Editorial – COVID-19 pandemic: is it time to learn about DPP-4/CD26?

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The rapid spread of SARS-CoV-2, a novel coronavirus that emerged in late 2019, and the resulting COVID-19 pandemic, has been labeled as a public health emergency of international concern by the World Health Organization. Individuals with diabetes mellitus are at high risk for severe manifestations of the disease, and COVID-19 mortality is increased in presence of major comorbidities, including diabetes¹. The rate ratio of diabetes among patients who died with SARS-CoV-2 infection compared to the general population was 1.75². DPP-4 inhibitors (saxagliptin, sitagliptin, vildagliptin, alogliptin and linagliptin) are used worldwide to treat type 2 diabetes. DPP-4 (dipeptidyl peptidase-4) is also known as CD26, a lymphocyte cell surface protein that plays an important role in T-cell immunity. Our group and others have shown that DPP-4 inhibitors have an immunosuppressive effect on T-lymphocyte differentiation and cytokine production³⁻⁵.

Overall risk of infections (including respiratory infections) with DPP-4 inhibitors has not been confirmed in all studies⁶⁻⁸. However, increased incidence of upper airway infections appears to be the most common⁶. Of note, MERS-CoV uses DPP-4 as a specific receptor for cellular entry, while SARS-CoV and SARS-CoV-2 appear to use the entry receptor ACE²⁰. Liu et al¹⁰ in a study of immunological characteristics of COVID-19, demonstrated that patients with severe disease had higher serum levels of IL-6, IL-10, IL-2, and IFN-γ and lower numbers of neutrophils and T cells (especially CD8+ T cells) than did patients with mild disease, suggesting that cytokine storm in general, and T cell-mediated dampening of exuberant immune responses in particular, participate in the pathophysiology of the severe disease. There appears to be an overactivation of T cells, manifested by increases in Th17 levels and high cytotoxicity of CD8+ T cells, partly accounting for the severe immune injury to lungs associated with COVID-19 infection¹¹.

DPP-4/CD26 is present and active in the lungs and is expressed constitutively by lung fibroblasts, where it exerts proliferative effects¹². DPP-4 inhibitors could ameliorate the inflammatory response in the lung, as evidenced by animal and in vitro studies¹⁵⁻¹⁸. Nevertheless, some case reports showed lung inflammatory effects and/or interstitial pneumonia with the use of DPP-4 inhibitors¹⁹⁻²². Of note, all these patients were Asian, and they were using vildagliptin. We demonstrated an in vitro immunosuppressive effect of sitagliptin on Th1 and Th17 lymphocyte differentiation that leads to the generation of regulatory TGF-beta-secreting cells with low CD26 gene expression that may beneficially modulate the inflammatory response³. Furthermore, type 2 diabetes patients treated with sitagliptin showed reduced levels of plasma markers of low-grade inflammation (C-reactive protein, IL-6, and TNF-α) and cell adhesion molecules (soluble intercellular adhesion molecule-1 and E-selectin); this effect was more pronounced in subjects with higher levels of inflammatory markers and cell adhesion molecules²³,²⁴.
At this point, it is critical to observe the evolution of COVID-19 disease in patients with diabetes using DPP-4 inhibitors. DPP-4 inhibitors may worsen or in some cases ameliorate the evolution of lung injury in these patients. Thus, the exact impact of different DPP-4 inhibitors on COVID-19 clinical outcomes remains uncertain. Further investigation in this area is, therefore, warranted to better understand the exact role of these drugs in lung disease in the context of COVID-19 infection. Understanding this relationship could help to improve the management of COVID-19 infection in patients with diabetes mellitus using DPP-4 inhibitors.

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REFERENCES


