Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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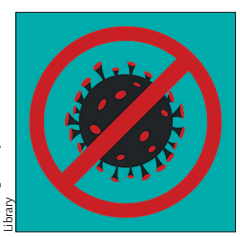
Early treatment to prevent progression of SARS-CoV-2 infection



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As of May, 2022, the SARS-CoV-2 virus has caused 521 million COVID-19 cases and at least 6 million deaths, worldwide.[1] Although the COVID-19 pandemic has led to breathtaking vaccine developments, early treatments to prevent progression of COVID-19, especially in those who are most vulnerable, are urgently needed. But to deploy such treatment will take a substantial change in the perception and management of upper respiratory infections, including COVID-19.

In *The Lancet Respiratory Medicine*, Hugh Montgomery and colleagues[2] report the use of a combination of monoclonal antibodies, tixagevimab and cilgavimab, to prevent the progression of SARS-CoV-2 infection. In a double-blind, randomised controlled trial, unvaccinated patients with documented SARS-CoV-2 infection were randomly assigned to receive 600 mg tixagevimab–cilgavimab intramuscularly within 7 days of onset of COVID-19 symptoms (n=456) or a placebo injection (n=454). Severe COVID-19 or death was reduced by 50·5% (95% CI 14·6–71·3) in those who received tixagevimab–cilgavimab compared with placebo. Severe COVID-19 or death occurred in 18 (4%) of 407 treated participants in the tixagevimab–cilgavimab group versus 37 (9%) of 415 treated participants in the placebo group. SARS-CoV-2 can be expected to cause severe disease most frequently in older patients with a variety of comorbidities[2–4] but the mean age of participants in this study was 46·1 years (SD 15·2).[2] Adverse events ascribed to tixagevimab–cilgavimab were mild, as has been the case for almost all the monoclonal antibodies directed against SARS-CoV-2.[2]

Montgomery and colleagues' trial follows an important study in which tixagevimab–cilgavimab reduced SARS-CoV-2 infection by 82·8% over 56 months in unvaccinated patients.[5] Tixagevimab–cilgavimab has a mutation in the FC portion of the molecule that extends the half-life,[6] allowing longer duration for prevention, and perhaps prevention of reinfection when used as early treatment. The study by Levine and colleagues[5] is ongoing to determine the ultimate duration of prevention provided by tixagevimab–cilgavimab.

Tixagevimab–cilgavimab was developed for prevention and treatment of the SARS-CoV-2 variant that launched the COVID-19 pandemic. However, the omicron SARS-CoV-2 variants have become dominant worldwide. Only tixagevimab–cilgavimab[7] and a newer monoclonal antibody, bebtelovimab,[8] have shown sufficient neutralisation activity in vitro to retain US Food and Drug Administration (FDA) emergency use authorization (EUA).[9] Tixagevimab–cilgavimab has EUA for pre-exposure prophylaxis of SARS-CoV-2 in patients at high risk who are unlikely to respond to a vaccine. Bebtelovimab has EUA for early treatment of COVID-19 in patients at risk for progression.

The potential use of tixagevimab–cilgavimab for treatment of early COVID-19 must be put into context. Older patients with comorbidities,[3] patients with host defense defects, and pregnant women[4] have the greatest risk for progression of COVID-19. Accordingly, clinicians should now help their patients with respiratory symptoms detect SARS-CoV-2 infection promptly and decide the best path forward.

Currently, the most popular treatment for COVID-19 is an oral combination of nirmatrelvir plus the CYP3A4 inhibitor, ritonavir, for 5 days within 5 days of symptom onset.[10] Another oral agent with FDA EUA for treatment, molnupiravir, provided only 30% protection from progression of disease.[11] Oral antiviral agents have a crucial advantage: they can be expected to work against all circulating variants

because they are not affected by mutations in the viral proteins that compromise neutralisation by monoclonal antibodies. In addition, they require no administration by a health-care provider. These agents represent the cornerstone of President Biden's test to treat programme.

The patients in greatest need of intervention are severely compromised hosts.[4] We have some difficulty in predicting who has responded to vaccination with accuracy, and who will have progression of COVID-19. But it seems clear that some patients with host defense defects have greater risk, and when unable to clear the viral infection might generate new and dangerous SARS-CoV-2 variants. It is possible that combination treatments will be required for some compromised hosts, and the idea of a monoclonal antibody, such as tixagevimab–cilgavimab, combined with an oral medication is a provocative option.

Perhaps most important, the COVID-19 pandemic will inevitably change management of respiratory infections. People can no longer simply suffer a cold. It is possible to envision that for a large segment of the population, rapid tests to separate COVID-19 from other pathogens will be essential, and better treatments for many of these diseases will be developed. If early interventions limit development of long COVID, the earliest possible treatments of this infection will be even more important. The best management of SARS-CoV-2 is still in development. Tixagevimab–cilgavimab and newer monoclonal antibodies and oral antiviral agents are examples of the many tools that will be needed.

MSC is co-chair of the HIV Prevention Trials Network and COVID Prevention Network supported by National Institutes of Health research funding. In addition, the author serves on an advisory board for Aerium, Atea, and GSK.

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