mTor inhibitors complication after renal transplantation

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History and Mechanisms of Action

Rapamycin was first described as an **antifungal** agent but is known for its **immunosuppressive** and **antiproliferative** properties in mammalian cells

Tablet / oral solution

hydrophobic compound

Extensively bound to blood cells especially RBC up o 95%

Less than 5% are free in plasma

Half life : 60 hours

Rapid absorption time : 1-2 h

Everolimus

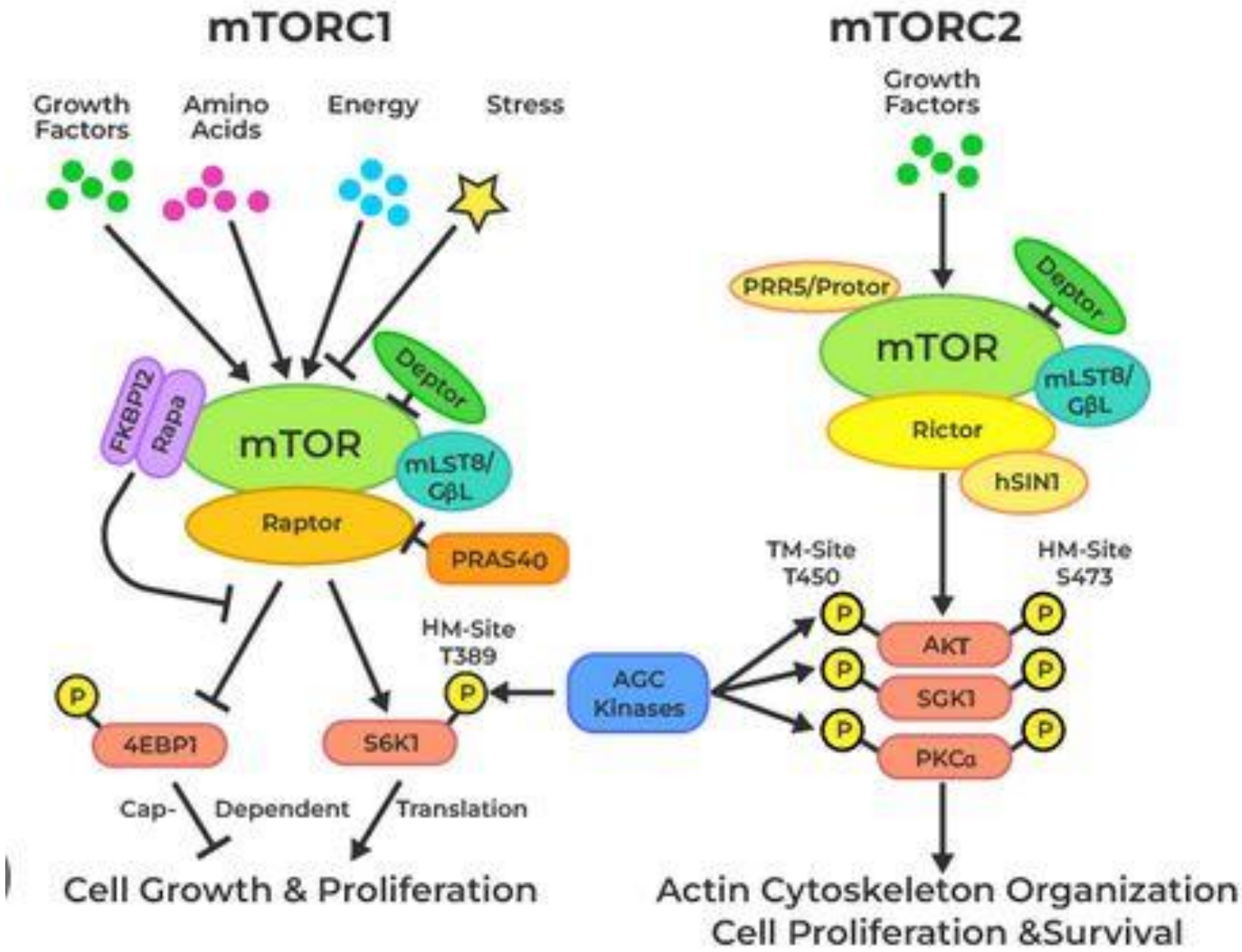
More water soluble

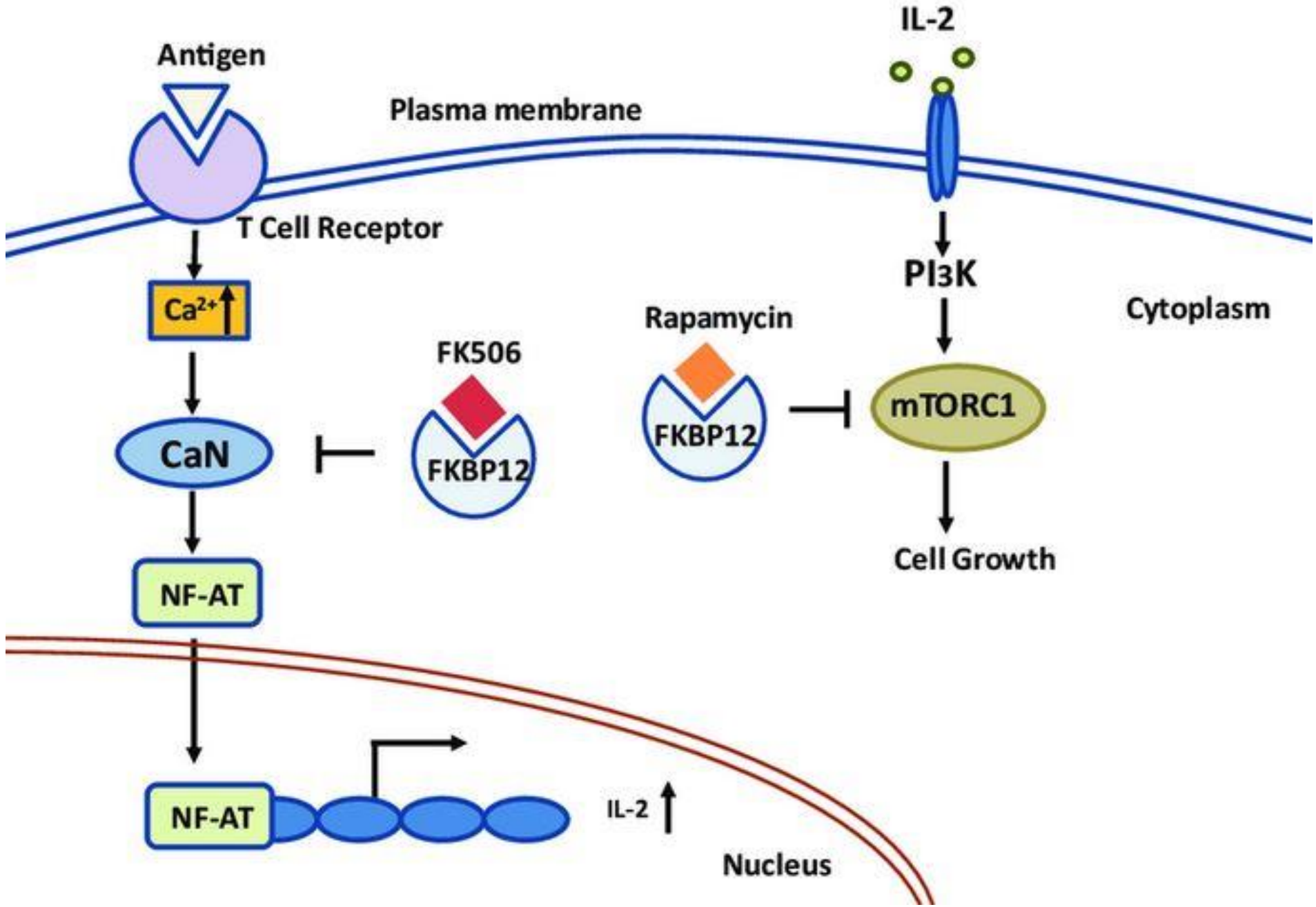
More than 75% partitioned into red blood cells (25%) is bound to plasma proteins

More bioavailability

Much shorter half life : 16-19 h

Rapid absorption (maximal concentration within 3 h)


mTORC1
Growth Factors
Amino Acids
Energy
Stress
FKBP12
Rapa
mTOR
Deptor
mLST8/ GβL
Raptor
PRAS40
HM-Site T389
P
4EBP1
S6K1
Cap-
Dependent
Translation
Cell Growth & Proliferation
mTORC2
Growth Factors
PRR5/Protor
Deptor
mTOR
mLST8/ GβL
Rictor
hSIN1
TM-Site T450
HM-Site S473
AGC Kinases
AKT
SGK1
PKCα
Actin Cytoskeleton Organization
Cell Proliferation &Survival



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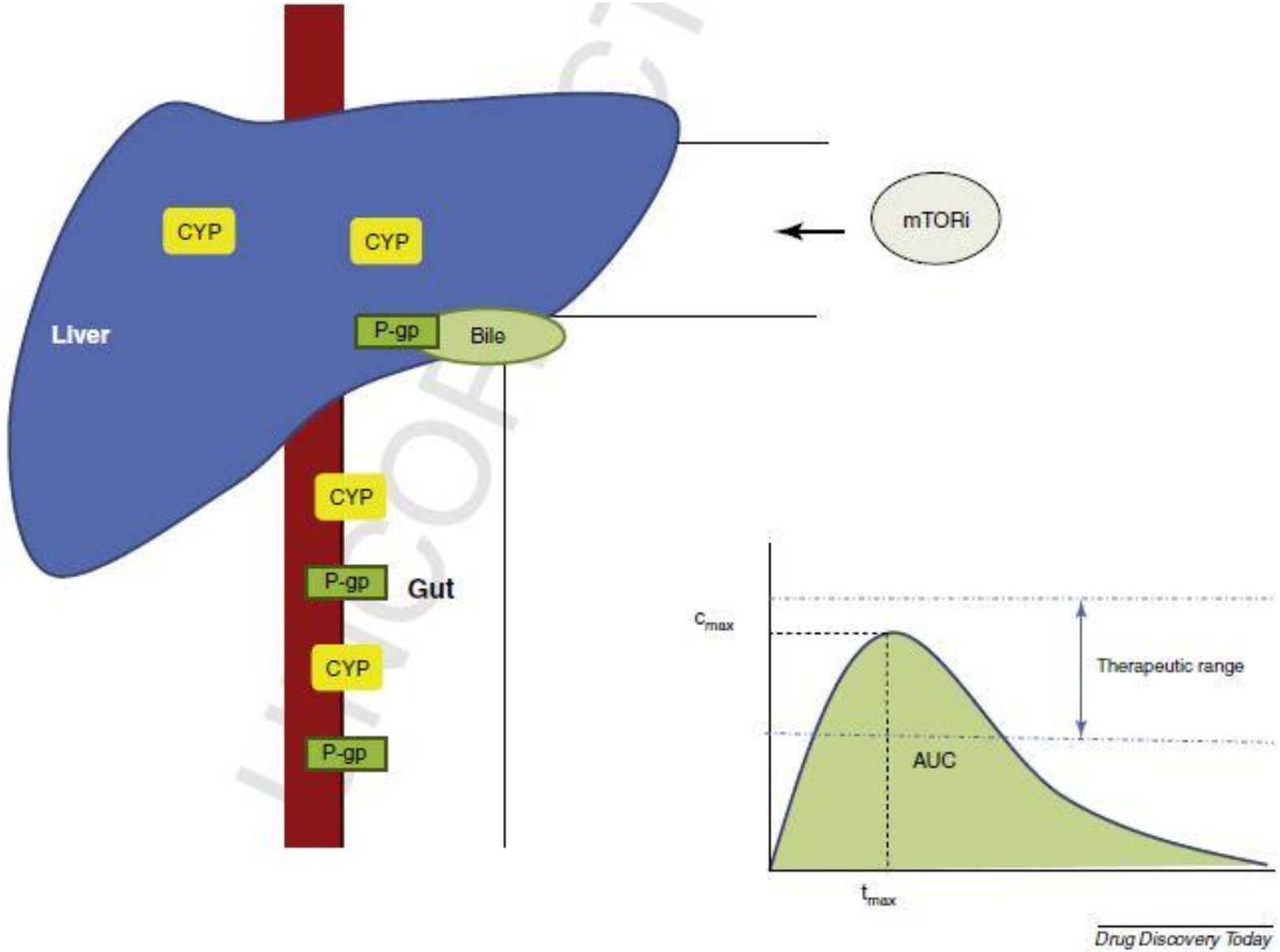
CYP
CYP
Liver
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AUC
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Drug Discovery Today

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Journal of Nephropathology

Everolimus induced pulmonary thromboembolism after kidney transplantation; a case report

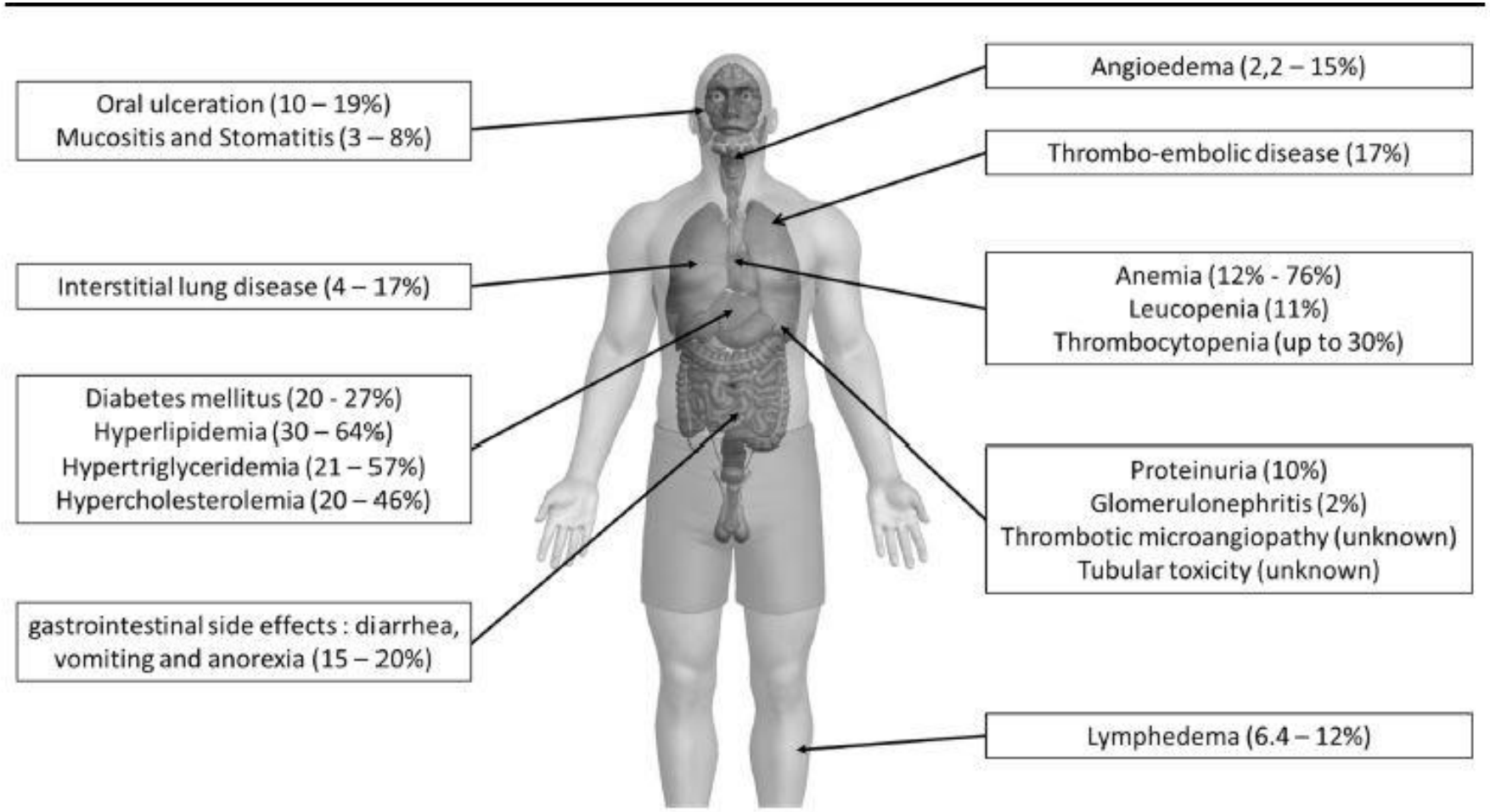
Fereshteh Saddadi[1*], Mohammad Hassan Fallahkohan[2]

48 Y/O male of kidney transplantation since 18 years ago from a deceased donor on Everolimus 0.75 twice a day and tacrolimus 2mg twice a day and prednisolone was admitted with dysnea and leg edema.

Venous thromboembolism and pulmonary thromboembolism was detected.

All secondary cause of VTE was rule out and use of mtori was the leading cause of VTE.

Known side effects associated with mechanistic target of rapamycin (mTOR) inhibitors



L. S. NGUYEN ET AL.

mTOR inhibitors—summary of toxicities

Toxicity	Temsirolimus [1–3, 15, 24]		Everolimus [4, 5, 25]	
	All grades (%)	Gr 3/4 (%)	All grades (%)	Gr 3/4 (%)
Mucositis	20–75	1–4	40–44	3–4
Skin rash	47–76	4	25–29	<1
Pulmonary toxicity[a]	2–36	9	8–14	3–4
Hyperglycemia	26–89	17–16	50–57	12–15
Hypercholesterolemia	21–87	1–21	76–77	3–4
Hypertriglyceridemia	21–83	3–4	71–73	<1
Hypophospatemia	13–49	13–18	32–37	4–6
Anemia	29–45	9–20	91–92	9–13
Thrombocytopenia	14–40	1–8	20–23	1
Neutropenia	7–19	3–5	11–14	0
Asthenia/fatigue[b]	38–51	8–11	31–38	4–5
Dysgeusia	20–21	0	7–10	0

TARG ONCOL (2011) 6:125–129

Hematologic Adverse Events

Anemia : 12–76% in the first year

Rapid onset after treatment initiation (about 1 month)

Microcytosis and characterized low serum iron

Altered iron metabolism (including digestive absorption)

Altered differentiation and proliferation of erythroid progenitor cells

Decrease globin synthesis

Hematologic Adverse Events

Leucopenia (11%) Concomitant use of mycophenolate may be confounding factor

Thrombocytopenia (up to 30%)

Venous thromboembolism

In lung transplantation, patients treated with a combination of tacrolimus and prednisone reported more venous thromboembolism events when treated with an mTOR inhibitor (sirolimus) than when receiving azathioprine

Hematologic Adverse Events

In kidney transplantation, anemia (12.5%) and leucopenia (13.9%) were reported more frequently in patients who switched from calcineurin inhibitors to everolimus than in patients who continued to receive calcineurin inhibitors

After liver transplantation, early withdrawal of tacrolimus with everolimus, compared with tacrolimus-based therapy, showed a higher rate of anemia (14.4 vs. 7.4%) but a lower rate of neutropenia (11.1 vs. 14.9%) and thrombocytopenia (8.9 vs. 10.6%)

New-onset diabetes after transplantation (NODAT)

Refers to the occurrence of diabetes in previously non-diabetic clinically stable kidney transplant recipients who had been discharged from the hospital and tapered to their maintenance immunosuppressive therapy

It occurs in almost 4% to 27% of kidney transplant recipients

It may induce the development of the chronic allograft damage by activating several pro-fibrotic mediators [including transforming growth factor beta (TGF-β)] and promoting mesangial matrix expansion and cell hyperplasia

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NODAT diagnostic criteria

Fasting glucose ≥126 mg/dL on more than one occasion,

Random glucose ≥ 200 mg/dL with symptoms,

Two-hour glucose after 75 g oral glucose tolerance test of ≥200 mg/dL hemoglobin A1C (HbA1c) ≥ 6.5%

Risk factors for PTDM

Risk factors for PTDM are similar to those for type 2 diabetes mellitus:

Increased age (>40 years), **family history** of type 2 diabetes, **ethnicity** (African-American, Asian, and Hispanic patients are at higher risk compared to Caucasian), abnormal glucose tolerance (expressed by fasting blood sugar levels between 90 and 100 mg/dL), and specific genetic factors

Metabolic syndrome and the **obesity**

Viral infections may increase the risk of PTDM

Hepatitis C virus (HCV) infection may trigger an immune-mediated reaction against β cells with consequent cytopathic effects, glucose uptake reduction

Cytomegalovirus (CMV) may directly damage beta-cells

Risk factors for PTDM

Corticosteroids and calcineurin inhibitors (CNIs; Tacrolimus and Cyclosporine A) are the main responsible for this complication, while the diabetogenic effects of mammalian target of rapamycin inhibitors (mTOR-Is) are still debated

As reported by the SYMPHONY study after 1 year and 3 years of follow-up patients treated with low-dose sirolimus (SRL) plus Mycophenolate Mofetil (MMF) presented a higher incidence of PTDM than those treated with low dose of CsA plus MMF (6.6% vs. 4.2% after the first year and 8% vs. 5% after 3 years of follow-up).

No differences were observed in the comparison between the standard dose of CsA vs. low dose SRL (in both groups the incidence was 8%).

New-onset diabetes after transplantation (NODAT)

Kreis et al. (ORION Study) also described no differences in the incidence of hyperglycemia and insulin-dependent PTDM in patients treated with SRL compared to CsA

The evaluation of two SRL-based regimens, one with CNI withdrawal (**SRL + TAC-Elim**) and the other with complete CNI avoidance (**SRL + MMF**), compared with a CNI-based regimen containing **TAC + MMF** in *de novo* renal allograft recipients demonstrated higher incidence of PTDM in TAC recipients confirming a diabetogenic effect of TAC compared to SRL

New-onset diabetes after transplantation (NODAT)

In both CONCEPT and ZEUS studies, the **early conversion** from CsA-based to SRL-based therapeutic regimen (3 or 4.5 months after transplantation) did not induce PTDM in a 12 months-period post-transplantation

Similarly, in the **late conversion** (CONVERT) study, where the renal allograft recipients were randomly assigned (2:1) to undergo conversion from CsA- or TAC-based immunosuppression to SRL or to continue receiving CNI-based therapy for 2 years, the frequency of PTDM was similar between the two study regimens (4.7% vs. 4.4%, $p = 1.000$)

New-onset diabetes after transplantation (NODAT)

Vitko et al. in a 36-month, multicenter, randomized, parallel-group equivalence trial of two oral doses of EVR (1.5 or 3 mg/day) vs. MMF (2 g/day) along with CsA microemulsion (Neoral) and corticosteroids in *de novo* renal transplant recipients, reported a higher incidence of PTDM in patients receiving 3 mg/day EVR (12.6%) compared to those receiving a low dose of EVR (6.7%) and MMF (5.6%)

New-onset diabetes after transplantation (NODAT)

In another 6-month, randomized, open-label, parallel-group, comparative trial comparing two regimens of TAC plus SRL (with either 0.5 or 2 mg) with a TAC plus MMF immunosuppressive schema, authors found that a larger number of patients treated with TAC plus SRL at 2 mg developed PTDM ($p = 0.005$). However, the number of patients requiring insulin for PTDM was similar in the TAC/SRL 2 mg and TAC/MMF groups ($p > 0.05$)

VITKO S, ET AL. TACROLIMUS COMBINED WITH TWO DIFFERENT DOSAGES OF SIROLIMUS IN KIDNEY TRANSPLANTATION: RESULTS OF A MULTICENTER STUDY. AM J TRANSPLANT. (2006)

New-onset diabetes after transplantation (NODAT)

In a multicenter trial, in which renal transplant recipients were randomized to TAC with fixed-dose SRL (*N* = 318) or TAC with MMF (*N* = 316), 6 months' creatinine clearance was comparable between the 2 immunosuppressive schemas. Biopsy-confirmed acute rejection was 15.1% (TAC/SRL) and 12.3% (TAC/MMF).

In both groups, graft survival was 93% and patient survival was 99%. Premature withdrawal due to an adverse event was twice as high in the TAC/SRL group (15.1% vs. 6.3%). The incidence of any antidiabetic treatment for >30 consecutive days in previously nondiabetic patients was 17.8% in TAC/SRL, and 24.8% in TAC/MMF

Conclusion

We cannot draw any definite conclusions about the diabetogenic impact of the mTOR-Is. However, we can encourage clinicians to lower the dose of these immunosuppressive drugs in patients at high risk of PTDM

Dyslipidemia

mTOR plays a key role in lipid metabolism, specifically lipogenesis in the liver, lipolysis in white adipose tissue and control of adipogenesis.

Hyperlipidemia has a reported prevalence of 30–64%, hypertriglyceridemia of 21–57% and hypercholesterolemia of 20–46%

Reports describe a median serum triglyceride increase of 65% and a median total cholesterol increase of 25% within 12 months of administration, with a dose-dependent effect

Mechanisms : reduced circulating lipoprotein catabolism via inhibition of lipase activity

mTORC2 inhibition may promote the metabolism of excess hepatic lipids

Renal Adverse Events

The incidence of proteinuria with sirolimus has been estimated at 10%, with complete nephrotic syndrome in 2% of the overall population.

Proteinuria was observed not only in patients who received de novo sirolimus therapy but also in patients who switched from a calcineurin inhibitor to mTOR inhibitor therapy (especially sirolimus).

Everolimus levels > 8 ng/ml were significantly associated with proteinuria

Renal Adverse Events

Specific toxicities include thrombotic microangiopathy, acute renal failure, glomerulonephritis, tubular toxicity, and chronic allograft nephrotoxicity associated with calcineurin inhibitors.

Pharmacokinetic studies showed a combined effect of sirolimus and calcineurin inhibitors, either through drug–drug interactions via cytochrome P450 (CYP) 3A4 and P-glycoprotein or through intracellular accumulation, resulting in direct tissue injury

Sirolimus increases the expression of transforming growth factor-β1. It also increases the toxicity of chronic calcineurin inhibitors and is often used in combination with these treatments

Renal Adverse Events

Proteinuria management of mTOR inhibitors :

Treatment discontinuation to decrease the risk of acute kidney injury. Generally, proteinuria resolves within a few months, and most patients later present with normal kidney function.

Switch to a regular calcineurin inhibitor: which may reverse proteinuria, regardless of its initial severity.

Nonspecific management : blood pressure control with either angiotensin II-receptor blockers or angiotensin-converting enzyme inhibitors; dietary restriction of sodium and protein intake; control of LDL cholesterol with statins; and general cardiovascular risk prevention

Dermatologic and Mucosal Adverse Events

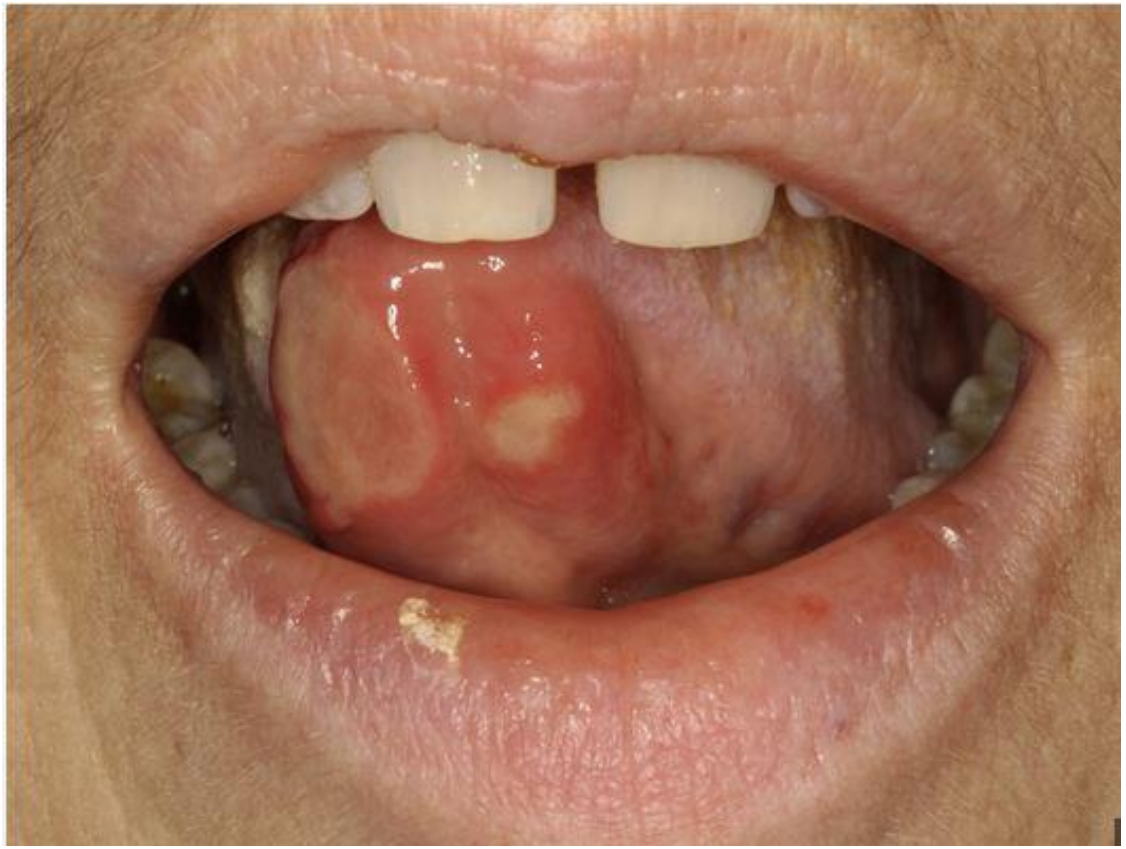
By frequency, mucositis and stomatitis are the most common reported side effects of mTOR inhibitors.

Mucositis usually has rapid onset, is mild to moderate in severity (grade 1–2) and does not result in discontinuation.

More severe lesions generally reverse with treatment cessation

Dermatologic and Mucosal Adverse Events

It presents as painful,ovoid, superficial ulcers surrounded by a specific erythematous margin. Lesions may be single or multiple and are 1 cm in diameter on the inner lips and ventral and lateral surfaces of the tongue as well as the buccal mucosa and soft palate.



Dermatologic and Mucosal Adverse Events

Stomatitis ulcers may form later after treatment initiation (about 1 week)

They may last up to 2 weeks if untreated and have the potential to relapse. They may be dose dependent , and it has been suggested that combined treatment with calcineurin inhibitors may exacerbate symptoms. mTOR inhibitors may have direct toxicity on oral mucous membranes.

Dermatologic and Mucosal Adverse Events

Prevention :

Oral hygiene (gentle brushing, mild toothpaste and mouthwashes);

Food and beverage adaptation (avoiding spicy, acidic or very hot food, alcohol), **Avoiding other eluding agents** such as iodine, peroxide and antifungals.

Laser or chemical cauterization may provide fairly rapid pain relief

Medical treatment of rapalog-associated aphthous ulcers includes: **topical steroids**, nonsteroidal anti-inflammatory drugs and anesthetics.

For more severe grades (grade 2 and higher), decreasing or withdrawing treatment may be necessary

Dermatologic and Mucosal Adverse Events

Recurrent or persistent stomatitis can be treated with intensive local (topical and intralesional) or systemic corticosteroids.

Other treatments include **colchicine**, **pentoxifylline** and **azathioprine**.

Discontinuation of mTOR inhibitor treatment may be considered if lesions persist after these treatments, and surgical biopsy may be deemed adequate.

Less severe dermatologic manifestations of rapalogs include acne-like dermatitis, pruritus, rash and nail changes.

They often resolve spontaneously, Rarer cases require local or systemic therapies

Wound-Healing Adverse Events

Postoperative complications :

Dehiscence, hernia, lymphoceles and wound infections .

15–32% in kidney transplantation, 8–40% in heart transplantation, and 1–12% in liver transplantation

Lymphoceles and hernias appear to be dose dependent.

Mechanisms involved include fibrosis restriction due to a lack of proliferation of endothelial cells and lowered expression of VEGF and nitric oxide-mediated pathways, T-cell proliferation and migration, and production of growth factors in epidermal layers

Pulmonary Adverse Events

mTOR-inhibitor-induced pneumonitis is a lung infiltration that is neither infectious nor malignant.

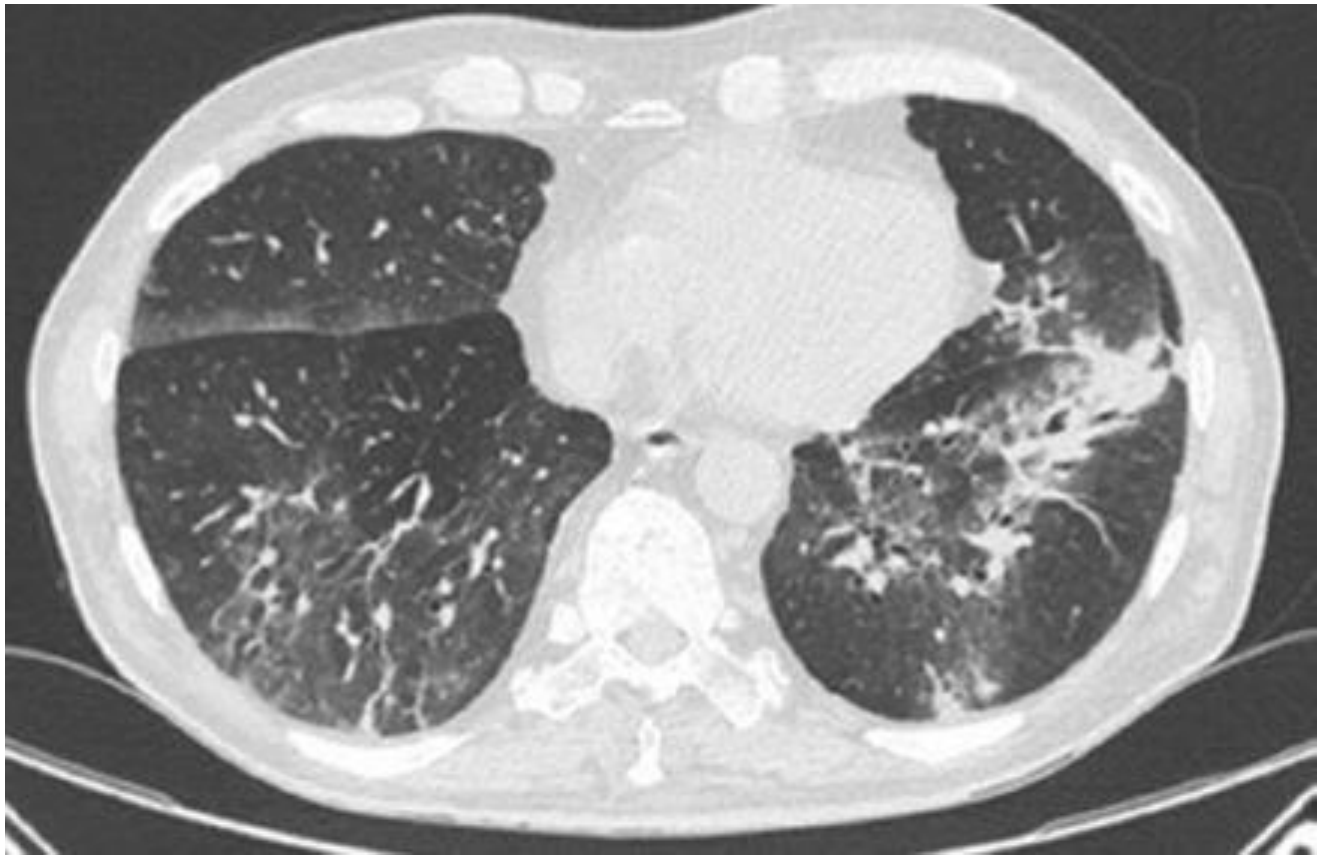
It clinically manifests as **dry cough** and **exercise dyspnea**.

Possible associated symptoms include hemoptysis and inflammatory syndrome (fever, night sweats)

Related to mTOR inhibitors, it is a form of immunologically mediated lung toxicity, and, although rare, is a serious side effect

Pulmonary Adverse Events

Diagnosis relies on imagery (X-ray and computed tomography scan) and histology (alveolar and focal fibrosis and alveolar hemorrhage).



Pulmonary Adverse Events

The incidence of interstitial lung disease is hard to estimate as patients are initially asymptomatic.

In kidney transplantation, the reported incidence ranges from 4 to 12.7%

Sirolimus seems to be less incriminated than everolimus in pneumonitis, notably after conversion from one to the other.

mTOR inhibitor-induced pneumonitis starts within 2–6 months after treatment introduction

Pulmonary Adverse Events

Mechanisms of pulmonary toxicity include **direct alveolar damage**, **immunogenic haptens** and **immunologic drug responses** (diagnosed by numerous cluster of differentiation (CD)-4-positive cells in bronchoalveolar lavage)

Sirolimus toxicity may expose cryptic antigens,which could then trigger an autoimmune response.

Whether this adverse event is due to dose-dependent toxicity or to an immune-mediated disorder is controversial

Pulmonary Adverse Events

Concentration-related toxicity is suggested by case series in renal transplantation, in which patients developing pneumonitis had higher sirolimus concentrations than did other patients

Supporting this dose dependence, a sexual dimorphism (with male predominance) was shown, which is consistent with the drug's longer half-life in men.

On the other hand, other case series showed that patients who developed pneumonitis did not have higher sirolimus concentrations, which then supports an immune-mediated disorder

PHAM PT,ET AL SIROLIMUS-ASSOCIATED PULMONARY TOXICITY. TRANSPLANTATION.

Pulmonary Adverse Events

Other risk factors for development of pneumonitis include :

age, male sex, late administration of sirolimus compared with de novo therapy and increased sirolimus dose and trough levels compared with baseline.

Diagnosis is by exclusion of infection or autoimmune disorders and malignancies

Resolution of symptoms occur within 3 months after drug cessation

Pulmonary Adverse Events

Management : When patients are asymptomatic, clinical and radiographic monitoring is warranted, with pulmonary function assessment once every 2 months

When symptomatic, it may be necessary to reduce the dosage and add corticosteroids (prednisone 1 mg/kg) and/or antibiotics

If the condition persists, treatment discontinuation resolves symptoms within 2–4 months

Angioedema

Angioedema typically presents as non-pitting isolated or diffuse edema localized on the face and the floor of the mouth and larynx.

Mechanisms are mediated by bradykinin, a vasoactive mediator that results from several pathways:

ImmunoglobulinE (IgE) mediated

Cyclooxygenase inhibition

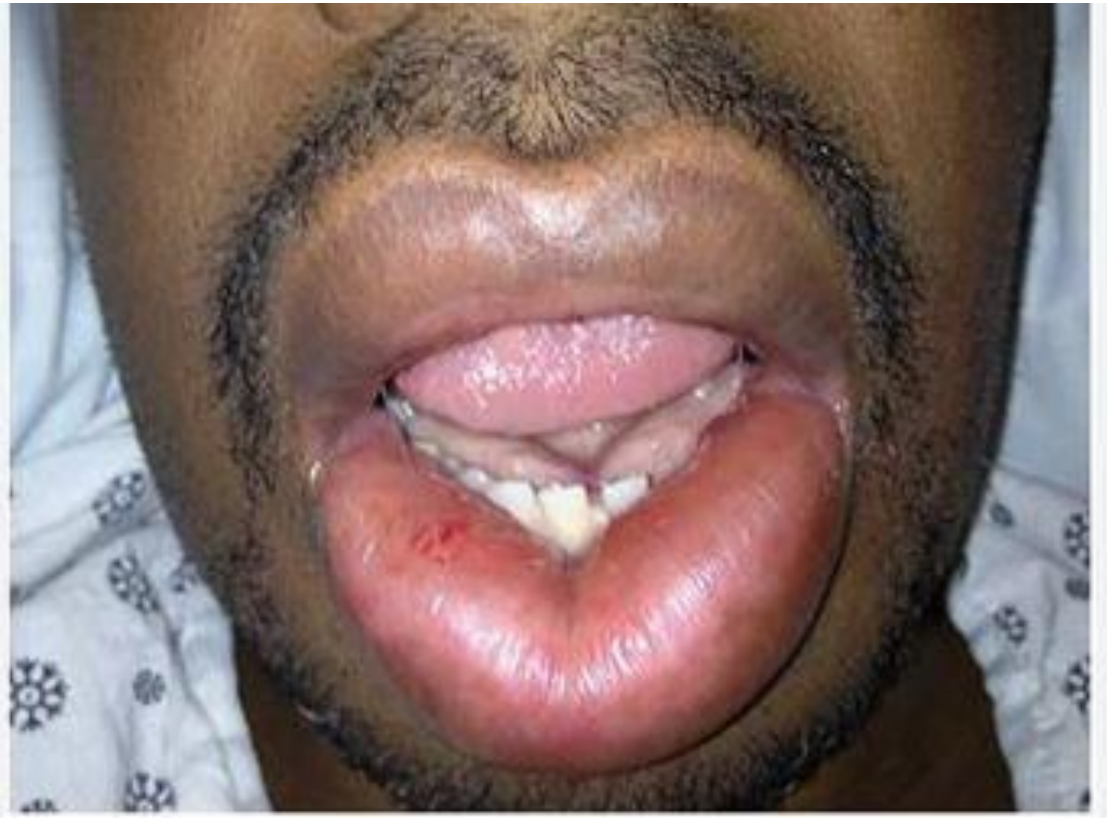
Kinin and complement metabolism activation

Bradykinin results in increased capillary permeability, with fluid accumulation in tissues.

Urticaria may be associated with angioedema

Angioedema

Concomitant use of sirolimus and ACE inhibitors was reported to dose-dependently increase the risk of angioedema (for trough level > 12 ng/ml), whereas symptoms resolved after trough level decreased to < 7 ng/ml



Lymphedema

Lymphedema typically presents as fluid retention localized to the limbs with associated tissue swelling.

Postoperative situations that may favor the appearance of lymphedema include congestive heart failure, extracellular volume expansion, associated nephrotic syndrome for bilateral edema, and—for unilateral peripheral edema—a vascular lesion.

Lymphedema may also appear in more atypical locations such as eyelids or upper limbs

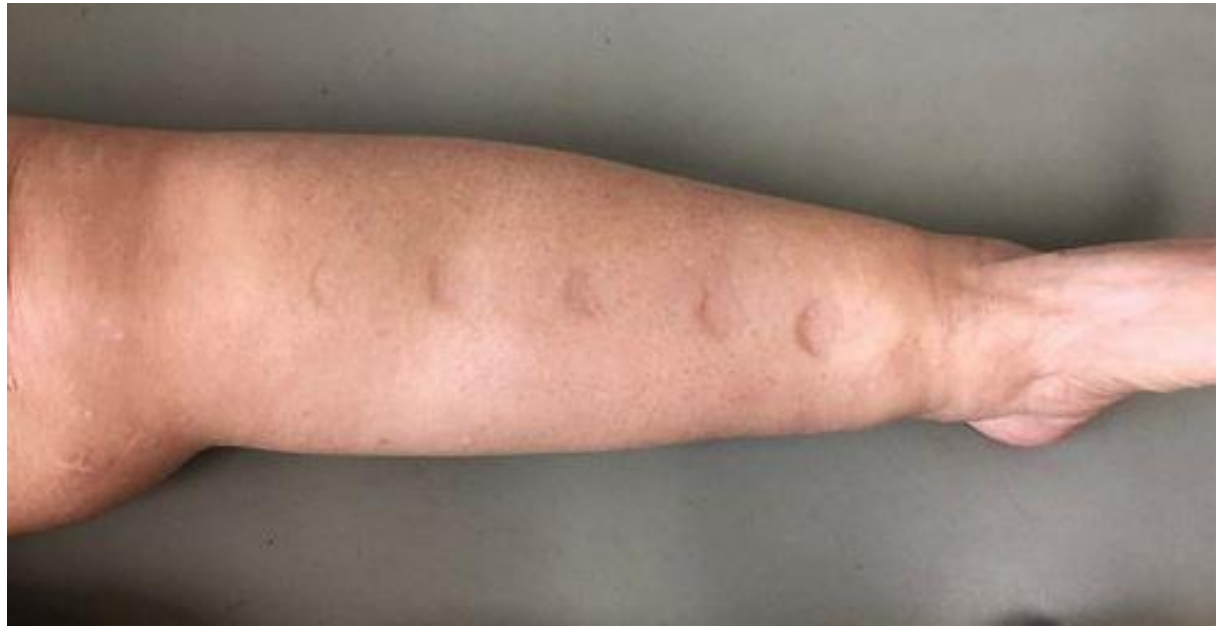
mTOR inhibitors blockade VEGF C and D and thus inhibit lymphoangiogenesis

Lymphedema

Lymphedema can be clinically monitored.

Most cases are reversible, a few may persist after treatment discontinuation, with some cases reported 7–30 months after transplantation.

Patients with preexisting lymphatic deficiencies may present a relative contraindication to mTOR inhibitors



Osteonecrosis

The role of mTOR inhibitors in the appearance of osteonecrosis is debated.

Several case reports describe osteonecrosis of the jaw in patients treated with everolimus for cancer.

In renal transplantation, a case series reported on patients who developed hip osteonecrosis.

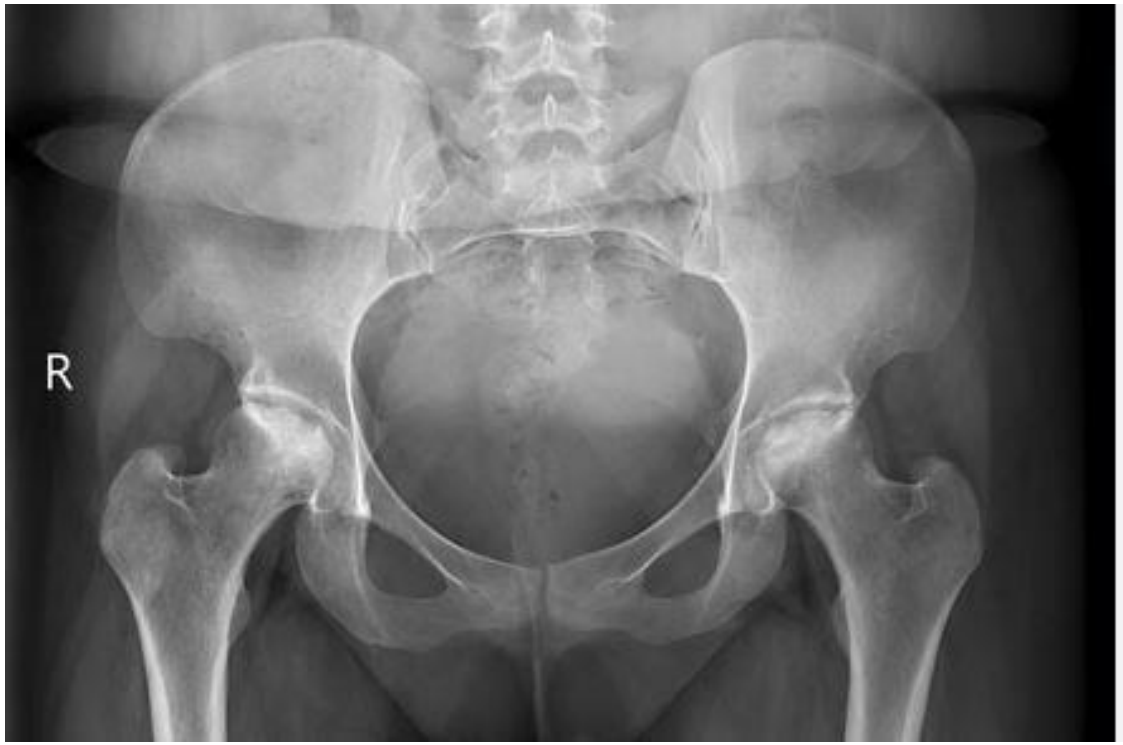
Mechanisms involved include treatment-related dyslipidemia combined with a potent bone marrow suppressive effect

The concomitant use of glucocorticoids remains a confounding factor

Osteonecrosis

Osteonecrosis has been reported 6–12 months after renal transplantation (with an estimated prevalence of 5%), which means the imputability of glucocorticoids is less likely because dosages of glucocorticoids decrease over time.

Finally, bone pain soon after surgery is thought to be related to such complications



Miscellaneous

Other mTOR complications include non-specific diarrhea, nausea and anorexia with weight loss.

Other common toxicities include alterations in taste and asthenia.

These symptoms are usually manageable with dosage reduction.

Gonadal dysfunction causing infertility was also reported with sirolimus after kidney transplantation

Thank you