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Are calcineurin inhibitors safer than mTOR inhibitors?

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Abstract

Isakova *et al.* report that kidney transplant recipients on mammalian target of rapamycin (mTOR) inhibitors do not have a lower risk of allograft failure but do have a higher risk of death than those on calcineurin inhibitors. Careful consideration is, therefore, required before converting to mTOR inhibitors to preserve renal function.

One of the abiding ironies of kidney transplantation is that calcineurin inhibitors—the mainstay of post-transplantation immunosuppression—are nephrotoxic. This problem, as well as the increased risk of cardiovascular disease associated with the use of calcineurin inhibitors, has spurred efforts to find alternative agents. Mammalian target of rapamycin (mTOR) inhibitors, which were first approved for use in kidney transplant recipients in 1999, were found to have reduced adverse effects on blood pressure and creatinine levels in the short-term compared with calcineurin inhibitors.¹ Moreover, initial concerns about potentially higher rates of acute rejection associated with the use of mTOR inhibitors compared with calcineurin inhibitors were not borne out in a meta-analysis of a decade of studies,¹ although the surrogate end points of patient outcomes, bone-marrow suppression and hyperlipidaemia (which could potentially lead to increased mortality as a result of infection and cardiovascular disease), were worse with mTOR inhibitors.¹

In an effort to investigate the long-term outcomes of mTOR inhibitors in kidney transplant recipients, Isakova and colleagues analysed data on the clinical outcomes of adult and paediatric patients who received single-organ kidney transplants in the US during 1999–2010.² Patients were categorized into either mTOR inhibitor (sirolimus or everolimus) without calcineurin inhibitor (cyclosporin or tacrolimus; $n = 3,237$), calcineurin inhibitor without mTOR inhibitor ($n = 125,623$) or calcineurin inhibitor plus mTOR inhibitor ($n = 10,510$) groups, according to their primary maintenance immunosuppressive regimen at the time of hospital discharge after transplantation. The primary outcomes were time to death-censored allograft failure, death, and a composite of the two. The researchers generated Kaplan–Meier survival curves and computed hazard ratios (Hrs) for each outcome using calcineurin inhibitor without mTOR inhibitor as the reference group. Even after adjusting for more than 30 covariates (including recipient demographics and comorbidities, donor risk factors, immuno-logical factors, transplant centre and year of transplantation), they found that treatment with an mTOR inhibitor without a calcineurin inhibitor was associated with a 1.11-fold (95% CI 0.99–1.24) increased risk of allograft failure, a 1.25-fold (95% CI 1.11–1.41) increased risk of death, and a 1.17-fold (95% CI 1.08–1.27) increased risk of the composite outcome 2–8 years post-transplantation. Patients who received a combination of both classes of drugs had intermediate risks of the primary outcomes.

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Competing interests

The authors declare no competing interests.

In the study by Isakova *et al.*, the increased risk of allograft failure at 2–8 years follow-up associated with the use of mTOR inhibitors rather than calcineurin inhibitors was not quite statistically significant.² However, the substantially increased risk of death in this group seems to be real, assuming that all selection bias was accounted for in the covariate analysis. This finding is disappointing, and also somewhat surprising, because mTOR inhibitors have been shown to prolong the lifespan of a variety of animals, including worms, fruit flies and mice.^{3,4} An understanding of why mTOR inhibitors are associated with improved survival in healthy animals but with reduced survival in kidney transplant recipients might help to determine which patients, if any, would benefit from mTOR inhibitor therapy, and at what time post-transplantation they would glean that benefit. The activation of mTOR by growth factors and amino acids drives cell growth and proliferation, and the lifespan extension induced by mTOR inhibitors in healthy animals might be related to the induction of autophagy—the scavenging of unnecessary or dysfunctional molecules and organelles, which simultaneously provides the cell with nutrients for vital functions and removes oxidized components that might otherwise cause damage. Inhibitors of mTOR also upregulate cap-independent translation, which is responsible for the production of proteins involved in the stress response that enable damaged cells to survive rather than undergo apoptosis.⁴ Thus, we might expect that mTOR inhibitor therapy would be especially beneficial during stressful events, such as transplant surgery, or at times of poor nutrition, such as during peri-operative fasting. However, mTOR is also inhibited by nutrient, ATP, and oxygen deficiency;⁵ therefore, pharmacologic mTOR inhibition during stressful periods might result in too much of a good thing.

Both the Kaplan–Meier curves and the plots of HR against time in the study by Isakova *et al.* show that the biggest difference in risk of death between patients on mTOR inhibitors and those on calcineurin inhibitors occurred during the first 2 years post-transplantation; the HR decreased steeply from 2.33 (95% CI 1.75–3.10) immediately post-transplantation to 1.29 (95% CI 1.08–1.55) at 2-year follow-up and then levelled out.² Is use of mTOR inhibitors associated with an increased risk of death particularly during the immediate post-transplantation period or is there a subset of patients at particularly high risk of death on mTOR inhibitors who die <2 years post-transplantation and are, therefore, removed from the pool of long-term survivors? In either case, the increased risk of death soon after transplantation could be a direct effect of mTOR inhibitor therapy or the result of an interaction with concomitant immunosuppression. An analysis of cause of death 0–2 and 2–8 years post-transplantation in patients who receive mTOR inhibitors versus those on calcineurin inhibitor therapy might be revealing. A possibility exists that much of the increased risk of death associated with the use of mTOR inhibitors might be abrogated by delaying mTOR inhibitor use after transplantation.

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mTOR inhibitors are often used over calcineurin inhibitors in transplant recipients to decrease the risk of allograft failure. However, the study by Isakova *et al.* does not show a decrease in the risk of allograft failure in patients treated with mTOR inhibitors.² Despite the potential benefit of mTOR inhibitors in slowing the development of chronic kidney disease, concerns exist about delayed recovery from acute kidney injury in patients treated with these agents. The role of mTOR in cell growth and proliferation means that mTOR inhibitors impair healing. This impairment is most obvious from a surgical standpoint in terms of wound issues, hernia, and lymphocele development,⁶ but can also have adverse effects on the transplanted kidney. In rats, mTOR contributes to the recovery of renal tubular cells following ischaemia–reperfusion injury,⁷ and in kidney transplant recipients, mTOR inhibitor exposure soon after transplantation is associated with substantially impaired recovery from delayed graft function.⁸ In this context, it is interesting that in the study by

Isakova *et al.*, the change in HR with time is even steeper for allograft failure than for death, with a HR for allograft failure of 3.1 (95% CI 2.44–3.94) immediately post-transplantation decreasing to 1.21 (95% CI 1.02–1.42) at 2 years follow-up.² However, these curves are unadjusted and whether the observations are due to post-transplantation complications resulting from mTOR inhibitor use, or reflect poor outcomes as a result of existing factors that drive the clinical decision to use mTOR inhibitors rather than calcineurin inhibitors, is unclear.

These new data also raise questions regarding the practice of converting from a calcineurin inhibitor to an mTOR inhibitor in patients who develop calcineurin-inhibitor-induced nephrotoxicity after nonrenal solid-organ transplantation. The realization that renal failure following transplantation of other organs substantially increases mortality⁹ has been a strong impetus to attempt to minimize the use of calcineurin inhibitors in patients with renal dysfunction induced by these agents—often by converting to mTOR inhibitor therapy.¹⁰ This point highlights one of the major limitations of the study by Isakova *et al.*; patients were assigned to calcineurin inhibitor or mTOR inhibitor groups according to their immunosuppression on hospital discharge without accounting for later changes in therapy. Thus, the major drug exposure of the patients during the 8-year follow-up is unknown. More importantly, the effect of conversion to mTOR inhibitor therapy versus remaining on calcineurin inhibitors was not analysed. A minor weakness is the fact that patients who died or had graft failure during the transplant admission were not included in the analysis. Although these patients represent a small percentage of the total study population, they account for approximately 20% of the deaths and allograft losses in the series.²

The available data clearly indicate that mTOR inhibitors are not an appropriate alternative to calcineurin inhibitors for all kidney transplant recipients. The analysis of HRs in single variable patient subsets by Isakova *et al.* did not identify any categories of recipients for whom mTOR inhibitors were beneficial in comparison to calcineurin inhibitors, although some subgroups did tend towards a lower HR for death associated with mTOR inhibitor use than other subgroups. For example, the HR for death 2–8 years post-transplantation was 1.16 (95% CI 0.67–2.00) for kidney transplant recipients with cancer compared with 1.27 (95% CI 1.11–1.45) in those without cancer, and patients with delayed graft function had a HR for death of 1.19 (95% CI 0.95–1.49) compared with 1.26 (95% CI 1.09–1.45) in those without.² These data suggest the possibility that a patient with cancer and/or [Au: OK?] delayed graft function might have a lower risk of death and allograft failure if started on mTOR inhibitor therapy 2 years post-transplantation rather than at the time of transplantation. Finally, it is important to note that mTOR inhibitors are not the only available alternative to calcineurin inhibitors; belatacept, which blocks T-cell costimulation, has also been approved for use in adult kidney transplant recipients.

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