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Editorial

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The Outcomes of Highly Sensitized Heart Transplant Patients in South Korea: Insights and Perspectives

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▸ See the article "Impacts of Pre-transplant Panel-Reactive Antibody on Post-transplantation Outcomes: A Study of Nationwide Heart Transplant Registry Data" in volume 54 on page 325.

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Stimulations of the humoral adaptive immune system can lead to antibody formation against human leukocyte antigens (HLA).[1] These 'stimulations' include prior surgery incorporating biologic graft materials, infection, blood and blood product transfusion, pregnancy, placement of durable mechanical circulatory support, repair surgery of congenital heart disease using a homograft and prior organ transplant.[2]

Non-specific circulating antibodies against class I and class II HLA used to be estimated by panel-reactive antibodies (PRAs), a recipient reactivity to antigens in a panel of random.[3] The calculated PRA (cPRA) is a quantitative measure, expressed as a percentage, indicating the portion of the general population for which a candidate recipient has circulating antibodies.[3] In 2015, the Immunology Division of the Korean Society of Laboratory Medicine developed a web-based cPRA calculator using data from Koreans (http://cpra.inforang.com/form/form.html). Presently, reporting cPRA using this tool has become standard in South Korea.

The degree of sensitization generally determines the probability that a potential recipient awaiting transplant will be matched with a compatible donor. For example, if a patient has a cPRA of 82%, it means that their antibodies are reactive against 82% of the donor population. In other words, out of 100 potential donors, there would be 82 positive cross-matches, implying a very high probability that the waiting time would be prolonged. The definition of 'highly sensitized patient' is diverse according to each expert, institute, and guidelines. In the International Society for Heart and Lung Transplantation (ISHLT) guidelines, they recommended cPRA of more than 50% as the desensitization threshold. Whereas, the Canadian allocation system suggests cPRA of more than 80% as highly sensitization as well as multiple positive prospective cross-matching in the waitlist.[4] The direct clinical impact of high cPRA is the matching failure in the wait-list. In an analysis of the United Network for Organ Sharing (UNOS) registry, heart transplant candidates with cPRA more than 80% had an almost 70% decreased chance of transplantation and a more than 2-fold increased risk of removal from the waitlist or death as compared with those with a cPRA less than 10%.[5]

Once transplantation has been performed, now that the genetic match for transplantation has been determined, what becomes crucial is the level of donor-specific antibody (DSA). For instance, even if cPRA is at 100%, there could be a match between the donor and the

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

recipient's HLA perfectly, or if the DSA level is ignorable, the importance of preformed HLA antibodies will be attenuated. Conversely, no matter how low the PRA may be, if the DSA level is notably high, the significance of the PRA percentage diminishes. Thus, once transplantation is already decided, clinical interests and focus move from cPRA level to preformed or de novo DSA and their intensity. However, it should be noted that in the Korean Network for Organ Sharing (KONOS) system, only donor HLA type A, B, DR, and DQ except C and DP, which suggests that such DSA could be excluded while they are at a significantly high level. Moreover, a high PRA value also suggests the presence of non-HLA antibodies such as angiotensin II type-1 receptor, endothelin receptor type A, and vimentin which can develop antibody-mediated rejection (AMR) themselves or synergize with HLA antibodies resulting in AMR.[1)]

Kim et al.[6)] published the clinical outcomes of recipients according to the intensity of sensitization in the Korean population using real-world, nation-wide, multicenter registry. During follow-up, patients with cPRA ≥50% had significantly lower freedom from AMR, but overall survival rate was comparable to those with cPRA <50%. These outcomes differ somewhat from previously published data. An analysis using the UNOS registry in 2007 (subsequent reports have been scarce) reported that as PRA increases, both mortality and the rate of 1-year post-transplant rejection also increase.[7)] Therefore, comparable mortality could be affected by the small sample size and the exclusion of highly sensitized and 'sick' patients due to early death before transplantation. Further analysis of mortality rates according to cPRA level among all patients listed in the KONOS also appears necessary in the future. Additionally, the clinical unmet needs and curiosity of the readers may be how to improve outcomes in highly sensitized recipients despite the limited reimbursement circumstances in South Korea. There were various efforts to desensitize recipients with various medications (intravenous immunoglobulins, plasmapheresis, rituximab, or bortezomib), selection of induction agents (e.g. anti-thymoglobulin antibody over basiliximab). Even though it has not been mentioned in the article, there should have been intensive control of complications along with each therapy. Therefore, survival without differences in this study groups should not be taken at face value.

In South Korea, the number of heart transplants directly bridged by extracorporeal membrane oxygenation (ECMO) has been growing sharply from around 25% to 45% recently.[8)9)] Highly sensitized ECMO patients do not have enough time to wait for the matching negative donors. Furthermore, they can hardly overcome the complications of desensitization therapy such as bone marrow suppression or severe infection. Then, will it be better to cross them first and desensitization intensively after transplantation? Still, we do not have any clear answer and should approach each case cautiously according to the patient's condition. Further investigation is warranted for this patient population.

The incidence of sensitized recipients is rising while awaiting transplantation according to the Organ Procurement Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) annual report.[10)] The characteristics of recipient are likely to become similar to those of Western countries, due to the growing number of left ventricular assist device and retransplant patients in our lists, which are well-known strong factors of allo-sensitization.[3)] Although numerous powerful desensitizing drugs such as tocilizumab are actively involved in desensitization in transplant expert centers,[2)3)] there is still a reimbursement issue in South Korea, making it challenging to prescribe them in reality. To improve the clinical outcomes for highly sensitized patients including AMR, now it's time to investigate the listing mortality

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of sensitized patients on the wait list as well as to discuss the extension of reimbursement for the desensitizing drugs with the government and the transplant society.

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