LETTERS

Renin–angiotensin–aldosterone system inhibitors to treat COVID-19?

I would like to respond to 2 statements in the commentary by Quinn and colleagues.[1]

"ACE inhibitors and ARBs exert opposite effects on angiotensin II"

Angiotensinogen is produced mainly in the liver and fat cells, in response to poor perfusion, and acts as a pro-signal in the complex downstream renin–angiotensin–aldosterone (RAAS) system. Angiotensinogen is cleaved to angiotensin I (Ang-[1–10]) by renin, which is found mostly in the juxtaglomerular apparatus of the kidney and is also considered to be a pro-signal peptide. Angiotensin I can be cleaved by 1 of 2 membrane proteases expressed by angiotensin-targeted cells: i) angiotensin-converting enzyme (ACE) to form angiotensin II, or ii) angiotensin-converting enzyme-2 to form Ang-(1–9). Angiotensin II is the main RAAS agonist and binds to angiotensin receptors expressed on the same targeted cells.

Thus, both ACE inhibitors and angiotensin receptor blockers (ARBs) exert down-regulating effects on angiotensin II activity. In essence, they complement the effect of ACE2, which is a naturally occurring protease that counters angiotensin II activity.

Improved outcomes during COVID-19 with ACE inhibitors and ARBs "are unlikely to be causal"

It is generally accepted that increased expression of ACE2 is advantageous for an ACE2-targeting virus such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which cycles through cells with membrane ACE2 proteases until those proteases are depleted. Higher ACE2 expression enables more viral cycling and thus a higher viral load, leaving the host acutely ACE2 depleted, with proportionally increased angiotensin II effects. This is equivalent to suddenly stopping ACE inhibitors or ARBs, or both at the same time.

Aiding an acute RAAS crisis by stopping angiotensin II–regulating drugs just as the natural ACE2 defence is destroyed is likely to increase morbidity and mortality.

In the study by Zhang and colleagues,[2] cited by Quinn and colleagues' commentary, the patients on ARBs who were maintained on treatment during their infections had a decreased mortality (adjusted hazard ratio 0.30; 95% confidence interval 0.12–0.70; $p = 0.01$) compared with matched hypertensive patients not on that particular class of drugs.

At this point in the pandemic, as hopes for a successful treatment strategy or a vaccine seem to be dwindling, we should take a closer look at the effect of ARBs during the critical inflammatory phase of coronavirus disease 2019 (COVID-19).

The current recommendations are to maintain patients on these drugs if they become infected with SARS-CoV-2. Equal consideration should be given to patients on downstream aldosterone-blocking drugs such as spironolactone, where discontinuing this medication, as with ARBs, could be detrimental.

Finally, as COVID-19 has a strong component of ACE2 depletion underlying the course of the illness, and as RAAS (angiotensin and aldosterone) stressors promote cytokine-mediated disease in the lungs and cardiovascular–renal system, introducing drugs to block those effects could offer a much-needed lifeline where a 0.3 risk of dying would be quite welcomed.

Richard A. Henry MBChB
Anesthesiologist, Queen's University, Kingston, Ont.

■ Cite as: *CMAJ* 2020 June 29;192:E728. doi: 10.1503/cmaj.76023

References

1. Quinn KL, Fralick M, Zipursky JS, et al. Renin–angiotensin–aldosterone system inhibitors and COVID-19. *CMAJ* 2020;192:E553-4.
2. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin–converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res* 2020; 126:1671-81.

Competing interests: Richard Henry has filed a provisional patent: Use of mineralocorticoid blockers in the treatment of COVID-19.