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Strategies for the management of adverse events associated with mTOR inhibitors

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A B S T R A C T

Mammalian target of rapamycin (mTOR) inhibitors are used as potent immunosuppressive agents in solid-organ transplant recipients (everolimus and sirolimus) and as antineoplastic therapies for various cancers (eg, advanced renal cell carcinoma; everolimus, temsirolimus, ridaforolimus). Relevant literature, obtained from specific PubMed searches, was reviewed to evaluate the incidence and mechanistic features of specific adverse events (AEs) associated with mTOR inhibitor treatment, and to present strategies to effectively manage these events. The AEs examined in this review include stomatitis and other cutaneous AEs, wound-healing complications (eg, lymphocele, incisional hernia), diabetes/hyperglycemia, dyslipidemia, proteinuria, nephrotoxicity, delayed graft function, pneumonitis, anemia, hypertension, gonadal dysfunction, and ovarian toxicity. Strategies for selecting appropriate patients for mTOR inhibitor therapy and minimizing the risks of AEs are discussed, along with best practices for identifying and managing side effects. mTOR inhibitors are promising therapeutic options in immunosuppression and oncology; most AEs can be effectively detected and managed or reversed with careful monitoring and appropriate interventions.

1. Introduction

The mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus are potent immunosuppressors used to prevent acute rejection following solid-organ transplantation [1]. These drugs target signal transduction pathways involved in cell-cycle progression, thereby inhibiting interleukin-2–induced T-cell proliferation. mTOR inhibitors also block enzymes in cell-cycle signal transduction pathways that play a role in the development and progression of certain cancers. The mTOR inhibitors everolimus, temsirolimus, and ridaforolimus have demonstrated antitumor activity in various cancers, most notably advanced renal cell carcinoma [2–4]. However, some mechanisms associated with the immunosuppressive and anticancer properties of mTOR inhibitors are also linked to the progression of many disorders, including metabolic (eg, diabetes, hyperlipidemia) [5], renal (eg, proteinuria, delayed graft function [DGF]) [6–8], dermatologic/mucosal (eg, stomatitis, rash) [9], hematologic (eg, anemia, microcytosis) [10], hemodynamic (eg, hypertension) [11], and hormonal conditions (eg, impaired gonadal function, ovarian toxicity) [12,13], as well as impaired wound healing (eg, lymphocele, hernia) [14]. This review explores the mechanistic causes of adverse events (AEs) associated with mTOR inhibitors and presents strategies for managing these events.

2. Literature search methods and results

An initial PubMed search was conducted to evaluate the overall scope of AEs associated with mTOR inhibitors using the following search criteria: {(everolimus OR sirolimus OR mTOR[Title]) AND adverse events [Title/Abstract]} AND English[Language]. Based on the initial literature review, additional PubMed searches were performed of the most common AEs and those of clinical interest using the following search terms: {(everolimus OR sirolimus) AND "AE name"[Title/Abstract]}, where "AE name" = proteinuria (196 articles), hypertension (183 articles), hyperlipidemia (132 articles), pneumonitis (128 articles), anemia (122 articles), wound healing (82 articles), stomatitis (82 articles), delayed graft function (74 articles), rash (72 articles), hyperglycemia (68 articles), new-onset diabetes (42 articles), lymphocele (32 articles), and follicle-stimulating hormone (FSH) OR luteinizing hormone (LH) (6 articles). Two recently published and relevant articles not identified in the PubMed searches also were included in this review. Articles were limited to those in the English language.

After removing duplicates, the identified abstracts were reviewed for potential relevance. Full-text articles were obtained for 104 references with details on the incidence of, mechanistic features of,

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and/or strategies for managing specific AEs. The following sections summarize the literature findings and present strategies to prevent and manage these AEs, based on the authors' clinical experience.

3. Dermatologic and mucosal adverse events

3.1. Stomatitis

Oral ulcerations are a common dose-limiting toxicity associated with mTOR inhibitors [9]. It is thought that these ulcers result from direct toxic effects of mTOR inhibitors on oral and nasal mucous membranes [15]. These AEs are distinct from the conventional mucositis seen with chemotherapy, with clinical findings resembling aphthous stomatitis [16]. mTOR inhibitor-associated stomatitis (mIAS) typically presents as distinct, painful, ovoid, superficial ulcers surrounded by a characteristic erythematous margin [16]. The ulcers are generally grayish-white lesions of <1 cm in diameter that form on the inner lip, ventral and lateral surfaces of the tongue, and the soft palate [16]. Unlike viral ulcers, mIAS lesions do not form on more keratinized mucosa, such as the gingiva and dorsal surface of the tongue [16]. mIAS ulcers usually form soon after initiation of mTOR inhibitor therapy (median time to onset with sirolimus is reportedly 1 week) [15].

In transplant recipients and cancer patients, the incidence of mIAS can be up to 60%, but most AEs are not severe (≤5% are Grade 3 or 4) and typically do not require discontinuation of therapy [15,17,18]. According to the prescribing information and safety results from pivotal Phase 3 transplantation studies, the incidence of stomatitis/mouth ulceration is between 3% and 8% with everolimus (Table 1) [18–30]. The incidence of oral ulceration in pivotal studies of sirolimus reportedly ranges from 10% to 19% (Table 1) [31]; however, the mucosal lesions were attributed to unconfirmed herpes simplex viral infection [19,20]. Further, there is wide variability across the literature in the incidence of AEs involving mucous membranes (ranging from 10% to 100% with sirolimus), possibly due to underreporting of mild AEs and/or to differences in underlying conditions (eg, psoriasis, diabetes mellitus), AE classifications (eg, herpes, aphthous ulceration, oral erosions, ulcerations), and treatment protocols [15,31]. Several studies showed no clear differences in the incidence or severity of mucositis AEs between everolimus, sirolimus, temsirolimus, or ridaforolimus [18,32].

Table 1
Incidence of adverse events of interest in pivotal transplantation studies of everolimus or sirolimus [18–30].

Adverse event	Everolimus (0.75 or 1.0 mg BID with reduced- or standard-dose TAC or CsA)[a]	Sirolimus (2 or 5 mg with CsA ± corticosteroids)
Dermatologic disorders		
Acne	5%–14%	10%–25%
Stomatitis/oral ulcers	3%–8%	10%–19%[b]
Rash	NR	5%–10%
Wound-healing disorders		
Any wound-healing event	11%–35%	3%–36%
Lymphocele	7%–16%[c]	5%–20%
Wound dehiscence	1.5%	NR
Incisional hernia	3%	18%
Metabolic disorders		
Hyperglycemia	12%–14%	NR
New-onset diabetes mellitus	5%–32%	20%–27%
Hyperlipidemia	21%–24%	30%–64%
Hypertriglyceridemia	4%	21%–57%
Hypercholesterolemia	16%–17%	20%–46%
Dyslipidemia	15%	NR
Renal disorders		
Proteinuria	3%–36%[c]	9%–10%
Nephrotic syndrome	NR	2%
Pulmonary disorders		
Pneumonitis	0%–7%	0%–5%
Blood and lymphatic disorders		
Anemia	8%–26%	11%–27%
Leucopenia	3%–12%	5%–12%
Thrombocytopenia	5%	6%–23%
Hemodynamic disorders		
Hypertension	17%–30%	21%–38%

Abbreviations: BID, twice daily; CsA, cyclosporine; NR, not reported; TAC, tacrolimus.
[a] Where possible, data are reported for approved doses: 0.75 mg BID for kidney transplantation and 1.0 mg BID for liver transplantation.
[b] Reported as unconfirmed herpes simplex virus.
[c] Range included everolimus up to 3.0 mg/d.

Aphthous ulceration is especially common in transplant recipients who are switched from a calcineurin inhibitor (CNI) to sirolimus and in patients on combination therapy with sirolimus and mycophenolate mofetil (MMF) [15,31]. The incidence of stomatitis in these patients is reportedly as high as 60% [31,33]. There are 2 possible explanations for the high incidence of stomatitis in such cases: (1) antiviral prophylaxis and high-dose steroid therapy given immediately after transplantation may reduce viral or inflammatory cofactors, thereby reducing the incidence of mIAS, and (2) long-standing CNI immunosuppressive therapy may result in mucous membrane fragility that is enhanced by introducing an mTOR inhibitor [15,33].

Strategies to prevent oral mIAS include maintaining good oral hygiene with gentle brushing, mild toothpaste (without sodium lauryl sulfate or strong flavors), and salt and baking soda rinses; avoiding spicy, acidic, hot, or hard foods; reducing stress; and avoiding harsh agents (eg, peroxide, antifungals, alcohol, iodine, thyme) [9,31,34–36]. If identified early, mIAS generally responds well to treatment [9,31,37]. Topical high-potency corticosteroids (eg, clobetasol, dexamethasone), nonsteroidal anti-inflammatory drugs (NSAIDs; eg, amlexanox paste), and anesthetics (eg, Miracle mouthwash, viscous lidocaine) can be used to promote healing and reduce pain [9]. Persistent or recurrent mIAS can be managed with intensive topical, intralesional, or systemic corticosteroids; or systemic colchicine, pentoxifylline, or azathioprine [9]. Grade 2 or higher mIAS is generally painful and may restrict oral intake of nutrients; in such cases, mTOR inhibitor dose reduction or cessation may be required [9]. If lesions persist after aggressive treatment and withdrawal of mTOR inhibitor therapy, patients should be referred to an oral surgeon to exclude cancer [31].

3.2. Other cutaneous adverse events

Other common dermatologic effects of mTOR inhibitors include acne-like dermatitis, pruritus, rash, and nail changes (Table 1) [31,38]. These AEs may result from mTOR inhibitor blockade of the epidermal growth factor pathway and may resolve spontaneously [39]. More persistent AEs typically can be managed with standard topical or systemic therapies and rarely lead to discontinuation of mTOR inhibitor therapy [31,39]. Physicians should actively monitor patients for dermatologic side effects because early intervention can minimize bothersome symptoms and cosmetic problems, and prevent more severe cutaneous AEs [31].

4. Wound-healing adverse events

Surgical complications, including wound dehiscence, incisional hernia, lymphocele, and infection, that can impair wound healing have been reported in 15% to 32% of kidney transplant and 8% to 40% of heart transplant recipients [14,40]. Higher rates of incisional hernia and lymphocele have occurred with mTOR inhibitors relative to other immunosuppressants when patients received a high loading dose of mTOR inhibitor [14,41,42]. However, more recent studies using lower doses of mTOR inhibitors without a loading dose have shown that rates of wound-healing complications do not differ significantly between mTOR inhibitors and other immunosuppressive therapies [14]. For example, in the H2304 study in which everolimus was initiated 30 days after liver transplantation, the rate of wound complication was 11.0% (27/245) for everolimus plus low-dose tacrolimus, compared with 7.9%

(19/241) for tacrolimus controls [21]. In a pooled analysis of 3 studies of everolimus 1.5 mg or 3.0 mg versus mycophenolic acid (MPA) initiated within 48 hours of kidney transplantation, the rate of wound complications was significantly greater for the higher everolimus dose compared to MPA (21.8% vs 14.3%; $p < 0.001$) but not for the lower dose (16.6% vs 14.3%; $p = 0.255$) [29]. Incidences of wound-healing complications in pivotal studies of solid-organ transplantation are listed in Table 1.

mTOR inhibitors block growth signals required for proliferation of endothelial cells and fibroblasts, thereby restricting fibrosis, which is a key factor in successful wound healing [14,43]. mTOR inhibitors also inhibit vascular endothelial growth factor (VEGF) and nitric oxide, which are mediators of angiogenesis, inflammation, and immune function in skin wounds [43,44]. Sirolimus has also been shown to disrupt skin T-cell proliferation, migration, and production of growth factors [45,46].

Factors that increase the risk of mTOR inhibitor-associated wound-healing AEs are advanced age, diabetes, malnourishment, corticosteroid or anticoagulant use, high body mass index (BMI), thymoglobulin induction, and long surgery duration [41,47]. Risk factors for incisional hernia in liver transplant patients receiving mTOR inhibitor therapy include male gender, BMI $\geq$ 29 kg/m^2, Model for End-Stage Liver Disease (MELD) score $\geq$ 22, hepatitis B virus positivity, and receipt of a deceased donor graft [44].

Delaying mTOR inhibitor therapy until 3 to 7 days posttransplantation and avoiding high loading doses (which is consistent with everolimus usage and administration guidelines) [27] have significantly reduced the risk of impaired wound healing, particularly for obese or diabetic patients [40,43,48]. Everolimus is not indicated for administration until at least 30 days after liver transplantation [27] because mTOR inhibitors dose-dependently impair vascularization [44]. Furthermore, most complications develop during the first few postoperative months. At $\geq$ 30 days posttransplantation, wounds should be somewhat healed and wound strength should be developing; the risks of wound complications associated with newly initiated mTOR inhibitor therapy at this stage should be minimal [42,44].

Reducing obesity before transplantation (if possible) may reduce the risk of wound complications [48]. For kidney transplant recipients, performing surgery prior to initiating dialysis is recommended [47]. Minimizing the use of corticosteroids is recommended to reduce the risk of wound-healing delays [47,48]. If patients require subsequent surgeries and mTOR inhibitor therapy can be safely interrupted, the risk of wound-related AEs may be reduced by stopping mTOR inhibitor therapy at least 1 week before surgery and resuming it 10 to 15 days afterward [49].

Surgical techniques reported to improve wound-healing outcomes in transplant recipients include placing closed-suction drains, using subcutaneous sutures, sealing or ligating lymphatic ducts, performing prophylactic peritoneal fenestration, and avoiding extensive dissection; careful attention to surgical technique also is important [41,43,47,49–51]. If used, staples can remain in place for 3 to 4 weeks to prevent skin dehiscence [41]. If a symptomatic lymphocele develops, ultrasonography should be performed to determine if intervention is required. Intervention is needed if flow to the kidney is impacted, hydronephrosis is found, there is radiologic or clinical evidence of an infected fluid collection, or the recipient develops unilateral swelling of the ipsilateral leg. Treatment options for symptomatic lymphoceles include percutaneous aspiration (with or without sclerotherapy) and surgical marsupialization of the lymphocele into the peritoneal cavity [50], which can be performed open or laparoscopically. If lymphoceles are associated with deep vein thrombosis, anticoagulation therapy or a vena caval filter may be required [50].

Incisional hernias can be repaired using laparoscopic or open techniques [52], with biologic or synthetic mesh closures [53]. Because the risk of infection is higher in immunosuppressed transplant recipients, biologic mesh is a viable option for them. If a mesh-related infection develops after hernia repair, having used biologic mesh allows for treating the infection with antibiotics as opposed to removing a synthetic mesh via another complex operation [54].

5. Lymphedema

mTOR inhibitors can impair lymphoangiogenesis, such that lymph fluid is not contained in the lymph system. This can lead to lymphocele development, as described above, and to the rare but serious AEs of lymphedema and capillary leakage [41,55]. Patients taking mTOR inhibitors should be monitored for lymphedema; treatment should be withdrawn promptly at the first sign of fluid accumulation because severe lymphedema is not always reversible and can be fatal [55]. Evidence suggests that patients with preexisting lymphatic deficiencies should not use mTOR inhibitors [55].

6. Metabolic adverse events

6.1. Hyperglycemia

Hyperglycemia and new-onset diabetes mellitus (NODM) are well-recognized posttransplant complications that increase cardiovascular events, all-cause mortality, and cardiovascular mortality [56]. There is a strong association between immunosuppression and NODM, particularly when immunosuppressive regimens include the CNI tacrolimus [57,58]. The association between mTOR inhibitors and NODM is less clear, and the risk of developing NODM may differ depending on whether a CNI is combined with an mTOR inhibitor. In a retrospective analysis of data from the US Renal Data System ($N = 20{,}124$ renal transplant patients), sirolimus was independently associated with an increased risk of NODM [59]. However, in randomized controlled trials of everolimus with low-dose cyclosporine (with or without basiliximab) in renal transplant recipients, the incidence of NODM was low ($\leq$5%) [60,61].

The pathophysiology of mTOR inhibitor-induced NODM is complex. mTOR and its downstream target S6 kinase 1 (S6K1) interact with various growth factors, hormones, and nutrients to regulate protein translation and cell growth, proliferation, and survival [5,62]. In animal models, sirolimus induces NODM by increasing insulin resistance, glucose intolerance, and gluconeogenesis, and reducing β-cell function [5,62].

Recent data suggest that patients with risk factors for diabetes (eg, advanced age, Black race, Hispanic ethnicity, obesity, family history of diabetes, hepatitis C positivity, transplantation from deceased donor) [59] be monitored closely for NODM throughout mTOR inhibitor therapy. Glucose monitoring (preferably fasting) should be performed regularly to identify new or worsening hyperglycemia [63]. Other symptoms that indicate hyperglycemia include increased thirst and urination [63–65]. Education strategies should be implemented so that patients learn to recognize these symptoms [65]. If possible, efforts should be made to establish normoglycemia before starting mTOR inhibitors [36,65].

The 2012 position statement from the American Diabetes Association and the European Association for the Study of Diabetes [66] provides practical guidelines for managing type 2 diabetes. Although these guidelines do not specifically address NODM associated with mTOR inhibitors in cancer or transplant patients, management strategies are similar for all causes of diabetes [66]. A patient-centered approach is emphasized, with individualized treatment goals based on each patient's overall health, medication tolerance, and preferences [66]. Treatment algorithms include diet and exercise modifications, followed by use of oral antihyperglycemic agents and insulin [36,51,65,66]. If sustained hyperglycemia develops despite diet and exercise modifications, metformin is usually recommended as first-line treatment; however, metformin is contraindicated in patients with renal impairment (estimated glomerular filtration rate [eGFR] < 60 mL/min), significantly impaired liver function, and states of decreased tissue perfusion (eg, myocardial infarction, sepsis) [63].

Hypoglycemia is a potentially life-threatening complication in transplant recipients and patients with advanced cancer. Patients treated with sulfonylureas or insulin should be monitored closely for hypoglycemia, and less aggressive glycemic goals (hemoglobin A1c level [$HbA_{1c} \leq 8\%$]) may be appropriate for critically ill patients compared with the general diabetes population ($HbA_{1c} \leq 7\%$) [63]. If patients discontinue mTOR inhibitor therapy for any reason, careful adjustment of antihyperglycemic treatments is needed to avoid hypoglycemia [63].

6.2. Hyperlipidemia

Hyperlipidemia is very common with mTOR inhibitors, with estimated prevalence of up to 75% [51,63]. Most lipid-related AEs are mild; patients rarely experience moderate or severe increases in cholesterol or triglycerides [36,51]. However, for patients with established hyperlipidemia, the risk/benefit ratio should be carefully considered before starting an mTOR inhibitor [26,27]. In clinical trials of sirolimus plus cyclosporine and sirolimus after cyclosporine withdrawal, up to 90% of patients required treatment for hyperlipidemia and hypercholesterolemia. Despite receiving lipid-lowering therapy, up to 50% of patients had fasting serum cholesterol levels > 240 mg/dL and triglycerides above the recommended target levels [26]. However, a retrospective analysis comparing the effects of everolimus versus sirolimus on blood lipid profiles and hematologic events in heart transplant patients with renal insufficiency ($N = 55$) demonstrated that everolimus 1.5 mg/day was associated with significantly lower levels of triglycerides ($p < 0.042$) and low-density lipoprotein ($p = 0.005$) at 6 months compared with sirolimus 3.0 mg/day [67]. Table 1 shows the incidence of lipid-related AEs in pivotal transplantation studies of these agents.

mTOR inhibition reduces the catabolism of circulating lipoproteins by inhibiting the activity of lipases, resulting in dyslipidemia [51]. In animal studies, sirolimus altered the expression of enzymes required for fatty acid uptake and storage and triglyceride synthesis [5]. By reducing lipid uptake and fat cell numbers, mTOR inhibition limits the capacity of adipose tissue for plasma lipid clearance, which likely contributes to hyperlipidemia [5].

Before initiating mTOR inhibitor therapy, lipidemic control should be optimized and patients should be evaluated for other potential causes of hyperlipidemia, such as hypothyroidism, nephrotic syndrome, and concomitant thiazide medication [36]. Patients should be advised to limit dietary intake of saturated fat, cholesterol, simple sugars, and alcohol, and to increase intake of soluble fiber and plant sterols [63]. Strategies to reduce weight and increase physical activity should be implemented, where possible, for overweight or obese patients [63]. Baseline lipid profiles should be determined for all patients [36,63].

Any patient taking an mTOR inhibitor should be monitored for hyperlipidemia [26,27]. If detected, interventions such as diet, exercise, and lipid-lowering agents should be initiated according to the National Cholesterol Education Program guidelines [26,27,68]. These guidelines take into account various risk factors and estimate the probability of a cardiovascular event over a period of years and provide recommendations accordingly [68]. Detailed clinical practice guidelines for managing dyslipidemias specifically in kidney transplant recipients have been issued by the National Kidney Foundation Kidney Disease Quality Outcomes Initiative [69].

Dyslipidemia can generally be managed with combinations of lifestyle changes, fibrates, extended-release niacin, statins, omega-3-acid ethyl esters (fish oil), and/or bile sequestrants [36,63,69]. If triglyceride levels exceed 500 mg/dL, patients should be treated with fibrates immediately to reduce the risk of pancreatitis [36].

Cyclosporine has been associated with rhabdomyolysis and other AEs, such as creatine phosphokinase elevation and myalgia, when combined with HMG-CoA reductase inhibitors (eg, lovastatin, simvastatin). Therefore, it is recommended that all patients taking a statin and/or fibrate with an mTOR inhibitor be monitored for similar side effects [26,27].

7. Renal adverse events

7.1. Proteinuria

De novo or exacerbated proteinuria occurs in up to 45% of patients following kidney transplantation and can adversely affect transplant outcomes [70–72]; however, the incidence of severe proteinuria is generally low [23,71]. It is hypothesized that proteinuria correlates with chronic allograft injury and development of glomerular lesions [73]. Although proteinuria has been observed in some studies in which patients received de novo sirolimus therapy [74], the condition is particularly common upon conversion from CNI to mTOR inhibitor therapy (especially sirolimus), possibly due to a reduction in the vasoconstrictive effects of CNIs [72,73]. The incidence of proteinuria and associated nephrotic syndrome in clinical studies of everolimus and sirolimus is shown in Table 1.

The exact mechanism by which mTOR inhibitors affect glomerular permeability is not known. Many mechanisms have been proposed, including decreased VEGF synthesis and expression, resulting in podocyte injury and focal segmental glomerulosclerosis; dose-related alteration of podocyte slit diaphragm-associated protein structure and function, resulting in loss of podocyte structural integrity; and activation of the innate immune system, resulting in an increased number of glomerular macrophages [6,7,73,75–77]. In preclinical studies, sirolimus (but not everolimus) enhanced the negative effects of cyclosporine on proximal tubule metabolism [78,79].

All patients on mTOR inhibitor therapy should be monitored for increased urinary protein excretion. Conversion from CNI to mTOR inhibitor therapy should be performed cautiously in patients with existing proteinuria (>800 mg/day), eGFR < 40 mL/min, or chronic allograft injury [6,49,73]. Immunostaining can be used to detect podocyte toxicity in the early stages of focal segmental glomerulosclerosis [73], and measurement of anti-human leukocyte antigen (anti-HLA) antibodies can serve as a marker for capillary damage, proteinuria, and reduced renal function. The presence of anti-HLA antibodies is also associated with poor graft survival and insufficient or ineffective immunosuppression [71].

Strategies for managing mild proteinuria include lowering blood pressure with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), dietary sodium and protein restriction, controlling obesity and lipids (with statins), and smoking cessation [70–73,80]. If proteinuria increases, drug withdrawal may be necessary to reduce the risk of acute renal failure; proteinuria is generally reversed within a few months of mTOR inhibitor discontinuation, and the majority of patients show no long-term residual kidney damage [72]. If massive proteinuria develops upon conversion from CNI to mTOR inhibitor therapy, reintroduction of CNI therapy may reverse urinary protein loss [72,73]. Plasmapheresis may be effective for managing patients who develop focal segmental glomerulosclerosis or membranoproliferative glomerulonephritis [71].

7.2. Hemodynamic effects

In an animal model of chronic cyclosporine toxicity produced by 1 week of salt depletion, adding sirolimus to cyclosporine immunotherapy was associated with worsening of renal function and structural injury [81]. These synergistic nephrotoxic effects may be due to sirolimus-induced hyperglycemia, which is known to accelerate renal tubulointerstitial fibrosis and tubular atrophy [81]. In addition, cyclosporine toxicity is related to the generation of reactive oxygen species, and when cyclosporine is coadministered with sirolimus, inhibition of mitochondrial energy metabolism and reactive oxygen species production are up-regulated. In contrast, everolimus antagonizes cyclosporine-induced mitochondrial dysfunction, which suggests

that, unlike sirolimus, everolimus may reduce the negative effects of cyclosporine on mitochondrial metabolism [82].

Although the effects of mTOR inhibition on CNI-induced fibrosis have not been verified clinically, hemodynamic effects have been observed in clinical trials of sirolimus and everolimus with standard-dose CNI therapy [19,20,83]. Therefore, to minimize the risk of nephrotoxicity, reduced doses of cyclosporine are required when used in combination with mTOR inhibitors [27], and careful monitoring of drug dosing and plasma concentrations is recommended [49]. For example, in an analysis of the association between everolimus and cyclosporine exposure levels and clinical events in renal transplant recipients, Shihab and colleagues [84] observed that the risk of nephrotoxicity and other AEs (eg, wound-healing AEs, NODM, dyslipidemia) were lowest when trough concentrations ranged from 3 to 8 ng/mL for everolimus and from 25 and 50 ng/mL for cyclosporine.

7.3. Delayed graft function

DGF, defined as the need for dialysis during the first week after transplantation, is a common complication in cadaveric renal transplantation [41,51]. Several studies have shown that sirolimus-containing regimens prolong recovery from DGF compared with other immunosuppressive protocols [8,85,86]. However, similar findings have not been observed with everolimus; the CALLISTO study showed that both de novo and delayed everolimus introduction strategies were associated with good renal function outcomes in patients at high risk for DGF [87].

Sirolimus is thought to prolong recovery from DGF because of its antiproliferative effects on growing renal epithelial cells, which inhibit regeneration of the epithelium following ischemia/reperfusion injury [51]. Risk factors for DGF that should be considered before using sirolimus include receipt of a kidney from a marginal donor or immunologic mismatch, along with patient age, body weight, ethnicity, gender, hypotension, and previous dialysis [41]. For high-risk patients, delaying sirolimus therapy until the transplanted kidney is functional can eliminate the risk of sirolimus-related prolongation of DGF [88]. The duration of sirolimus-induced DGF effects is thought to be dose-dependent, so high loading doses of sirolimus should be avoided, and target trough concentrations of 6 to 10 ng/mL are recommended [41].

If persistent DGF develops during sirolimus treatment, transplant biopsies should be performed every 1 to 2 weeks to exclude the possibility of acute rejection. Sirolimus doses should be reduced to trough levels of 4 to 8 ng/mL or, in severe cases, a different immunosuppressive regimen should be used. If graft function improves, low-dose sirolimus can be restarted 5 to 10 days after kidney function is restored [41].

8. Pulmonary adverse events

Pneumonitis, or interstitial lung disease, is another potential complication of mTOR inhibitors. Pneumonitis appears to be more common in oncology than in transplant settings, possibly due to differences in dosing regimens or more frequent radiographic monitoring of cancer patients, leading to increased detection [80,89]. Among patients with advanced renal cell carcinoma, pneumonitis rates of up to 14% have been reported with everolimus [89]. In solid-organ transplant recipients, pulmonary toxicity is considered a rare but serious side effect of sirolimus and everolimus, described primarily in case reports [90–92]. Case reports of pneumonitis are much less common in transplant patients receiving everolimus versus sirolimus, and sirolimus-related pneumonitis reportedly resolves after conversion to everolimus [80,92].

Pneumonitis is a noninfectious, nonmalignant infiltration of the lungs that presents as ground-glass opacities and focal consolidation on x-ray [34,36]. The most common symptoms of interstitial lung disease include dry cough and exertional dyspnea; fever, night sweats, fatigue, respiratory distress, and hemoptysis also may occur [90,91]. Arterial blood gas measurements often reveal hypoxemia, and pulmonary function tests may show reduced capacity for diffusing carbon monoxide [90]. Histologic changes associated with mTOR inhibitor-related pulmonary toxicity may include organizing pneumonia, pulmonary alveolar proteinosis, focal fibrosis, and alveolar hemorrhage [91]. The onset of mTOR inhibitor-related pneumonitis typically occurs within 2 to 6 months after treatment initiation [36].

The exact pathogenic mechanism of mTOR inhibitor-induced pulmonary toxicity is not known. Possible mechanisms include direct damage to alveolar structures, formation of immunogenic haptens, and direct immunologic drug responses (based on observed high levels of CD4-positive cells in bronchoalveolar lavage) [91]. Pulmonary toxicity appears to be dose-related, and an observed slight male predominance of sirolimus-related pulmonary AEs is consistent with the drug's longer half-life in males versus females [90].

In patients with respiratory symptoms at baseline, pulmonary function tests should be performed prior to starting mTOR inhibitor therapy; treatment should be initiated only if lung function is normal [36]. mTOR inhibitors should be avoided in patients with significant pulmonary fibrosis or severe chronic obstructive pulmonary disease [36]. If mTOR inhibitor-related pneumonitis is suspected, it is important to rule out infection, parasites, autoimmune disorders, and other pulmonary diseases [90,91]. mTOR inhibitor-associated pulmonary toxicity should be a diagnosis of exclusion [90,91]. If patients present with fever, titration of infection biomarkers (eg, procalcitonin) may help discriminate between infectious and noninfectious disease [36].

Grade 1 (asymptomatic) interstitial lung disease should be monitored closely with frequent (every 4–8 weeks) radiographic and pulmonary function assessments [65]. mTOR inhibitor dose reductions, corticosteroids (eg, prednisone 1 mg/kg), and antibiotics may be required for Grade 2 (symptoms not interfering with daily activities, and oxygen support not required) or Grade 3 (symptoms interfere with daily activities and/or oxygen support required) toxicities [34,65,90]. Clinical improvement is often rapid after mTOR inhibitor discontinuation; complete radiographic resolution of pneumonitis is frequently observed within 2 to 4 months [91,92].

If pneumocystis pneumonia is suspected in patients with mTOR inhibitor-associated pneumonitis, treatment with pentamidine should be avoided because interactions with sirolimus reportedly cause drug-induced phospholipidosis and rapid clinical deterioration. Instead, treatment with trimethoprim/sulfamethoxazole or clindamycin/primaquine is recommended [93].

9. Hematologic adverse events

9.1. Anemia

Posttransplant anemia occurs in 12% to 76% of renal transplant recipients [94]. Immunosuppression with mTOR inhibitors can promote anemia and delay improvement in hemoglobin levels after surgery [94]. Anemia associated with mTOR inhibitors is characterized by microcytosis (ie, marked decline in mean corpuscular volume of red blood cells [RBCs]) and low serum iron levels [10,95,96]. It is generally mild, dose-dependent, and reversible upon discontinuation of treatment [10]. Anemia generally presents early in the course of mTOR inhibitor therapy (within a month of initiation) and is sustained throughout treatment [10]. Other risk factors for anemia include advanced age, low iron status, malignancies, inflammation, renal dysfunction, viral infections, and combined use of mTOR inhibitors and MMF (MMF is associated with significantly higher rates of anemia vs other immunosuppressants) [94,96–98].

It is hypothesized that mTOR inhibitor-related anemia results from disruptions in iron homeostasis and gastrointestinal iron absorption, as well as effects on erythroid progenitor cell differentiation and erythropoietin receptor-mediated proliferation of erythroid precursors

[10,94]. mTOR inhibitors may cause early differentiation of the erythroid precursors and reduced globin synthesis [94].

Anemia screening every 1 to 3 months is recommended for patients taking mTOR inhibitors. If anemia is detected, its cause should be determined. Stools should be tested for the presence of occult blood, and screenings should be conducted to detect possible malignancies. RBC indices, reticulocyte count, and levels of vitamin B_{12} and folate should be measured [94]. Patients should also be evaluated for hemolytic–uremic syndrome, a rare complication of cyclosporine treatment [94]. If there is no evidence of infection, inflammation, malignancy, or nutritional defects, mTOR inhibitor-related anemia should be considered, especially if microcytosis is present.

If iron deficiency is present (eg, serum ferritin < 100 ng/mL and transferrin saturation < 20% or reticulocyte hemoglobin content < 29 pg/cell), oral supplementation should be considered (≥200 mg/day of elemental iron), with careful monitoring to avoid iron overload [94,98]. If oral supplementation is not effective, intravenous iron should be considered [94]. Erythropoiesis-stimulating agents may also be effective for managing mTOR inhibitor-associated anemia [98]. If iron supplementation and/or erythropoiesis-stimulating agents are not sufficient to manage anemia, mTOR inhibitor therapy should be reduced or discontinued [94].

9.2. Thrombocytopenia and leucopenia

Thrombocytopenia and leucopenia/neutropenia have been reported with mTOR inhibitor therapy, especially when combined with mycophenolate therapy [99]. These AEs frequently occur simultaneously and usually resolve spontaneously [100]. Complete blood counts should be obtained regularly to monitor for these AEs. Management of thrombocytopenia involves minimizing procedures that increase bleeding risk and avoiding aspirin, ibuprofen, and NSAIDs [35]. To prevent infections, patients with neutropenia should be counseled to wash their hands frequently and avoid exposure to germs. Grade 3 or higher neutropenia or thrombocytopenia may require temporary interruption of mTOR inhibitor therapy [35,49].

10. Hypertension

Posttransplant hypertension is associated with immunosuppressive therapy and declining renal function, along with a range of other factors, such as renal artery stenosis, antibody-mediated rejection, chronic allograft injury, and proteinuria [11,101]. Donor age and graft quality, as well as recipient age, gender, diabetes, BMI, pretransplant hypertension, and primary kidney disease, are factors that can influence the risk of hypertension [101]. CNIs are known to promote hypertension because they increase oxidative stress and sympathetic activation, which may cause afferent arteriolar vasoconstriction [101]. Nephrotoxicity and chronic allograft injury associated with CNI therapy may also increase the risk of hypertension [101]. It has been postulated that CNI minimization with mTOR inhibition may reduce the incidence of hypertension compared with standard-dose CNI, but data are conflicting, and randomized controlled trials are needed to confirm this [101]. Hypertension is a common side effect of mTOR inhibitors (Table 1), but pivotal clinical trials showed no meaningful increase in the incidence of hypertension versus comparator agents [21,22,25].

Optimal management of hypertension after transplantation includes manipulating immunotherapy (when possible) to reduce exposure to cyclosporine, often with conversion to sirolimus or everolimus [11]. However, even with an optimized immunosuppressive regimen that minimizes drug-related hypertension, most patients still require at least one antihypertensive medication to control blood pressure. Vasodilatory calcium-channel blockers (eg, nifedipine) are often considered first-line agents for posttransplant hypertension because positive interactions with immunosuppressants may reduce the requirement for CNIs or mTOR inhibitors and reduce nephrotoxicity. Beta-blockers are also recommended, particularly for patients with congestive heart failure or history of myocardial infarction. Although ARBs and ACE inhibitors may also be effective, and can reduce the incidence of proteinuria, they should be used cautiously because they can exacerbate reductions in GFR, hyperkalemia, and anemia [11]. In addition, increased rates of angioedema were noted when ACE inhibitors were combined with mTOR inhibitors [102].

11. Reproductive endocrine adverse effects

11.1. Effects in Men

Sirolimus and everolimus have been shown to delay the improvement of gonadal function after transplant surgery, resulting in decreased fertility, sexual hormone dysfunction, decreased ejaculate volume, and low sperm count or azoospermia [103,104]. Testosterone deficiency is also associated with increased levels of FSH and LH [13,105]. The incidence of gonadal AEs is not known with certainty; these AEs were not reported in pivotal controlled trials. Sirolimus prescribing information lists reversible azoospermia as a possible AE [26], and decreased serum testosterone and increased FSH have occurred with everolimus, with 5% of patients reporting erectile dysfunction compared with 2% of controls [27].

The underlying mechanism of adverse gonadal effects is thought to relate to mTOR inhibitor suppression of p70 S6 kinase, which regulates germ-cell proliferation, meiosis, and apoptosis [13]. In animal models, sirolimus reduced testicular weight, altered the morphology of seminiferous tubules, and decreased spermatogenesis and testosterone levels. These effects were dose-related and worsened over time, but were reversed within 8 weeks of cessation of sirolimus [103].

Data on the clinical implications of reduced fertility and erectile function in men treated with mTOR inhibitors are limited. No published guidelines were identified for the management of gonadal AEs. Discontinuation of mTOR inhibitor therapy is suggested to reverse these effects; limited evidence suggests that replacing mTOR inhibitors with tacrolimus may normalize hormone levels. Glucocorticoids may worsen the gonadal effects of mTOR inhibitors because they are known to decrease testosterone synthesis [105].

11.2. Effects in women

Menstrual-cycle disturbances, including amenorrhea and menorrhagia, have occurred in women treated with sirolimus [12,26], and ovarian cysts have been reported with sirolimus and everolimus [26,27]. High rates of ovarian cysts (52%) and oligoamenorrhea (57%) have been noted for patients receiving low doses of sirolimus (mean doses: 1.2–1.5 mg/day) [12]. However, such AEs were not assessed in pivotal clinical trials of mTOR inhibitors [12].

In animal models, sirolimus amplified signaling in ovarian follicles through the phosphatidylinositol-3 kinase pathway [12]. However, serum FSH and LH levels were similar for sirolimus recipients and controls [12].

Treatment guidelines for the management of female endocrine AEs are limited, but evidence suggests that these effects generally resolve after withdrawal of mTOR inhibitor therapy (eg, cyst size was reduced in 80% of patients) [106]. Observed ovarian cysts are generally benign, but may require surgery and may recur [106,107]. The risks of ovarian toxicity should be discussed with mTOR inhibitor candidates, and patients should be monitored for the development of these AEs [12,106].

12. Conclusions

Although challenges are associated with managing the AEs caused by mTOR inhibitors, these immunosuppressants significantly reduce the risk of nephrotoxicity and malignancy in solid-organ transplant recipients relative to CNIs. mTOR inhibitors have become the standard

of care for patient with advanced renal cell carcinoma, with good tolerability compared with other chemotherapeutic agents.

This article summarized the current understanding of the mechanisms associated with mTOR inhibitor-related AEs, and described strategies to effectively manage many common AEs. As with all immunosuppressive and antineoplastic therapies, careful proactive monitoring is required to reduce the risk of serious or irreversible AEs. However, most AEs associated with mTOR inhibitors are moderate or mild and dose-related, and many are reversible upon cessation of treatment. Patients should be well educated on the potential side effects of mTOR inhibitors, and the decision for their use should be based on individual patient characteristics and risk factors.

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