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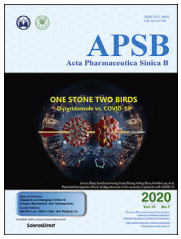

LETTER TO THE EDITOR

Letter to the editor: Comment on GLP-1-based drugs and COVID-19 treatment

To the Editor:

The coronavirus disease 2019 (COVID-19) pandemic is now spreading over 187 countries or territories, taking away hundreds to thousands of lives each day. The lack of specific and effective therapeutics is the major challenge in dealing with patients that are suffering from severe symptoms, *i.e.*, acute respiratory distress syndrome (ARDS). Drug development with conventional drug-discovery pipelines will not meet the immediate needs. Thus, it is essential and urgent to develop repurposed therapeutics. Furthermore, type 2 diabetes (T2D) is one of the major comorbidities of COVID-19 patients who developed ARDS[1,2]. Treatment of those patients represents additional complexities. Since T2D therapeutic agents known as glucagon-like peptide-1 (GLP-1)-based drugs possess the strong anti-inflammatory effect in the lung and elsewhere, we suggest that these drugs are among potential repurposed drugs for COVID-19. We also suggest that large scale retrospective studies should be conduced, which may reveal whether administration of this type of drugs have beneficial effects on clinical outcomes of T2D patients who suffered from COVID-19, with or without ARDS.

1. GLP-1-based drugs can ameliorate lung injury in animal models

Gut endocrine L cells produce the incretin hormone known as glucagon-like peptide-1 (GLP-1). Studies on function of GLP-1 led to the development of GLP-1-based therapeutic agents including exendin-4 (Byetta), liraglutide (Victoza), semaglutide (Ozempic) and others, utilized world widely for diabetes treatment. GLP-1-based drugs exert their functions mainly *via* GLP-1 receptor (GLP-1R), which is most abundantly expression in the lung epithelia as well as certain immune cells[3,4]. Native GLP-1 and GLP-1-based drugs exert a broad spectrum of extra-pancreatic effects including the anti-inflammation and immunity regulatory effect in the lung and elsewhere. Liraglutide was shown to reduce mortality and improve lung function in a mouse chronic obstructive pulmonary disease (COPD) model[5]. Interestingly, in a mouse model, GLP-1 was demonstrated to reduce blood pressure by stimulating production and release of atrial natriuretic peptide (ANP), a natriuretic peptide hormone known as a potent pulmonary vasodilator[6]. In lipopolysaccharide (LPS)-induced acute lung inflammatory injury mouse model, several studies have shown the "therapeutic" effect of liraglutide or exenatide. Beneficial effects of GLP-1-based drugs in the lung include the repression of pro-inflammatory cytokine and chemokine expression, the stimulation of eNOS/sGC/PKG signalling cascade, and the inactivation of the NF-κB signalling. We have identified that a key inflammasome component, known as thioredoxin-interacting protein (TxNIP), is a novel therapeutic target of liraglutide in LPS-induced acute lung injury mouse model. LPS injection significantly increased lung TxNIP levels, associated with upregulation of pro-inflammatory cytokine and chemokine gene expression; while liraglutide pre-treatment attenuated TxNIP elevation, as well as expression of cytokine and chemokine genes (manuscript submitted).

2. GLP-1-based drugs as candidates for treating COVID-19 and/or ARDS

Based on available information to date, diabetes subjects are more vulnerable to SARS-CoV-2[1,7,8]. In diabetes patients, elevated blood glucose level can stimulate the inflammasome component TxNIP, while circulation GLP-1 level could be reduced in T2D subjects. Thus, the utilization of GLP-1-based drugs could improve metabolic defects in these patients. Moreover, in case these patients are infected with SARS-CoV-2, these treatments may also ameliorate acute lung injury. It is also essential for physicians to have cross-disciplinary discussions, providing proper GLP-1-based drugs for individual patient. The most serious pathological changes of COVID-19 pneumonia are ARDS, that is, excessive inflammation, with a so-called "cytokine storm", which attacks endothelial cells in multiple organs, and also attacks alveolar epithelial cells in the lung, damages the blood gas exchange, inactivates pulmonary surfactant, resulting in formation of hyaline membrane in the alveolar space, severe pulmonary edema and disruption of lung parenchyma structure and functions. As we have learned from animal model studies, GLP-1-based drugs exert multiple beneficial effects on excessive inflammation-induced acute lung injury. These include the stimulation of local

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expression of potent pulmonary vasodilator ANP, facilitation of SP-A and TTF-1 expression, prevention of PMN−endothelial adhesion, and inhibition of multiple cytokines and chemokines in the lung. These beneficial effects, along with their anti-inflammatory effects *via* reducing TxNIP levels and increasing eNOS expression, make GLP-1-based drugs excellent candidates for the treatment of COVID-19 patients with or without T2D. This speculation is very exciting and could be tested with coronavirus-induced SARS murine model we have reported previously[9].

3. Diabetes patients with COVID-19: retrospective studies

In addition to pre-clinical animal experimentation, clinical epidemiology studies should also be considered. Up to date, there are nearly 3 million confirmed COVID-19 cases world widely. In China alone, confirmed cases are over 83,000. Since the prevalence of T2D is about 11% in China[10], among confirmed COVID-19 cases, the incidence of T2D could be 8800 or higher. Retrospective studies to compare the clinical process and outcomes between patients who have taken GLP-1-based drugs, especially liraglutide, with those who did not receive such treatment may reveal clinical benefits if any. These studies should focus on patient's distributions from mild, moderate, severe to critically ill, especially on the development of ARDS. Moreover, one could study patient mortality, use of ECMO, days on ventilator, days in ICU, days in hospital, etc. Information gained from this kind of study may allow us to judge whether T2D patients under GLP-1-based drug treatment had better clinical outcome. Such studies will provide valuable information to the whole world in combating the pandemic; and add our knowledge in personal and precise medicine.

The rapid spread of this disease with increasing mortality worldwide urges the development and discovery of new therapeutics. We propose to systemically determine the potential clinical benefits of GLP-1-related drugs *via* retrospective studies on COVID-19 patients with T2D in China as well as in other countries. We propose to test these drugs in coronavirus-induced acute lung injury models. Positive results from these studies could lead to clinical applications, as the pharmacokinetics, toxicology, safety of these drugs have been tested in T2D patients. Repurposing this category of medicines may provide clinically applicable medications for the urgent needs in treatment of COVID-19 disease.

Author contributions

Both Mingyao Liu and Tianru Jin have contributed to this review manuscript composition.

Conflicts of interest

The authors have no conflict of interest to claim.

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