EDITORIAL

Is the immunosuppression protocol related to aortic dilation in patients after kidney transplantation? A conundrum still unsolved

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The etiology and pathogenesis of aortic aneurysms is complex and still poorly understood. It is believed to depend on a combination of numerous factors such as aging, hypertension, atherosclerosis, smoking, valvular disease, trauma, inflammation, family history, or specific genetic disorders.[1-3] In brief, aneurysm progression is facilitated by systemic inflammatory response, which promotes proteolytic imbalance within the aortic wall. There are also many other mechanisms of progressive aortic dilation in patients with chronic kidney disease, which is associated with an increased global risk of cardiovascular morbidity and mortality. It is well documented that arterial dilation and increase in arterial stiffness occur in parallel with the decline in renal function.[4] Hence, the observations on aortic aneurysm growth in chronic kidney disease are particularly interesting. There is evidence that aortic aneurysms in kidney transplant recipients on immunosuppressive treatment expand more than twice as fast as those in healthy patients and have a higher risk of rupture,[5] which is associated with poor clinical outcomes in this population. Nonetheless, the effect of different immunosuppressive regimens used in kidney transplant recipients is still poorly understood.

In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Obremska et al[6] report not only high prevalence of aortic root dilation in patients after kidney transplantation (46% of patients with aortic root enlargement and 68% of patients with a dilated ascending aorta), but also suggests that the use of mammalian target of rapamycin inhibitors (mTORi) may contribute to the increased aortic diameter in comparison with calcineurin inhibitors (CNIs), which did not show a similar effect. Interestingly, the opposite effect has been recently observed in an animal model study, which showed mTORi to stabilize atherosclerotic lesions and prevent aortic expansion.[7] However, the presented results support the previous observations of other authors reporting a high prevalence of aortic dilation, which provides the rationale for strict monitoring of the aorta in this group due to potential risk of aortic complications. High-quality noninvasive imaging is a must, with choices spanning transthoracic or transesophageal echocardiography, computed tomography, or magnetic resonance imaging.

Although accelerated progression of aortic diameter and threatening rupture in kidney transplant recipients was documented,[5,8] it is still unknown whether it is related to the effect of steroids on the matrix turnover or rather it is associated with other immunosuppressive drugs. Of note, less than a half of the analyzed group (18 of 41 patients) received mTORi de novo after kidney transplantation, and in the remainder these drugs were introduced later, on average 5 years after transplantation, due to neoplastic disease or CNI nephrotoxicity. Additionally, the treatment protocols included also steroids combined with mycophenolic acid or alone, and some patients also additionally received low dose of CNIs. Similarly, drug protocol was also incoherent in the CNI group, and included combinations with various immunosuppressive drugs (mycophenolic acid, azathioprine). These facts, along with a relatively small study group, represent an evident limitation of the study. Therefore, the findings must be interpreted with caution, especially if a causative effect of mTORi on the progression of aortic dilation is suggested. Clearly, there is too much heterogeneity in used treatment protocols.

New-onset hyperlipidemia, diabetes, and hypertension are also all common posttransplant issues due to the side effects of immunosuppressant drugs. However, their incidence was not reported by Obremska et al,[6] and it might likely affect the aortic dilation rates over time.

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The growth of the kidney transplant recipient population represents a challenge for medical researchers (and obviously practitioners) to understand and address issues related to the obligatory use of immunosuppressive treatment, especially regarding cardiovascular complications. The presented study, along with other previous reports on the aggressive clinical course of aortic aneurysm in patients receiving solid-organ transplant and, later, lifelong immunosuppressive regimen,[5,8] questions the interventions considered as the most promising approach allowing pharmacological stabilization of growing aortic aneurysm. It even suggests that some immunosuppressants may have an adverse effect on aortic dilation progression. The clinical research, especially head-to-head comparisons of uniform immunosuppressive treatment protocols in organ transplant recipients, is highly warranted to elucidate the relationship between posttransplant status and aortic aneurysm progression.

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