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EDITORIAL COMMENT

Galectin-3 After Heart Transplantation

Does it Get Better?*

Alan Maisel, MD,[a] Paul Kim, MD,[b] William Stendardi, MD[c]

Galectin (Gal)-3 has generated significant interest since the seminal paper by Sharma et al. (1) as a culprit biomarker that not only reflects acute and chronic inflammation but also is also integrally involved in fibrosis (1,2). In addition to representing cardiac fibrosis, Gal-3 also has been shown to be involved in hepatic, pancreatic, pulmonary, and renal fibrosis (3). Gal-3 has a complex interaction with the innate immune system that helps protect the host in acute inflammation but may contribute to pathological fibrosis through chronic inflammation (3,4).

Prior studies have demonstrated an association between increased serum Gal-3 and cardiovascular mortality and morbidity (5–7). Additional studies have shown a relationship between Gal-3 and renal function (8–10). Although Gal-3 may reflect renal dysfunction, similar to cystatin-C (11), it has been shown to predict as well as cause renal dysfunction through fibrosis (12). Dang et al. (13) previously demonstrated that Gal-3-null mice that underwent kidney transplantation had preservation of tubules and reduced interstitial fibrosis compared with normal mice.

Milting et al. (14) first demonstrated that none of the group of fibrosis-related biomarkers, including tissue inhibitor of metalloproteinases-1, tenascin, osteopontin, or Gal-3, were reduced after mechanical circulatory support (MCS). Similarly, a decrease in Gal-3 levels was not seen after MCS in subsequent studies (15,16). When evaluating myocardial tissue at the time of left ventricular assist device implantation compared with tissue at the time of left ventricular assist device explantation, myocardial fibrosis was shown to have increased, consistent with persistently elevated Gal-3 levels (15).

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In this context, in this issue of *JACC: Heart Failure*, Grupper et al. (17) pose an interesting question of whether Gal-3, intricately related to inflammation and fibrosis, would decrease after "reversing" cardiac fibrosis and inflammation through heart transplantation. The study consisted of 62 patients, the majority of whom (n = 50) underwent heart-only transplantation; there were 6 heart-kidney and 6 heart-liver transplantations. The etiologies of heart failure from this single large referral center were restrictive cardiomyopathy (37%), dilated cardiomyopathy (26%), ischemic heart disease (21%), valvular heart disease (8%), and arrhythmogenic cardiomyopathy (3%). Serum Gal-3 levels were measured twice, 23 to 798 days before and 54 to 767 days after heart transplantation. The major finding of the study was that Gal-3 levels did not significantly change before and after heart transplantation. The study showed that the glomerular filtration rate was significantly lower in patients with elevated Gal-3 levels, using 17.8 ng/ml as the threshold value, compared with patients with normal levels. No correlation between Gal-3 levels, before or after heart transplantation, and Gal-3 staining measured in myocardial tissue from endomyocardial biopsies at 1 year post-transplantation was demonstrated. Additionally, there was no correlation between Gal-3 levels and myocyte hypertrophy and interstitial fibrosis. After adjustment for age, body mass index, and pre-heart transplantation glomerular filtration rate, Gal-3 levels were no longer associated with reduced functional capacity by cardiopulmonary

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From the [a]Division of Cardiology, Department of Medicine, Veterans Affairs San Diego Healthcare System, La Jolla, California; [b]Division of Cardiology, University of California, San Diego, San Diego, California; and the [c]Department of Medicine, University of California-San Diego, San Diego, California. Dr. Maisel is a consultant for Critical Diagnostics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

exercise testing. As a result, the investigators conclude that Gal-3 is less likely a cardiac-specific biomarker but more likely a marker that is influenced by renal function. This, plus the fact that levels rarely change with treatment, makes this biomarker less suitable for treatment guidance in the clinical setting. Of particular interest was the demonstration that ST2 and N-terminal pro-brain natriuretic peptide levels were significantly reduced post-transplantation.

A limitation of this study, also acknowledged by the investigators, is that it was a retrospective study in a small patient population. Consequently, the study itself was not powered to detect smaller differences that may exist. Additionally, because the study was performed at a single large referral center, a disproportionate number of patients with restrictive cardiomyopathy were represented (18). This is important to note because Gal-3 may reflect ongoing systemic inflammation and fibrosis that is not necessarily "reversed" after heart transplantation, such as in patients with sarcoidosis. Despite immunosuppression post-transplantation, patients with systemic diseases may continue to have subclinical inflammation and fibrosis in other organ systems, particularly after tapering and discontinuation of steroids, that is reflected in persistently elevated Gal-3 levels. Third, the measurements of Gal-3 pre- and post-transplantation varied considerably and were measured up to 2 years before and after heart transplantation. Timely measurement of Gal-3 is important, as previously described (5,19,20), and certainly the heart failure as well as the post-transplantation state can change significantly over a period of 2 years. Fourth, as suggested by the investigators, Gal-3 may also be reflective of renal dysfunction. This needs to be explored further, as it may be that Gal-3 has decreased clearance in subjects with chronic kidney disease, as do many other biomarkers such as the natriuretic peptides. A more detailed evaluation of the observed renal dysfunction would be helpful, as heart transplantation patients not uncommonly have diastolic dysfunction and associated cardiorenal syndrome. Patients with elevated Gal-3 levels post-transplantation may have evidence of elevated filling pressures that could be shown in right heart catheterization that is done routinely. Last, though post-transplantation outcomes including cardiac allograft function, cardiac allograft vasculopathy, and rejection episodes were assessed, other primary outcomes, including all-cause mortality (presumably none), hospitalizations for heart failure, and retransplantation, would be useful to consider, particularly as the investigators reviewed clinical data 3 years after heart transplantation. Prior studies in patients with heart failure demonstrated a relationship between elevated Gal-3 and all-cause mortality and heart failure hospitalization (5,6), and it would be of interest to see if this relationship continued after heart transplantation.

An interesting and notable result described by the investigators was that ST2 significantly decreased after transplantation. ST2 is also a biomarker reflective of fibrosis that appears to be more specific for cardiac fibrosis than Gal-3 (21–23), as also suggested by this study. ST2 has the distinct advantage of being easy to measure, with a low coefficient of variation and reference change value (24). Many studies have demonstrated that a value of 35 ng/ml represents an important cut point for ongoing risk in the setting of heart failure (25,26). The fact that ST2 decreases in response to good therapy for heart failure and is additive to natriuretic peptide values suggests that ST2 levels may be useful in following patients with heart failure, as well as after mechanical circulatory support and transplantation (27–29).

In summary, although a specific association of Gal-3 with cardiac fibrosis and inflammation was not seen in this study, and Gal-3 instead appears to be elevated because of either altered renal clearance or renal dysfunction, further studies must be performed to better understand the underlying cause for persistently elevated Gal-3 levels after heart transplantation. Moreover, the findings reported suggest that additional studies are needed to evaluate ST2 after transplantation as a more specific marker of cardiac fibrosis.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Alan Maisel, San Diego VA Healthcare, Division of Cardiology, 3350 La Jolla Village Drive, San Diego, California 92161-0002. E-mail: amaisel@ucsd.edu.

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