Mammalian Target of Rapamycin Inhibitors and Nephrotoxicity: Fact or Fiction

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Abstract
Mammalian target of rapamycin inhibitors, such as rapamycin and more recently everolimus, have substituted calcineurin inhibitors in many minimization strategies. Despite their acclaimed renal safety profile, several lines of evidence are emerging on their potential nephrotoxic effect. Predisposing conditions for nephrotoxicity involve a complex interplay between several environmental and genetic factors in the donor-recipient pair. Renal injury may be enhanced by pharmacodynamic interactions when combined with other drugs such as calcineurin inhibitors or nutrients that are predominantly related to an increase in local tissue exposure. These toxic interactions may occur within adequate doses and therapeutic blood levels. This explains the occurrence of nephrotoxicity in some but not all cases. Here, we postulated that activity of a low permeability glycoprotein efflux pump related to low protein expression and/or inhibition enhanced immunosuppressive drug entry in different cells. A rise in intracellular drug concentration increases bioactivity, leading to greater immunosuppression and more immune-related, nonrenal adverse events in the recipient and increased nephrotoxicity in the kidney graft. Under specific isolated or combined environmental and/or genetic conditions in both the recipient and donor affecting the glycoprotein efflux pump and/or the mammalian target of rapamycin pathway, these renal injuries may be aggravated by heightened drug tissue concentrations despite adherence to therapeutic drug and blood levels. Mammalian target of rapamycin inhibitors may induce predominantly a dose-dependent renal epithelial cell injury affecting either the glomerular or the renal tubular epithelial cells, leading to cell death and apoptosis. Epithelial mesenchymal transition-mediated interstitial fibrosis and tubular atrophy observed with these drugs may be the result of a cumulative toxic renal tubular injury induced by the direct insult of the drug itself and/or podocytopathy-associated proteinuria. The resulting glomerular tubular damage will ultimately lead to graft failure and loss, if exposure persists.

Key words: Intracellular drug level, Grapefruit juice, Permeability glycoprotein pump, Pharmacogenetics

Introduction
Calcineurin inhibitors (CNIs) are associated with acute and chronic nephrotoxicity. Calcineurin inhibitor-sparing regimens have yielded conflicting short-term and long-term results that were sanctioned by greater rates of acute rejection and, in some patients, evidence of chronic transplant glomerulopathy. Many of these CNI minimization strategies have involved mammalian target of rapamycin (mTOR) inhibitors such as rapamycin and everolimus.1 Evidence is emerging on their potential nephrotoxic effect.2 In this study, we describe a 47-year-old diabetic male recipient of a deceased-donor kidney transplant who had everolimus-induced graft dysfunction after prolonged grapefruit juice ingestion. We also highlight the complexity of the kidney transplant patient milieu, which is the result of intricate interactions between 2 distinct
donor-recipient genetic backgrounds and their exposure to several environmental stress factors along the life of the graft after transplant. The implications of these parameters on the development of a spectrum of adverse events that we observed concomitantly in both the recipient and the graft after transplant also are discussed. Finally, we review our own observations and recent reports from the literature and propose a mechanism for mTOR inhibitor-associated nephrotoxicity, emphasizing the important role of local tissue, rather than systemic exposure, in the pathogenesis of the associated renal injury and the extrarenal manifestations.

Case Description
A 47-year-old man who underwent a deceased-donor kidney transplant from a 65-year-old woman was initially treated with a triple immunosuppressive regimen of tacrolimus, mycophenolate mofetil, and prednisone. At 5 months posttransplant, treatment was converted to a CNI-free regimen because of biopsy-proven tacrolimus-induced acute nephrotoxicity. At hospital discharge, his serum creatinine level was 1.6 mg/dL. During the early follow-up (Figure 1), he exhibited a rise in serum creatinine levels that was associated with 2 episodes of adequately treated urinary tract infections and concomitant increase in whole blood tacrolimus level up to 20 ng/dL. Because of persistent deterioration in graft function despite tapering of tacrolimus dose, the patient underwent his first kidney graft biopsy at 4 months posttransplant, which revealed significant tubular isometric vacuolization (TIV) with 30% glomerulosclerosis, arterial and hyaline arteriolar sclerosis, and 15% interstitial fibrosis and tubular atrophy (IFTA). Tests for panel reactive antibodies, C4d and viral stains, and serology were all negative. The patient’s histologic lesions were consistent with a superimposed acute CNI nephrotoxicity on a baseline of expected chronic changes in a graft from an older donor. These findings prompted the discontinuation of tacrolimus, and his treatment regimen was converted to everolimus at a starting dose of 3 mg/day with mycophenolic mofetil continued at the same dose of 2 g/day.

Early after treatment conversion, the patient developed several extrarenal adverse events attributed to everolimus therapy, such as hypertriglyceridemia, mouth ulcerations, tremor, ankle edema (Figure 1), and anemia with lymphopenia (Figures 2 and 3), despite a noticeable improvement in renal function.

Figure 2. Extrarenal Adverse Events Postconversion to Everolimus Therapy

Note the worsening thrombocytopenia and higher epoetin requirement to maintain hemoglobin levels after introduction of grapefruit juice and despite the same level of minimal immunosuppressive therapy.

At 9 months after conversion to everolimus therapy, the patient exhibited a slight rise in serum creatinine levels, along with its adverse effects, and thrombocytopenia, prompting a second graft biopsy that revealed a worsening in TIV (Figure 5A) in the absence of any immunologic or viral infections, that was reflected by a gradual decline in serum creatinine levels, reaching the nadir value at discharge 2 months later. Most of these adverse events occurred while the patient was within therapeutic everolimus whole blood levels (Figure 4) and on standard mycophenolic mofetil dose, with some adverse events persisting despite the gradual tapering of both immunosuppressive agents.

At 9 months after conversion to everolimus therapy, the patient exhibited a slight rise in serum creatinine levels, along with its adverse effects, and thrombocytopenia, prompting a second graft biopsy that revealed a worsening in TIV (Figure 5A) in the absence of any immunologic or viral infections,
suggesting again some form of drug-induced nephrotoxicity. During this period, the patient’s total lymphocyte count was persistently below 1000/μL (Figure 3), indicating a significant state of immunosuppression that was associated with an adequate mycophenolic mofetil dose and therapeutic everolimus whole blood level (Figure 4).

Overall, the patient’s serum creatinine level remained stable for 1 year after conversion to a low dose of mycophenolic mofetil (1 g/d) and everolimus (1 mg/d) and within therapeutic blood levels until the patient started dieting because of weight gain. Three months later, he presented with a rapid and unexplained deterioration in graft function and a rise in serum creatinine levels to 2.5 mg/dL. A third graft biopsy revealed an improvement; however, TIV had persisted (Figure 5B) and IFTA had doubled up to 30% (Figure 5C) with minimal focal effacement of the epithelial cell foot process, with electron microscopy examination showing mild glomerular and peritubular capillaries and endothelial cell swelling with focal loss of endothelial cell fenestrations (Figure 6). Tests for panel reactive antibodies, serology tests, and viral and C4d stains were all negative. When further questioned, the patient admitted drinking 2 or 3 glasses of grapefruit juice per day over the last 3 months.

Case Discussion and Review of the Literature
Everolimus is an mTOR inhibitor used in kidney transplant. Mammalian target of rapamycin inhibitors

Figure 3. Total Lymphocyte Counts Before and After Conversion to Everolimus Therapy

Abbreviations: EVR, everolimus; MMF, mycophenolate mofetil; TAC, tacrolimus

Note the drop in lymphocyte count below 1000 that occurred after the conversion and the steady increase in the total count after the minimization of both everolimus and mycophenolate mofetil dose that was followed by a new decrease in the count after the introduction of the grapefruit juice while being on the same level of immunosuppression.

Figure 4. Everolimus Pharmacokinetic Whole Blood Level Monitoring and Mycophenolic Mofetil Dose Adjustment in the Postconversion Period

Abbreviations: BW, body weight; EVR, everolimus; MMF, mycophenolate mofetil; TAC, tacrolimus

Figure 5. Light Microscopy of Second and Third Graft Biopsies

(A) Accentuation in tubular isometric vacuolization from second graft biopsy.
(B) Attenuation in tubular isometric vacuolization in third graft biopsy. With (C) Increase in interstitial fibrosis and tubular atrophy to 30% from a baseline of 15% on previous biopsy.

Figure 6. Electron Microscopy of Third Graft Biopsy

(A) Focal effacement of epithelial cell foot process. (B) Mild glomerular and peritubular capillaries and endothelial cell swelling and focal loss of endothelial cell fenestrations.
are being safely and effectively used in several renal transplant protocols, in particular in certain CNI predisposing nephrotoxicity settings such as the case of our patient, the “old-for-old” kidney transplant and in other CNI sparing regimen. The main mechanism of action is inhibition of mTOR, a regulatory protein kinase involved in lymphocyte proliferation. Because of their specific pharmacologic characteristics and their relative lack of nephrotoxicity, these inhibitors are valid options to CNI as maintenance immunosuppressive therapy in renal transplant recipients with nonimmunologic chronic allograft dysfunction. Despite the acclaimed nephroprotective profile, recent evidence has suggested that mTOR inhibitor-based therapy is associated with a wide range of renal and extrarenal adverse effects, such as anemia, thrombocytopenia, leukopenia, dyslipidemia, posttransplant diabetes, lymphedema, stomatitis, fibrointerstitial pneumonitis, viral infection, and infertility. Although most of these adverse effects are dose dependent, it is extremely important for clinicians to recognize these early to reduce or discontinue mTOR inhibitor treatment, thereby avoiding the development and onset of severe clinical complications.

Mammalian target of rapamycin inhibitor-associated proteinuria has been reported in different clinical settings: (1) in de novo mTOR inhibitor treatment in combination with a CNI, (2) in de novo mTOR inhibitor treatment without a CNI, (3) in treatments requiring early conversion from a CNI-based regimen to an mTOR inhibitor-based regimen, (4) in treatments requiring late conversion from a CNI-based regimen to an mTOR inhibitor-based regimen, and (5) in nonrenal solid-organ transplants. High-dose of everolimus in animal models are associated with glomeulosclerosis and tubulointerstitial fibrosis. The exact molecular and/or biologic mechanisms associated with these profibrotic effects remain unknown. Suppression of mTOR Complex 1 activity may lead to a marked inhibition of the endothelial cell through an alteration in vascular endothelial growth factor balance at the podocyte and may cause reduced expression of several slit diaphragm-associated proteins and key podocyte structures, such as nephrin, podocin, and CD2ap, leading to disruption of the filtration barrier, proteinuria, and glomerulosclerosis. Epithelial to mesenchymal transition (EMT), a phenotypic conversion of epithelium to a fibroblastic or myofibroblastic phenotype, induced by suppression of the Akt protein kinase signaling pathway, may play a central role in the mTOR inhibitor-associated profibrotic process. Masola and associates recently demonstrated that high concentrations of everolimus induced an up-regulation of all EMT markers in human renal epithelial proximal tubular cells, including alpha-smooth muscle actin, vimentin, fibronectin, and matrix metalloproteinase 9, at both the gene and protein levels. The promotion of EMT may be facilitated or not by a transforming growth factor β-dependent mechanism and appears to be mediated through a heparanase-stimulating process known to be involved in the pathogenesis of several proteinuric nephropathies. In contrast, low dose of everolimus, commonly used during organ transplant, failed to induce EMT in the same experimental settings.

Therefore, mTOR inhibitor-associated nephrotoxicity is characterized predominantly by a possible apoptotic renal epithelial cell injury that affects both podocytes and renal tubular epithelial cells in the tubulointerstitial compartment. Consequently, the IFTA observed with mTOR inhibitor therapy may be the result of a cumulative toxic renal tubular injury induced by the podocytopathy-associated proteinuria and/or by the direct toxic tubular insult of the drug itself. Moreover, the IFTA commonly observed with kidney graft biopsies is often multifactorial. It is frequently found at the time of transplant in kidney grafts from older donors and may be aggravated or induced by other nonimmunologic factors involving one or more of the following: CNI, recurrent native kidney diseases, viral infections, and reflux nephropathy. Chronic rejection, however, represents a common cause of IFTA, but the exact contribution of each of these insults, combined with the overall IFTA load, remains unknown. Interstitial fibrosis, tubular atrophy, and glomerulosclerosis also are commonly observed along with other lesions of both immune and nonimmune origin, such as arterial fibrointimal hyperplasia, medial arteriolar hyalinosis, and TIV.

In our case, the patient exhibited evidence of acute kidney injury on the first graft biopsy related to tacrolimus and manifested mainly by TIV that overlapped with the chronic baseline changes
(glomerulosclerosis, IFTA, and arterial and hyaline arteriolar sclerosis). These acute histologic lesions were presumed to be reversible, given the slow and gradual return of serum creatinine levels to baseline several months after CNI therapy was stopped. However, the patient’s second graft biopsy unexpectedly showed worsening of TIV, which affected nearly 50% of the tubules (Figure 5A), along with the same and unchanged chronic lesions, despite the discontinuation of tacrolimus for more than 9 months and without any evidence of immune-related or viral-mediated causes. This could be explained by the additive toxic renal tubular effect of everolimus that was superimposed on a preexisting and lasting CNI-induced acute injury. Histologic lesions suggestive of acute CNI nephrotoxicity are known to persist for several months after drug discontinuation, even with improvements in graft function.38-40 The worsening of TIV and deterioration in graft function coincided with several extrarenal manifestations (hypertriglyceridemia, ankle edema, mouth ulcers, tremor, skin infections with anemia, thrombocytopenia, and lymphopenia). Interestingly, these recipient-related (immune and extrarenal) and donor-related (renal) toxicities occurred within therapeutic dose and whole blood levels of everolimus, indicating a poor association between current pharmacokinetics therapeutic monitoring parameters and efficacy and safety patient profiles.38,41-43 The absence of proteinuria may be explained by the introduction of the angiotensin receptor blocker telmisartan during the early posttransplant period for treatment of hypertension and the gradual tapering of everolimus levels.7,8,11,44,45

The third graft biopsy was prompted by a sudden rise in serum creatinine levels in the absence of proteinuria after nearly 1 year of stable renal function and reduced maintenance immunosuppressive therapy. Histologic findings in the third biopsy included a partial regression in TIV (Figure 5B) that was associated with doubling in IFTA to 30% (Figure 5C), with electron microscopy showing mild glomerular and peritubular capillaries and endothelial cell damage with focal effacement of the foot processes (Figure 6) but no presence of microinflammation or lamellation. The deterioration in graft function was unexplained in the absence of any other immunologic or viral cause. More importantly, podocyte injury and worsening in IFTA occurred in the context of a sudden drop in the total lymphocyte count, a rough indicator of reduced immunity, despite continuation on the same minimal levels of immunosuppressive drug, which was maintained within therapeutic blood levels (Figures 3 and 4). Control of blood pressure using an angiotensin receptor blocker and the gradual reduction to a minimal level of the immunosuppressive agent may explain the absence of proteinuria despite the mild glomerular lesions. These histologic findings have been reported to be associated with mTOR inhibitor monotherapy or in combination therapy with CNI and at therapeutic concentrations, in both animal and human models.7,11,16-23,46,47 In fact, Piao and associates47 recently demonstrated, using an in vivo experimental animal model, that combined treatment with cyclosporine and the mTOR inhibitors (rapamycin and everolimus) significantly increased cyclosporine or mTOR inhibitor concentrations in kidney tissue versus treatment with cyclosporine or mTOR inhibitor alone, despite similar whole blood levels of either drug. This increase in tissue concentration of both drugs was associated with an exaggeration in oxidative stress and an aggravation in renal injury with significant deterioration in renal function in the combination therapy group versus with monotherapy. These observations suggested a potential intrarenal pharmacodynamic interaction between the mTOR inhibitor and CNI that caused a greater degree of tubulointerstitial fibrosis in the kidneys from animals receiving combination therapy. This aggravation of nephrotoxicity with combination therapy appears to be dose dependent and the result of the additive direct toxic effect of both classes of drug on the renal tubular epithelial cell. Our suggestions are in agreement with earlier observations on the synergistic effect of cyclosporine and rapamycin combination on the greater and disproportionate increase in intrarenal cell drug concentration in relation to whole blood levels and the consequent exacerbation of renal dysfunction in the combination-treated animals versus use of either drug alone.21

This enhanced renal tissue exposure when both drugs are combined appears to be mediated by P-glycoprotein (P-gp) inhibition in renal tubular cells.46 In an in vitro human epithelial renal cell model, Anglicheau and associates46 demonstrated that rapamycin exerted an inhibitory effect on P-gp and increased intracellular cyclosporine concen-
trations and cell death in a dose-dependent manner. The P-gp efflux pump, an ABCB1 (previously multidrug resistance 1) gene product, is a membrane protein that functions as an ATP-dependent exporter. It has a protective role against toxicity of many substances, such as xenobiots, antibiotics, and chemotherapeutic agents, by extruding them from cells. In the kidney, P-gp is constitutively expressed mainly on the brush border of the proximal and distal tubular cells. Low activity of this efflux pump caused by either low protein expression induced by a genetic mutation such as the ABCB1 3435C→T TT genotype or its inhibition by a drug or a natural substance such as grapefruit juice, a well-established potent P-gp inhibitor, can lead to renal toxicity within therapeutic drug blood level ranges as a result of increased intracellular drug concentration and can lead to an exaggerated deleterious injury, when unfavorable genetics, demographics, and environmental conditions are combined. Chronic cyclosporine nephrotoxicity is inversely related to P-gp expression in the renal tubule. Conversely, P-gp up-regulation appears to protect proximal renal tubular cells from cadmium-induced apoptosis. Although mTOR inhibitors are well known to act simultaneously like CNIs as substrates, and as inhibitors for P-gp, similar associations between P-gp expression and everolimus nephrotoxicity have not been reported so far.

P-glycoprotein is located and widely expressed on many other cell surfaces, including the small intestine, liver, blood-brain barrier, placenta, and lymphocyte. Therefore, P-gp can regulate the content of specific drugs in several cells. Asnermot and associates have shown in healthy volunteers that the concentration of cyclosporine in lymphocytes was influenced by the level of P-gp activity and was inversely related to P-gp expression. Moreover, they have shown that cyclosporine whole blood levels did not predict intracellular levels. This finding was confirmed in kidney, liver, and lung transplant. Kidney, heart, and liver transplant recipients who carry the ABCB1 3435C→T TT genotype (low-P-gp expressers) are less likely to develop acute rejection than their counterparts, carriers of CC or CT genotypes (high P-gp expressers), regardless of the whole blood level of CNI. These findings suggest that, despite maintenance of drug concentrations in the therapeutic range, some patients could have either increased intracellular levels and therefore could be overimmunosuppressed or have inadequate intracellular concentrations and therefore underimmunosuppressed. Depending on the level of P-gp activity, this could lead to either immune-related or other nonrenal adverse events (for patients with low activity) or to increased risk of rejection (for patients with high activity). These observations are in agreement with our earlier report of cyclosporine-treated kidney transplant patients, which was later confirmed by other investigators in cyclosporine-treated renal transplant recipients and everolimus-treated cardiac transplant recipients, on the weak association between whole blood levels of immunosuppressive drugs and their corresponding lymphocyte concentrations and on the stronger correlation of the latter with the rate of biopsy-proven acute rejection. Interestingly, no such associations have been yet described with mTOR inhibitors despite their similar effects to both CNIs on P-gp.

When the clinical course from conversion of tacrolimus to everolimus is observed more closely, our patient exhibited a spectrum of intermittent clinical extrarenal manifestations reflecting a state of heightened immunosuppression, including mouth ulcerations and plantar infections that occurred shortly after the conversion and were associated with lymphopenia (Figures 2 and 3). In addition, he developed neurologic (tremor) and hematologic adverse effects, including thrombocytopenia and anemia, with the latter requiring a maintenance recombinant erythropoiesis-stimulating agent. Although these manifestations partially subsided, most persisted after transplant despite progressive minimization of immunosuppressive agents. This was paralleled by a gradual improvement in graft function and return of serum creatinine levels to the patient’s discharge level. Interestingly, the introduction of grapefruit juice triggered a new rise in serum creatinine levels of toxic origin that was associated with the emergence of new evidence of bone marrow suppression, reflected by worsening lymphocyte count (Figure 3), thrombocytopenia, and anemia (Figure 2), with the latter requiring a higher dose of erythropoiesis-stimulating agent to maintain the same low hemoglobin level. All these toxic immune, renal, and extrarenal manifestations occurred without any change in an already reduced immunosuppressive state and with everolimus whole blood levels within the therapeutic dose
range. These observations suggest an exaggerated renal and hematopoietic tissue exposure to everolimus that was potentially induced by grapefruit juice-mediated inhibition of P-gp. Unfortunately, the measurement of tissue levels of mTOR inhibitors is not readily available in routine clinical practice and critical intracellular levels are not known.\textsuperscript{71,72} To our knowledge, no study evaluating the link between mTOR inhibitor concentrations in lymphocytes and clinical effect has been published.

The enhanced sensitivity to immunosuppression reflected by worsening lymphopenia after conversion to everolimus and before grapefruit juice introduction despite adequate blood levels and minimal drug dose levels could imply a state of baseline constitutive low mTOR and/or P-gp activity related to an unidentified mutation in the mTOR pathway and/or the ABCB1 gene of the recipient. Moreover, the persistence and exaggeration on the second graft biopsy in TIV, a marker of acute drug nephrotoxicity, several months after the discontinuation of tacrolimus and the doubling in IFTA in addition to the podocyte injury observed in the third graft biopsy could imply a possible state of impaired baseline P-gp expression in the donor graft that was aggravated by the prolonged exposure to grapefruit juice. Unfortunately, we could not establish genetic profiles in the recipient or donor. In any case, no study on the consequences of genetic polymorphisms in ABCB1 regarding the biologic effects of everolimus has been reported in solid-organ transplant, and the efficacy of the mTOR inhibitor or adverse effects of polymorphisms in the proteins of the mTOR pathway have not yet been investigated.\textsuperscript{73,74}

**Mechanism of mTOR Inhibitor Adverse Events**

We postulated that low P-gp activity may be related to low protein expression caused by one or more specific genetic mutation and/or to inhibition induced by drugs or nutrients. This reduced activity enhances immunosuppressive drug entry in different cells (lymphocytes and nonimmune cells in the recipient and renal cells in the graft). The rise in drug influx results in an increase in intracellular drug concentration and exaggerated bioactivity without any change in whole blood level, an indicator of bioavailability; therefore leading to greater immunosuppression and more extraintestinal, nonrenal adverse events in the recipient and increased nephrotoxicity in the kidney graft (Figure 7). This scenario is in agreement with the posttransplant course that we observed in our patient before and after long-term ingestion of grapefruit juice. It highlights the complexity of the transplant recipient setting, which represents a hybrid milieu involving the combination of 2 distinct genetic backgrounds of the recipient and the donor. The ultimate outcome in terms of efficacy and safety is the result of a complex interaction between these genetics parameters and the environmental factors arising in the recipient after transplant.\textsuperscript{43}

**Figure 7. Effect of P-Glycoprotein Inhibition on Immunosuppressive Drug Disposition**

Based on our observations and recent reports in the literature, we propose the following mechanism for mTOR inhibitor-induced nephrotoxicity. Everolimus, like rapamycin, may induce predominantly a dose-dependent renal epithelial cell injury affecting the glomerular and/or the renal tubular epithelial cells, leading to cell death and apoptosis. The EMT-mediated IFTA observed with these drugs may be the result of a cumulative toxic renal tubular injury induced by the direct toxic tubular insult of the drug itself and/or podocytopathy-associated proteinuria. The resulting glomerulosclerosis in combination with IFTA ultimately will lead to graft failure and loss, if exposure persists. Under specific isolated or combined environmental and/or genetic conditions
in both the recipient and donor, already discussed above, affecting both the efflux pump P-gp and/or the mTOR pathway, these renal injuries may be aggravated by a heightened drug tissue concentration despite therapeutic drug and whole blood levels (Figure 8).

Figure 8. Mechanism of Mammalian Target of Rapamycin Inhibitor Nephrotoxicity

Abbreviations: EMT, epithelial mesenchymal transition; IFTA, interstitial fibrosis tubular atrophy; mTOR-I, mammalian target of rapamycin inhibitor; P-gp, permeability glycoprotein

Mammalian target of rapamycin inhibitors mainly induce dose-dependent renal epithelial cell injury that affects either the glomerular or the tubular epithelial cells leading to slit diaphragm disruption and cell death and apoptosis. The epithelial mesenchymal transition-mediated interstitial fibrosis and tubular atrophy observed with these drugs may be the result of a cumulative renal tubular injury induced by the direct toxic tubular insult of the drug itself and/or the podocytopathy-associated proteinuria. Under specific isolated or combined environmental and/or genetic conditions, mainly in the kidney graft, affecting both the efflux pump P-glycoprotein and/or the mammalian target of rapamycin pathway, these renal injuries may be aggravated by heightened drug tissue concentration despite adherence to therapeutic drug dose and whole blood levels. The resulting glomerulosclerosis in combination with interstitial fibrosis and tubular atrophy will ultimately lead to graft failure and loss, if exposure persists.

To our knowledge, this is the first case describing kidney graft injury associated with mTOR inhibitor therapy after prolonged ingestion of grapefruit juice. It highlights the complexity of monitoring immunosuppression in the kidney transplant patient and the importance of distinguishing between the mechanisms of the different adverse events affecting concomitantly the recipient and the kidney graft. Kidney transplant and probably all organ transplant patients should be cautioned and warned against the ingestion of grapefruit or other herbal products that might interfere with immunosuppressive drug disposition. Further studies are needed to identify the effect of genetic mutations affecting the P-gp efflux pump and/or the mTOR pathway on the efficacy and safety of mTOR inhibitors in solid-organ transplant.

References


