Sacubitril/valsartan: potential impact of ARNi "beyond the Wall" of ACE2 on treatment and prognosis of heart failure patients with COVID-19

Speranza Rubattu[1], Giovanna Gallo[1], and Massimo Volpe[2]

[1]Sapienza University of Rome
[2]University of Rome La sapienza

October 1, 2020

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Speranza Rubattu [1,2], Giovanna Gallo[1], Massimo Volpe [1,2]

1 Cardiology Unit, Department of Clinical and Molecular Medicine, Sapienza University of Rome, Sant'Andrea Hospital, Rome, Italy.

2 IRCCS Neuromed, Pozzilli (IS), Italy

Running title: ARNi and COVID-19 in HFrEF

Total word count (excluding references): 835

Corresponding address:

Speranza Rubattu, M.D.

Department of Clinical and Molecular Medicine,

School of Medicine and Psychology,

Sapienza University of Rome;

IRCCS Neuromed, Pozzilli (Isernia), Italy

e-mail: speranzadonatella.rubattu@uniroma1.it

From the beginning of the SARS-CoV-2 pandemic and of its related COVID-19 outbreak, the angiotensin-converting enzyme 2 (ACE2), probably the most "unloved and neglected" member of the renin-angiotensin-aldosterone system (RAAS) family, has attracted increasing attention since it has been shown as the cell receptor through which the virus enters into the cells (Iaccarino, Grassi et al., 2020).

The physiological action of ACE2 consists in degrading angiotensin II (Ang II) to angiotensin (1-7), a heptapeptide with a potent vasodilator function through the Mas receptor able to counterbalance the Ang II effects on vasoconstriction, sodium retention, and fibrosis (Gallagher, Ferrario et al., 2014).

Previous studies have shown that angiotensin type 1 receptor (AT1R) blockers (ARBs), ACE inhibitors (ACEI) and mineralocorticoid receptor antagonists (MRA) may up-regulate the expression of ACE2 both in acute and chronic settings of cardiovascular diseases (CVDs) such as hypertension, heart failure (HF) and myocardial infarction (MI) (Gallagher, Ferrario et al., 2014).

These data have generated concern during the early phases of the pandemic, since it has been speculated that the increase in ACE2 level may have contributed to disease virulence and to adverse outcomes particularly in those subjects affected by chronic coexisting CVDs who commonly received treatment with RAAS inhibitors and who were characterized by a worse clinical course (Iaccarino, Grassi et al., 2020).

On the other hand, it has been observed that the binding between coronavirus and ACE2 leads to

ACE2 downregulation, resulting in an unopposed production of angiotensin II by ACE, contributing to lung damage as a consequence of AT1R mediated inflammation, fibrosis, thrombosis, vasoconstriction and increased vascular permeability. According to these findings, RAAS inhibitors and in particular ARBs may even protect against COVID-19 acute lung injury (Iaccarino, Grassi et al., 2020). As a matter of fact, epidemiological studies conducted in large populations of COVID-19 patients demonstrated that ARBs or ACEI had no association with a severe or fatal course of the disease (Iaccarino, Grassi et al., 2020).

In such a context, natriuretic peptides (NPs), which include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), along with their N-terminal counterparts, may play an important protective role in COVID-19 disease. NPs are released as a consequence of increased volume overload and myocytes stress and, through their vasorelaxant, diuretic and natriuretic effects, are able to counterbalance RAAS and sympathetic nervous system actions, ultimately regulating blood pressure, electrolytes and water homeostasis (Volpe, Rubattu et al, 2014). At the vascular level, NPs reduce cellular growth and proliferation, preserving endothelial function and integrity as well as vascular tone, and they oppose blood clotting, inflammation, angiogenesis and atherosclerosis progression (Volpe, Rubattu et al, 2014). Besides their well-described systemic haemodynamic and autocrine/paracrine functions within the cardiovascular system, NPs play an important protective role in the lungs. It fact, ANP is able to reduce lung endothelial permeability caused by inflammation and oxidative stress, avoiding the development of acute respiratory distress syndrome and improving arterial oxygenation during mechanical ventilation. According to these evidences, it has been proposed that COVID-19 patients with deficiencies in the NP system, mainly obese and black subjects, may have an increased risk of developing severe lung complications.

A bidirectional interaction between ANP and ACE2 has been demonstrated in experimental models. ANP, through cyclic guanosine monophosphate (cGMP) production, inhibited the Ang II-mediated decrease of ACE2 mRNA synthesis. On the other hand, Ang-(1-7), the product of ACE2 activity, stimulated ANP secretion (Gallagher, Ferrario et al., 2014).

In such a context, a field of great interest is represented by the potential impact on the clinical course of the COVID-19 disease and on its outcome of a treatment with sacubitril/valsartan (S/V), a member of the new pharmacological class of AT1R/neprilysin inhibitors (ARNi) and currently recognized as a cornerstone of the therapeutic management of HF with reduced ejection fraction (HFrEF). With regard to the trend of different NPs levels after the initiation of S/V, NT-proBNP level decreases as a consequence of the improvement of cardiac function; BNP level slightly increases due to its relatively low affinity to neprilysin, whereas ANP level consistently and substantially increases, mediating most of the benefits of neprilysin inhibition (Ibrahim, McCarthy et al., 2019).

According to these evidences, an approach based on early administration of S/V has been proposed in the therapeutic management of COVID-19 hospitalized patients (Acanfora, Ciccone at al., 2020). This intriguing hypothesis appears devoid of any practical value in non CVD patients, due to the undesirable haemodynamic effects of this drug and to the lack of indication for S/V administration in the absence of HFrEF.

In our opinion, a more specific and rational approach to test the expected beneficial role of S/V would be to retrospectively investigate in existing registries of hospitalized COVID-19 patients whether, among subjects affected by HFrEF, those who were treated with S/V presented a lower disease incidence, a better prognosis and clinical course, compared to patients who received other medications, including ACEI/ARBs. A call to action is required to test the potential benefits of S/V in HFrEF patients affected by COVID-19 through new prospective randomized clinical trials.

Acknowledgements

No fundings to disclose.

Conflict of interest statemente

Authors have no conflicts of interest to disclose.

Authorship

All Authors substantially contributed to the conception and design, acquisition of data, or analysis and interpretation of data, drafted the article and approved the final version to be published.

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