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EDITORIAL COMMENT

Renin-angiotensin-aldosterone system inhibitors and the COVID-19 epidemic

Os inibidores do sistema Renina-Angiotensina-Aldosterona e a epidemia Covid-19

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This editorial comment refers to the article ''Impact of renin-angiotensin-aldosterone inhibitors withdrawal on mortality in COVID-19 patients'' by Caro-Codón et al., published in this issue of the Revista Portuguesa de Cardiologia.[1]

The anchor-point of SARS-CoV-2 in human cell membranes, specifically in the respiratory epithelium, is a protein called angiotensin-converting enzyme-2 (ACE-2). Once attached to this protein, internalization vesicles are formed and the virus enters the cytoplasm. The consequence of SARS-CoV-2 virus binding to ACE-2 and the resulting internalization of these molecules is a decrease in ACE-2 on the epithelial cells' surface.[1–3]

Contrary to angiotensin-converting enzyme-1 (ACE-1), which promotes the conversion of angiotensin-I into angiotensin-II, thus increasing serum concentrations of the latter, ACE-2 reduces angiotensin-II levels by transforming it into angiotensin.[1–7] Angiotensin-II has deleterious effects which include vasoconstriction, sodium retention, cell proliferation, apoptosis, fibrosis, and inflammation. Angiotensin[1–7] has diametrically opposed protective effects.[2,3]

Lung damage, cardiac remodeling, inflammation, and vasoconstriction are harmful consequences of an overproduction of angiotensin-II.[2,3]

SARS-CoV-2, by docking on ACE-2, with the consequent internalization of the virus/ACE-2 complex, reduces the number of ACE-2 molecules available at the cell surface (specifically at the respiratory epithelium level), leading to a decrease in the amount of protective angiotensin 1-7 molecules and an increase in harmful angiotensin-II molecules, with a consequent exaggerated inflammatory response.[2–5]

At the beginning of the SARS-CoV-2 epidemic, it was thought that this infection could be aggravated by ACE inhibitors (ACEi) and by angiotensin receptor blockers (ARB), which supposedly could facilitate SARS-CoV-2 infection by increasing ACE-2 levels at epithelial cells' surface, creating an opportunity for SARS-CoV-2 to anchor and then be internalized into target cells, specifically those of the respiratory epithelium, infecting them.[6,7] In fact, a paper published in Circulation in 2005[8] showed that ACEis did increase ACE-2 molecules at the epithelial cells' surface and the same occurred with ARBs.[6] It was, therefore, assumed that these drugs could indeed create greater opportunities for SARS-CoV-2 to cause injury.[6,7]

This created a wave of suspicion regarding these drugs leading to their discontinuation, particularly in patients with

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cardiovascular diseases, in which they play a central role in improving prognosis.[1]

However, the study by Caro-Codón et al. now published in the Journal, showed that, in patients with cardiovascular disease infected with SARS-CoV-2, the discontinuation of ACEis or mineralocorticoid receptor antagonists (MRAs) was in fact associated with an increase in all-cause mortality, compared to patients in whom these drugs were not withdrawn.[1]

This study is consistent with others previously published, especially one by Savarese et al.,[8] demonstrating, in an extensive cohort of 1.4 million patients with arterial hypertension, heart failure, diabetes, kidney disease, or coronary heart disease, that the use of ACEIs/ARBs was associated with a reduced risk of hospitalization/mortality due to COVID-19 infection.[8] Therefore, the study by Savarese et al.[8] does not confirm the fears of a possible negative association of ACEIs/ARBs with a worsened COVID-19 infection prognosis.[5,8]

Despite these reassuring data, randomized studies are needed to determine the role of renin-angiotensin-aldosterone system inhibitors (RAASi) in patients infected with COVID-19.[5,8] The BRACE CORONA study, including 659 cardiovascular patients with mild to moderate forms of COVID-19 infection who were randomized to continuation *vs.* discontinuation of ACEis/ARBs, proved that the maintenance of these drugs was safe, and was not associated with increased mortality.[9]

In summary, current evidence does not demonstrate that RAASi are effective against COVID-19 infection, but it clearly suggests that, in this context, they are safe and, therefore, they should be maintained in patients with heart failure, hypertension, diabetes, coronary heart disease and kidney disease, even if infected with COVID-19, taking into account their proven positive prognostic impact in patients with these cardiovascular disorders.[1,5,8,9]

Conflicts of interest

The author has no conflicts of interest to declare.

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