Galectin-3 and ST2 in Cardiology

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Gal3 is a protein that belongs to the family of galectins, which are beta-galactoside binding proteins. Gal3 is broadly expressed in tissues, including all types of immune cells, epithelial cells, and sensory neurons. Furthermore, it participates in a wide variety of processes involved in the genesis of fibrosis, such as apoptosis, angiogenesis, and inflammation. ST2 is a protein that is part of the interleukin-1 receptor, and there are two isoforms, a transmembrane receptor (ST2L) and a soluble receptor (sST2, denoted as ST2). Interleukin-33 plays a cardioprotective role. It prevents fibrosis and cardiac hypertrophy through ST2L. In addition, ST2 reduces the cardioprotective effect of the Interleukin-33/ST2L pathway by binding to free interleukin-33.

Keywords: ST2 ; galectin-3 ; biomarkers ; cardiology

1. Introduction

Biomarkers are molecules used as indicators of biological processes that can be objectively observed in a sample. In most cases, these are obtained from peripheral blood. Biomarkers are commonly used in clinical practice both in the diagnosis and assessment of the response to treatment of a variety of cardiovascular diseases. There are biomarkers that have been widely studied, validated, and used in cardiology, such as NT-proBNP or troponins, and other more novel and not yet well studied, such as Galectin-3 (Gal3) and ST2. The objective of this review is the analysis of these two biomarkers in the main heart diseases.

2. ST2 and Galectin-3 in Ischemic Heart Disease

There are conflicting studies regarding Gal3 expression levels in acute myocardial infarction (AMI). Higher Gal3 values have been identified in patients with AMI than in patients with unstable angina and, in turn, higher values than in stable angina. Furthermore, a higher expression of Gal3 has been observed in multivessel coronary artery disease [1]. Likewise, in high cardiovascular risk patients referred for coronary angiography, Gal-3 is a strong independent predictor of cardiovascular death [2].

Patients with AMI who present higher expression of ST2 have been associated with a greater probability of cardiovascular death and HF. ST2 levels provide not only prognostic information independent of traditional risk factors, but it is also complementary to NT-proBNP, and its combination offers better risk stratification compared to the TIMI risk scale [3]. In a recent article by Aleksova et al. [4], an algorithm was proposed in AMI (type 1 and type 2) in which ST2 values <35 ng/mL translate to the absence of activation of fibrosis cascades, with which adverse remodeling is unlikely, levels between 35–70 ng/mL translate to moderate activation of fibrosis cascades and adverse remodeling is likely, and finally, ST2 levels >70 ng/mL translate to the activation of fibrosis mechanisms and neurohormonal activation. By determining these biomarkers, those patients with a higher risk of adverse left ventricular remodeling could be identified in order to adapt the management of these patients.

3. ST2 and Galectin-3 in Heart Failure

In a study that included patients who were admitted for dyspnea, a cut-off value of Gal3 of 9.2 ng/mL was suggested to distinguish acute HF from other causes of dyspnea. Furthermore, the patients who died during the follow-up presented higher values of Gal3 than those who survived (12.9 vs. 9.0 ng/mL, $p < 0.001$) [5]. In the GALA study (GALectin-3 in Acute heart failure) that included 115 patients with acute HF, the values of three biomarkers, Gal3, NT-proBNP, and troponin I, were compared in the prediction of all-cause mortality at 30 days and at the 1-year follow up. This study concluded that only Gal3 was useful for predicting all-cause mortality 30 days after hospital admission for acute HF, although it had no prognostic usefulness for mortality at one year, which did show NT-proBNP. In contrast, troponin I was not useful in predicting mortality at 30 days or one year after admission [6]. In the COACH study (Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure), Gal3 was a highly useful biomarker in predicting the absence of

events within 180 days after hospital discharge due to acute HF. It also presented a high sensitivity with values below 11.8 ng/mL and higher values (>17.8 ng/mL) have been related to an increased risk of new hospitalization for HF (up to 2–3 times higher) [7].

In contrast, in other studies, Gal3 has shown limited utility. In the RELAX-AHF (RELAXin in Acute Heart Failure) study that included 1161 patients with acute HF in whom Gal3 values were determined at different times, Gal3 values were stable over time, so no usefulness was established in event prediction [8]. Gal3 appears to be an additional risk biomarker in acute HF. However, it is not a specific cardiac biomarker, as it performs many other systemic functions, which may explain the contradictory results.

In the Val-HeFT study (Valsartan Heart Failure Trial), which included 1346 patients with chronic HF, it was concluded that both the Gal3 values measured at baseline and the measurement performed 4 months after inclusion were significantly correlated with hospitalization for HF and all-cause mortality. Furthermore, Gal3 levels below 16.2 ng/mL were related with lower admissions for HF [9]. In another study, the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) that included 1329 patients with chronic HF, it was observed that Gal3 values measured at baseline and those measured at 3 months of follow-up were related to increased mortality and rehospitalization for HF [10]. A meta-analysis published in 2017 showed a significant increase in the risk of cardiovascular mortality for each increase in the standard deviation of Gal3 in patients with HF [11].

On the contrary, other studies have not demonstrated the predictive capacity of Gal3 in patients with chronic HF. In the study by Miller et al. [12], which included 180 patients with chronic HF with reduced left ventricular ejection fraction (LVEF) with a two-year follow-up, no relationship was found between Gal3 values and mortality events or heart transplantation after adjusting the results for clinical variables and other biomarkers, such as ST2 and troponin T. When analyzing ST2 and Gal3 as continuous variables, both were independent predictors, which did not occur when they were included separately in the multivariate analysis, where Gal3 lost its predictive value, possibly because Gal3 is influenced by other biomarkers.

4. ST2 and Galectin-3 in Atrial Fibrillation

Gal3 has also been studied in patients with persistent AF without structural heart disease undergoing catheter ablation. The patients in whom AF recurred had significantly higher Gal3 values than those who remained in sinus rhythm. This suggests that Gal3 could be a useful marker to identify suitable candidates for pulmonary vein ablation [13].

In addition, the usefulness of ST2 is not established in AF. Although significantly higher ST2 values have been evidenced in patients with both persistent and permanent AF compared to subjects in sinus rhythm, no significant differences were found between patients with paroxysmal and persistent AF [14].

The determination of this biomarker could be useful to detect patients with AF originating in the pulmonary veins and who would obtain greater benefit from ablation than those patients with more advanced disease. In this sense, the relationship between ST2 levels and recurrence of AF has been studied in a group of 100 patients with paroxysmal AF who underwent cryoablation of pulmonary veins. For this, peripheral blood samples were collected prior to ablation. The biomarkers they studied were urate, NT-proBNP, high-sensitivity C-reactive protein, and ST2. ST2 was the only biomarker that was independently and significantly related to AF recurrence. This fact is explained by the authors as a form of expression of extensive fibrosis in the left atrium, and these patients obtain less benefit from ablation [15].

A performance algorithm has been described in maintaining sinus rhythm based on ST2 values [16]. This algorithm was based on the hypothesis that elevated ST2 levels translate into excess myocardial fibrosis. Thus, patients with high levels (considering the cut-off point of 35 ng/mL) would not benefit from performing electrical cardioversion and should be evaluated in a specialized consultation to assess pulmonary vein ablation.

In a recent study [17] in which 115 patients with persistent nonvalvular AF who underwent electrical cardioversion were included, seven biomarkers were analyzed (Gal3, ST2, ultrasensitive troponin T, CRP, urate, fibrinogen, and NT-proBNP) at baseline (prior to performing electrical cardioversion) and at the 6-month follow-up, and its possible relationship with electrical recurrence of arrhythmia was evaluated at the 6-month follow-up. The patients were evaluated with a holter-ECG at 3 months, electrocardiogram at 6 months, in addition to other possible eventual records in their clinical history. None of the biomarkers measured at baseline were related to the presence of recurrence at follow-up. However, ST2 and NT-proBNP measured at the 6-month follow-up were related to the presence of recurrence. The authors suggested that this fact may be due to the existence of mechanisms of inflammation and fibrosis in the acute phase of the fall in AF and

that these mechanisms diminish over time. In this sense, no relationship was found with the biomarkers measured at baseline, but there was at follow-up. Gal3 did not show a relationship with recurrence at baseline or at follow-up, possibly due to the variability of the processes in which it is involved.

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