MTOR SIDE EFFECTS & MONITORINGS

By:

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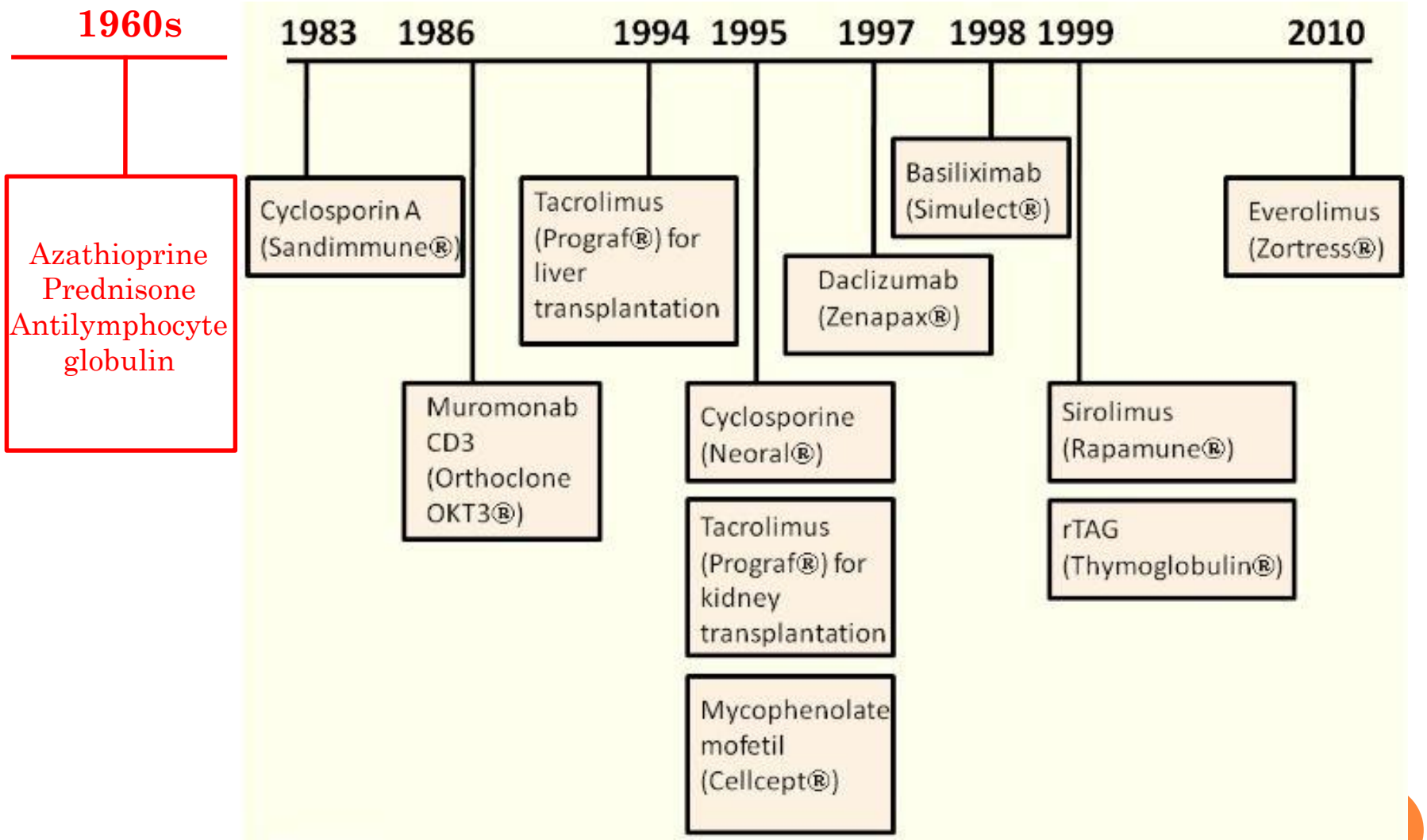
Introduction

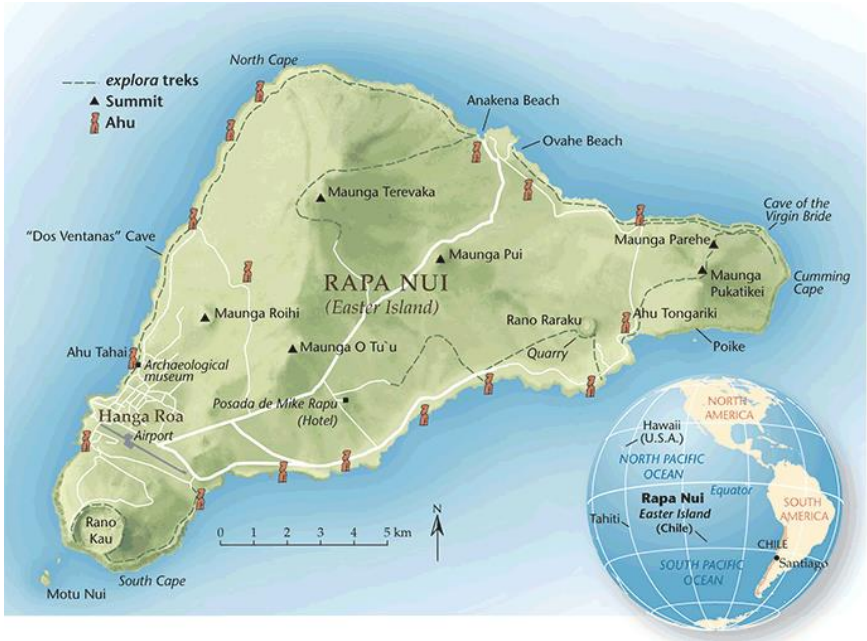
Timeline of approval of maintenance and induction therapy agents used for immunosuppression in solid-organ transplantation

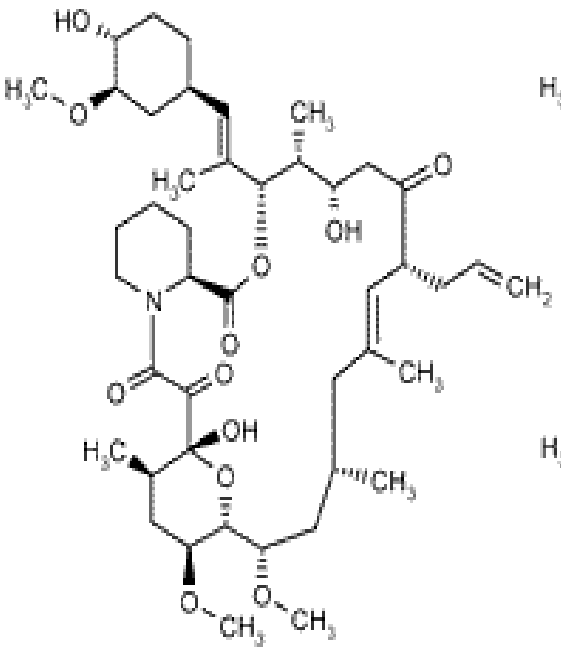


Herwig-Ulf Meier-Kriesche, Sundus A. Lodhi. Organ Transplant Immunosuppression in the Era of Calcineurin Inhibitors. CME/CE Released: 08/13/2010

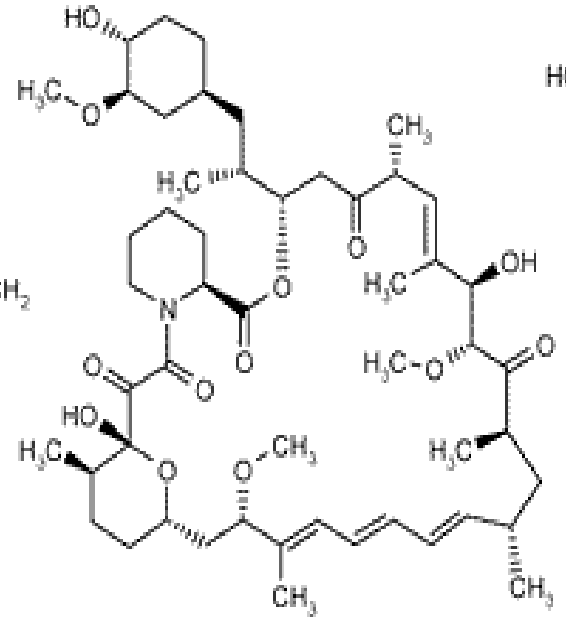
Sirolimus & Everolimus

- Sirolimus (C51H79NO13) with molecular weight of 913.7 Da was isolated from soil samples on **Rapa Nui (Easter Island)** and is a **macrolide**, structurally related to **tacrolimus**.

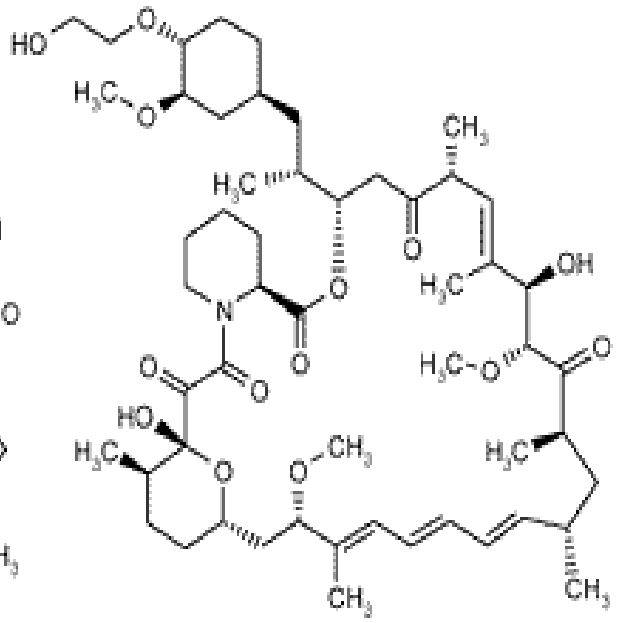




Tacrolimus



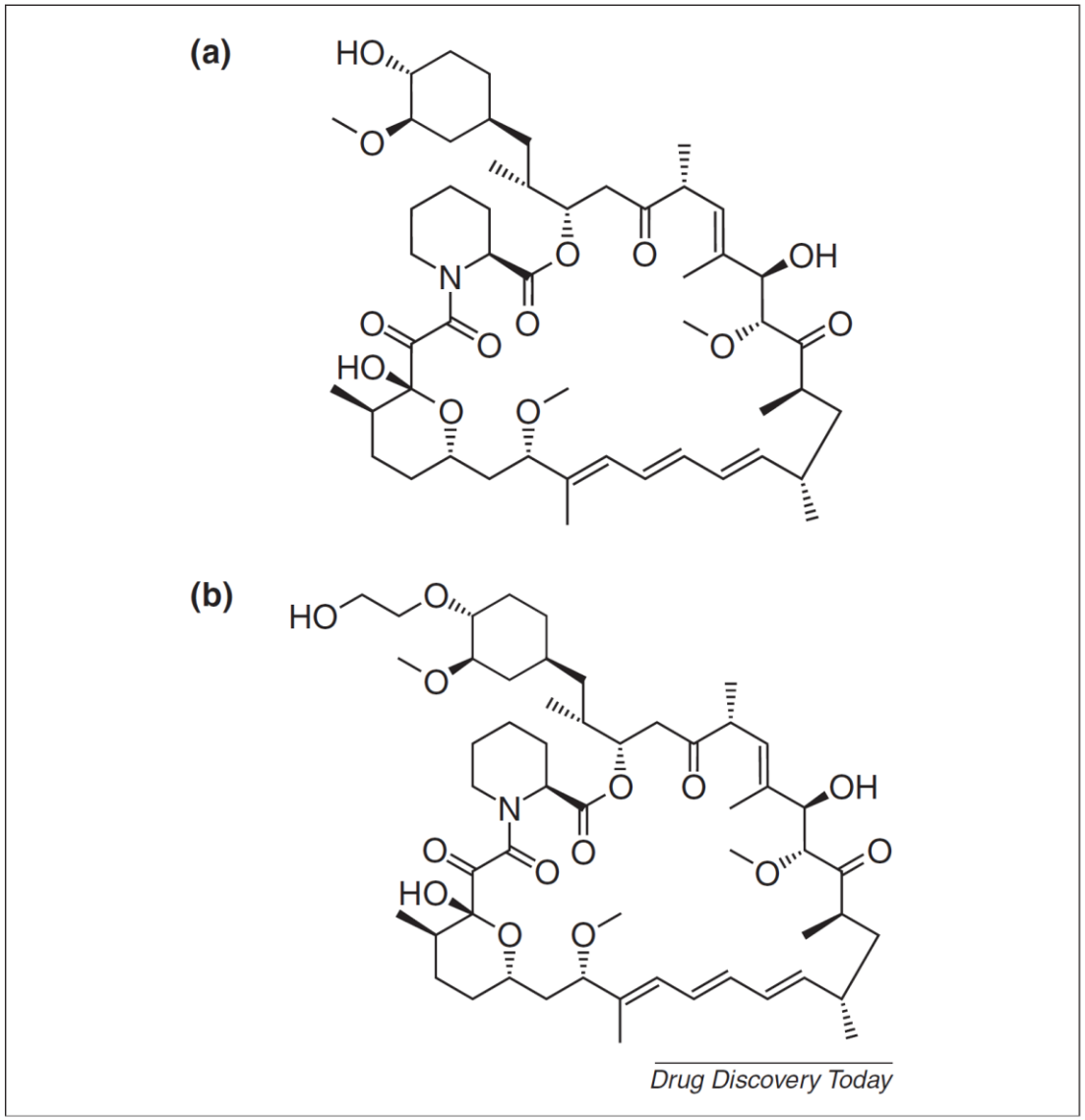
Sirolimus



Everolimus

Immunotherapy in Transplantation: Principles and Practice, First Edition. Edited by Bruce Kaplan, Gilbert J. Burckart and Fadi G. Lakkis. 2012 Blackwell Publishing Ltd

Chemical structures of (a) sirolimus and (b) everolimus



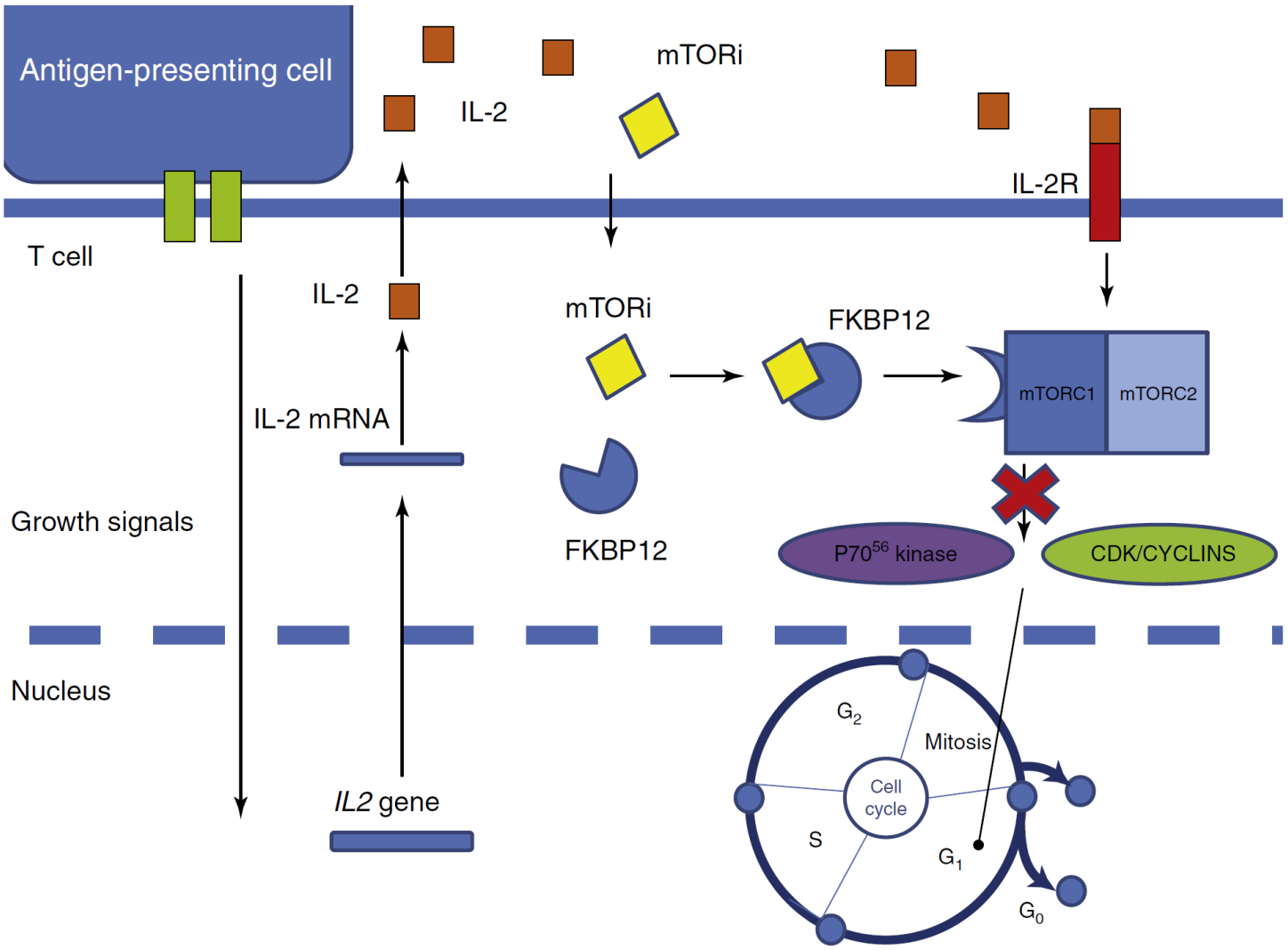
Moes DJ, Guchelaar HJ, de Fijter JW. Sirolimus and everolimus in kidney transplantation. Drug Discov Today. 2015;20(10):1243-9.

Sirolimus was introduced into clinical transplantation in the United States in 1999, after a series of clinical trials demonstrated that, when used in combination with cyclosporine and prednisone, it produced a significant reduction in the incidence of acute rejection episodes in the early post-transplantation period, compared with either azathioprine or placebo.

In Europe, its introduction was delayed (2002) because of concerns regarding impairment of kidney function documented in similar trials. It was eventually approved for use in Europe in a protocol based on withdrawal of cyclosporine starting 3 months after transplantation.

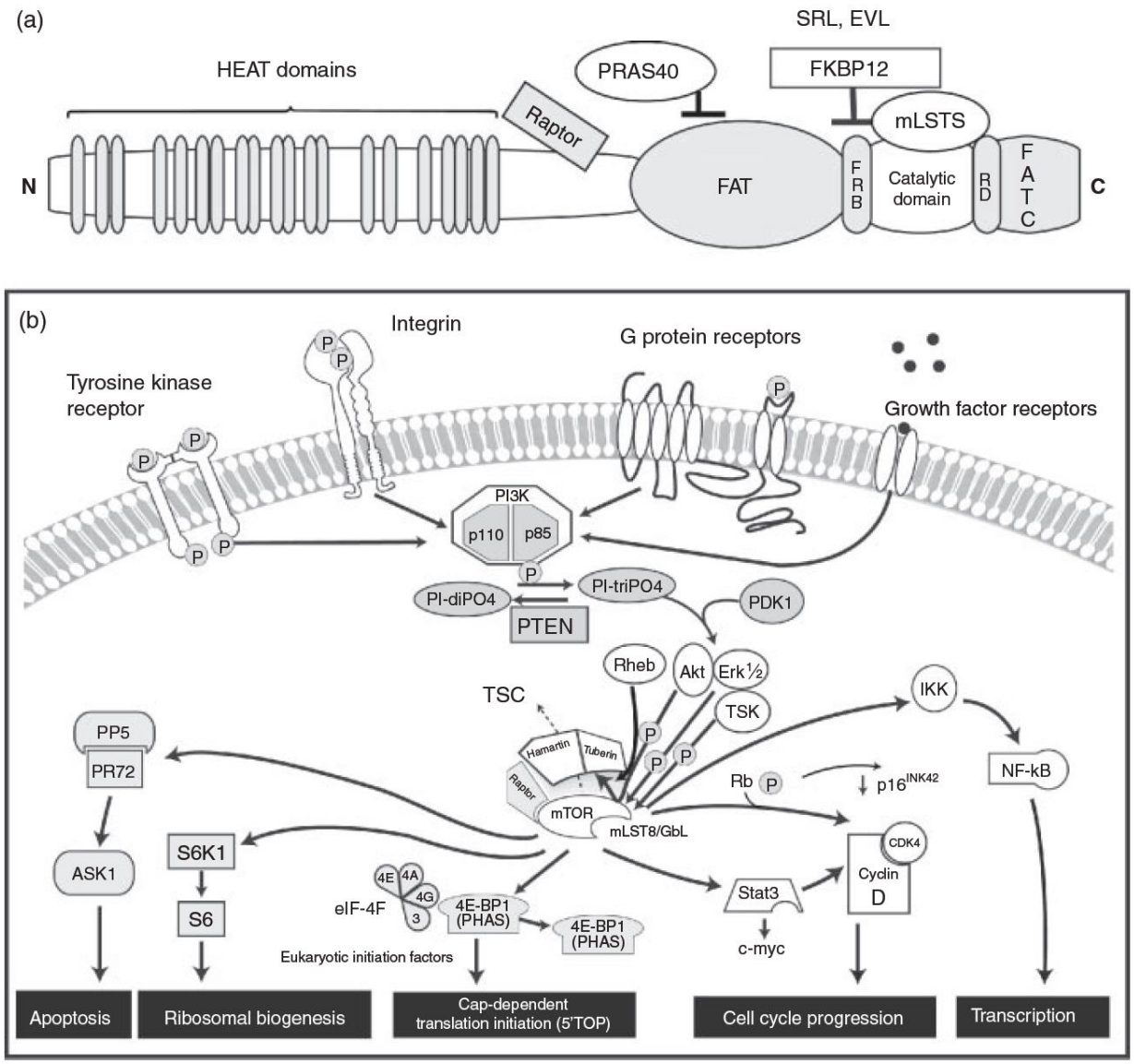
Mechanism of action

Simplified schematic representation of mammalian target of rapamycin inhibitor (mTORi) mechanism of action

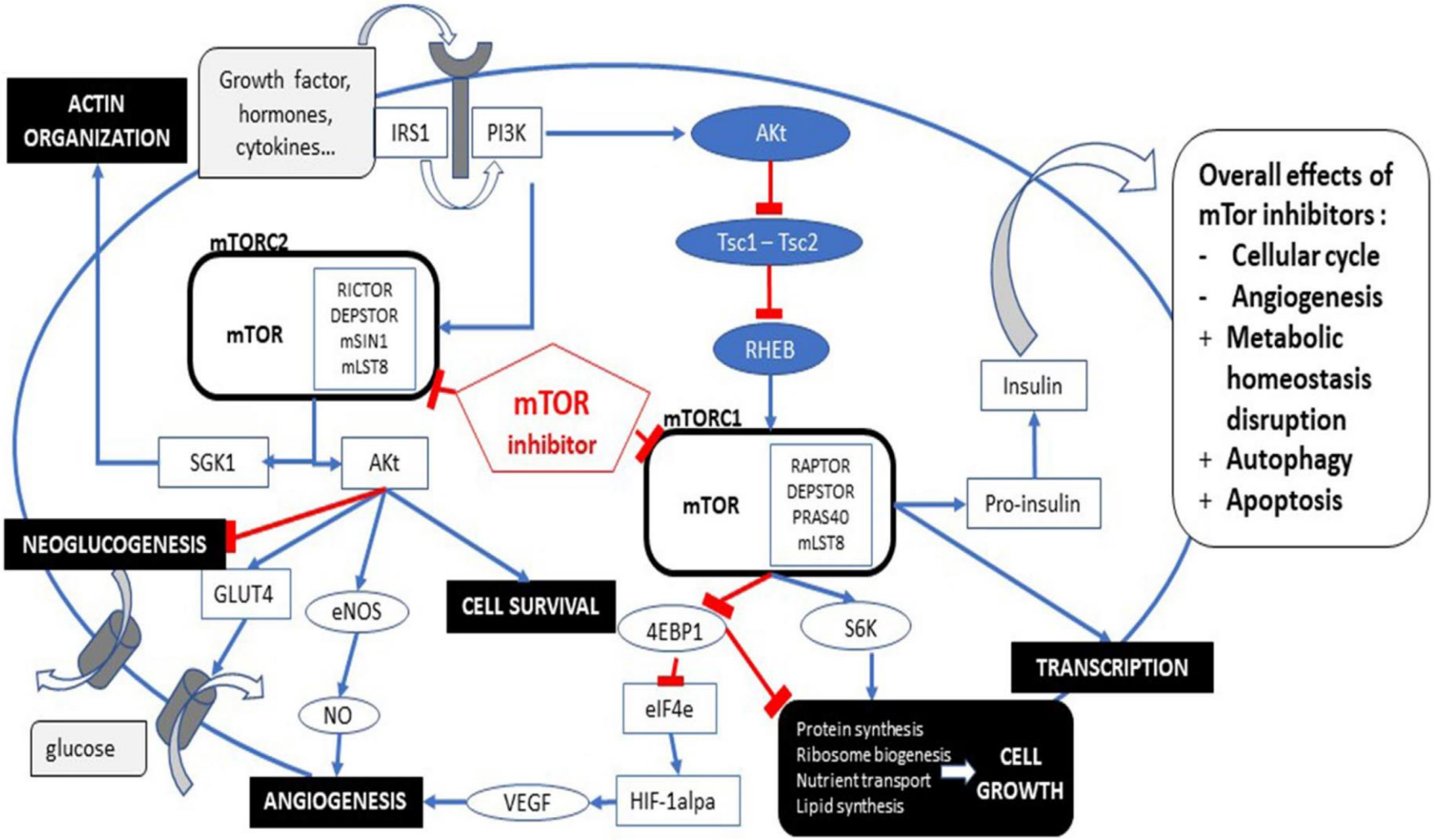


Moes DJ, Guchelaar HJ, de Fijter JW. Sirolimus and everolimus in kidney transplantation. Drug Discov Today. 2015;20(10):1243-9.

Schematic structure and central role of mammalian target of rapamycin (mTOR) in cellular responses



Immunotherapy in Transplantation: Principles and Practice, First Edition. Edited by Bruce Kaplan, Gilbert J. Burckart and Fadi G. Lakkis. 2012 Blackwell Publishing Ltd


ACTIN ORGANIZATION
Growth factor, hormones, cytokines...
IRS1
PI3K
AKt
Tsc1 – Tsc2
RHEB
mTORC2
mTOR
RICTOR
DEPSTOR
mSIN1
mLST8
mTOR inhibitor
mTORC1
mTOR
RAPTOR
DEPSTOR
PRAS40
mLST8
SGK1
AKt
Insulin
Pro-insulin
Overall effects of mTor inhibitors :
- Cellular cycle
- Angiogenesis
+ Metabolic homeostasis disruption
+ Autophagy
+ Apoptosis
NEOGLUCOGENESIS
GLUT4
eNOS
CELL SURVIVAL
4EBP1
S6K
TRANSCRIPTION
glucose
NO
eIF4e
Protein synthesis
Ribosome biogenesis
Nutrient transport
Lipid synthesis
CELL GROWTH
ANGIOGENESIS
VEGF
HIF-1alpa

Dosage forms

DOSAGE AND USE: See accompanying prescribing information.

Store at room temperature, 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature.] Dispense in tight (USP), light-resistant (USP), and child-resistant containers.

Distributed by
Wyeth Pharmaceuticals Inc
A subsidiary of Pfizer Inc
Philadelphia, PA 19101

MADE IN JAPAN

FPO UPC 80% x 5.5 mm
N3 0008-1040-05 7

ALWAYS DISPENSE WITH MEDICATION GUIDE

Pfizer

NDC 0008-1040-05

Rapamune®
(sirolimus) Tablets
0.5 mg

For oral use only.

100 Tablets **Rx only**

Usual Dosage: See enclosed prescribing information.

Store at room temperature, 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature.] Dispense in a tight, light-resistant container as defined in the USP.

Keep out of reach of children.

U1041-05-3

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

FPO (01) 00300081041054

NDC 0008-1041-05 **100 Tablets**

Rapamune®
Rx only (sirolimus)
1 mg Tablets

For oral use only.

Wyeth® Wyeth Pharmaceuticals Inc.

The appearance of these tablets is a trademark of Wyeth Pharmaceuticals.

U.S. Patents: See package insert.

FPO

NDC 0008-1042-05 100 Tablets

Rapamune®

℞ only (sirolimus)

2 mg Tablets

For oral use only.

Wyeth® Wyeth Pharmaceuticals Inc.

The appearance of these tablets is a trademark of Wyeth Pharmaceuticals.

U.S. Patents: See package insert.

FPO

Usual Dosage: See enclosed prescribing information.

Store at room temperature, 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature]. Dispense in a tight, light-resistant container as defined in the USP.

Keep out of reach of children.

U1042-05-2

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

(01)00300081042051

NDC 0008-1030-04 60 mL

Rapamune®

(sirolimus)

Oral Solution 1mg/mL

℞ only

For oral use only.
Each mL of RAPAMUNE contains 1 mg sirolimus.
1.5%-2.5% ethanol
Also contains a mixture of propylene glycol and phosphatidylcholine derived from soy lecithin (and other components) and polysorbate 80.

Wyeth®

Store refrigerated at 2°-8°C (36°-46°F). Protect from light.
Use contents within 1 month after opening.

U.S. Patents: See package insert.

LB-5561/S

LOT
EXP.

Usual dosage: See accompanying information
Keep out of reach of children.

U1030-04-3

Manufactured for:
Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101
MADE IN CANADA

(01)00300081030041

FPO

TORISEL®
(temsirolimus) injection

28 Tablets

Carton contains
4 individual blister cards
of 7 tablets.

NDC 0078-0566-51

Rx only

AFINITOR®
(everolimus) tablets

Each tablet contains
5 mg
everolimus

NOVARTIS

28 Tablets

Carton contains
4 individual blister cards
of 7 tablets.

NDC 0078-0567-51

Rx only

AFINITOR®
(everolimus) tablets

Each tablet contains
10 mg
everolimus

NOVARTIS


NOVARTIS
CERTICAN® 0,25 mg
everolimus
60 Tabletten/comprimés


NOVARTIS
CERTICAN® 0,5 mg
everolimus
60 Tabletten/comprimés


NOVARTIS
CERTICAN® 0,75 mg
everolimus
60 Tabletten/comprimés
CHEAP DRUGMART.com

Pharmacokinetics

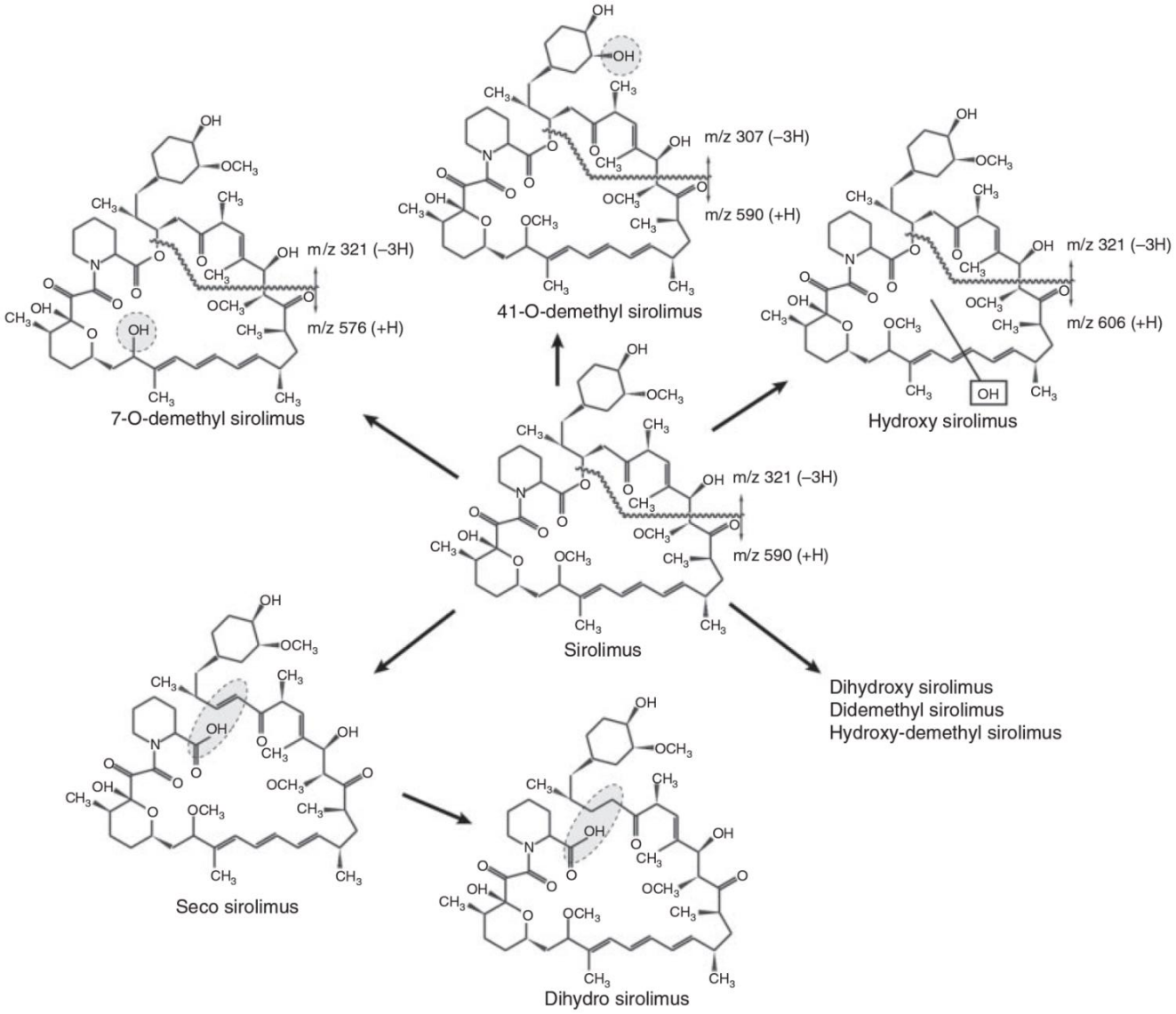
Pharmacokinetics Variable	Sirolimus	Everolimus
Bioavailability	Liquid formulation: 14% Tablet formulation: 18%	20%
Time to peak (Tmax)	Liquid formulation: 1-3 hours Tablet formulation: 1-6 hours	1 to 2.2 hours
Maximum concentration (Cmax)	14 to 344 mcg/L	2.3 to 179 mcg/L
Distribution	Protein binding: ~92%, primarily to albumin 94% in blood is sequestered into erythrocytes (RBC : Plasma ratio is 36:1)	Protein binding: ~74% 75% in blood is sequestered into erythrocytes
Volume of Distribution	12 L/kg (5.6-16.73 L/kg)	2.1 L/kg
Half-life elimination	Mean: 62 hours (range: 46 to 78 hours)	~30 hours
Loading dose	Three times the maintenance dose (6-15 mg)	Not required

Pharmacokinetics Variable	Sirolimus	Everolimus
Metabolism	Extensive; in intestinal wall via P-glycoprotein and hepatic via CYP3A4 to 7 major metabolites (Metabolites contribute to <10 percent of immunosuppressive activity of the parent compound)	Extensively metabolized in the liver via CYP3A4; forms 6 weak metabolites
Clearance	139 to 221 ml/kg/hr	?
Excretion	Feces (91% due to P-glycoprotein-mediated efflux into gut lumen); urine (2%)	Feces (80%, based on solid organ transplant studies); Urine (~5%,
Therapeutic range (Renal transplant)	With cyclosporine: 5-15 or 6-12 ng/mL Without cyclosporine: 16 to 24 ng/mL for the first year; 12 to 20 ng/mL after 1 year	3-8 ng/mL

Pharmacologic features of sirolimus and everolimus

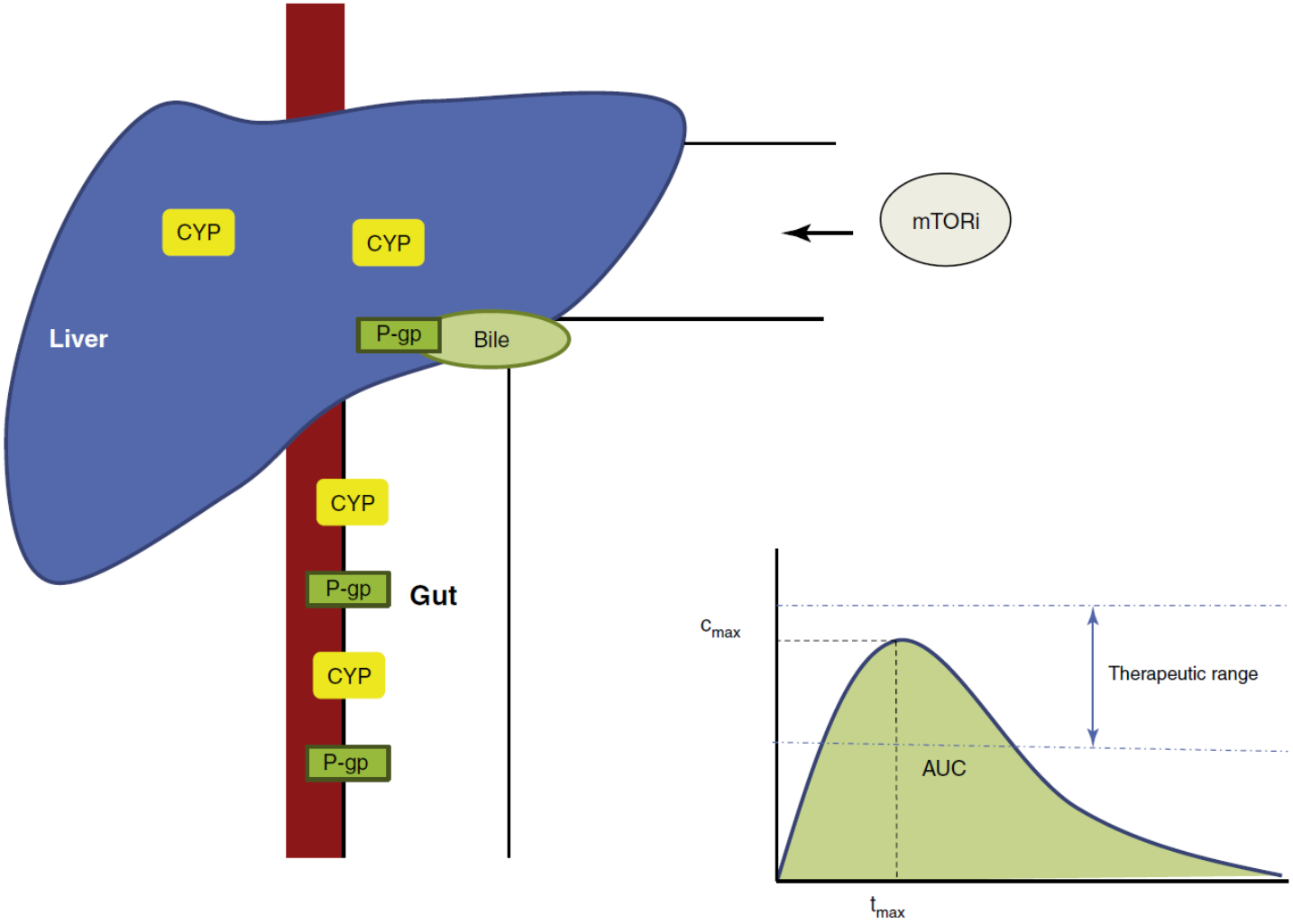
Pharmacologic feature	Sirolimus	Everolimus
Indications related to solid organ transplantation	Prevention of renal graft rejection. In patients at low or moderate risk of rejection: in combination with a calcineurin inhibitor and corticosteroids; withdrawal of the calcineurin inhibitor is possible after 2–4 months. In high-risk patients, the combination must continue for at least 12 months	Prevention of renal, cardiac and liver graft rejection. In patients at low or moderate risk of rejection: in combination with a calcineurin inhibitor (tacrolimus in liver transplantation) and corticosteroids; withdrawal of the calcineurin inhibitor is possible after 2–4 months. In high-risk patients, the combination must continue for at least 12 months
Dosage	6 mg on day 1, then 2 mg daily	0.75 mg bid in renal and cardiac transplantation; 1 mg bid 4 weeks after hepatic transplantation
Bioavailability, ethnic group, food	14% (10%); clearance is 20% higher in Black than in non-Black patients. A high-fat meal reduces the rate of absorption	90% (16%); clearance is 20% higher in Black than in non-Black patients. A high-fat meal reduces the rate of absorption
Protein binding (%)	92	74
Half-life (h)	63	30
Time to peak concentration (h)	1–3	1–2
Metabolism	Sirolimus is a substrate of CYP3A4 and P-glycoprotein. It is metabolized in the intestinal wall and liver and returns from the small intestine to the gut lumen via counter-transport by enterocytes. It is metabolized by O-demethylation and hydroxylation, leading to several metabolites, including hydroxy-, demethyl- and hydroxydemethyl-sirolimus, which can be detected in whole blood. Seven major metabolites may be detected in plasma, fecal and urine samples. However, sirolimus remains the major component in human whole blood, and the main component of sirolimus accounts for 90% of its immunosuppressive activity	Everolimus is a substrate of CYP3A4 and P-glycoprotein. After oral intake, everolimus is the main circulating component in human blood and the only active component. Metabolites of everolimus are inactive (three monohydroxylated metabolites, two hydrolytic ring-opened products and a phosphatidylcholine conjugate of everolimus)
Excretion	91 ± 8% in feces and 2.2 ± 0.9% in urine	98% in the bile and 2% in urine
Interaction	CYP3A4 and P-glycoprotein	CYP3A4 and P-glycoprotein
Therapeutic target (C_{min})	4–12 ng/ml with and 12–20 ng/ml without anticalcineurin inhibitors	3–8 ng/ml
Dosage adjustment	5–7 days after dosage modification	4–5 days after dosage modification
Initial FDA approval	1999	2009

Metabolic pathways of sirolimus



Immunotherapy in Transplantation: Principles and Practice, First Edition. Edited by Bruce Kaplan, Gilbert J. Burckart and Fadi G. Lakkis. 2012 Blackwell Publishing Ltd

Schematic representation of oral administration of mammalian target of rapamycin inhibitors (mTORi), interaction with metabolic enzymes, and effect on blood levels



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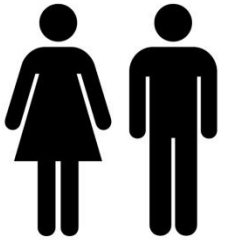
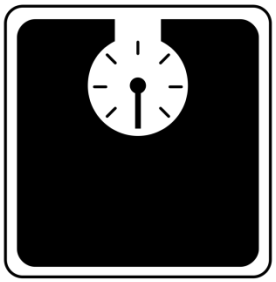


Demographic factors, such as sex, age, or body weight do not affect the pharmacokinetics of sirolimus in adults.



Whereas the tablets are not bioequivalent to the liquid formulation, the 2 mg dose is clinically equivalent and dose adjustment is clinically necessary.

Ingestion with high-fat meals decreases peak concentrations but increases AUC of sirolimus by 23% to 35%.

Take consistently sirolimus (either with or without food) to minimize variability.

We prefer to have patients take sirolimus at 8 AM, usually one to two hours after food ingestion.

Since mTOR inhibitors are highly lipid soluble, has large volume of distribution, extensively protein bound, and partitions into blood, they are not removed by either hemodialysis or continuous hemofiltration.

Therapeutic drug monitoring & Time to sample

- An **excellent correlation** exists between **trough whole-blood levels** and the **area under the time-concentration curve (AUC)** for **sirolimus**.
- It has **narrow therapeutic window** and **variable oral bioavailability**.
- Mean values of **intra-** and **inter-patient variability** in AUC has been determined to be **64%** and **60%**, respectively.
- Because it has a **longer half-life** than the CNI, concentrations are obtained **less frequently** and only **5 to 7 days** after a dose change.

Routine therapeutic drug monitoring of sirolimus blood concentrations is recommended for all patients.

Iranian Journal of Pharmaceutical Sciences
Autumn 2011: 7(4): 237-245
ijps.sums.ac.ir

Original Article

Therapeutic Drug Monitoring of Sirolimus, Correlation With Laboratory Parameters In Transplant Patients

Hashem Montaseri[a], Hasan Merrikhi[b], Mohammad Javad Khoshnoud[b,*], Bita Geramizadeh[c]

Abstract

Sirolimus is a potent immunosuppressive agent administered as prophylactic agent to prevent rejection after organ transplantation. Sirolimus must be used within a narrow therapeutic window. Due to inter- and intra-variability, sirolimus blood concentrations may be affected, therefore, there is no possibility of predicting the sirolimus blood concentrations based on the dose patients received. Therapeutic drug monitoring (TDM) of whole blood is an important part of immunosuppressive therapy and is mandatory for sirolimus dosage individualization. The objective of this study was to present a validated method for the analysis of sirolimus in human blood by LC/MS spectrometry and also evaluation of correlation between blood sirolimus concentration and laboratory parameters. We examined a group of 32 patients receiving sirolimus at different stages after organ (kidney, liver or pancreas) transplantation. The mean sirolimus concentration was 10.2 ng/ml (range: 1.3-30.1 ng/ml). The assay was validated for a linear dynamic range of 1-50 ng/ml. The correlation coefficient (r) was 0.995. The within-run imprecision CV(%) for concentrations (1 and 10 ng/ml) were 14.7 and 2.2%, respectively. The between-run imprecision CV(%) for the same concentrations were 14.8 and 3.4%, respectively. Limit of quantification (LOQ) and limit of detection (LOD) were defined as 1 and 0.3 ng/ml, respectively. Analytic recovery was 98±2% over a range of 1-50 ng/ml. Statistical results showed no correlation between sirolimus blood concentration and the dosage in patients receiving sirolimus. Also, no relationship between drug concentration in blood and laboratory parameters was seen.

Therapeutic drug monitoring & Time to sample

- In clinical practice, sirolimus whole-blood concentrations are being measured by both **chromatographic** and **immunoassay** methodologies.

- The recommended time for collection is **one hour** prior to the **next oral dose**.

- High performance liquid chromatography with ultraviolet detection (**HPLC UV)** or high performance and/or liquid chromatography with **tandem mass spectrometric** detection **(HPLC or LC/MS/MS)** will be **about 20%** lower than **immunoassay techniques** for whole blood concentration.

Whole-blood samples should be collected in tubes with ethylenediaminetetraacetic acid (EDTA) and protected from light.

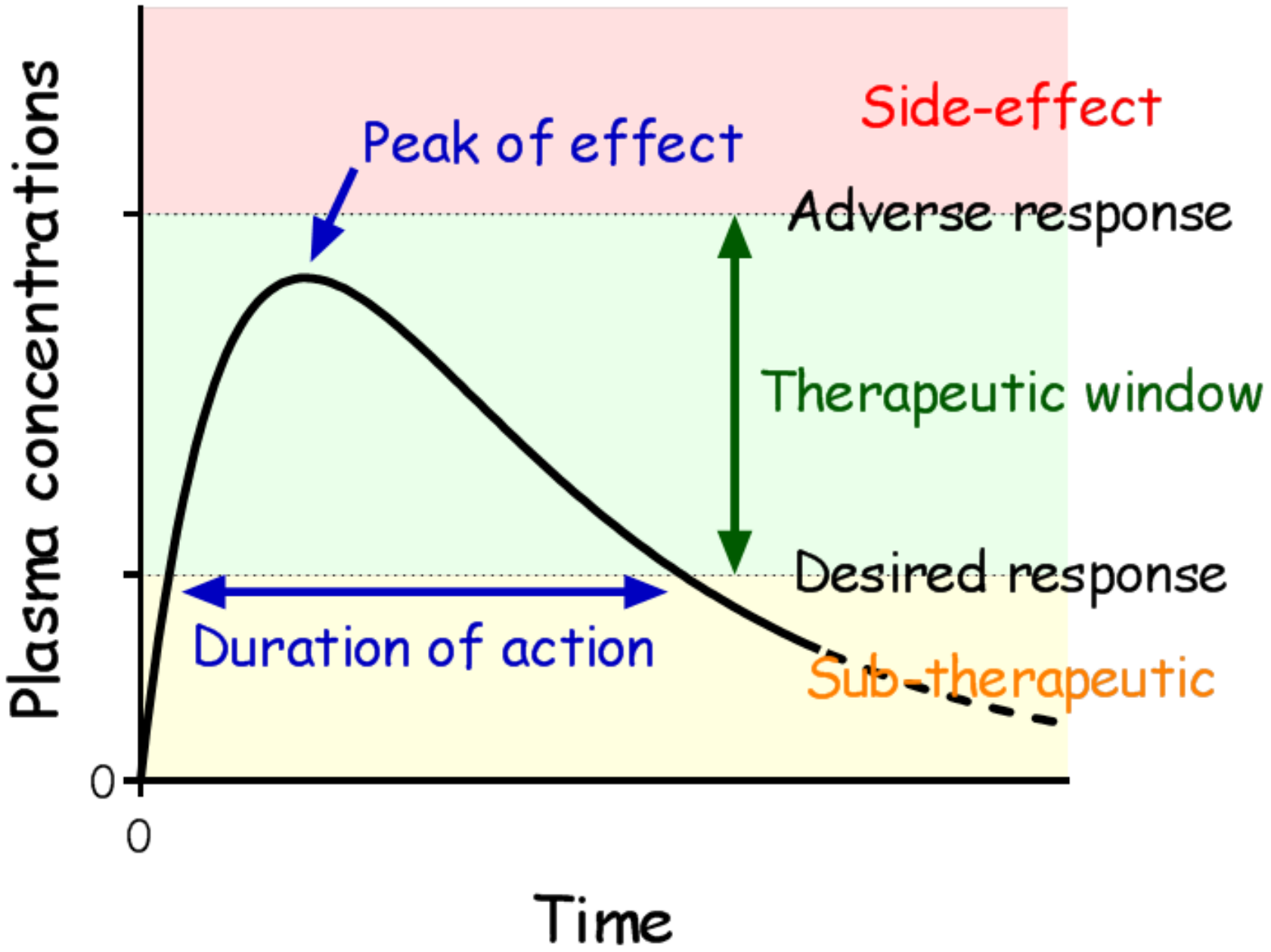
For 24 hours at room temperature

Up to one week at refrigerator

Up to three months at -20°C

Once the **initial dose** titration is complete, monitoring sirolimus trough concentrations **weekly** for the **first month** and **every 2 weeks** for the **second month** appears to be appropriate.

After the **first 2 months** of dose titration, routine TDM of sirolimus is **not necessary** in all patients, but may be warranted to achieve target concentrations in **certain populations** of patients, but the **frequency of further monitoring remains to be determined** and should be individualized.


Plasma concentrations
Side-effect
Peak of effect
Adverse response
Therapeutic window
Desired response
Duration of action
Sub-therapeutic
0
0
Time

- **Serum trough concentration goals for renal transplantation (based on HPLC methods)**

In combination with cyclosporine and prednisone	In combination with azathioprine and prednisone
5 to 15 ng/mL (4 to 12 ng/mL)	**30 ng/mL (16 to 24 ng/mL) for the first two months post-transplant, then reduced to 15 ng/mL (12 to 20 ng/mL) thereafter**

- **Serum trough concentration goals for renal transplantation (based on HPLC methods)**

In combination with tacrolimus and mycophenolate mofetil without steroids

6- 8 ng/mL

In combination with mycophenolate mofetil and steroids
(As a substitute for tacrolimus (starting 4 to 8 weeks post-transplant)

8-12 ng/mL

Conversion from tacrolimus to sirolimus >6 months post-transplant due to chronic allograft nephropathy

4 to 6 ng/mL

Drug interactions

Drug interactions between immunosuppressant agents

Drug interaction	Effect on drug exposure (not unequivocally demonstrated)	Mechanism (presumed)	Clinical risk
Tacrolimus + sirolimus/everolimus	Unchanged or reduced	(CYP3A/P-glycoprotein)	Undetermined
Tacrolimus + corticosteroids	Reduced	CYP3A/P-glycoprotein	Minimal
Ciclosporin + sirolimus/everolimus	Increased	CYP3A/P-glycoprotein	Nephrotoxicity
Ciclosporin + corticosteroids	Unchanged		
Mycophenolic acid + ciclosporin	Reduced	MRP2 inhibition	Graft rejection
Mycophenolic acid + tacrolimus	Unchanged		
Mycophenolic acid + sirolimus	Unchanged		
Mycophenolic acid + corticosteroids	(Reduced)	UGT induction	Minimal
Sirolimus/everolimus + ciclosporin	Increased	CYP3A/P-glycoprotein	Nephrotoxicity
Sirolimus/everolimus + tacrolimus	Unchanged or reduced	(CYP3A/P-glycoprotein)	Undetermined
Sirolimus/everolimus + corticosteroids	Unchanged		

a See text for details.

CYP = cytochrome P450; **MRP2** = multidrug resistance-associated protein 2; **UGT** = uridine diphosphate-glucuronosyltransferase.

Kuypers DR. Immunotherapy in elderly transplant recipients: a guide to clinically significant drug interactions. Drugs Aging. 2009;26:715-37.

Clinically relevant drug interactions with proliferation signal inhibitors

Type of concomitant drug	Concomitant drug	Effect on sirolimus/everolimus exposure	Clinical relevance
Antacids	Magnesium hydroxide	Reduced	Not demonstrated
	Sodium bicarbonate	Reduced	Not demonstrated
	Aluminium hydroxide	Reduced	Not demonstrated
Antiepileptics	Phenytoin	Reduced	High
	Carbamazepine	Reduced	Not demonstrated
	Phenobarbital	Reduced	Not demonstrated
Antifungals	Fluconazole	Increased	High
	Ketoconazole	Increased	High
	Voriconazole	Increased	High
	Itraconazole	Increased	High
	Posaconazole	Increased	Not demonstrated
Antibacterials	Erythromycin	Increased	High
	Clarithromycin	Increased	High
	Azithromycin	Increased	High
	Chloramphenicol	Increased	Not demonstrated
	Rifampicin	Reduced	High
Calcium channel antagonists	Verapamil	Increased	High
	Diltiazem	Increased	High
Food constituents	Grapefruit juice	Increased	Not demonstrated
Herbal preparations	St John's wort (*Hypericum perforatum*)	Reduced	Not demonstrated
Protease inhibitors	Lopinavir/ritonavir	Increased	Not demonstrated
	Nelfinavir	Increased	High
	Saquinavir	Increased	Not demonstrated

Kuypers DR. Immunotherapy in elderly transplant recipients: a guide to clinically significant drug interactions. Drugs Aging. 2009;26:715-37.


DINEM
Nervoxin
Tablet
50 Coated Tablets
Antidepressant
Anxiolytic
Hypericum perforatum

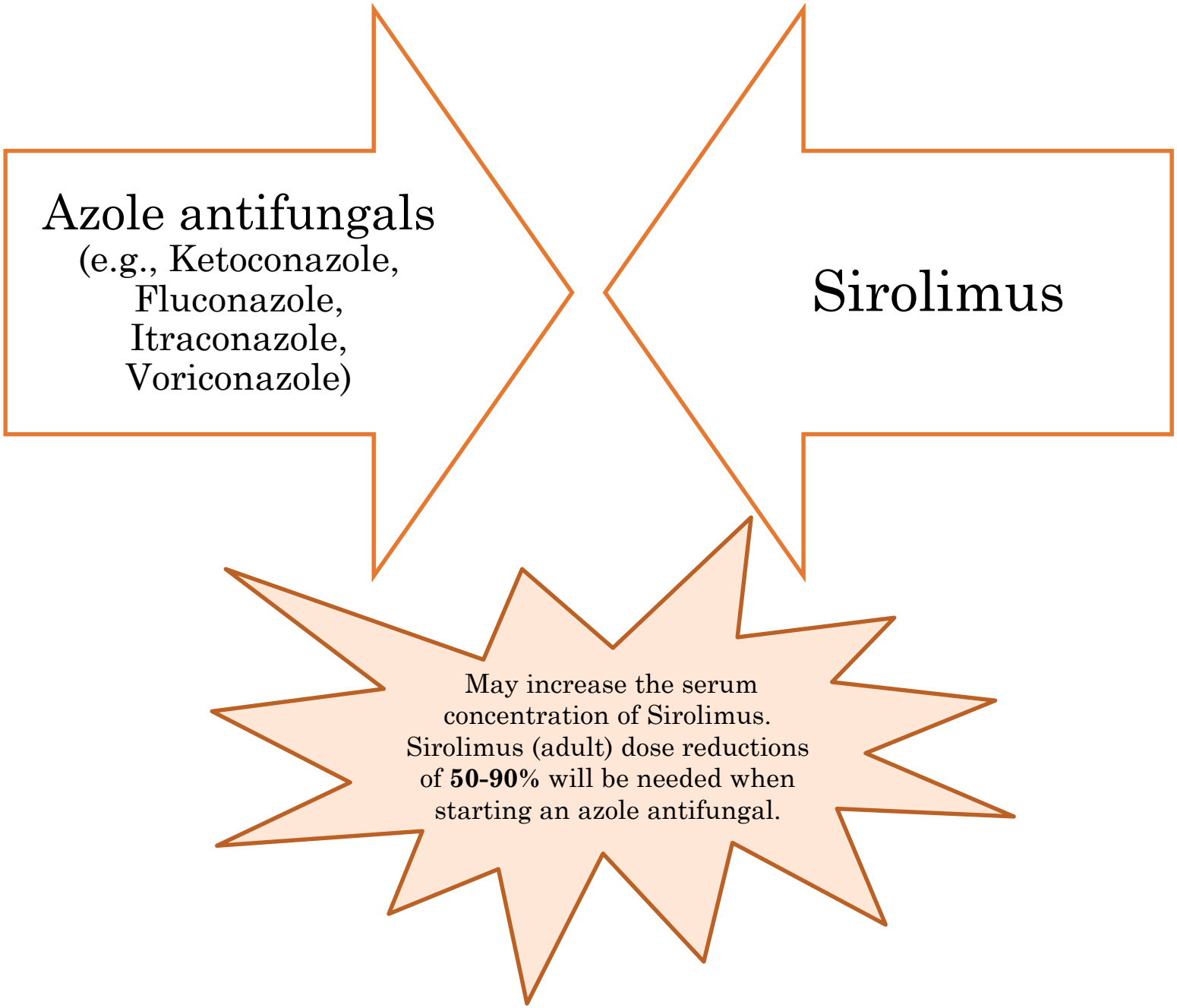

PERFORAN
پرفوران
۲۴
پرفوران

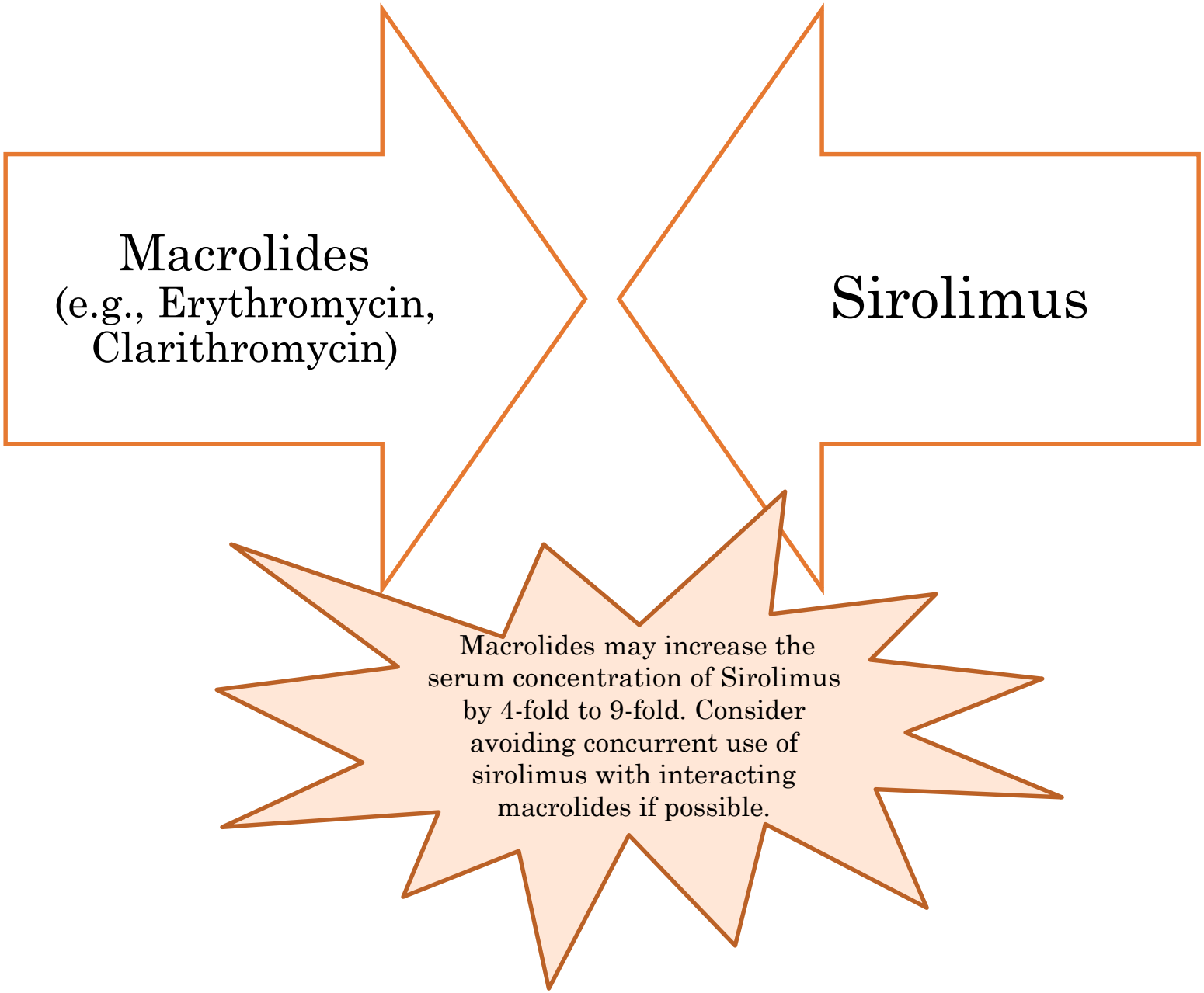

HYPIRAN
هایپیران
۸۴
هایپیران
هایپیران

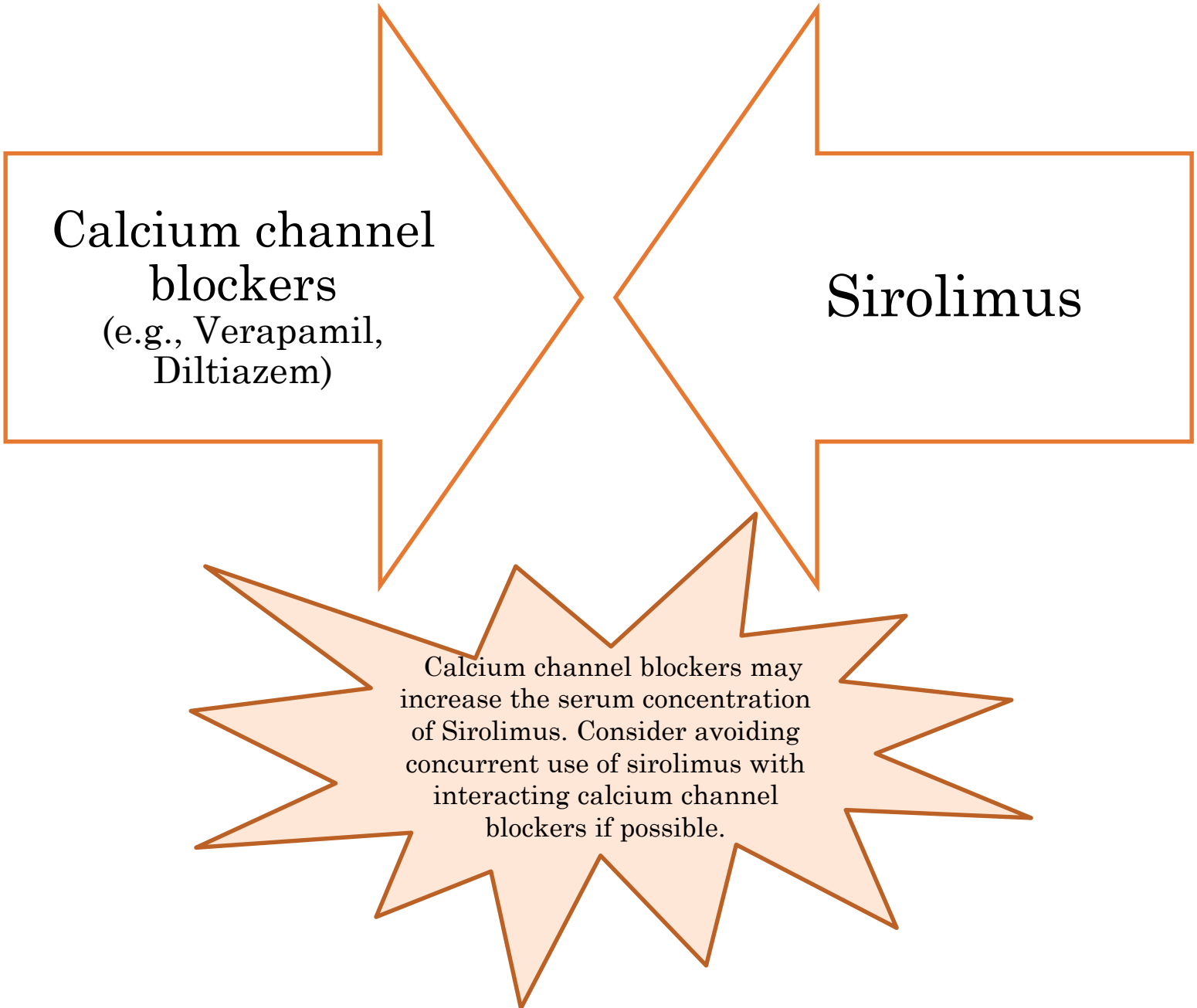

© Alamy

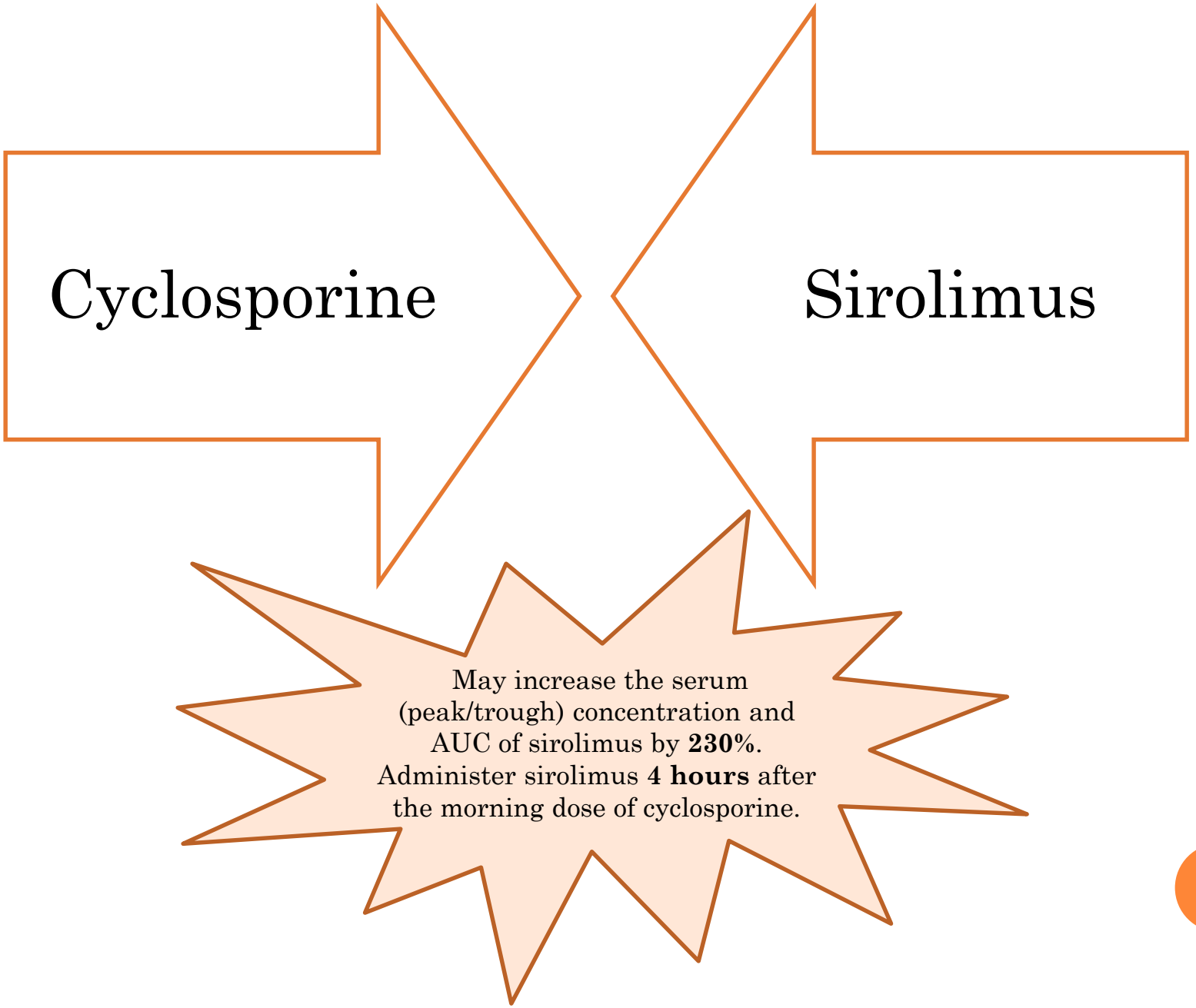
Because rapamycin occupies the same binding protein as tacrolimus, it was originally presumed that it would impair the action of tacrolimus; the drug was thus developed in clinical trials as an adjunctive agent with cyclosporine

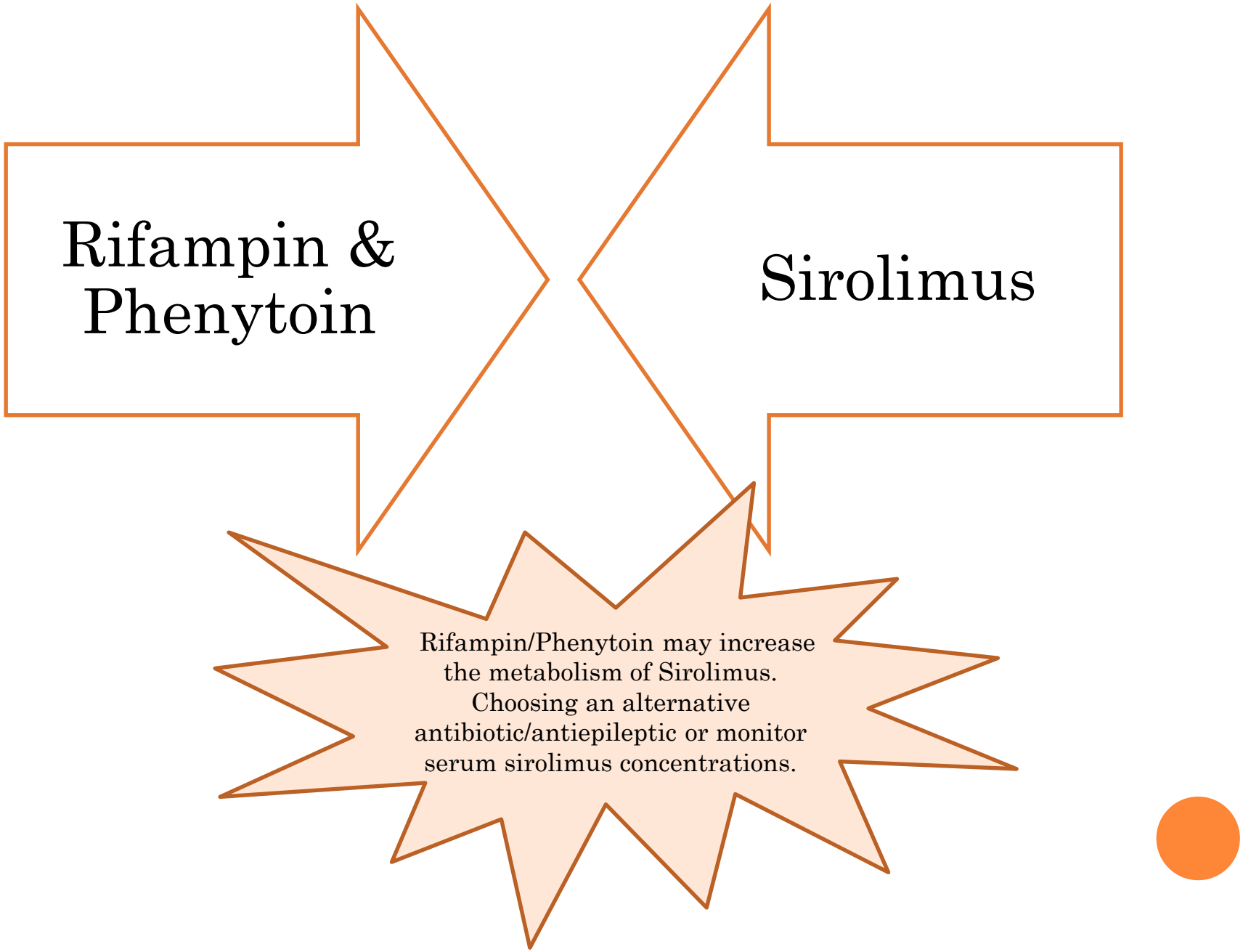
It now appears that the abundance of FKBP in vivo makes it unlikely that there would be inhibitive competition of tacrolimus and sirolimus for their receptor, and the drugs are often used in combination.


Azole antifungals
(e.g., Ketoconazole, Fluconazole, Itraconazole, Voriconazole)
Sirolimus
May increase the serum concentration of Sirolimus. Sirolimus (adult) dose reductions of **50-90%** will be needed when starting an azole antifungal.


Macrolides
(e.g., Erythromycin, Clarithromycin)
Sirolimus
Macrolides may increase the serum concentration of Sirolimus by 4-fold to 9-fold. Consider avoiding concurrent use of sirolimus with interacting macrolides if possible.

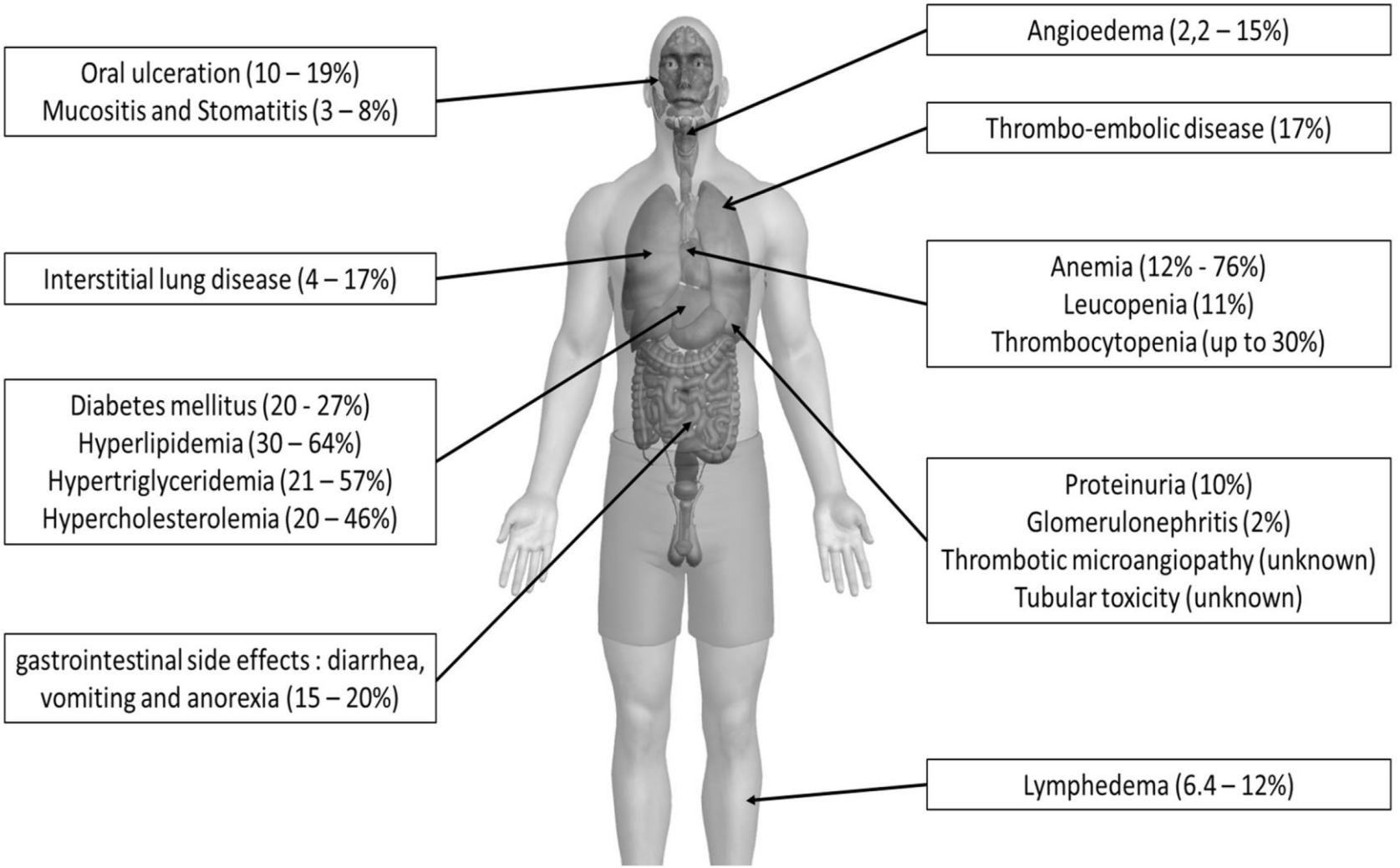

Calcium channel blockers
(e.g., Verapamil, Diltiazem)
Sirolimus
Calcium channel blockers may increase the serum concentration of Sirolimus. Consider avoiding concurrent use of sirolimus with interacting calcium channel blockers if possible.


Cyclosporine
Sirolimus
May increase the serum (peak/trough) concentration and AUC of sirolimus by **230%**.
Administer sirolimus **4 hours** after the morning dose of cyclosporine.


Rifampin & Phenytoin
Sirolimus
Rifampin/Phenytoin may increase the metabolism of Sirolimus. Choosing an alternative antibiotic/antiepileptic or monitor serum sirolimus concentrations.

Adverse drug reactions

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



Side effects

- **Gastrointestinal**

- Common gastrointestinal adverse events include:

  - ✓ Constipation (**28 to 36 percent**)
  - ✓ Diarrhea (**25 to 42 percent**)
  - ✓ Dyspepsia (**17 to 25 percent**)
  - ✓ Nausea (**25 to 36 percent**)
  - ✓ Vomiting (**19 to 25 percent**)

Side effects

- **Hematologic Adverse Events**

- Anemia is characterized by **microcytosis, low serum iron,** and **high serum ferritin levels**.

- It is reported to be **dose dependent**.

- The onset of anemia is rapid after treatment initiation (**about 1 month**), and may persist after treatment cessation.

- Suggested mechanisms include **altered iron metabolism** (including digestive absorption), **increased levels of IL-6 and TNF-α** and **altered differentiation and proliferation of erythroid progenitor cells** via erythropoietin signals.

Side effects

- **Hematologic Adverse Events**

- Concomitant use of **mycophenolate** may be confounding as it is also a known purveyor of **leucopenia**.

- Although **leucopenia** and **thrombocytopenia** may be severe, they resolve after **treatment discontinuation**.

- **Anemia (12.5%)** and **leucopenia (13.9%)** were reported more frequently in patients who switched from c**alcineurin inhibitors to everolimus** than in patients who continued to receive **calcineurin inhibitors**.

Side effects

- **Hyperglycemia**

- Rapamycin has been independently associated with an increased risk of **new-onset diabetes mellitus**.

- In renal transplantation, several trials have reported a marked **increase in new-onset diabetes mellitus** in patients who converted to mTOR inhibitor.

- A combination of **insulin resistance** and **dysfunctional insulin secretion,** as in the general population, remains the most likely mechanism of mTOR inhibitor-induced diabetes.

Side effects

- **Hypophosphatemia**

- **Phosphate levels** are often reduced during mTORi therapy.
- Symptoms of hypophosphatemia, including **fatigue** and **muscle weakness**, are not specific and are **rarely severe**.
- **Oral supplementation** is sufficient in the vast majority of the cases.
- The **exact mechanism** of this toxicity is **not known**.

Side effects

- **Dyslipidemia**

- In patients treated with mTOR inhibitors, **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.

- Several mechanisms may contribute to dyslipidemia via mTOR inhibition, including **reduced circulating lipoprotein catabolism** via **inhibition of lipase activity**.

The annual risk of a cardiovascular event is almost 50-fold greater for a kidney transplant patient than for the general population, and these events account for over one-third of all deaths.

Immunosuppressive strategies to minimize sirolimus doses may help control hyperlipidemia.

Statins and fibrates are effective in reducing hypercholesterolemia and hypertriglyceridemia, respectively.

Side effects

- **Renal Adverse Events**

- In clinical studies with sirolimus, the incidence of **proteinuria** has been estimated at **10%**, with **complete nephrotic s**yndrome in **2%** of the overall population.

- **Proteinuria** has been associated with chronic allograft injury and development of glomerular lesions.

- **Everolimus** increased the risk of **proteinuria** as compared with **mycophenolate** in kidney transplantation.

- This risk seems dose dependent, as **everolimus levels > 8 ng/ml** were significantly associated with **proteinuria**.

mTOR inhibitors may induce de novo proteinuria or aggravate pre-existing proteinuria.

Side effects

- **Renal Adverse Events**

- Sirolimus enhances **thrombotic microangiopathy (TMA)** by inhibiting the **repair of endothelial lesions** produced in marginal kidneys exposed to the drug in the context of transplantation.

Downregulation of vascular endothelial growth factor (VEGF)	Potentiating the effects of calcineurin inhibitors
Increases the expression of transforming growth factor-β1	Inhibits mitochondrial energy metabolism

After proteinuria onset, management of mTOR inhibitors relies on 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.

An alternative to treatment discontinuation is to switch to a regular calcineurin inhibitor, which may reverse proteinuria, regardless of its initial severity.

Side effects

- **Renal Adverse Events**

- Nonspecific management of proteinuria:

1. Blood pressure control with either angiotensin II-receptor blockers or angiotensin-converting enzyme inhibitors
2. Dietary restriction of **sodium target (1.5 to 2 g per day) and protein intake (0.8 to 1 g/kg per day)**
3. Control of LDL cholesterol with statins

Patients with GFRs < 40 mL/min was halted because of excess pneumonia and death among those in whom the sirolimus substitution had been performed.

We do not use sirolimus in patients with proteinuria >110 mg/day, unless there are other overriding concerns.

Side effects

- **Dermatologic and Mucosal Adverse Events**

- **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**.

- Mucositis 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.

Side effects

- **Dermatologic and Mucosal Adverse Events**

- More rarely, **larger lesions > 1 cm in diameter** may **last longer** and affect the **dorsum of the tongue**, **hard palate** or **gingiva**.

- **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**.

- It is **unclear** whether the incidence of these events is related to the **type of mTOR inhibitor used**.

Side effects

- **Dermatologic and Mucosal Adverse Events**

- Less severe dermatologic manifestations of rapalogs include **acne-like dermatitis (up to 46%)**, **pruritus**, **rash** (**3-68%**), and **nail changes**.

- **Acne-like lesions** and **folliculitis** have a strong **male predominance** and **do not seem** to be related to the **dose of mTORi.**

- They often **resolve spontaneously**, as the **epidermal growth factor** is blockaded by the treatment.

Side effects

- **Dermatologic and Mucosal Adverse Events**

- Preventive measures include:

1. Oral hygiene (gentle brushing, mild toothpaste and mouthwashes)
2. Food and beverage adaptation (avoiding spicy, acidic or very hot food, alcohol)
3. Avoiding other eluding agents such as iodine, peroxide and antifungals

Side effects

- **Dermatologic and Mucosal Adverse Events**

- Medical treatments of aphthous ulcers include:

1. Topical steroids (e.g., clobetasol, triamcinolone)
2. Non-steroidal anti-inflammatory drugs
3. Anesthetics
4. Decreasing or withdrawing treatment

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

Other treatments include colchicine, pentoxifylline and azathioprine.

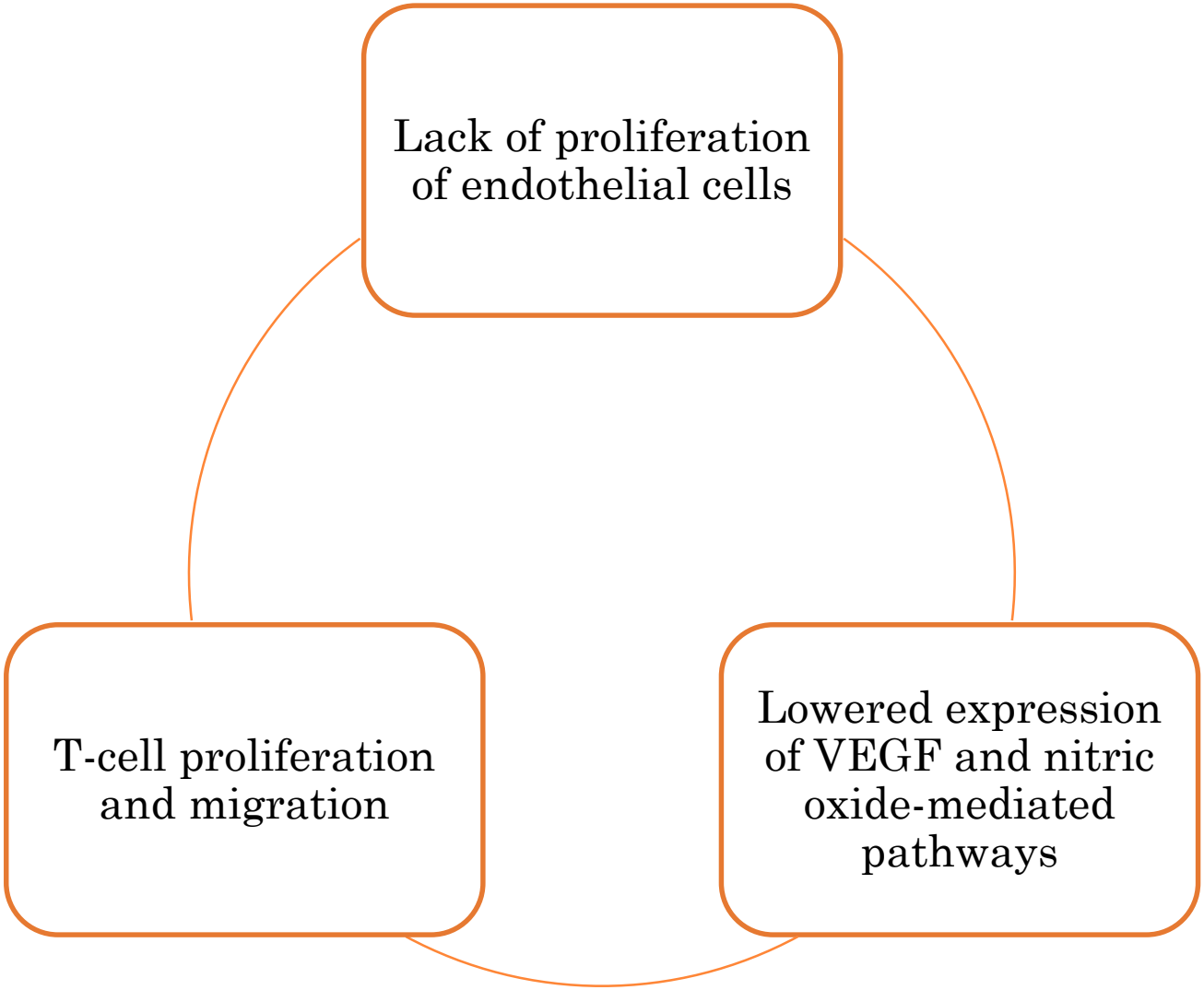
Side effects

- **Wound-Healing Adverse Events**

- As healing processes are altered, **dehiscence, hernia, lymphoceles** and **wound infections** may occur.

- Reported rates of these kinds of events are **15–32%** in kidney transplantation.

- **Lymphoceles** and **hernias** appear to be **dose dependent**.


Lack of proliferation of endothelial cells
Lowered expression of VEGF and nitric oxide-mediated pathways
T-cell proliferation and migration

For patients scheduled for certain elective surgical procedures (e.g., bowel anastomosis, hernia repair, skin flap) it may wise to switch patients off mTORs a week prior to the procedure and recommence after wound healing.

For emergent surgery, the switch from mTORs to CNI, mycophenolate or azathioprine can take place immediately postoperatively.

Side effects

- **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)**.

Side effects

- **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**.

Whether interstitial lung disease is due to "dose-dependent" toxicity or to an immune-mediated disorder is controversial.

Side effects

- **Pulmonary Adverse Events**

- Causal relationship may be considered using the usual rules: **delayed occurrence**, **differential diagnosis** has been performed and **resolution of symptoms within 3 months after drug cessation.**

- 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 (2-3 weeks) 2-4 months.

Side effects

- **Angioedema**

- Case reports in renal transplantation suggest a **causal role** for sirolimus due to **temporal association** (appearance after introduction, resolution after discontinuation).

- 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.**

Side effects

- **Lymphedema**

- It presents as **fluid retention** localized to the **limbs** or **eyelids** with associated **tissue swelling**.

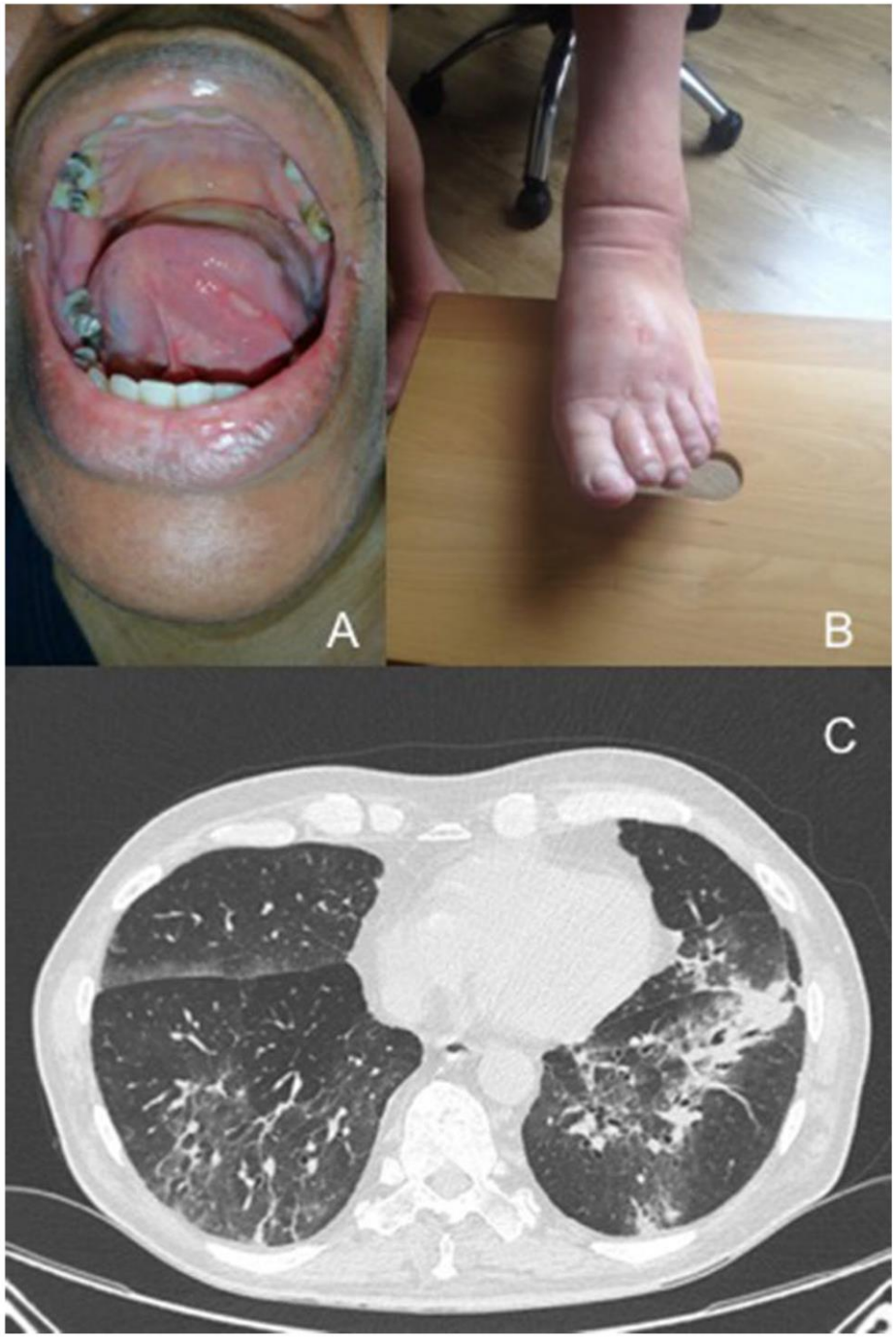
- The involvement of mTOR inhibitors via the impairment of **lymphoangiogenesis** explains how **lymphatic fluid leaks** and how lymphocele may occur.

- mTOR inhibitors blockade **VEGF C** and **D** and thus inhibit **lymphoangiogenesis**.

- **Lymphatic healing** after surgery may be **further impaired**.

Unlike other adverse events, although 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.


A
B
C

Side effects

- **Fertility**

- The spontaneous fathered **pregnancy rate** was found to be **decreased** by **15-fold** with mTORi treatment compared with a sirolimus-free regimen.

- The **testicular insufficiency** related to mTOR inhibition is due to the **abolition of spermatogonial cell proliferation** by blocking the PI3K/AKT pathway.

- The **full recovery of spermatogenesis** is **uncertain** and may take **many months**.

Pregnancy & Lactation

1. • Pregnancy Risk Factor: C
2. • Adverse events have been observed in animal reproduction studies.
3. • Effective contraception must be initiated before therapy with sirolimus and continued for **12 weeks** after discontinuation.
4. • Women post-transplant who wish to conceive be switched prior to conception **from sirolimus** to **cyclosporine** or **tacrolimus**.

Because almost no information is available on the use of sirolimus during breastfeeding, an alternate drug may be preferred, especially while nursing a newborn or preterm infant.


Thank
You