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Editorial

Does the Use of mTOR Inhibitors Increase Long-Term Mortality in Kidney Recipients?

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Well-designed randomized, placebo-controlled clinical trials are critical for assessing the safety and effectiveness of immunosuppressive therapy (1). However pivotal immunosuppressive trials have generally had relatively short follow-up: from 6 months in the case of MMF to 2 years in the case of belatacept. Despite the estimated half-life of more than a decade for a kidney transplant, the long-term impact of immunosuppressive therapy is largely unknown. Furthermore, surrogate markers and composite endpoints are often used but their association with long-term outcomes is uncertain. As the main focus of organ transplant has shifted to long-term graft and patient survival, we need longer term follow-up studies.

In this issue of AJT, Cortazar et al. compared the long-term outcomes in kidney recipients who received and did not receive mTOR inhibitor containing regimens at Semmelweis University in Hungary (2). Despite the limitations noted by the authors, this study raises concern about long-term sequelae of immunosuppression and also illustrates the fact that we currently do not have long-term studies on mTOR inhibitors.

This observational cohort study included 993 primarily Eastern European Caucasians whose median time at study entry was 72 months posttransplant with a median follow-up of 37 months. One hundred and one received mTOR inhibitor containing regimens. We do not have details on what proportion of the mTOR inhibitor use was *de novo* or conversion but the study suggested that the majority were already converted to mTOR inhibitors at study entry primarily for the presumed CNI nephrotoxicity or malignancy. Use of mTOR was associated with double the mortality risk in patients with no previous history of malignancy (n = 943). The differences in mortality started early and continued to diverge to the end of the follow-up. There are important strengths and weaknesses of this study which contains novel data on long-term outcomes of mTOR inhibitor use long-term posttransplant. The authors used several relevant statistical models to adjust for potential confounding factors including multivariate analyses controlling for individual covariates and the propensity score, propensity score matching and the left-truncated model. The major limitations of this study include the relatively small number of mTOR inhibitor users, the lack of detail on both the confounders and causes of mortality. The use of a cross-sectional cohort also potentially introduced the bias that some patients may have died or lost their graft before the recruitment. Of 101 recipients with mTOR inhibitor use, we do not have sufficient detail on how many were *de novo* use or conversion, the rationale for why recipients were placed on mTOR inhibitors and how long they received mTOR inhibitors. This information was not apparently available and therefore not accounted for in their multivariate analyses. A major concern is the lack of data on the cause of death. Without knowing the causes of death, one could not be able to hypothesize on why the mortality rate was higher in the mTOR inhibitor group.

Even with these limitations in mind, can we explain the association of mTOR inhibitors and mortality in this study? The shorter follow-up study of mTOR inhibitor used in both *de novo* and conversion setting consistently showed no differences in survival compared to those on CNI maintenance therapy (3,4). Is it possible that the differences in fact occur late post-transplantation? The leading causes of death among renal transplant recipients are cardiovascular disease, infection and cancer. Given the side effects of mTOR inhibitor including hyperlipidemia, diabetes and worsening renal function (when used concomitantly with CNI), one could postulate that mTOR inhibitor use may lead to adverse long-term cardiovascular outcomes. However, bearing in mind the shorter follow-up of two trials comparing sirolimus conversion from CNI regimens, patient survival was not different in the 4-year follow-up of the postconcept and 2-year follow-up of the CONVERT study (3,4). The other questions include who are at risk for mortality with mTOR inhibitor and what is the optimal timing for conversion if any? Is the regimen consisting of both mTOR inhibitor and CNI overimmunosuppressive resulting in an increase in infectious death risk?

The lack of positive or negative impact of mTOR inhibitors among kidney recipients with a prior history of malignancy deserves a careful examination. We would have expected favorable outcomes among those who received mTOR inhibitors due to its antineoplastic effect. Is it possible that putative beneficial effect on malignancy is negated by an increase in mortality from other causes?

The results of this study do raise concerns about the long-term safety data of mTOR inhibitor beyond what is available from clinical trials. We should encourage publications of adequate sample size, well-designed and executed longer term transplant outcomes on mTOR inhibitor users. The linking of registry to clinical trial databases in patients who were initially involved in previous randomized trials of both *de novo* and conversion to examine longer term outcomes will lessen the treatment and indication bias. With more data, one could re-examine the impact of mTOR inhibitors using tools such as metanalysis. In the mean time, there is not enough evidence to conclude that mTOR inhibitor use was associated with higher mortality rates.

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. S. B. has received grant funding and speaker honorarium from Novartis.

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