In the Name of GOD

The Role of mTOR in Solid Organ Transplant & SPK

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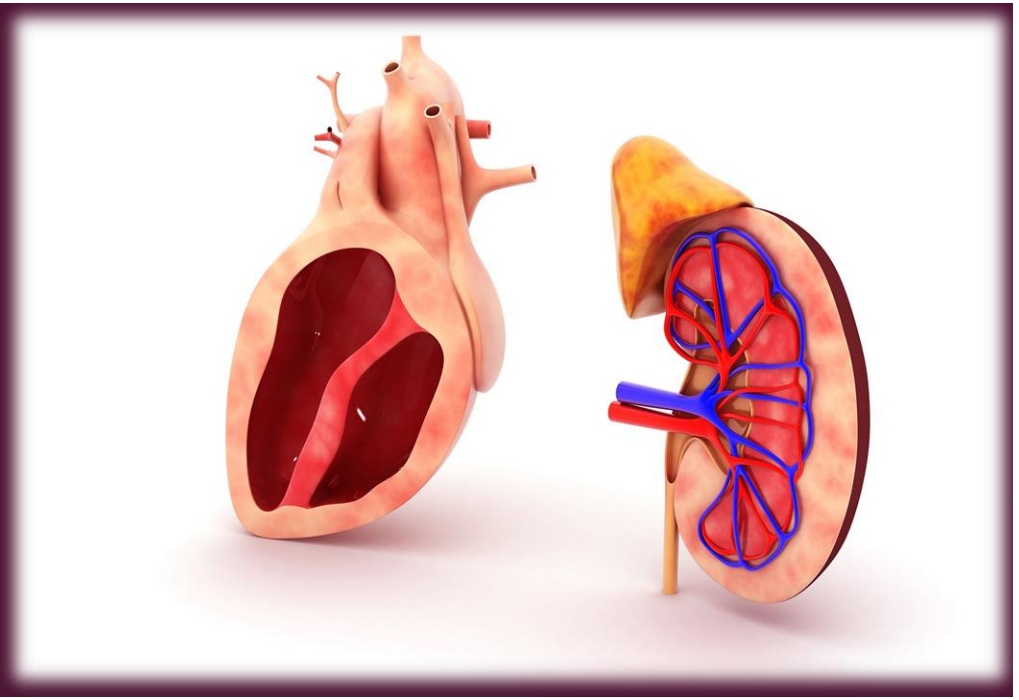
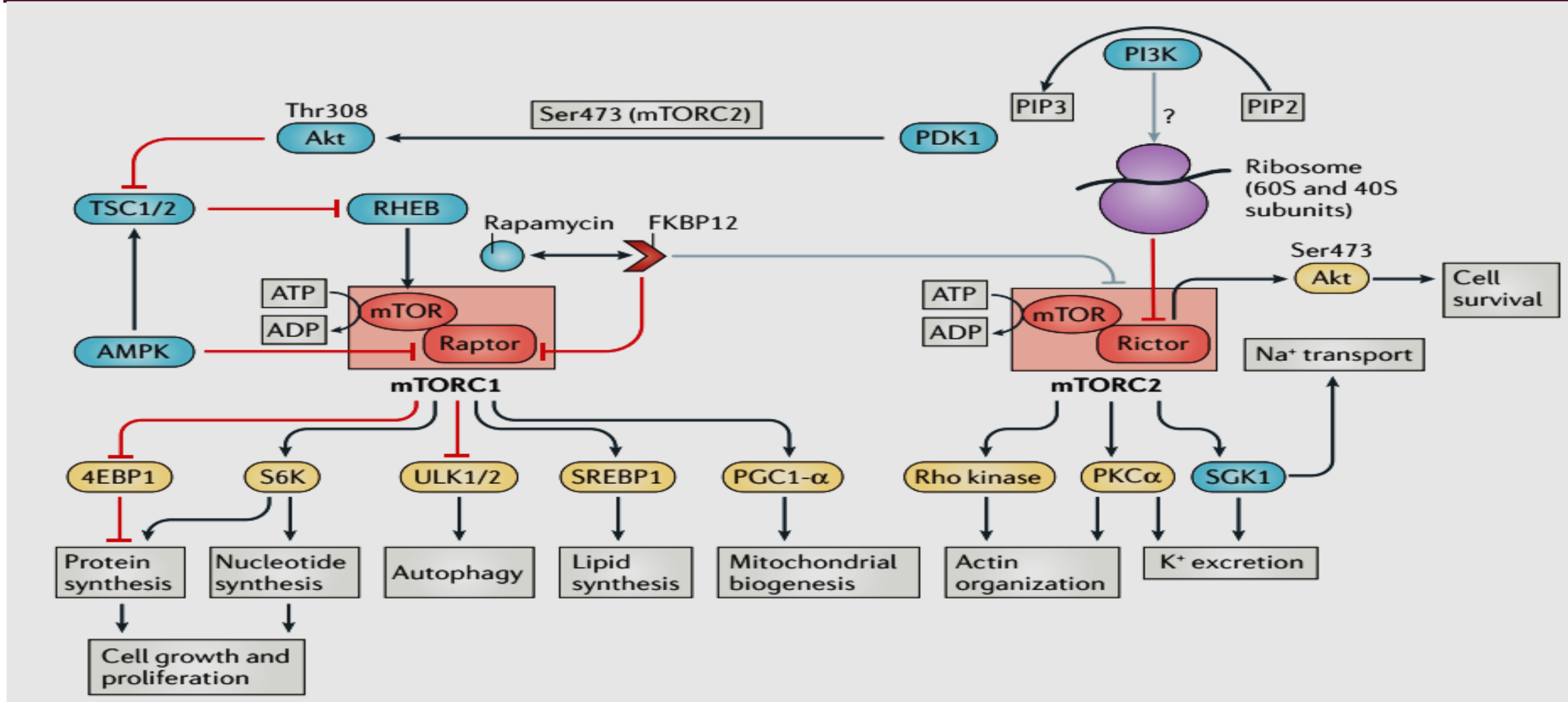


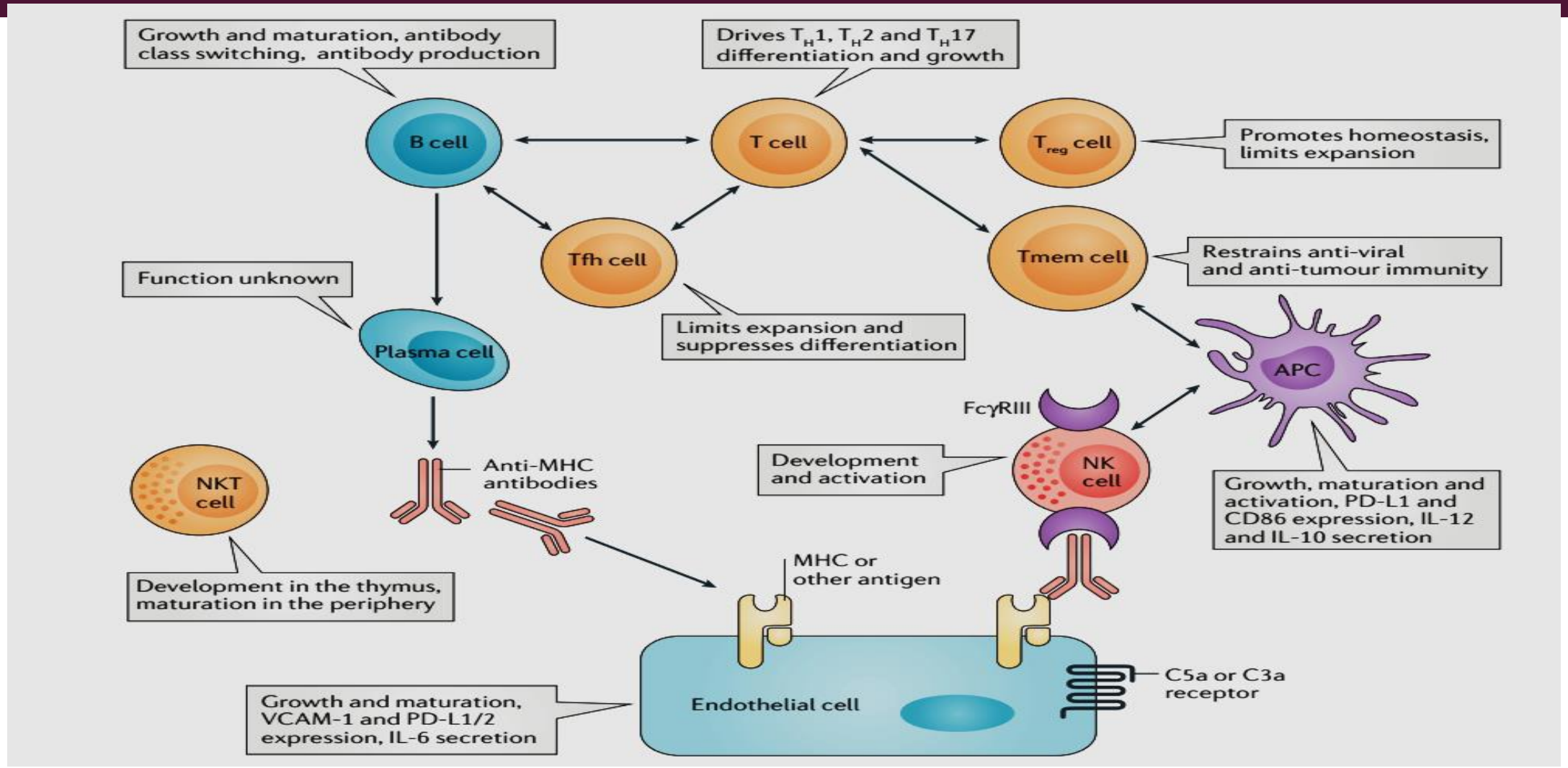
Introduction

- mTOR is an evolutionarily conserved serine–threonine kinase that regulates cell growth, proliferation and metabolism.
- Increasing evidence indicates that mTOR has an important role in the regulation of renal cell homeostasis and autophagy.
- Moreover, this kinase has been implicated in the development of glomerular disease, polycystic kidney disease (PKD), acute kidney injury (AKI) and **solid organ transplant rejection**.

mTOR operates in at least two distinct, multiprotein complexes: mTOR complex 1 (mTOR C1) and mTOR complex 2 (mTOR C2)



Roles of mTOR in Immune Cells and Vascular Endothelial Cell Homeostasis



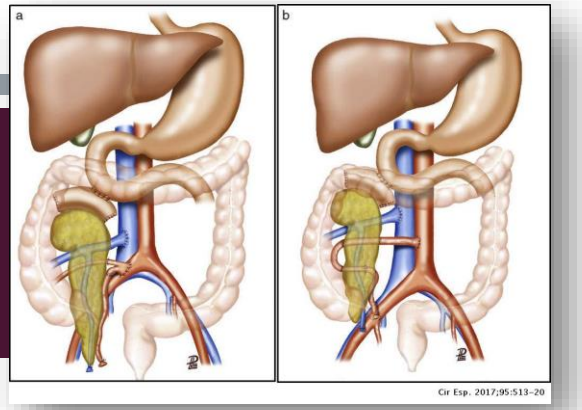
Putative Roles of mTOR Complexes in Immune Cell Populations in The Setting of Transplantation

Immune cell	Role of mTOR	
	Physiological role	**Role in clinical transplantation**
Conventional DCs	Promotes growth, proliferation, maturation, alters proinflammatory/anti-inflammatory cytokine secretion[68,70], suppresses inflammation (mTORC2)[72,283] and restrains T-cell responses in human myeloid DCs (mTORC1)[284,285]	May either promote (ACR) or restrain (pneumonitis) immune hyper-responsiveness
Plasmacytoid DCs	Promotes activation (TLR9) and type-I IFN production; restrains (TLR7) Tmem cell and T_{reg} cell proliferation[286,287]	May regulate function including interaction with T_{reg} cells
Effector T cells	Drives T_H1 (mTORC1), T_H2 (mTORC2 +/– mTORC1), and T_H17 (mTORC1) cell differentiation and growth[81,82,288]	Promotes expansion with role in rejection (ACR, acute and chronic ABMR)
Follicular helper CD4 T cells	Restrains differentiation (mTORC1)[83]	May prevent alloantibody formation and ABMR
CD8 memory T cells	Restrains anti-viral and anti-tumour immunity[124,126,289]	May promote viral infections, including CMV, human herpesvirus 8 and BK virus[127,290]
T_{reg} cells	Promotes homeostasis and function (mTORC1)[80], limits expansion (mTORC1 +/– mTORC2)[79]	May restrict role in promotion of tolerance
Neutrophils	Formation of neutrophil extracellular traps[291], promotes endothelial cell and extracellular matrix adhesion (mTORC1)[292], promotes chemotaxis (mTORC2)[293,294]	May promote role in rejection (ACR, acute and chronic ABMR)
NK cells	Promotes development in the bone marrow, activation in the periphery and IL-15-induced function[90]	May promote role in rejection (ACR, acute and chronic ABMR)
NKT Cells	Promotes thymic and peripheral iNKT development (mTORC1 (REF. 295) and mTORC2 (REF. 296)) and fate of NKT17 cells (mTORC2)	May promote role in rejection (ACR, acute and chronic ABMR) and restrict role in tolerance
B cells	Promotes growth, proliferation, maturation, antibody class switching and production (mTORC1 and mTORC2)[86,87,297,298], but decreases IL-7 receptor and RAG recombinase gene expression (mTORC2)[299]	May promote role in rejection (ACR, acute and chronic ABMR)
B_{reg} cells	Unknown	Unknown
Plasma cells	Unknown	Alloantibody generation in acute and chronic ABMR
Endothelial cells	Promotes growth, proliferation, maturation, alters pro-inflammatory/anti-inflammatory cytokine secretion, negatively regulates T_{reg} cell expansion and increases VCAM-1 expression (mTORC2)[300,301]	May promote role in rejection (ACR, acute and chronic ABMR)

mTOR Inhibitors in Solid Organ Transplant & SPK

- Current U.S. FDA approved of mTORi-based protocols include:
  - **Calcineurin inhibitors (CNIs)** withdrawal with **sirolimus (SRL)**
  - **Reduced CNI** with **de novo everolimus (EVR)**
- mTORi is used in immunosuppressive maintenance regimen in ~ 20% of SPKT recipients.
- Switching from CNIs to mTORi is associated with worsening or de novo proteinuria in the post-transplant setting.
- Low risk immunologic risk patients with estimated glomerular filtration ratio > 40 ml/min and no significant proteinuria (< 500 mg/day) are potentially good candidates for conversion.
- Despite the fact that mTORi, SRL or EVR, were reported to have less toxicity to the kidney and β-cells, routine use of these agents in maintenance regimens was reported in less than 20% of pancreas transplants at discharge and one year post-transplant.

Role of mTOR in Maintenance therapy



- Following induction with a T cell-depleting agent, some centers administer maintenance immunosuppression therapy to all SPK and PAK transplant recipients.
- Maintenance immunosuppression is given to help prevent acute rejection and loss of the pancreas and kidney allografts.
- Maintenance therapy is similar for patients receiving an SPK or PAK transplant and typically includes a calcineurin inhibitor, an antimetabolite or mTOR inhibitor, and generally a tapering dose of glucocorticoids.

Maintenance Regimen for SPK Transplant Recipients

- For most simultaneous pancreas-kidney (SPK) transplant recipients, administer a maintenance regimen consisting of triple immunosuppression therapy.
- This includes a calcineurin inhibitor (usually **tacrolimus**), an antimetabolite (**mycophenolate**), and **prednisone**.
- At some centers, **mTOR inhibitors** are used either in addition to or in place of any of the above agents.

Mechanisms of mTOR Inhibitors Effects

- In addition to immunosuppressive effects, mTOR inhibitors have anti-tumor, anti-viral, and anti-fungal properties.
- Sirolimus is administered once daily because of a long half-life, and everolimus is administered twice daily; both agents are dosed to achieve target trough levels of
  3 to 8 ng/mL:
  - ✓ A single-center study reported one-year kidney and pancreas survival rates of 100 percent among 20 SPK transplant patients administered a tacrolimus/sirolimus maintenance regimen after induction therapy.

Mechanisms of mTOR Inhibitors Effects

- In one study of 59 SPK transplant recipients: rates of death-censored pancreas survival and biopsy-proven acute T cell-mediated rejection were similar between both groups.
- In a United Network for Organ Sharing (UNOS) registry study 25,387 pancreas or SPK transplant recipients: The use of mTOR inhibitors was associated with a 7 percent risk reduction in allograft failure and higher patient survival rates up to 10 years.
- By contrast, randomized, controlled trials comparing mTOR inhibitors with standard immunosuppressive regimens have yielded conflicting results.
- The available data suggest that the role of mTOR inhibitors may be better suited to replace an antimetabolite rather than a calcineurin inhibitor, which may then permit glucocorticoid weaning and withdrawal.
- A common theme in most studies with mTOR inhibitors has been a high incidence of drug-related side effects resulting in either dose reductions or discontinuation with conversion to another agent.

Data on Liver & Heart Transplants

- Data on liver transplants showed that with the focus on calcineurin inhibitor (CNI) minimization, native renal function is preserved.
- Recent data on the use of mTOR inhibitors in heart transplantation, under CNI minimization and conversion strategies aiming to preserve renal function and to prevent the development of graft vasculopathy, CMV infection, and malignancy.
- The role of mTORi in the management of viral infections after solid organ transplant, not only the potential role in the management of cytomegalovirus, poliomavirus, herpes virus 8, -related Kaposi sarcoma but also the lack of evidence for use of mTORi in EBV-mediated posttransplant lymphoproliferative disease or hepatitis C virus viral replication.

Data on Liver & Heart Transplants

- In addition to renal dysfunction, long-term complications associated with liver transplantation include the development of de novo malignancies and the recurrence of HCV and HCC.
- Late conversion to sirolimus in liver transplant recipients is associated with generally low rates of acute rejection.
- The use of mTOR inhibitors, either as conversion or de novo immunosuppression, results in generally low rates of patient death, graft failure, and acute rejection that are comparable to those observed with CNIs and MMF.
- The majority of studies that we retrieved involved conversion to sirolimus or everolimus and most of these demonstrated a benefit on renal function.
- Comparative studies suggest that sirolimus-based immunosuppression is associated with higher rates of survival after liver transplantation for HCC compared to an alternative immunosuppressant.

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Thanks for your attention