Modest but impactful: Commentary on immunosuppressive drugs for nontransplant comorbidities are not associated with abdominal aortic aneurysm growth

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Challenging case studies and studies with a limited sample size can provide strong translational clues and valuable mechanistic insight. Inflammation is a key aspect of abdominal aortic aneurysms (AAAs). Aspects of the innate and adaptive immune responses will be abundantly present in the wall of larger AAAs and constitute an overarching core aspect of the murine models of AAA disease and clinical AAA disease.[1] However, although diverse anti-inflammatory interventions can effectively prevent AAA formation and/or disease progression in experimental models, all clinical interventions targeting progression of larger AAA have failed to date.[2] The malignant AAA progression observed after solid organ transplantation has even suggested that aspects of the inflammatory response can be beneficial in clinical AAA disease.[3,4]

Thus, the report by Thanigaimani et al[5] has filled the knowledge gap with respect to a possible association between the inflammatory and/or immunologic responses and AAA progression. The authors performed a retrospective analysis of AAA progression in 34 patients (from a surveillance cohort of 621 patients) who had been prescribed one or more immunosuppressant drugs. Although it could be argued that the study was heterogeneous with respect to the therapy prescribed and that the group size was limited, the observed differences in AAA growth and the associated 95% confidence intervals were notably small. As such, it is unlikely that larger studies would result in fundamentally different conclusions.

Based on the apparent absent effect of immunosuppressant drugs on AAA progression,[1,5] the question arises regarding why solid organ transplantation has been found to be associated with malignant AAA progression.[3,4] The immunosuppressant drugs evaluated in the analysis by Thanigaimani et al[5] mainly represented nonspecific immune-modifying agents (ie, steroids, colchicine, and/or methotrexate). Only one patient had been prescribed cyclosporine, and none had been prescribed mycophenolate, both cornerstones of immunosuppression after solid organ transplantation.[5] Thus, it could be tempting to speculate that the apparent contrasting effects of immunosuppressant therapies used in the context of chronic inflammatory disorders and those prescribed after solid organ transplantation reflect a highly specific immunologic effect or, alternatively, are related to a nonimmunologic (pleiotropic) action of immunosuppressant drugs used after solid organ transplantation. In this, the bioenergetic reprogramming—with a switch from oxidative phosphorylation to glycolytic metabolism—induced by cyclosporine stands out.[1,6]

Although not excluding a role in disease initiation, the apparently absent effect of immunosuppressant therapy on AAA progression has challenged the perpetual role of inflammation on AAA disease progression and characterizes inflammation in late-state disease as a bystander phenomenon. Thus, it is important to remember that AAA formation in murine models of the disease relies critically on strains with specific genetic backgrounds,[7,8] hallmarked by Th1-skewed (pro-) inflammatory responses[9] and, consequently, that aspects of inflammation are an inherent prerequisite for aneurysms to develop in these models. The clinical data presented by Thanigaimani et al[5] is a further call to the field for a critical reevaluation of the validity of the preclinical models used and have dampened the optimism with respect to anti-inflammatory strategies (including colchicine) as a medical strategy for AAA stabilization.[10]

The opinions or views expressed in this commentary are those of the authors and do not necessarily reflect the opinions or recommendations of the JVS — Vascular Science or the Society for Vascular Surgery.

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