AN OPEN LETTER TO THE SCIENTIFIC COMMUNITY ON THE POSSIBLE ROLE OF DYSREGULATED BRADYKININ SIGNALING IN COVID-19 RESPIRATORY COMPLICATIONS

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Dear Colleagues,

This is with reference to the current COVID-19 pandemic and its high Case Fatality Rate (CFR). According to data reported by the World Health Organization through its COVID-19 homepage; as of April 7, 2020, 2:00 AM CEST, out of 1,279,722 confirmed cases over time, there have been 72,616 deaths, putting the CFR at ~5.67%.[1]

As the COVID-19 pandemic is rapidly spreading, and emergency rooms are being overwhelmed by the large numbers of patients needing acute care for breathing difficulty, it is imperative that alternate pharmacotherapeutic strategies are explored expeditiously to improve survival.[2, 3]

It is in this context that the off-label use of the bradykinin B2 receptor blocker, icatibant, seems promising. Icatibant (Trade Name: FIRAZYR; Takeda, Tokyo, Japan) is a drug that has been approved by the United States Food and Drug Administration (FDA) and other regulatory bodies, for the treatment of angioedema episodes in patients (18 years and older) with hereditary angioedema (HAE).[4] Icatibant is thought to work by binding to bradykinin B2 receptors and blocking the downstream activity of bradykinin in a variety of cells, including those present in blood vessels and the airway.[5] Icatibant is effective in treating breathing difficulty in patients presenting with angioedema, including angioedema caused by angiotensin converting enzyme (ACE) inhibitors taken for hypertension.[6] It might be purely coincidental that COVID-19 causes a “dry cough” - a rare but characteristic side effect of ACE inhibitors, which is linked to bradykinin.[7]

However, it is compelling to speculate that, dysregulated bradykinin signaling might be involved in COVID-19 respiratory distress and might be treatable by icatibant, for the following reasons:

1. The SARS-CoV-2 virus, which causes COVID-19, is known to enter host cells in the respiratory system via the transmembrane protein, angiotensin converting enzyme 2 (ACE2) [8]

2. SARS coronaviridae infection depletes ACE2 [9]

3. ACE2 depletion increases levels of des-Arg(9)-bradykinin, which is a bioactive metabolite of bradykinin that is associated with lung injury and inflammation [10, 11]

4. des-Arg(9)-bradykinin not only binds strongly to bradykinin B1 receptors, through which it exerts downstream effects; but also binds weakly to bradykinin B2 receptors in certain tissues, and exerts downstream effects, which are blocked by the bradykinin B2 receptor blocker, icatibant [12, 13]

5. A possible role for bradykinin in COVID-19 respiratory distress is consistent with established evidence that, bradykinin, histamine, and serotonin, have for long been known as key mediators of acute lung inflammation and respiratory distress [14]

Currently, due to the pandemic situation with COVID-19, time is of the essence, to repurpose drugs that are safe and likely to be effective in mitigating refractory respiratory distress in COVID-19.[2, 3] Icatibant has been shown to be safe and effective, with side effects and adverse reactions being rare when used in the context of angioedema.[15] A human study on the off-label use of icatibant to treat allergic rhinitis showed that, the drug significantly reduced grass pollen antigen-induced hyperresponsiveness to histamine, which was linked to icatibant inhibiting interleukin-8 (IL-8) release.[16] Given that IL-8 is implicated in acute lung injury and respiratory distress, it would be worth considering the experimental use of icatibant in the treatment of unremitting respiratory distress in COVID-19.[17] It might also be useful to retroactively obtain data on patients who have been treated recently with icatibant for angioedema, while having COVID-19 as a comorbidity, to ascertain whether or not COVID-19 respiratory symptoms decreased after icatibant administration. Additionally, it would be worth closely monitoring outcomes in patients with COVID-19 who take ACE inhibitors (for hypertension), DPP4 inhibitors (for diabetes mellitus), or neprilysin inhibitors (for heart failure), since these drugs are known to interfere with bradykinin breakdown and thus increase bradykinin bioavailability.[18]

It is possible that molecules other than icatibant, which act on bradykinin signaling pathways, might also be able to reduce respiratory distress in COVID-19. For example, blocking des-Arg(9)-bradykinin's main target, the bradykinin B1 receptor, might produce better outcomes.[19] However, at this time, potent bradykinin B1 receptor blockers (e.g. orally-active H1-113823) have only been tested in animals.[20] Nonetheless, bradykinin B2 receptor blockade has been shown to be effective in the context of airway hyper responsiveness and respiratory distress in animal models; and, des-Arg(9)-bradykinin has been shown to act on the bradykinin B2 receptor in some tissues.[12, 13, 19] Upstream inhibition of bradykinin production with the FDA-approved drug, ecallantide, also seems promising, albeit with a risk of anaphylaxis in some patients.[21] Increasing plasma aminopeptidase-P (APP) levels with hormonal therapy could also be tried as a benign intervention aimed at accelerating bradykinin and des-Arg(9)-bradykinin degradation.[22]

From a scientific standpoint, analyzing plasma levels of bradykinin and des-Arg(9)-bradykinin, and plasma activity of APP, in patients with breathing difficulty from COVID-19, might help support or refute the bradykinin hypothesis for COVID-19 breathing difficulty.[23, 24]

In Figure 1, we propose a model for the role of bradykinin in COVID-19 respiratory distress and the possible benefit of pharmacotherapy with the bradykinin antagonist, icatibant.

We thank you for your time and consideration.

Sincerely,

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FIGURE 1. Proposed model for the role of bradykinin in COVID-19 respiratory distress and the possible benefit of pharmacotherapy with the bradykinin antagonist, icatibant

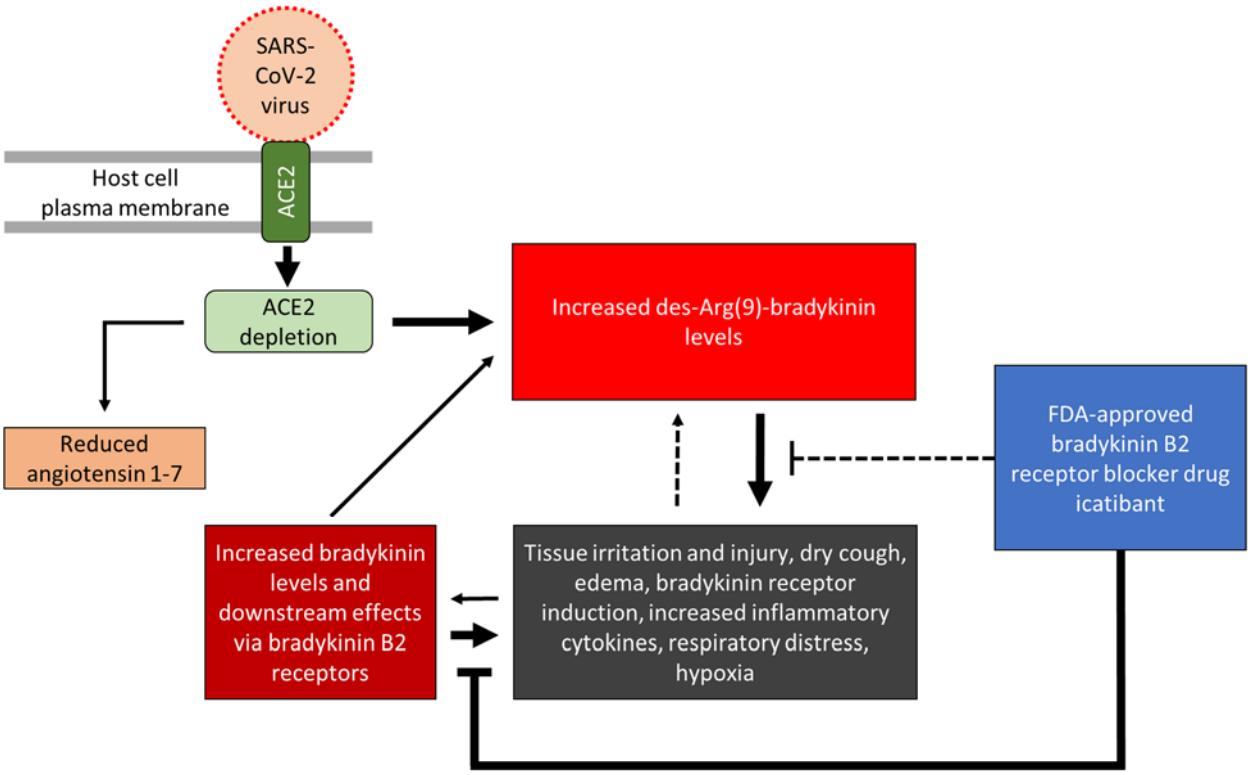

FIGURE LEGEND

Figure 1. Proposed model for the role of bradykinin in COVID-19 respiratory distress and the possible benefit of pharmacotherapy with the bradykinin antagonist, icatibant

SARS-CoV-2, the virus that causes coronavirus disease 19 (COVID-19), is known to enter host cells in the respiratory system via the transmembrane protein, angiotensin converting enzyme 2 (ACE2).[8] SARS coronaviridae infection via ACE2 depletes this enzyme.[9] ACE2 depletion increases levels of des-Arg(9)-bradykinin, which is a bioactive metabolite of bradykinin that is associated with airway inflammation.[10] des-Arg(9)-bradykinin not only binds strongly to the bradykinin B1 receptor, through which it exerts downstream effects; but also binds weakly to bradykinin B2 receptor in certain tissues, and exerts effects that are blocked by the bradykinin B2 receptor blocker, icatibant.[12, 13] Since icatibant is already approved for treating bradykinin-mediated angioedema, it might be worth considering its off-label experimental use to treat unremitting respiratory distress in COVID-19. In the proposed model, bold lines have been used to depict pathways that are directly supported by previous studies; light lines have been used to depict pathways that are inferred from previous studies; and, dotted lines have been used to indicate pathways that might exist but have not yet been tested directly.

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