## Lopinavir/ritonavir/sirolimus interaction

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### Hepatitis following an off-label use: case report

A 59-year-old man developed hepatitis following concomitant administration of sirolimus and an off-label lopinavir/ritonavir for COVID-19.

The man was admitted with sudden aggravation of dyspnoea and fever. Previously, he was diagnosed with end-stage renal disease due to immunoglobulin A nephropathy and underwent living related donor kidney transplant 18 years prior to admission. He received immunosuppressive treatment with sirolimus 6 mg/day [*routes not stated*] and prednisolone. His comorbidities included diabetes, dyslipidaemia and hypertension. He complained of sputum production and mild cough and was tested positive on RT-PCR for COVID-19. His oxygen saturation was 96% with 2 L/min oxygen administered via a nasal cannula and body temperature was 38.0°C. His laboratory tests showed decreased lymphocyte count, elevated serum creatinine and increased C-reactive protein (CRP) level. Chest radiography revealed infiltrative patch opacities in both lungs. Chest CT scan showed bilateral multifocal ground-glass opacities that were consistent with COVID-19 pneumonia. For COVID-19 pneumonia, he started receiving an off-label lopinavir/ritonavir 400mg/100mg daily along with ceftriaxone for prophylactic antibiotics. Sirolimus and prednisolone doses were maintained the same. Two days later, his fever persisted, CRP level increased and hypoxaemia continued. However, over the next 3 days, his lymphocyte rate increased, serum creatinine and CRP levels decreased and fever rapidly resolved. On day 5, his multifocal consolidation on chest radiography was nearly resolved. His COVID-19 results were negative 4 consecutive times from hospital day 6. His laboratory tests showed an increase in aspartate aminotransferase 647 U/L, alkaline phosphatase 439 U/L, total bilirubin 5.41 mg/dL and alanine aminotransferase 357 U/L on day 5. His viral hepatitis infection markers was negative, and liver ultrasonography did not show any abnormal findings to explain the increased hepatic enzymes levels. Sirolimus levels abruptly increased to 122.9 ng/mL. Sirolimus-induced hepatitis due to potential interaction of lopinavir/ritonavir with sirolimus was suspected.

The man's treatment with lopinavir/ritonavir was discontinued and dose of sirolimus was reduced to 2 mg/day. Thereafter, his sirolimus trough levels decreased and liver enzymes began to normalize. During the hospitalisation, prednisolone was continued. Finally, he was discharged on day 22 of the hospitalisation.

Ra R, et al. COVID-19 and Sirolimus Treatment in a Kidney Transplant Recipient. Experimental and Clinical Transplantation 19: 977-980, No. 9, Sep 2021. Available from: URL: http://doi.org/10.6002/ect.2021.0232

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