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INVITED COMMENTARY

Another step in defining the role of mTOR inhibitors in kidney transplantation

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RE: Efficacy and safety of *de novo* or early everolimus with low cyclosporine in deceased donor kidney transplant recipients at specified risk of delayed graft function: 12-month results of a randomized, multicenter trial [1].

At the present time, important new advances in clinical kidney transplantation are limited by a number of practical and ethical constraints that govern transplant practice around the world. New information is dependent on randomized controlled trials performed either at single centers, at a group of centers in one region, or at multiple sites around the world in which small differences are tested against a standard or 'best local therapy.' The wider the accrual, the more applicable will be the results to populations with demographic variables. Studies that analyze the role of immunosuppressive agents have a number of additional limitations. Trials are virtually never designed using a single agent versus another, and must then compare the impact of an agent as part of a multidrug regimen. Therefore, transplant clinical trials either focus on a measure of efficacy (patient and graft survival, acute rejection rates, and renal function), or safety and tolerability (measured by the frequencies of certain side effects and/or drug discontinuations thought to be related to the study drug). In addition, funded transplant clinical trials usually vary from 6 to 24 months, are limited by high cost and complexity of follow-up, and may miss important differences that emerge after the study window has closed. For these reasons, 10 years after the initial approval of the first in class mammalian target of rapamycin inhibitor (mTORi) sirolimus and the recent introduction of the mTORi everolimus, we are still asking the question of how to use these agents most effectively. We have learned that important advantages of mTORi class are slowing the degree of fibrosis after inflammation, prevention of certain cancers, possibly lower rates of viral infections, and diminished injury to allograft kidneys [2,3]. Important side effects attributed to these agents include dyslipidemia, bone marrow suppression, impaired healing of certain wounds, fluid collections, oral ulcers and skin rashes, pneumonitis, more proteinuria in damaged allografts, and hypogonadism [2–5]. In addition, some have suggested that mTORi prolong the recovery from acute tubular necrosis after organ preservation. These advantages and disadvantages must be weighed in each patient individually, compared with the use of alternative agents.

In this issue of Transplant International, the investigators of the French CALLISTO study provide 1-year data from their randomized prospective trial of 139 Deceased Donor kidney-only transplant recipients at intentional higher risk for delayed graft function (DGF). It should be noted that having one or more of the risk factors chosen, donor age >55 years, cold ischemia time range 24–40 h, and prior kidney transplant were quite modest. All patients were given a nondepleting IL2 receptor induction antibody, cyclosporine, and steroids. The two randomized groups

were given either immediate everolimus (IE, $n = 64$) at 0.75 mg bid adjusted to C_0 in the range 3–8 ng/mL, or delayed everolimus (DE, $n = 75$) commencing at week 5 at 0.75 mg bid adjusted to C_0 in the range 3–8 ng/mL. For the DE group, mycophenolic acid was given from day one until discontinuation at the fifth week of introduction of everolimus. In addition, the DE group received about twice the exposure to cyclosporine in the first month until both groups were targeted at C_2 500–700 ng/mL. Therefore, after 1 month, all patients received the same immunosuppressive regimen. The thrust of this trial asked the question whether there is a benefit to the delayed introduction of the mTOR inhibitor everolimus compared with its immediate introduction. For this purpose, the authors derived a rather unusual composite endpoint summing the events of patient death, graft loss, acute rejection, DGF, wound complications, and lost to follow-up. At 1 year, they found no significant difference for the composite endpoints for IE 64.6% and DE 66.2% groups; and no significant differences in the six components of the composite endpoint for either the IE or the DE groups. An interesting finding was that Adverse Events led to study drug discontinuation in fewer IE patients (17; 26.2%) than DE patients (28; 37.8%), although the difference was not significant. The authors concluded that there was no benefit in delaying the introduction of everolimus when used in combination with IL2R, cyclosporine, and steroids; and no difference in DGF.

The use of mTORi drugs in kidney transplantation remains a work in progress, with no doubt newer approaches on the horizon. While the CALLISTO study seems to support early use, the trial was carried out in a predominantly white population (93%), with a low BMI mean of 24 kg/m^2 (excluding BMI >32), only 11% diabetic, low mean cold ischemia time of 21 h, a small number of retransplants (6%), few sensitized recipients (3%), and excluding donation via cardiac death. This study population may be the very group that will benefit most from the *de novo* use of an mTORi demonstrating the best combination of efficacy, safety, and tolerability. In centers where these demographics represent the majority of recipients, early everolimus use appears safe. Additional indications would be recipients with a prior history of skin or solid organ cancers [6]. However, caution for the early use of mTORi drugs should be considered for recipients with high immunologic risk, severe early oligoanuria, lipid-lowering drug-resistant dyslipidemia, renal failure caused by glomerular disease with significant recurrence rates, prior pelvic surgery or radiation, or young males seeking paternity [7].

The CALLISTO study also points out the need for clinical trials to validate assumptions regarding the delivery of combinations of immunosuppressants. The dosing range of cyclosporine used in this trial in combination with everolimus was three- to fivefold lower than doses administered 20 years ago. During the pivotal trials of sirolimus and earlier trials using everolimus, higher dosing ranges for cyclosporine in combination with mTORi led to more nephrotoxicity [8,9]. As everolimus use increases, more individualized dosing strategies and ranges will be important. Especially, as calcineurin inhibitor minimization and/or avoidance strategies evolve. When improper dosing of mTORi drugs is employed in calcineurin inhibitor-free regimens, as in the Symphony study, higher rates of acute rejection can be expected [10]. Therefore, the target C_0 ranges of 3–8 ng/ml for everolimus with low-dose cyclosporine and steroids used in the CALLISTO trial should remain the guidepost until new validated information becomes available.

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