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Letters to the Editor

The Multiple Effects of SGLT2 Inhibitors Suggest Potential Benefit in COVID-19 Patients

To the Editor:

Recent evidence has shown that inflammation is a potential contributor to the progression and exacerbation of COVID-19.[1] Indeed, SARS-CoV-2 often induces a robust immune response and releases cytokines, which might contribute to multiorgan dysfunction and mortality.[1] Growing evidence suggests that COVID-19 is not solely a respiratory illness, and that the infection can directly or indirectly infect organs or vascular endothelial cells causing endotheliitis. Because of the urgent need for additional therapies and because COVID-19 disproportionately affects individuals with cardiovascular/cardiometabolic comorbidities, herein we discuss the rationale for using the antidiabetic sodium-glucose cotransporter 2 (SGLT2) inhibitors, namely dapagliflozin and empagliflozin, as a unique approach to potentially treat severe COVID-19 symptoms.

Although originally intended to treat diabetes, cardiovascular outcome trials of SGLT2 inhibitors showed a profound reduction in cardiovascular mortality and heart failure hospitalization in diabetic patients, and more recently, also in nondiabetic heart failure patients. Interestingly, some of the cardiovascular benefits of SGLT2 inhibitors might be because of off-target, non-antihyperglycemic effects.[2] Although these mechanisms remain elusive, evidence suggests that SGLT2 inhibitors can directly or indirectly act on cardiac, renal, endothelial, and immune cells, or systemically, to reduce inflammation.[2] In fact, we recently reported that use of empagliflozin reduced cardiac inflammation in a model of heart failure,[3] and lessened renal damage, systemic inflammation, and mortality in a model of sepsis.[4] Heart failure and sepsis also increased cardiac and renal macrophage infiltration, respectively, which was reduced with empagliflozin treatment. Similarly, it has been reported that macrophage interleukin-1β and tumour necrosis factor α secretion is also reduced in patients treated with SGLT2 inhibitors. This is relevant for COVID-19 when considering that endothelial/organ damage caused by SARS-CoV-2 results in immune cell activation and cytokine secretion, which can be reduced with the anti-inflammatory properties of SGLT2 inhibitors. Thus, SGLT2 inhibitors might potentially improve outcomes in COVID-19 patients by reducing the organ and/or systemic inflammatory response. This rationale led to the initiation of the **Da**pagliflozin in **Re**spiratory Failure in Patients With COVID-19 (DARE-19) trial (ClinicalTrials.gov: NCT04350593), in which dapagliflozin for respiratory failure in COVID-19 patients with cardiometabolic comorbidities is currently being tested. However, because excessive inflammation is common in severely affected COVID-19 patients, SGLT2 inhibitors might also be effective in COVID-19 patients without underlying comorbidities.

Overall, because SGLT2 inhibitors are not merely antidiabetic drugs, have minimal side effects, excellent safety and tolerance, and multifaceted benefits, they are worthy of consideration as a potentially effective treatment for COVID-19 patients with or without cardiometabolic comorbidities.

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Disclosures

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