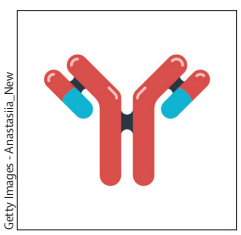
The insights from SARS-CoV-2 antibody treatment for future emerging infectious diseases



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Antibodies have pivotal roles in the immune response to infection. Laboratory-created SARS-CoV-2 antibody treatment is an emerging approach to treat COVID-19. Early treatment with these antibodies can reduce COVID-19-related hospitalisation or death in patients at high risk.[1–3] These antibodies can also provide targeted prophylaxis for individuals at high risk, and interrupt transmission of viruses in populations.[4]

A major concern of SARS-CoV-2 antibodies is the limited commercial value compared with current small-molecule drugs, such as nirmatrelvir plus ritonavir (Paxlovid) and molnupiravir. Small-molecule drugs (typically 0·1–0·6 kilodalton) can penetrate the cell membrane and bind intracellular targets; they are generally more stable than biological drugs and can be administered orally. Therefore, the target population that would benefit from SARS-CoV-2 antibodies rather than small-molecule drugs needs to be identified.

Currently, SARS-CoV-2 antibody treatment might be effective in immunocompromised patients with COVID-19.[5] However, large phase 3 trials are difficult to conduct to establish the efficacy of SARS-CoV-2 antibody treatment in the highest-risk patients, who have negligible ability to produce endogenous antibodies. Examples of such patients include those with haematological malignancies treated with anti-CD20 monoclonal antibodies (mAbs) or chimeric antigen receptor T-cell immunotherapy. For these patients, systemic administration would be more helpful than inhalation due to their almost non-existent humoral immunity.

Another promising use of SARS-CoV-2 antibodies is in prophylactic treatment for patients at high risk. The necessary condition is that the antibodies require an extended half-life to be effective.[6] It is reasonable to position the objective of the phase 1/3 trial of AZD3152 (NCT05648110), a combination of two mAbs (AZD1061 and AZD3152), as evaluating its safety and neutralising activity for pre-exposure prophylaxis of COVID-19. However, theoretically, inhaling the antibodies might not provide long-lasting exposure in the lungs. Therefore, the use of the inhalation route for antibodies needs to be explored for its potential value and scenarios for SARS-CoV-2 infection, because it might also be helpful for other infectious diseases.

The evasion of mAb-induced protection to all SARS-CoV-2 antibodies is the biggest threat because of the evolution of the spike protein of new SARS-CoV-2 variants.[7] At the time of writing, the omicron variant (BA.5) has evaded almost all available mAb-based drugs.[8] Efforts are still being coordinated to quickly identify and develop better antibodies.[9]

Maranda and colleagues[10] did a phase 1/2 trial to test the safety and explore the efficacy of IBIO123. This treatment consists of a fully human, recombinant, monoclonal IgG in a mixture of two antibodies binding to the S1 subunit and one antibody binding to the S2 subunit of the receptor-binding domain. IBIO123 showed neutralisation potency against SARS-CoV-2 from the original strain isolated in Wuhan, China, up to XBB1.5. The authors raised a hypothesis that direct delivery of neutralising antibodies via inhalation might provide additional respiratory clinical benefits. Thus, in this phase 1/2 trial, IBIO123 and a placebo were administered via oral inhalation to outpatients with COVID-19.

The main findings of the study indicate that oral inhalation of IBIO123 did not result in more adverse events or serious adverse events than the placebo. The results also showed that the proportion of participants with respiratory symptom resolution on day 8 was 33 (41%) of 81 in the IBIO123 group, compared with five (17%) of 29 in the placebo group (p=0·024) in the overall population. However, no significant reduction in viral load was observed on day 5.

The study showed the safety of inhaling antibodies. However, several key questions remain unanswered, including whether inhalation of antibodies is more beneficial than systemic administration, how inhalation of antibodies neutralises SARS-CoV-2 in other organs, how antibody exposure should be evaluated in the lungs and plasma, and how the optimal dosage of antibody could be identified in phase 1 trials.

The extended development time required for new small-molecule drugs makes it challenging for them to address emerging infectious diseases quickly. Although

SARS-CoV-2 antibodies face the aforementioned challenges, the rapid development of mAbs is poised to contribute more substantially in the future. The insights gained from antibodies for SARS-CoV-2 will probably be applicable to the creation of antibodies for other infectious diseases too.

We declare no competing interests.

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The power and pressure placed on clinicians and guideline panels

The trial reported by William Schilling and colleagues[1] in *The Lancet Infectious Diseases* adds crucial data to guide treatment decisions between clinicians and patients at this stage of the COVID-19 pandemic. This appears to be the first published randomised trial of molnupiravir and ritonavir-boosted nirmatrelvir versus placebo in low-risk adults. In this trial, molnupiravir caused viral mutations and ritonavir-boosted nirmatrelvir caused symptom rebound in individuals at low risk. This information should be discussed with patients when weighing risks and benefits of treatment options.

Clinicians and guideline panels should balance the potential for clinical benefit in individuals at low risk with the potential harm to populations. With molnupiravir, viral clearance (measured as half-life) occurred 3·9 h faster than placebo; however, molnupiravir caused more viral mutations than placebo. With nirmatrelvir, viral clearance occurred 7·0 h faster than placebo but nirmatrelvir caused more viral rebound than placebo. Rebound symptoms, which might be a clinical manifestation of a virus responding to a selective pressure, occurred in all three groups but was most common in the nirmatrelvir group. Because neither medication shortened the duration of illness in this low risk, relatively young population, symptom rebound might cause overall more days of illness and therefore harm from treatment.

Patients should be fully informed of the risks and benefits of these and other outpatient treatments for COVID-19. The world deserves several treatment options for SARS-CoV-2, and researchers worked together to quickly identify several options. Considering the symptom and viral rebound reported here by Schilling and colleagues, patients might choose metformin instead, which was less likely to cause viral rebound compared with placebo. This makes sense, because metformin's antiviral activity is mediated by host proteins, not viral proteins.[2,3] Metformin also prevented severe clinical outcomes (emergency department visits, hospitalisation, or death), as well as the long-term outcome of post-COVID-19 condition (also known as long COVID).[3–5]

Beyond the addition of these important data from a randomised trial, the authors make several points about this stage in the pandemic. Their assertion that "the increasing rarity of deterioration requiring hospitalisation and death mean that prohibitively large comparative studies are needed to detect clinically important differences"[1] is nuanced. Consensus on what

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