Icatibant in Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A Case Report

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The coronavirus SARS-CoV-2 was identified in Wuhan, China in late 2019 [1]. The World Health Organization named the disease induced by the virus COVID-19. There is evidence that excessive activity of bradykinin in the lungs correlates with the pathogenesis of severe interstitial involvement and severe acute respiratory syndrome. Binding of bradykinin to bradykinin 2 receptors (BK2R) increases vascular permeability, leading to pulmonary edema and release of proinflammatory mediators. SARS-CoV-2 uses angiotensin-converting enzyme (ACE) 2 (ACE2) as the most suitable receptor for infecting human cells [2]. Lack of ACE2 function results in the accumulation of angiotensin II (ANG II), which may lead to a secondary reduction in the activity of ACE, with a consequent increase in bradykinin levels. Indeed, ACE not only catabolizes ANG I to ANG II, but is also able to inactivate bradykinin [3].

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

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

We report the case of a 56-year-old man admitted with COVID-19 pneumonia and no comorbid conditions. The patient developed dyspnea 10 days after the onset of symptoms. At admission, his arterial blood gas values were as follows: pH, 7.5; PaO_2, 53 mmHg; pCO_2, 32 mmHg; PaO_2/FiO_2, 252; and the alveolar–arterial gradient, 57.

A computed tomography scan of the chest revealed extensive peripheral dense ground-glass opacities with >50% involvement. The patient received treatment with darunavir/cobicistat, hydroxychloroquine, and antibiotic therapy (Supplementary Figure).

The patient's respiratory condition worsened rapidly in the first 24 hours after arrival at the hospital—PaO_2/FiO_2 decreased to 205 despite high-flow oxygen therapy—and he required treatment with noninvasive ventilation (helmet CPAP, PEEP 5 cmH_2O, and FiO_2 0.40 mmHg).

Because his respiratory symptoms worsened despite these treatments, icatibant was started on the second day of hospitalization (off-label icatibant 30 mg subcutaneously every 8 hours for 3 days).

The patient's clinical condition subsequently improved, with reduced values for C-reactive protein (from 67 to10 mg/L), IL-6 (IL-6, from 111 to 6 pg/mL), IL-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 from noninvasive ventilation was started on the fourth day of admission, when the patient's arterial blood gas analysis (Venturi mask) values were as follows: FiO_2, 0.40 mmHg; pH, 7.53; PaO_2, 109 mmHg; pCO_2, 33 mmHg; PaO_2/FiO_2, 290. The patient was discharged on day 12 with no need for supplemental oxygen.

Icatibant is effective in angioedema caused by ACE inhibitors and in treating dyspnea in patients presenting with angioedema. It is important to bear in mind that COVID-19 causes dry cough, a typical adverse effect of ACE inhibitors that is linked to increased bradykinin levels [6].

In the case we report, there was a significant reduction in inflammatory cytokine and C-reactive protein values, suggesting a potential anti-inflammatory effect of icatibant as a complementary treatment in COVID-19. Furthermore, icatibant reduced IL-8 levels; in fact, IL-8 may be stimulated by bradykinin in the airways. This finding supports the empirical use of icatibant in the treatment of unremitting respiratory distress in patients with COVID-19 [7].

The present case report is limited by the fact that its findings cannot be extrapolated and by the absence of a cause-effect relationship between the use of icatibant and the clinical improvement observed. It is also limited by the absence of support for the safety of icatibant at the dose used (30 mg every 8 hours for 3 days). The summary of product characteristics shows that ≤8 icatibant injections per month

have been administered in clinical trials. The package insert recommends an interval of ≥6 hours between doses and no more than 3 doses in 24 hours [8]. However, data from the Icatibant Outcome Survey registry show that among 10 patients who received ≥9 injections in 1 month, no adverse effects were reported in 4 patients who received icatibant more frequently than 3 times in 24 hours [8]. To our knowledge, the dose of 30 mg administered 3 times daily for 3 consecutive days has never been used in clinical practice. Given the drug's short half-life (1.48 [0.35] hours), repeated subcutaneous administrations of 30 mg at 6-hour intervals in healthy volunteers did not result in an appreciable accumulation of the drug [9].

van de Veerdonk et al [10] recently treated 10 patients with 3 doses of 30 mg of subcutaneous icatibant at 6-hour intervals. Treatment was well tolerated by all 10 patients, and in 8 patients the need for oxygen was reduced.

Gas exchange improved in the present case, as seen in the arterial blood gas analysis, thus enabling early weaning from noninvasive ventilation.

However, the patient was admitted to 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, bradykinin could play a relevant role in COVID-19 by binding to BK2R, thus mediating vascular permeability and leading to vasodilation and edema.

In conclusion, off-label use of icatibant, a BK2R blocker, seems to be promising for the treatment of patients with respiratory distress caused by SARS-CoV-2.

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Conflicts of Interest

Dr Tascini has received funds for speaking at symposia organized on behalf of Pfizer, Novartis, Merck, Angelini, Zambon, Thermo Fisher, Biotest, Gilead, Hikma, Biomerieux, and Astellas. Dr Zanichelli has received speaker/consultancy fees and/or has been a member of advisory boards for CSL Behring, Shire/Takeda, and SOBI. The remaining authors declare that they have no conflicts of interest.

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