Letter to the Editor

Recombinant Human Angiotensin-Converting Enzyme 2 and COVID-19 Acute Respiratory Distress Syndrome: A Theoretical or a Real Resource?

Mirko Barone,[1] Claudio Ucciferri,[2,5] Giuseppe Cipollone,[3,4] Felice Mucilli[3,4]

[1]Department of General and Oncological Surgery, SS. Annunziata Hospital, Chieti, Italy
[2]Department of Infectious Diseases, SS. Annunziata Hospital, Chieti, Italy
[3]Department of General and Thoracic Surgery, SS. Annunziata Hospital, Chieti, Italy
[4]University Department of Medical, Oral and Biotechnological Sciences, Gabriele d'Annunzio University of Chieti-Pescara, Chieti, Italy
[5]University Department of Medicine and Health Sciences, University of Molise, Campobasso, Italy

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly emergent beta-coronavirus closely linked to SARS virus, characterized by interstitial lung infiltrate, whose intensive care unit related admission rate is of 5%. Its natural history can be complicated by mild to severe respiratory failure till the onset of a fearsome life-treatening acute respiratory distress syndrome (ARDS). Given the interaction with host ACE2 type II pneumocytes receptors, dysregulation of the renin-angiotensin system may serve a central role both in the onset and progression of lung injury.[1, 2] The complex SARS-CoV-2 Spike (S) glycoprotein and ACE2 receptor primed by the cellular protease TMPRSS2 is a critical step for ectodomain virion entry by suppressing ACE2 activity and altering the ACE/ACE2 balance to a predominant ACE/AngII axis with a reduction of Ang(1-7)-Mas complex and subsequent vaso-constriction, cytokines-bradykinin inflammatory response, Fas-induced apoptosis, fibrogenesis and oxidative damage.[3] As reported by Liu et al.,[4] in a small monocentric case series including twelve patients, serum Ang II levels in COVID-19 patients were significantly higher than in non-infected individuals with a linear association with both viremia and lung severity injury. Since ACE2 exerts cytoprotective effects on pulmonary parenchyma by an antagonistic action of Ang II, we speculated about both direct (restorative of the renin angiotensin system) and indirect (chimeric receptor effect) therapeutic effects in the treatment of COVID-19 related ARDS. Khan A et al.,[5] in a double-blind two-part phase II trial comparing the effect of the administration of a recombinant form of human angiotensin-converting enzyme 2 (GSK2586881) in forty-six patients with acute respiratory distress syndrome, reported a significant reduction of Ang II levels after scalar infusion with a long standing 48-hours plateau phase. Moreover, surfactant protein D increased as far as interleukin-6 concentrations decreased. The authors reported no significant differences in either peak or plateau pressures between recombinant human angiotensin-converting enzyme 2 (rhACE2) and placebo group in the first 72 hours, but an equally increase at the end of the five-day observation period. No adverse haemodynamic effects were reported; however, hyperna-tremia, rush and dysphagia were noted. However, some

concerns may rise dealing with enrollment process in the trial, such as the inclusion of only hemodynamically stable patients with recent diagnosis (within 48 hours) of respiratory distress without any reference to the radiological severity and extension of the pulmonary injury. This aspect could theoretically limit the adoption in COVID-19 patients for various reasons, such as the not negligible prevalence of concurrent related cardiomyopathies (17-23%) and the relative late onset of a full-blown ARDS (10-12 days from the onset of the first symptoms).[6] A correct stratification and monitoring would therefore appear essential in order to envisage the adoption only in selected cases.

In our opinion, further elements of reflection arise about the genetic susceptibility of enzymatic mechanisms, as ACE2 gene (Xp22; 39.98kb) exhibits a high degree of genetic polymorphisms,[7] which would justify the co-presence of responder and non-responder patients. Finally, the last limit is reserved for therapeutic feasibility both in terms of effective doses required (low rhACE2 half-life) and clinical monitoring (delayed effects on ventilatory pressures). On the other hand, the adoption of a target therapy for COVID-19 ARDS is promising as it could ensure both an anti-inflammatory (like interleukin-inhibitors, such as Tocilizumab) and regenerative (restoration of surfactant homeostasis, prevention of post-injury fibrotic remodelling) effects.

In conclusion, the development of target therapies acting on the renin-angiotensin system appear promising although theoretically limited only to selected patients. In order to extend indications, we believe it could be essential to establish early therapy in patients who meet ARDS criteria without concomitant hemodynamic instability. However, some concerns still claim debate about protocols as well as individual genetic sensitivity which could result into an unspecified estimation of non-responder cases. Finally, the cytoprotective and remodeling aspects that could theoretically be clinically associated with a reduced incidence of post-treatment sequelae, such as pulmonary fibrosis and chronic post-injury respiratory failure, is fascinating.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

References

1. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study. medRxiv 2020. [CrossRef]

2. Wan Y, Shang J, Graham R, Baric RS, Li F. 2020. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020;94:e00127–20. [CrossRef]

3. 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. [CrossRef]

4. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020;63:364–374. [CrossRef]

5. Khan A, Benthin C, Zeno B, et al. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care 2017;21:234. [CrossRef]

6. Zhou F, Yu T, Du R, Fan G, Liu Y, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–1062. [CrossRef]

7. Luo Y, Liu C, Guan T, et al. Association of ACE2 genetic polymorphisms with hypertension-related target organ damages in south Xinjiang. Hypertens Res 2019;42:681–9. [CrossRef]