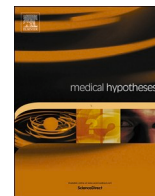




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Correspondence

Closing the portal to SARS-CoV-2 cellular entry: *May open newer avenues...*

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Dear Editor,

Amidst the wide range of challenges posed by COVID-19 associated thrombosis, the Kumar et al proposition of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) cellular entry based angiotensin converting enzyme 2 (ACE2) signalling alterations being at the cornerstone of endothelial dysfunction and vascular pro-thrombotic environment, can have potentially important therapeutic implications [1,2]. Taking account of their molecular level description, we wish to highlight a few points to substantiate the clinical perspective of the discussion.

- (i) Akin to Kumar and colleagues, the essential role of transmembrane protease serine 2 (TMPRSS2) co-expression in mediating the SARS-CoV-2 cellular entry, has captivated the attention of the fraternity [3–6].
- (ii) In this context, the TMPRSS2 inhibitors such as camostat mesylate (CM) and nafamostat mesylate (NM) are being currently envisaged as promising repurposed drugs (approved for treating pancreatitis in Japan) in COVID-19 for their anti-inflammatory and antiviral properties owing to serine protease inhibition and resultant viral cellular entry block [3–6]. A few researchers cite an incremental value to the therapeutic inclusion of a critical host factor blocker like TMPRSS2 inhibitor over an isolated antiviral regimen, in conferring a subsequent resilience to the rapidly developing viral resistance. They opine that the isolated viral point mutations are unlikely to accommodate for such a critical host component block [7].
- (iii) A recent retrospective observational case-series by Hofmann-Winkler et al outlined an attenuation of the COVID-19 disease severity marked by lower sepsis-related organ failure assessment (SOFA) scores paralleled by an ameliorated inflammatory profile in the six ICU patients who received CM compared to the five ICU patients treated with hydroxychloroquine [3]. The maximum CM dose administered in their evaluation amounted to 2×100 mg pills three times daily for 5 days which was in accordance with the protocol of a large Denmark randomized controlled trial

- (RCT, CamoCo-19, NCT04321096). In addition to the aforementioned, a number of double to quadruple blinded RCTs are also ongoing with the aim of evaluating the role of CM as a monotherapy or as an add-on therapy in COVID-19 patients [4].
- (iv) Centralizing the focus on thrombosis as in Kumar et al discussion [1], NM has additional anticoagulant and antifibrinolytic effects with Asakura and Ogawa suggesting a heparin and NM combination therapy in COVID-19 patients [5,6]. Interestingly, three elderly high-risk SARS-CoV-2 pneumonia patients with a progressive disease despite antiviral therapy demonstrated an improved clinical profile following administration of 200 mg NM over a span of 24 h [6].

To conclude, the therapeutic armamentarium against COVID-19 is doubtlessly going to become more SARS-CoV-2 specific as an augmented comprehension of the disease related mechanisms transpires. This is heralded by the exemplar of a comprehensive SARS-CoV-2 cellular level patho-physiological description staged by Kumar et al [1], in opening distinctly novel and selective therapeutic avenues aimed at the highest priority societal goal of mitigating the COVID-19 associated morbidity and mortality.

CRediT authorship contribution statement

Ridhima Sharma: Conceptualization, Writing - original draft. .
Rohan Magoon: Conceptualization, Writing - original draft, Conceptualization, Writing - original draft.
Brajesh Kaushal: Writing - review & editing.

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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References

- [1] Kumar A, Narayan RK, Kumari C, Faiq MA, Kulandhasamy M, Kant K, Pareek V. SARS-CoV-2 cell entry receptor ACE2 mediated endothelial dysfunction leads to vascular thrombosis in COVID-19 patients. *Med Hypotheses* 2020;145:110320. <https://doi.org/10.1016/j.mehy.2020.110320>.
- [2] Magoon R, ItiShri, Kohli JK, Kashav R. Inhaled milrinone for sick COVID-19 cohort: a pathophysiology driven hypothesis! *Med Hypotheses* 2020:110441. <https://doi.org/10.1016/j.mehy.2020.110441>.
- [3] Hofmann-Winkler H, Moerer O, Alt-Epping S, Bräuer A, Büttner B, Müller M, et al. Camostat mesylate may reduce severity of Coronavirus disease 2019 sepsis: a first observation. *Crit Care Explor* 2020;2(11):e0284. <https://doi.org/10.1097/CCE.0000000000000284>.
- [4] Breining P, Frølund AL, Højen JF, Gunst JD, Staerke NB, Saedder E, et al. Camostat mesylate against SARS-CoV-2 and COVID-19—rationale, dosing and safety. *Clin Pharmacol Toxicol* 2020. <https://doi.org/10.1111/bcpt.13533>.
- [5] Asakura H, Ogawa H. Potential of heparin and nafamostat combination therapy for COVID-19. *J Thromb Haemost* 2020;18(6):1521–2. <https://doi.org/10.1111/jth.14858>.
- [6] Jang S, Rhee J-Y. Three cases of treatment with nafamostat in elderly patients with COVID-19 pneumonia who need oxygen therapy. *Int J Infectious Diseases* 2020;96: 500–2. <https://doi.org/10.1016/j.ijid.2020.05.072>.
- [7] Prussia A, Thepchatri P, Snyder JP, Plemper R. Systematic approaches towards the development of host-directed antiviral therapeutics. *Int J Mol Sci* 2011;12:4027–52. <https://doi.org/10.3390/ijms12064027>.

Ridhima Sharma^a, Rohan Magoon^b, Brajesh Kaushal^{c,*}

^a Department of Paediatric Anaesthesia, Superspeciality Paediatric Hospital & Postgraduate Teaching Institute, Noida 201301, India

^b Department of Cardiac Anaesthesia, Atal Bihari Vajpayee Institute of Medical Sciences (ABVIMS) and Dr. Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi 110001, India

^c Department of Anaesthesia, Gandhi Medical College and Hamidia Hospital, Bhopal 462001, Madhya Pradesh, India

* Corresponding author.

E-mail address: brajeshkaushal3@gmail.com (B. Kaushal).