proBNP (r = 0.30, p = 0.003) and with ΔNT-proBNP (r = -0.24, p = 0.022).

Galectin-3 and Biomarkers

Correlative analysis of galectin-3 concentrations and the sampled biomarkers is detailed in Table 2. At baseline, there was significant correlation between galectin-3 and MMP-3, TIMP-1, MCP-1 and IL-8. The only parameter that correlated significantly with change over time in galectin-3 was change in apelin concentration.

Effect of Eplerenone on Galectin-3

At baseline, serum galectin-3 was 14.0 (4.6) ng/mL in patients randomized to placebo and 15.3 (6.0) ng/mL in those randomized to eplerenone (p = 0.26). There was a non-significant trend towards increase in galectin-3 in the placebo group (+1.1 [4.4] ng/mL, p = 0.074), while the increase in galectin-3 levels in eplerenone-treated patients reached significance (+2.1 [6.7] ng/mL, p = 0.039). There was no significant treatment effect of eplerenone on serum galectin-3 levels over the 24-week study period (p = 0.23). In the parent study, eplerenone had a modest anti-remodeling effect, but only after covariate adjustment.14

Discussion

A potential role for galectin-3 in the pathophysiology of LV remodeling has been suggested by a variety of animal and human studies, although a causal effect has yet to be proven. Data on circulating levels of galectin-3 in the early post-AMI period in humans are lacking, however, as are detailed cardiac structural data in relation to galectin-3 concentrations in
survivors of AMI and in patients with CHF. Galectin-3 has been shown to be elevated in 49% of a cohort of patients with NYHA class III-IV CHF and reduced LVEF; levels of galectin-3 were unchanged over 6 months in a subset of these patients who underwent serial sampling.\textsuperscript{15} Galectin-3 was similarly unchanged over 18 months in patients with CHF, reduced LVEF and interventricular conduction defects enrolled in the Cardiac Resynchronization in Heart Failure Trial (CARE-HF) trial.\textsuperscript{16} Among the novel findings in this study we have shown that around one-fifth of a cohort of patients admitted with AMI, with reduced LVEF at baseline, had an elevated plasma galectin-3 when sampled on average 2 days after symptom onset. Moreover, despite a high revascularization rate and greater uptake of anti-remodeling drug therapy than any other post-AMI trial to date (reflected in the observation that LVEF rose significantly over the study follow-up and LV volumes decreased), plasma galectin-3 was found to increase significantly over time. While this may suggest an uncoupling of galectin-3 and serial change in LV function, there were interesting observations when galectin-3 levels were analyzed in relation to remodeling in this cohort.

We found that galectin-3 had no correlation with LVEF or LV volumes on the baseline CMR scan. This is consistent with echocardiographic studies in CHF patients which have consistently failed to demonstrate any relationship between galectin-3 and LVEF, although galectin-3 has been shown to correlate with parameters of LV stiffness (‘diastolic’ function) and RV function in such patients.\textsuperscript{13,15} However, subgroup analysis of patients stratified by median baseline LVEF revealed significant relationships between baseline galectin-3 and change in both LVESVI and LVEDVI over time in those with relatively preserved LV function early after AMI (ie. those with LVEF greater than the median) but not in those with median or lower baseline LVEF. This study was underpowered for biomarker analysis thus these findings may simply be spurious, or may simply reflect findings from a recent ACS.
study and a number of CHF trials that galectin-3 is an adverse prognostic marker.\textsuperscript{12,13,15,17} Galectin-3 has, however, been shown to be a more powerful prognostic indicator in patients with HF-PEF than in those with HF-REF.\textsuperscript{12} Galectin-3 is related to certain echocardiographic markers of ‘diastolic’ but not systolic dysfunction.\textsuperscript{13} In the failure-prone hypertrophied rat heart, myocardial biopsy prior to development of overt heart failure showed that galectin-3 expression was highest in the rats that later developed heart failure.\textsuperscript{7} We have found a possible association between higher galectin-3 levels and greater remodeling in patients with relatively preserved LV function early after AMI but not in those with more severe LV dysfunction.

Why might galectin-3 appear to be of greater significance prognostically (and perhaps pathophysiologically) in patients with relatively preserved LV function in CHF (and possibly following AMI)? Galectin-3 has been demonstrated to be pro-fibrotic in animal models. It is released by activated macrophages and is required for normal phagocytosis, but in pathological states such as (experimental) myocarditis and myocardial hypertrophy (in murine and rat models), galectin-3 stimulates macrophage migration and may also stimulate cardiac fibroblastic proliferation.\textsuperscript{11,12,18} Infusion of galectin-3 into the pericardium of healthy rats promoted extensive myocardial fibrosis and progressive LV dysfunction, effects that were completely obviated by the antifibrotic agent N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP).\textsuperscript{7,19} Although a pro-fibrotic effect in human myocardium has yet to be confirmed, galectin-3 has been shown to correlate significantly with MMP-2, TIMP-1 and PIIINP, all markers of ECM turnover, in patients with HF-REF.\textsuperscript{20} In the current cohort, we have previously demonstrated associations between TIMP-4, MMP-3, MCP-1 and sST2 and remodeling; of these biomarkers, galectin-3 was significantly associated with MMP-3 and MCP-1 at baseline in the current analysis.\textsuperscript{14,21-23} Galectin-3 may thus influence a variety of
separate pathways of ECM turnover, and may provide the link between macrophage activation and fibrosis, although this requires further investigation. Whether galectin-3 may activate certain pro-fibrotic, pro-remodeling pathways in patients with preserved LV function that, perhaps, are already highly activated (via other means) in those with depressed LV function is unknown, but clearly the determination of whether galectin-3 plays a definite role in remodeling merits further study.

NT-proBNP is elevated in symptomatic and asymptomatic LVSD and predicts mortality across all grades of CHF (both HF-REF and HF-PEF).\textsuperscript{24-26} It also predicts major adverse cardiac events following AMI.\textsuperscript{27} NT-proBNP was elevated early after AMI in the present study and, although it decreased significantly over time, remained elevated at 24 weeks. We found that galectin-3 correlated significantly with NT-proBNP at baseline. Similar findings have been reported following ACS and in patients with CHF.\textsuperscript{12,13,28} Baseline galectin-3 also correlated inversely with ΔNT-proBNP, although galectin-3 subsequently rose over time. This presumably reflects the difference between the pro-fibrotic effects of galectin-3 and the load-dependent nature of natriuretic peptide release, NT-proBNP (and BNP) tending to fall with reduction in myocardial stretch and in the presence of off-loading therapies such as ACE inhibitors and diuretics. Indeed, in patients with advanced CHF requiring left ventricular assist device (LVAD) support, galectin-3 and BNP were significantly elevated at baseline but, while BNP fell significantly after LVAD implantation, galectin-3 did not (although galectin-3 was highest in those who died).\textsuperscript{11}

The present study is the first to date that has assessed the effect of anti-remodeling drug therapy on galectin-3 levels – in either AMI or CHF – in a randomized, controlled manner. We analyzed whether 24 weeks of therapy with eplerenone influenced plasma galectin-3
levels following AMI. The study was powered for CMR end-points rather than drug effects on biomarkers. Within these confines, we found that galectin-3 increased over 24 weeks in patients treated with eplerenone but not in those receiving placebo, although overall the treatment effect did not reach statistical significance. In a recent sub-study of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), use of an aldosterone antagonist was associated with higher concentrations of galectin-3 in patients with chronic systolic heart failure. These data may suggest potential interplay between galectin-3 and the aldosterone pathway, although such findings would need to be explored in a larger, appropriately-powered study. That the pro-fibrotic effects of galectin-3 were blocked by Ac-SDKP in an experimental model of cardiac remodeling suggest that further research is warranted into both the development and possible clinical applications of galectin-3-modifying therapy in the attempt to ameliorate remodeling in CHF and following AMI.

**Limitations**

The main limitation of this study is that the clinical trial on which the current analysis is based was powered for CMR end-points, not biomarker effects. The results are therefore hypothesis-generating only. It is, however, the only study using serial CMR scanning – the current gold standard imaging modality for LVEF and LV volume measurement (and which allows significant sample size reduction compared to echocardiography and other modalities) – in relation to galectin-3. We measured galectin-3 only once at baseline, on average 2 days after AMI. It is not known whether galectin-3 levels fluctuate in plasma early after AMI, or indeed over the 24-week period that served as follow-up in our study. Similar limitations are relevant to studies of galectin-3 in CHF. Our findings are applicable to patients with AMI and depressed LV function on echocardiography performed within 48 hours of infarction, and without clinical heart failure, and therefore cannot be extrapolated to all patients with AMI.
We measured galectin-3 concentrations in plasma only, which provide no information on tissue levels. Finally, the correlations reported do not necessarily indicate direct biological relationships but do provide directions for further study.

Conclusions

This is, to our knowledge, the first study reporting serial galectin-3 concentrations in human plasma following AMI. Galectin-3 was elevated in only around one-fifth of survivors of AMI with reduced LVEF. Higher galectin-3 concentrations at baseline were significantly associated with lower LVEF at 24-week follow-up, although there was no significant relationship between galectin-3 and remodeling per se. Whether a relationship does exist between galectin-3 and remodeling after AMI remains unclear and will require to be analyzed further in larger, appropriately powered studies. Galectin-3 appears to be related to natriuretic peptides following AMI similar to findings from CHF trials, and correlated significantly with certain biomarkers involved in the inflammation-fibrosis cascade, although it remains unclear whether galectin-3 plays a direct role in remodeling. We found no significant effect of therapy with the aldosterone antagonist eplerenone on serum galectin-3 levels over 24 weeks after AMI in this (under-powered) study, but further projects assessing the effects on remodeling (and indeed on cardiovascular outcomes) of specific galectin-3-modifying therapies are undoubtedly warranted as we continue to target remodeling as a therapeutic strategy in both AMI and CHF.

Sources of Funding

Parent study funded by Pfizer UK Ltd., Walton Oaks, Dorking Road, Walton on the Hill, Surrey KT20 7NS, England, UK.
Disclosures

RAP Weir received a modest research grant from Pfizer UK to fund the study and is currently on the end-point committee for the REMINDER trial, using eplerenone; JJV McMurray has received modest Speakers Bureau fees from Pfizer and has recently served on the executive committee for EMPHASIS-HF, using eplerenone. There are no other relevant disclosures.

References


Table 1. Baseline characteristics of study patients. Continuous data are expressed as mean (SD), while categorical data are expressed as percentages of the cohort at baseline.

<table>
<thead>
<tr>
<th></th>
<th>Total cohort (n=100)</th>
<th>r*</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.9 (12.0)</td>
<td>0.29</td>
<td>0.004</td>
</tr>
<tr>
<td>Male (%)</td>
<td>77 (77%)</td>
<td>0.15</td>
<td>0.13</td>
</tr>
<tr>
<td>BMI</td>
<td>30.8 (4.2)</td>
<td>-0.08</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>39 (39%)</td>
<td>0.08</td>
<td>0.43</td>
</tr>
<tr>
<td>Smoker</td>
<td>55 (55%)</td>
<td>-0.07</td>
<td>0.49</td>
</tr>
<tr>
<td>Previous AMI</td>
<td>7 (7%)</td>
<td>0.02</td>
<td>0.83</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35 (35%)</td>
<td>0.11</td>
<td>0.27</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>25 (25%)</td>
<td>-0.11</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>54 (54%)</td>
<td>-0.13</td>
<td>0.19</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>27 (27%)</td>
<td>0.05</td>
<td>0.62</td>
</tr>
<tr>
<td>Rescue PCI</td>
<td>26 (26%)</td>
<td>-0.02</td>
<td>0.82</td>
</tr>
<tr>
<td>Angiography performed</td>
<td>85 (85%)</td>
<td>-0.10</td>
<td>0.32</td>
</tr>
<tr>
<td>PCI performed</td>
<td>74 (74%)</td>
<td>-0.10</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>ceCMR measurements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVESVI (mL/m²)</td>
<td>43.8 (15.2)</td>
<td>0.04</td>
<td>0.68</td>
</tr>
<tr>
<td>LVEDVI (mL/m²)</td>
<td>84.3 (18.1)</td>
<td>0.03</td>
<td>0.72</td>
</tr>
<tr>
<td>LVEF (%)^Δ</td>
<td>48.9 (8.7)</td>
<td>-0.10</td>
<td>0.33</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>74.4 (14.9)</td>
<td>0.10</td>
<td>0.36</td>
</tr>
<tr>
<td>Infarct volume (mL/m²)</td>
<td>33.2 (20.7)</td>
<td>0.03</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Renal function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>100.1 (21.3)</td>
<td>0.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Admission medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>25 (25%)</td>
<td>0.17</td>
<td>0.09</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>18 (18%)</td>
<td>0.06</td>
<td>0.55</td>
</tr>
<tr>
<td>ACE inhibitor/ARB</td>
<td>12 (12%)</td>
<td>0.20</td>
<td>0.049</td>
</tr>
<tr>
<td>Statin</td>
<td>15 (15%)</td>
<td>-0.05</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Discharge medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>96 (96%)</td>
<td>0.22</td>
<td>0.03</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>82 (82%)</td>
<td>0.18</td>
<td>0.07</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>93 (93%)</td>
<td>-0.12</td>
<td>0.23</td>
</tr>
<tr>
<td>ACE inhibitor/ARB</td>
<td>94 (94%)</td>
<td>0.19</td>
<td>0.05</td>
</tr>
<tr>
<td>Statin</td>
<td>98 (98%)</td>
<td>-0.06</td>
<td>0.52</td>
</tr>
<tr>
<td>Furosemide</td>
<td>21 (21%)</td>
<td>0.17</td>
<td>0.09</td>
</tr>
</tbody>
</table>

PCI – percutaneous coronary intervention; CABG – coronary artery bypass graft; Δ normal range 58-68%; *correlative analysis with baseline galectin-3 (Spearman correlation coefficients for continuous variables, or paired samples correlation for categorical variables).
Table 2. Spearman correlation coefficients for biomarkers, sampled at baseline and 24 weeks, and simultaneous galectin-3 concentrations over 24 weeks post-AMI in the 93 patients who completed the study.

*p<0.05   **p<0.01 (p values are SPSS Bonferroni-adjusted)  ΔChange in each biomarker between baseline and 24 weeks. Note: all biomarker data logarithmic-transformed prior to correlative analysis.

<table>
<thead>
<tr>
<th></th>
<th>Gal-3</th>
<th>MMP-2</th>
<th>MMP-3</th>
<th>MMP-9</th>
<th>TIMP-1</th>
<th>TIMP-2</th>
<th>TIMP-4</th>
<th>sST2</th>
<th>Apelin</th>
<th>IL-1Ra</th>
<th>IL-2R</th>
<th>IL-4</th>
<th>IL-5</th>
<th>IL-6</th>
<th>IL-7</th>
<th>IL-8</th>
<th>IL-10</th>
<th>IL-12</th>
<th>IL-15</th>
<th>IL-21</th>
<th>MCP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>0.33**</td>
<td>0.18</td>
<td>0.22*</td>
<td>0.15</td>
<td>0.18</td>
<td>-0.15</td>
<td>0.01</td>
<td>0.03</td>
<td>0.18</td>
<td>0.38</td>
<td>0.16</td>
<td>0.05</td>
<td>0.15</td>
<td>0.34**</td>
<td>-0.02</td>
<td>0.18</td>
<td>0.10</td>
<td>0.04</td>
<td>0.23*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 wk</td>
<td>0.02</td>
<td>0.22*</td>
<td>0.08</td>
<td>0.25*</td>
<td>0.05</td>
<td>0.24*</td>
<td>0.32*</td>
<td>0.18</td>
<td>-0.06</td>
<td>0.03</td>
<td>-0.07</td>
<td>0.04</td>
<td>0.08</td>
<td>0.09</td>
<td>0.29*</td>
<td>-0.10</td>
<td>0.13</td>
<td>0.05</td>
<td>-0.01</td>
<td>0.14</td>
</tr>
<tr>
<td>Δ</td>
<td>0.05</td>
<td>-0.11</td>
<td>-0.19</td>
<td>0.02</td>
<td>-0.09</td>
<td>0.12</td>
<td>0.12</td>
<td>0.24*</td>
<td>0.07</td>
<td>-0.05</td>
<td>-0.08</td>
<td>-0.08</td>
<td>-0.08</td>
<td>-0.08</td>
<td>-0.01</td>
<td>-0.07</td>
<td>-0.01</td>
<td>0.18</td>
<td>-0.07</td>
<td>0.03</td>
<td>-0.03</td>
</tr>
</tbody>
</table>
Figure Legend

**Figure.** Mean (±SEM) change from baseline in galectin-3 concentration in relation to (A) left ventricular end-systolic volume index (ΔLVESVI) and LV end-diastolic volume index (ΔLVEDVI), (B) LV ejection fraction (ΔLVEF), (C) LV infarct volume index and (D) LV mass index. Correlation coefficients and significance levels are shown for each cardiac magnetic resonance parameter in relation to change in galectin-3.
ΔInfarct volume index (mL/m²)

ΔGalectin-3 (ng/mL)

Time from MI (weeks)
Galectin-3 and Cardiac Function in Survivors of Acute Myocardial Infarction
Robin A.P. Weir, Colin J. Petrie, C. Aengus Murphy, Suzanne Clements, Tracey Steedman, Ashley M. Miller, Iain B. McInnes, Iain B. Squire, Leong L. Ng, Henry J. Dargie and John J.V. McMurray

Circ Heart Fail. published online March 15, 2013;
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/early/2013/03/15/CIRCHEARTFAILURE.112.000146

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/