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Official statement of the Italian Society of Pharmacology on the use of ACE-inhibitors or angiotensin receptor blockers in COVID-19 infection

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The coronavirus 2019 (SARS-CoV-2) pandemic is spreading around the world and is a matter of great concern. In this situation, it is more important than ever to make evidence-based decisions concerning pharmacological treatment. Some editorials (Gurwitz D, 2020; Zheng YY et al, 2020; Watkins J, 2020) have reported conflicting hypotheses on the potential benefit/risk profile of anti-hypertensive drugs acting on the renin-angiotensin system. The relevance of these drugs is related to the involvement of the angiotensin converting enzyme 2 (ACE2) in the invasion process of SARS-COV-2 in the host lung cells. It is therefore critical to clarify the potential impact of these drugs in SARS-CoV-2 infection and to promote a clear understanding of the assumptions in favor of or against switching patients treated with ACE-inhibitors or angiotensin II receptor blockers (ARBs) to other anti-hypertensive agents or vice-versa, in order to prevent potentially inappropriate therapeutic regimens.

ACE2 and ACE-inhibitors/ARBs

The angiotensin-converting enzyme 2 (ACE2) is an aminopeptidase membrane protein that plays an important role in the regulation of the cardiovascular and immune systems. It is involved in the regulation of cardiac activity and in the development of chronic illness, such as hypertension and diabetes mellitus (Turner AJ et al, 2004). ACE2 is highly expressed on the surface of cardiac and pulmonary cells, and it is used by coronaviruses, such as SARS-CoV and SARS-CoV-2, to enter host cells (Hoffmann M et al, 2020). Specifically, the interaction between the “spike” protein of coronaviruses and ACE2 has been identified as a key factor for the virus transmission.

SARS-CoV-2 mainly infects the epithelial cells of the alveoli, leading to significant respiratory symptoms that are particularly severe in patients affected by cardiovascular diseases. In vitro studies have demonstrated that both the ACE-inhibitor lisinopril and the ARB losartan can significantly increase the expression of cardiac ACE2 (by 5- and 3-fold, respectively) (Ferrario CM et al, 2005). For these reasons, some authors suggested carefully evaluating the

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potential risks and benefits of using ACE-inhibitors or ARBs in patients infected by SARS-CoV-2 (Zheng YY et al, 2020; Watkins J, 2020).

However, several studies conducted on SARS-CoV, which are generalizable to SARS-CoV-2, have suggested the opposite to be true (Gurwitz D, 2020). It has been demonstrated that the bond between the spike protein and ACE2 stimulates a down-regulation of ACE2 that leads to an excessive production of the angiotensin II. This excessive production is mainly due to the absence of the conversion of the angiotensin II into the angiotensin 1-7 (a vasodilator peptide) by ACE2. This phenomenon contributes to lung damage as the stimulation of angiotensin receptors causes an increase in pulmonary vascular permeability (Imai et al, 2005; Kuba et al, 2005). As a result, there is a paradoxical increase in the expression of ACE2 induced by chronic treatment with ARBs which may protect patients infected by SARS-CoV-2 from more severe pulmonary symptoms. This might be related to two complementary mechanisms: 1) ARBs can block the effect of angiotensin receptors; 2) ARBs can induce upregulation of ACE2 and consequently increase the level of angiotensin 1-7 (Gurwitz D, 2020, de Wit et al, 2016).

Clinical evidence on the switch from or to ACE-inhibitors and ARBs

ACE-inhibitors and ARBs are currently approved (with some differences among single drugs) for the treatment of high-impact chronic illnesses such as hypertension, heart failure and diabetic glomerular nephropathy, as well as for the secondary prevention of acute myocardial infarction. To date, there is no scientific evidence from clinical studies, nor is there any approved indication to support the substitution of an ACE-inhibitor or an ARB with other anti-hypertensive agents (or vice-versa) in patients with SARS-CoV-2 infection whose hypertension is adequately controlled with their current anti-hypertensive medication/s. The Chongqing Medical University is conducting a retrospective observational study to evaluate clinical differences among adult hypertensive patients affected by COVID-19, who are treated or not treated with ACE-inhibitors. This study will be concluded on April 30th, 2020 (clinicaltrials.gov, NCT04272710). Moreover, the aforementioned editorials suggested that "*Whether patients with COVID-19 and hypertension who are taking an ACE inhibitor or angiotensin-receptor blocker should switch to another antihypertensive drug remains controversial, and further evidence is required*" (Zheng YY et al, 2020) and "*The tentative suggestion to apply [angiotensin receptor 1] antagonists such as losartan and telmisartan as SARS-CoV-2*

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therapeutics for treating patients prior to the development of acute respiratory syndrome remains unproven until tried " (Gurwitz, 2020).

In conclusion, therapeutic switching between different anti-hypertensive classes which are known to be effective in the treatment of chronic diseases such as hypertension, heart failure, diabetes, and renal failure, is unjustified as it exposes frail patients to an increased risk of cardiovascular events or a worsening of the aforementioned clinical conditions, considering that existing evidence is derived from molecular hypotheses or in vitro experiments. The conduction of pharmacoepidemiology studies and, where possible, clinical trials, which evaluate the role of ACE-inhibitors/ARBs in patients infected by SARS-COV-2, are needed.

With regards to the hypothesis that ACE-inhibitors and ARBs can be used in healthy people to prevent SARS-CoV-2 infection, it is worth reminding clinicians that these drugs should just be used to manage the conditions for which they are indicated. Furthermore, there is no biological or clinical evidence in favor of their protective effect in COVID-19. No regulatory authority in the world has, to date, recommended any kind of therapeutic switch from or to ACE-inhibitors/ARBs. Many Scientific Societies have also expressed their opinion in this regard (see the position statement of the Italian Society of Hypertension, 2020; the clinical guidelines of the Italian Society of Cardiology, 2020; the position statement of the European Society of Cardiology – Hypertension Council).

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