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INVITED COMMENTARY

Increased risk of infection-associated death with incompatible kidney transplantations

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In times of organ shortage, transplantation over the blood group A/B and HLA antibody barriers helps increasing the living donor pool in kidney transplantation. Waiting times are reduced, while patient survival may be improved. By desensitization, both blood groups A/B as well as HLA antibodies are eliminated from the patient's circulation using plasmapheresis, double filtration plasmapheresis or selective or unselective immunoadsorption. In addition, antibody production and post-transplant antibody rebound are prevented by powerful immunosuppression and induction therapy with or without B-cell eliminating anti-CD20 antibody rituximab. Death-censored graft survival does not appear to be impaired after ABO incompatible kidney transplantation. In contrast, a reduced death-censored graft survival was reported in patients who were transplanted after desensitization for HLA antibodies, most likely as a consequence of an increased rate of antibody-mediated rejection episodes. Recent data suggests that patient survival after ABO (and HLA) incompatible kidney transplantations is reduced due to infectious complications and infection-associated death [1].

In the current issue of *Transplant Int*, Ko and coworkers [2] present data from 46 kidney transplantation centers reporting to the Korea Organ Transplantation Registry (KOTRY) on the outcomes of 1964 living donor kidney transplant recipients who were transplanted during the period 2009–2012. Outcome of patients desensitized for ABO incompatible ($N = 248$), HLA incompatible ($N = 144$), or ABO and HLA incompatible ($N = 31$) kidney transplantations were compared with outcomes of standard risk recipients ($N = 1541$). HLA incompatibility was defined as the presence of panel reactive antibodies together with either a positive cross-match result or Luminex-detected donor HLA-specific antibodies. Desensitization was achieved by plasmapheresis with or without intravenous immunoglobulins and rituximab administration.

As expected, the incidence of biopsy-proven acute rejection was with 22.8% in ABO as well as HLA incompatible patients and with 18.1% in HLA incompatible patients higher than the 12.1% rate in ABO incompatible and the 10.4% rate in compatible standard risk recipients (HR for biopsy-proven acute rejection in

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HLA incompatible transplantations 1.99, $P = 0.007$), with also an increased number of late acute rejection episodes. However, this higher rate of (late) rejection episodes did not translate into a higher rate of death-censored graft loss. It is difficult to speculate on the reasons for the comparable graft survival in HLA incompatible patients compared with the other groups as no data on cross-match results or HLA antibody strength are provided. A short follow-up period may be one possible explanation. Other studies on HLA incompatible kidney transplantations showed higher overall rejection rates with antibody-mediated rejection episodes in the range of 20–30% and increased death-censored graft loss, again, making the interpretation of this part of the manuscript not easy [3]. During the study period, 20 patient deaths were recorded in living donor kidney transplant recipients, with a 3.2% death rate (one of 31) in ABO and HLA incompatible kidney transplant recipients, a 1.4% rate (two of 144) in HLA incompatible patients and a 2.4% rate (six of 248) in ABO incompatible patients; these rates are higher than the 0.7% rate (11 of 1541) in standard risk recipients. The increased death rate in this Korean cohort of desensitized patients was most likely explainable by the higher rate of infection-associated death. Although the numbers in each group are small, more than 80% of patient deaths in the ABO and HLA incompatible, the HLA incompatible and the ABO incompatible groups were due to infection, whereas infection was the cause in only 27.3% of the deaths in standard risk recipients. In the multivariate analysis, pretransplant desensitization with plasmapheresis and rituximab was identified as the driving cause of infection-associated death (HR = 3.40, $P = 0.002$).

Higher rates of infection-associated deaths have also been identified in several other recent studies: Barnett and colleagues from London reported on reduced patient survival 1 and 3 years after ABO incompatible kidney transplantation with four deaths in 62 desensitized patients (Log rank $P = 0.018$ for patient survival) [4]. One patient death was due to sepsis, while the other three patient deaths were attributable to pneumocystis jirovecii pneumonia (PcP). In contrast, the four patient deaths in 167 ABO compatible kidney transplant recipients were not attributable to infection. Comparable results were found in a cohort of 1420 patients from the Collaborative Transplant Study (CTS) [1]. Approximately one additional patient death due to infection occurred in 100 ABO incompatible patients during the first 3 years after surgery (Log rank $P = 0.022$ for death due to infection, Fig. 1). Not only infection-associated death but infection rates per se seem to be increased after incompatible transplantations. Increased rates of viral infections such as CMV, HSV, VZV, and BK viruses (replication and nephropathy) as well as increased rates of PcP pneumonia, wound, severe urinary tract infections, and a higher frequency of colonization with multidrug-resistant bacteria were reported after ABO incompatible kidney transplantations [5–7]. While infectious complications are increased also after HLA incompatible procedures [8], it is currently a matter of debate whether the recipients of ABO incompatible grafts may rather be prone to infectious complications such as BK virus-associated nephropathy. In a recent study, Sharif and colleagues found a three times higher BK virus nephropathy rate in ABO incompatible than in HLA incompatible transplantations despite comparable immunosuppressive regimens [9]. Bentall hypothesized that different blood group antigens may influence the binding of viral pathogen receptors to sialic acid on renal tubular cells [10].

While it is not possible to receive further detailed information on the infectious complications from the registry study of Ko and coworkers, this work delivers further evidence that the rate of infectious complications is higher after ABO or HLA incompatible kidney transplantations. Questions that remain to be elucidated are as follows:

1 Are ABO incompatible kidney transplant recipients particularly prone to infectious complications or is the increase solely a result of the added therapy

2 Which part of therapy is responsible for the increased infection risk: Desensitization procedure by

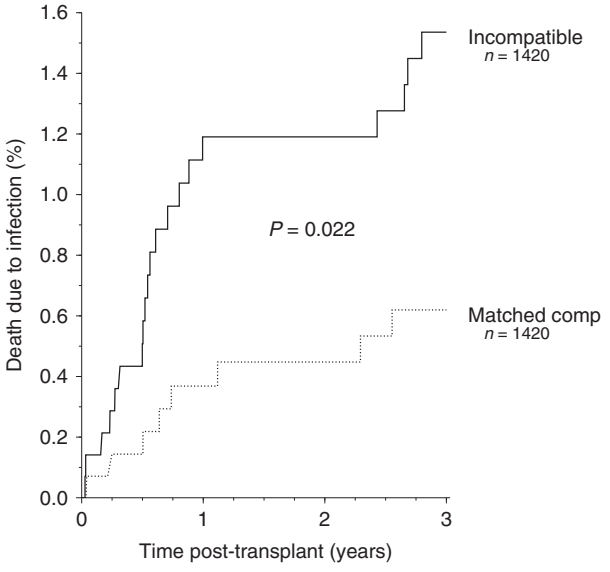

Figure 1 Cumulative incidence of death due to infection in recipients of an ABO incompatible living donor graft and matched controls receiving an ABO compatible living donor graft [11].

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plasmapheresis or immunoadsorption, antibody induction therapy with T- or B-cell depleting antibodies or the more frequent use of tacrolimus as compared to cyclosporine in incompatible transplant recipients

3 Can toxicity of desensitization strategies be reduced, e.g. by avoiding anti-CD20 antibody rituximab induction, or would this on the other hand, cause increased graft loss as our recent work suggests

There is further room for improvement in the management of desensitized patients who, due to the application of more potent immunosuppression, are more susceptible to infectious complications.

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Conflicts of interest

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