COVID-19 and mTORi in Renal Transplant

Dr.Leila Sabetnia

assistant professor of nephrology

AJUMS

Genaral Consideration in Kidney Transplant Patients

- Clinical manifestations, therapeutical options, and prognosis of COVID-19 in kidney transplant recipients would differ from normal population

- During current pandemic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), KTRs have been considered as patients at higher risk of disease severity and mortality

Genaral Consideration in Kidney Transplant Patients

- Early diagnosis of the infection in these patients has great importance
- Lymphopenia does not assist physicians in kidney transplant recipients since a preceding drug-related lymphopenia exists in these patients
- Due to immunosuppressive therapy, KTRs are considered low responders to vaccines and were not included in pre-authorization clinical trials for SARS-CoV-2 vaccine

Genaral Consideration in Kidney Transplant Patients

- It remains challenging how to manage immunosuppressive agents in transplant recipients infected with COVID-19 ideally

- Several factors effect selection of a given regimen; the chief aim is induction of equilibrium between the benefit of rejection inhibition and over-immunosuppression risk

Immunosuppression in COVID-19

Mild infection

- In case of mild infection symptoms and the possibility of a ***high risk*** of rejection the patient's immunosuppression regimen should continue as usual :

1. *First two months after transplantation*
2. *patients with a history of more than one organ transplant*
3. *patients transplanted with a high-risk immunological reaction*

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Immunosuppression in COVID-19

Mild infection

- If the patient's immunological risk is low and immunosuppression can be reduced, it is recommended that antiproliferative agents (mycophenolate, azathioprine) and mTOR inhibitors (everolimus, sirolimus) be discontinued

- Continue administration of prednisolone and CNI with minimal effective blood concentration

- In mycophenolate+ mTOR inhibitor receiving patients, replace mTOR inhibitor with CNIs

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Immunosuppression in COVID-19

Moderate to severe infection

- Continue prednisolone regimen with stress dose or replace it with intravenous hydrocortisone/methylprednisolone
- discontinue antimetabolite agents (mycophenolate, azathioprine)/mTOR inhibitors
- CNI (tacrolimus or cyclosporine) is recommended to be discontinued, and in case of high risk of rejection, minimal concentration
- In lupinavir/ritonavir or atazanavir/ritonavir treaed patients, usually even with discontinuation of mTOR and CNI inhibitors

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mTOR inhibitors

- mTOR inhibitors are generally metabolized via cytochrome P450 enzyme 3A4 (CYP3A4) and Pglycoprotein (P-gp)

- The coadministration of hydroxychloroquine with mTORi (CYP3A4 inhibitors) may theoretically increase their blood concentrations with the development of potential adverse effects/toxicities (including QT-prolongation)

- In patients treated with Lopinavir/Ritonavir 50–90% reduction in dose of sirolimus and discontinuation of everolimus has been proposed

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Potential positive effects of mTORi in viral infections

- The mTOR exists in two distinct complexes, defined as mTOR complex 1 (mTORC1) and 2 (mTORC2)
- Activated mTORC1 induces metabolic effects such as mRNA translation, ribosome biogenesis, protein synthesis, mitochondrial metabolism, and adipogenesis
- mTORC2 promotes cell survival, regulates the actin cytoskeleton, ion transport, and cell growth

Coquillard et al SOJ Immunol. 2005;3(1):1-10

Potential positive effects of mTORi in viral infections

- mTOR inhibitors bind to the intracellular protein FKBP-12, forming a complex that inhibits the activity of mTORC1 and mTORC2

- This inhibition interferes with translation and protein synthesis, which regulate the proteins involved in the cell cycle, angiogenesis, and glycolysis

J Med Virol. 2021 April ; 93(4): 1843–1846.
doi:10.1002/jmv.26728

Potential positive effects of mTORi in viral infections

- mTOR inhibitors have been identified as potential therapeutic agents given their known antiviral properties
- mTOR inhibitors have been shown antiviral effects on some viruses, such as CMV and BK virus
- Everolimus has been used to treat Kaposi's sarcomas associated with human herpesvirus 8 (HHV-8)

J Med Virol. 2021 April ; 93(4): 1843–1846.
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Potential positive effects of mTORi in viral infections

- It is well documented that both DNA (i.e., adenoviruses, CMV, and HSV) and RNA (i.e. MERS-CoV, influenza, HIV, West Nile virus, and Zika virus) viruses modulate the mTOR pathway

- There is ample evidence to suggest that mTOR inhibition suppresses viral protein synthesis in addition to interfering with virus-mediated transcription events

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Potential positive effects of mTORi in viral infections

- In vitro mTOR inhibitors have been shown to reduce the replication of another coronavirus, the Middle East respiratory syndrome-related coronavirus (MERS-CoV)
- This effect has been also observed in rapamycin-treated cells infected influenza A virus
- In patients with severe H1N1 pneumonia, early adjuvant treatment with rapamycin and corticosteroids was associated with a rapid virus clearance and a significant clinical improvement

published: 23 August 2021 doi: 10.3389/fphar.2021.710543

Potential positive effects of mTORi in COVID-19

- A recent study identified the mTOR–PI3K–AKT pathway as a key signaling pathway in SARS-CoV-2 infection
- Some studies reported mTOR as a highly effective molecule in COVID-19 progression
- The authors evaluated mTOR inhibitors in vitro and identified significant viral inhibition of SARS-CoV-2 with nanomolar drug concentrations of each drug

bioRxiv preprint doi:
https://doi.org/10.1101/2020.06.24.150326

Potential positive effects of mTORi in COVID-19

- Dysregulation of the mTOR pathway seems to enhance SARS-CoV-2 pathogenicity, which may result in severe COVID-19

- Thus, targeting this pathway might reduce SARS-CoV-2 pathogenicity

Appelberg et al Emerg Microbes Infect. 2020;9(1):1748-60.
Zhou et al Cell Discov. 2020;6:14.

Potential positive effects of mTORi in COVID-19

- The mTOR exerts a vital role in regulating inflammation within the immune system, and controls multiple effector T cells
- mTOR pathway, in fact, has a central role in B and T cells development and proliferation
- The mTORC1 mediates T-Helper 1 and T-Helper 17 differentiation at the time of viral antigenic presentation by dendritic cells (DCs)
- mTORC2 mediates T-Helper 2 differentiation
- While both complexes restrict differentiation of the regulatory T-cell

published: 23 August 2021 doi: 10.3389/fphar.2021.710543

Potential positive effects of mTORi in COVID-19

- Data reported in the literature suggest that in patients with severe COVID-19, TH17 cells were increased, while Treg count was below normal value
- SARS-CoV-2 infection can cause an imbalance in TH17/Treg cells by dysregulation of the mTOR pathway
- Treg cells are responsible for maintaining the immune homeostasis by suppressing the activation, proliferation, and proinflammatory function of most T and B lymphocytes, and natural killer cells

Chen et al. J Clin Invest. 2020;130(5):2620-9

Pulmonary Fibrosis

- Namerous clinical data have reported an incidence of pulmonary complications in mTORi treated kidney transplant recipients of 2–11%, with the onset of symptoms until 5 years after the initiation of sirolimus or everolimus therapy

- There are several lung manifestations including :

➢ lymphocytic interstitial pneumonitis

➢lymphocytic alveolitis

➢bronchiolitis obliterans with organizing pneumonia

➢focal pulmonary fibrosis

➢diffuse alveolar hemorrhage

Pulmonary Fibrosis

- Pulmonary toxicity seems to be dose-dependent since clinical and radiologic improvement has been observed in a large number of kidney transplant recipients after mTORi dose reduction

- Some studies have reported that mTOR-I, when administrated at low dosage, may exert anti-fibrotic effects

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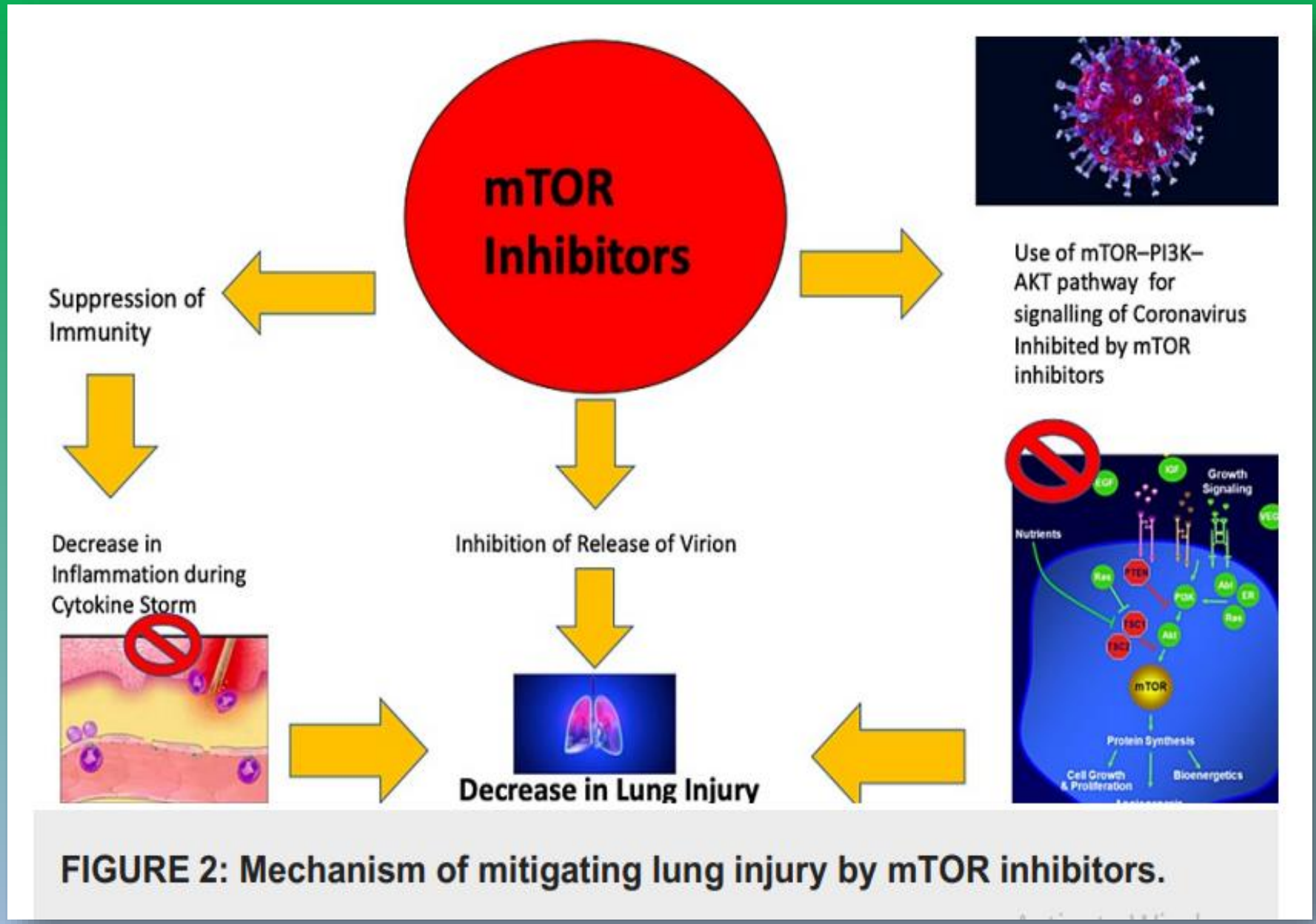

FIGURE 2: Mechanism of mitigating lung injury by mTOR inhibitors.

2021 Talwar et al. Cureus 13(8): e17102

Therefore, it is unquestionable that mTORi could act as a double edge sword in patients with COVID-19 and a correct use of this medication may have a beneficial clinical effects

The ongoing trials (NCT04341675, NCT04461340, NCT04948203) that evaluates the effects of sirolimus treatment in hospitalized COVID-19 patients will provide more information in the next future

- In COVID-19 kidney transplant recipients, we do not have enough evidence to support the hypothesis that mTOR-I may antagonize recovery or promote pulmonary complications

- Therefore, mTORi discontinuation should be reserved to kidney transplant recipients with severe COVID-19

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- In mild to moderate COVID-19 symptoms, a “wait and see approach” or a reduction of the dosage of these agents may be useful to minimize the risk of acute allograft rejection and to exploit their potential anti-viral and anti-fibrotic effects

- The reduction of the dosage may partially restore the host immunity facilitating the disease recovery, antagonize/mitigate the onset of cytokine storm, and preserve Treg growth and activity, which could reduce the progression to severe COVID-19.

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CASE REPORT

COVID-19 and Sirolimus Treatment in a Kidney Transplant Recipient

Ri Ra, Jin Sug Kim, Kyung Hwan Jeong, Hyeon Seok Hwang

A 59-year-old man was admitted with fever and sudden aggravation of dyspnea and mild cough and sputum production. He underwent living related donor kidney transplant 18 years prior
His maintenance immunosuppressive regimen included 6 mg/day sirolimus and 5 mg/day prednisolonee

We started lopinavir/ritonavir (400 mg/100 mg daily) for COVID-19 pneumonia and ceftriaxone (2 g daily) for prophylactic antibiotics . We maintained sirolimus and prednisolone at the same doses.

Two days later, the patient's fever persisted, hypoxemia continued, and CRP level increased considerably; however, over the next 3 days, his fever rapidly resolved, lymphocyte rate increased, and serum creatinine and CRP levels decreased.

CASE REPORT

COVID-19 and Sirolimus Treatment in a Kidney Transplant Recipient

We reported the successful treatment of COVID-19 pneumonia while maintaining sirolimus treatment in a renal transplant recipient. Sirolimus is an effective treatment option for renal transplant recipients with COVID-19, and pharmacologic interactions between immunosuppressants and lopinavir/ritonavir should be carefully monitored

We suspected sirolimus-induced hepatitis and discontinued lopinavir/ritonavir because of the potential interaction with sirolimus. We also reduced the sirolimus dose to 2 mg/day. The sirolimus trough levels decreased, and the liver enzymes began to normalize

Case report

Complete recovery from COVID-19 of a kidney-pancreas transplant recipient: potential benefit from everolimus?

Vanessa C Heron ,[1] Cindy-Anne T Bach,[2] Natasha E Holmes ,[3] John B Whitlam [1,4]

- 45-year-old man patient with T3 paraplegia underwent kidney-pancreas transplantation 18 years ago, followed by a subsequent kidney transplant 9 years ago, and presented with fever, hypoxia and hypotension after exposure to two confirmed cases of COVID-19
- History of solid organ transplant, pre-existing renal impairment, asthma, and an elevated D-dimer were identified as established risk factors for severe COVID-19
- Immunosuppressive regimen comprised everolimus 2mg two times per day and prednisolone 5mg daily

Case report

Complete recovery from COVID-19 of a kidney-pancreas transplant recipient: potential benefit from everolimus?

Vanessa C Heron [1], Cindy-Anne T Bach,[2] Natasha E Holmes [3], John B Whitlam [1,4]

We hypothesise that the relatively low level of baseline immunosuppression, in addition to the antiviral properties of everolimus, contributed to the relatively mild disease course in this case, despite multiple predictors of severe disease

Witl
and he remains well in the community 3months after his initial presentation

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BRIEF COMMUNICATION

AJT

mTOR inhibitors improve both humoral and cellular response to SARS-CoV-2 messenger RNA BNT16b2 vaccine in kidney transplant recipients

- Evaluated the association between mTOR-inhibitors (mTOR-I) and immune response to mRNA BNT162b2 (Pfizer-BioNTech) vaccine in KTR.

The presence of mTOR-I is associated with a better immune response to COVID-19 vaccine in KTR compared to therapy without mTOR-I, not only by increasing vaccine-induced antibodies but also by stimulating anti-SARSCoV-2 T cell respons

Moreover, SARS-CoV2-specific T cell–derived IFNγ release was significantly increased in patients treated with mTOR-I ($p < .001$), than in those without

Conclusion


Thanks for your attention