Pharmacological Research 157 (2020) 104826

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Darunavir does not prevent SARS-CoV-2 infection in HIV patients

In 2003, the screening of approved drugs identified lopinavir, the inhibitor of HIV type 1 aspartate protease, as a potential treatment of severe acute respiratory syndrome (SARS) caused by coronavirus (SARS-CoV) [1,2]. Lopinavir and also darunavir, the most recent HIV protease inhibitor, are the current proposed drugs also for the treatment of COVID-19 caused by SARS-CoV-2 [3]. In this paper we report three HIV-positive subjects on antiretroviral (ARV) regimen containing darunavir with good immunovirological status, diagnosed with COVID-19.

On March 10th 2020, a 62-years-old HIV-positive man was admitted at our emergency department referring dry cough and fever up to 38.8 °C for at least 7 days. His ARV regimen consisted of darunavir/cobicistat 800/150 mg and lamivudine 300 mg once daily. Blood tests performed less than 2 months earlier showed an undetectable viral load (< 20 copies/mL) and a CD4+ count of 0.441 × 10^3/μL. He was also on maintenance therapy with doxazosin, metoprolole and amlodipine for arterial hypertension and ischemic heart disease. Chest x-ray evidenced a bilateral reticular interstitial thickening. No contacts with known cases of COVID-19 were reported by the patient but, considering the ongoing epidemic in Lombardy [4], a nasopharyngeal swab for SARS-CoV-2 was performed retrieving a positive result. Darunavir/cobicistat was replaced by lopinavir/ritonavir plus hydroxychloroquine. In the following days, the patient's respiratory function quickly worsened despite Venturi mask and continuous positive airway pressure therapy and, one week after admission, the patient required mechanic ventilation. In the intensive care unit lopinavir/ritonavir plus hydroxychloroquine were replaced by tocilizumab (two doses) and remdesivir (withdrawn for acute liver injury after 5 days) with improved respiratory conditions. At the last available follow-up (April 1), the patient is still inpatient with no fever and requiring only low-flow oxygen delivery.

The second case was a 63-years old HIV-infected man on darunavir-based antiretroviral therapy (given at 800 mg coformulated with cobicistat, tenofovir alafenamide and emtricitabine); at the last outpatient visit he had an undetectable viral load (< 20 copies/mL) and a CD4+ count of 0.743 × 10^3/μL. He was also on active treatment with irbesartan for arterial hypertension. On March 18 the patient was admitted to the emergency department reporting fever up to 38.0 °C for at least 11 days with no signs of respiratory distress; he also reported that some members of his family living near Bergamo [4] were tested positive for SARS-Co-V-2 infection. The chest x-ray evidenced a bilateral reticular interstitial thickening and the nasopharyngeal swab for SARS-CoV-2 resulted positive. At hospital admission darunavir/cobicistat was replaced with lopinavir/ritonavir (plus tenofovir alafenamide plus emtricitabine) and hydroxychloroquine given for 5 days. On March 28 he was successfully discharged.

A third case of a 57-years old HIV-infected woman on darunavir-based antiretroviral therapy (given at 800 mg combined with cobicistat and raltegravir) and on nebivolole and atorvastatin, developing SARS-CoV-2 infection was admitted to our hospital on March 24 reporting fever and cough from at least 10 days. The chest x-ray evidenced reticular interstitial thickening at the right lung. The nasopharyngeal swab for SARS-CoV-2 resulted positive. In this case darunavir/cobicistat was maintained (not replaced with lopinavir/ritonavir for patient history of poor drug tolerability) and hydroxychloquine was added for 7 days. At the last available follow-up (April 1), she is still inpatient waiting for the results of the nasopharyngeal swab to confirm SARS-CoV-2 absence before her discharge.

In all three cases, therapeutic drug monitoring of darunavir plasma trough concentrations measured before the diagnosis of Covid-19, showed in every instances, optimal drug exposure (1043, 628 and 1683 ng/mL, respectively; therapeutic range: > 500 ng/mL). Taken together, darunavir pharmacokinetic data allowed us to exclude poor patient compliance to antiretroviral therapies in all cases.

Lopinavir and darunavir, two protease inhibitors used for HIV infection, have been proposed as a suitable treatment for SARS-CoV-2 infected patient [3]. Lopinavir showed efficacy against SARS-CoV both in patients and in tissue culture, dropped viral titers, and ameliorated disease progression in marmosets infected with MERS-CoV [5,6]. A recent publication in Korea suggested that lopinavir/ritonavir might reduce COVID-19 viral load and improve clinical symptoms [7].

Given the structural similarity with lopinavir, darunavir is a potentially effective treatment against SARS-CoV-2 and is currently under investigation in phase III clinical trials [3]. However, with these clinical reports, we provide preliminary evidence that darunavir, at least at the currently adopted dosage of 800 mg, did not prevent SARS-CoV-2 infection in people living with HIV and, at least in one case, did not protect from the worsening of respiratory function.

Declaration of Competing Interest

There are no conflicts to declare.

https://doi.org/10.1016/j.phrs.2020.104826
Received 1 April 2020
Available online 20 April 2020

References

[1] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.

[2] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (2020) 507–513, https://doi.org/10.1016/S0140-6736(20)30211-7.

[3] G. Li, E. De Clercq, Therapeutic options for the 2019 novel coronavirus (2019-nCoV), Nat. Rev. Drug Discov. 19 (2020) 149–150, https://doi.org/10.1038/d41573-020-00016-0.

[4] Integrated surveillance of COVID-19 in Italy -11 March 2020 UPDATE. Available at https://www.epicentro.iss.it/coronavirus/bollettino/Infografica_30marzo%20ENG.pdf.

[5] C.M. Chu, V.C. Cheng, I.F. Hung, M.M. Wong, K.H. Chan, K.H.S. Chan, R.Y. Kao, L.L. Poon, C.L. Wong, Y. Guan, J.S. Peiris, K.Y. Yuen, HKU/UCH SARS study group, Thorax 59 (2004) 252–256.

[6] J.F. Chan, Y. Yao, M.L. Yeung, W. Deng, L. Bao, L. Jia, F. Li, C. Xiao, H. Gao, P. Yu, J.P. Cai, H. Chu, J. Zhou, H. Chen, C. Qin, K.Y. Yuen, Treatment with Lopinavir/Ritonavir or Interferon-β1b improves outcome of MERS-CoV infection in a non-human primate model of common marmoset, J. Infect. Dis. 212 (2015) 1904–1913, https://doi.org/10.1093/infdis/jiv392.

[7] J. Lim, S. Jeon, H.Y. Shin, M.J. Kim, Y.M. Seong, W.J. Lee, K.W. Choe, Y.M. Kang, B. Lee, S.J. Park, Case of the index patient who caused tertiary transmission of Coronavirus disease 2019 in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 pneumonia monitored by quantitative RT-PCR, J. Korean Med. Sci. 35 (2020) e79, https://doi.org/10.3346/jkms.2020.35.e79.

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