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EDITORIAL COMMENT

Is it Time for Trials on Preventing Immune-Mediated Myocardial Damage?*

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Myocarditis—a primary inflammatory injury of the myocardium—has been recognized as a distinct pathologic entity since the 19th century. Unfortunately, a comprehensive understanding of myocarditis that encapsulates why it happens, how it happens, and how to make it better remains stubbornly elusive. The enigmatic nature of myocarditis arises largely from its heterogeneity, with myocardial damage arising from diverse etiologies, presenting as an array of clinical manifestations, and resulting in a variety of long-term outcomes. Compounding these issues of heterogeneity are a lack of reliable and standardized diagnostic frameworks, creating a combination of "difficult-to-define" and "difficult-to-diagnose," which has made myocarditis difficult to effectively treat in multiple clinical trials. The lack of clear efficacy in clinical investigations has appropriately led investigators from the clinic back to the bench in efforts aimed at parsing the various, distinct aspects of immune-mediated myocardial damage that might be suitable for targeted therapy. Although myocarditis remains a relatively uncommon disease, the public health impact of the disease should not be overlooked nor the need for continued mechanistic research undersold. Myocarditis is a significant cause of sudden death in the young, and when presenting as a reduction in left ventricular function, has a significant risk of progressing to permanent cardiomyopathy with chronic heart failure (1).

In this issue of *JACC: Basic to Translational Science*, Shiheido-Watanabe et al. (2) present a thorough experimental examination of the dipeptidyl peptidase (DPP)-4 inhibitor linagliptin as an emerging therapeutic option for myocarditis. Although the cardiovascular benefits of antihyperglycemic therapy in the form of sodium-glucose co-transporter-2 inhibition has been established by recent clinical trials, large trials of DPP-4 inhibitors have yielded variable and contradictory findings in several heart failure outcomes studies (3). However, interest in DPP-4 inhibitors as a potential immune-modulating therapy is supported by many years of research in animal and human tissues (4), owing largely to the presence of DPP-4 as a costimulatory molecule on the surface of T cells. This interest has extended to myocarditis, with prior research demonstrating a disease-modifying effect for linagliptin in an experimental autoimmune myocarditis (EAM) mouse model (5). In the present research (2), the investigators investigate the molecular mechanisms through which linagliptin might exert this disease-modifying effect. In controlled experiments using 2 distinct murine models of immune-mediated, noninfectious myocarditis—an EAM model conditioned to generate anti-myosin heavy chain antibodies, and an immune checkpoint inhibitor myocarditis (ICIM) model conditioned with high-dose anti-PD1 and anti-PD-L1 antibodies—the investigators clearly demonstrate that linagliptin therapy mitigates both ventricular dysfunction and cardiac fibrosis. The investigators then carefully explore mechanisms by which DPP-4 inhibition may exert cardioprotective effects, revealing for the first time that DPP-4 physically interacts with proinflammatory cathepsin G on granulocytes, and through this interaction, protects cathepsin G from inactivation by the serine protease

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SerpinA3N. A decrease in DPP-4 activity, either via direct experimental manipulation or via linagliptin-induced inhibition, is shown to decrease cathepsin G activity, with a resultant decrease in inflammation as measured by granzyme activity and a decrease in profibrotic effectors as measured by angiotensin II production (angiotensin I being a known substrate of cathepsin G). Taken together, these study findings describe a fairly detailed and highly plausible overview of the role of DPP-4 in promoting cardiac inflammation and deleterious remodeling, and convincingly demonstrate interruption of these mechanisms with linagliptin therapy.

The experimental models used by Shiheido-Watanabe et al. (2) represent complementary approaches to exploring immune-mediated cardiac damage. The EAM model is an antibody-driven autoimmune process, whereas the ICIM model—through inhibition of tolerogenic T-cell costimulation—represents a cell-mediated autoimmune response. From a translational perspective, a framework that focuses on the specific immunologic mechanism of injury is quite relevant. In other autoimmune diseases, the disease-modifying treatments of choice typically focus on suppression of the offending immunologic arm (eg, anti-cellular-immunity therapies in the case of inflammatory bowel diseases, or anti-humoral-immunity therapies in multiple sclerosis). Concerted efforts within myocarditis research to interrogate the specific immunologic actors that instigate and perpetuate inflammation may aid in identifying new classes of highly specific treatments for different types of myocarditis. In the present study, linagliptin appeared to provide benefit in both a primary antibody-mediated disease process and a primary cell-mediated disease process. This may be due to exerting effects on multiple pathways (eg, effects on T-cell-mediated inflammation and on angiotensin II inhibition), though it may also be a consequence of experimental design. In these experiments, treatment arms in both model systems had continuous exposure to linagliptin. Because sustained antibody-mediated immune responses generally involve initial T-cell priming, it may be that the benefits in seen in the EAM model are largely due to effects on T-cell/cathepsin G interactions rather than direct effects on humoral auto-immunity.

The experiments conducted by Shiheido-Watanabe et al. (2) have limitations that should temper enthusiasm about linagliptin as a trial-ready intervention in primary immune-mediated (eg, noninfectious) myocarditis. As already mentioned, in the intervention arm of these experiments, linagliptin administration was a continuous process initiated well before the expected onset of cardiac inflammation. This experimental design therefore represents a prevention strategy rather than a treatment/rescue strategy that would require treatment only after the onset of overt inflammatory injury (as myocarditis is typically encountered in clinical settings). Because it is not typically possible to predict the onset of myocarditis, it remains unclear whether linagliptin has real-world potential as a myocarditis therapy for patients presenting with active injury. Additionally, as the investigators convincingly demonstrate, DPP-4 inhibition may exert some of its cardioprotective benefits by reducing angiotensin II levels. Although this mechanism has established clinical value, given that patients with overt myocarditis are already treated with neurohormonal blockade targeting angiotensin II production as part of consensus guidelines, it is uncertain whether linagliptin provides value above and beyond the current standard of care. This concern is reinforced by data from the current experiment that demonstrates no significant difference in fibrosis or ejection fraction between hearts treated with linagliptin + losartan versus losartan alone. Future efforts should attempt to investigate the effects of linagliptin after myocardial damage has occurred and should also further distinguish between the benefits of DPP-4 inhibition and those of angiotensin II blockade.

Although large clinical studies of linagliptin across a broad population of myocarditis patients may be premature, it is tempting to envision investigations in more select populations for whom future risk of immune-mediated cardiac injury might be more predictable. In considering translation from animal models to human subjects, it is worth noting that DPP-4 inhibitors have a favorable side-effect profile as compared with the powerful immunosuppressant therapies (corticosteroids, calcineurin inhibitors, etc.) often used when disease-modifying treatment is considered. This modest risk profile alone makes the possibility of another myocarditis clinical trial far more palatable for DPP-4 inhibitors than for other, more traditional myocarditis therapeutic classes. Moreover, the focus on ICIM in the present research by Shiheido-Watanabe et al. (2) opens up the possibility of ICIM prevention or mitigation trials. This subgroup of myocarditis patients has a known exposure at a known time, and could potentially be provided with linagliptin in a prospective fashion which mirrors the experimental design of the ICIM experiment. Although the risk of ICIM is relatively low, immune checkpoint inhibitors occupy a very large and growing niche across all cancer types, and adequately powered clinical

investigations—perhaps only focusing on diabetic subgroups for whom linagliptin could otherwise be indicated—may be feasible.

Additionally, although not typically considered in discussions of immune-mediated myocarditis, alloimmunity in heart transplantation represents another potential population for focused clinical translation of DPP-4 inhibitor therapy. Alloimmune responses resulting in transplant allograft rejection manifest through the many of the same immunologic mechanisms as those studied in the article by Shiheido-Watanabe et al. (2) (albeit due to different antigenic triggers). Allograft rejection can occur through either cell-mediated or humoral mechanisms, and prior research has demonstrated convincing roles for an imbalance of pro- and anti-inflammatory T-cell subsets and for depletion of the immune checkpoint system in driving the severity of alloimmune reactions (6). Additionally, due to high doses of corticosteroids and comorbid conditions, heart transplant recipients have a high incidence of diabetes during the first year after transplant, which might provide a particular opportunity to explore the benefits of DPP-4 inhibition on transplant recipient outcomes.

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