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Fluvoxamine for outpatients with COVID-19: where do we stand?

Published Online
October 27, 2021
https://doi.org/10.1016/S2214-109X(21)00501-5

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Advances in vaccine development have had a major effect on reducing the number of new symptomatic cases, hospitalisations, and deaths due to COVID-19, the viral disease caused by SARS-CoV-2, globally.[1] Nevertheless, because of the unequal distribution and access to vaccines, a relevant proportion of individuals remain at risk for COVID-19, especially in low-income and middle-income countries.[2] Therefore, the identification of beneficial interventions to prevent clinically relevant outcomes among patients with COVID-19 still represents a major medical need. This is particularly true for outpatients, who comprise the largest population of individuals infected with the SARS-CoV-2, and for whom few effective therapies exist.

Fluvoxamine is a selective serotonin reuptake inhibitor commonly indicated for the management of depression, obsessive-compulsive disorders, and other mental-health conditions. Owing to potential anti-inflammatory effects observed in initial experimental non-clinical studies,[3] fluvoxamine has been proposed as a potential therapy for COVID-19. Accordingly, observational evidence has suggested favourable results of fluvoxamine with respect to symptom resolution and hospitalisations at 14 days.[4]

In trial results published in 2020, 152 outpatients with mild COVID-19 were randomly assigned to receive 100 mg fluvoxamine three times daily or matching placebo for 15 days.[5] The primary outcome was clinical deterioration, defined as shortness of breath or hospitalisation for shortness of breath or pneumonia, and oxygen saturation less than 92% on room air or need for supplemental oxygen to achieve oxygen saturation of 92% or greater. Within 15 days, none of the participants who received fluvoxamine and 8·3% of those who received placebo reached the primary endpoint (absolute risk difference 8·7%; 95% CI 1·8%–16·5%; p=0·009). Despite the promising results, limitations such as low statistical power and missing data for the primary outcome precluded definitive conclusions about the efficacy of fluvoxamine for the treatment of COVID-19.

In *The Lancet Global Health*, Gilmar Reis and colleagues report the results of TOGETHER, a randomised, adaptive, platform, placebo-controlled trial.[6] A total of 1497 participants were randomly allocated to fluvoxamine, 100 mg twice daily, or matching placebo. All included participants had a positive test for SARS-CoV-2 and known risk factors for disease progression (including age ≥50 years, diabetes, hypertension, obesity, smoking, conditions associated with immunosuppression, unvaccinated status, or comorbidities such cancer, cardiovascular, pulmonary, and kidney disorders). Enrolment occurred in 11 cities in Brazil. The primary endpoint was a composite of COVID-19 emergency setting retention for greater than 6 h or hospitalisation (defined as either retention in a COVID-19 emergency setting or transfer to tertiary hospital) from COVID-19 up to 28 days. Using a Bayesian analytical approach, the authors found that the proportion of patients reaching the primary endpoint was lower for the fluvoxamine group compared with placebo (11% *vs* 16%; relative risk: 0·68; 95% Bayesian credible interval 0·52–0·88), with a probability of superiority of 99·8%.

The TOGETHER trial had low risk of bias. The allocation was concealed, participants, investigators, and caregivers were unaware of treatment assignments, and the main analyses followed the intention-to-treat principle. It should also be noted that TOGETHER constitutes the largest randomised trial completed to date aimed at testing the effect of fluvoxamine for outpatients with COVID-19. Conversely, the main study limitations are related to the lack of event adjudication and to the inconclusive effects on patient-important outcomes such as hospitalisation and mortality.

What are the lessons learned from the TOGETHER trial? From a research perspective, the TOGETHER trial reinforces the concept that it is possible to rapidly generate high-quality, randomised evidence even during a pandemic such as COVID-19. Undeniably, key factors for the success of this initiative rely on the scientific exchange between academic groups from Brazil and Canada and on the use of an adaptive, platform, randomised design. This research methodology allows simultaneous and efficient assessment of different potential therapies for COVID-19. From a clinical practice

perspective, the results represent an important step in understanding the role of fluvoxamine for outpatients with COVID-19. In this sense, the study strongly suggests that fluvoxamine constitutes an effective, safe, inexpensive, and relatively well tolerated option for the management of ambulatory patients with COVID-19, which is particularly useful for (but not limited to) low-resource settings.

Despite the important findings from the TOGETHER trial, some questions related to the efficacy and safety of fluvoxamine for patients with COVID-19 remain open. The definitive answer regarding the effects of fluvoxamine on individual outcomes such as mortality and hospitalisations still need addressing. In addition, it remains to be established whether fluvoxamine has an additive effect to other therapies such as monoclonal antibodies[7] and budesonide,[8] and what is the optimal fluvoxamine therapeutic scheme. Finally, it is still unclear whether the results from the TOGETHER trial extend to other outpatient populations with COVID-19, including those without risk factors for disease progression, those who are fully vaccinated, and those infected with the delta variant or other variants.

I declare research grants outside of the submitted work paid to my institution from AstraZeneca, Bayer, Amgen, Servier, Novartis, Pfizer, and Boehringer-Ingelheim.

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