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INVITED COMMENTARY

Toward a better risk stratification for late antibody-mediated rejection in ABO incompatible kidney recipients

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During the last 25 years, increasing organ shortage enforced the development for living donor programs including ABO incompatible (ABOi) renal transplantation, paired donor exchange program, and transplantation across a positive cross-match. ABOi kidney transplantation has become a routine procedure with death-censored graft survival rates comparable to the rates in compatible transplantation. ABOi transplantation protocols have evolved to specific isoagglutinin elimination techniques without the need for splenectomy, reduction in isoagglutinin production, and modulation of immune response. Various preconditioning protocols differ with respect to isoagglutinin removal techniques, accepted and target isoagglutinin titer, method of isoagglutinin detection, and immunosuppression maintenance. The aim of desensitization protocols is the reduction and maintenance of anti-A/B isoagglutinins during the early period after transplantation below a threshold that is considered to be safe. In fact, accommodation appears to be a frequent phenomenon after ABOi kidney transplantations and is often associated with C4d deposition in peritubular capillaries of allograft biopsies. By contrast, little is known regarding the impact of (ABOi) renal transplantation on late immunological events.

In the current issue of *Transplant Int*, Lonze *et al.* [1] report the results of an original study that aimed to provide the overall incidence and risk stratification for late antibody-mediated rejection (AMR) in recipients of ABOi kidney transplants.

In this study, they retrospectively evaluated a single-center cohort of 115 ABOi kidney transplant recipients, of which 32% were also HLA incompatible (ABOi/HLAi) with their donors.

Using an adjusted negative binomial model to evaluate risk factors for late AMR, patients were assigned either into high- and low-risk groups for the development of late AMR. They observed that ABOi/HLAi recipients and patients with early AMR were the two main determinants of the high-risk recipients. These recipients exhibited a sixfold increased incidence of late AMR versus low-risk recipients. According to this risk

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stratification, the overall incidence of late AMR was strongly different between both groups (20.8% in the high-risk and 1.5% in low-risk recipients, respectively).

Another original finding of this report is the absence of correlation between changes in anti-A/B titer and global risk of late AMR.

Much of the reports regarding ABOi transplantation has focused on the experience at Japanese centers, where this practice has been more widely adopted than in the US and in Europe. However, these inferences may not generalize to other populations. In other countries, experience regarding ABOi outcomes has largely consisted of smaller, single-center studies. Although good outcomes have been reported, such studies may be underpowered to detect subtle differences and to conduct subgroup analysis and in particular to better define long-term immunological risk and outcome. In fact, ABOi recipient population has evolved into a heterogeneous one combining the detrimental effect of anti-A/B and anti-HLA antibodies, defining a so called 'double-barrier' transplant.

Thus, an accurate risk stratification according to each subgroup is necessary in order not only to optimize clinical, immunological, and histological monitoring but also to better define our graft allocation program. In fact, ABOi transplantation can yield options that both shorten waiting times and provide a novel approach to transplanting the ultra-highly sensitized patient, particularly when combined with the use of paired kidney exchange programs. The current study clearly identifies a high-risk subpopulation and thus could enable us to define an acceptable risk across the HLA barrier by selecting the best HLA matched donor and to adapt our desensitization protocols.

The final lesson from this study concerns the immunosuppressive regimen. The occurrence of an early episode of AMR in the ABOi/HLAi recipients should clearly not prompt us taper over time the maintenance immunosuppression and to strengthen our long-term surveillance practices in the same subgroup.

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Conflict of interest

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REFERENCE

1. Lonze BE, Bae S, Kraus ES, Holechek MJ, King KE, Alachkar N. *et al.* Outcomes and risk stratification for late antibody mediated rejection in recipients of ABO-incompatible kidney transplants: a retrospective study. *Transpl Int* 2017; **30**: 874.