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Commentary: Suppressing the inflammatory response—can it be an alternative to surgical aortic valve replacement and transcatheter aortic valve replacement for patients with calcific aortic stenosis?

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Currently, there are no medical therapies available to treat calcific aortic stenosis (AS). Surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement are the only therapeutic options available to augment blood flow across a stenotic, calcific aortic valve. This has led to an increased interest in determining the pathophysiology of calcific AS with the goal of developing medical therapies to limit, and even reverse, calcification and fibrosis of aortic valve leaflets. There is now increasing evidence that acute inflammatory processes resulting in the infiltration of T lymphocytes, macrophages, and osteoblast-like valvular interstitial cells contribute to the formation of calcified AS.¹ The expression of the immune checkpoint protein, programmed cell death 1 protein and its ligand (PD-L1) have been found to inhibit T cell receptor-mediated lymphocyte proliferation and cytokine secretory function.²

In this issue of the *Journal*, Erkhem-Ochir and colleagues³ report the results of an immunohistochemical analysis of aortic valve leaflets in 53 patients undergoing SAVR for severe AS to examine the association of PD-L1 expression and active inflammation in severe calcific AS. PD-L1 expression was significantly associated with infiltration of CD8⁺ T lymphocytes and CD163⁺ macrophages in aortic

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CENTRAL MESSAGE

Immune checkpoint proteins may play a role in delaying or reversing the progression of calcific aortic stenosis.

leaflet tissue. Greater infiltration of CD8⁺ T lymphocytes were associated with higher (>40 mm Hg) aortic mean pressure gradients. In contrast, less calcified valves exhibited lower expression of PD-L1 and decreased infiltration of CD8⁺ T lymphocytes and CD163⁺ macrophages. CD163⁺ macrophages have been associated with calcified aortic valves and contributes to calcific bone formation by valvular interstitial cell activation and inflammatory cytokine secretion.⁴ Erkhem-Ochir and colleagues also found that the infiltration of Foxp3⁺ regulatory T (Treg) cells in the resected AS specimens was negatively associated with calcification. Treg cells have been shown to be protective of calcification by either secreting immunosuppressive cytokines or competing with effector T lymphocytes, similar to what has been observed in atherosclerotic pathophysiology.⁵ Treg inhibitors have been proposed as a strategy for improving survival in patients with advanced malignancies.⁶ Therefore, future studies will need to determine whether Treg inhibitors may inadvertently lead to severe AS.

Erkhem-Ochir and colleagues found that increased PD-L1 level was associated with nonsmoking but not with other cardiac comorbidities such as diabetes, coronary artery disease, hypertension, and hyperlipidemia, and that PD-L1 level was not predictive of postoperative morbidity or mortality. Therefore, it is not clear as to whether the expression of PD-L1 can be useful for identifying high-risk SAVR patients. Interestingly, CD8 infiltration was associated with a significantly increased incidence of postoperative atrial fibrillation.

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This study by Erkhem-Ochir and colleagues adds to the accumulating evidence that mechanisms related to the inflammatory response play an important role in the development of calcific AS. Further studies are needed to determine whether immune checkpoint proteins such as PD-L1 can be used as anti-inflammatory agents to delay or even reverse the progression of calcific AS.

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