

Icatibant in Severe Acute Respiratory Syndrome Coronavirus 2: a case description

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Palabras clave: COVID-19, Icatibant, Síndrome respiratorio agudo severo. SARS-CoV-2. Sistema de contacto.

In late 2019, the coronavirus SARS-CoV-2 was identified in Wuhan, China [1]. The WHO named COVID-19 the disease induced by the virus. There is evidence that excessive activity of bradykinin (BK) at pulmonary level correlates to severe interstitial and Severe Acute Respiratory Syndrome (SARS) pathogenesis. BK binding to Bradykinin 2 Receptors (BK2R) increases vascular permeability leading to pulmonary edema and release of proinflammatory mediators. SARS-CoV-2 uses Angiotensin-Converting enzyme 2 (ACE2) as the most suitable receptor to infect human cells [2]. Lack of ACE2 function results in the accumulation of Angiotensin II (ANG II) and this may cause a secondary reduction in the activity of Angiotensin-Converting Enzyme (ACE), with consequent increase of BK. Indeed, ACE catabolizes not only ANG I to ANG II conversion but it is also able to inactivate BK [3].

ACE2 is needed to inactivate des-Arg9 bradykinin (DABK), a bioactive metabolite of BK [4] that binds the bradykinin receptor type 1 (BK1R). In contrast to BK2R, the BK1R on endothelial cells is upregulated by proinflammatory cytokines. Lack of ACE2 leads to the inactivation of BK1R ligands, thus increasing DABK levels.

Furthermore, DABK weakly binds BK2R in certain tissues, and exerts effects that are blocked by the BK2R blocker Icatibant [4]. Icatibant is a selective antagonist of the BK2R, approved for treatment of acute attacks of hereditary angioedema [5]. Icatibant may interrupt the positive feedback loop of DABK- and BK-mediated inflammation and injury, improving clinical outcomes in patients with COVID-19 respiratory complications [4]. The use of off-label Icatibant (FIRAZYR[®], manufactured by Shire, Zug - Switzerland, and now part of Takeda), blocking the increase in vascular permeability mediated by BK, may inhibit pulmonary edema in COVID-19.

We describe the case of a 56-year-old man, admitted for COVID-19 pneumonia in absence of comorbidity. Ten days after the onset of symptoms dyspnea occurred. At the hospital admission, the patient had the following arterial blood gas analysis: pH 7.5, PaO₂ 53 mmHg, pCO₂ 32 mmHg, with PaO₂/FiO₂ 252 and the alveolar–arterial gradient of 57.

The chest-CT revealed extensive peripheral dense ground-glass opacities with > 50% involvement. The patient received treatment with darunavir/cobicistat, hydroxychloroquine and antibiotic therapy (see Supplementary Figure).

The patient's respiratory condition rapidly worsened in the first 24 hours upon arriving at the hospital: PaO₂/FiO₂ decreased to 205 despite high-flow oxygen therapy. Patient needed to be treated with non-invasive ventilation (helmet CPAP – PEEP 5 cmH₂O – FiO₂ 0.40 mmHg).

Because of the respiratory symptoms worsening despite these treatments, Icatibant was started on the second day of hospitalization: the patient received off-label Icatibant 30 mg subcutaneously every 8 hours for 3 days.

After administration of Icatibant, the patient presented a progressive clinical improvement and a reduction in: C reactive protein (from 67 to 10 mg/L), Interleukin 6 (IL-6, from 111 to 6 pg/ml), Interleukin 8 (IL-8, from 70 to 24 pg/ml), TNF- α (from 20 to 13 pg/ml) and IFN- γ (from 9,9 to 5,6 pg/ml).

Weaning by non-invasive ventilation occurred on the fourth day upon hospital admission when the patient had the following arterial blood gas analysis in Venturi Mask, with FiO₂ 0.40 mmHg: pH 7.53, PaO₂ 109 mmHg, pCO₂ 33 mmHg, with PaO₂/FiO₂ 290. Patient was discharged on day 12 without need of supplemental oxygen.

Icatibant is effective in angioedema caused by ACE-inhibitors and in treating breathing difficulty in patients presenting with angioedema; we have to keep in mind that COVID-19 causes dry cough, a typical side effect of ACE-inhibitors, linked to increase bradykinin level [6].

In our clinical case, there was a significant reduction of inflammatory cytokines and C reactive protein, suggesting a potential anti-inflammatory effect of Icatibant as a complementary treatment in COVID-19 SARS. Furthermore, Icatibant therapy was able to reduce IL-8 level, in fact this cytokine may be stimulate by BK in airway. Also, this finding supports the empirical use of Icatibant in the treatment of unremitting

respiratory distress in COVID-19 [7].

This case-report has some limitations, such as incapability to generalize and no possibility to establish cause-effect relationship between the use of Icatibant and the observed clinical improvement in patient.

Another limitation is the absence of support for the safety of Icatibant at the dose used (30 mg every 8 hours for 3 days). The Icatibant summary of product characteristics show that ≤ 8 Icatibant injections per month have been administered in clinical trials. The Icatibant package information recommends an interval of ≥ 6 h between doses and no more than three doses in 24 h [8]. However, in the *Icatibant Outcome Survey* registry, among 10 patients who received ≥ 9 Icatibant injections in 1 month, no adverse effects were reported in four patients who received Icatibant more frequently than three times in 24h [8]. As far as we know, the dose of 30 mg thrice a day for three consecutive days has been never used before in clinical practice. Due to the short half-life (1.48 ± 0.35 hours), repeated subcutaneous administrations of Icatibant 30 mg at 6-hour intervals in healthy volunteers did not result into appreciable drug accumulation [9].

In the recent experience of van de Veerdonk et al., 10 patients were treated with 3 doses of 30 mg of Icatibant by subcutaneous injection at 6-hour intervals. Icatibant treatment was well tolerated in all 10 patients and in 8 patients a reduction of oxygen implementation was observed [10].

In our case report, the patient had an improvement of gas exchanges documented by arterial blood gas analysis and this allowed early weaning by non-invasive ventilation.

However, our patient was admitted to the hospital 10 days after the onset of symptoms. The second stage of COVID-19 is often characterized by pulmonary inflammation and coagulopathy. In this stage BK could play a relevant role in COVID-19: BK binds to B2-receptors, mediating vascular permeability, vasodilation and edema.

In conclusion, the off-label use of Icatibant, a B2R blocker, seems to be promising in the treatment of patients with respiratory distress caused by SARS-COV2.

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References

- [1] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020
- [2] Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11:875-9.
- [3] Meini S, Zanichelli A, Sbrojavacca R, Iuri F, Roberts AT, Suffritti C, et al. Understanding the Pathophysiology of COVID-19: Could the Contact System Be the Key? *Front. Immunol*. 11:2014. doi: 10.3389/fimmu.2020.02014
- [4] Roche JA, Roche R. A hypothesized role for dysregulated bradykinin signaling in COVID-19 respiratory complications. *FASEB J*. 2020;34:7265-9.
- [5] Zanichelli A, Mansi M, Periti G. Icatibant Exposure During Pregnancy in a Patient With Hereditary Angioedema. *J Investig Allergol Clin Immunol*. 2015;25:447-9.
- [6] Al-Shamlan F, El-Hashim AZ. Bradykinin sensitizes the cough reflex via a B2 receptor dependent activation of TRPV1 and TRPA1 channels through metabolites of cyclooxygenase and 12-lipoxygenase. *Respir Res*. 2019;20:110.
- [7] Allen TC, Kurdowska A. Interleukin 8 and acute lung injury. *Arch Pathol Lab Med*. 2014;138:266-9.
- [8] Zanichelli A, Maurer M, Aberer W, et al. Long-term safety of icatibant treatment of patients with angioedema in real-world clinical practice [published correction appears in *Allergy*. 2018 Sep;73(9):1929]. *Allergy*. 2017;72(6):994-998. doi:10.1111/all.13103
- [9] Leach JK, Spencer K, Mascelli M, McCauley TG. Pharmacokinetics of single and repeat doses of Icatibant. *Clin Pharmacol Drug Dev* 2015;4:105-11.
- [10] van de Veerdonk FL, Kouijzer IJE, de Nooijer AH, et al. Outcomes Associated With Use of a Kinin B2 Receptor Antagonist Among Patients With COVID-19. *JAMA Netw Open*. 2020;3(8): e2017708. Published 2020 Aug 3. doi:10.1001/jamanetworkopen.2020.17708.