Letter to the Editor

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Persistent Preformed Donor-Specific Antibodies and Clinical Risks of *de novo* Donor-Specific Antibody Development after Kidney Transplantation

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To The Editor

Methods used to identify alloantibodies have become increasingly more sensitive and specific over time, evolving from complement-dependent cytotoxicity crossmatch (CDCXM), flow cytometry crossmatch (FCXM), and solid phase assays performed using Luminex platforms [1].

It is widely recognized that preformed anti-human leukocyte antigen (HLA) donor-specific antibodies (DSA) increase the risk of antibody-mediated rejection (ABMR) and graft failure after kidney transplantation. Caillard et al. [2] analyzed the sera on the day of transplantation of 239 patients who received kidney transplantation. Thirty-seven patients (15.5%) had performed DSA detected on the day of transplantation. After 5 years, the preformed DSA disappeared in 22 patients whereas they persisted in 12. Variables associated with DSA persistence were age <50 years, a history of previous transplantation, the presence of class II DSA, mean fluorescence intensity (MFI) of preformed DSA >3500, and the presence of two or more DSA. They concluded that DSA persistence was associated with a higher risk of graft loss and ABMR [2]. Redondo-Pachon et al. [3] analyzed post-transplant evolution of preformed DSA identified retrospectively and their impact on outcomes of 370 kidney transplantations. Antibodies were monitored prospectively at 1, 3, and 5 years after kidney transplantation. Preformed DSA Class-II persisted more frequently than class I/I+II. Risk factor independently associated with persistence was pre-transplant MFI. They concluded that persistent preformed DSA was a very important risk factor for ABMR, and the ABMR rates of patients with preformed DSA that disappeared were intermediate between persistent DSA and no DSA [3].

The development of *de novo* DSA (dnDSA) post-transplantation is also associated with higher rates of graft loss. Compared with preformed DSA, Aubert et al. [4] reported that dnDSA patients with ABMR showed inferior graft survival compared with performed DSA patients with ABMR. Our previous study evaluated the impact of persistent preformed DSA and dnDSA detected at 1 year post-transplantation on long-term death-censored graft survival [1]. One hundred and sixty adult patients who received living kidney allograft with pre-transplant-negative T-cell CDCXM, and without periodic screening for DSA, were eligible the study. The presence of DSA was analyzed in stored serum samples collected at 1 year post-transplantation. Death-censored allograft survival rates of patients with persistent preformed DSA, dnDSA, and those without DSA at 9 years were 60.0, 51.4, and 92.0%, respectively. The graft survival rate was lower in patients with persistent preformed DSA and dnDSA.

Despite many reports about treatment for dnDSA, no specific intervention has been established as effective. Therefore, it is important to identify risk factors for dnDSA production after renal transplantation and reduce these risks. Many risk factors for dnDSA have been reported, including a younger recipient age, frequent nonadherence, early blood transfusion, viral infections, and suboptimal immunosuppressive therapy. We analyzed the association of immunosuppressive agents and clinical events for the development of dnDSA within 1 year post-transplantation [5]. In multivariate analysis, a low trough level of tacrolimus, discontinuation of mycophenolate mofetil, and treatment of cytomegalovirus (CMV) infection within 1 year after transplantation were independently associated with the detection of dnDSA at 1 year. In patients with or without dnDSA at 1 year, the 10-year allograft survival rate was 51.4 versus 87.9%, respectively. CMV infection enhanced natural killer (NK) cell alloreactivity, which might adversely influence graft survival. Further evaluation of NK cell alloreactivity should be done in renal transplant patients with CMV infection.

Since April 2018, the costs of annual screening for post-transplant anti-HLA antibodies has been covered by health insurance in Japan and a DSA is also covered if the screening test is positive. Further study is needed to evaluate whether periodic DSA monitoring and characterization using the Luminex assay improve long-term graft survival.

Conflicts of Interest

The authors declare no conflicts of interest.

Compliance with Ethical Standards, Human and Animal Rights

This article does not contain any studies with human participants and we utilized the data described in our previous studies [1,4]. IRB approval is not applicable for an opinion-based letter.

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