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Antihypertensive drugs and risk of COVID-19?

Authors' reply

We thank Joshua Brown, Kevin Lo and colleagues, and Christopher Tignanelli and colleagues for their responses to our Correspondence[1], and we welcome the opportunity to reply.

The fast-developing pandemic of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported from Wuhan, China,[2] and has spread globally. As of March 22, 2020, 307 297 people have been infected by SARS-CoV-2, with 13 049 deaths and 92 382 people recovered. Several reports have summarised the clinical and epidemiological features of COVID-19 and have shown specific comorbidities associated with increased risk of infection and developing into a severe or fatal case. Of 1099 infected patients, 173 had severe disease, in whom the most common co-morbidities were hypertension (24%), diabetes (16%), coronary heart disease (6%), and cerebrovascular disease (2%).[3] In a second cohort of 41 patients hospitalised with COVID-19,[4] diabetes (20%), hypertension (15%), and cardiovascular disease (15%) were frequent comorbidities. Among 191 patients hospitalised with COVID-19,[5] the most common comorbidities with significant effects on mortality were hypertension (30%; p=0·0008), diabetes (36%; p=0·0051), and coronary heart disease (15%; p=0·0001). In an analysis of 201 patients with COVID-19,[6] 84 (42%) patients developed acute respiratory distress syndrome, with hypertension (27%) and diabetes (19%) as the most common comorbidities.

Hypertension, diabetes, and cardiovascular disease, which seem to be the most common comorbidities in patients with COVID-19, are typically treated with drugs that inhibit the renin–angiotensin system (RAS), including angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). The long history of use and thorough investigation of these drugs means that efficacy and safety of RAS inhibitors is very well documented, not only for management of blood pressure but also for protection from disease-associated inflammation and organ remodelling.[7] The high proportion of patients with severe COVID-19 and these comorbidities suggests a causative link and led to our hypothesis,[1,8] which has also been presented by others.[9,10] Based on the drugs most frequently given to patients to treat these comorbidities (ie, ACEIs and ARBs), we postulated whether these drugs might further increase risk for severe or fatal COVID-19.[1] This hypothesis is supported by the observation that organ-specific expression of angiotensin converting enzyme 2 (ACE2) correlates with the vulnerability to infection by SARS-CoV-2.[11] Our concern was initiated after investigating the molecular mechanism by which SARS-CoV-2 attaches to and infects cells. Both SARS-CoV-2 and severe acute respiratory syndrome coronavirus (SARS-CoV) bind to the host cell's membrane via ACE2,[12] which is specifically highly expressed by epithelial cells in oral mucosa.[13] ACE2 is a widely expressed protein in lung, intestine, kidney, and blood vessels, and on immunoreactive cells.[11] Moreover, circulating amounts of ACE2 are increased in patients with hypertension or diabetes, and levels are further increased by different drugs, including ACEIs and ARBs.[14,15] It should also be emphasised that specific alleles control ACE2 expression, activity, and response to ACEIs.[15] In addition to animal models, humans given ACEIs, ARBs, or both, had increased ACE2 levels on intestine luminal cells.[16]

In this context, it should be noted that modification of glycosylation is essential for binding of SARS-CoV-2 spike protein. Inhibition of ACE2 glycosylation by either chloroquine, hydrochloroquine, or a serine protease inhibitor significantly reduces the infection of host cells by SARS-CoV and SARS-CoV-2 in vitro.[17–19]

We are aware of the beneficial effects of ACEIs and ARBs protecting the heart and kidney for patients with hypertension and diabetes. An opposing hypothesis has suggested that upregulation of ACE2 expression or infusion of human recombinant ACE2 might protect against SARS-CoV-2 infections.[20,21] However, it has to be emphasised that the role of ACE2 in these protective effects are not well understood.[12–14]

Furthermore, it should be noted that ACEIs have been reported to modify the adaptive immune response,[22] suggesting that long-term use of ACEIs might suppress the adaptive immune response, which is a key defence against viral infections. Similar effects on the adaptive immune response are known for most non-steroid anti-inflammatory drugs. These effects need to be addressed in an extended discussion and investigated with clinical trials in the context of the COVID-19 pandemic.

Available published data indicate that ACE2 is a double-edged sword, particularly when considering patients with SARS-CoV-2 infection and comorbidities of hypertension, diabetes, and cardiovascular disease. The final answer as to whether drugs to treat these comorbidities (ie, ACEIs or ARBs) are more beneficial than harmful in this current pandemic is unclear, and all hypotheses should be investigated rather than being interpreted as evidence. This work is of special importance because coronaviruses in general have always been a part of the common influenza season and, in the future, new SARS-CoV will probably develop.

The overinterpretation of our hypothesis should not lead to changing drugs for patients with hypertension or diabetes without first consulting with an expert clinician. Nevertheless,

Published Online
March 26, 2020
https://doi.org/10.1016/S2213-2600(20)30159-4

it is of utmost urgency for the scientific and medical community to work together to find evidence-based proof to address these concerns.

We declare no competing interests.

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Related links

- The latest guidance from WHO on ibuprofen and COVID-19 (dated: 19.03.2020)
- Statement from Prof Michael Roth on how to interpret the original letter