## Hydroxychloroquine/immunosuppressants

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### Nosocomial coronavirus disease 2019 (COVID-19), leucopenia and prolonged persistence of COVID-19 following off-label use: case report

A 62-year-old man developed nosocomial COVID-19, leucopenia and prolonged persistence of COVID-19 during immunosuppressive treatment with ciclosporin, mycophenolate-mofetil and prednisone. Additionally, off-label treatment with hydroxychloroquine for nosocomial COVID-19 was considered to have contributed to the persistent course of COVID-19 [*routes and times to reactions onsets not stated; not all dosages and outcomes stated*].

The man, who had undergone heart transplantation on 2 November 2019 for arrhythmogenic cardiomyopathy of the right ventricle, continued to remain hospitalised at a centre in Germany due to a series of complications, which included pneumonia, acute respiratory distress syndrome (ARDS), respiratory failure and renal failure on haemodialysis. He required 56 days of mechanical ventilation, and he also needed intermittent renal replacement therapy. Following transplantation, he had been receiving immunosuppressive therapy with ciclosporin [cyclosporine A; target range 135±30 ng/mL), mycophenolate mofetil 500mg twice daily and prednisone 10mg once daily. He was noted to have anaemia [*aetiology unknown*] and leucopenia on blood count, and the leucopenia was considered to have been likely caused by immunosuppressive medications (ciclosporin, mycophenolate-mofetil and prednisone).

The doses of immunosuppressive medications were reduced; however, the leucopenia did not improve significantly under dose reduction. Concomitantly, he received cotrimoxazole, and he had received ganciclovir for 4 months following transplantation due to cytomegalovirus (CMV) high-risk constellation (D + R−). He had been also receiving ganciclovir for 4 months after transplantation that was then switched to prophylactic valganciclovir. On 13 March 2020 (day 1), he developed fever (39.9°C), sore throat and tachycardia (105 bpm). PCR from throat swab showed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, which indicated COVID-19. Weaning from haemodialysis was successful (day 1). Body temperature was noted to have quickly normalised within the first 12 hours, and blood oxygen saturation levels were noted to remain stable (96–100%) without oxygen supplementation at a respiratory rate of 16 breaths/minute. He also had mild rhinorrhoea and impaired exercise capacity. On day 7, he developed a second increase in temperature up to 38.4°C (fever), which spontaneously resolved. Along with this episode of fever, lymphopenia and a mild rise and peak of CRP, interleukin-6 (IL-6) and pro-B-type natriuretic peptide (proBNP) levels were observed. A CT scan revealed regressive post-inflammatory alterations after bacterial pneumonia and ARDS, without any clear signs of COVID-19 pneumonia and bacterial superinfection. Also, procalcitonin level was low. He therefore received off-label treatment with hydroxychloroquine at a loading dose 400mg twice daily, followed by 200mg twice daily from day 7 to day 14. He was free of marginal residual clinical symptoms since day 20; however, he showed positive SARS-CoV-2 RT-PCR (from oropharyngeal swab) on days 1, 5, 7, 11, 18, 21, 25, 28, 33 and day 35. Concurrent with the second onset of fever, an increased viral load following day 7, that slowly returned to the level of infection onset, was observed. Virus cultures on day 18 and day 21 confirmed active virus replication, while he was asymptomatic. Based on increase and decrease in proBNP levels simultaneously with the inflammation parameters, a COVID-19-related myocardial infection was suspected. Urine output and body weight were noted to remain stable. The dose of ciclosporin was adjusted several times over the course of COVID-19 infection to achieve a therapeutic range of 135±30 ng/mL. The dose of prednisone was increased to 50mg for 3 days and 25mg for another 3 days from day 14 for the treatment of acute gout in the left knee, and all the medications including immunosuppressants were continued unchanged. He developed a mild nosocomial COVID-19 secondary to immunosuppressive treatment with ciclosporin, mycophenolate-mofetil and prednisone. Also, he demonstrated prolonged virus persistence due to immunosuppression, and hydroxychloroquine was considered to have also contributed to the persistent mild course of disease (without symptoms) after the first week of SARS-CoV-2 infection.

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