Commentary

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Listing of the neutralizing antibodies amubarvimab and romlusevimab in China: Hopes and impediments

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SUMMARY The coronavirus disease 2019 (COVID-19) pandemic continues to ravage the world, and the virus' constant evolution has made it increasingly difficult to contain. The combination of the neutralizing antibodies amubarvimab and romlusevimab has recently been introduced as a treatment for COVID-19 in China. Based on its potential to effectively combat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its Omicron variant at a modest cost and under medical insurance, this controversial biotherapy is anticipated to be widely available in China. Hopefully, whether and how the proposed medication will alter the treatment of COVID-19 in China will be apparent soon, as well as if it will help to reduce hospitalizations, reduce the incidence of severe illness, or even act as pre-exposure prophylaxis.

Keywords COVID-19, SARS-CoV-2, Omicron variant, neutralizing antibody, monoclonal antibody

Coronavirus disease 2019 (COVID-19), a global epidemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to flare up three years later. As a result of the emergence of Alpha, Beta, Gamma, Delta, and now Omicron variants, COVID-19's level and speed of transmission have substantially increased (*1,2*). Repeated infections and severe, prolonged symptoms pose significant social and economic concerns and cast serious doubts on the efficacy of vaccination. Other than vaccination against COVID-19, systemic treatment options are quite limited in terms of safety and expense. Small molecules and neutralizing antibodies are reliable and effective therapies for COVID-19. Combining neutralizing antibodies in a cocktail therapy decreases the possibility of a resistant virus strain emerging in individuals with COVID-19 and maintains neutralization activity against several emerging mutant strains. Therefore, the successful development of combination therapies with neutralizing antibodies could play a critical role in reshaping the world's ability to combat the epidemic.

The first neutralizing antibody cocktail therapy for COVID-19 to be commercially marketed in China was introduced on July 7, 2022. It consisted of two non-competing, anti-SARS-CoV-2 monoclonal antibodies, amubarvimab (BRII-196) and romlusevimab (BRII-198), obtained from the B cells of eight patients recovering from COVID-19 in the early stages of the 2020 pandemic. In response to promising results of a phase 1 clinical trial conducted in China, BRII-196 and BRII-198 were selected for inclusion in NIH's Accelerating COVID-19 Therapeutic Interventions and Vaccines 2 (ACTIV-2) international multicenter clinical trial. As reported in the ACTIV-2 study, the combination of BRII-196 and BRII-198 reduced hospitalization and the risk of death by 78% compared to a placebo (*3*). After this trial demonstrated the safety and effectiveness of the treatment for COVID-19, the FDA granted it an Emergency Use Authorization (EUA). In December 2021, the State Drug Administration of China approved the combination therapy for the treatment of adult and adolescent patients with mild or general COVID-19 with risk factors for progression, and the National Health Commission included it in the Diagnosis and Treatment Protocol for COVID-19 (Tentative 9th ed.) in March 2022 (*4,5*). These advances have contributed to improved treatment options for COVID-19 and bolstered clinicians' confidence in their ability to combat SARS-CoV-2 in China.

As a thriving avenue of drug discovery, many monoclonal antibodies either singly or in combination have been granted an EUA by authorities in various countries (*6*). Hundreds of monoclonal antibodies are in different stages of clinical studies as COVID-19 therapies. However, the widespread adoption of neutralizing antibodies poses major obstacles. The most

significant problem is loss of neutralizing antibodies' efficacy against emerging SARS-CoV-2 variants, such as Omicron and its sub-variants (BA.1, BA.2, BA.3, and BA.4/5). Among the more than 50 mutations present in Omicron, 32 occurred in the receptor binding domain of the spike protein (*7*). Since the receptor binding domain is the primary target of neutralizing antibodies following infection and immunization, these modifications may result in Omicron's evasion of antibody therapy. Studies have indicated that most of the therapeutic antibodies licensed under an EUA lose their binding and neutralizing properties when combined with Omicron variants. This will provide a serious challenge to the efficacy of neutralizing antibodies. This might be overcome by the newly listed amubarvimab and romlusevimab. A live virus neutralization assay revealed that amubarvimab had reduced neutralizing activity against the Omicron variant while romlusevimab displayed enhanced neutralizing action against the Omicron variant (*8*). The total concentrations of the two drugs in the blood remained 60 times higher than the amount needed to neutralize the live virus isolate BA.2 by 90%.

The normal use of neutralizing antibodies is dependent on availability and affordability, which are ongoing concerns for policymakers and patients. Due to a combination of technical advancements and market demand, the capacity for and price of antibody preparations have changed radically, and once prohibitive prices have become more affordable. As a medication that must be used long-term, the combination therapy will place a significant financial burden on patients. Moreover, injectables pose an obvious challenge for patients at home. Amubarvimab and romlusevimab are covered by medical insurance in China, but if their use is driven by medical necessity, this will put pressure on the Chinese health insurance system.

Overall, the use of neutralizing antibodies to treat COVID-19 presents both opportunities and challenges. Existing policies in China to combat the epidemic have been adjusted in light of the country's economic and social development. A broader selection of therapeutic options will make the strategy more adaptable and flexible, so the healthcare system will not become overburdened or better preventative measures can be taken to reduce the spread of the disease. Amubarvimab and romlusevimab, along with their derivatives, are expected to contribute to achieving these goals.

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