EDITORIAL

Reducing Antibody Levels in Patients Undergoing Transplantation

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The advent of solid-organ transplantation for the treatment of patients with end-stage organ failure has been one of the most exciting medical advances in the late 20th and early 21st centuries. Thousands of lives have been saved or improved by transplantation, allowing terminally ill patients to rejoin society, work productively, and have a meaningful life.[1,2]

Unfortunately, transplantation has been an imperfect and expensive therapy. The financial burden of transplantation has limited its widespread application in the developed world; furthermore, therapeutic failure occurs all too often, owing to side effects or inadequacy of immunosuppression. Fortunately, in recent years, the potency of the newer immunosuppressive medications has improved, and the ability to prevent or treat acute cellular (i.e., T-cell–mediated) rejection has led to a reduction in early rejection rates to less than 15%, and most of the episodes are reversible.[3]

Less progress has been made with B-cell, or antibody-mediated, rejection, which has become an increasingly important problem after transplantation. Although good therapies exist, involving a combination of plasmapheresis and intravenous immune globulin,[4] they are expensive, nonspecific, and not always successful. Furthermore, these approaches have their own associated complications.

Preformed anti-HLA antibodies have remained a major problem for many years, especially in patients awaiting renal transplantation.[5] High levels of antibodies against HLA (sensitization) may develop, as a function of a failed previous transplant, blood transfusion, or pregnancy. Sensitized patients now account for a substantial percentage (currently, about 30% in the United States) of those on renal-transplant waiting lists. Waiting times for such patients are much longer than those for nonsensitized patients, and the immunologic obstacle to transplantation in such patients often becomes a death sentence, as they remain, and die, on dialysis.

Attempts to reduce antibody levels in candidates for transplantation with high titers are therefore important. Methods used have included plasmapheresis,[4,6] protein A immunoadsorption,[7] intravenous immune globulin,[8] immunosuppression with B-cell–specific agents,[9] or various combinations of these.[4,6] The two most popular and successful therapies have included the combination of plasmapheresis and low-dose (100 mg per kilogram of body weight per dose) intravenous immune globulin,[4,6] or the use of high-dose (2 g per kilogram per dose) intravenous immune globulin alone.[8] Plasmapheresis with low-dose intravenous immune globulin has only been feasible in the context of living donation, with the goal of abrogating a cross-match already known to be positive to allow transplantation to go forward. High-dose intravenous immune globulin has been used in patients on the deceased-donor waiting list as well as in patients with living donors and a positive cross-match. Although some of these various approaches to decrease antibody levels have been successful, they have either been associated with significant morbidity and mortality, high rates of humoral rejection after transplantation, or limited efficacy and substantial expense, and none have been used in large numbers of sensitized transplant candidates.

In this issue of the *Journal*, Vo et al.[10] have provided exciting preliminary evidence in a small number of sensitized patients (ClinicalTrials.gov

number, NCT00642655), using the combination of intravenous immune globulin (which this and other groups have used in the past[8]) and rituximab, a chimeric anti-CD20 (anti–B cell) monoclonal antibody.[9] Using an accelerated regimen of intravenous immune globulin (2 g per kilogram on days 0 [the day of infusion] and 30) and rituximab (1 g regardless of weight [or, in children, 375 mg per square meter of body-surface area] on days 7 and 22), they were able to perform transplantation in 16 of 20 patients (80%).

Sensitization was measured by the panel-reactive antibody level — a standard assessment of sensitization to a panel of cells encompassing most of the known HLA antigens. Sensitization was decreased in the patients, with mean panel-reactive antibody levels falling from 77% to 40%. One-year survival rates of patients and grafts were 100% and 94%, respectively (with 1 graft of 16 lost), and the mean serum creatinine at 1 year was 1.3 mg per deciliter (115 μmol per liter). The mean waiting time before desensitization through the combined regimen by Vo et al.[10] was 12 years, and the subsequent waiting time was approximately 5 months. The incidence of rejection was high (50%) and that of antibody-mediated rejection was also substantial (31%). Most rejection episodes occurred early and were treated successfully. In addition, the profile of infectious complications was favorable and was not higher than that seen in most renal-transplant recipients; no instances of infection with cytomegalovirus, Epstein–Barr virus, parvovirus, or polyomavirus BK, which may cause serious illness after transplantation, were reported.

Despite this study's limitations, which include a small number of patients, a relatively short follow-up period, and a high rate of early rejection, the implications are important. The desensitization regimen described by the authors was short, used agents approved by the Food and Drug Administration (admittedly in an off-label manner), and was associated with a high rate of transplantation. Over 80% of the patients who received a transplant had cross-matches that were not completely negative; flow-cytometric cross-matches were positive in 69% of the patients, and 19% also had positive complement-dependent cytotoxicity cross-matches. The resulting high incidences of acute rejection and antibody-mediated rejection are, consequently, not surprising, and attempting transplantation under such circumstances is not for the faint of heart. Caring for these highly sensitized patients requires careful, long-term monitoring after transplantation. The authors do not discuss this requirement for increased vigilance, but it is implicitly necessary.

As the authors note, their observations need to be confirmed and validated by other centers and in larger numbers of patients and during longer periods of follow-up. However, their approach may represent a breakthrough in the care of sensitized patients awaiting transplantation and may have the potential to help thousands of patients who are languishing on waiting lists around the world.

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1. Port FK, Wolfe RA, Mauger EA, Berling DP, Jiang K. Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. JAMA 1993;270:1339-43.
2. Simmons RG, Anderson CR, Kamstra LK. Comparison of quality of life of patients on continuous ambulatory peritoneal dialysis, hemodialysis, and transplantation. Am J Kidney Dis 1984;4:253-5.
3. Andreoni KA, Brayman KL, Guidinger MK, Sommers CM, Sung RS. Kidney and pancreas transplantation in the United States, 1996–2005. Am J Transplant 2007;7:1359-75. [Erratum, Am J Transplant 2007;7:2214.]
4. Montgomery RA, Zachary AA, Racusen LC, et al. Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. Transplantation 2000;70:887-95.
5. Organ Procurement Transplantation Network. Scientific registry of transplant recipients: OPTN: data. (Accessed June 27, 2008, at http://www.optn.org/data/.)
6. Gloor JM, DeGoey SR, Pineda AA, et al. Overcoming a positive crossmatch in living-donor kidney transplantation. Am J Transplant 2003;3:1017-23.
7. Palmer A, Taube D, Welsh K, et al. Extracorporeal immunoadsorption of anti-HLA antibodies: preliminary clinical experience. Transplant Proc 1987;19:3750-1.
8. Jordan SC, Tyan D, Stablein D, et al. Evaluation of intravenous immunoglobulin as an agent to lower allosensitization and improve transplantation in highly sensitized adult patients with end-stage renal disease: report of the NIH IG02 trial. J Am Soc Nephrol 2004;15:3256-62.
9. Vieira CA, Agarwal A, Book BK, et al. Rituximab for reduction of anti-HLA antibodies in patients awaiting renal transplantation. 1. Safety, pharmacodynamics, and pharmacokinetics. Transplantation 2004;77:542-8.
10. Vo AA, Lukovsky M, Toyoda M, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med 2008;359:242-51.