In a recent *New England Journal of Medicine* article, Jordan et al. (1) report the results of a case series making use of an IgG endopeptidase derived from *Streptococcus pyogenes* to desensitize patients with donor-specific antibodies (DSAs) to an incompatible deceased donor kidney at the time of transplantation. In distinction from immune cell-depleting antibodies, such as thymoglobulin and rituximab (anti-CD20), which target and remove peripheral T and B cells, and plasmapheresis, which removes antibody in bulk, IgG endopeptidase destroys antibody by degrading it. This represents a potentially important advance for deceased donor kidney transplantation, because this agent can be given at the time that the patient is brought in to receive a donor organ and results in near-complete removal of all antibodies, including DSAs, from the circulation. The current practice to desensitize a patient waiting for a deceased donor kidney transplant is for a center to attempt to anticipate when organ offers will begin to occur. Then, an opened process of intravenous immune globulin (IVIG) therapy with or without plasmapheresis is initiated in an effort to reduce DSAs while waiting for an appropriate organ. Additionally, this manuscript shows a proof of concept that IgG endopeptidases can be used safely in humans and cause rapid and complete short-term removal of antibody from the circulation. Although not assessed in this study, it is a logical extension to investigate the utility of this in the treatment of acute antibody-mediated rejection. As promising as this approach to treating sensitized patients awaiting kidney transplantation may be, it must be placed in the proper context, because in constructing their hypothesis, the authors overlook the current reality of deceased donor allocation.

This manuscript follows a similar pattern as others reporting the results of recent desensitization trials (2). That is, it fails to acknowledge that, since December 4, 2014, the kidney allocation system (KAS) prioritizes highly sensitized patients and, hence, has dramatically reduced the mean waiting time for an organ offer (3). As Stewart and Klassen (4) report, the median waiting time for patients with calculated panel reactive antibodies (cPRAs) 98%–100% has fallen from >19 years pre-KAS to 3.2 years post-KAS (Figure 1). This has a significant bearing on how desensitization trials are interpreted, because the central tenet of this approach is that the risk of more intense immunosuppression (5) and poorer graft survival with an incompatible organ (6) is offset by more rapid transplantation. If a sensitized patient can receive an organ to which he/she has no preformed DSAs in a short period of time, there is no clinical justification for desensitization. Since the implementation of the KAS, access to kidney transplantation has been greatly improved for all but the most extremely sensitized patients: those with cPRAs of 99.95%–100% (3). These individuals have antibodies to almost all HLA s and require a phenotypic, 0 HLA-mismatched organ to be transplanted. Additionally, in the post-KAS era, waitlist candidates in all cPRA categories are being transplanted in proportion to their representation on the waitlist; therefore, it is difficult to justify an intervention that will both allow some individuals to jump the line and result in worse overall outcomes.

When considering a therapy, such as desensitization, it is necessary to compare the risks of the therapy with those of the alternative. In the pre-KAS era, the alternative was waiting on dialysis, with the morbidity and mortality risks associated with it. After the waiting time for a highly sensitized patient approximates that of a patient with low or zero cPRAs, the risk benefit decision shifts to the risks of the procedure compared with the incremental increase in the amount of time spent on dialysis. The first notable risk in the study by Jordan et al. (1) is that 11 of 24 patients had rejection, ten of whom were antibody mediated or had cellular rejection with an antibody component. This preliminary rate of rejection exceeds the observed rejection rate of 10% seen with compatible transplants. This is nearly a fivefold increase in the rate of rejection. Hariharan et al. (7) showed that, in the modern era of calcineurin inhibitor–based immunosuppression, one episode of acute rejection cuts the expected graft survival in one half. Moreover, antibody-mediated rejection may be associated with even worse long-term graft survival (6).

Finally, the rebound at 1 month after transplantation in DSAs is of potential concern. Even in those individuals who did not experience antibody-mediated rejection or cellular rejection, the persistence of DSA is associated with a significantly worse long-term outcome (8). Therefore, when considering the benefit of IgG endopeptidase to shorten time on the waitlist by achieving a short-term reduction in DSAs and allowing transplantation with a noncompatible donor, it is necessary to weigh it against the increased risk of having inferior long-term graft survival.

Outcome measures addressing renal function are reported as 6-month creatinine values, and they are reported as “generally good.” However, most patients appear to have creatinine estimates of 2 mg/dl at 6 months. Serum creatinine values at 1 year after transplantation correlate strongly with 5-year graft survival.
As serum creatinine at 1 year increases above 1.5 mg/dl, there is a stepwise and significant reduction in 5-year graft survival (9). Therefore, although desensitization therapy in the short term allows for kidney transplantation sooner, it does not seem to confer the same benefit of longer-term graft survival achieved through compatible kidney transplants. Premature allograft failure results in greater sensitization, making subsequent transplants more challenging, with resultant worse 1-, 3-, and 5-year graft survival compared those rates of first-time transplant recipients (10).

Finally, the use of IgG endopeptidase at the time of transplantation results in challenges when administering immunosuppression. In the Swedish cohort, recipients received horse antithymocyte globulin (Atgam), because this is not digested by endopeptidase. In the United States, rabbit antithymocyte globulin (Thymoglobulin) is used for induction therapy in highly sensitized patients, but there are no data presented on its resistance to digestion by endopeptidase. Patients in the United States trial received alemtuzumab (anti-CD52) for induction, but it was delayed until 4 days after transplantation. Finally, most protocols in highly sensitized patients also involve administration of human IVIG and rituximab at the time of transplantation; these would be rendered ineffective by IgG endopeptidase. In this trial, rituximab and IVIG are delayed 1–3 weeks. This delay in achieving full immunosuppression creates a window for the cellular immune response to be initiated and predisposes the patient to an increased risk of future rejection episodes. Therefore, because using this new therapy for desensitization causes such a large deviation from common practice (5), the results need to be interpreted cautiously. Ultimately, it must be studied in a randomized and controlled fashion before any conclusions can be made.

There are clearly evident clinical scenarios that require further investigation into the utilization of this novel agent. For patients who have the highest level of sensitization, those with cPRAs 99.9%–100%, this agent may represent the only viable opportunity for timely kidney transplantation. Another clinical scenario where this agent could provide great value is in the treatment of antibody-mediated rejection, where rapid reduction in antibody is necessary to prevent permanent allograft injury. IgG endopeptidase in this situation has the potential to immediately shut off an episode of antibody-mediated rejection and allows time for conventional immunosuppression to abrogate the immune response. However, with the success of the KAS and kidney paired donation in transplanting all but the most highly sensitized patients in a timely manner with a compatible kidney, the demonstrated risks and subpar outcomes of desensitization no longer have a place in routine clinical kidney transplantation.

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References


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