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Outcomes of Mammalian Target of Rapamycin Inhibitor Regimens in Kidney Transplant Recipients with Pre- Transplant Primary Diagnosis of Hypertension and Other Etiologies: An Observational Study

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Abstract

We aimed to look at the outcomes related to the mammalian target of rapamycin inhibitor (sirolimus or everolimus), (m-TORi) regimens in kidney transplant recipients (KTR) with primary diagnoses of hypertension: In this retrospective observational study, 187,381 adult KTRs were classified into the hypertension or non-hypertension cohort supported their primary renal diagnosis pre-transplant. Cox regressions were used to analyze the risks for death and graft loss associated with the following regimens: m-TORi with or without steroids combined with cyclosporine (m-TORi+CSA), mycophenolate (m-TORi+MPA) or tacrolimus (m-TORi+Tac); cyclosporine with or without steroids combined with mycophenolate (CSA+MPA); and other regimens.Results: the danger of death-with-graft-function didn't differ between mTORi regimens in KTRs with a primary diagnosis of HTN [mTORi+CSA vs: mTORi+MPA (HR=0.88; 95% CI=0.68-1.14) and mTORi+Tac (HR=1.16; 95% CI=0.91-1.47); and mTORi+MPA vs. mTORi+Tac (HR=1.31; 95% CI=1.00-1.72)]. However, in KTRs with a primary diagnosis other than HTN, mTORi+CSA is associated with a lower risk of death-with-graft-function than mTORi+MPA or mTORi+Tac [mTORi+CSA vs. mTORi+MPA: HR=0.81; 95% CI=0.71-0.92] and [mTORi+CSA vs. mTORi+Tac: HR=0.76; 95% CI=0.66-0.87]. In both primary diagnosis cohorts, the risks of overall and death-censored graft loss are higher with m-TORi+MPA than the other m-TORi regimens.Conclusion: MTORi+MPA is associated with higher risks of graft loss regardless of pre-transplant primary diagnosis. MTORi+CSA is said to a far better likelihood of survival with a functioning graft in KTRs with a non-HTN primary diagnosis, a benefit not seen among KTRs with a primary diagnosis of HTN. Therefore outcomes related to mTORi regimens vary with the pre-transplant primary diagnosis classification of hypertension or non- hypertension: these associations could even be considered in mTORi regimen selection after kidney transplantation.

Keywords

Graft survival; Hypertension; Immunosuppressant; Calcineurin inhibitor; MTOR inhibitor; Patient survival

Introduction

The success of modern immunosuppressant drugs in improving kidney transplant survival through prevention of rejection have been reflected in the reduction of acute rejection rates and increase in allograft survival rates [1]. However, the same agents have contributed to increased morbidity and mortality in kidney transplant recipients (KTR). Since the most common cause of renal allograft loss is death with a functioning graft, clinical measures aimed at decreasing this complication, including a systematic selection of immunosuppression regimen would be beneficial [2,3]. Hypertension, a leading cause of renal failure leading to kidney transplantation that

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commonly recurs after kidney transplantation is associated with multiple cardiovascular risk factors and morbidities that increase the risks of post-transplant mortality and allograft failure [4,5]. Post-transplant hypertension contributes to allograft and multi-system vasculopathy that can lead to poor patient and graft outcomes [6,7]. are implicated in the pathogenesis of post-transplant hypertension through multiple mechanisms [8]. On the other hand; other rejection prophylaxis drugs such as mycophenolic acid, azathioprine and the mammalian target of rapamycin inhibitors such as sirolimus and everolimus (m-TORi) are believed to be not intrinsically pro-hypertensive [9]; although, when combined with CNI's, mTOR-inihibitors could promote nephrotoxicity and hypertension [7,8]. In US, the triple drug combination of tacrolimus+mycophenolate+steroids has been the most utilized immunosuppression regimen in kidney transplantation [10]. However, when clinical indications dictate the use of alternative regimens, the m-TORi drugs have been combined with the CNIs, cyclosporine or tacrolimus or the antimetabolite, mycophenolate [10]. Hence, we aimed to study the kidney transplant and patient outcomes associated with the interactions between mTOR-i regimens and primary diagnosis classification of HTN or non-HTN. Utilizing existing data of the US Organ Procurement and Transplantation Network (OPTN) we conducted this observational study analyzing the risks of overall graft loss (OAGL),

Discussion

In this study, we analyzed the risks of (overall and death-censored) graft loss and death with graft function associated with the mammalian target of rapamycin inhibitor regimens in KTRs stratified based on their primary diagnosis of hypertension or another etiology. The study found that the risks of graft loss and patient death varied between different m-TORi regimens used in kidney transplantation. Specifically, m-TORi+MPA was associated with higher risks of overall and death-censored graft loss than other m-TORi regimens irrespective of the primary renal diagnosis classification. On the other hand, m-TORi+CSA was associated with a lower risk of death- with-graft-function (DWGF) than other m-TORi regimens in KTRs with primary diagnoses other than hypertension.

Conclusion

In summary, our study suggests that in a kidney transplant recipient with clinical indication for an m-TORi (steroids) immunosuppressant regimen, m-TORi+MPA is not a desirable choice due to its higher risks for overall and death-censored graft losses than m-TORi+CSA or m-TORi+Tac. When choosing between last two foregoing regimens, a primary diagnosis of HTN may indicate that either may be used; while, a primary diagnosis other than hypertension may indicate the preferential use of m-TORi+CSA. We conclude that the classification of the KTR's pre-transplant renal diagnosis into HTN or another (non-HTN) etiology could be a useful baseline pre-transplant factor to consider in the selection of an m-TORi regimen for maintenance immunosuppression.

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