Fluoxetine and Molnupiravir: A Synergistic Combination for COVID-19 Treatment?

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To the Editor,

The current 2019 novel coronavirus disease (COVID-19), an emerging global health threat, caused by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), has had a calamitous effect on the world's population resulting in more than 5.49 million deaths worldwide. COVID-19 has also led to diverse mental health problems, such as anxiety (panic attacks and post-traumatic stress) and depression. While awaiting a vaccine, we need new or repurposed pharmacological treatment options for COVID-19. A widespread use of such drugs could decrease hospitalizations and, ultimately, morbidity, and mortality. Therefore, we suggest that fluoxetine and molnupiravir may show a synergistic and complementary action if administered simultaneously for treatment of COVID-19 patients. When SARS-CoV-2 enters human cells, the inflammatory response plays a key antiviral role, but a strong cytokine storm, corresponding to an unopposed generation of both pro-inflammatory and anti-inflammatory cytokines by the innate immune system, can be very damaging to the COVID-19 patients. Therefore, targeting cytokines during the management of patients could improve survival percentages and reduce mortality percentages. The current data (including the in vivo and in vitro data) demonstrate that many selective serotonin reuptake inhibitor (SSRI) antidepressants, especially fluoxetine (Prozac) and fluvoxamine (Luvox), reduce levels of several pro-inflammatory cytokines/chemokines (such as IL-6, TNF-α, IL-1β, NF-κB, and CCL-2), decrees of anti-inflammatory cytokines IL-10 and TGF-β, and direct suppression inflammatory cells (such as platelets, T cells, and macrophages).[1,2] In this context, fluoxetine, with a favorable safety and tolerability profile, showed a promising adjuvant therapeutic option against SARS-CoV-2 infection by reducing the secretion of IL-6 and cytokine storms, and modulating immune system responsiveness to infection.[3-5] Also, several in vitro and in vivo studies reported the potential anti-viral activity of fluoxetine alone or in combination with antiviral drugs (such as remdesivir) on SARS-CoV-2.[6,7] A pharmacokinetic study showed efficient inhibition of SARS-CoV-2 at a commonly well-tolerated concentration of fluoxetine used for treatment of depression.[8] In addition, an in vitro study showed that fluoxetine inhibited acid sphingomyelinase (ASM), a lysosomal phosphodiesterase catalyzes the hydrolysis of sphingomyelin into ceramide and phosphorylcholine, and the formation of ceramide-enriched membrane domains (serve as entrances for the virus), and prevented Vero cells from being infected with SARS-CoV-2.[9]

Because of its promising results in SARS-CoV-2 patients, fluoxetine (20 mg daily for 1 week and then 60 mg daily for 2 weeks to 2 months depending on symptom duration) has now entered into Phase-4 clinical trials (Clinical Trial Number: NCT04377308). The appropriate timing is crucial in any intervention in COVID-19 treatment. A meaningful benefit of fluoxetine (with inhibitory effect on IL-6, IL-1β, TNF-α, and NF-κB) over other IL-6 receptor antagonists (such as tocilizumab and sarilumab) might be the possibility of early oral outpatient fluoxetine treatment, which could cause the host's immune balance in the later stages of disease.[10] More recently, a systematic review and meta-analysis demonstrated that mental health disorders were associated with mortality in COVID-19.[11] This may be explained by the particular immunological profile of these patients. Since fluoxetine has anti-inflammatory and immunomodulatory effect independent of its potent antidepressant action, it seems to be an appropriate choice for treating COVID-19 patients' depression and low mood. SARS-CoV-2 is a single strand positive-sense RNA virus that requires an RNA-dependent RNA polymerase (RdRp) for replication of its viral genome. Molnupiravir (formerly EIDD-2801/MK-4482), the prodrug of the active antiviral ribonucleoside analog β-d-N4-hydroxycytidine, which also targets RdRp, blocks SARS-CoV-2 transmission in ferrets, inhibits SARS-CoV-2 replication, and enhances the efficacy of favipiravir in a Syrian hamster SARS-CoV-2 infection model, halts SARS-CoV-2 replication and prevents infection of human cells in a new mouse model containing human lung tissue.[12] In a Phase-2a clinical trial, Fischer et al. investigated the antiviral efficacy of molnupiravir (200 mg, 400 mg, or 800 mg twice a day for 5 days) in symptomatic SARS-CoV-2-infected adults.[13] The study identified that molnupiravir (800 mg orally every 12 h for 5 days) was effective in terms of viral RNA clearance. Molnupiravir is currently being tested in a

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Phase-3 clinical trial for the treatment of nonhospitalized patients with laboratory-confirmed COVID-19 (Clinical Trial Number: NCT04939428). According to interim Phase-3 trial data, molnupiravir reduced the risk of hospitalization or death by approximately 50%. The combination of fluoxetine (which is on the WHO's Model List of Essential Medicines and has the greatest in vitro inhibitory effect on the ASM/ceramide system among SSRI drugs) with molnupiravir (which has shown very encouraging results in clinical trials so far) has still not been studied; intuitively, known functions of fluoxetine and molnupiravir can be beneficial in combating the pandemic. Therefore, we invite researchers and clinicians to explore the synergistic effect of fluoxetine and molnupiravir to potentiate the emerging quest for life-saving COVID-19 treatments.

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