Exceptional treatment of COVID-19 pneumonia with icatibant

Tratamiento de la neumonía COVID-19 con acetato de icatibant: una vía de tratamiento inusual

To the editor:

Icatibant acetate acts as a competitive bradykinin type 2 receptor antagonist. It is approved for the treatment of acute attack of hereditary angioedema and can be administered in repeated doses depending on clinical course.[1-3] Angiotensin converting enzyme (ACE) is one of the enzymes that degrade bradykinin, consequently the use of ACE inhibitors (ACE inhibitors) inhibits bradykinin degradation, producing an increase in its concentration, and in some patients causes bradykinergic angioedema that responds to the administration of icatibant.[4-6] In the case of SARS-CoV-2 infection, viral endocytosis occurs through the ACE receptor type 2 (ACE2), reducing the

expression of this enzyme, which leads to a decrease in the degradation of bradykinin, thus elevating its concentration. In the lungs, this bradykinin increases vascular permeability and inflammatory activation, and results in inflammatory edema, which is expressed radiologically in the form of pulmonary infiltrates. Blockade of the bradykinin receptor with icatibant may have beneficial effects on the clinical course of these patients by halting this pulmonary permeability and inflammatory activation.[7-8] We describe the case of a patient with pneumonia due to SARS-CoV-2 infection and concomitant bradykinergic angioedema, who was being treated with enalapril. Administration of icatibant halted the progression of angioedema, along with rapid improvement of pulmonary infiltrates, as well as rapid normalization of D-dimer levels.

A 70-year-old man with a history of arterial hypertension, on enalapril treatment, and dyslipidemia on atorvastatin treatment consulted the emergency department (ED) with fever, odynophagia and dysgeusia of 4 days evolution, and no other symptoms. Chest X-ray examination showed normal results, and blood tests showed no relevant data. The reverse transcriptase polymerase chain reaction (RT-PCR) test taken by nasopharyngeal swab was positive for SARS-CoV-2, and he was discharged with the usual measures of isolation, symptomatic treatment and rules on alarm symptoms to return to the ED. After 48 hours the patient came back with angioedema of the upper lip and dorsum of the tongue. The radiological study showed bilateral peripheral pulmonary infiltrates of left predominance, suggestive of SARS-CoV-2 pneumonia (Figure 1). Oxygen saturation was 97% (FiO_2 0.21). Laboratory tests showed AST 45 IU (normal values -NV-: < 40), D-dimer 1,141 mcg/L (VN: < 250), ferritin 418 mcg/L (VN: 39-400), LDH 273 IU (VN: < 199), C-reactive protein 78.9 mg/L (VN: < 5), and 1,140 lymphocytes/µl. Given the persistence of angioedema, a single intravenous dose of 2 mg dexchlorpheniramine and 40 mg methylprednisolone was administered. During his stay in the emergency room he presented progression of angioedema of the tongue which, given the lack of response to the treatment administered, was classified as bradykinergic angioedema due to ACE inhibitors with airway compromise. It was decided to administer 30 mg of subcutaneous icatibant acetate, a dose that was repeated at 8 and 24 hours due to recurrence of angioedema. The patient was hospitalized and, since he did not present respiratory failure, he did not receive specific treatment for SARS-CoV-2 infection. After 24 and 48 hours the control radiological study showed an improvement of pulmonary infiltrates, as well as normalization of D-dimer (< 250 ug/L), C-reactive protein 18.3 mg/l and disappearance of angioedema on the lip and dorsum of the tongue, with oxygen saturation of 100%. The rest of the analytical parameters showed no substantial changes. He was discharged from the hospital on the 4th day and a follow-up visit was made two weeks later, when he was asymptomatic.

We believe that this clinical case is exceptional in that it is plausible that the improvement of the pneumonic process could be due to the use of icatibant. There are different mechanisms by which bradykinin receptor inhibition with icatibant can produce an effect in SARS-CoV-2 infection, and especially in its most severe form of presentation, adult acute respiratory distress syndrome (ARDS). In general, in ARDS there is activation of the contact system leading to bradykinin synthesis, which increases vascular permeability with consequent recruitment and activation of inflammatory mediators ultimately responsible for pulmonary edema.[9] In SARS-CoV-2 infection, the virus enters the respiratory epithelial cell through the ECA2 receptor 7, and produces a decrease in its expression, which causes a decrease in its expression, which causes an inhibition of bradykinin catabolism. To these two mechanisms we must add another suggested mechanism which consists in the fact that icatibant could produce an inhibition of SARS-CoV-2 protease M, a key enzyme in the replication of the coronavirus. This circumstance has been investigated for several drugs, including icatibant, by analyzing the molecular structure of protease M and a virtual computer simulation.[10]

Although we must recognize that corticosteroids were initially administered to the patient, and we know that they have a beneficial effect on the evolution of SARS-CoV-2[11] infection, only a punctual dose was administered at the beginning of the picture, as treatment for angioedema. The radiological involvement of the patient was mild and it could be that its natural evolution was towards spontaneous resolution and no further progression, but we think that in our clinical case the doses of icatibant had a positive effect on the radiological evolution since there is also a rapid normalization of the D-dimer, expression of the activation of the contact system. It is true that there are some cases reported in the literature in relation to this hypothesis of icatibant use, however, they are cases in which the patients presented mostly severe involvement. Our hypothesis

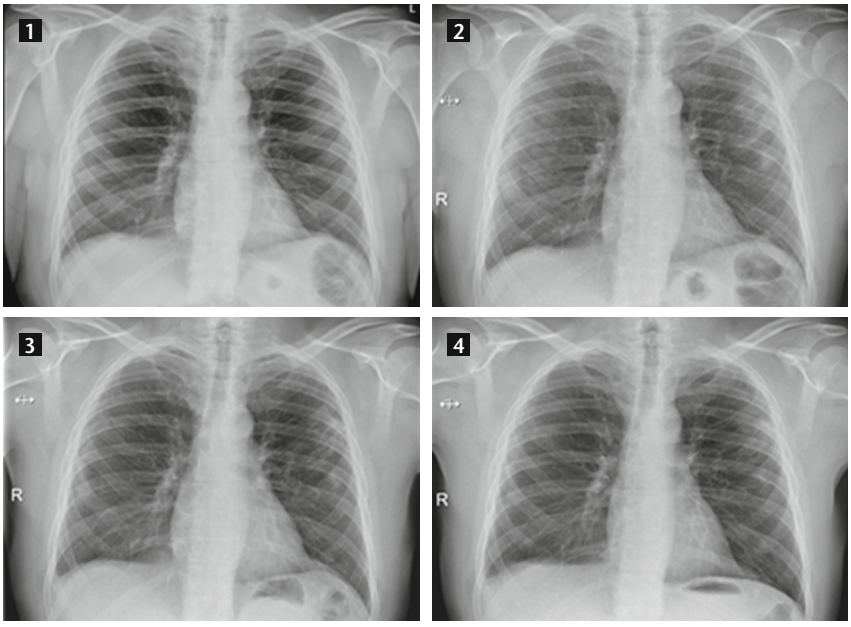

Figure 1. Radiological study of the patient. Chronological order: Chest X-ray number 1 corresponds to clinical day +4 and shows no pulmonary infiltrates. Chest X-ray number 2 corresponds to day +7 and shows a peripheral patchy infiltrate in the left lobe. Number 3 corresponds to day +8 and number 4 to day +9 and shows a progressive radiological improvement, with attenuation of the pulmonary patches.

is that the benefit of this treatment probably lies in its use in the initial phases of the inflammatory period.[12,13] In order to provide scientific evidence of the role of icatibant treatment in SARS-CoV-2 infection, we have promoted a phase II clinical trial to investigate the efficacy and safety of icatibant in patients infected with SARS-CoV-2 and admitted to inpatient units, without invasive mechanical ventilation, compared to the standard of care (ICAT-COVID), whose recruitment will be carried out in the emergency departments of the participating centers.[14]

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References

1 Maurer M, Magerl M, Ansotegui I, Aygören-Pürsün E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. Allergy. 2018;73:1575-96.
2 Busse PJ, Christiansen SC. Hereditary Angioedema. N Engl J Med. 2020;382:1136-48.
3 Leach JK, Spencer K, Mascelli M, McCauley TG. Pharmacokinetics of single and repeat doses of icatibant. Clin Pharmacol Drug Dev. 2015;4:105-11.
4 Baş M, Greve J, Stelter K, Havel M, Strassen U, Rotter N, et al. A randomized trial of icatibant in ACE-inhibitor-induced angioedema. N Engl J Med. 2015;372:418-25.
5 Bova M, Guilarte M, Sala-Cunill A, Borrelli P, Rizzelli GM, Zanichelli A. Treatment of ACEI-related angioedema with icatibant: a case series. Intern Emerg. 2015;10:345-50.
6 Jacob J, Bardes I, Palom X, Carrizosa M, Fuentes E. Angiotensin-converting enzyme inhibitor-induced angioedema and icatibant: a new hope. Intern Med J. 2015;45:1093-94.
7 Tolouian R, Vahed SZ, Ghiyasvand S, Tolouian A, Ardalan M. COVID-19 interactions with angiotensin-converting enzyme 2 (ACE2) and the kinin system; looking at a potential treatment. J Renal Inj Prev. 2020;9:e19.
8 Yang G, Tan Z, Zhou L, Yang M, Peng L, Liu J, et al. Effects of Angiotensin II Receptor Blockers and ACE (Angiotensin-Converting Enzyme) Inhibitors on Virus Infection, Inflammatory Status, and Clinical Outcomes in Patients With COVID-19 and Hypertension: A Single-Center Retrospective Study. Hypertension. 2020;76:51-8.
9 Hess R, Wujak L, Hesse C, Sewald K, Jonigk D, Warnecke G, et al. Coagulation factor XII regulates inflammatory responses in human lungs. Thromb Haemost. 2017;117:1896-909.
10 Liu X, Wang X. Potential inhibitors agains 2019-nCoV coronavirus M protease from clinically approved medicines. J Genet Genomics. 2020;47:119-21.
11 RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2021;384:693-704.
12 Pecori D, Della Siega P, Sozio E, Barbano E, Mazzoran L, Zanichelli A, et al. Icatibant in Severe Acute Respiratory Syndrome Coronavirus 2: a case description. J Investig Allergol Clin Immunol. 2021;31:451-2.
13 van de Veerdonk FL, Kouijzer IJE, de Nooijer AH, van der Howven HG, Maas C, Netea MG, et al. Outcomes Associated With Use of a Kinin B2 Receptor Antagonist Among Patients With COVID-19. JAMA Netw Open. 2020;3:e2017708.
14 Clinical trials register.eu. Randomized, open, multicenter phase II clinical trial, proof of concept, to evaluate efficacy and safety of Icatibant in hospitalized patients with SARS-COV-2 (COVID-19) without assisted ventilation compared with standard care. (Consultado 2 Marzo 2021). Disponible en: https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002166-13/ES