Editorial

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Impact of Low-level Donor-specific Antibody Determined With a Positive Luminex and Negative Flow Cytometric Crossmatch on Kidney Transplantation Outcomes

Since the introduction of the Luminex technique to detect donor-specific antibodies (DSAs) in kidney transplantation, efforts have been made to determine the risk of pre-operative low-level DSAs. The risk of low-level DSAs can be stratified by the mean fluorescence intensity (MFI), based on the highest level or sum [1]. However, the relative amount of antigen expressed on Luminex beads for each HLA locus varies from that expressed *in vivo* [2]. Therefore, caution is needed when applying the same MFI criteria to each HLA locus. Accordingly, the flow cytometric crossmatch test, which detects the actual binding of a DSA to donor lymphocytes, remains an important pre-transplantation test despite recognized limitations such as inter-laboratory and person-to-person variations or false positives due to non-HLA antibodies [3]. Therefore, it is meaningful to analyze the clinical impact of pre-operative low-level DSAs determined by a positive Luminex result but negative flow cytometric crossmatch (PLNF) on kidney transplantation outcomes.

Previous studies demonstrating these effects reported diverse results [4, 5]. In 2012, a meta-analysis including seven studies concluded that the risk of antibody-mediated rejection (AMR) and graft failure increased in patients with PLNF results compared to that in patients without DSAs, even when using the Luminex assay [4]. However, a subsequent meta-analysis published in 2019 also analyzing seven studies showed no significant increase in the risk of acute rejection, 1-year graft survival, or 5-year graft survival [5].

The major contributor to these discrepant results is the use of different criteria for selecting patients among studies. First, the type of kidney donor could be different (living vs. deceased-donor). Clinical outcomes of deceased-donor transplantation are known to be worse than those of living-donor transplantation [6, 7]. Second, the inclusion or exclusion of patients with pre-operative desensitization treatment can affect the study results [8-10]. Third, the collection of serum before or after desensitization prior to transplantation will have a large impact. DSA levels were found to be lower for samples collected after desensitization, which would result in more favorable clinical outcomes as the risk of DSAs is minimized [8, 11]. Conversely, studies using sera after desensitization or excluding patients who underwent desensitization indicated an increase in the risk of AMR, although the risk of graft failure did not increase [9, 11].

In this issue of *Annals of Laboratory Medicine*, Lee, *et al.* [12] reported the results of an analysis of 1,090 kidney transplantation patients (629 living and 398 deceased donors), wherein 178 patients (127 living and 51 deceased donors) had undergone desensitization before transplantation. In these 178 pa-

tients, sera collected after desensitization prior to transplantation were used for DSA analysis using the Luminex assay and flow cytometric crossmatch approach. The authors found the risk of AMR to be increased in patients with PLNF compared to that in patients without DSAs, whereas the risk of graft failure did not, when using the Luminex assay. In particular, the impact of AMR was more pronounced in patients who underwent deceased-donor transplantation than in those who underwent living-donor transplantation. This result was concordant with those of previous studies reporting worse outcomes in deceased-donor transplantation [5, 6]. In this study by Lee, *et al.* [12], a higher proportion of low-level DSA (PLNF) patients with living donors received desensitization treatment, including not only rituximab but also plasmapheresis/intravenous immunoglobulin, which might have contributed to a better allograft outcome. Desensitization treatment did not increase the risk of post-transplant infection in their study. Given its well-known association with better allograft outcomes despite the presence of DSAs, several institutions consider desensitization treatment. Lee, *et al.* [12] showed that patients who received desensitization treatment to achieve low-level DSA (PLNF) before transplantation did not have a notable increase in the risk of graft failure, and there was also no increased risk of post-transplant infection.

Despite the main limitation of the study by Lee, *et al.* [12] as a single-institution study, this work has the advantage of accurately determining the effect of low-level DSA (PLNF) on kidney transplantation outcomes using a unified immunosuppressive treatment protocol. The authors did not analyze the peak MFI before desensitization, which might have affected the study results. Further evaluation of low-level DSA based on PLNF and the MFI strength of DSAs using sera collected both before and after desensitization would be warranted, as it is known that the peak MFI strength of DSAs before desensitization can affect transplantation outcomes [13, 14].

In summary, pre-operative PLNF might (or might not) increase the risk of AMR, depending on several factors such as the type of donor or desensitization protocol employed. Nevertheless, PLNF seems to have minimal impact on graft survival. Further studies including multiple centers with unified desensitization, immunosuppressive regimens, and treatment for rejection protocols are needed for validation of these results.

AUTHOR CONTRIBUTIONS

Nam M drafted the manuscript; Song EY designed, reviewed, and revised the manuscript. Both authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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