Title page

Hydrogen therapy as an effective and novel adjuvant treatment against COVID-19

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Dear Editor,

We read with great interest the recent article by Wang et al [1], which showed that 45 minitues hydrogen gas (XEN) inhalation once attenuated airway inflammation in asthma and COPD patients by mainly inhibiting the pro-inflammatory cytokines of MCP-1, IL-4 and IL-6. High IL-6 level had also been found closely correlated with the incidence of detectable serum severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load and the vital signs of coronavirus disease 2019 (COVID- 19) patients[2,3]. As of September 14, 2020, 28 637 952 confirmed cases of COVID-19 patients have been reported with 917 417 deaths in 212 countries globally[4], and COVID- 19 has caused an unprecedented global public health crisis[5]. However, to date, effective therapeutic approach or antiviral drugs for COVID- 19 remain limited[6].

Hydrogen (H_2) is colorless, odorless, and the lightest of gas molecules in the universe. Since the first reported hydrogen therapy in a skin squamous carcinoma mouse model, studies in the past ten years have indicated that H_2 has therapeutic effects in diverse animal models and human disease, including metabolic syndrome, organ injury(respiratory system, nervous system, reproductive system, etc.), radiation damage and cancer, from acute illness to chronic illness[7,8]. We hypothesize that hydrogen therapy may be as an effective and novel adjuvant treatment against COVID-19, and exhibit beneficial potential to prevent COVID-19-associated cytokine storm and multiple organ

damage through following multiple mechanisms[8]. First, H_2, as an important physiological regulatory factor with antioxidant effects on cells and organs, could activate the Nrf2 signaling pathway, provide cytoprotective activity and reduce tissue damage caused by SARS-CoV-2 infection[9,10]. Additionally, oxidative stress induced by viral infections could exacerbate the DNA methylation defect which may result in further ACE2(a functional receptor for the viral spike glycoprotein that allows the entry of SARSCoV-2 into cells) hypomethylation and enhanced viremia[11]. H_2, as an antioxidant, may downregulate ACE2 expression through epigenetic control of the ACE2 gene. Second, SARS-CoV-2 induced activation of apoptosis and p53 signalling pathway in lymphocytes may play an important role in the development of patients' lymphopenia[12], while H_2 could exert anti-apoptotic effects in lymphocytes attributed to its free radicals scavenging capacity, which may prevent disease progression and be used for prevention and treatment in COVID-19 patients[13]. Last, but definitely not least, H_2 can suppress proinflammatory gene expression(TNF-α, IL-1β, IL-6, IL-10 and ICAM-1) via NF-κb pathway, while these pro-inflammatory cytokines could be overexpressed in COVID-19 infection and play important roles in the progress of diseases [14,15].

In conclusion, with the effects on selective anti-oxidation, anti-apoptosis, anti-inflammation, gene expression alterations, and as a gaseous signal modulator[8], hydrogen therapy may be a novel, promising and effective adjuvant treatment against COVID-19. Although additional experiments and clinical studies are required to confirm this hypothesis, we hope that hydrogen therapy would provide an emerging and good option for the currently limited prevention and treatment strategy of COVID-19.

Conflict of interest： None declared.

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