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Angiotensin II Type 1 Receptor Antibodies Trigger Inflammation in Renal Transplantation

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Transplantation medicine was initially focused on the effects of anti-human leukocyte antigen (HLA) antibodies in graft rejection. These donor-specific antibodies (DSA) initiate rejection through complement-mediated and antibody-dependent cell-mediated cytotoxicity.[1] However, it became apparent that HLA antibodies do not explain all rejection cases: 40% to 50% of rejections with severe vascular changes, such as fibrinoid necrosis, are C4d negative, implicating involvement of non–complement fixing antibodies.[2] Moreover, recipients of HLA-identical kidneys have been reported to develop features of refractory rejection with vascular pathology, implicating putative pathogenic antibodies that are not directed against the HLA system.[3]

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In 2005, such non-HLA antibodies targeting a G-protein coupled receptor, the Angiotensin II type 1 receptor (AT_1R), were reported in 16 kidney transplant patients with refractory vascular allograft rejection and malignant hypertension without HLA-DSA.[4] Further studies have contributed to reveal that AT_1R-antibodies (AT_1R-Ab) can promote antibody-mediated rejection (AMR) either alone or together with HLA-DSA.[5]

In this issue of *Kidney International Reports*, Pearl and colleagues[6] investigated the inflammatory cytokine profiles associated with AT_1R-Ab in pediatric renal transplantation. They monitored 65 pediatric kidney transplant recipients for 2 years and gathered blood following transplantation (within the 3 first months), along with biopsy samples at 6, 12, and 24 months posttransplantation, and on suspicion of rejection. The patients received a standardized immunosuppressive strategy, namely (i) an induction with antithymocyte globulin either when panel-reactive antibodies were at or exceeded 30% or in case of delayed graft function, or (ii) either rapid-steroid withdrawal protocol or anti-CD25 monoclonal antibody if panel-reactive antibodies were inferior to 30%. Immunosuppression maintenance consisted of steroid-free or steroid-based immunosuppressors, a calcineurin inhibitor, and an antimetabolite. Antibodies directed against HLA or AT_1R were titrated in the blood samples using Luminex single-bead assay (Immucor, Stamford, CT) or enzyme-linked immunosorbent assay (OneLambda, Canoga Park, CA), respectively. Patients were considered HLA-DSA positive when the mean fluorescence intensity exceeded 1000 and AT_1R-Ab positive when the antibody levels were greater than 17 U/ml. The study revealed that 58% of the patients showed AT_1R-Ab after transplantation and 29% HLA-DSA, with no evident demographic differences observed between the antibody-positive and antibody-negative groups. Further analyses of the blood samples underlined an association between the presence of AT_1R-Ab and elevated cytokine levels for all the proinflammatory cytokines measured (tumor necrosis factor α, interferon-γ, interleukin [IL]-8, IL-1β, IL-6, and IL-17). On the contrary, HLA-DSA was not associated with any increase in cytokine levels. To see whether AT_1R-Ab and HLA-DSA positivity could act synergistically on the cytokine levels, the patients were segregated into subgroups. AT_1R-Ab association with cytokine elevations remained similar with or without HLA-DSA (Figure 1) and after controlling relevant clinical variables. On the other side,

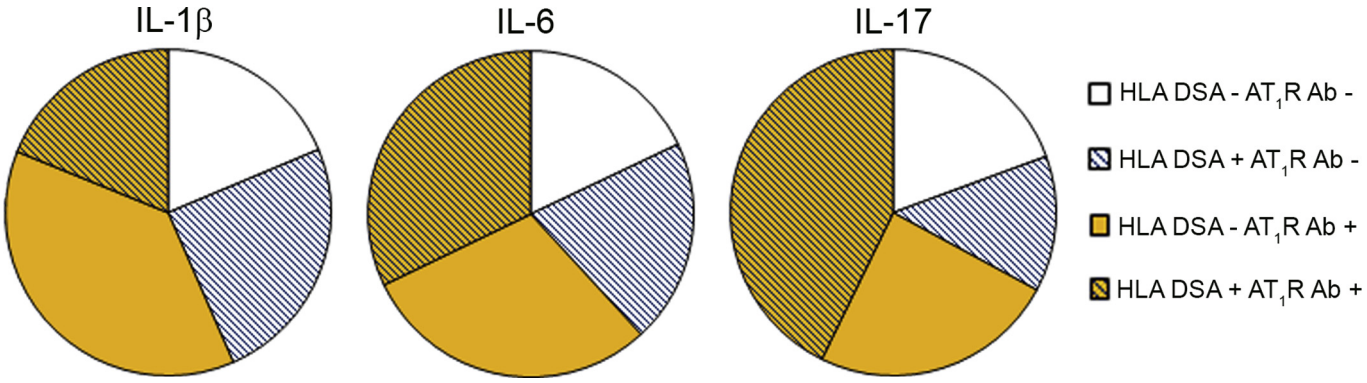

Figure 1. Percentage of patients positive for interleukin (IL)-1β, IL-6, or IL-17 levels in blood depending on human leukocyte antigen–donor-specific antibody (HLA-DSA) and Angiotensin II type 1 receptor antibody (AT_1R-Ab) positivity. Adapted with permission from Pearl MH, Grotts J, Rossetti M, et al. Cytokine profiles associated with angiotensin II type 1 receptor antibodies. *Kidney Int Rep*. https://doi.org/10.1016/j.ekir.2018.12.011.[6]

HLA-DSA positivity influence varied depending on the cytokine considered, and these effects were not significant when a regression model was applied.

Pearl and colleagues[6] finally tried to link the elevated cytokine levels with histologic signs of antibody-mediated rejection. Because of a small number of biopsy samples, a putative association between IL-8 levels and biopsy-proven acute rejection could not be verified. However, blood samples, which were collected up to 6 weeks around biopsy, and came from patients with arteritis and glomerulitis, showed significantly higher IL-8, IL-1β, and IL-6 levels.

This study raises 2 important points. First, it shows the association of antibodies targeting AT_1R with inflammatory cytokines, bringing a possible explanation for the involvement of AT_1R-Ab in antibody-mediated rejection. As described in a recent review from the *New England Journal of Medicine*,[5] microvascular inflammation is a key feature of AMR. AT_1R-Abs are associated in the present work with elevated cytokine levels independently from the presence of HLA-DSA, starting in the early posttransplantation stages. Hence, AT_1R-Ab could cause or participate in the increase of cytokine levels at the systemic level. Higher concentrations of cytokine in the transplanted organ could facilitate the development of microvascular lesions, leading to the occurrence of AMR; however, further studies are needed to elucidate how AT_1R-Ab functionally affect the cytokine levels. Second, the present study could not demonstrate a synergistic effect between AT_1R-Ab and HLA-DSA. Whether such effect exists is indeed controversial: in 2013, 2 studies published back to back in the *American Journal of Transplantation* raised the question of whether HLA-DSA and AT_1R-Abs effects might add up.[7,8] In their work, Giral and colleagues[7] showed that patients positive for AT_1R-Ab alone or together with pretransplantation HLA-DSA had a higher risk of developing AMR. In parallel, Taniguchi and colleagues[8] found a synergistic effect of AT_1R-Ab and HLA-DSA, which led to the worst graft survival in patients positive for both kinds of antibodies. A recent study, published in 2018 by Malheiro and colleagues[9] on 76 kidney transplant recipients, demonstrated an association between AT1R-Ab and HLA-DSA toward acute rejection and graft outcome.

The present study sheds light on the possible mechanisms of action of the antibodies targeting AT_1R and opens new research fields on the link between these antibodies, microvascular lesions, and antibody-mediated rejection.

DISCLOSURE

The author declared no competing interests.

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