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EDITORIAL COMMENT

Cathepsin A Inhibitors to Treat Heart Disease

Much Potential, Many Questions*

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Cathepsin A is a ubiquitously expressed, multifunctional lysosomal protein. In the lysosome, it binds to neuraminidase and β-galactosidase to activate the former and stabilize the latter, functions that led to the term "lysosomal protective protein." It also possesses serine carboxypeptidase activity at acidic pH as well as deamidase and esterase activities at neutral pH. Mutations that disrupt its "protective" functions are known to cause the lysosomal storage disease, galactosialidosis, in humans (summarized by Hiraiwa [1]). However, its enzymatic activity has garnered the most attention in recent years. Although localized to lysosomes intracellularly, cathepsin A can also be secreted. Extracellularly, it is capable of degrading many bioactive peptides that function in the cardiovascular system, including endothelin-1, bradykinin, and angiotensin I. Because the enzymatic activity of cathepsin A can be targeted separately from its "protective" functions (2), there has been interest for at least a decade in clinically targeting cathepsin A in patients with cardiovascular disease, and novel β-amino acid inhibitors were synthesized for this purpose (3).

In the paper by Hohl et al. (4) in this issue of *JACC: Basic to Translational Science*, the investigators examine the effect of 1 of these inhibitors, SAR164653 ((S)-3-{[1-(2-fluoro-phenyl)-5-methoxy-1H-pyrazole-3-carbonyl]-amino}-3-o-tolyl-propionic-acid), in ischemic cardiomyopathy. Analysis of left ventricle specimens of patients with end-stage ischemic cardiomyopathy revealed significant increases in cathepsin A mRNA and protein levels (~50% increase over tissue from healthy donor hearts), although details of these patients were not available. Using a rat model of myocardial infarction, cathepsin A mRNA levels in the remote left ventricular myocardium and left atrial myocardium were significantly increased 8 weeks after left anterior descending artery ligation (1.5- and 1.8-fold, respectively). Using an ischemia/reperfusion rat model (30-min ischemia followed by 10-week reperfusion), these increases were 1.7- and 2.9-fold, respectively. The up-regulated cathepsin A levels were associated with increased atrial natriuretic peptide mRNA levels. Treatment of the ischemia/reperfusion rats with SAR164653 had no effect on infarct size or normalized heart weight, but did improve ejection fraction and reduce plasma brain natriuretic peptide levels. Magnetic resonance imaging analysis revealed better contractility in the SAR164653-treated rats than in the placebo-treated rats, which seemed to be caused by preservation of remote myocardium with SAR164653 treatment (i.e., there was better wall motion in these areas).

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Regarding the left atrium, SAR164653 did not affect chamber dimensions in the ischemia/reperfusion rats, but fractional shortening was significantly higher compared with that of the placebo-treated controls. With respect to left atrial remodeling at 10 weeks,

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fibrosis was increased, accompanied by increased procollagen mRNA levels and an increased collagen I/collagen III ratio; SAR164653 treatment significantly reduced the fibrosis, collagen ratio, and Col1A1 mRNA levels. Polar and lateral connexin 43 expression was increased in the left atria of the ischemia/reperfusion rats, and SAR164653 treatment significantly reduced lateralization of the connexin 43. In the left atrium post-ischemia/reperfusion, the duration of atrial fibrillation, total activation time, and areas of slow conduction increased, and all of these values were significantly reduced by SAR164653 treatment. As a comparison, treatment with the angiotensin-converting enzyme (ACE) inhibitor ramipril produced similar results as those with SAR164653, although, overall, the latter was more efficacious. As a notable exception, echocardiographic estimations of left ventricular mass suggested that SAR164653 was less effective at reducing post-ischemic hypertrophy than ramipril (although direct measures of left ventricular cardiomyocyte size were not shown).

Hohl et al. (4) have certainly shown an association of cathepsin A levels with dilated cardiomyopathy, and SAR164653 was able to improve cardiac structural/functional parameters post-infarct in the rat models. Targeting cathepsin A holds a lot of promise in this regard, especially the attenuation of atrial and remote site remodeling that can lead to heart failure progression. However, many questions remain unanswered, and 2 are critical in order to move this from the bench to the bedside: 1) What is the mechanism?; and 2) What will this mean for patients and potential therapies? Regarding the mechanism(s) of activity, the investigators (or a subset of them) have studied the effect of SAR164653 in rat experimental infarct models (the focus of this editorial), a rat model of type 2 diabetes (5), and a mouse model of myocardial infarction (6). All of these studies have shown significant improvements or trends toward improvement with SAR164653 treatment, yet no mechanism has been determined. Together, cathepsin A, neuraminidase, and an enzymatically inactive splice variant of β-galactosidase form the cell-surface elastin receptor, and inhibition of cathepsin A catalytic activity has been shown to lead to reduced elastic fibers in the lungs, skin, and aortic adventitia of mice (2). However, how this is related to tissue remodeling and fibrosis in the heart is unclear. Mechanistically, the authors appear to be favoring the tissue-specific stabilization of protective bioactive peptides, such as bradykinin, which is a reasonable hypothesis. However, tissue-specific stabilization of endothelin-1 may also occur and could be detrimental, as it could lead to vasoconstriction, prolonged inflammation, and fibrosis (7,8). For these reasons, determining tissue-specific mechanisms of the efficacy of cathepsin A inhibitors is crucial for future translational studies.

Finally, what does this mean for patients and potential therapies? The trajectory of SAR164653 in this regard is unclear at the moment. Sanofi was originally going to use this compound to treat cardiovascular-related complications in diabetic patients, but abandoned this in 2013 in order to evaluate the compound in pulmonary hypertension (9). A phase I trial was conducted in the United Kingdom (no later than 2014) on 45 healthy subjects (20 to 82 years of age), and no adverse effects were noted over 14 days up to the maximum dose of 800 mg daily (10). However, to the best of my knowledge, there have been no further updates on relevant clinical trials. Although tissue expression levels can vary, the rather ubiquitous expression of cathepsin A emphasizes the importance of long-term safety studies in human patients. The outcomes can be hard to predict and need to be assessed empirically. However, a lessen can be garnered from the positive outcomes on morbidity and mortality of the combined neutral endopeptidase (neprilysin) inhibitor and angiotensin receptor blocker, sacubitril/valsartan, in heart failure with reduced ejection fraction (i.e., the PARADIGM-HF [Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure] trial) (11). The trials and tribulations of this treatment strategy, from the efficacy failures of neprilysin inhibitors (e.g., ecadotril) to the unacceptably high angioedema associated with neprilysin/ACE dual inhibition (with omapatrilat) to the eventual success of switching from ACE inhibitor to angiotensin receptor blocker in order to target the renin-angiotensin system, have been summarized very thoroughly in Eugene Braunwald's 2015 review (12). The important message here is that scientific and medical advances rarely take a linear path, with some successes and many more failures. However, even in the failures, there can be something of value, some knowledge to be gained, albeit sometimes not what was originally intended. I am unsure of what is to come of cathepsin A inhibition to treat cardiovascular disease, but I am positive that much will be learned in the process. The current study by Hohl et al. (4) is an important step in that direction.

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