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LETTER TO THE EDITOR

Old drug fluvoxamine, new hope for COVID-19

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The coronavirus disease 2019 (COVID-19) is an acute respiratory disease caused by the novel coronavirus SARS-CoV-2. Despite the second vaccination for SARS-CoV-2, the number of individuals infected with SARS-CoV-2 variants (i.e., delta and lambda) has markedly increased worldwide. Although approximately 80% of individuals infected with SARS-CoV-2 is mild to moderate, a part of them may convert to severe clinical stages in about 1 week, ultimately resulting in the intubation or death. Using drug repurposing, it is, therefore, necessary to discover drugs that can prevent clinical deterioration [1]. Here, we discuss the emergent use of the old antidepressant fluvoxamine which may block clinical deterioration in mild to moderate patients infected with SARS-CoV-2.

In November 2020, Dr. Lenze and his colleagues reported that fluvoxamine could prevent clinical deterioration in adult outpatients infected with SARS-CoV-2. In the study, clinical deterioration occurred in 0 of the fluvoxamine group ($n=80$) and in 6 of placebo group ($n=72$) [2]. Although sample size of this study was small, this study strongly encouraged further trials using a large sample size. In February 2021, Dr. Seftel and his colleague reported a prospective, non-randomized observational cohort study of fluvoxamine in outpatients ($n=113$) infected with SARS-CoV-2 at the Golden Gate Fields horse racing track in Berkeley, California [3]. Incidence of hospitalization was 0 of the fluvoxamine-treated group ($n=65$) and 6 of the observation alone group ($n=48$). Two patients required intensive care unit stay with mechanical ventilation, one of them died. On April 23, 2021, fluvoxamine was added in the US National Institutes of Health (NIH) COVID-19 Guidelines Panel although there is insufficient evidence for the efficacy of fluvoxamine.

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On August 6, 2021, the interim results of TOGETHER trial (NCT04727424) by a multinational group in Canada and Brazil were presented at the NIH symposium. They compared three compounds, fluvoxamine, the antidiabetic drug metformin, and the antiparasitic drug ivermectin. Although metformin and ivermectin did not show beneficial effects, fluvoxamine was much more promising. Among the randomized participants ($n=1{,}480$), fluvoxamine significantly reduced the risk of disease progression by 29% (95% confidence interval 0.54–0.93) [4].

Detailed mechanisms of action of fluvoxamine for COVID-19 are currently unknown. In 1996, we reported that fluvoxamine binds to endoplasmic reticulum (ER) protein sigma-1 receptor with high affinity, suggesting a role of sigma-1 receptor in the mechanisms of its action [5]. Subsequent studies suggest that fluvoxamine is a potent agonist at sigma-1 receptor which plays a key role in inflammation [1, 5, 6]. Among the antidepressants, fluvoxamine was the most potent at sigma-1 receptor [1, 5, 6]. Furthermore, fluvoxamine has several beneficial effects, including reduction in platelet aggregation by serotonin transporter inhibition, decreased mast cell degranulation, interference with lysosomal trafficking of virus, inhibition of acid sphingomyelinase (ASM), and increased levels of metatonin by cytochrome P450 inhibition [7].

In October 2020, Gordon et al. [8] identified the sigma-1 receptor (encoded by *SIGMAR1*) as a functional host-dependency factor for SARS-CoV-2. Knockout or knockdown of *SIGMAR1* produced robust reductions in SARS-CoV-2 replication, indicating a key role of the sigma-1 receptor in SARS-CoV-2 replication (Fig. 1). In 2019, Rosen et al. [9] demonstrated that the sigma-1 receptor is essential for the cytokine production in a mouse model of septic shock, and that fluvoxamine could protect against inflammatory response and lethal septic shock. Taken together, it is likely that the potent sigma-1 receptor agonists, such as fluvoxamine, might ameliorate inflammatory events (i.e., cytokine storm) associated with ER stress due to SARS-CoV-2 replication (Fig. 1) [1].

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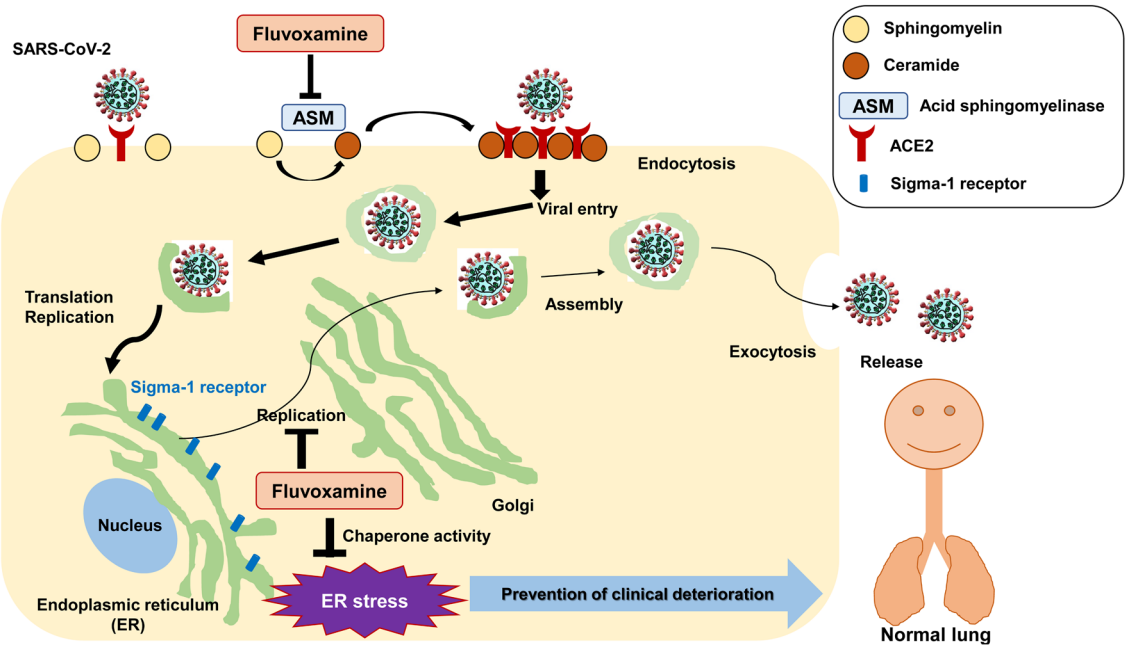

Fig. 1 Proposed biological mechanisms of fluvoxamine in the treatment of SARS-CoV-2-infected patients. SARS-CoV-2 binds to ACE2 receptor on the cells, resulting in activation of the acid sphingomyelinase (ASM) which converts sphingomyelin to ceramide. ASM/ceramide system can facilitate viral entry. Antidepressants such as fluvoxamine inhibit ASM and formation of ceramide-enriched membrane domains, resulting in decreased viral entry. Recent study shows that sigma-1-receptor ligands can attenuate SARS-CoV-2 replication [8]. Through sigma-1 receptor chaperone activity [1], the sigma-1-receptor agonist fluvoxamine may attenuate ER stress due to SARS-CoV-2 replication in cells, thus resulting in a blockade against inflammatory events (i.e., cytokine storm). Thus, early intervention using fluvoxamine may block or delay clinical deterioration in individuals with SARS-CoV-2 infection. A slight modification with Fig. 1 in the reference [10] and Fig. 3 in the reference [1]

A recent observational multicenter study ($n = 2846$) showed association between the use of functional inhibitors of ASM and reduced risk of intubation or death in hospitalized patients with severe COVID-19 [10]. The functional inhibitors of ASM include the antidepressants such as fluvoxamine, fluoxetine, and escitalopram. Interestingly, fluoxetine and escitalopram are also sigma-1 receptor agonists although they are less potent than fluvoxamine [1]. Considering the role of sigma-1 receptor and ASM in biological actions of SARS-CoV-2 in cells (Fig. 1), both fluoxetine and escitalopram may be prophylactic drugs for mild to moderate patients infected with SARS-CoV-2 although further clinical study is needed.

The advantages of fluvoxamine are favorable safety profiles, widespread availability, very low cost, oral administration and use for children and adolescents. If fluvoxamine is used in individuals with COVID-19 as quickly as possible after confirmation of SARS-CoV-2 infection, clinical deterioration might be prevented [1]. Importantly, fluvoxamine could be a prophylactic drug for COVID-19 in countries with low vaccination rates or low health system.

Author contributions The authors did the reference search and wrote the commentary.

Declarations

Conflict of interest Dr. Y. Hashimoto and Dr. Suzuki have no conflict of interest. Dr. K. Hashimoto has received speakers' honoraria from Abbott and Meiji Seika.

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