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Sacubitril/valsartan in COVID-19 patients: the need for trials

Keywords COVID • RAAS inhibitors • Sacubitril

We thank Luigi Petramala and Claudio Letizia for their comment[1] on our letter about the possible role of sacubitril/valsartan in patients with coronavirus disease 2019 (COVID-19).[2]

The authors rightly affirm the need for continuing previous therapies with angiotensin-converting enzyme inhibitors (ACE-Is) or sartans in patients with COVID-19, as outlined by recent international consensus papers.[3] There is no definite evidence about the harmful or protective use of ACE-Is/sartans in COVID-19 patients.[4,5] Dedicated, randomized controlled trials are needed in order to verify the possible worsening of lung infection and/or systemic involvement in patients with COVID-19 who are chronically treated with ACE-Is/sartans. Furthermore, we do not intend to pressurize the indiscriminate change of previous treatments towards sacubitril/valsartan in the absence of evidence from randomized trials. The COVID-19 pandemic forced the scientific community to think about possible, alternative solutions to counteract the multiorgan damage by the virus.

We do agree that interrupting specific treatments would increase adverse clinical outcomes in patients, independently from the course of COVID-19, but trying to improve therapeutic solutions is challenging. Sacubitril/valsartan has already demonstrated superiority over standard therapies in patients suffering from heart failure with reduced ejection fraction (HFrEF), regardless of any comorbidities.[6] Moreover, post-hoc analysis from the Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) trial revealed a 42% relative risk reduction in the composite endpoint of death from any cause, re-hospitalization for heart failure, left ventricular assist device implantation, or listing for cardiac transplant, a 42% relative risk reduction in the composite endpoint of cardiovascular death or re-hospitalization for heart failure, and a 39% relative risk reduction in re-hospitalization for heart failure after 8 weeks of treatment with sacubitril/valsartan administered early in patients stabilized during hospitalization for acute decompensated heart failure.[7] Furthermore, a significant 50% reduction in NT-proBNP is evident after the first week of treatment with sacubitril/valsartan.[8]

The need for early administration of sacubitril/valsartan in acute heart failure is probably becoming mandatory in pharmacological management of heart failure patients, although not yet covered by the guidelines.

In recent days, the characteristics of cardiac injury during COVID-19 infection have been made available to the medical and scientific community.[9,10] In COVID-19 patients, with and without symptoms attributable to pneumonia, there is evidence of a significant increase in NT-proBNP, regardless of left ventricular dysfunction. NT-proBNP levels are also the results of acute renal injury and pro-inflammatory molecules such as interleukin-1 and C-reactive protein, which are independent of cardiac function. Shi *et al.* showed that patients with cardiac injury had a higher rate of mortality during the interval both from symptom onset to admission and from admission to clinical endpoint. Increased death rates were associated with higher levels of NT-proBNP. [9] Gao *et al.* reported that higher NT-proBNP was an independent risk factor for in-hospital death in patients with severe COVID-19 after adjusting for sex, age, hypertension, coronary heart disease, chronic obstructive pulmonary disease, myoglobin, creatin kinase-MB, high sensitivity troponin-I, white blood cell count, lymphocyte count, C-reactive protein, and procalcitonin.[10]

Based on the evidence and in relation to the hypotheses generated from our previous correspondence,[2] we thought about the possibility of early adoption of sacubitril/valsartan in patients with COVID-19, to maximize the anti-inflammatory effects of an enhanced natriuretic peptide system and contain the effects of angiotensin II. Clinical trials in COVID-19 patients are needed in order to validate our hypothesis.

Conflict of interest: none declared,

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