Sirolimus & mTORIs in Solid Organ Transplantation: Case Presentation

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Objects

1. Introduction
2. Pharmacologic Features of Sirolimus & Everolimus
3. Conversion from CNI to mTORI
4. Known side effects associated with mTORIs
5. Some adverse effects of mTORIs with case presentation

Springer Link

Review Article | Published: 13 March 2019

Sirolimus and mTOR Inhibitors: A Review of Side Effects and Specific Management in Solid Organ Transplantation

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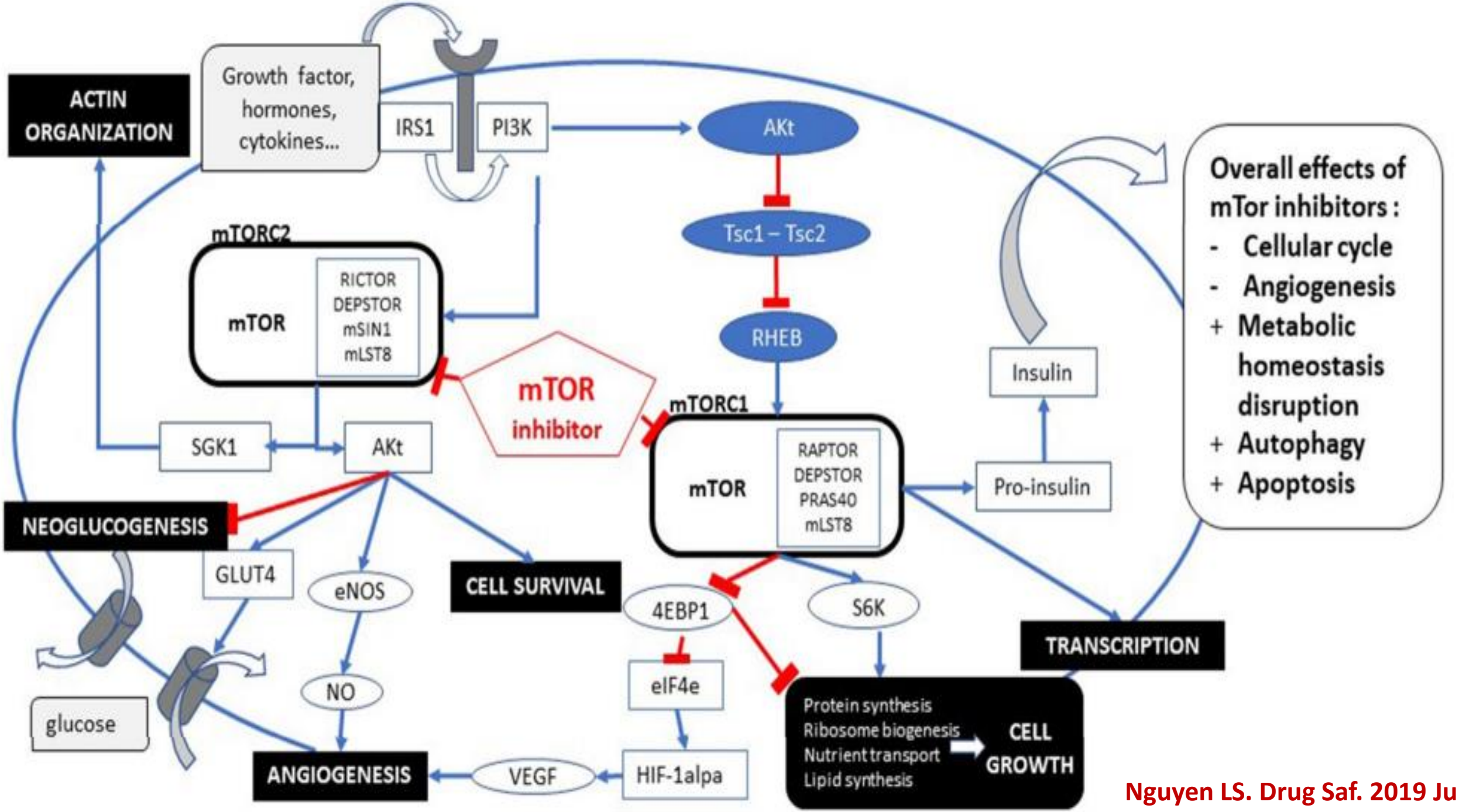
Drug Safety **42**, 813–825 (2019) | Cite this article

Abstract

Inhibitors of mechanistic target of rapamycin (mTOR inhibitors) are used as antiproliferative immunosuppressive drugs and have many clinical applications in various drug combinations.

Introduction

- mTORIs are also called **rapalogs**.
- First-generation rapalogs include sirolimus, everolimus & temsirolimus.
- They represent an alternative to other inhibitors of cytokine-driven proliferation of lymphocytes, acting at a later stage of T-lymphocyte activation than the related compound FK506 or cyclosporin, which block interleukin IL2 transcription.



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Introduction

- While mTORC1 is sensitive to rapamycin in acute administration,

  mTORC2 requires more chronic exposure

Pharmacologic Features of Sirolimus & Everolimus

Pharmacologic feature	Sirolimus	Everolimus
Indications related to SOT	Prevention of renal graft rejection. In patients at low or moderate risk of rejection: in combination with a CNI & corticosteroids; withdrawal of the CNI is possible after 2–4 ms. In high-risk patients, the combination must continue for at least 12 ms	Prevention of renal, cardiac & liver graft rejection. In patients at low or moderate risk of rejection: in combination with a CNI & corticosteroids; withdrawal of the CNI is possible after 2–4 ms. In high-risk patients, the combination must continue for at least 12 ms

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Dosage	~~6 mg on day 1, then~~ 2 mg daily	0.75 mg bid in renal & cardiac Tx 1 mg bid 4 ws after hepatic Tx
Protein binding (%)	92	74

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Pharmacologic Features of Sirolimus & Everolimus

Pharmacologic feature	Sirolimus	Everolimus
Half-life (h)	63	30
Time to peak concentration (h)	1–3	1–2

Pharmacologic Features of Sirolimus & Everolimus

Pharmacologic feature	Sirolimus	Everolimus
Half-life (h)	**63**	**30**
Time to peak concentration (h)	**1–3**	**1–2**
Metabolism	Sirolimus is a substrate of CYP3A4 & P-glycoprotein. It is metabolized in the intestinal wall & liver & returns from the small intestine to the gut lumen via counter-transport by enterocytes.. Sirolimus remains the major component in human whole blood, & the main component of sirolimus accounts for 90% of its immunosuppressive activity	Everolimus is a substrate of CYP3A4 & P-glycoprotein. After oral intake, everolimus is the main circulating component in human blood & the only active component. Metabolites of everolimus are inactive.

Pharmacologic Features of Sirolimus & Everolimus

Pharmacologic feature	Sirolimus	Everolimus
Excretion	91±8% in feces & 2.2±0.9% in urine	98% in the bile & 2% in urine
Interaction	CYP3A4 & P-glycoprotein	CYP3A4 & P-glycoprotein

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Interaction	CYP3A4 & P-glycoprotein	CYP3A4 & P-glycoprotein
Therapeutic target (Cmin)	4–12 ng/ml with & 12–20 ng/ml without CNI	3–8 ng/ml
Dosage adjustment	5–7 days after dosage modification	4–5 days after dosage modification
Initial FDA approval	1999	2009

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سوال

- کدامیک از روشهای آزمایشگاهی کنترل Trough level سیرولیموس ، سطح خونی را ۱۵٪ بالاتر نشان می دهد؟

A. Chromatographic

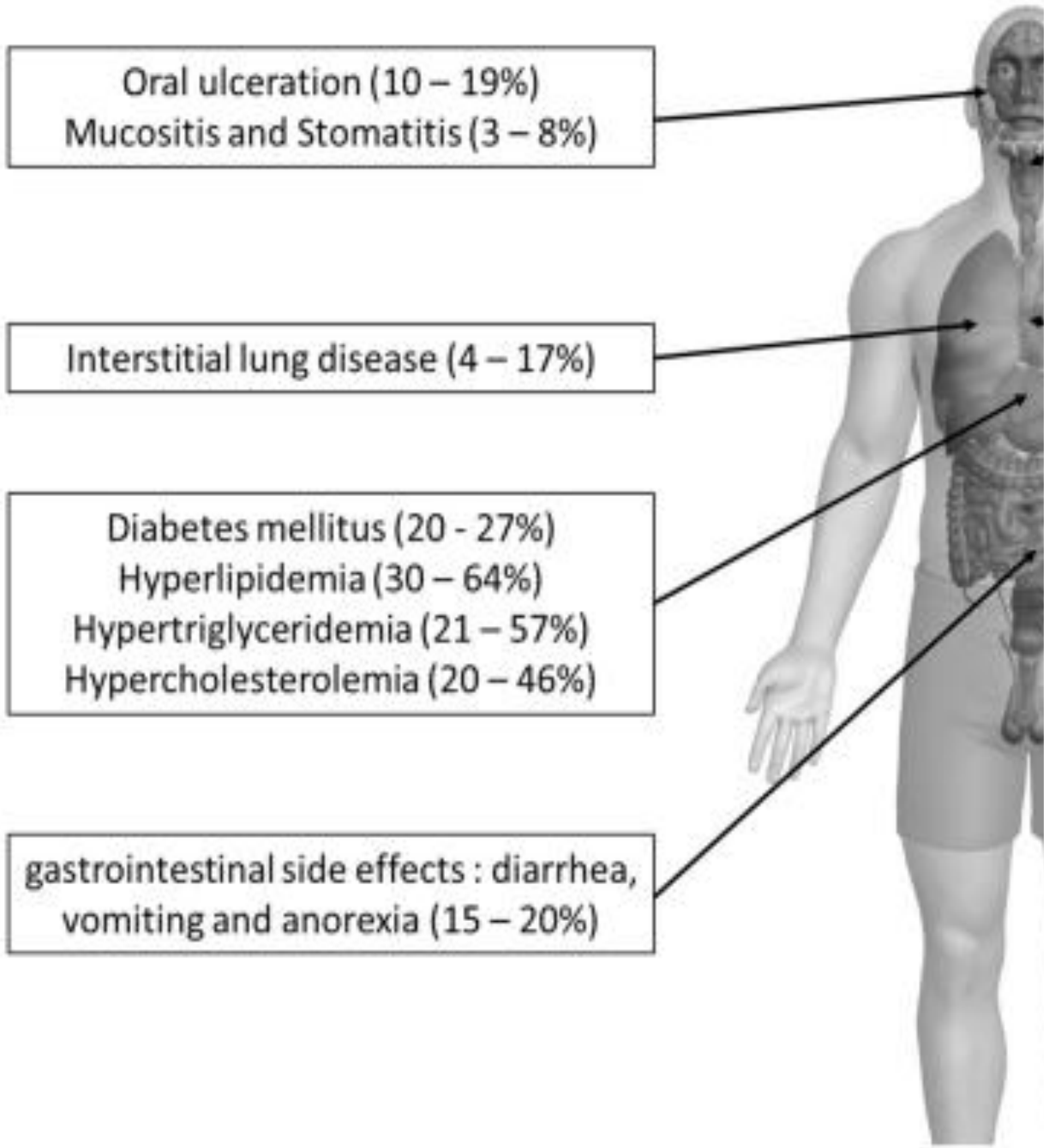
B. Immunoassay

C. CMIA

D. الف و ج

Conversion from CNI to mTORI therapy should be performed cautiously in patients with:

1. Existing proteinuria (> 800 mg/day)
2. eGFR < 40 mL/min
3. Chronic allograft injury



Known side effects associated with mTORIs

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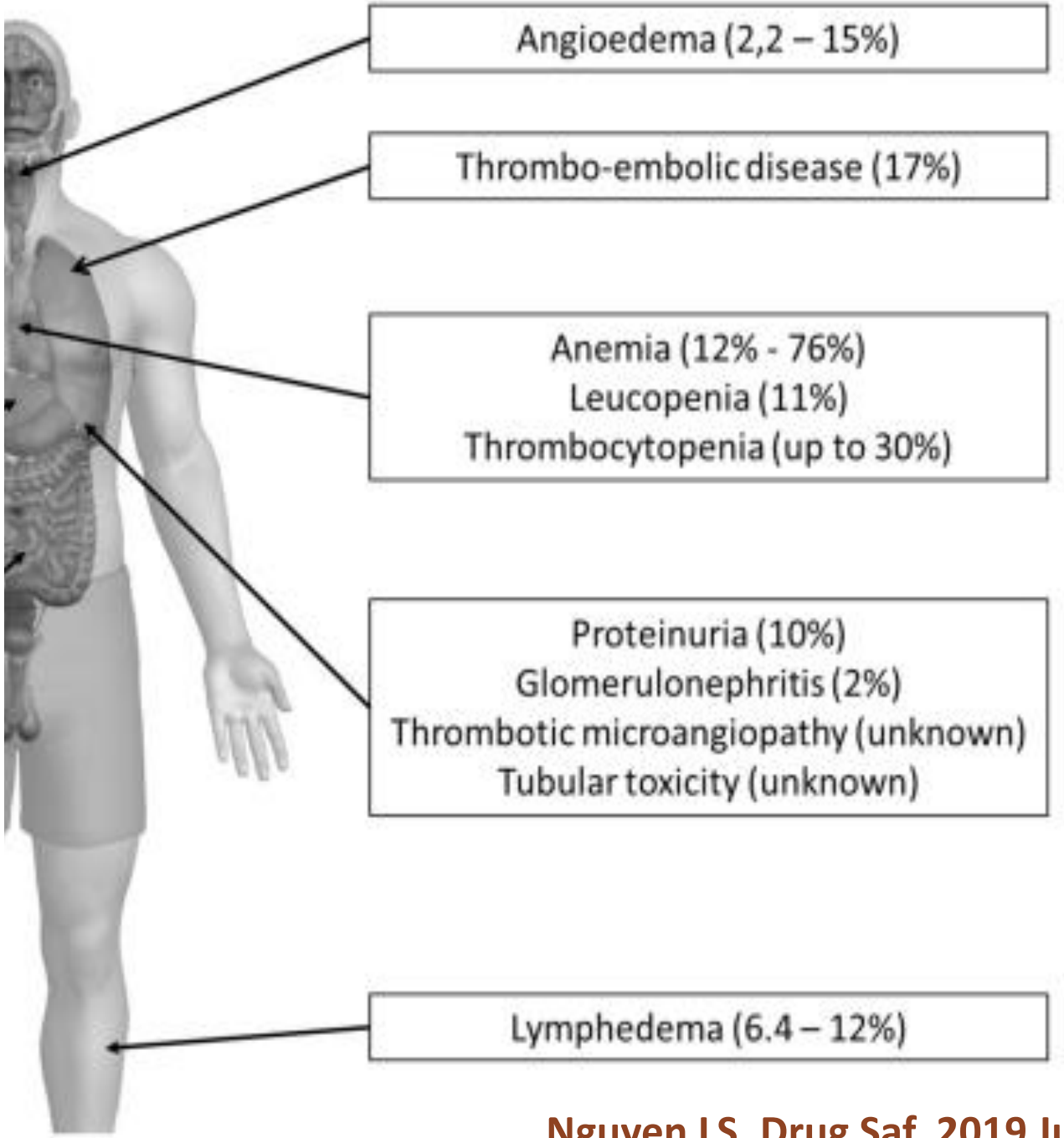
Known side effects associated with mTORIs



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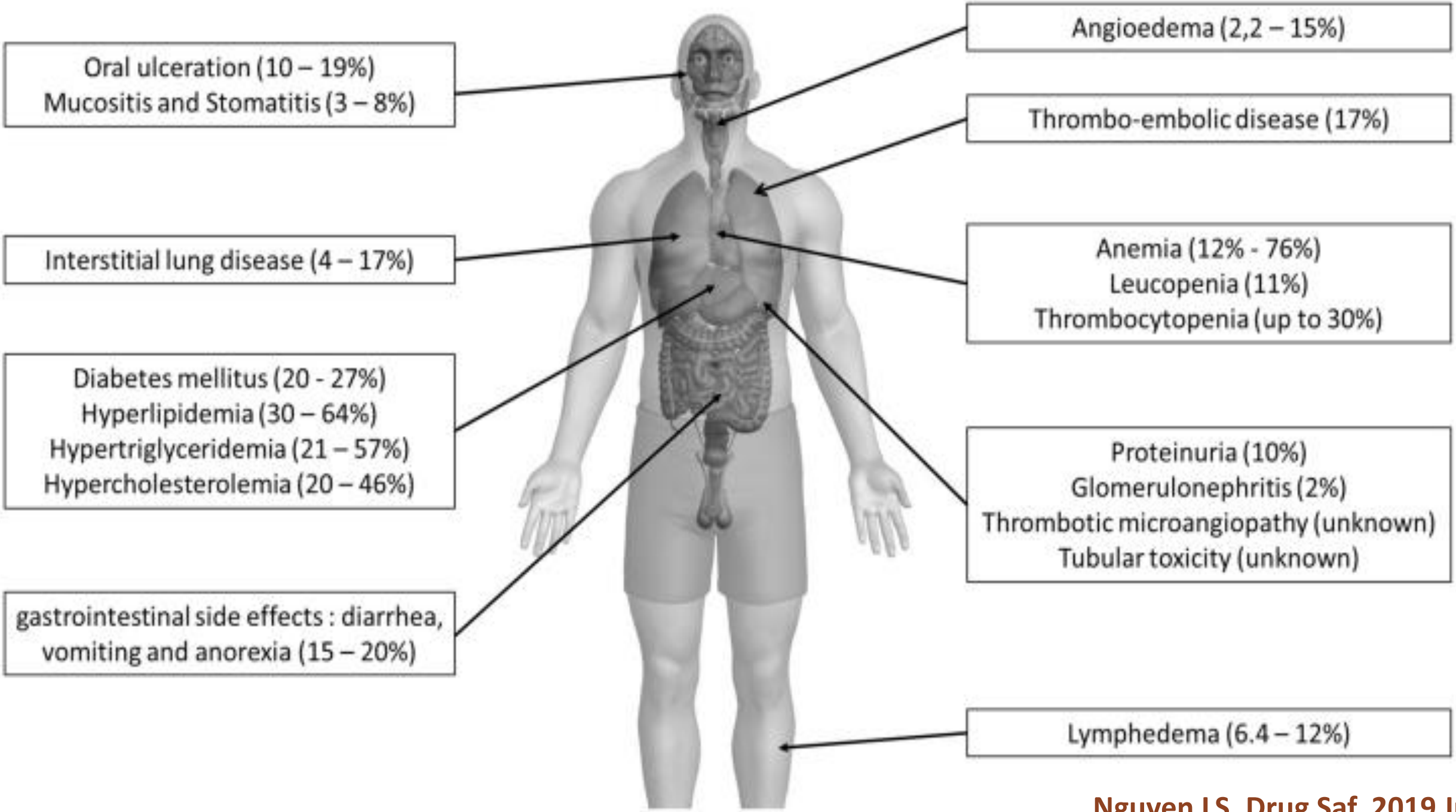

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Strategies for the management of adverse events associated with mTOR inhibitors

Article *in* Transplantation reviews (Orlando, Fla.) · March 2014

DOI: 10.1016/j.trre.2014.03.002 · Source: PubMed

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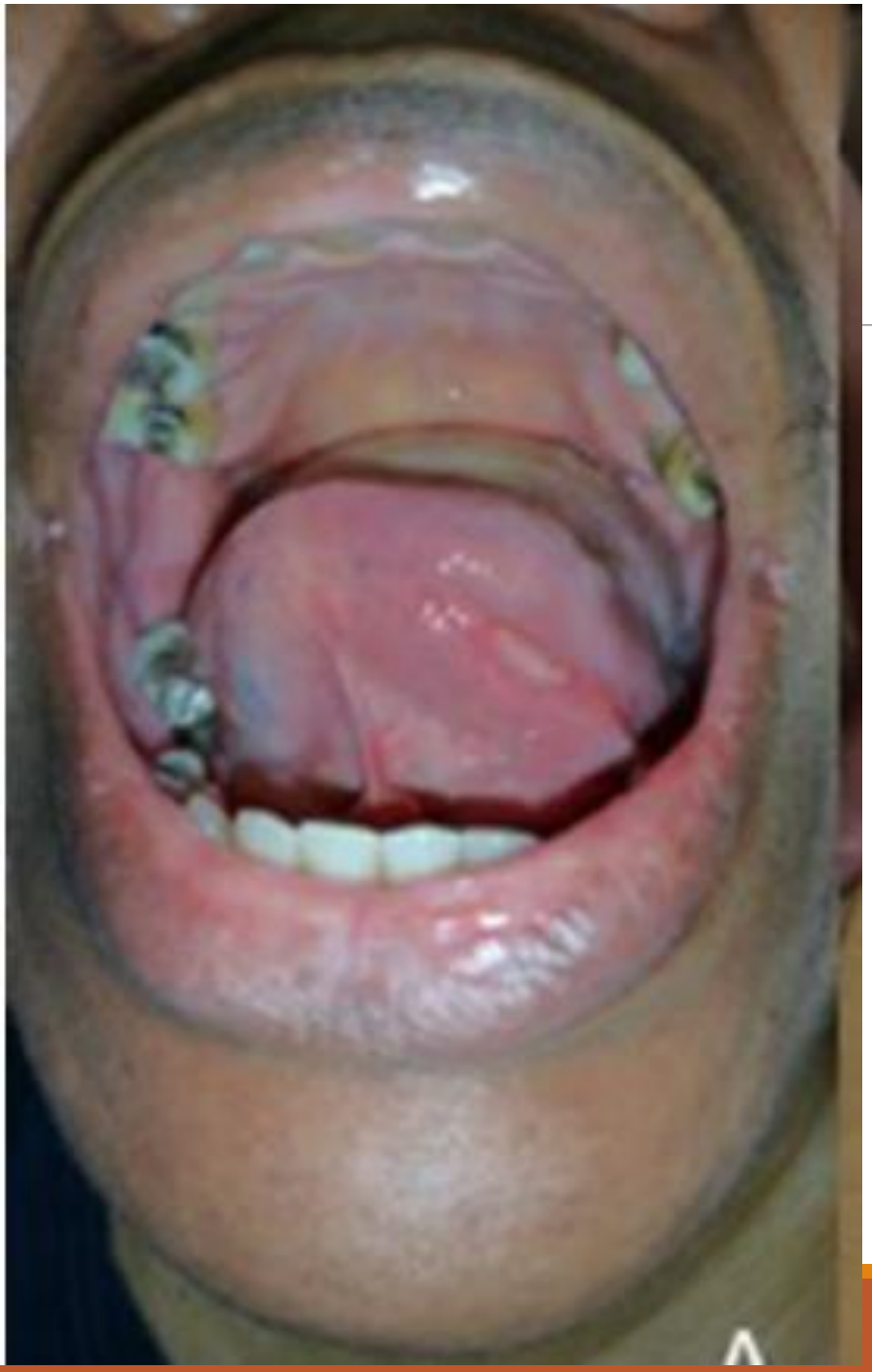
Adverse event	Everolimus (0.75 or 1.0 mg BID with reduced- or standard-dose TAC or CsA)[a]	Sirolimus (2 or 5 mg with CsA ± corticosteroids)
Dermatologic disorders		
Acne	5%–14%	10%–25%
Stomatitis/oral ulcers	3%–8%	10%–19%[b]
Rash	NR	5%–10%
Wound-healing disorders		
Any wound-healing event	11%–35%	3%–36%
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%

Renal Adverse Events: Proteinuria

- Sirolimus increases the expression of **TGF-β1**.
- It also **increases** the toxicity of chronic CNIs & is often used in combination with these treatments.
- Moreover, the cumulative nephrotoxic effects of sirolimus & cyclosporine may be increased by sirolimus-induced **hyperglycemia**, known to accelerate renal IF & TA.
- Sirolimus was also associated with inherent lesions of **FSGS** de novo.
- Moreover, the combination of sirolimus & cyclosporine inhibits mitochondrial energy metabolism. This leads to the generation of **reactive oxygen species** as byproducts of incomplete oxidation.
- Conversely, everolimus is not associated with such findings & may even reduce the effects of cyclosporine on mitochondrial metabolism

Renal Adverse Events: Proteinuria

- After proteinuria onset, management of mTORIs relies on **treatment discontinuation** to decrease the risk of AKI.
- Generally, proteinuria resolves within **a few ms**, & most patients later present with normal kidney function.
- An alternative to treatment discontinuation is to switch to a regular **CNI**, which may reverse proteinuria, regardless of its initial severity.
- **Nonspecific management** is the same as for proteinuria unrelated to rapalogs:
  1. BP control with either ARBs or ACEIs
  2. Dietary restriction of Na & pr intake
  3. Control of LDL cholesterol with statins
  4. General CV risk prevention



Mucositis & stomatitis

- Are the **most common** reported side effects of mTORIs .
- Mucositis usually has rapid onset, is mild to moderate in severity (grade 1–2) & does not result in discontinuation.
- It presents as painful, ovoid, superficial ulcers surrounded by a specific erythematous margin.
- Stomatitis ulcers may form later after treatment initiation (about 1 w). They may last up to 2 ws if untreated & have the potential to relapse.

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Dermatologic & Mucosal Adverse Events

- Preventive measures include:
  - Oral hygiene (gentle brushing, mild toothpaste & mouthwashes)
  - Food & beverage adaptation (avoiding spicy, acidic or very hot food, alcohol), & if possible, avoiding other eluding agents such as iodine, peroxide & antifungals.
- Laser or chemical cauterization may provide fairly rapid pain relief, which has been attributed to disruption of local nerve endings or reductions in inflammatory mediators.

سوال

- مرد ۵۹ ساله با سابقه پیوند کلیه از ۱۰ سال قبل قرار است عمل جراحی الکتیو هرنیورافی اینگوایینال شود بیمار تحت درمان با سیرولیموس ، سل سپت و پردنیزولون می باشد چه مدت قبل از عمل جراحی بهتر است سیرولیموس قطع شود؟

A. یک روز

B. یک هفته

C. ده روز

D. نیاز به قطع دارو نیست

سوال

- مکانیسم احتمالی Brawny limb edema به دنبال مصرف mTORIs

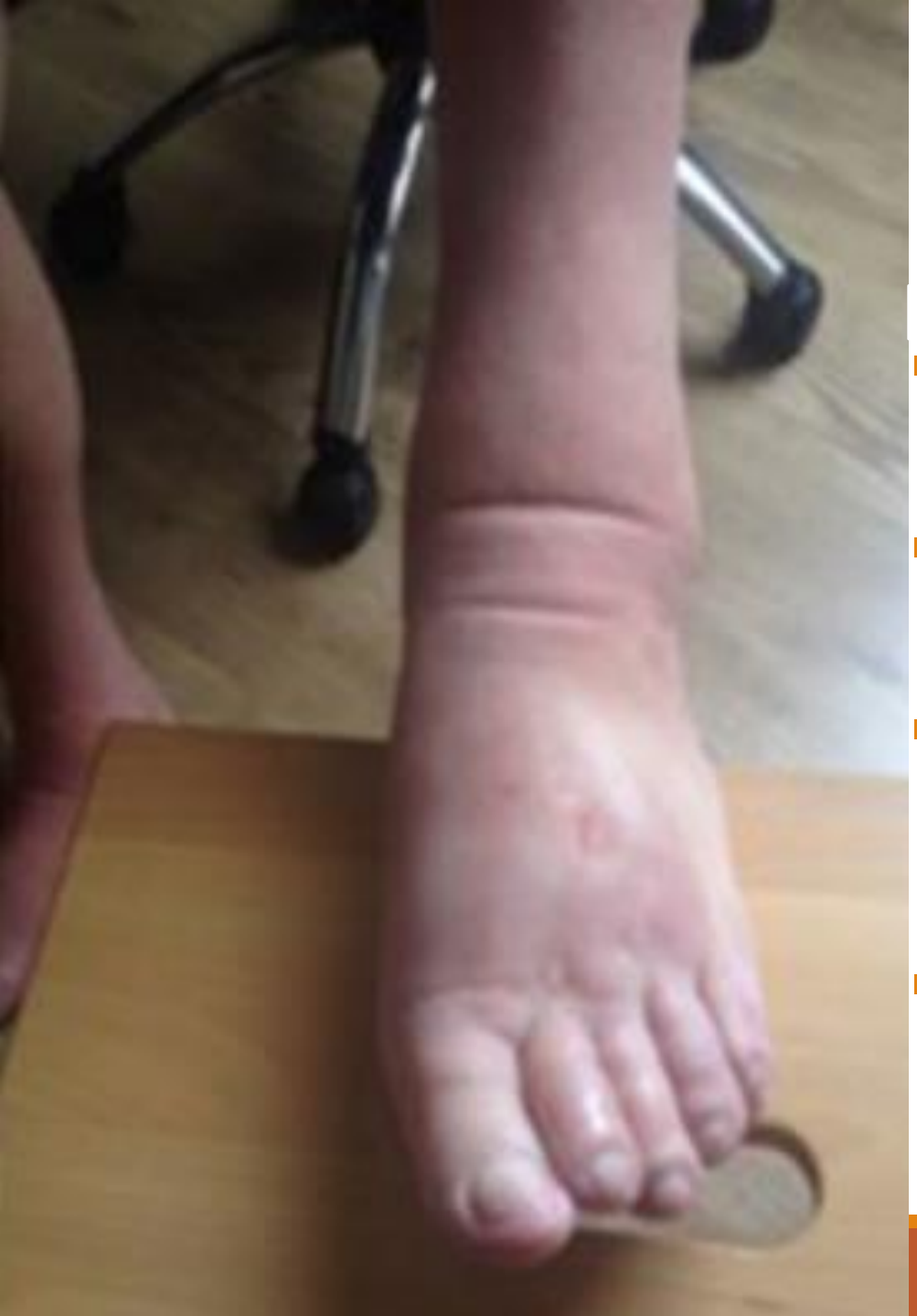
کدامیک از موارد زیر است؟

A. Heart failure

B. Impaired lymphangiogenesis

C. Overload

D. Nephrotic syndrome



Lymphedema

- mTORIs blockade **VEGF C & D** & thus inhibit lymphoangiogenesis.
- Therefore, lymphatic healing after surgery may be further impaired.
- Although most cases are reversible, a few may persist after treatment discontinuation, with some cases reported **7–30 ms** after Tx.
- Patients with preexisting lymphatic deficiencies may present a relative contraindication to mTORIs.

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Lymphedema of the Transplanted Kidney and Abdominal Wall with Ipsilateral Pleural Effusion Following Kidney Biopsy in a Patient Treated with Sirolimus: A Case Report and Review of the Literature

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 32
Final Diagnosis: Sirolimus induced congestion of kidney and overlying abdominal wall
Symptoms: Abdominal pain • abdominal swelling • dyspnea
Medication: —
Clinical Procedure: Improvement of symptoms with drug withdrawal

Case Report

- A 32 y woman ESRD of unknown etiology had undergone KT from an URLD, 8 ys ago.
- She was referred with dyspnea, localized abdominal pain, & swelling of the transplanted kidney.
- 4 ms before admission, a kidney biopsy had been performed for asymptomatic proteinuria & mild allograft dysfunction.
- The serum Cr level at the time of performing the needle biopsy was **1.4 mg/dL.**
- The histopathology findings from the renal biopsy included proliferative GN & suspected cyclosporine toxicity.
- Following the renal biopsy results, cyclosporin treatment was switched to **sirolimus**, 1 mg twice a day. Her other immunosuppressive therapy included prednisone & MMF.

Case Report

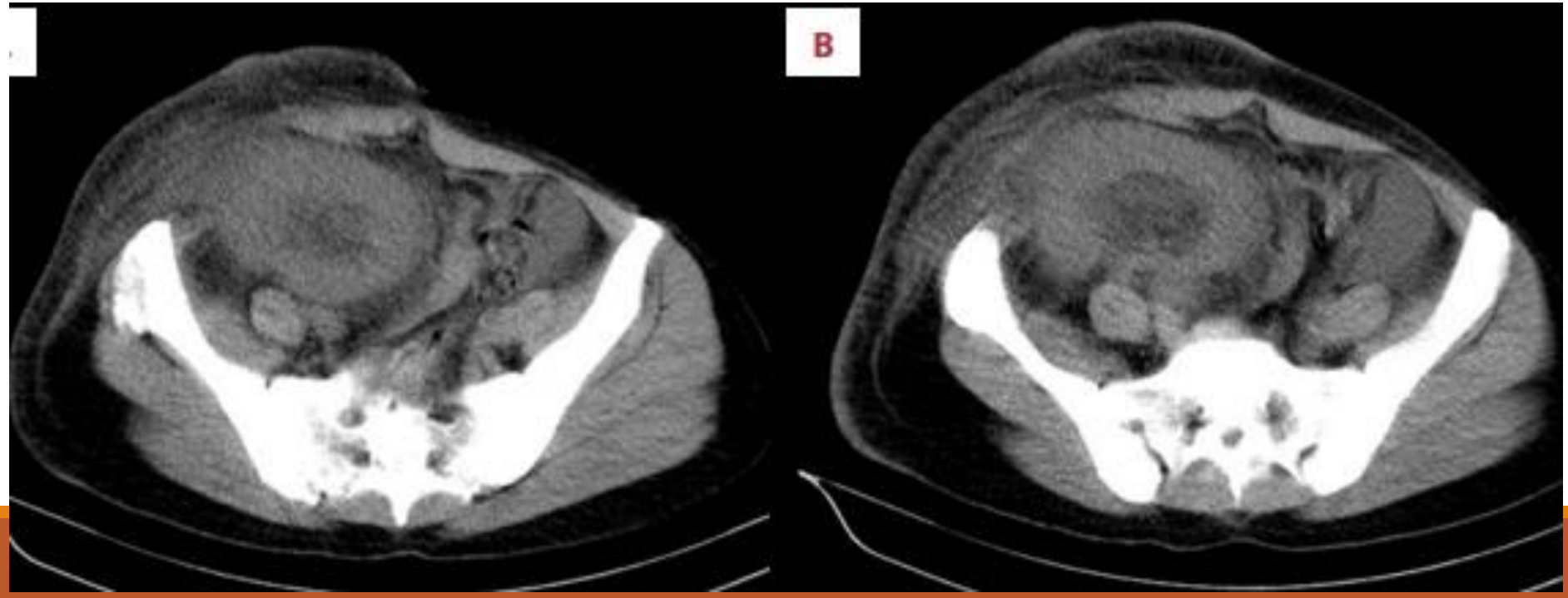
- Several days after the kidney biopsy procedure & change to sirolimus therapy, swelling & pain appeared at the site of the kidney biopsy in the RLQ & progressed over the following 4 ws.
- She developed symptoms of dyspnea 2 ws before admission.
- On hospital admission, PE showed a normal BP, reduced breath sounds over the lower & central the right lung, localized non-pitting swelling, & tenderness of the RLQ associated with an enlarged right-sided transplanted kidney.
- CXR confirmed a right-sided pleural effusion.
- Lab: mild anemia, proteinuria, & a transudate PE. Serum & pleural fluid Cr levels were 1.2 mg/dL & 1.0 mg/dL, respectively.
- The serum sirolimus level was **15.6 ng/mL**.
- While the length of the transplanted kidney, measured by US was 120×62 mm at the time of performing the kidney biopsy 4 ms previously; on the day of hospital admission, it was **160×83** mm in length.

Case Report

- In this case presentation, severe enlargement of the transplanted kidney could have been due to lymphatic congestion of the transplanted kidney.
- A normal kidney has **2 connected lymphatic systems**; the **first** drains lymph from the cortex to the subcapsular networks & perinephric lymphatics; the **second** is the hilar system that collects lymph from the renal cortex & medulla to the hilar lymphatic ducts, & so ligation of hilar lymphatic ducts during surgery leads to drainage of lymph through subcapsular lymphatics.

Case Report

- After surgery, lymphangiogenesis can connect perinephric lymphatics to the lymphatics of the abdominal wall, & this may be an explanation for simultaneous congestion & swelling of the kidney & overlying abdominal wall, as well as the development of ipsilateral PE in our patient.



سوال

- به نظر شما جالب بودن این بیمار کدام عارضه سیرولیموس می باشد که باعث چاپ مقاله شده است؟

A. اولین مورد پلورال افیوژن یکطرفه

B. اولین مورد لنفادم یک طرفه

C. اولین مورد لنفانژکتازی کلیه پیوندی

D. اولین مورد ادم یک طرفه

Case Report: Conclusion

- Lymphedema in the skin of the extremities, abdominal wall, face, & breast, have previously been reported as a relatively rare complication of mTORI use but may involve internal organs such as the kidney.
- In patients treated with sirolimus, **lymphatic damage** caused by kidney needle biopsy may be a predisposing factor for this complication.
- This case report has shown that lymphedema of the transplanted kidney can involve the adjacent abdominal wall & become associated with an ipsilateral PE.

Pulmonary Adverse Events

- It clinically manifests as **dry cough & exercise dyspnea**.
- Possible associated symptoms include **hemoptysis** & inflammatory syndrome (**fever, night sweats**).
- Sirolimus seems to be less incriminated than everolimus in pneumonitis, notably after conversion from one to the other.
- mTORI-induced pneumonitis starts within **2–6 ms** after treatment introduction.
- **Mechanisms** of pulmonary toxicity include direct alveolar damage, immunogenic haptens & immunologic drug responses.

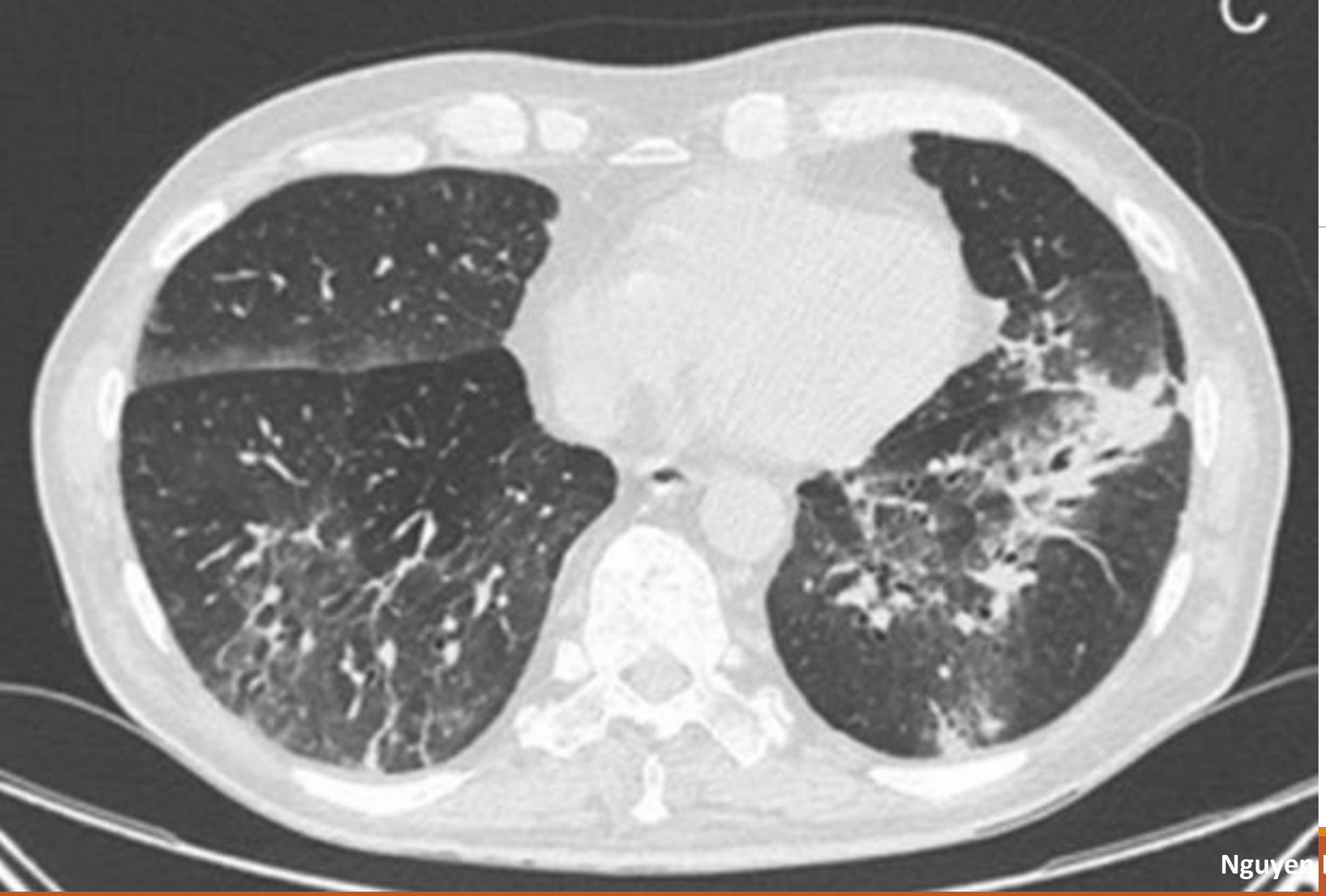
Pulmonary Adverse Events

- Other risk factors for development of pneumonitis include:
  - Age
  - Male sex
  - Late administration of sirolimus compared with de novo therapy
  - Increased sirolimus dose & trough levels compared with baseline

Pulmonary Adverse Events

- **Grade 1** (asymptomatic) interstitial lung disease should be monitored closely with frequent (every 4–8 weeks) radiographic & pulmonary function assessments.
- **Grade 2** (symptoms not interfering with daily activities, & oxygen support not required) mTORI dose reductions, corticosteroids (eg, prednisone 1 mg/kg), & antibiotics may be required.
- **Grade 3** (symptoms interfere with daily activities &/or oxygen support required). Clinical improvement is often rapid after mTORI discontinuation; complete radiographic resolution of pneumonitis is frequently observed within 2 to 4 ms.

B. Kaplan et al. Transplantation Reviews. 2014



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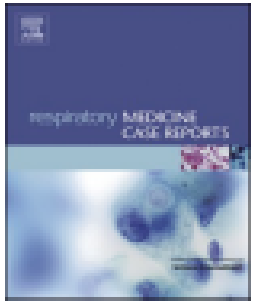

Sirolimus-induced interstitial lung disease and resolution after conversion to everolimus

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ARTICLE INFO

Keywords:
Sirolimus
Everolimus
Drug induced pneumonitis

ABSTRACT

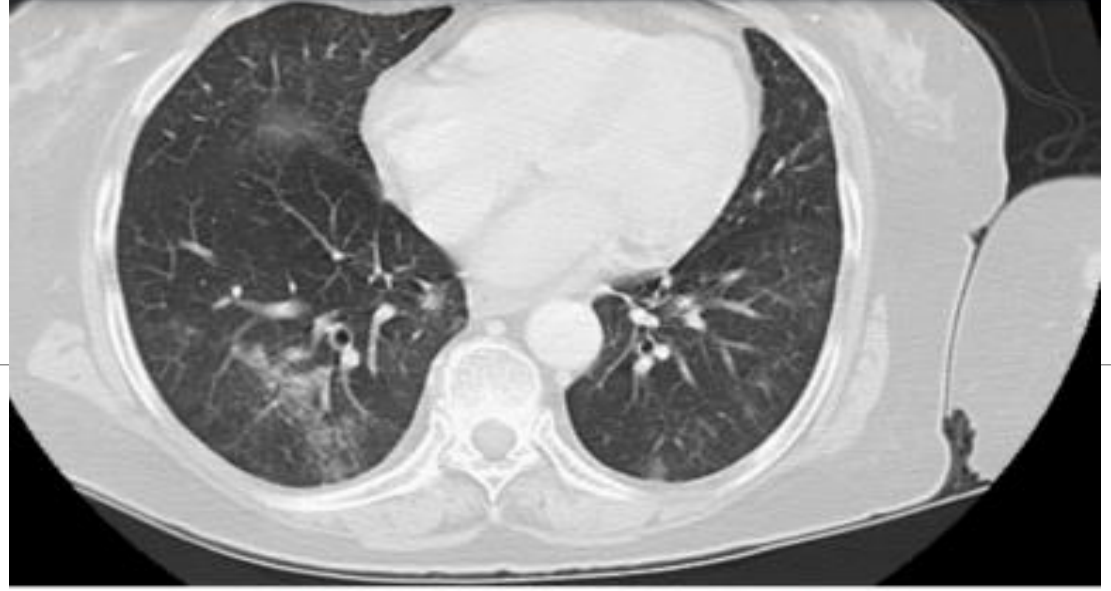
Mammalian target of rapamycin inhibitors (mTORi) are used to treat a variety of malignancies and have an established role in organ transplantation. Interstitial lung disease (ILD) is one of the complications of mTORi and is believed to be a class effect. More cases of ILD have been reported with sirolimus than with everolimus in the literature, possibly due to earlier introduction and wider use of sirolimus. We report the case of a kidney transplant recipient who developed ILD secondary to sirolimus and improved rapidly after switching to everolimus.

Case Report

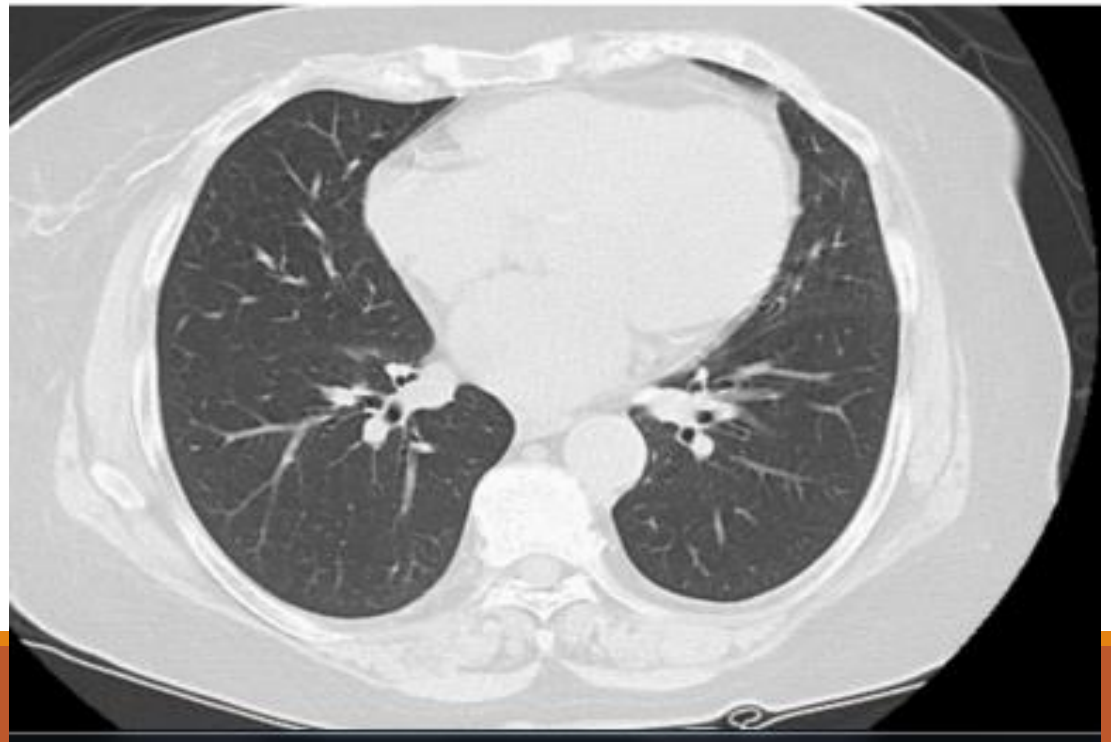
- 67 ys female with history of ESRD, most likely secondary to CGN. She underwent a URLD in July 1998.
- She received a triple immunosuppressive regimen consisting of cyclosporine, azathioprine & prednisone.
- SCr of 0.7–1 mg/dL & no proteinuria.
- In August 2016 she was diagnosed with aggressive diffuse large B cell lymphoma, plasmablastic subtype involving the left nostril, stage 1AE.
- Her immunosuppressive agents were discontinued & she received lymphoma treatment with Etoposide, Prednisone, Vincristine, Doxorubicin and cyclophosphamide.
- In **February 2017**, after completion of chemotherapy she was started on sirolimus 2mg daily. The level was maintained at 5–10 ng/ml.
- In **July 2017**, the patient presented with dry cough, fever & dyspnea on exertion for 6 ws.
- There was no hemoptysis. CXR showed patchy infiltrates in the left lung.

Case Report

- Chest CT revealed multiple patchy, predominantly GGO scattered in a peribronchovascular distribution throughout the lung fields bilaterally, mainly involving the left upper & both lower lobes.
- Broncho alveolar fluid analysis revealed cloudy fluid with WBC 310/mm3 , 10% PMNs, 76% lymphocytes & 14% monocytes.
- The gram stain was negative & so was the bacterial, viral and fungal culture.
- After an **exhaustive work-up** to exclude infectious causes & other pulmonary diseases, the diagnosis of sirolimus-associated pulmonary toxicity was made.
- In **November 2017**, sirolimus was discontinued & she was switched to everolimus at 0.75 mg twice daily.
- The level was maintained at 4–8 ng/ml. Within one week the patient experienced improvement in her symptoms and she was back to her baseline level of activity after 2 ms. A repeat chest CT scan revealed significant decrease of the interstitial infiltrates.
- 2 ys after conversion to everolimus the patient has excellent graft function with a SCr of 1.0 mg/dL, no proteinuria, & no respiratory symptoms.



1. Chest CT showing peribronchovascular ground glass opacities scattered throughout the lung fields



Case Report: Conclusion

- Everolimus is **more hydrophilic** which results in different tissue distribution, different affinities to drug transporters & metabolizing enzymes, as well as differences in drug-target protein interactions .
- It is also more potent in terms of interaction with the mTOR complex 2 than sirolimus.
- Our case supports the idea that in cases of **sirolimus induced ILD**, **switching to everolimus** is a viable option in order to benefit from the antiproliferative effect of mTORi & to avoid CNIs side effects.

Angioedema

- Mechanisms are mediated by **bradykinin**, a vasoactive mediator that results from several pathways: IgE mediated, cyclooxygenase inhibition & kinin & complement metabolism activation.
- Concomitant use of **sirolimus & ACEIs** 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

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Other mTORIs Complications

- Non-specific **diarrhea, nausea & anorexia** with weight loss.
- Other common toxicities include **alterations in taste & asthenia**.

  These symptoms are usually manageable with dosage reduction.
- **Gonadal dysfunction causing infertility** was also reported with sirolimus after KT.

Iranian Journal of Kidney Diseases | Volume 5 | Number 5 | September 2011

TRANSPLANTATION IJKD

Sirolimus-Based Immunosuppression for Treatment of Cutaneous Warts in Kidney Transplant Recipients

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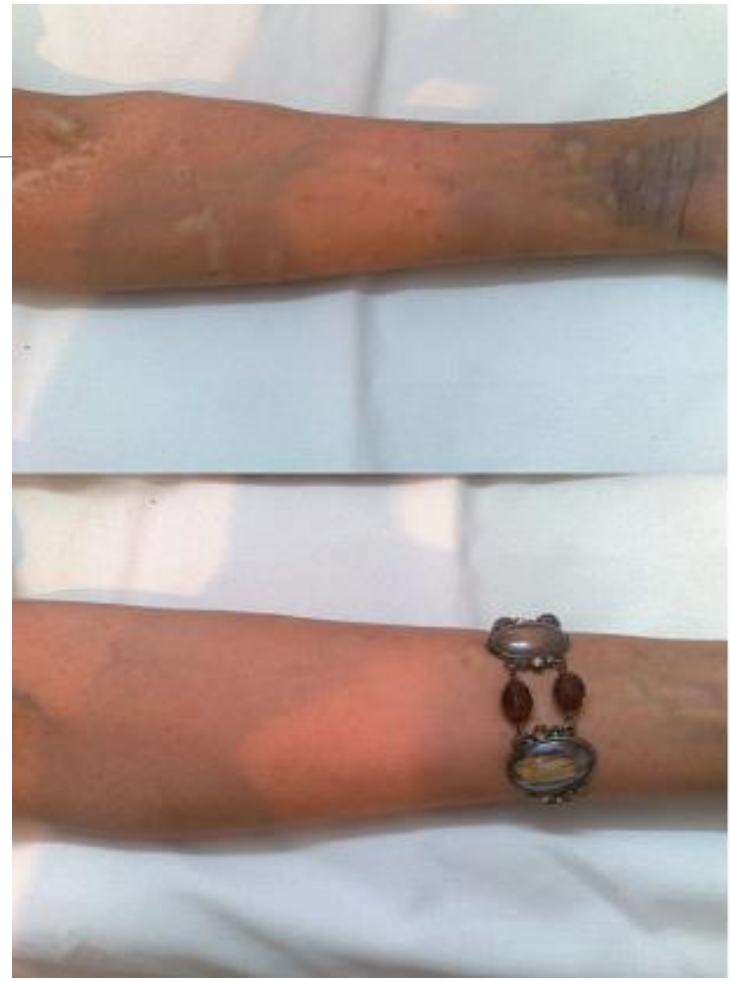
Keywords. human papillomavirus, kidney transplantation, sirolimus, viral infections, warts

Dermatological complications, especially skin infections, are very common following organ transplantation, and result in a lot of distress in the recipient. Herpes zoster, herpes simplex, and human papillomavirus infections are common infections in kidney transplant recipients, and therapeutic management is usually disappointing in immunosuppression state. We report here 2 cases of kidney transplant recipients who developed diffuse human papillomavirus-induced cutaneous warts with no response to conventional treatments. According to similar reports in organ transplant recipients, we modified the immunosuppressive regimen by converting to sirolimus, which led to a rapid relief

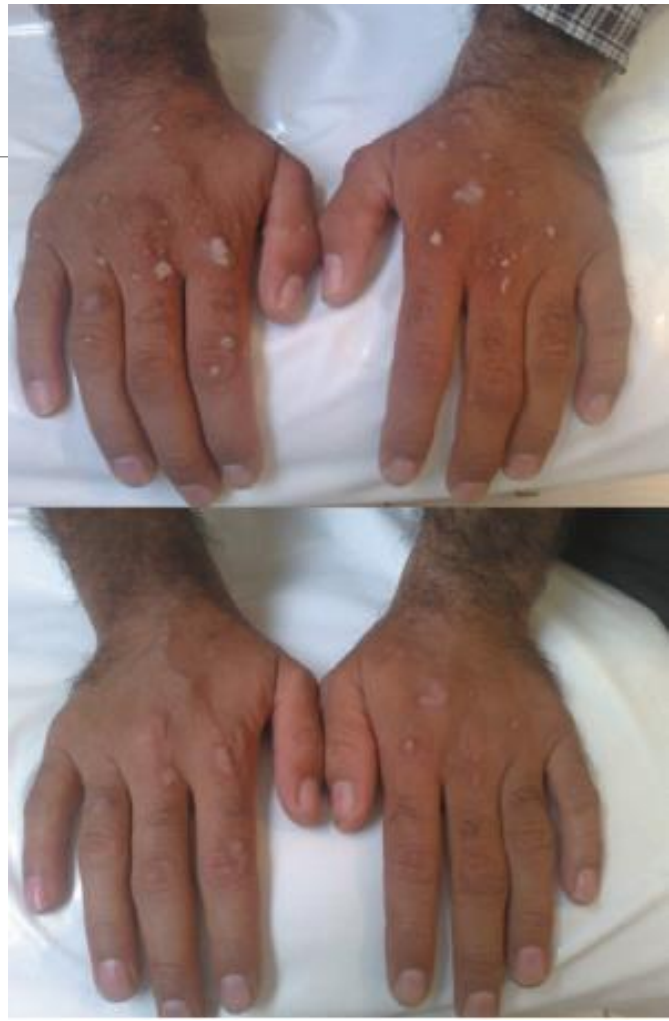
Case Report

- 18 ys woman with ESRD due to VUR received a kidney allograft from a RLD in 1998 & was on cyclosporine, 175 mg/d; prednisolone, 7.5 mg/d; & azathioprine, 50 mg/d, with changing dosages during the treatment period according to side effects.
- In 2000, she experienced multiple skin warts on her arms & hands & was referred to a dermatologist. She received intensive topical therapies & cauterization.
- As no improvement was observed, cyclosporine was substituted by sirolimus, 2 mg/d, in 2008, which resulted in gradual disappearance of the warts until in less than 1 year



Case Report

- 21 ys man with ESRD due to SLE received a kidney allograft from an URLD in 2004. He was on cyclosporine, 250 mg/d; MMF, 2 g/d; & prednisolone, 7.5 mg/d.
- In 2006, the patient experienced multiple skin warts on his hands & fingers. He was referred to a dermatologist & received topical therapies & cauterization.
- Simultaneously, cyclosporine dose was reduced to 100 mg/d. Since the warts did not improve, cyclosporine was replaced with sirolimus, 2 mg/d, in 2008. Two months later, sirolimus dosage was decreased to 1 mg/d due to diarrhea & vomiting.
- The warts gradually disappeared within 3 ms.



Case Report

- The exact mechanism by which mTORIs can interfere with HPV replication is not clear.
- Evidence showed that mTOR pathway activation is essential for the replication of mammalian DNA viruses.
- The function of HPV E7 oncoprotein is essential for viral replication, & it is reported that the mTOR kinase inhibitor, rapamycin, decreases the level of E7 protein by blocking phosphorylation of the translation inhibitor, 4E-BP1.

Case Report: Conclusion

Current evidence suggest that conversion of the immunosuppressive regimen from CNIs to mTORIs can be helpful in the treatment of transplant recipients with severe skin warts.

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Sirolimus Dose Requirement in Kidney Transplant Recipients in Iran

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Introduction. Sirolimus (Rapamune) is an important immunosuppressive drug in kidney transplant patients. The usual maintenance dose of Sirolimus in these patients is 2 to 5 mg/d and its optimal maintenance trough level is 5 to 10 ng/mL. The required Sirolimus doses may differ markedly from patient to patient. It is because of high inter and intrapatient variability in its pharmacokinetics. There have been no studies in Iran on the correlation of Sirolimus blood level and its target dose. This study has been done to show the target dose of Sirolimus in kidney transplanted patients in Isfahan.

Methods. This is a longitudinal cross-sectional study conducted from June 2018 to September 2019. The study population included

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- Longitudinal cross-sectional study.
- Sirolimus was prescribed for 73 patients.
- 57 renal transplanted patients were included in the study.
- The mean starting dose of Sirolimus in these patients was 2 ± 0.19 mg/d.
- At the time of study the mean of the Sirolimus dose was **1.2 ± 0.44** mg/d.
- There was > 20% GFR improvement in 68% of the patients after changing the CNI to Sirolimus ($P < .05$)

Ghasemi G, et al. IJKD. 2020

سوال

- در مورد اختلاف نیمه عمر سیرولیموس در دو جنس کدام صحیح است؟

A. در مردها طولانی تر است
B. درخانمها طولانی تر است
C. در هر دو یکسان است

Table 4. Mean of Sirolimus Dose

Variable	Classification	Frequency	Sirolimus Dose	*P*	F.
Sex	Female	14 (24.6)	1.4 ± 0.5	< .05	4.1
	Male	43 (75.4)	1.1 ± 0.4		
Age, y	≤ 42.0	15 (26.3)	1.3 ± 0.5	> .05	0.4
	43.0 to 53.0	16 (28)	1.1 ± 0.5		
	54.0 to 62.0	12 (21.1)	1.2 ± 0.3		
	≥ 63.0	14 (24.6)	1.1 ± 0.4		

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

*Nguyen LS. Drug Saf. 2019 Jul

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Conclusion

Contrary to the recommended dose of Sirolimus in the references (2 to 5 mg/d) Iranian kidney transplant recipients needed lower daily doses of Sirolimus (**1.2 mg/d**) to achieve the desired whole blood level.

Take-home Message

- Sirolimus & mTORIs are associated with a wide array of adverse events that require persistent vigilance to ensure early diagnosis to manage dosages & modify treatment when required.
- Mechanisms involved in specific toxicities are not fully understood, but the growing use of more specific second-generation mTORIs such as ATP-competitive inhibitors may contribute to a better understanding of these adverse events.
- Finally, although mTORIs are associated with potentially severe adverse events, they remain indicated in SOT so require close monitoring.

با تشکر از توجه دوستان