Costimulatory Blockade and Use of Mammalian Target of Rapamycin Inhibitors: Avoiding Injury Part 1

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Although calcineurin inhibitor drugs have been the mostly used therapy in modern immunosuppression in kidney transplantation, their effect on kidney allograft dysfunction has been suboptimal as far as preservation of kidney function is concerned. Additionally, there are metabolic and other nonmetabolic effects including increased risk of malignancy that has necessitated the use of mammalian target of rapamycin inhibitors to reduce exposure to calcineurin inhibitors. Mammalian target of rapamycin inhibitors, both sirolimus and everolimus, have been studied in several trials to facilitate preservation of kidney function with variable effects on kidney allograft function and immunogenicity. Preservation of kidney function is increasingly becoming the mainstay of immunosuppression not only in kidney transplantation, but also in extrakidney transplantation. The best kidney outcomes have been reported in calcineurin inhibitor withdrawal studies using mammalian target of rapamycin inhibitors, in kidney transplant recipients with stable kidney function. This review article summarizes data from several studies in which mammalian target of rapamycin inhibitors have been used to reduce exposure to or withdraw calcineurin inhibitors in an attempt to preserve kidney function.

Key Words: Target of rapamycin, Inhibitors, Calcineurin inhibitors, Kidney transplantation

BACKGROUND

The mammalian target of rapamycin (mTOR) is a multifunctional kinase that catalyzes critical steps in the transduction cascade that leads to cell cycle progression mediated by a variety of cytokine, hormonal, and nutrient signals. By decreasing the proliferation of lymphocytes, mTOR inhibitors serve as potent immunosuppressive drugs. However, these agents also inhibit proliferation of other cells and the effects of many other cytokines and growth factors—resulting in a myriad of side effects including impaired wound healing, bone marrow suppression (especially anemia and thrombocytopenia), mouth sores, leg edema, hyperlipidemia, proteinuria, and interstitial pneumonitis. Currently available mTOR inhibitors include sirolimus and everolimus, a hydroxyethyl congener of sirolimus. In early pivotal trials, the combination of sirolimus and cyclosporine (CsA) significantly reduced the incidence of acute rejection in kidney transplant recipients compared to rates observed with CsA combined with either azathioprine or placebo.[1-3] Because the mTOR inhibitors do not exhibit the classic nephrotoxic effects of the calcineurin inhibitors (CNIs) manifested by decreases in kidney blood flow and glomerular filtration rate (GFR), they have been used in a number of protocols designed to minimize exposure to CNIs. Herein, we focus on the outcomes of the major randomized prospective trials reported during the past 2 decades. The mTOR inhibitor–based strategies used in these studies can be classified as those that facilitate CNI avoidance, CNI withdrawal, or CNI minimization.

USE OF mTOR INHIBITORS TO AVOID CNIs

Two early multicenter European trials examined the potential benefits of sirolimus to facilitate avoidance of CsA. Groth and associates[4] randomized 161 patients to receive either sirolimus or CsA in combination with azathioprine and steroids. The incidence of acute rejection in the first year was comparable between groups (41%, sirolimus arm; 38%, CsA arm). However, the estimated GFR was significantly lower in the sirolimus arm at 3 months. Kreis and associates[5] performed a similar study in 78 patients randomized to either sirolimus or CsA but receiving mycophenolate mofetil (MMF) instead of azathioprine. Again, acute rejection rates were similar in each group. However, the calculated GFRs were better in the sirolimus arm after 2 months. Morales and associates[6] combined data from the above two trials and looked at 2-year end points in the pooled study groups. The cumulative incidence of acute rejection was numerically higher in the sirolimus arms (34.6% vs 28.7%; P = NS). However, calculated GFR was statistically better in the pooled sirolimus arms (69.3 vs 56.8 mL/min; $P = 0.004$).

Two early single-center studies performed in the United States extended these observations. Flechner and associates studied 61 adult kidney transplant recipients who were randomized to receive either CsA or sirolimus in addition to basiliximab, MMF, and steroids.[7] After 18 months of follow-up, the cumulative incidence of acute rejection was numerically lower in the sirolimus arm (6.4% vs 16.6%). At 12 months, eGFR (calculated by the Cockroft-Gault equation) was also better in the sirolimus arm (81 ± 24 vs 61 ± 15 mL/min; $P = 0.008$). In contrast, Larson and associates[8] performed a single-center trial and enrolled 165 patients randomized to receive either sirolimus or tacrolimus in addition to

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Financial Disclosure: Fillin.

Support: Fillin.

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1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2016.09.003

rabbit antithymocyte globulin, MMF, and steroids. The incidence of acute rejection was similar in each group (tacrolimus, 14%; sirolimus, 19%). At 12 months, GFR measured by iothalamate clearance was similar in each group (56 ± 16 in the sirolimus arm [$n = 64$] vs 55 ± 17 mL/min in the tacrolimus arm [$n = 65$]). Notably, the study drug discontinuation rate was 38% for sirolimus vs 16% for tacrolimus. In a follow-up study of kidney biopsies performed on patients who remained on their initially assigned therapy, those on sirolimus exhibited lower Banff ci and ct scores and exhibited a trend toward less interstitial fibrosis (Table 1).[9]

In the multicenter SPEISSER trial, 145 kidney transplant recipients were randomized to receive either sirolimus or CsA.[10] All patients received polyclonal antibodies, MMF, and steroids. The primary end point, GFR estimated by the Nankivell formula was not significantly different between the groups at 12 months. There were also no differences in graft or patient survival rates or in the incidence of acute rejection. Study drug discontinuation was higher in the sirolimus arm (28.2% vs 14.9%).

The ORION study was an open-label randomized multicenter trial in which 469 kidney transplant recipients were randomized into three groups: (1) de novo sirolimus and tacrolimus with gradual weaning and discontinuation of tacrolimus after 3 months; (2) de novo sirolimus and MMF with no CNI; and (3) de novo tacrolimus and MMF.[11] All three groups also received induction therapy with daclizumab and maintenance therapy with steroids. The primary end point of the trial was eGFR at 1 year, measured by the Nankivell formula. Study of patients randomized to the CNI avoidance arm (group 2) was terminated prematurely by the sponsor because of a high rate of biopsy-proven acute rejection. In group 1, withdrawal of tacrolimus was accomplished in 59% of patients and was not attempted in remaining patients who had either prior acute rejection or graft dysfunction at 3 months. By intent-to-treat analysis, there were no differences in eGFR at 1 year (group: 1 59 + 24 mL/min, group 2: 59 + 24 mL/min, group 3: 62.22 mL/min). At 2 years, the cumulative incidence of acute rejection was 17.2% in group 1, 32.8% in group 2, and 12.3% in group 3 ($P < 0.001$ for group 2 vs 3).

The ELITE-Symphony study was an open-label, randomized, multicenter trial in which 1645 kidney transplant recipients were randomized into four groups: (1) no induction, standard CsA (based on trough levels); (2) reduced CsA; (3) reduced tacrolimus; and (4) sirolimus.[12] Groups 2-4 received induction therapy with daclizumab. All patients received MMF and steroids. The primary end point was GFR at 12 months, estimated by the Cockcroft-Gault formula. Ironically, the CNI avoidance group (group 4) exhibited the lowest eGFR and also the highest rate of acute rejection among the four arms, reaching statistical significance when compared to patients receiving reduced tacrolimus (group 3).

Collectively, these trials utilizing sirolimus in an effort to avoid CNIs demonstrate variable effects on kidney function based on estimated or measured GFR. The greatest benefit was observed in early studies in which CsA was used as the CNI in control arms. The benefit is much less apparent when sirolimus is compared to tacrolimus. For patients who are not withdrawn from therapy because of side effects, long-term use of sirolimus with avoidance of CNIs may confer a modest benefit in reducing chronic histological changes in the allograft.

Table 1. Histologic Features of 1-Year Surveillance Biopsies of Kidney Transplant Recipients Managed Continuously With Tacrolimus- or Sirolimus-Based Immunosuppression.

Histologic Index (mean ± SD)	Tacrolimus ($n = 57$)	Sirolimus ($n = 38$)	*P* value
ci*	0.86 ± 0.79	0.53 ± 0.60	0.03
ct*	1.26 ± 0.55	1.03 ± 0.37	0.02
cv*	0.68 ± 0.66	0.63 ± 0.63	0.6
ci + ct + cv*	2.81 ± 1.51	2.18 ± 1.33	0.04
% interstitial fibrosis	11.0 ± 11.5	6.9 ± 7.8	0.06

Abbreviation: SD, standard deviation.
*Banff scores: ci, chronic interstitial score; ct, chronic tubular score; cv, chronic vascular score.
Adapted from Dean et al.[9]

CLINICAL SUMMARY

- Use of mammalian target of rapamycin inhibitors to reduce exposure to calcineurin inhibitors has had variable effects on preservation or improvement of kidney function.
- The benefits have been modest in avoidance protocols.
- The best kidney functional outcomes have been reported in withdrawal studies in stable patients.
- The potential benefits of mammalian target of rapamycin inhibitor therapy must be weighed against the risk of side effects.

USE OF mTOR INHIBITORS TO WITHDRAW CNIs

Withdrawal of CNIs Without Conversion to Another Agent

Two randomized multicenter trials assessed the benefits and risks of CsA withdrawal in kidney transplant recipients initially treated with CsA, sirolimus, and corticosteroids. In a study (the Wyeth 310 trial) originally published by Johnson and associates,[13] patients were randomized at 3 months after transplantation to CsA withdrawal ($n = 215$) or CsA continuation ($n = 215$). Two years after randomization, the incidence of acute rejection was 9.8% in the withdrawal group and 5.1% in the continuation group. At 12 months, the serum creatinine concentration was significantly better in the withdrawal group (142 vs 158 μmol/L, $P < 0.001$). Analysis of the 4-year outcomes of patients enrolled in this trial continued to suggest better kidney function in the group of patients randomized to CsA withdrawal.[14] In a similar study (the Wyeth 212 trial) performed with only 1 year of follow-up, Gonwa