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Letter to the Editor

A severe COVID-19 despite ongoing treatment with Lopinavir-Ritonavir

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To the Editor

Since December 2019, an outbreak of a novel human severe acute respiratory syndrome coronavirus (SARS-CoV-2) has become pandemic [1]. In Europe, no antiviral treatment is specifically authorized to date for patients with COVID-19. Lopinavir/ritonavir has been proposed to treat patients with COVID-19 (Coronavirus Disease 2019) although no randomized study has proven its efficacy yet [2]. We report here for the first time a case of severe COVID-19 in a patient receiving ongoing treatment with lopinavir/ritonavir for Human Immunodeficiency Virus (HIV) infection.

A 65-year-old patient was admitted to Cochin Hospital (Paris, France) for fever, dry cough and shortness of breath that started 7 days prior to admission. He had a past medical history of hypertension, overweight and HIV infection currently treated with abacavir/lamivudine and Lopinavir/Ritonavir (200/50 mg, 2 tablets twice a day). Viral load was undetectable and $CD4^+$ count was $810/mm^3$ 3 months prior to admission. On admission, oxygen saturation was 84% in room air. Laboratory findings showed high inflammatory markers (C-reactive protein 350 mg/L; fibrinogen 9.6 g/L), lymphopenia (lymphocyte count 0.89×10^9/L) and moderate hepatic cytolysis and cholestasis. HIV viral load was under the detection threshold and the CD4/CD8 lymphocyte ratio was normal (1.31 for normal range 1–3.6). Unenhanced chest CT scan showed bilateral peripheral diffuse ground glass opacities, highly suggestive of COVID-19 pneumonia (Fig. 1A). The reverse transcription polymerase chain reaction on nasopharyngeal swab was positive for SARS-CoV-2. The patient was treated with intravenous cefotaxime and spiramycin and lopinavir/ritonavir was continued. Low-dose enoxaparin (4000 IU per day) was administered for thromboprophylaxis. Therapeutic dose monitoring for blood lopinavir and ritonavir concentrations measured 2 days after admission showed that both drugs were overdosed respectively at 25,982 ng/mL (normal range 1,000-8,000 ng/mL) and 1,194 ng/mL (target around 500 ng/mL). Day 9 after symptom onset, patient's condition required to increase oxygen therapy up to 7 L/min to maintain an oxygen saturation > 94%. D-dimer level was high at 2,414 ng/mL. A pulmonary CT angiography did not show any pulmonary embolism but a rapid progression of the pneumonia with more extensive lesions combining consolidations and ground glass opacities (Fig. 1B). Day 13 after symptom onset, further impairment of the respiratory status required to initiate high-flow nasal oxygen therapy (HFNOT) with a FiO_2 up to 75%. Fibrinogen level had increased to 10.9 g/L and D-dimer level was over 10 000 ng/mL. A second pulmonary CT angiography showed critical lung parenchyma involvement with diffuse large bilateral consolidations with air-bronchogram (Fig. 1C) and pulmonary embolism in a segmental artery of the right upper lobe (Fig. 1D). Curative enoxaparin was started. He subsequently improved and could be weaned from HFNOT after one week and from oxygen 34 days after symptom onset. Patient was discharged quickly afterwards.

To our knowledge, this is the first published case of severe COVID-19 in a patient already treated with lopinavir/ritonavir for chronic HIV infection with good immunovirological status. In our patient, not only lopinavir/ritonavir failed to prevent SARS-CoV-2 infection, but it also failed to prevent rapid progression to severe pneumonia. To support these findings, 3 cases of COVID-19 were recently reported in HIV patients despite antiretroviral regimen containing darunavir, a protease inhibitor similar to lopinavir and currently under investigation in phase III trial for patients with COVID-19 [3]. Yet, no clinical data support antiretroviral therapy regimen modification (i.e. to include a protease inhibitor like lopinavir or darunavir) in HIV patients with COVID-19 [4].

Preliminary results from patients treated with lopinavir/ritonavir for COVID-19 have been equivocal [5,6]. A large randomized controlled trial including patients with severe COVID-19 indicated that the addition of lopinavir/ritonavir to standard care did not decrease the time to clinical improvement compared with standard care alone [2]. There was a trend towards decreased mortality with lopinavir/ritonavir, and the numerical difference in mortality was greater among those who were randomized within 12 days of symptom onset, but neither difference was statistically significant. However, this study was underpowered to show effects on mortality. Recently, Yan et al. reported that lack of lopinavir/ritonavir treatment was independently associated with prolonged viral shedding in patients with COVID-19 [7], suggesting that earlier administration of lopinavir/ritonavir could shorten viral shedding and disease duration in COVID-19 [8].

So far, HIV infection has not emerged as a risk factor for severe COVID-19 [9]. Blanco et al. reported a prevalence of HIV infected patients of 1% among those hospitalized for severe COVID-19 (5 out of 543) in Barcelona, however, none of them had lopinavir/ritonavir-containing antiretroviral regimen [10]. Among the 5 patients, 4 recovered and one remained in intensive care unit. However, reliable data on prevalence or clinical characteristics of COVID-19 in patients with HIV infection are still missing [4].

In our patient, we cannot state that the disease severity would not have been greater if lopinavir/ritonavir combination had not been administered. We can only notice that, despite this treatment,

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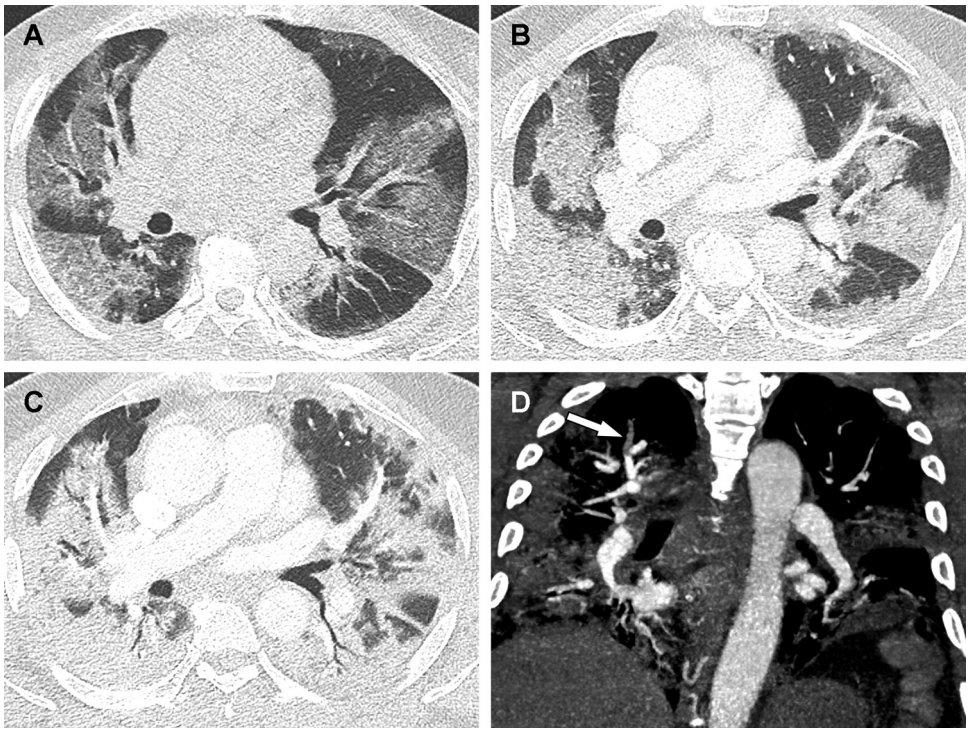

Fig. 1. Chest computed tomography (CT) scan findings over time in a 65-year-old patient, previously treated by lopinavir/ritonavir for chronic HIV infection and presenting with typical pneumonia secondary to SARS-COV-2 infection. Eight days after symptom onset: axial unenhanced CT image of lung parenchyma showing peripheral bilateral ground glass opacities (A). Nine days after symptom onset: axial enhanced CT image of lung parenchyma showing rapid progression of the pneumonia with a mixed pattern combining consolidations and ground glass opacities (B). Thirteen days after symptom onset (C and D): (C) pulmonary CT angiography showing large bilateral consolidations with air-bronchogram; (D) coronal maximum intensity projection reformation showing pulmonary embolism in a segmental artery of the right upper lobe (arrow).

the disease became very severe, as assessed by oxygen requirements, CT-scan images and occurrence of pulmonary embolism, a now classical complication of severe COVID-19 [11].

In conclusion, this observation questions the efficacy of lopinavir/ritonavir combination for preventative or curative treatment in patients with COVID-19. The results of ongoing clinical trials assessing the effects of lopinavir/ritonavir for the treatment of COVID-19 infection are needed to confirm this observation.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgment

None of the authors have an association that might pose a conflict of interest to report.

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H. Joumaa [a,1]
L. Regard [a,b,1]
N. Carlier [a]
G. Chassagnon [b,c]
E. Alabadan [a]
E. Canouï [d]
A. L'honneur [e]
F. Rozenberg [e]
P.-R. Burgel [a,b]
N. Roche [a,b,*]

[a] *Service de pneumologie, hôpital Cochin, AP–HP, 27, rue du Faubourg-Saint-Jacques, 75014 Paris, France*
[b] *Université de Paris, institut Cochin, Inserm U1016, 24, rue du Faubourg-Saint-Jacques, 75014 Paris, France*
[c] *Service de Radiologie, hôpital Cochin, AP–HP, 27, rue du Faubourg-Saint-Jacques, 75014 Paris, France*
[d] *Équipe mobile d'infectiologie, centre université de Paris, site Cochin, AP–HP, 27, rue du Faubourg-Saint-Jacques, 75014 Paris, France*

[e] *Service de virologie, hôpital Cochin, AP–HP, 27, rue du Faubourg-Saint-Jacques, 75014 Paris, France*

[*] Corresponding author at: Service de pneumologie, hôpital Cochin, AP–HP, 27, rue du Faubourg-Saint-Jacques, 75014 Paris, France.
E-mail address: nicolas.roche@aphp.fr (N. Roche)

[1] These authors equally contributed to this article.

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