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Editorial

The role of everolimus in treatment of cardiac allograft vasculopathy

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Cardiac allograft vasculopathy (CAV) remains one of the most important causes of late graft failure and death in heart transplant recipients [1]. CAV is a progressive coronary artery disease characterized by diffuse and progressive thickening of the intima along the entire length of the epicardial and intramyocardial arteries [2]. CAV is largely caused by various immunologic factors, which act on the wall of the graft coronary vessels damaging the endothelium and triggering the release of proliferative substances and the adhesion of platelets and mononuclear cells [3]. According to the official report of the International Society for Heart and Lung Transplantation, with a registry of more than 65 000 heart transplants, a CAV prevalence of 7% was found at the first year, 32% at 5 years, and 53% at 10 years after transplantation [4]. The symptoms do not usually appear until advanced stages of CAV because of cardiac denervation produced during transplantation. Therefore, silent myocardial infarction, heart failure, and sudden death are the most common forms of presentation [5]. Because of possible lack of symptoms, various methods of evaluating CAV have been employed. Intravascular ultrasound (IVUS) has been used as the gold standard for the detection and monitoring of CAV [5]. Since sensitivity of coronary angiography is low, an apparently normal angiography can underestimate the presence of advanced CAV.

Recently, the use of proliferation signal inhibitors such as everolimus has been shown to significantly prevent CAV compared to other immunosuppressive regimens [6,7]. A combination of a calcineurin inhibitor, mycophenolate mofetil, and a glucocorticoid is commonly used for maintenance immunosuppression after heart transplantation. Chou et al. [8] showed that an everolimus regimen can significantly suppress lumen diameter and circumference assessed by IVUS compared to a mycophenolate mofetil regimen. It was suggested that everolimus can improve established CAV as well as prevent the progression of CAV [7,9]. In the present study, Nakatani et al. clearly showed a case with remarkable plaque regression associated with everolimus administration [10]. Although serial angiographies did not detect obvious stenosis during the follow-up period, an increased focal eccentric plaque was observed by IVUS at 1 and 2 years after transplantation. They added everolimus to the patient's existing regimen and withdrew mycophenolate mofetil. It is established that an increase of $\geq$0.5 mm in intimal thickness is significantly associated with higher rates of cardiac events and a poorer prognosis [11]. In a randomized, multicenter trial, conversion to everolimus combined with reduced calcineurin inhibitor did not influence CAV progression among maintenance heart transplantation recipients [12]. However, patients with everolimus combined with azathioprine demonstrated attenuated CAV progression and a decline in inflammatory markers, whereas the opposite pattern was seen with everolimus combined with mycophenolate mofetil. On the other hand, everolimus combined with mycophenolate improves renal function, whereas everolimus combined with reduced cyclosporine deteriorates renal function [13]. The optimal combination regimen has not yet been established. According to virtual histology assessment of CAV in a multicenter Scandinavian study [14], conversion to everolimus combined with reduced calcineurin inhibitor is associated with a significant increase in calcified and necrotic intimal components and is more prominent in patients with a longer time after heart transplantation. Everolimus has not yet been approved by the US Food and Drug Administration to prevent organ rejection in heart transplantation recipients. Everolimus may be an alternative immunosuppressive drug for maintenance therapy with good results. Further investigations are needed to investigate long-term efficacy and safety [15].

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