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Possible Role of Selective Serotonin Reuptake Inhibitors (SSRIs) in Clinical Outcome of COVID-19 Patients

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To the Editor-in-Chief:

In February 2020, the World Health Organization officially named the disease caused by the new corona virus as COVID-19. For COVID-19 patients, there are usually four phases of the disease. The first one is virus reproduction phase. The second phase is accompanied with mild symptoms and usually includes flu-like symptoms. The third phase is associated with the development of acute respiratory distress syndrome (ARDS) and is characterized by its symptoms. The fourth phase is associated with high fever, systemic inflammatory responses, especially in the lungs, and eventual respiratory failure (1). COVID-19 is associated with upregulations of inflammatory cytokines. In the acute phase of COVID-19, the function of TCD4+ cells are impaired and the production of interferon-gamma (IFN-γ) and Tumor Necrosis Factor-alpha (TNF-α) in these cells is reduced. With impaired immune function, virus replication continues, and damaged lung cells induce excessive inflammatory responses and overproduction of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 from immune cells (2). This eventually induce cytokine storm with systemic inflammatory responses and end organ damage. The level of inflammatory cytokines such as IL-1β, IL-6 and IL-10 in COVID-19 patients has been reported to be higher in COVID-19 patients admitted in ICU (3).

The lack of effective treatment for the severe infection caused by COVID-19 has led scientists and physicians to repurpose popular medications that are indicated for other similar conditions. No effective modality to successful management of this viral disease has yet been identified. Immunosuppressive and anti-inflammatory drugs have been suggested for acute patients with cytokine storms and severe lung involvement.

Recently, due to the anti-inflammatory effects of selective serotonin reuptake inhibitors (SSRIs), their therapeutic effects have been proposed for COVID-19 patients. This group of drugs are usually prescribed to treat depressive disorders. SSRIs have been shown to reduce inflammation and the expression of inflammatory cytokines such as TNFα and IL-1β (4). The decrease in inflammatory cytokines such as IL-1β and TNF-α in the cerebral tissue has been shown as a result of sertraline administration (5), indicating the anti-inflammatory effects of this drug. In another study, Fluvoxamine could lower IL-1β, IL-6, and TNFα expression in the striatum in depressed mice (6). Much attention is paid to sertraline due to its very low anticholinergic activity which is especially desirable for the elderly with coronary heart diseases. Moreover, the anti-inflammatory properties of this compound is attributed to prevention of the expression of pro-inflammatory cytokines.

Recently, it was demonstrated that treatment of patients with major depression with SSRIs could reduce the expression of inflammatory cytokines, such as IL-10, TNF-α, and IL-6 in these patients (7). The expression of these inflammatory mediators increase in critically ill COVID-19 patients. Therefore, the use of this class of medications in the management of COVID-19 patients could be considered, especially for acute patients with cytokine storms. In a recently published study, the use of antidepressants SSRI and paroxetine and SNRI venlafaxine in hospitalized patients due to COVID-19 reduced the risk of intubation and death (8). This therapeutic effect on COVID-19 could be attributed to the inhibition of acid sphingomyelinase activity, which prevents epithelial cell from being infection by SARS-CoV2.

It has also been suggested that S1A (σ-1- receptor) agonists can prevent cytokine storms in severe COVID-19 (9). SSRIs, especially fluvoxamine and to a lesser extent sertraline have a moderate to high affinity for this receptor. Antidepressants are associated with decreased plasma levels of pro-

inflammatory cytokines which elevate in COVID-19. Furthermore, the antiviral activity of some antidepressants such as fluoxetine has been reported in COVID-19 patients. In a randomized clinical trial on adult outpatients with COVID-19, administration of 100 mg of fluvoxamine reduced the likelihood of clinical deterioration over 15 days (10). This has been attributed to the high affinity of fluvoxamine for S1R, which reduces the inflammatory responses.

It seems that SSRIs are potential candidates for COVID-19 due to their anti-inflammatory properties. Future clinical studies will determine the exact role of this class of medications in clinical outcomes of COVID-19 patients.

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Author contribution

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Conflict of interest

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