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MINI-REVIEW

Role of dipeptidyl peptidase-4 inhibitors in patients with diabetes infected with coronavirus-19

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Abstract: The pandemic infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is widely increasing the patients affiliated with coronavirus disease 2019 (COVID-19) from last December of 2019. It is reported that the entry receptor of SARS-CoV-2 has been confirmed to be angiotensin-converting enzyme 2 (ACE2). Notably, whether the ACE-related inhibitors or drugs modulated ACE2 activity in affecting the viral activity and disease severity of SARS-CoV-2 is still an open question. Dipeptidyl peptidase-4 (DDP-4), a well-known anti-diabetic drug, has been widely used to control the glycemic condition in patients with diabetes. In this article, we are focusing on the impact of ACE inhibitors (ACEI) and DPP4 inhibitors used on SARS-CoV-2 activity and discussions about those drugs that may be related to infectious condition of COVID-19 diseases.

Keywords: Coronavirus disease 2019; Dipeptidyl peptidase-4 inhibitors; Severe acute respiratory syndrome coronavirus 2

The continuous outbreak of coronavirus infections since the 2000s has shown that humans lack awareness and prevention of new viral infections, which has caused disasters for humans. Severe acute respiratory syndrome coronavirus (SARS-CoV-1) was the first epidemic coronavirus threat infected more than 8000 people with case-fatality rate (CFR) about 11%.[1] Fortunately, no more new case of SARS-CoV-1 was reported and World Health Organization (WHO) had declared that the chain of human-to-human transmission was broken since 2004. The second novel coronavirus outbreak, middle east respiratory syndrome coronavirus (MERS-CoV), epidemic spreads with more than 2200 infected patients and possesses a high CFR of 35.5% from June 2012 to June 2019.[2] More contagious than the former coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is steadily pandemic spreading worldwide and more patients died owing to the outbreak since last 2019.

According to the situation reports of WHO, there have been approximately 2 million infected cases with more than 123 000 deaths due to coronavirus disease 2019 (COVID-19) until April 15, 2020. Most of the infected patients are symptomless or only present with mild disease activity, but these characteristics make the virus be more likely to widespread. Although COVID-19 has lower fatal rate as compared with SARS-CoV and MERS-CoV, patients with more comorbidities tend to have more severe disease and worse prognosis, especially in those with diabetes mellitus, cardiovascular disease, and cancers along with elderly.[3]

The entry routes of different viruses often lead to differences in clinical manifestations and are also related to the possible therapeutic targets of the virus. Previous experiments had confirmed that angiotensin-converting enzyme 2 (ACE2) is the entry receptor in SARS-CoV-1 and dipeptidyl peptidase-4 (DPP4, also known as CD26) is the entry receptor in MERS-CoV. Recently, the entry receptor of SARS-CoV-2 is also identified to be ACE2, similar to SARS-CoV-1.[4] Therefore, it is highly concerned that drugs that may affect ACE2 activity are also associated with viral activity and disease severity. Currently, the main issue is to focus on the impact of ACE inhibitors (ACEI)/angiotensin receptor blockers (ARB) use on COVID-19 disease activity and the cardiovascular benefits come from ACEI/ARB. However, there are relatively few discussions about other drugs that may be related to viral activity.

Patients with diabetes are the group more vulnerable severe COVID-19 infection.[3] In order to reduce the impact of COVID-19 on diabetics, aggressive prevention strategies to break the human-to-human transmission of virus are imperative. Moreover, adequate glycemic control is beneficial in restoring the dysregulation of the immune system and preventing both viral and secondary bacterial infections. Among numerous anti-diabetic drugs, DPP4 inhibitors might play an important role during coronavirus infection, including pandemic COVID-19. DDP-4 is an enzyme that degrades incretins glucagon-like peptide-1 and gastric inhibitory protein, which are endogenous hormones that stimulate the secretion of insulin from β-cells and suppress the secretion of glucagon from α-cell of pancreas in

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response to serum glucose change.[5] Clinical use of DPP4 inhibitors can block the degradation of incretins and thus prolong the response of insulin stimulation in response to elevated serum glucose concentration. Besides, the risk of hypoglycemia is relatively lower in using DPP4 inhibitors, avoiding unfavorable hypoglycemic episodes that occur during active COVID-19. Apart from the role in glucose regulation, DPP4 is expressed on immune cells and is thought to be associated with maintaining lymphocyte composition and function, T-cell activation and co-stimulation, memory T-cell generation, and thymic emigration patterns during immune-senescence.[6] DPP4 is also associated with modulating cytokines, chemokines, and peptide hormones.[7] The clinical immune response to SARS-CoV-2 may be divided into two phases, an earlier phase of adaptive immune to eliminate the virus and a later phase of innate inflammation triggered by damaged alveolar cells.[8] The most lethal complication of COVID-19, acute respiratory distress syndrome, may be associated with the later immune phase, and treatment to reduce inflammation at the phase may be helpful in attenuating lung damage. DPP4 inhibitors may potentially act the role to modulate the overactive immune reaction and prevent devastating lung injury.[7] Furthermore, DPP4 is the entry receptor of MERS-CoV and may also participate in the pathogenesis of SARS-CoV-2 despite not being its primary entry receptor. Just like other RNA viruses inherit with high mutation rate, SARS-CoV-2 is found to have mutations in the receptor-binding domain in the spike protein, which is responsible for facilitating the entry of virus.[9] Phylogenetic network analysis also finds three central variants distinguished by amino acid changes of SARS-CoV-2.[10] These pieces of evidence suggest that the SARS-CoV-2 may continually mutate to adapt the changes in the environment and the types of invading cells. What should be more worrying is the SARS-CoV-2 may also mutate to another novel coronavirus which invades cell via coupling with DPP4, the viral receptor of MERS-CoV and carry higher fatality. The easy mutation characteristics of SARS-CoV-2 also make DDP-4 inhibitor effective prevention against mutant coronavirus.

Whether DPP4 inhibitors may affect the activity of COVID-19 and bring in beneficial effects may need more evidence to demonstrate. However, one of the best strategies to deal with the highly variable coronavirus outbreak is to carefully examine every possible influence factor, especially the factors associated with highly comorbid patients. As more and more patients are infected with SARS-CoV-2, there is still a lack of promising effective treatments or vaccines. The focus of the researches should be extended to all treatment which possible linked to the pathogenesis of the virus, including DPP4 inhibitors.

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