ACE inhibitors and COVID-19: we don't know yet

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Abstract

The SARS-CoV-2, the causative agent of COVID-19, has been established to gain access to the human cell via the ACE2 receptor similar to its familial coronavirus SARS-CoV which led to the outbreak in 2003. A concern with the newer 2019 coronavirus is its 10-20-fold higher affinity to the ACE2 receptor that of SARS-CoV, aiding its effective human-to-human transmission which has led to this pandemic. ACE2 receptor expression is thought to be upregulated in use with ACE inhibitors. As ACE inhibitors are known to be a used extensively in the treatment of hypertension it was a concern regarding the risk of using these medications alongside a SARS-COV-2 infection. ACE inhibitors are also used in the treatment regime of other common conditions including diabetes and Cardiovascular disease (CVD). It is worth noting that ACE2 expression has found to be upregulated by the use of thiazolidinediones and ibuprofen too. Consequently, the increased expression of ACE2 would facilitate infection with COVID-19. Therefore, it would hypothesise that diabetes and hypertension treatment with ACE2-stimulating drugs would increase the risk of developing severe and fatal COVID-19.

Running Head: COVID-19 and ACEi

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Abstract:

The SARS-CoV-2, the causative agent of COVID-19, has been established to gain access to the human cell via the ACE2 receptor similar to its familial coronavirus SARS-CoV which led to the outbreak in 2003. A concern with the newer 2019 coronavirus is its 10-20-fold higher affinity to the ACE2 receptor that of SARS-CoV, aiding its effective human-to-human transmission which has led to this pandemic. ACE2 receptor expression is thought to be upregulated in use with ACE inhibitors. As ACE inhibitors are known to be a used extensively in the treatment of hypertension it was a concern regarding the risk of using these medications alongside a SARS-COV-2 infection. ACE inhibitors are also used in the treatment regime of other common conditions including diabetes and Cardiovascular disease (CVD). It is worth noting that ACE2 expression has found to be upregulated by the use of thiazolidinediones and ibuprofen too. Consequently, the increased expression of ACE2 would facilitate infection with COVID-19. Therefore, it would hypothesise that diabetes and hypertension treatment with ACE2-stimulating drugs would increase the risk of developing severe and fatal COVID-19.

Dear Editor,

The recent Chinese clinical studies detailing the clinical characteristics of patients infected by the novel COVID-19 infection have confirmed many of these concerns [1]. A study included 1099 patient's laboratory-confirmed Covid-19 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China through January 29, 2020, of which 261 had an associated comorbidity [2]. Hypertension yet again was the most common comorbidity with 165 patients, followed by 81 patients with diabetes. A meta-analysis [3] evaluating the comorbidities associated with COVID19 found similar results, however noted that in comparison to the prevalence of both diabetes and hypertension in china, the percentage of each comorbidity presenting with COVID19 was similar. These statistics raise the question of whether hypertension itself a high-risk comorbidity is or is the use of ACEI specifically as treatment responsible for these statistics.

Coronary heart disease (CHD) being the most common chronic condition worldwide, a small percentage of COVID-19 patients had the disease as a comorbidity. The lower rates of CHD could be associated with the lower ACE2 receptor expression found to be supressed in patients with the development of heart failure [4]. Lower ACE2 expression then, would reduce the ability of the COVID-19 virus to bind and infect the cell. Large cohort studies factoring in ACE2 expression as a variable while comparing progression of COVID19 infection in patients would indicate the relevance of the ACE2 receptor in COVID19 mortality and fatality.

According to data from the above study, 23·7% of patients with hypertension were assessed to have a severe COVID19 infection, followed by diabetes mellitus (16·2%), coronary heart diseases (5·8%), and cerebrovascular disease (2·3%). A high percentage of 35.9% of who had hypertension had an end point at ICU, with the use of mechanical ventilation or death. 26.9% of diabetic patients had a similar end point. As ACE inhibiters are dominantly used in hypertension this could potentially explain the high percentage of COVID19 positive patients who develop severe infection. Diabetic patients could also be on ACE inhibitors slowing down the progression of the vascular complications associated with diabetes hence, the high percentage of diabetic patients developing a severe infection. Still, however much less than hypertension which could be due to the lower use of ACE inhibitors in diabetes in comparison. It has been shown that contracting COVID19 is equal in both hypertensive and diabetic, however hypertensive patients are likely to develop a severe infection in comparison.

On the other hand, studies [5] have suggested the use of ACE inhibitor might be protective against respiratory complications. The binding of SARS-CoV-2 to ACE2 exhausts ACE2, leading to an imbalance of the renin-angiotensin-aldosterone system which spirals into acute severe pneumonia. Blocking the renin-angiotensin-aldosterone system by ACEI might therefore reduce inflammation in COVID-19 pneumonia, potentially reducing mortality. A recent study [5] compared inflammatory marker found in COVID19 positive patients on ACE inhibitors versus non-ACE inhibitors. It was found that Interleukin 6 a pro-inflammatory marker levels were reduced in the ACEI group. Large studies are needed to delineate the role of ACEI in treating

COVID-19, ideally both in patients naïve to ACEI, and chronic users of ACEI. Since small centres may have difficulty amassing enough cases, inter-institutional collaborations should be strongly encouraged. These would indicate whether the use of ACE inhibitors in COVID-19 positive cause more harm than good or vice versa which would shine a light on the use of hypertensive medication in these patients.

In short, both the concerns regarding ACE inhibitor use predisposing to infection by SARS-CoV-2 and the idea that ACEI may help treat COVID-19 have valid theoretical bases. At this point, there is insufficient clinical evidence pointing to either being true, further studies are urgently required. Given the known, significant cardiovascular benefits of ACEI, patients should not stop taking them over the above theoretical concerns. These guidelines nonetheless are due to lack of evidence for the use of ACE inhibitors in COVID19 positive patients. Medical workers and researchers worldwide are strongly encouraged to report any available data regarding the relationship between ACEI and COVID-19.

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