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https://doi.org/10.1016/j.amjcard.2020.05.038

Angiotensin Converting Enzyme 2 May Mediate Disease Severity In COVID-19

Identification of vulnerability to *severe* coronavirus disease 2019 (COVID-19) is extremely important and might allow optimized shielding and easing of lockdown. The disease is attributed to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which enters host cells through binding to angiotensin converting enzyme 2 (ACE2) on the cell surface. Clinical syndromes such as hypertension that display reduced ACE2 expression tend to correlate with a more severe disease course, whereas treatments which upregulate ACE2 such as the use of angiotensin converting enzyme inhibitors (ACE-i) appear to have a protective effect against COVID-19. Preclinical studies have shown that plasma soluble ACE2 could render SARS-CoV-2 inactive in a dose-dependent manner. The association of clinical syndromes or treatments that impact ACE2 expression and clinical severity of COVID-19 infection combined with the reduction in viral load with human recombinant serum ACE2 shown in preclinical studies indicate a key role for ACE2 in determining COVID-19 severity. In conclusion, we propose that measurement of ACE2 level may help identify individuals at risk of severe infection where targeted shielding can be used and could provide a novel therapeutic target.

Identification of vulnerability to *severe* COVID-19 is extremely important, and might allow optimized shielding and easing of lockdown. We propose a pathological role for soluble angiotensin converting enzyme (sACE2) modulating COVID-19 disease severity, which could be used in screening and treatment.

Hypertension, diabetes, and obesity are risk factors for severe disease.[1] SARS-CoV-2 enters the host cell through the spike (S) protein binding to ACE2,[2] and since ACE-inhibitors (ACE-i) and angiotensin-II receptor blockers (ARB) upregulate cellular ACE2 expression, this could theoretically facilitate SARS-CoV-2 binding and severe disease manifestation, whereas renin-angiotensin-aldosterone inhibition appears protective.[3]

After SARS-CoV-2 binds to host cells, ACE2 expression and enzymatic activity are significantly reduced through enhanced shedding, with the extracellular component of ACE2 cleaved and resultant soluble protein released. The resultant increased sACE2 may act as a "dummy" receptor, binding the S protein on circulating virus. Thus, higher numbers of ACE2 receptors expressed before first binding event may lead to higher sACE2 level and reduced circulating SARS-CoV-2 with "active" S protein sites, reduced numbers of affected host cells, and less systemic impact. Therefore, conditions that upregulate ACE2 may confer protection, whereas reduced ACE2 expression may result in more severe disease.

Clinical findings support such pathological role for reduced ACE2 levels in mediating disease severity. Patients with hypertension, exhibiting marked ACE up-regulation and ACE2 downregulation, are at higher risk of severe disease, whereas those taking ACE-i/ARB exhibit less disease severity and lower mortality.[3] The ACE2 gene is linked to metabolic syndrome and obesity.[4] ACE2 gene knockout leads to metabolic syndrome in mice. In patients with diabetic renal disease, ACE2 expression is reduced compared with patients with nondiabetic renal disease or controls. Lower ACE2 expression in obese patients and metabolic syndrome may explain worse outcomes with COVID-19.[1]

The ACE2 gene is located on the X-chromosome, and ACE2 activity and expression in rats was decreased by oophorectomy and restored by oestrogen. Thus, women would be expected to have higher ACE2 activity, which might explain better outcomes. Recent studies show that human recombinant sACE2 (hrsACE2) can bind and neutralise SARS-CoV-2 S protein,[5] reducing SARS-CoV-2 entry into cells in a dose-dependent manner.[2]

The association of clinical syndromes and treatments that impact ACE2 expression and the reduction in viral load with hrsACE2, indicate a key role for ACE2 in COVID-19 severity. We propose that measurement of ACE2 level may help identify individuals at risk of severe infection and provide a novel therapeutic target.

Disclosures

The authors have no financial associations or other possible conflicts of interest to report.

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8 May 2020
26 May 2020

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https://doi.org/10.1016/j.amjcard.2020.06.002

Recent Findings on Cardiovascular Safety With the Use of Chloroquine and Hydroxychloroquine for COVID-19

In a recent review article, Aggarwal et al[1] discussed the implications for cardiovascular safety of the potential therapies for the treatment of patients with COVID-19. The authors highlight the potential toxicities and cardiovascular side effects of the controversial use of chloroquine (CQ) and hydroxychloroquine (HCQ) that should be taken into consideration before its use. At this time, other implications for cardiovascular safety, along with the prolongation of QT interval reported in small size studies,[2–7] have recently been addressed in regard to the use of CQ and HCQ, alone or in combination with a second-generation macrolide antibiotic (azithromycin or clarithromycin), for the treatment of COVID-19 and the discussion of the potential harm of these drugs is highly relevant and worthy of careful review.

Rosenberg et al[8] conducted a retrospective cohort study of 1,438 patients from 25 different hospitals in New York City, treated with HCQ plus azithromycin (AZ) (n = 735), HCQ alone (n = 271) AZ alone (n = 211), and none of these drugs (n = 221). and found no significant differences in the likelihood of abnormal electrocardiogram findings (defined as arrhythmia or prolonged QT interval) between groups, however, the researchers highlight that cardiac arrest was more likely in the group treated with HCQ plus AZ (adjusted odds ratio [OR] 2.13; 95% confidence interval [CI] 1.12 to 4.05). No significant differences in in-hospital mortality were found. To elucidate if the finding of cardiac arrest was mediated or not by mechanical ventilation, the authors performed a stratified analysis and indicated that in the group of patients who did not receive mechanical ventilation, the risk for cardiac arrest remained increased for HCQ alone compared with AZ alone (adjusted OR 3.01 95% CI 1.07 to 8.51). The analysis performed in this study was adjusted for likely confounders, including co-morbidities, demographics and disease severity. However, due to the observational study design it is possible that some amount of unmeasured confounding remains.

Later on, Mehra et al[9] reported a large international observational registry including data from 96,032 patients from 671 hospitals in 6 continents (mainly North America and Europe) who received CQ (n = 1,868); CQ plus macrolide (n = 3,783); HCQ (n = 3,016); HCQ plus macrolide (n = 6,221) versus none of these drugs (n = 81,144) and found that the use of CQ or HCQ with or without macrolides was independently associated with a higher risk of in-hospital mortality and an increased frequency of de-novo ventricular arrhythmia (nonsustained or sustained ventricular tachycardia or ventricular fibrillation). The authors state that the combination of CQ or HCQ with a macrolide increased the hazard of de-novo ventricular arrhythmias: CQ with a macrolide (hazard ratio [HR] 4.01; 95% CI 3.34 to 4.81); CQ alone (HR 3.56; 95% CI 2.76 to 4.59); HCQ with a macrolide (HR 5.10; 95% CI 4.10 to 5.98), and HCQ alone (HR 2.36; 95% CI 1.93 to 2.90). Predictors of ventricular arrhythmia were also investigated and the variables found to be independently associated with higher risk of de-novo ventricular arrhythmias were CQ or HCQ with or without macrolides and baseline co-morbidities such as coronary artery disease, congestive heart failure, history of cardiac arrhythmia, and chronic obstructive pulmonary disease. The researchers argue that the presence of underlying cardiovascular disease could represent a partial explanation of the cardiovascular toxicity associated with the use of CQ or HCQ particularly with the combination of macrolides. Notably, a propensity score matching analysis was conducted to mitigate potential confounders. Moreover, Cox proportional hazards models and a tipping-point analysis were performed to assess the robustness of the estimates. Clearly, this study represents a potential landmark regarding safety and efficacy of CQ and HCQ, either alone or in combination with macrolides, for the treatment of COVID-19. However, the observational retrospective design limits the study's implications.

In addition to the cardiotoxic considerations mentioned by Aggarwal et al,[1] relevant cardiovascular side effects and toxicities associated with the use of repurposing drugs for the treatment of COVID-19 have been stated by researchers of cardiovascular disease who stress the risk of QT interval prolongation, thrombocytopenia and anemia specifically with the use of CQ and HCQ.[10] In conclusion, it is not clear whether the risk of toxic effects may outweigh the benefits of potential COVID-19 treatments. A decisive answer still awaits the results of high quality large randomized controlled trials.

Disclosures

The authors have no conflicts of interest to disclose.

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27 May 2020

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