Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother
doi:10.1093/jac/dkaa213

Failure of hydroxychloroquine pre-exposure prophylaxis in COVID-19 infection? A case report

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Sir,

The use of hydroxychloroquine against COVID-19 is controversial following the report of a case series of COVID-19 patients with inflammatory diseases [i.e. systemic lupus erythematosus (SLE), rheumatoid arthritis or sarcoidosis] treated with hydroxychloroquine.[1]

We report the case of a man in his seventies (95 kg, 1.83 m, BMI 28.4 kg/m^2) admitted to the Emergency Department of a hospital for fever, dyspnoea and polypnoea. Upon arrival, he was conscious, oriented and without cardiac disorders. He presented with fever (38°C), with 98% oxygen saturation and resting respiratory rate at 26 cycles/min, blood pressure at 150/83 mmHg and plasma C-reactive protein (CRP) at 77 mg/L. The patient reported the onset, 9 days earlier, of a cough (without sputum), with feverish sensation, myalgia, rhinitis and confusional syndrome with memory loss. His GP ordered a cough suppressant. His medical history included sarcoidosis affecting the lungs, skin and heart requiring the installation of a pacemaker and prescription of hydroxychloroquine 200 mg q12h and prednisone 7 mg q24h for 1 year. Since that day, the multivisceral sarcoidosis was controlled by this dual therapy. Given the clinical picture in the Emergency Department, empirical antibiotic and antiviral therapy [ceftriaxone (1 g q24h), spiramycin (1 MIU q8h) and oseltamivir (75 mg q12h)] was prescribed with 2–3 L/min oxygen (via mask). The chest CT scan showed small areas of ground-glass opacities, i.e. typical lesions of SARS-CoV-2 infection, and a nasopharyngeal sample returned positive for SARS-CoV-2 by RT–PCR (Ct = 16.53). In light of the latter results, he was then referred to the Infectious Diseases Department, where antibiotics and oseltamivir were discontinued. Hydroxychloroquine was maintained for his sarcoidosis.

Two days after his hospitalization (D2), he had severe acute respiratory distress. Lopinavir/ritonavir (400/100 mg q12h orally for 10 days) and dexamethasone (IV, 10 mg for 3 days then 5 mg for 7 days) were added.

At D4, and towards the presumption of lack of efficacy of hydroxychloroquine against SARS-CoV-2, we first performed the determination of hydroxychloroquine blood trough concentration (C_{trough}) for the sarcoidosis indication (usual target C_{trough} of 950 ng/mL in inflammatory diseases)[2] using LC-coupled fluorescence detection (Waters Alliance, Milford, MA, USA).[3]

The blood C_{trough} of hydroxychloroquine was <200 ng/mL, suggesting a lack of previous treatment adherence with the absence of visceral progression of the sarcoidosis.

In parallel, we determined lopinavir and ritonavir plasma C_{trough} using LC coupled with tandem MS: 19 672 and 1744 ng/mL, respectively (UPLC-MSMS Xevo, Waters, USA).[4]

At D10, we determined the plasma concentration of hydroxychloroquine, on top of lopinavir/ritonavir, using UPLC-MSMS Xevo (limit of quantification <3 ng/mL).[5] Hydroxychloroquine, lopinavir and ritonavir plasma C_{trough} were 242, 6430 and 261 ng/mL, respectively. At the same time, CRP was 3 mg/L.

Hydroxychloroquine plasma C_{trough} was >100 ng/mL suggesting an adequate penetration in the pulmonary compartment with an expected unbound inhibitory quotient in tissue >80.[6]

Indeed, hydroxychloroquine, as a weak base, demonstrates an extensive volume of distribution attributed to tissue binding.[7] It enters erythrocytes via passive diffusion and accumulates in blood cells, with a mean ± SD blood to plasma ratio of 7.2±4.2.[7] Hydroxychloroquine presents a long terminal elimination half-life (50±16 days)[7] probably in relation to its extensive volume of distribution. With the latter data on the blood to plasma ratio of hydroxychloroquine, at D10, we might expect a blood concentration of at least 3-fold higher than in plasma, confirming the initial long-term adherence difficulties. However, Mathian *et al.*[1] reported a case series of COVID-19 in 17 SLE patients treated with hydroxychloroquine. Blood concentrations of hydroxychloroquine were 648 ng/mL (median; range = 254–2095 ng/mL). Those results might put at risk the benefit of hydroxychloroquine as SARS-CoV-2 prophylaxis.

At D14, all symptoms disappeared and the nasopharyngeal sample returned negative by RT–PCR. At D21, the patient was discharged from the Infectious Diseases Department.

The high lopinavir and ritonavir C_{trough} might probably be explained by the inhibition of the CYP450 activity consecutive to the cytokine storm.[8] Considering the usual upper limit of lopinavir C_{trough} of 8000 ng/mL,[9] as reported in HIV-infected patients, the lopinavir C_{trough}, at D4, was 2-fold higher than in those patients. However, recent data reported a high EC_{50} of lopinavir for SARS-CoV-2 (9.1–26.6 μM; 5722–16745 ng/mL).[10] Moreover, few data on lopinavir/ritonavir penetration in the lung compartment are available,

particularly for such a short-course treatment. Finally, the use of dexamethasone probably helped to reduce the inflammatory process and improved lopinavir/ritonavir disposition since, at D10, CRP and lopinavir/ritonavir C_{trough} were in the usual range. No Cushing's syndrome was observed despite lopinavir/ritonavir and dexamethasone drug–drug interaction, which is probably due to the short-course treatment.

In conclusion, at first glance, we were surprised by a SARS-CoV-2 infection in a patient treated with hydroxychloroquine 200 mg q12h for 1 year for his sarcoidosis. The use of therapeutic drug monitoring might have explained such an outcome by a lack of adherence to treatment, preventing us from jumping to the wrong conclusion.

Funding

None to declare.

Transparency declarations

M.P.L. has received travel grants from Bristol Myers Squibb and Janssen. B.V. has received travel grants from Gilead and Janssen, and payment for giving a lecture for Gilead. D.D. has received fees for participating in advisory boards for Gilead Sciences, ViiV Healthcare, Janssen-Cilag and MSD. J.G. has received travel grants, consultancy fees, honoraria or study grants from various pharmaceutical companies, including Gilead Sciences, Janssen, Merck and ViiV Healthcare. G.P. has received travel grants, consultancy fees, honoraria or study grants from various pharmaceutical companies, including Bristol Myers Squibb, Gilead Sciences, Janssen, Merck and ViiV Healthcare. All other authors: none to declare.

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