Immunosuppressive Drugs In the setting of liver transplantation

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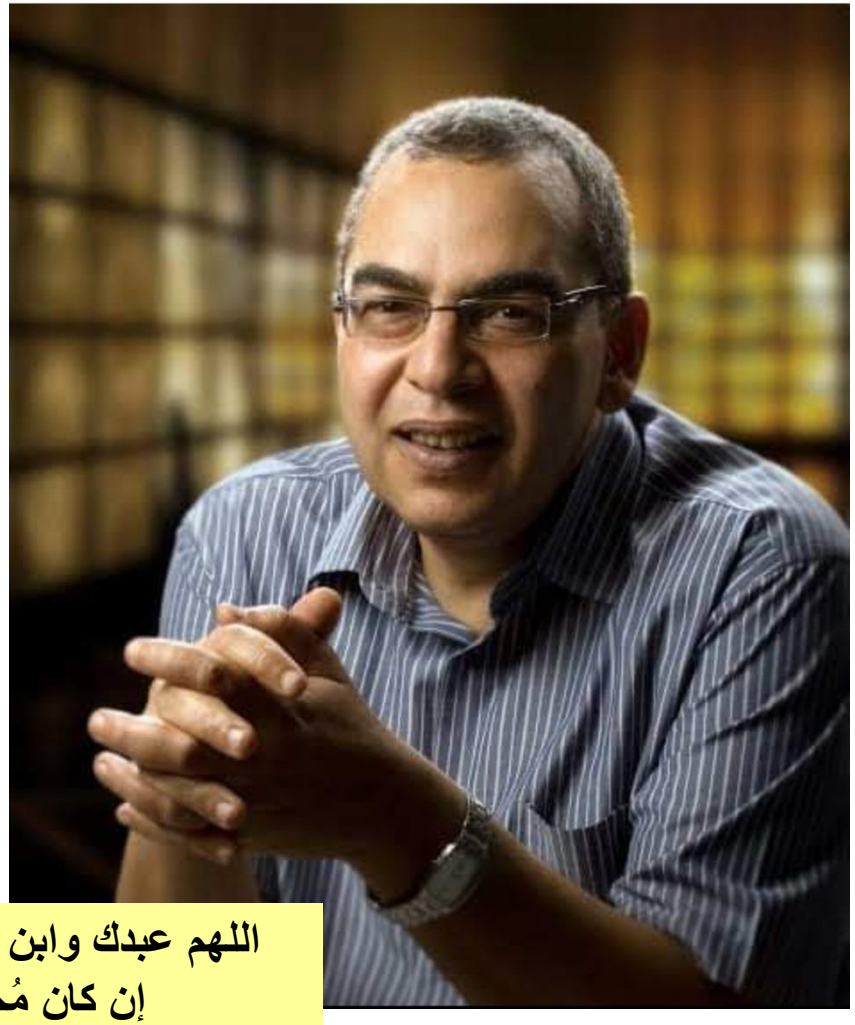
"لست متأكداً من وجودي طويلاً بالدنيا، لكنني أتمنى أن أكون قد غرست داخل الجميع ذكرى طيّبة تبقى للأبد."

#أحمد_خالد_توفيق



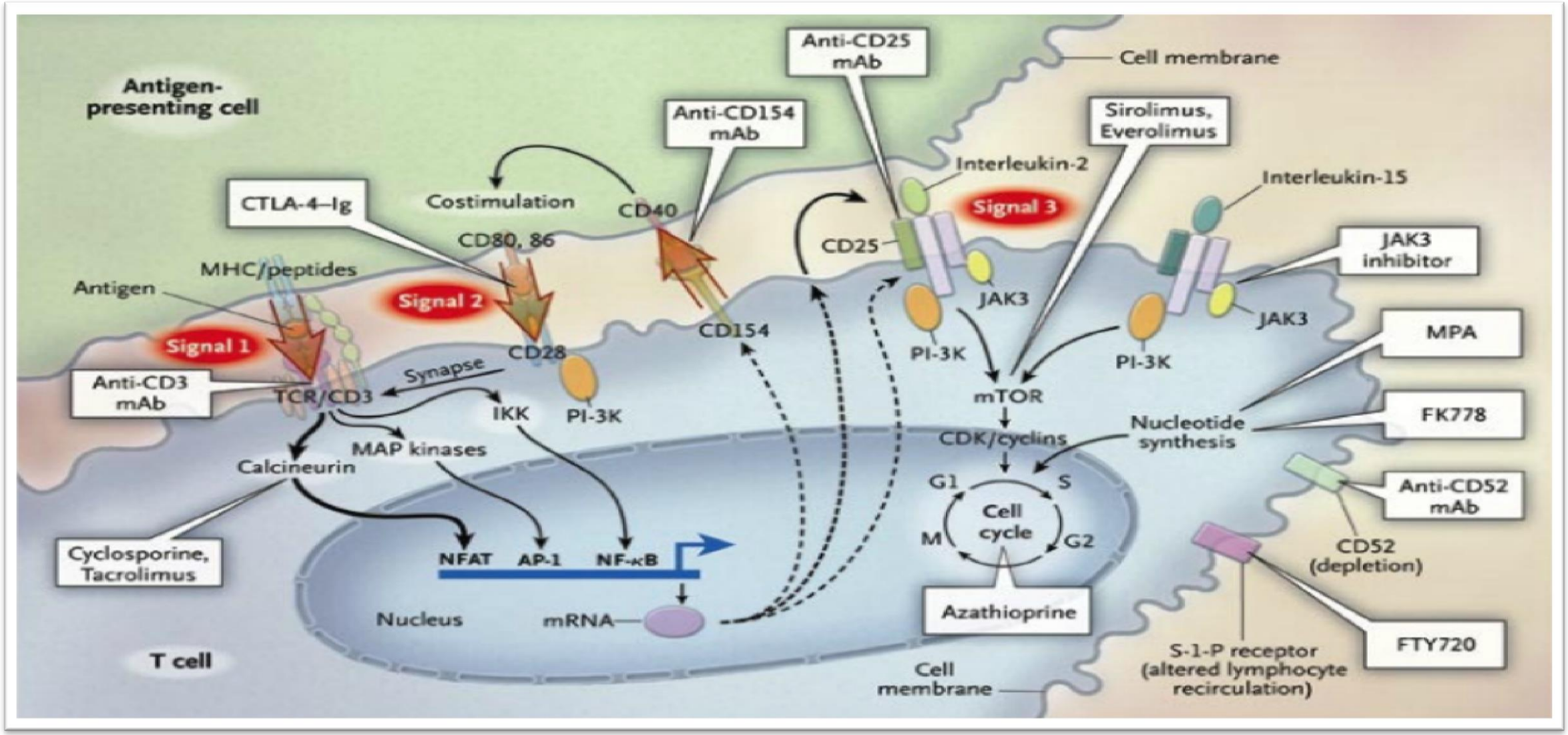
اللهم عبدك وابن عبدك وابن أمتك احتاج إلى رحمتك وأنت غني عن عذابه، إن كان مُحسناً فزده في حسناته، وإن كان مُسيئاً فتجاوز عنه

Why do we use immunosuppressive drugs

The answer

To prevent and treat acute cellular rejection

To keep the health of the graft


Antigen-presenting cell
Anti-CD25 mAb
Cell membrane
Anti-CD154 mAb
Sirolimus, Everolimus
Interleukin-2
Interleukin-15
Costimulation
CD40
CTLA-4–Ig
CD80, 86
Signal 3
CD25
JAK3 inhibitor
MHC/peptides
Antigen
Signal 2
JAK3
JAK3
Signal 1
CD154
MPA
CD28
PI-3K
PI-3K
Synapse
Anti-CD3 mAb
TCR/CD3
IKK
PI-3K
mTOR
FK778
Nucleotide synthesis
MAP kinases
CDK/cyclins
Calcineurin
G1
S
Anti-CD52 mAb
Cell cycle
M
G2
CD52 (depletion)
Cyclosporine, Tacrolimus
NFAT
AP-1
NF-κB
Azathioprine
Nucleus
mRNA
FTY720
S-1-P receptor (altered lymphocyte recirculation)
T cell
Cell membrane

Immunosuppressive agent	Target pathway
PHARMACOLOGICAL	
Corticosteroids	(a) Inhibits cytokine transcription by antigen presenting cell (b) Selective lysis of immature cortical thymocytes
Calcineurin inhibitors (cyclosporine/neoral and tacrolimus/Prograf/Fk506)	Inhibits Signal 2 transduction via T cell receptor
Mammalian Target of rapamycin inhibitors (sirolimus/rapamycin, everolimus)	Inhibits signal 3 transduction via IL-2 receptor
Azathioprine (Imuran)	Inhibits purine and DNA synthesis
Mycophenolic acid (cellcept)	Inhibits purine and DNA synthesis
BIOLOGICAL	
Anti-CD3 monoclonal antibodies (OKT3)	(a) Causes depletion and receptor modulation in T cell (b) Interferes with signal 1
Antithymocyte globulin (ATG)	(a) Causes depletion and receptor modulation in T cells (b) Interferes with signal 1, 2 and 3 (c) Inhibits lymphocyte Trafficking
Anti IL-2 alpha chain receptor antibodies (Basiliximab, Daclizumumab)	Inhibits T cell proliferation to IL-2 (signal 3)
Anti-CD52 monoclonal antibodies (campath 1-H)	Causes depletion of thymocytes, T cells, B cells (not plasma cells) and monocytes

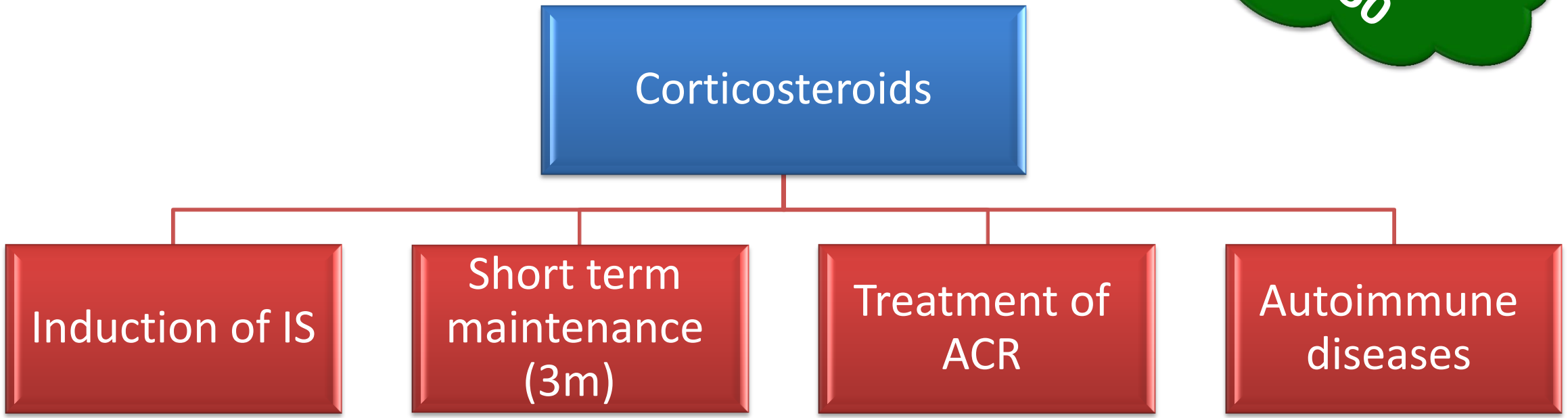
Hard"s" of LT

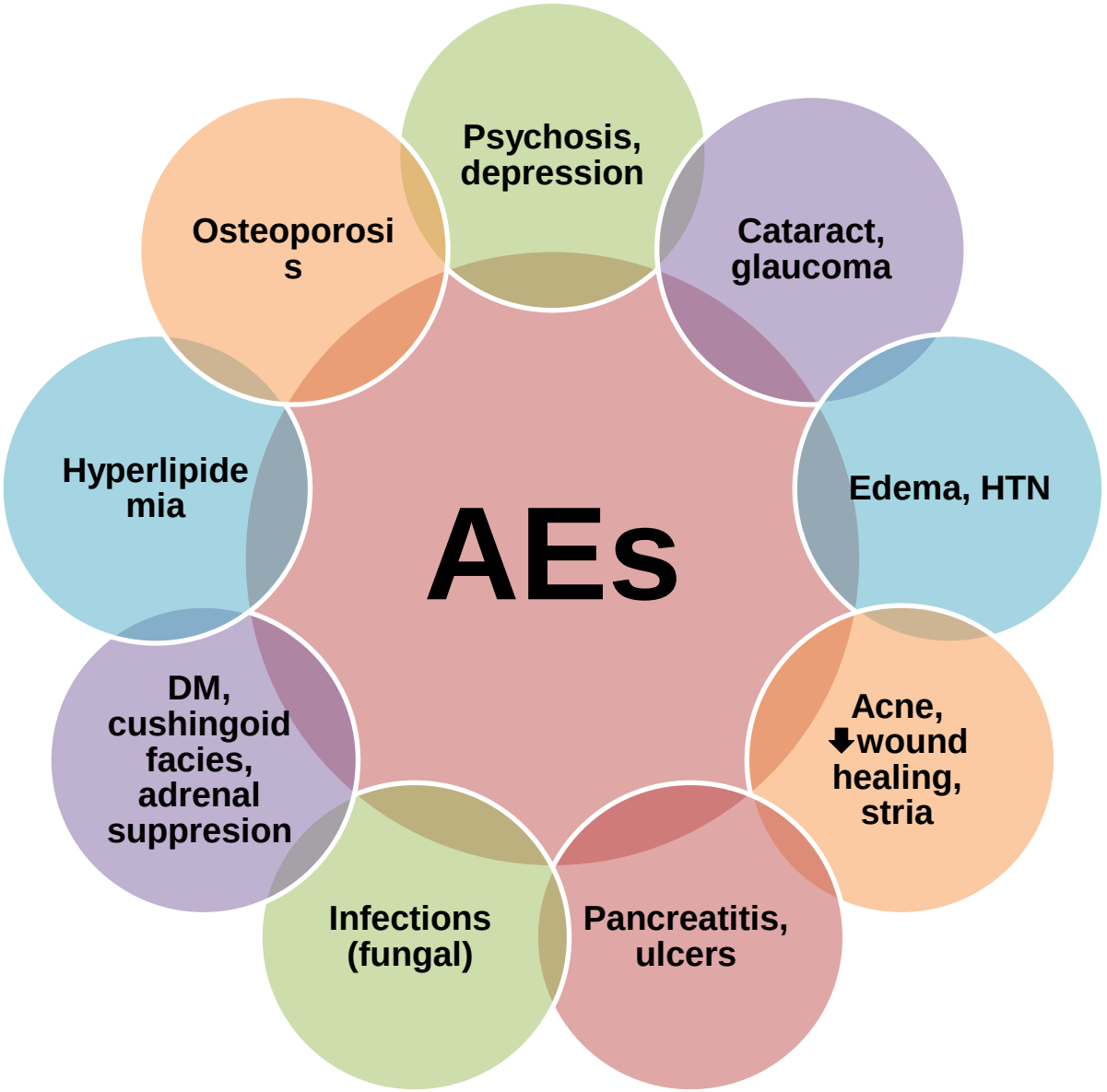
- **Hard** for the patient to hear he needs LT
- **Hard** to find donor
- **Hard** operation
- **Hard** times with immunosuppressive drugs.
- **Hard** times with complications
- **IF YOU WANT LIFE YOU HAVE TO PAY:**
  - Money
  - Stressful life
  - Cope with AEs


DEPTH
GAUGE
90 ft.

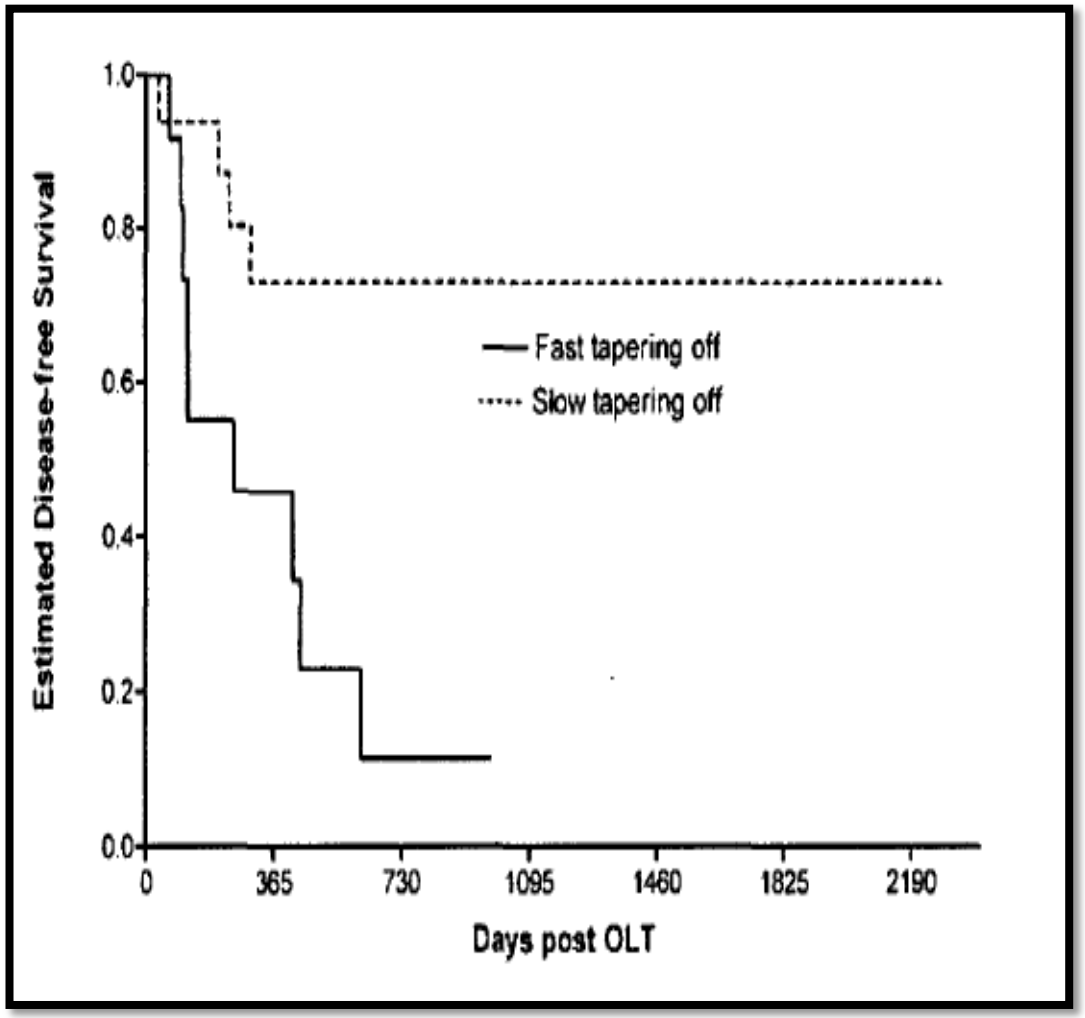
1st Group

Steroids: first used IS drug 1940-50





HCV recurrence during tapering



? Steroids minimization protocols

Calcineurin Inhibitors (CNIs)


Prograf 1 mg Capsules
1 mg
tacrolimus
Immunosuppressant
Reg. No. : DKI1108000201B1
5 blisters @ 10 capsules
astellas


Prograf 0.5 mg Capsules
0.5 mg
tacrolimus
Immunosuppressant
Reg. No. : DKI1108000201A1
5 blisters @ 10 capsules
astellas

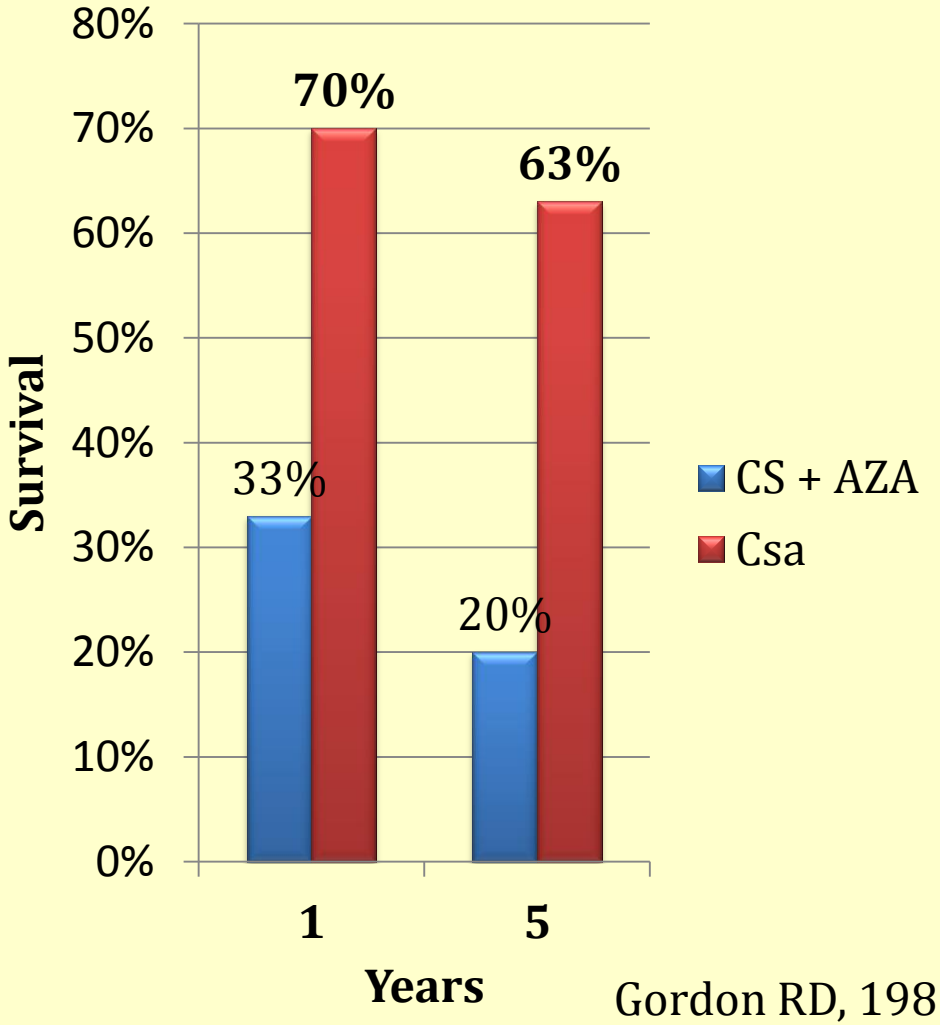

Prograf® Granules
(tacrolimus for oral suspension)


Advagraf 5 mg
Advagraf 3 mg
Tacrolimus
Advagraf 1 mg
Advagraf 0,5 mg

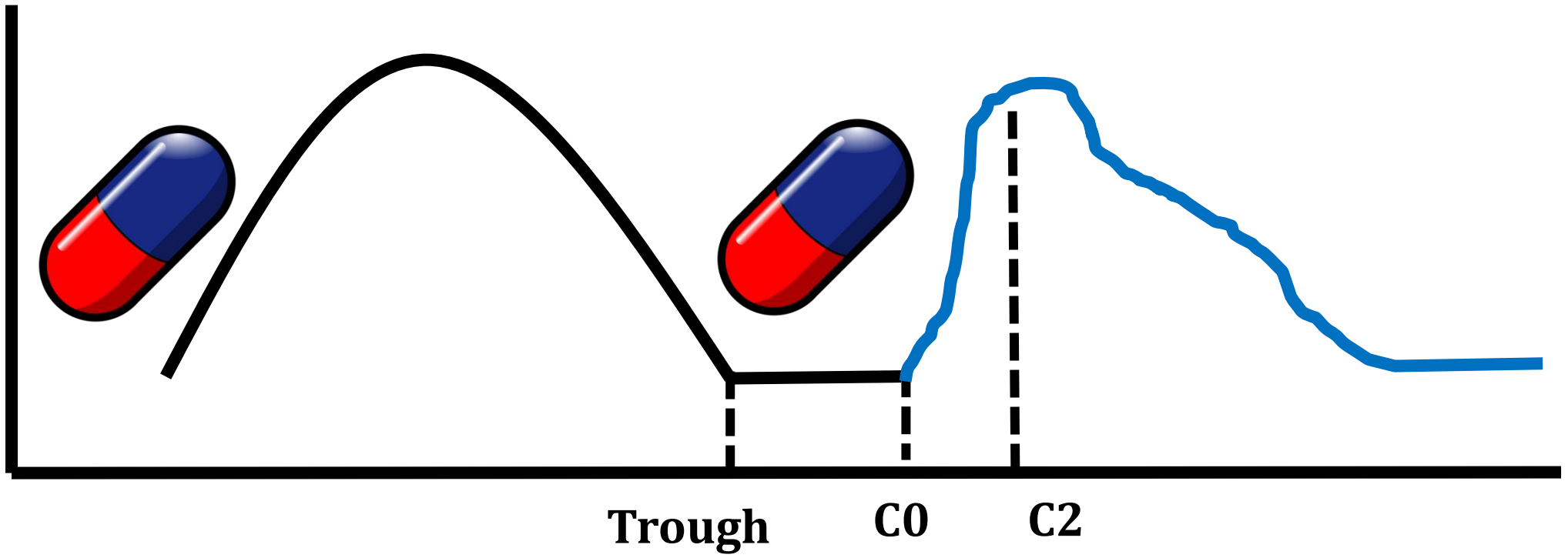

NOVARTIS
Sandimmun Neoral®
Ciclosporin
100 mg/ml
50 mg
100 mg
10 mg
25 mg

Cyclosporine (Csa)

- It is derived from *Tolypocladium inflatum*.
- **1976:** discovery of immunosuppressive activity.
- **Breakthrough in IS.**
- **1982:** approved in LT.



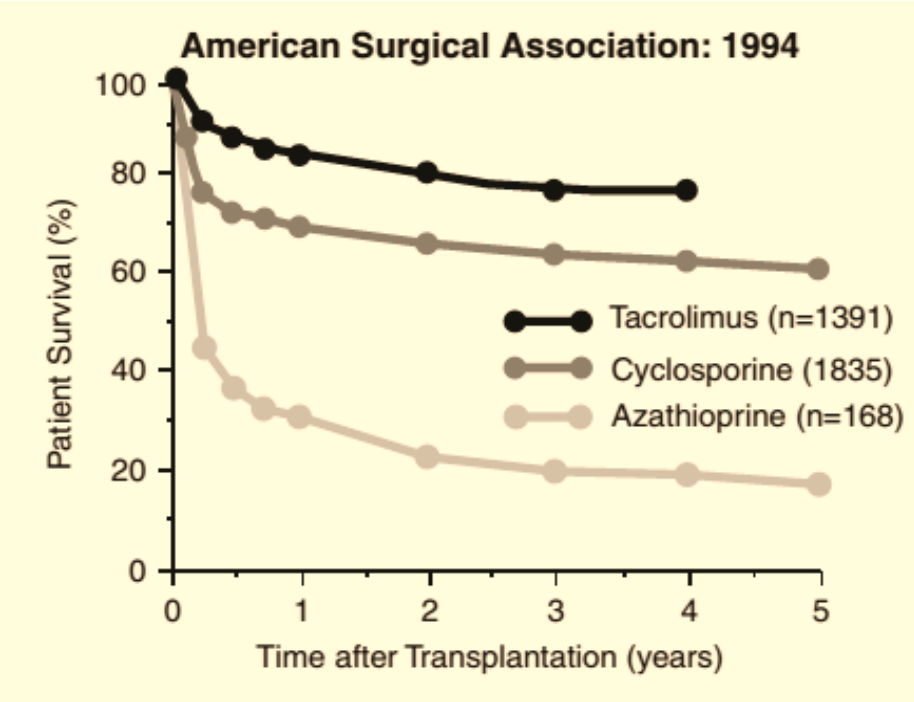
Gordon RD, 1987



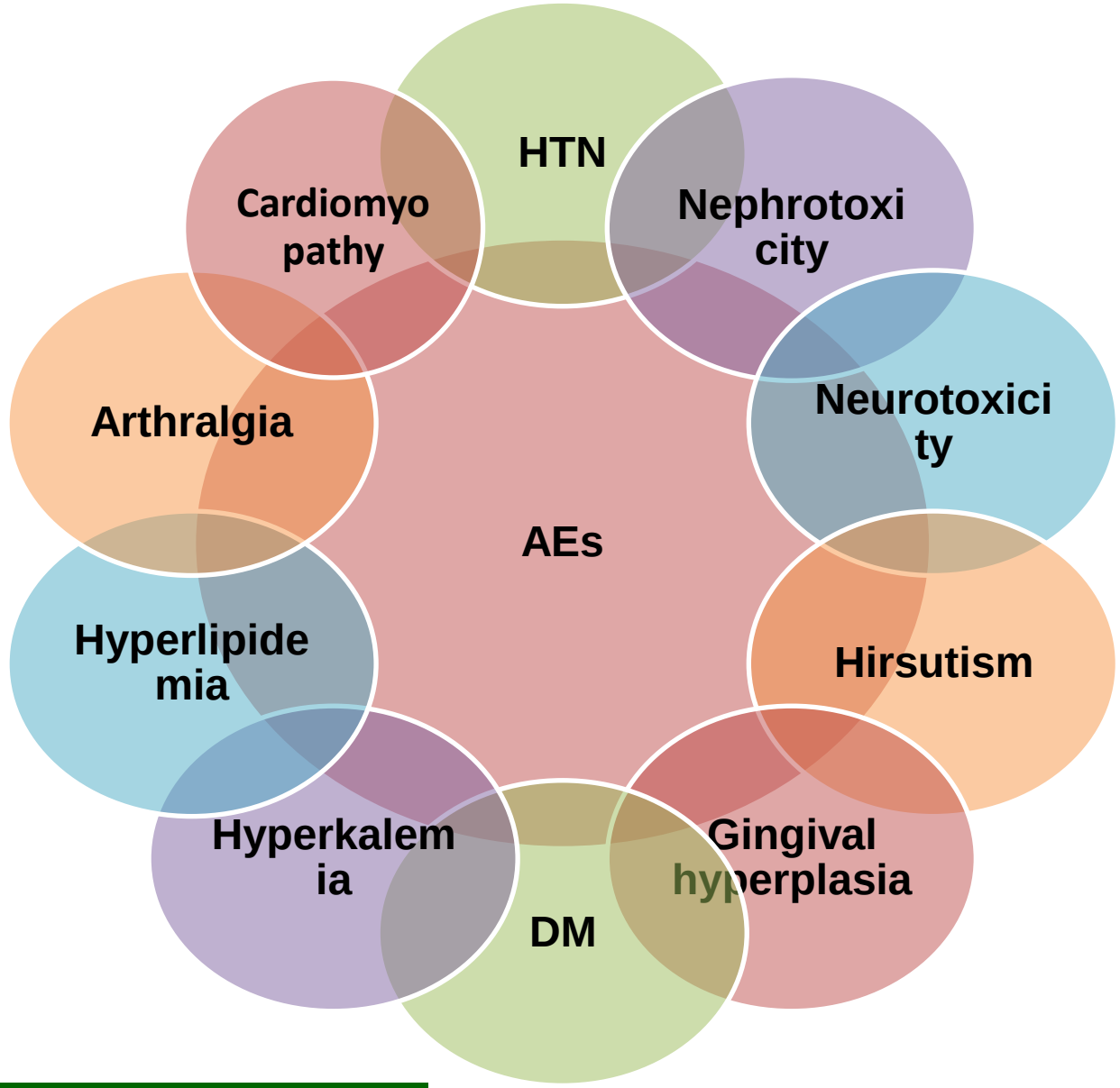
- Dosage: 10-15 mg/kg/day divided into 2 doses.
- **Adjustment of the oral dose is based on:**
- **C0:**
  - 12-hour trough level.
  - Target trough levels vary widely; do not accurately reflect the area under the curve for cyclosporine exposure in individual patients.
  - 250-350 ng/mL during weeks 1-2
  - 200-300 ng/mL during weeks 3-4
  - 150-250 ng/mL during weeks 5-24
  - 100-200 ng/mL during weeks 25-52.
- **C2:**
  - blood concentration at 2 hours after the dose.
  - a better measure of the area under the curve, and may be more useful in controlling toxicity and enhancing efficacy.
  - 850 to 1400 ng/mL at 2 hours after dose from 0 to 3 months posttransplant.

Tacrolimus (TAC).

- **Tacrolimus (Prograf, FK506)**
- It is derived from the fungus *Streptomyces tsukabaensis*.
- **100 times more potent than Csa.**
- **1994: approved in LT**
- **Trough Goals**
  - Early Post-OLT – 10-15 ng/ml
  - 3-6 Months – 8-10
  - >6 Months – 5-7 (variable)



? ADVAGRAF



TAC more diabetogenic and neurotoxic than Csa

Drugs That May Increase Tacrolimus and Cyclosporine Blood Concentrations (inhibit the P450 pathway)

Calcium Channel Blockers	Antifungal Agents	Macrolide Antibiotics
• Diltiazem • Nicardipine • Nifedipine • Verapamil	• Fluconazole • Itraconazole • Ketoconazole • Voriconazole. • Clotrimazole	• Clarithromycin • Erythromycin • Troleandomycin • Azithromycin • Telithromycin
Prokinetic Agen	Miscellaneous Agents	
• Cisapride • Metaclopramide	• Amiodarone • Cimetidine • Methylprednisolone • Omeprazole • Protease inhibitors Nefazodone • Ethinyl estradiol	• Grapefruit • grapefruit juice

Drugs That May Decrease Tacrolimus and Cyclosporine Blood Concentrations (stimulate P450 Pathway)

Anticonvulsants	Antibiotics	Herbal Preparations	Miscellaneous Drugs
• Carbamazepine • Phenobarbital • Phenytoin • Fosphenytoin	• Rifabutin • Rifampin • Rifapentine	• St. John’s Wort	• Probucol • Terbinafine • Orlistat. • Octreotide • ticlopedine

No Interaction Expected

Ledipasvir/Sofosbuvir

Tacrolimus

No Interaction Expected

Daclatasvir

Ciclosporin (Cyclosporine)

Potential Interaction

Daclatasvir

Everolimus

Coadministration has not been studied but may increase everolimus concentrations due to P-gp inhibition by daclatasvir. Concentration of daclatasvir may also increase due to inhibition of CYP3A4 by everolimus. If coadministration cannot be avoided, therapeutic drug monitoring of everolimus should be performed along with close monitoring for daclatasvir related side effects and toxicities.

Do Not Coadminister

Ombitasvir/Paritaprevir/r + Dasabuvir

Everolimus

No Interaction Expected

Ledipasvir/Sofosbuvir

Ciclosporin (Cyclosporine)

No Interaction Expected

Daclatasvir

Ciclosporin (Cyclosporine)

Do Not Coadminister

Ombitasvir/Paritaprevir/r + Dasabuvir

Tacrolimus

No Interaction Expected

Ledipasvir/Sofosbuvir

Sirolimus

Potential Interaction

Ledipasvir/Sofosbuvir

Everolimus

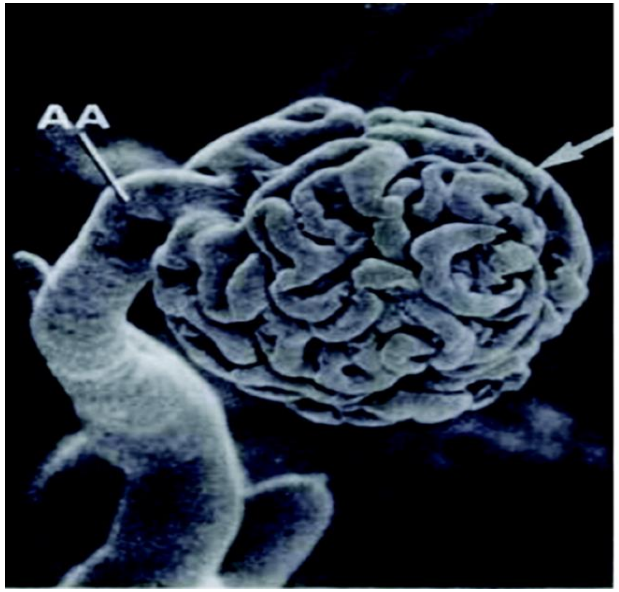
No Interaction Expected

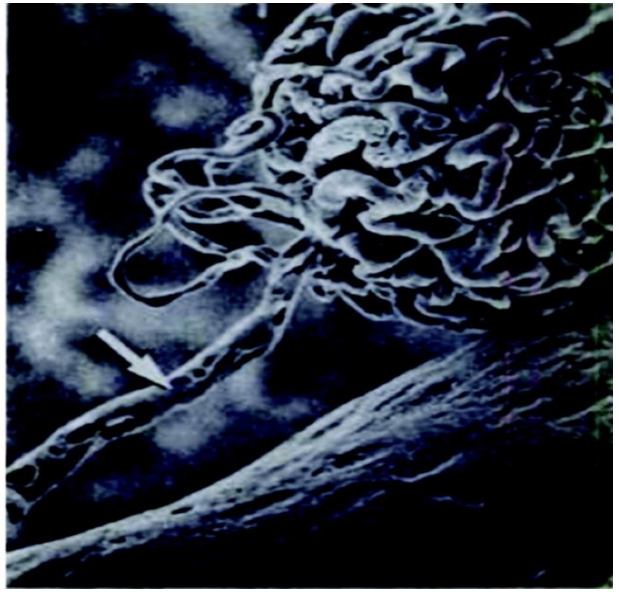
Daclatasvir

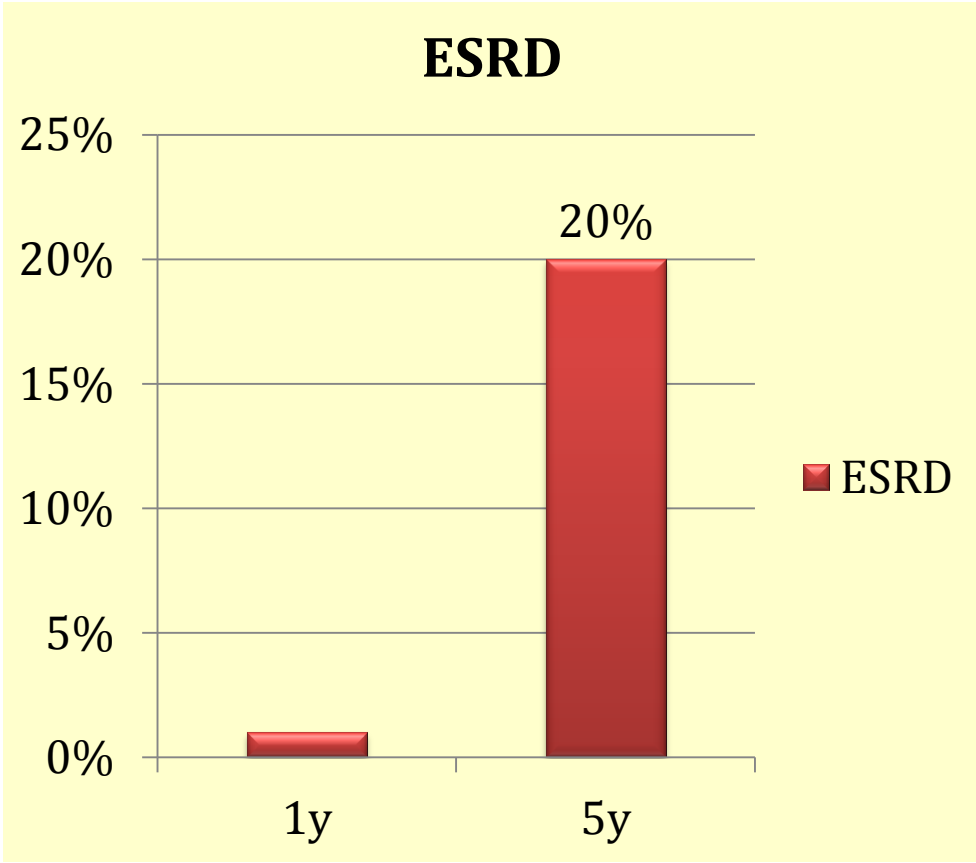
Tacrolimus

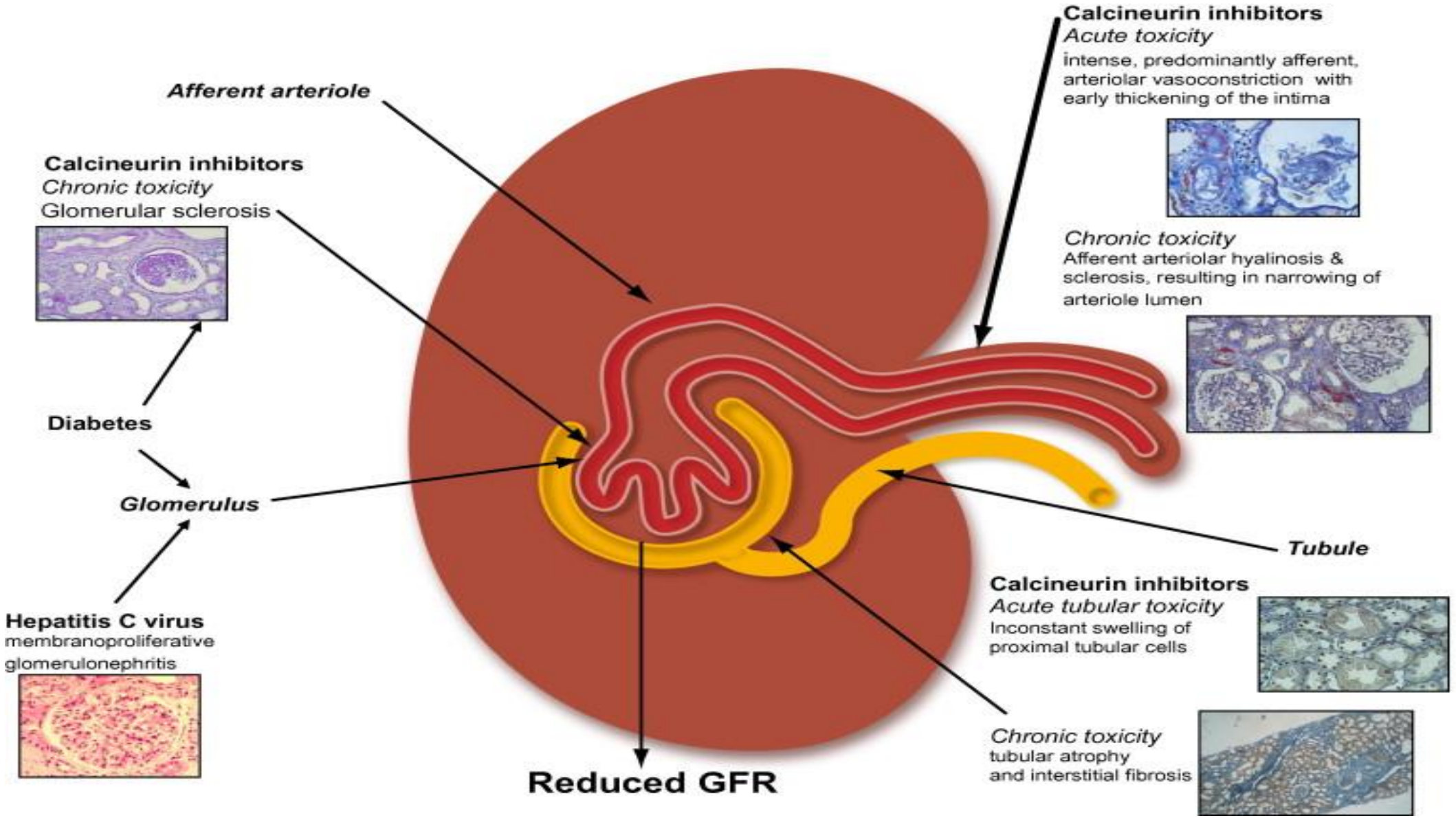
CNIs and Kidney.

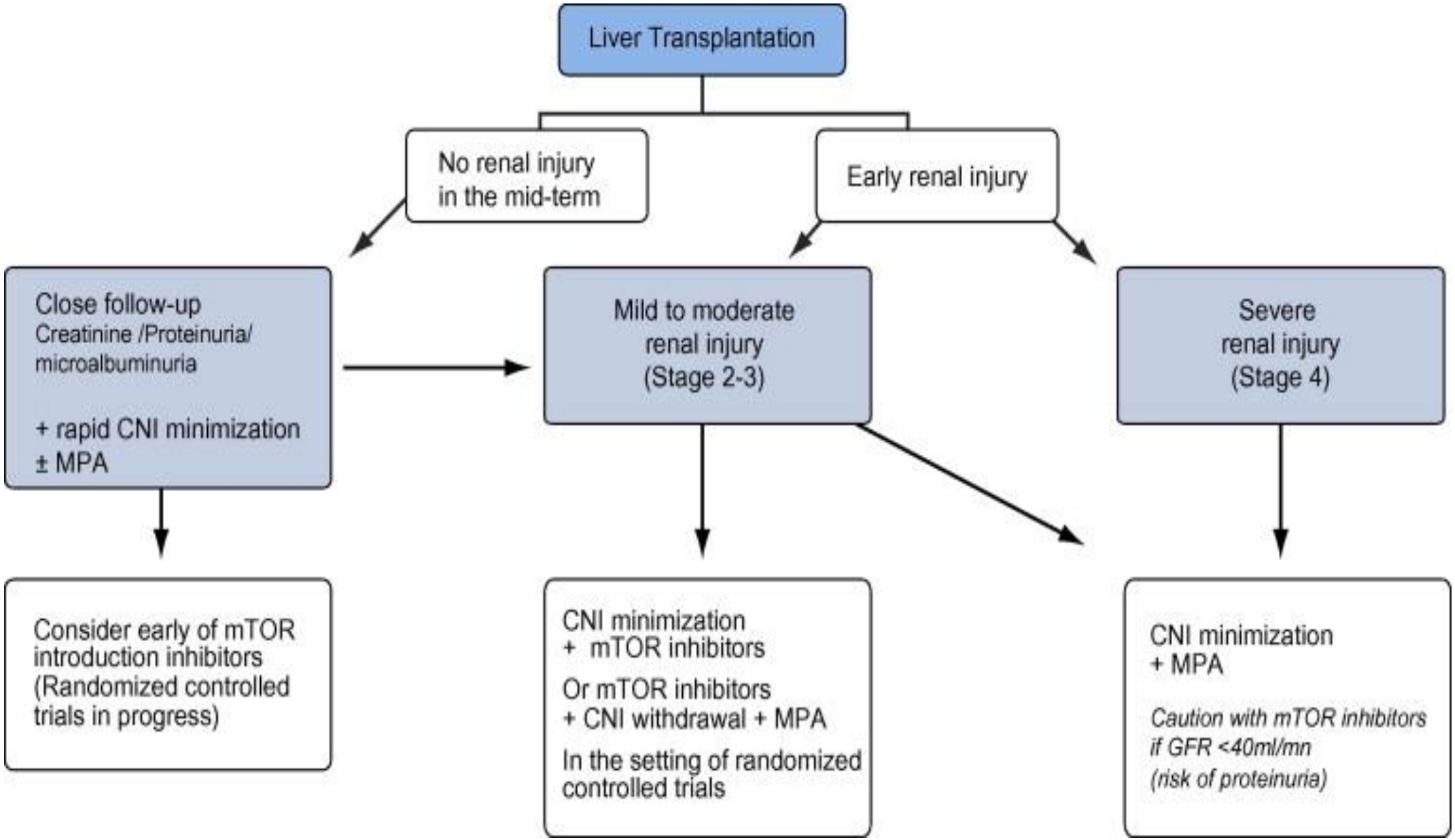
- **CNI:**
  - Nephrotoxic.
  - Renal artery vasoconstriction (reversible)
  - Tubular interstitial fibrosis and scarring (irreversible)








Calcineurin inhibitors
Acute toxicity
intense, predominantly afferent, arteriolar vasoconstriction with early thickening of the intima
Afferent arteriole
Calcineurin inhibitors
Chronic toxicity
Glomerular sclerosis
Chronic toxicity
Afferent arteriolar hyalinosis & sclerosis, resulting in narrowing of arteriole lumen
Diabetes
Glomerulus
Tubule
Hepatitis C virus
membranoproliferative glomerulonephritis
Calcineurin inhibitors
Acute tubular toxicity
Inconstant swelling of proximal tubular cells
Chronic toxicity
tubular atrophy and interstitial fibrosis
Reduced GFR


Liver Transplantation
No renal injury
in the mid-term
Early renal injury
Close follow-up
Creatinine /Proteinuria/
microalbuminuria
+ rapid CNI minimization
± MPA
Mild to moderate
renal injury
(Stage 2-3)
Severe
renal injury
(Stage 4)
Consider early of mTOR
introduction inhibitors
(Randomized controlled
trials in progress)
CNI minimization
+ mTOR inhibitors
Or mTOR inhibitors
+ CNI withdrawal + MPA
In the setting of randomized
controlled trials
CNI minimization
+ MPA
Caution with mTOR inhibitors
if GFR <40ml/mn
(risk of proteinuria)

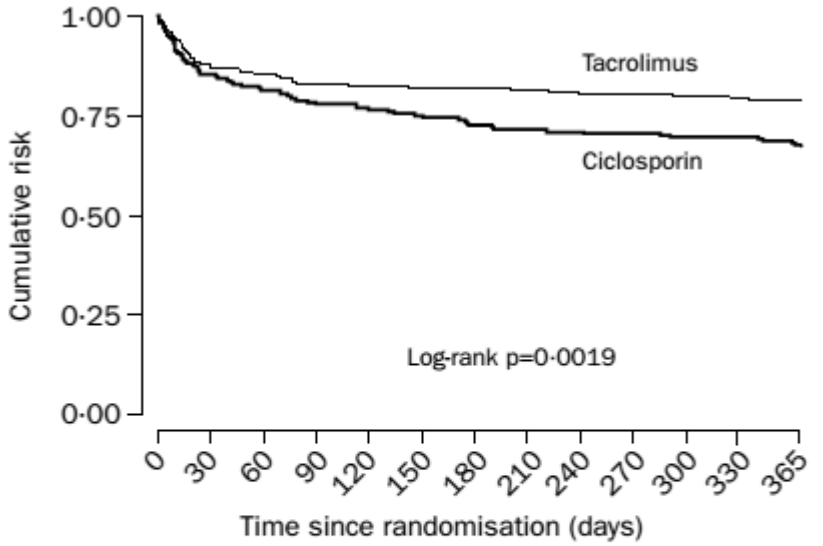
CNIs, Fibrosis and HCC.

- CNIs ➡⬆ TGFb production ➡ fibrosis.
- CNIs ➡⬆ TGFb production ➡ tumour cell invasiveness.
- Csa ➡⬆ tumour angiogenesis ➡⬆risk for HCC recurrence.

CNI and HCV

- Before DAAs era meta-analysis:
  - ***Tacrolimus is diabetogenic.***
  - Tacrolimus and cyclosporine are equal for HCV treatment by INF/RBV therapy.

Tacrolimus versus Cyclosporine

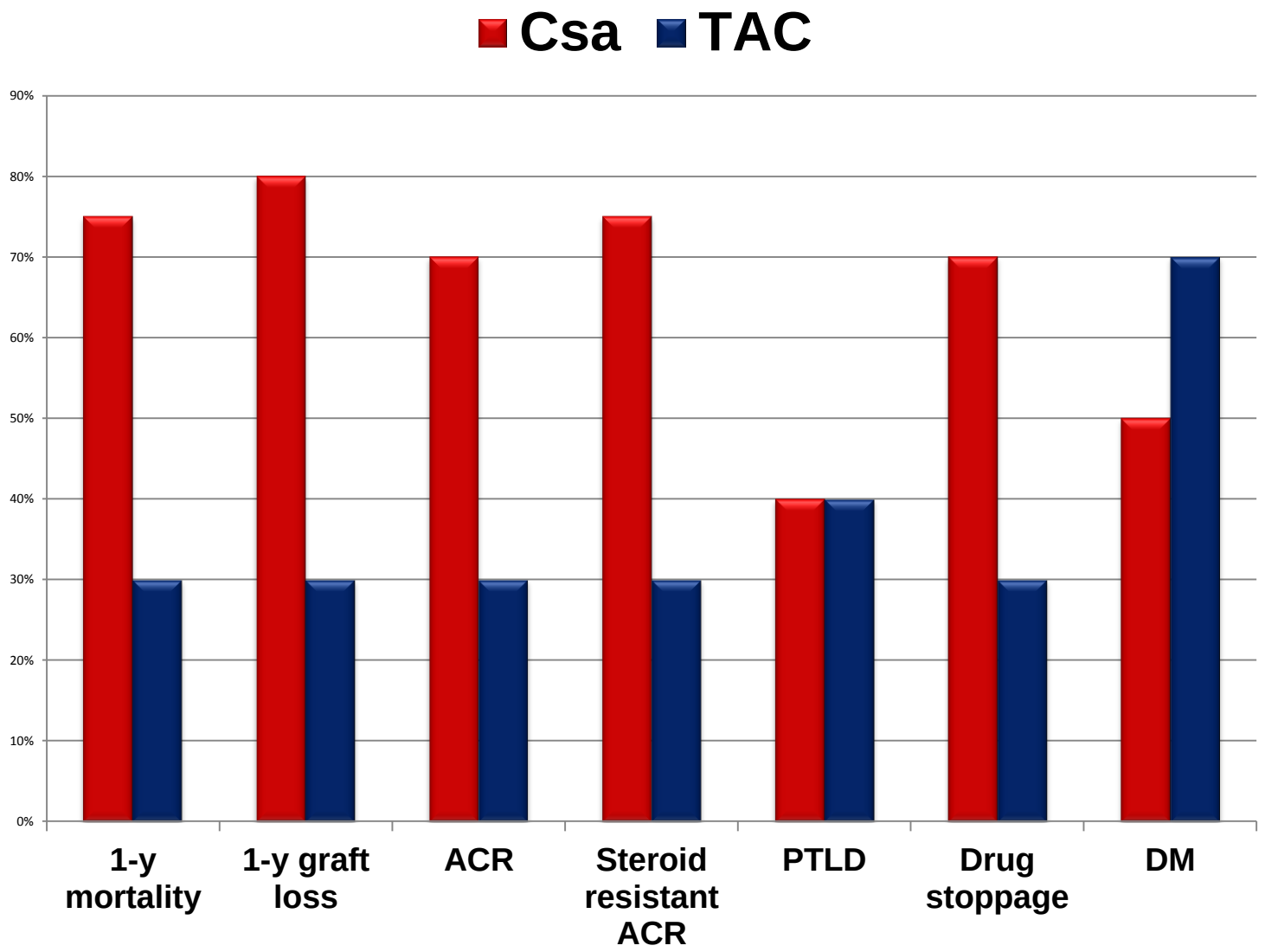


Number of patients at risk

Tacrolimus	301	262	258	251	250	247*	246	245	242	241*	239	238	237
Ciclosporin	305	261	247*	236†	230	226	219	215	213	212	210	209	204

Figure 2: **Survival plot showing freedom from primary endpoint (combined treatment failure, retransplantation, or death)**
*Includes 1 patient lost to follow-up.
†Includes 2 patients lost to follow-up

O'Grady, J. et al (2002). Tacrolimus versus microemulsified ciclosporin in liver transplantation: the TMC randomised controlled trial. The Lancet, 360(9340), 1119–1125. doi:10.1016/s0140-6736(02)11196-2



McAlister, et al. Cyclosporine versus tacrolimus as primary immunosuppressant after liver transplantation: a meta-analysis. Am J Transplant 2006; 6:1578.


3rd
Group


mTor
inhibitors


Sirolimus
(SRL)

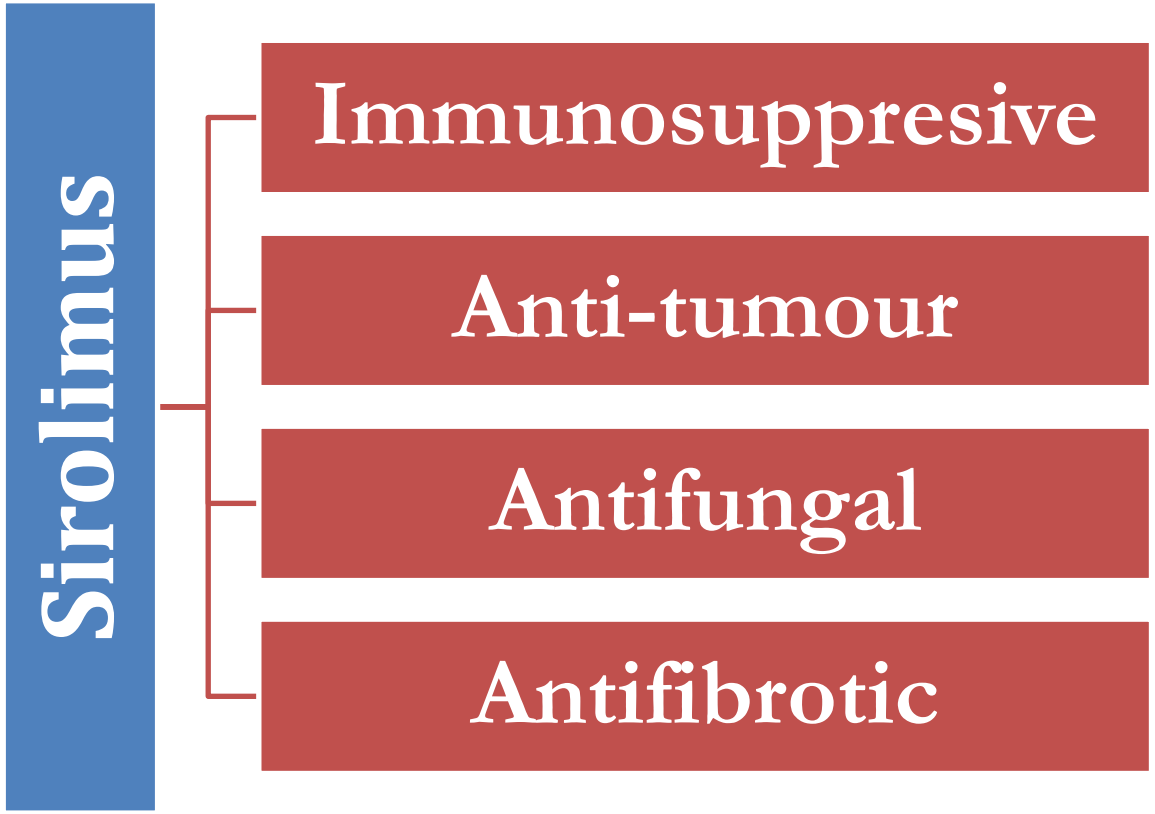

Everolimus
(EVL)


10 x 10 coated tablets
Rapamune® 1 mg
coated tablets
sirolimus
雷帕鳴™
100 x 1 mg
Wyeth


NOVARTIS
CERTICAN® 0,25 mg
Everolimus
60 Tabletten/comprimés/
tablets/comprimidos
NOVARTIS
CERTICAN® 0,5 mg
Everolimus
60 Tabletten/comprimés/
tablets/comprimidos
NOVARTIS
CERTICAN® 0,75 mg
Everolimus
60 Tabletten/comprimés/tablets/comprimidos

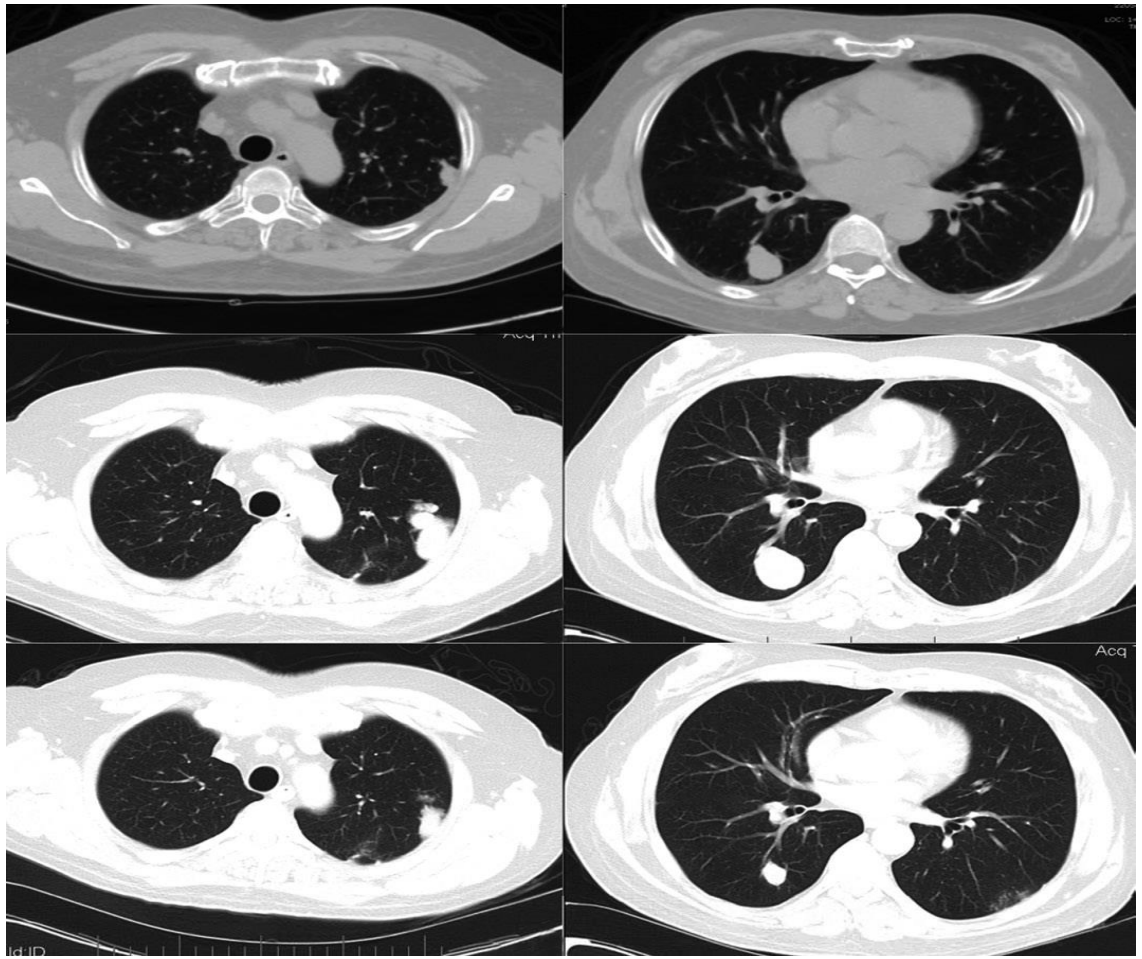
Sirolimus (Rapamycin)

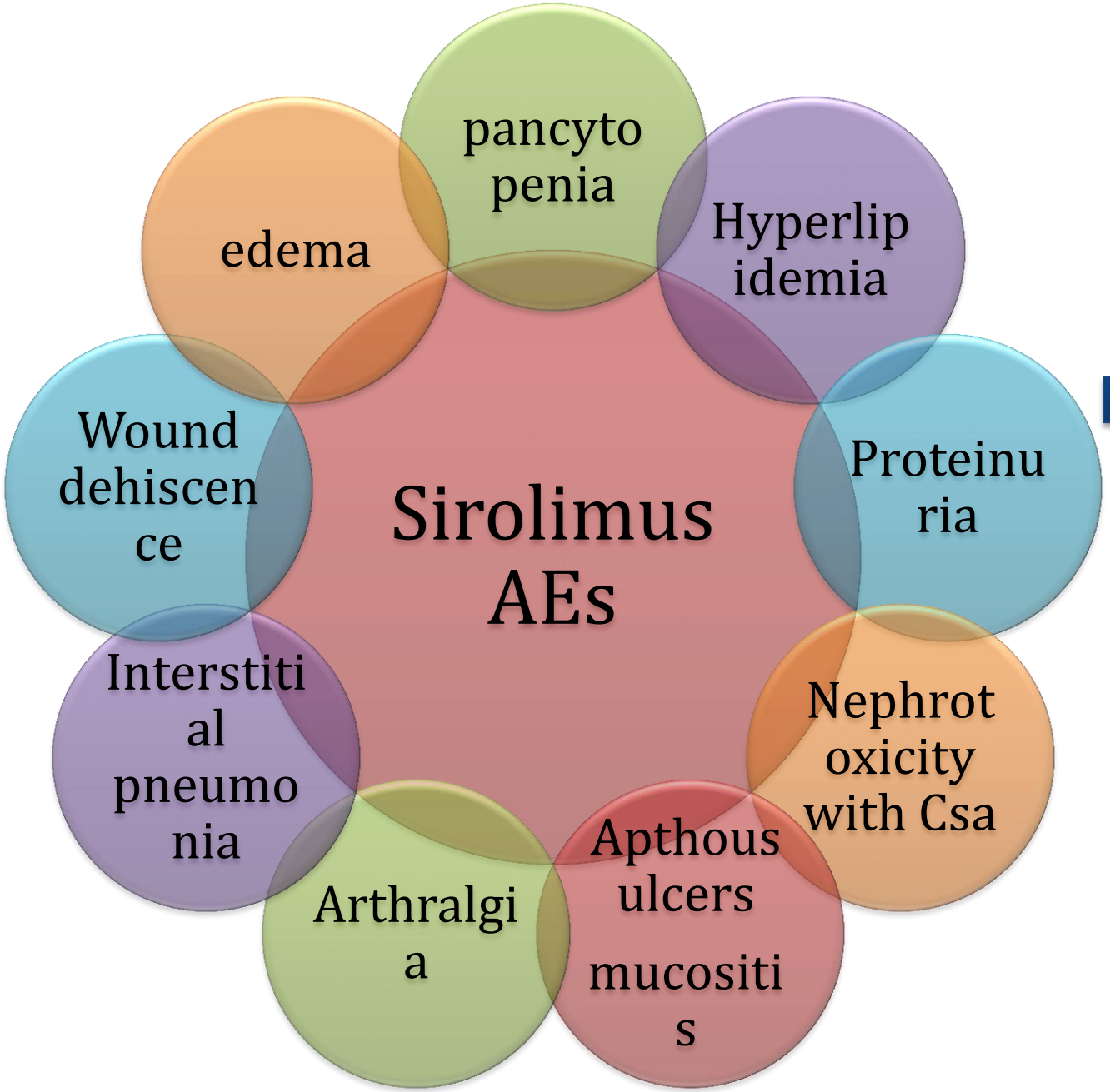
- Sirolimus is derived from the *actinomycete Streptomyces hygroscopicus*.
- *Structural homology between sirolimus and tacrolimus*
- **1965:** discovery.
- **1999:** approved in LT.



- Fat decreases absorption
- Long t1/2 and narrow therapeutic window.
- The immunosuppressant effect of sirolimus can last for up to six months after discontinuation in some animal studies
- Drug drug interaction as with CNI
- Can be used as monotherapy or combined with low dose tacrolimus.

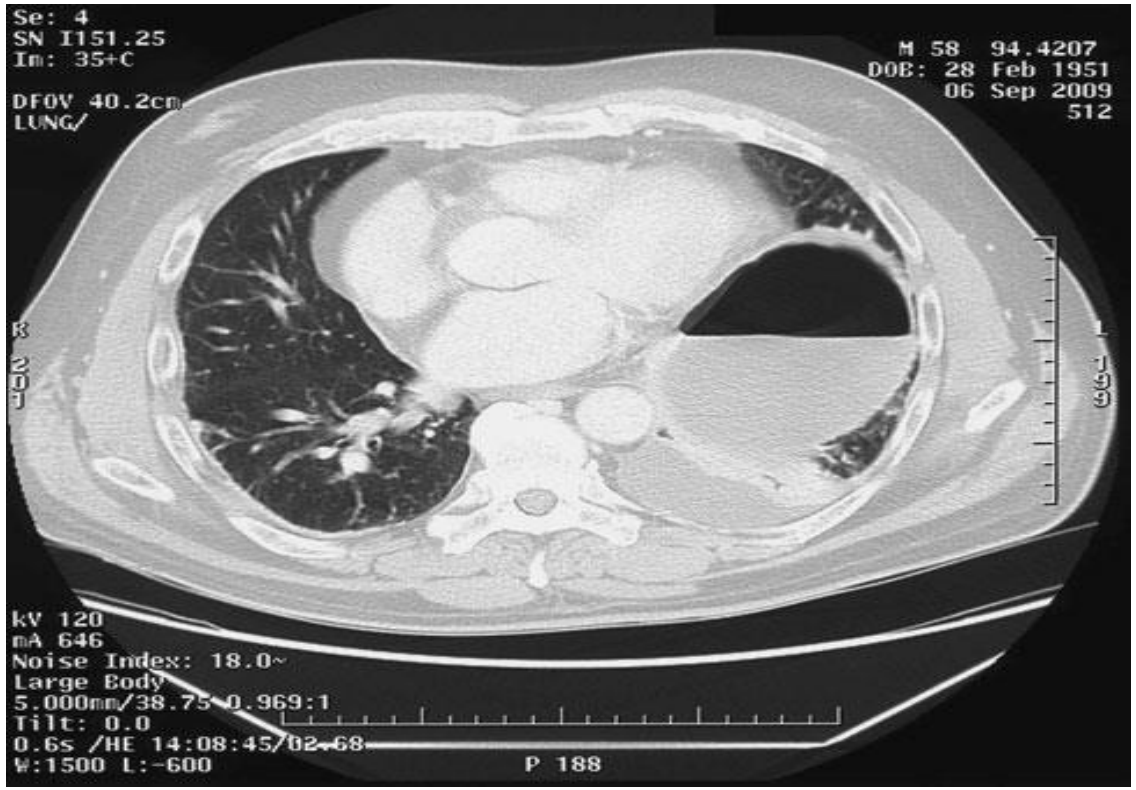
CT of chest at different time points of the treatment. The lung lesions were increased in size after sorafenib therapy but significantly reduced in size after sirolimus was introduced in combination with sorafenib. The dates were August 6, 2008 (A), January 26, 2009 (B) and August 26, 2009 (C).



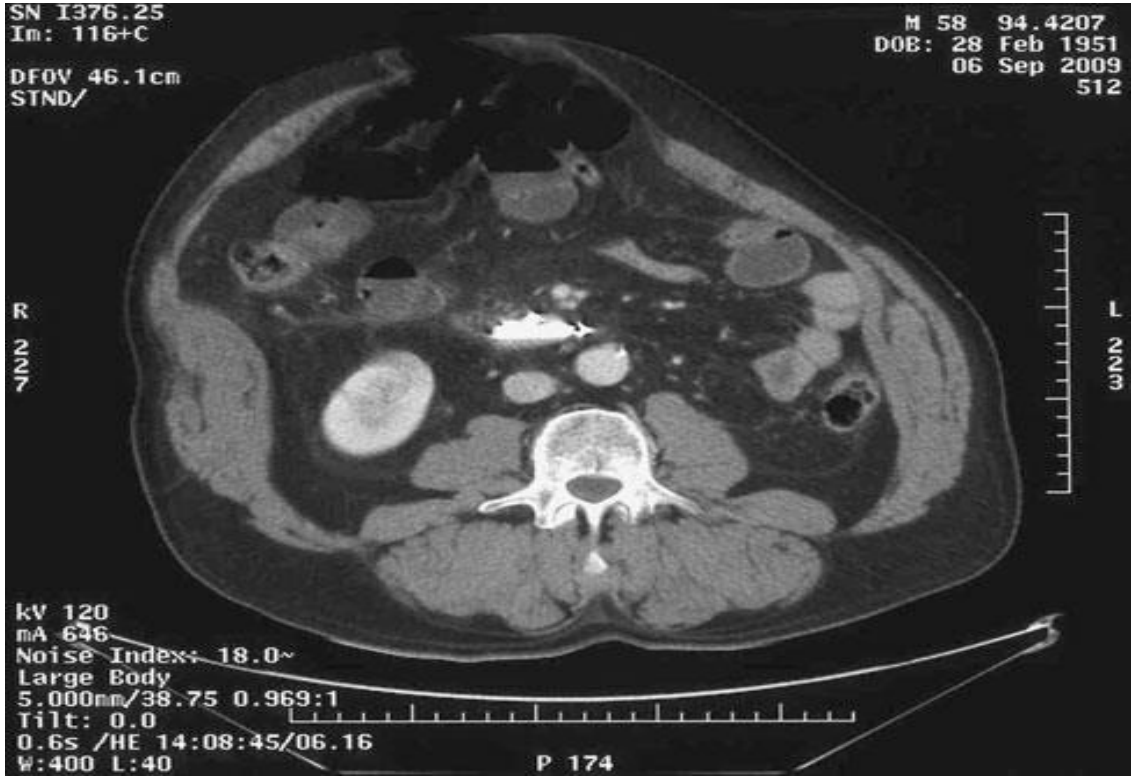


Hepatic Artery Thrombosis	**black box warning**

CT-scan of the thorax showing a large herniation of the gastric fundus in the left-sided hemithorax with pleural effusion and lung parenchymal compression on the same side



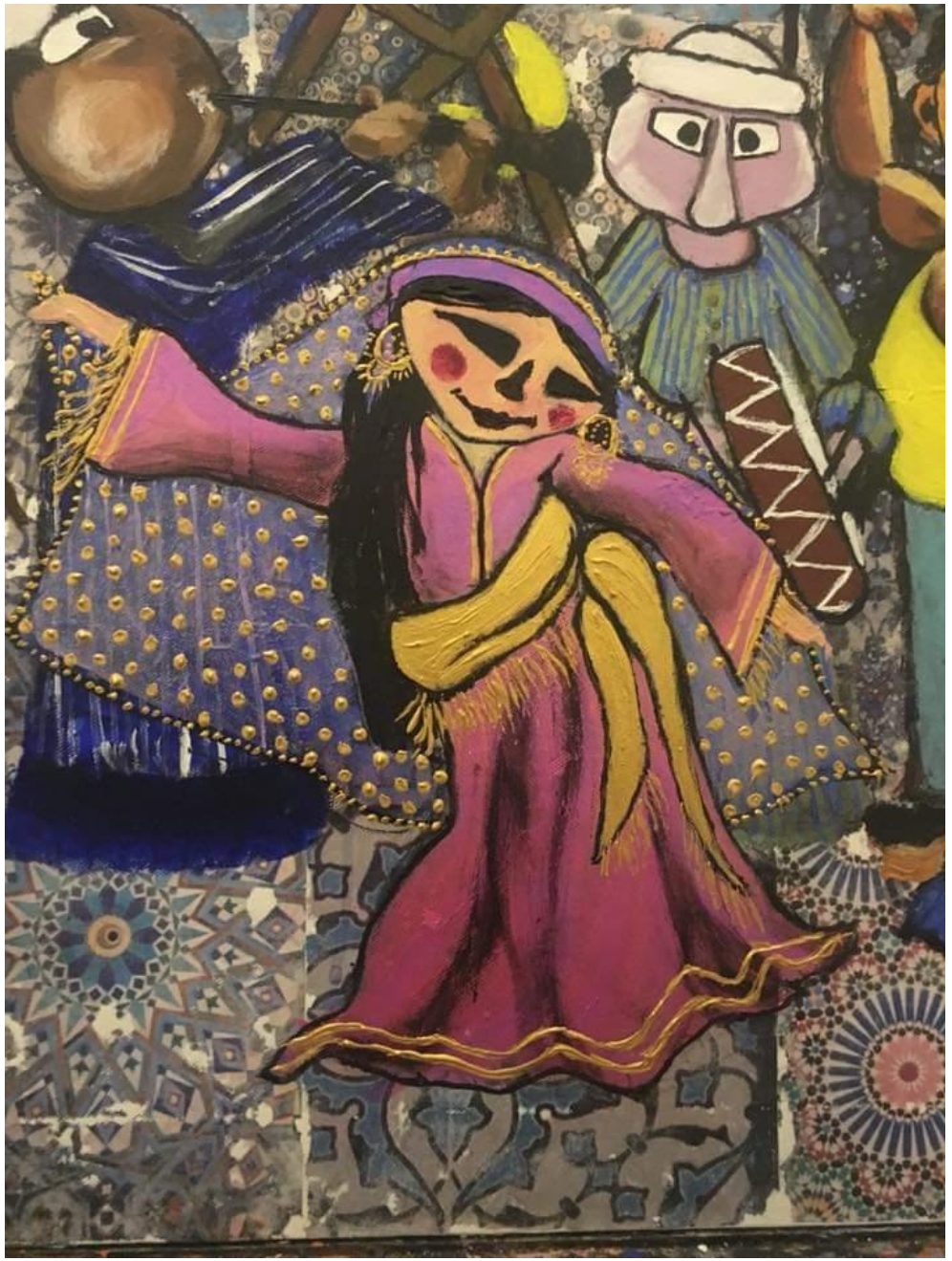
CT-scan of the abdomen showing a large incisional hernia



Everolimus

- It is a semisynthetic form of sirolimus.
- It has same mechanism of action of sirolimus.
- ***Three times more powerful than sirolimus.***
- The half-life of everolimus is approximately 28 hours (60 hours for sirolimus),

Everolimus is the new star of IS



Use of Everolimus in Liver Transplantation: Recommendations From a Working Group

Transplantation ■ February 2017 ■ Volume 101 ■ Number 2

Renal functions

- **Renal-sparing immunosuppressive strategies for LT recipients include the following options:**
  - A triple or a quadruple regimen with use of induction agents in association with antimetabolites and delayed introduction of CNI (within 5-10 days after surgery) ± steroids;
  - **EVR-facilitated CNI reduction starting 30 (±5) days after transplantation;**
  - **Early (≤10 days) use of EVR to reduce CNI exposure.**

- **EVR-facilitated reduction of CNI early (30±5 days) or very early (≤10 days) after transplantation improves renal function at 1 and 3 years**

- Delaying renal-sparing intervention strategies until glomerular filtration <60 mL/min per 1.73 m^2 is associated with only minor improvement in renal function

Time of EVR Introduction, CNI Reduction and Elimination, and Risk for Graft Rejection

- In LT, **early (30 ± 5 days) CNI reduction with EVR introduction is as effective and safe as standard-exposure CNI immunosuppression.** CNI reduction facilitated by EVR can be implemented

- CNI withdrawal is associated with a 10− 20% risk of acute rejection of the liver graft depending on time of discontinuation after LT.

- **Conversion to EVR monotherapy for CNI-related renal toxicity is feasible in 80% of patients at ≥12 months after liver transplantation.** The impact on renal function of conversion strategies is dependent on the severity of renal impairment and timing of conversion.

- Due to different pharmacokinetic interactions, TAC should not be reduced before EVR is in the target blood range (≥3 ng/mL), whereas cyclosporine A (CyA) should be reduced upon administration of EVR

Antiproliferative Effects of EVR

- **EVR and SIR share similar antiproliferative properties** both in vitro and in vivo, with EVR presenting advantages due to its shorter half-life.
- Use of mTORi is associated with a **reduced incidence of de novo malignancies after kidney, heart, and LT**
- In LT, mTORi can be used as immunosuppressants to **reduce the risk of posttransplant HCC recurrence**
- Use of mTORi is **recommended for patients with de novo malignancies after LT.**
- In patients with **recurrent HCC after LT**, it is recommended to **introduce EVR together with CNI reduction or withdrawal**, due to its combined immunosuppressive and antiproliferative properties.
- In patients with recurrent HCC after LT, use of **EVR is recommended unless clinically contraindicated and irrespective of implementation of other treatment modalities** (eg, surgery, radiology-guided tumor ablation, transarterial chemoembolization, or transarterial radioembolization)
- For LT patients with **recurrent HCC not amenable to surgical or radiological treatment, a combination regimen with EVR and sorafenib** shows a pathophysiological rationale.

Management of EVR-Related Adverse Events

- In transplant patients, **EVR-related dyslipidemia is dose-dependent.**
- When dyslipidemia is observed in LT recipients on treatment with EVR at trough levels higher than the recommended ranges (>8 ng/mL), prompt reduction of EVR oral dose is warranted.

- Dyslipidemia occurring in LT recipients should be treated (with EVR dose reduction if trough levels are >8 ng/mL) irrespective of the time from transplantation

- **The risk of EVR-related proteinuria (as per >1 g/d) in LT recipients is about 3% at 3 years.**

- In LT recipients with **severe neutropenia** (<1000 mm^3), **leukopenia** (<2000 mm^3), or **thrombocytopenia** (<50 000 mm^3) **dose adjustments of EVR or withdrawal are recommended.**

- **EVR-based immunosuppressive regimens are not associated with an increased risk of infections compared with standard CNI-based immunosuppression.**

Purine Synthesis Inhibitors

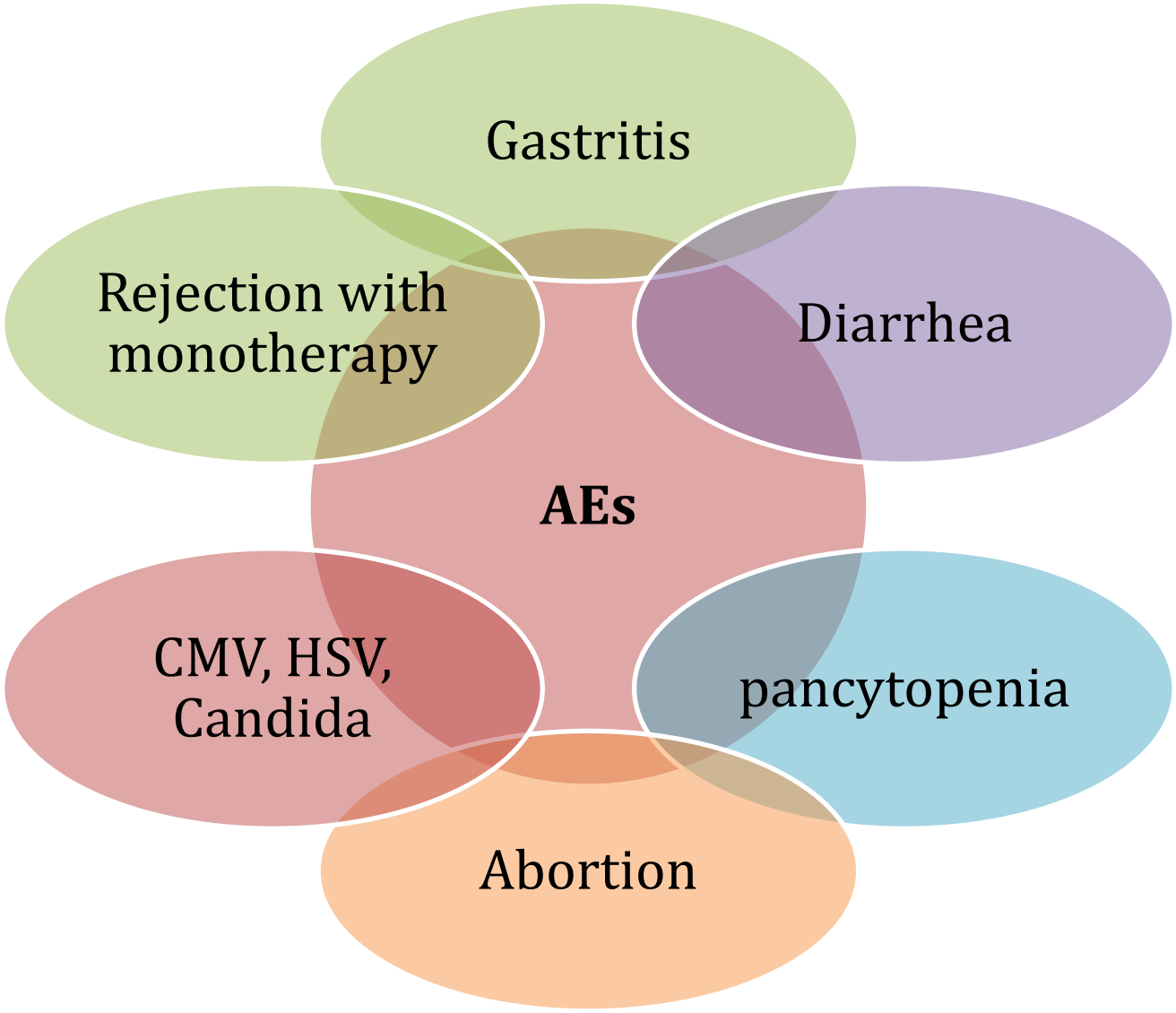
- Azathioprine (no longer used in LT).
- Cyclophosphamide (no longer used in LT).
- **Mycophenolic acid:**
  - **Mycophenolate mofetil (MMF, CellCept)**
  - **mycophenolic acid (MPA, Myfortic)**


NOVARTIS
myfortic
Mycophenolsäure
acide mycophénolique
360 mg
180 mg


CellCept
Mycophenolate mofetil
500 mg
50 tablets
Roche

- **MMF (cellcept):**
  - is produced by several species of the *fungus Penicillium*.
  - 1896: discovery.
  - food decreases MPA concentrations so MMF should be administered at least one hour before or two hours after meals.

- **Mycophenolic acid (MPA, Myfortic)**
  - prodrug of MPA
  - delayed-release drug formulation that allows release of MPA in the small intestine via a pH-dependent dissolution.
  - Although MPA was conceived to reduce gastrointestinal symptoms, side effects appear to occur independently of gastrointestinal resorption.

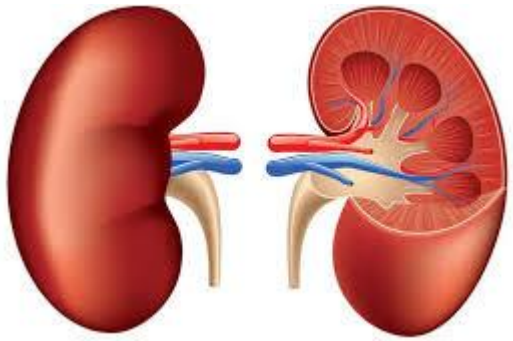


- ***Drugs increasing MPA levels:***
  - acyclovir, ganciclovir, probenecid, salicyaltes and sirolimus.
- ***Drugs decreasing MPA levels:***
  - antacids containing aluminium or magnesium,
  - cholestyramine, iron, metronidazole, norfloxacin and rifampin.

- *MPA* also *decreases protein binding* to *phenytoin* and *theophylline* leading to *elevated levels of both drugs*.

- MMF also markedly *potentiates* the *anti-herpetic activities of acyclovir and ganciclovir* and should *not be given with other anti-metabolites such as AZA*.

- **MMF does not cause nephrotoxicity or neurotoxicity (CNI-sparing agent)**
- **Routine monitoring of MPA levels is not generally employed in clinical practice**



International Liver Transplantation Society Consensus Statement on Immunosuppression in Liver Transplant Recipients

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TABLE 1.

The impact of IS on metabolic syndrome

	Hyperlipidemia	Hypertension	Obesity	Diabetes mellitus
CNIs	+ Population studied: Liver transplant	++ Population studied: Liver transplant	+ Population studied: Liver transplant	++ Population studied: Liver transplant Caveats: (Tac > CsA)
Mycophenolate/azathioprine	–	–	–	–
Corticosteroids	+ Population studied: Liver transplant	+ Population studied: Liver transplant	+ Population studied: Liver transplant	+++ Population studied: Liver transplant
mTOR inhibitors	++ Population studied: Liver transplant	+ Population studied: Renal transplant	–	–
Thymoglobulin	–	–	–	–
IL2-receptor antibodies	–	–	–	–

Side effects of immunosuppressive drugs								
	BM	hyperlipidemia	HTN	CNS	osteoporosis	DM	Kidney	GIT
Azathioprine	+++							++
MMF	++							+++
Sirolimus	++	+++						+
Steroids		+	++		++	+		+
Cyclosporine		+	+	++	+	+	+++	
Tacrolimus		+	++	+++	+	++	+++	+

Biological immunosuppresion

- **Antilymphocytic Ab Therapy**
  - Monoclonal antibodies
    - Muromonab-CD3 (OKT3)
      - Treatment of steroid resistant rejection.
  - Polyclonal antibodies
    - Antithymocyte globulin (ATG)
      - Induction therapy
      - Treatment of steroid resistant rejection.
- **Interleukin-2 receptor antibodies**
  - basiliximab (Simulect).
    - Induction therapy (steroid sparing, CNI minimization

Cytokine Release Phenomenon

- fever, hypotension, headache (aseptic meningitis), dyspnea (flash pulmonary edema) and gastrointestinal complaints (nausea, diarrhea and vomiting).

Post transplant lymphoproliferative disease

- occur commonly in patients transplanted for HCV

Infections

Expensive

Thanks a lot