Transformation in Immunosuppression: Are We Ready for it?

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doi: https://doi.org/10.1681/ASN.2018050491

Over the past 25 years there has been a dramatic reduction in biopsy-proven acute kidney allograft rejection rates, from 35%–50% to 10%–15% at 1-year post transplant. This is remarkable, given the increasing complexity of both donor and recipients with an increase in average donor age to over 50 years, the use of donors with hypertension and diabetes, an increase in recipient average age to over 70 years, and that recipients with increased comorbidities is inversely correlated with estimated patient transplant survival. The transplant community has applauded itself on the 1-year graft and patient survival of over 95%. However, the 5-year patient and graft survival of a deceased donor transplant is about 81% and 72%, respectively, on the basis of recent reports from the Scientific Registry of Transplant Recipients. This is less than the survival of cancers such as breast cancer and localized colorectal cancer.

Compared with the dramatic decrease in acute rejection rates, the reasons for the relatively poor outcomes in renal transplant are multifactorial and include immunologic and nonimmunologic causes. Immunologic causes include rejection, mixed infections, and recurrent malignancies. A leading cause of graft failure is antibody-mediated rejection (ABMR), which can present even decades after transplantation. However, T cell-mediated rejection almost never occurs after 10 years post-transplant, suggesting that a state of partial adaptive tolerance develops over time. Immunologic causes include rejection, mixed infections, and recurrent malignancies. A leading cause of graft failure is antibody-mediated rejection (ABMR), which can present even decades after transplantation. However, T cell-mediated rejection almost never occurs after 10 years post-transplant, suggesting that a state of partial adaptive tolerance develops over time.

Nonimmunologic causes include the quality of the donor kidney; interstitial fibrosis and tubular atrophy; arteriolar hyalinosis (which was previously thought to be only related to calcineurin inhibitors [CNIs]); and medication nonadherence for a variety of reasons such as side effects, intolerance, toxicity, financial and social reasons, genetic racial polymorphisms for genes such as APOL1, and issues with drug metabolism (e.g., the CyP3A5*1 and *3 mutations, which are associated with the rapid metabolism of many drugs, including CNIs). CNI toxicity has long felt to contribute to chronic rejection, particularly with the use cyclosporine A (CsA). With the introduction of tacrolimus, there has been less early CNI nephrotoxicity and fewer rejection episodes. Einecke et al. studied 562 biopsy specimens and found that arterial hyalinosis often indicates adequate CNI exposure, not toxicity, and unexpected ah0 lesions should point physician attention toward drug nonadherence and inadequate immunosuppression.

We continue to struggle with the role of rejection. When treated, T cell-mediated rejection is no longer felt to be relevant for long-term outcomes. There is considerable dissatisfaction with Banff borderline rejection criteria. The recognition of the importance of ABMR is new, but we do not have a stable standard definition, adequate diagnostic criteria or standard effective treatment. And so, investigators and clinicians are left desiring a transplant transformation. It is in this context that the mechanistic target of rapamycin (mTOR) inhibitors were introduced into the transplant immunosuppressive armamentarium.

Rapamycin is the prototype of the first generation of mTOR inhibitors. The US Food and Drug Administration (FDA) approved it in 1997 for use in transplantation to prevent allograft rejection. Everolimus (EVL) is the second novel rapamycin analog. It was approved by the FDA in 2010 as a replacement, or used in combination with other immunosuppressants, including CNI. With full dose combination of mTOR and CNI, side effects were common and efficacy was not clearly evident, therefore low doses of each were investigated. The CRAD001AUS92 study demonstrated that EVL use with low-dose tacrolimus was associated with an increased rejection rate. A follow-up study by Shihab et al. supported maintaining an EVL trough concentration of 3–8 ng/ml when combined with low-dose tacrolimus, and was found to be safe in renal transplant recipients.

It is with this background that the TRANSFORM (Advancing renal TRANSplant efficacy and safety Outcomes with an eveRoliMus-based regimen) study was designed. This multicenter, international, randomized, controlled trial used a novel primary end point of treated BPAR or eGFR<50 ml/min per 1.73 m2 at month 12 post-transplant, which was 48.2% in EVL group versus 45.1% in the mycophenolic acid group. The triple end point of BPAR, death, and graft loss was 14.9% versus 12.5%. De novo donor-specific antibody was evident in 10.2% versus 13.6%, but ABMR was recorded in 7.8% versus 5.8% despite the higher de novo donor-specific antibody rate. Cytomegalovirus disease was lower at 3.6% versus 13.3%. BK nephropathy was lower at 4.3% versus 8.0%. Medication was discontinued significantly more often in the EVL group because of side effects in 23.0% versus 11.9%. Prominent side effects including peripheral edema, proteinuria, stomatitis/mouth ulceration, thrombocytopenia, thrombotic/thromboembolic events, wound healing events/complications, hypokalemia, and proteinuria were seen more commonly in the EVL group. However, diarrhea, nausea, vomiting, tremor, leukopenia, and insomnia were more frequent in the mycophenolic acid and higher tacrolimus dose group.

Various strengths of the TRANSFORM study are that it is an international, multicenter, randomized large trial with 2037
de novo kidney transplant patients, making it the largest de novo study in kidney transplantation. The study used contemporary immunosuppression as standard, with allowance for rabbit-antithymocyte globulin and basiliximab induction, and <20% CsA maintenance. It also included both living and deceased donor recipients. EVL was maintained at generally tolerable levels of 3–8 ng/ml to reduce side effects. The study has a relatively long follow-up time of 1 year, with plans to continue follow-up for 2 years.

This trial has some concerns, namely, the 10% noninferiority margin, which although used in previous trials, is generous, given the improvement in care over time and the novel end point. The Consolidated Standards of Reporting Trials guidelines recommend showing a figure comparing the confidence interval of the relative risk with a predefined margin to improve interpretation of the study. Fairly high tacrolimus troughs were used in the standard arm, with initial troughs of 8–12 ng/ml, which may have lowered the eGFR and affected the end point. The target tacrolimus troughs in the EVL arm were initially 4–7 ng/ml, and were not lowered to the prespecified average of 2–4 ng/ml, minimizing differences in acute rejection rates. Although the study compound end point is novel (BPAR and eGFR<50 ml/min per 1.73 m²), it is hard to interpret any study in which two variables are changed at the same time (in this trial, the antimetabolite and the tacrolimus targets). The exclusion criteria also limit generalizability of the results by excluding multiorgan transplantation (7% of transplanted organs, nationally), HLA-identical living and related donations (5% of transplants, nationally), cold ischemia time >30 hours, high risk of rejection (on the basis of variable local assessment of donor-specific antibodies), high panel-reactive antibodies, presence of preexisting donor-specific antibodies, the recipient or donor is positive for the hepatitis C virus, or a donor body mass index >35 kg/m².

There are some other questions of interpretation and practice that deserve comment. The cytomegalovirus-protective effect of the mTOR inhibitors has a well defined mechanism of action and has been described in numerous studies. The BK-protective effect is not a consistent finding and the lower incidence of BK in the TRANSFORM study seems to be more easily explained by the lower tacrolimus dose and the absence of mycophenolate in the EVL group. The mTOR inhibitors had been thought to be less diabetogenic than CNIs; however, sirolimus-based immunosuppression is associated with a significantly higher 3-year risk of diabetes than CsA or tacrolimus. Initially, mTOR inhibitors were also felt to be less oncogenic, but this has not been evident in outcome studies. The incidence of post-transplant lymphoproliferative disorder is as much or more, and the TUMORAPA study showed that switching from a CNI to sirolimus decreased the risk of new cutaneous squamous cell carcinoma, but not if the patient had more than one cutaneous squamous cell carcinoma. Kaposi sarcoma, on the other hand, is not very common and mTOR inhibitors do not work for all patients. The use of mTOR inhibitors also requires therapeutic drug monitoring, which when used in combination with a CNI, doubles the cost of immunosuppressive monitoring.

Large, randomized, controlled trials such as the TRANSFORM study are rare in transplantation and should be applauded. Similar to previous studies of mTOR inhibitors, the TRANSFORM study had many dropouts from side effects. The increased cost of monitoring both CNI and EVL levels should also be considered. The TRANSFORM study investigated the EVL and low-dose CNI combination and found that this combination is better tolerated than before, but is still not very well tolerated. For the transplant community, it is important to ask if we are ready for this transformation.

DISCLOSURES

A.A. has nothing to disclose. D.C.B. has been a consultant for, or has been on the speaker bureau in the last 24 months for Alexion, CareDx, Novartis, Sanofi, and Veloxis.

REFERENCES


See related article, “Everolimus with Reduced Calcineurin Inhibitor Exposure in Renal Transplantation,” on pages 1797–1911.