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Letter to the Editor

Rho kinase inhibitors for SARS-CoV-2 induced acute respiratory distress syndrome: Support from Bartter’s and Gitelman’s syndrome patients

Renin-Angiotensin system (RAS) plays a role as part of the CoV-2 infection process via Angiotensin Converting Enzyme 2 (ACE2) which serves as the entry point of SARS-CoV-2. The involvement of ACE2 has given rise to conflicting suggestions as to how ACE2 and RAS in general should inform the treatment of COVID-19 [Supplemental refs. 1,2]. These concerns arise as a result of the need to weigh the roles of ACE2 in the infection process and subsequent morbidity and mortality in light of the protective counter-regulatory role of the ACE2-Angiotensin (Ang) 1-7-MasR axis versus the classical ACE-Ang II-AT1R regulatory axis of RAS [Supplemental ref. 3].

The potential protective role of ACE2 in SARS-CoV-2 infection-induced acute respiratory distress syndrome (ARDS), the major cause of COVID-19 mortality as well as other risk factors such as hypertension, diabetes and cardiovascular disease that are linked to COVID-19 morbidity and mortality have been recently reviewed [Supplemental ref. 4].

We read with great interest the recent publications of Abedi and coworkers who recently reviewed the relationship between Rho kinase, acute lung injury and ARDS and the beneficial effect of Rho kinase inhibitors on lung injury [1]. They subsequently noted the increased activity and levels of ACE2 caused by Rho kinase inhibitors [Supplemental ref. 5], leading them to suggest that clinical studies on Rho kinase inhibitors effects on the respiratory complications induced by SARS-CoV-2 infection should be conducted [2].

Our studies in Bartter’s and Gitelman’s syndrome patients (rare genetic tubulopathies) to explore and better define the human RAS and RhoA/Rho kinase systems [3,4] provide further background as to the protective effects of increased levels of ACE2 along with Rho kinase inhibition and how those might be of use against SARS-CoV-2 infection (COVID-19)-induced respiratory complications. Specifically, these patients have an activated RAS and high Ang II levels, yet blunted Ang II-mediated cardiovascular effects and normotension or hypotension. Moreover, our cohort of Gitelman’s and Bartter’s patients provides evidence, admittedly anecdotal and circumstantial, that increasing ACE2 by Rho kinase inhibition is unlikely to raise the risk of COVID-19 infection, as has been suggested [Supplemental ref. 1]. The results of a telephone survey contacting over 100 of our Gitelman’s and Bartter’s patients, all of whom were from the hotspots of the COVID-19 pandemic in Italy (Veneto, Lombardy and Emilia Romagna), found none of them infected with COVID-19 [6]. This suggests that increased ACE2 and reduced Rho kinase activity likely provide benefits in terms of reduced risk of COVID-19 such as those we found in Gitelman’s and Bartter’s patients.

Our findings therefore support Abedy and coworkers’ [2] call for human clinical trials to confirm their hypothesis regarding the benefits of ACE2 increases driven by Rho kinase inhibitors with respect to protection against the respiratory complications associated with SARS-CoV-2 infection.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found in the online version, at doi:https://doi.org/10.1016/j.phrs.2020.104903.

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2