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Medical Hypotheses 141 (2020) 109792

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Letter to Editors

# Why not consider an endothelin receptor antagonist against SARS-CoV-2?

## Background

On 12 January 2020, the World Health Organization named a new 2019-nCoV as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. About 15% of cases progress to a life-threatening severe phase with lung inflammation and a cytokine storm, driven by interleukin (IL)-6 [2,3]. Bilateral interstitial pneumonia in chest computed tomography were found in 98% of cases [1] and high percentage of patients develop lung fibrosis after recovery from respiratory syndrome [4]. Since there are no registered vaccines for the disease, the straight control of the sources of infection remains crucial. Antivirals and anti-malarian drugs have been proved to be effective for 2019-nCoV treatment. Chinese guidelines in the latest 6th edition, recommend: interferon (IFN)-α, lopinavir/ritonavir, ribavirin, chloroquine phosphate, arbidol [5–8]. In addition, tocilizumab has been used as a new therapeutic opportunity results targeting IL-6 [9].

## Hypothesis

In the last two decades, many publications have shown that Endothelin-l (ET-1) has a key role in inflammatory cascade [10]. Bosentan is a dual endothelin-receptor antagonist approved for the treatment of pulmonary arterial hypertension (PAH) in New York Heart Association functional classification (NYHA) II-IV and in scleroderma patients [10]. Bosentan significantly reduced profibrotic and proinflammatory cytokines: IL-2, IL-6, IL-8 and IFN-γ levels in scleroderma patients, slowing progression to fibrosis and vascular damage [10]. IL-6 has been identified as the main cytokine in the genesis of PAH lesions, even in human immunodeficiency virus (HIV) patients [11]. Bosentan was also studied for its antiviral effect. An important reduction of viral RNA copy number (70–90%) was detected in human umbilical vein endothelial cells pretreated with 56 cmax Bosentan or 106 cmax Valsartan, even with low dosages [12]. Guo et al [13] described a case of 57-year-old man with influenza A (H7N9) virus infection initially treated with empirical antibacterial therapy and oseltamivir with progression to acute respiratory distress syndrome and mechanical ventilation. After bosentan administration patient's right ventricular systolic pressure improved rapidly with successful weaning from mechanical ventilation [13]. In patients with HIV infection, PAH is a life-threatening complication [14]. These patients present high levels of ET-1 that also correlates with severity of the disease [14]. Ritonavir and lopinavir, given together to suppress HIV-replication, have been associated with bosentan to treat PAH in HIV-infected patients without dosage adjustment of protease inhibitors with good tolerability [14]. In conclusion, we think bosentan could be considered, in association with other approved drugs, in the treatment of SARS-CoV-2 to improve hemodynamics, potentiate antiviral effects and to prevent lung fibrosis.

## Sources of support in the form of grants

None.

## Acknowledgement

The authors have no funding sources to disclose.

## Conflict of interest statement

The authors declare that they have no financial or personal relationships with other people or organisations that could inappropriately influence this work.

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https://doi.org/10.1016/j.mehy.2020.109792
Received 29 March 2020; Accepted 24 April 2020

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