Multiple drugs

X S

Various toxicities: case report

A 35-year-old man developed COVID-19 during immunosuppressive treatment with prednisolone and everolimus, and respiratory deterioration with respiratory insufficiency secondary to pulmonary interstitial disease and renal function deterioration due to everolimus toxicity following concomitant administration of everolimus and off-label lopinavir/ritonavir. Paracetamol use was a contributory factor for renal function deterioration [*not all routes and dosages stated; durations of treatments to reactions onsets not stated*].

The man, who had a history of end-stage renal disease of unknown origin, underwent renal transplant in 2016. Thereafter, he started receiving immunosuppressive therapy with SC alemtuzumab 15mg QD on two consecutive days and autologous mesenchymal stromal cells for induction followed by dual maintenance immunosuppressive therapy with everolimus 3mg twice daily and prednisolone 7.5mg once daily. Trough concentrations of everolimus were targeted between 3–8 µg/L. On 29 February 2020, he developed a cough, fever, muscle pain, malaise and headache. General practitioner treated him with paracetamol [acetaminophen] and tramadol. However, his complaints progressed. Therefore, he was hospitalised in Netherlands, on 10 March 2020. At that time he complained of dyspnoea with tachypnoea, rhinorrhoea, productive cough with sputum, muscle ache, headache, vomiting, nausea and loose stools without abdominal pain. Laboratory examination revealed lymphopenia, acute on chronic kidney injury, increased inflammatory markers, increased transaminases, rhabdomyolysis, a high anion gap metabolic acidosis due to renal insufficiency and acute respiratory alkalosis with hypoxaemia. Chest radiography revealed peripheral consolidations in multiple lobes in the lung, raising suspicion of COVID-19 pneumonia. Nasopharyngeal swab for SARS-CoV-2 and urine pneumococcal antigen test were positive.

Strict viral isolation followed. The man was given oxygen by nasal cannula and off-label IV cefuroxime was started. However, dyspnoea with tachypnoea persisted leading to admission in the ICU. He remained respiratory stable on 5L of oxygen through nasal cannula. Additionally, he started receiving off-label oral chloroquine 300mg twice daily following 600mg loading dose and off-label antiviral therapy with lopinavir/ritonavir 400/100mg twice daily. Considering possibility of interaction between everolimus and lopinavir/ritonavir, the dose of everolimus was reduced to 2mg twice daily. Cefuroxime therapy was switched to off-label ceftriaxone. He was discharged to the inpatient clinic on 12 March 2020. Despite everolimus dose reduction at ICU admission, he exhibited supratherapeutic trough concentration on 12 March 2020. Therefore, everolimus was stopped. On 14 March 2020, his renal function and respiratory status deteriorated, requiring transfer to transplant center for further management. Everolimus level was persistently elevated despite discontinuation of everolimus 2 days earlier. Further novel deterioration with respiratory insufficiency led to ICU admission and rapid intubation. A positive end expiratory pressure (PEEP) in combination with a fraction inspired oxygen (FiO2) of 60% was given. A repeated thoracic radiograph revealed progressive bilateral consolidations, most prominent in the right upper lobe. Lopinavir/ritonavir and chloroquine, which he had received for 4 days, were stopped. Off-label antibiotics were continued and unspecified loop diuretics were started. Four days later, he was successfully extubated while on supplemented oxygenation and discharged to the COVID-19 ward. Everolimus concentrations were decreasing and reached below the detection limit on 23 March 2020. Given the association between everolimus trough levels, and appearance and reversibility of respiratory deterioration, pulmonary interstitial disease due to everolimus toxicity in combination with pulmonary oedema was considered as a contributory factor to respiratory deterioration. From 23 March 2020, ciclosporin-based immunosuppressive therapy was started. Thereafter, he recovered steadily. However, his renal function had not returned to baseline, probably due to a combination of everolimus toxicity, paracetamol use, viral tubulo-interstitial nephritis and/or rhabdomyolysis. Twenty-four-hour urinalysis revealed 630mg proteinuria with no leucocyturia or erythrocyturia. On 24 March 2020, 15 days following admission, he was discharged with self-quarantine precautions.

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