

Sacubitril, valsartan and SARS-CoV-2

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10.1136/bmjebm-2020-111497

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Dear Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (COVID-19) is responsible for the current global pandemic. To date, no antivirals directed against the virus or effective vaccines are available.¹ It is essential to recognise the risk factors and components that may play a protective role. There is no clear evidence on the correlation between changes in the renin-angiotensin system (RAS) by treatment with ACEIs, ARBs or DRIs and COVID-19 infection.²⁻⁴ Randomised controlled trials are needed to verify the involvement of COVID-19 viral infection and chronic treatment with these drugs. A possible scientific hypothesis to investigate is the role of the neprilysin inhibitor sacubitril in association with valsartan in the more severe stages of COVID-19 infection. The challenge to defeat the current pandemic poses several objectives, among them trying to give added values to therapeutic solutions; in this direction, the association with sacubitril/valsartan has already demonstrated therapeutic efficacy in the treatment of chronic symptomatic heart failure with reduced ejection fraction in several studies⁵; indirectly, the therapeutic benefits of the cardiovascular type are also directed to a decrease in the risk of infection and complications from COVID-19. Furthermore, there is evidence of a significant increase in N-terminal pro hormone BNP (NT-proBNP) in patients with COVID-19.⁶ Studies show that higher NT-proBNP was an independent risk factor for death in patients with severe COVID-19⁷; moreover, NT-proBNP is associated with proinflammatory effects.^{8,9} Sacubitril, through its mechanism of action, increases neprilysin-degraded peptides, such as natriuretic peptides (NPs), peptide natriuretic atrial (ANP) and peptide natriuretic brain (BNP)¹⁰; evidence associates these peptides with anti-inflammatory, antihypertrophic and antifibrotic effects. Recent evidence shows that interleukin-1 β secretion is strongly inhibited by the BNP/ Natriuretic peptide receptor (NPR-1)/ cyclic guanosine monophosphate (cGMP) axis to all molecular mechanisms closely controlling its production and release, Nuclear factor NF- κ B, extracellular regulated kinases ERK 1/2 and all elements of the NALP3/ASC/ caspase-1 inflammasome cascade, and that NALP3 inflammatory inhibition is directly related to the deregulatory effect of BNP on the activation of NF- κ B/ERK 1/2¹¹; also, the decrease of NT-proBNP by sacubitril is known. Valsartan in association, by blocking the AT-1 receptor of Ang II, decreases profibrotic and proinflammatory activities mediated by AT-1r and indirectly increases the action of Ang II on AT-2r with antifibrotic, anti-inflammatory effects. Based on the evidence and in relation to our generated hypothesis, we believe that the use of sacubitril/valsartan in the most severe stages of COVID-19 infection could have therapeutic efficacy, with anti-inflammatory and antifibrotic effects mediated by NPs. Clinical studies are required to confirm this hypothesis.

Contributors AV, the undersigned, and any other author, declares that the manuscript was written

entirely by the authors; all authors made equal contributions to the development of the paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

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To cite: Vitiello A, La Porta R, Ferrara F. *BMJ Evidence-Based Medicine* 2021;26:205.