

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

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SUMMARY

We present a kidney-pancreas transplant recipient who achieved complete recovery from COVID-19. A 45-year-old 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. Supportive management was provided, baseline immunosuppression with everolimus was continued, and oral prednisolone was increased. A complete recovery was observed. Given the favourable outcome despite risk factors for severe COVID-19, we identify and review the potential mitigating roles of immunosuppression and mammalian target of rapamycin (mTOR) inhibitors in this disease. Further investigation is required to establish whether mTOR inhibitors could be used as therapeutic agents to treat COVID-19, or as alternative immunosuppression implemented early in the COVID-19 disease course.

BACKGROUND

The first case of COVID-19 caused by SARS-CoV-2 was described in December 2019,¹ and the disease was declared a pandemic by the WHO on 11 March 2020.² There is evidence that the elderly, those with existing comorbidities and those with compromised immune systems³ are at greater risk of severe disease. The outcomes of solid organ transplant (SOT) recipients infected with COVID-19 remain under study, but preliminary reports indicate that outcomes are significantly poorer than the general population.⁴ While immunosuppression has been hypothesised to be associated with poor prognosis, mammalian target of rapamycin (mTOR) inhibitors, which can be used for transplant immunosuppression, may influence outcomes of SOT recipients with COVID-19. mTOR inhibitors have been previously investigated as potential antiviral therapeutics, including treatment for coronaviruses and influenza.⁵

CASE PRESENTATION

A 45-year-old man presented for investigation of a 2-day history of fever on the background of a simultaneous kidney-pancreas transplant 18 years ago complicated by allograft-associated renal cell

carcinoma. He had undergone a graft nephrectomy and a subsequent living-related kidney transplant 9 years ago. A motor vehicle accident 4 years ago caused complete T3 paraplegia with requirement for long-term intermittent self-catheterisation. His medical history also included type 1 diabetes, Epstein-Barr Virus-associated post-transplant cerebral lymphoma that was treated with rituximab 9 years ago (now in remission), BK and cytomegalovirus viraemia, pulmonary embolus (on rivaroxaban), asthma, and thalassaemia trait. His transplant immunosuppressive regimen comprised everolimus 2 mg two times per day and prednisolone 5 mg daily. His preadmission baseline creatinine was 79 $\mu\text{mol/L}$ (60–110 $\mu\text{mol/L}$), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimated glomerular filtration rate was $>90 \text{ mL/min/1.73 m}^2$ and everolimus level was 4.3 $\mu\text{g/L}$. Other medications included fludrocortisone, pantoprazole, pregabalin, tapentadol and sertraline.

Vital signs on presentation included temperature of 40.1°C, blood pressure of 130/80, heart rate of 97 beats per minute and oxygen saturation of 97% on ambient room air, which dropped to 87% several hours after admission. He required 2 L/min of oxygen administered by nasal prongs to maintain oxygen saturation $\geq 96\%$. He did not require any supplemental oxygen after the first day of admission. He became hypotensive (blood pressure 80/50) 3 hours after admission, and this was managed with intravenous crystalloids and increased dose of oral prednisolone to 15 mg daily. Intravenous fluids were not continued due to concern for potential worsening of his respiratory status in the setting of COVID-19.

INVESTIGATIONS

Investigations revealed a stable anaemia (haemoglobin 102 g/L; 130–170 g/L), with a normal white cell count (9.4×10^9 ; $4\text{--}11 \times 10^9$) and lymphocyte count (2.5×10^9 ; $1\text{--}3.5 \times 10^9$). His creatinine was 93 $\mu\text{mol/L}$ (60–110 $\mu\text{mol/L}$), and his lipase was normal at 28 units/L (10–60 units/L). His C reactive protein was elevated (91 mg/L; 0–5 mg/L). Given his presentation with a febrile illness and recent exposure to two confirmed cases of COVID-19, combined oropharyngeal and nasopharyngeal swab was obtained and SARS-CoV-2 was detected by nucleic acid testing. Chest X-ray on admission and after 48 hours did not demonstrate any evidence of pneumonia or pulmonary infiltrates, and he did



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not require further supplemental oxygen after day 1 of admission. He had an elevated D-dimer of 1163 ng/mL (<500 ng/mL), ferritin of 429 µg/L (30–340 µg/L) and lactate dehydrogenase of 310 units/L (120–250 units/L).

TREATMENT

Baseline immunosuppression was continued apart from the short course of stress-dose prednisolone given for 3 days due to hypotension shortly after admission. Meropenem was initiated for treatment of polymicrobial urinary tract infection (UTI) in the setting of recurrent UTIs and intermittent self-catheterisation. He did not receive other medications with putative activity against COVID-19 such as lopinavir/ritonavir or hydroxychloroquine in accordance with local treatment guidelines at the time. In the absence of supportive criteria for cytokine release syndrome, an interleukin 6 inhibitor was not given. His everolimus level was 6.7 µg/L.

OUTCOME AND FOLLOW-UP

With supportive care, the patient was discharged home 8 days after admission (day 10 of COVID-19 illness), and he remains well in the community 3 months after his initial presentation. The patient had presumed low level viral shedding, as evidenced by discrepant PCR results (detected/not detected) on different platforms, up until 3 months after initial admission.

DISCUSSION

The first case reports of COVID-19 in SOT recipients came from China, where two heart transplant recipients made complete recovery from their illness.²

The outcomes of COVID-19-infected kidney transplant recipients remain under study. Columbia University reported 15 cases in kidney transplant recipients.⁶ Of the cases 27% needed mechanical ventilation and two died; however, not all cases had recovered at the time of publication. This group concluded that the outcomes in this cohort were similar to the general population.⁶ On the other hand, an Italian cohort including 20 kidney transplant recipients reported a 25% mortality rate and hypothesised that kidney transplantation may be associated with unfavourable outcomes.⁴ Seven cases have been reported in South London hospitals, including one death.⁷ Long-term outcomes and consequences for kidney transplant function remain to be seen.

According to the US Centers for Disease Control and Prevention, SOT recipients are at high risk of severe COVID-19.⁸ Pre-existing chronic kidney disease, prior haematological malignancy, chronic lung disease and the presence of an elevated D-dimer are all features of the described case associated with increased likelihood of severe disease.⁹ Additionally, there was a history of several opportunistic viral infections in our case. The impact of spinal cord injury on COVID-19 outcomes is not known. Unexpectedly, apart from the initial hypoxia and hypotension that responded quickly to conservative measures, this case did not have severe or complicated disease course. This may be because COVID-19 has a variable clinical presentation and may not necessarily follow a serious course of infection despite underlying risk factors or organ transplantation.¹⁰ However, it is plausible that outcomes in SOT recipients are influenced by the type of baseline immunosuppression.

There is debate about whether immunosuppression is protective or harmful in COVID-19. It has been suggested that there are two phases of the disease.¹¹ First, there is an incubation period and viral replication. During the second phase, there is

systemic inflammation, driven by T cell activation, which can cause cytokine storm and lung injury.¹¹ While immunosuppressive medications may promote viral replication, the anti-inflammatory effects could dampen the systemic inflammatory response and lessen disease severity during the second phase of illness.^{11 12} The modification of immunosuppression may therefore have variable effects at different stages of the disease, and the withdrawal of immunosuppression at the point of critical illness may be counterproductive.

Many case reports of infected transplant recipients described management with immunosuppression reduction.^{4 7 8 13} Of the 40 cases of COVID-19-infected transplant patients Johnson *et al*⁸ reviewed in the literature, only 3 were managed without alteration to pre-existing immunosuppression doses, with 30 cases completely ceasing calcineurin inhibitor (CNI) and anti-proliferative treatment. Given the stable clinical picture and the relatively low level of baseline immunosuppression in the presented case, a decision was made to continue immunosuppression without modification.

There are few cases of COVID-19 in kidney transplant recipients treated with mTOR inhibitors. Guillen *et al*¹³ reported a case of a 50-year-old man with a history of kidney transplant, splenectomy and post-transplant lymphoproliferative disease managed with tacrolimus, everolimus and prednisolone. Following a COVID-19 diagnosis, tacrolimus and everolimus were stopped, and he was treated with lopinavir, ritonavir and hydroxychloroquine. On day 6 of admission (day 10 of illness), he was intubated and interferon beta was commenced. His outcome is unknown.¹³

While mTOR inhibitors are less commonly used as first-line immunosuppression, case series of kidney transplant recipients with COVID-19 appear to be under-represented by individuals on mTOR inhibitors. From a series of 20 kidney transplant recipients, 2 were on mTOR inhibitor maintenance immunosuppression.⁴ These included a 70-year-old woman, also on a CNI, who survived to home discharge, and a 44-year-old man on a CNI and mTOR inhibitor who was an inpatient at the time of reporting but stable on room air. The first case was managed with lopinavir/ritonavir and hydroxychloroquine, while the second received darunavir, ritonavir and hydroxychloroquine. Both cases had their baseline immunosuppression withdrawn.⁴

A Spanish group reported 1 kidney transplant recipient and 2 liver transplant recipients treated with everolimus in a cohort of 18 patients. The kidney transplant recipient was also taking prednisolone and tacrolimus, and developed severe acute respiratory distress syndrome necessitating high-flow oxygen administration. Some radiological improvement was noted prior to publication. One liver transplant recipient usually managed with everolimus alone recovered, while another died.¹⁴

The prior emergence of Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus prompted investigation into therapeutic targets for coronaviruses. mTOR inhibitors have been identified as potential therapeutic agents given their known antiviral properties. Everolimus has been used to treat Kaposi's sarcomas associated with human gammaherpesvirus 8.¹⁵ Furthermore, analysis of the MERS-CoV infection found that it modulated the ERK/MAPK and PI3K/AKT/mTOR signalling responses, which play a significant role in the host response to infection.⁵ Everolimus was found to have an inhibitory activity against MERS-CoV.⁵ Additionally, sirolimus, another mTOR inhibitor, was found to stop viral protein expression and virion release in MERS-CoV.^{16 17} mTOR signalling also appears to be important in H1N1 influenza infections, where sirolimus administration in those with respiratory

failure improved prognosis.¹⁶ Studies have shown that sirolimus in addition to steroids improved outcomes in humans infected with H1N1,^{17 18} although this was not replicated in a subsequent study.¹⁹ Martins *et al*²⁰ found in vitro that the mTOR pathway played a role in internalising the parasite *Trypanosoma cruzi*. It remains to be demonstrated if mTOR inhibitors could hinder the internalisation of a virus such as SARS-CoV-2, thereby modifying the disease course. However, it is plausible that everolimus, given as maintenance immunosuppression, could have contributed to the favourable outcome in this case, despite risk factors for severe disease and prior evidence of poor antiviral immune responses. Continuation of pre-existing maintenance everolimus immunosuppression should therefore be considered in transplant recipients who have contracted SARS-CoV-2.

In conclusion, the potential mitigating role of mTOR inhibitors was identified and reviewed in a case of COVID-19 infection in a kidney-pancreas transplant recipient. 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. This proposition is supported by previous research showing that mTOR inhibitors can have antiviral effects, including for coronaviruses. Further investigation is required to establish whether mTOR inhibitors could be used as therapeutic agents to treat COVID-19, or as alternative immunosuppression implemented early in the COVID-19 disease course. Until further research is available clinicians should continue or adjust immunosuppression based on the clinical course, risk factors for severe disease and immunosuppressive regimen.

Learning points

- ▶ Mammalian target of rapamycin (mTOR) inhibitors can have antiviral effects, including for coronaviruses.
- ▶ Further investigation is required to establish whether mTOR inhibitors could be used as therapeutic agents to treat COVID-19, or as mitigating alternative immunosuppression implemented early in the COVID-19 disease course.
- ▶ While immunosuppressive medications may promote viral replication, the anti-inflammatory effects could dampen the systemic inflammatory response and lessen disease severity during the second phase of the COVID-19 illness.
- ▶ The modification of immunosuppression may have variable effects at different stages of COVID-19, and the withdrawal of immunosuppression at the point of critical illness may be counterproductive.

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