Antibody therapies to prevent and treat COVID-19

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There are numerous biological and small-molecule therapies currently under investigation for the prevention and treatment of COVID-19. This article focuses on antibody therapies that target the virus itself, including convalescent plasma and monoclonal antibodies against SARS-CoV-2, and discusses their efficacy in clinical trials and likely future role.

The pandemic has brought an unprecedented urgency to basic and clinical research to identify and evaluate new treatments for COVID-19. While it is clear that vaccination is the primary means of prevention, NICE is monitoring research on over 60 potential pharmacological treatments. At the time of writing, NICE has made recommendations for 14 of these treatments, among the management options for community and hospital care of COVID-19 (see Table 1).

The number and diversity of drugs under surveillance show how wide the net is now being cast for immediately available treatments; other agents are at various stages of investigation and development. The range includes immunosuppressants such as corticosteroids as well as many drugs in current use for other indications but whose properties might be beneficial against COVID-19 or its complications (e.g., tyrosine kinase inhibitors such as baricitinib, androgen-receptor antagonists, ACE inhibitors, statins and biological therapies such as ravulizumab). Novel biological therapies have been developed specifically to treat COVID-19, either by targeting the virus itself or the cytokines that promote the hyperinflammatory response associated with severe disease, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL-6).

There is evidence from clinical trials that corticosteroids reduce all-cause mortality in patients with severe COVID-19. There is also evolving evidence for the efficacy of IL-6 blocking agents such as tocilizumab in severe disease.

Antibody therapies

Antibody therapies evaluated as treatments for COVID-19 include neutralising antibodies obtained from infected patients (convalescent plasma) and monoclonal antibodies derived from these natural antibodies that have been engineered to target viral antigens. It is believed that the potential for anti-SARS-CoV-2 antibodies to prevent and treat COVID-19

![Figure 1. Role for anti-SARS-CoV-2 antibodies at various stages of the COVID-19 disease course. From: Shapiro AE, Bender Ignacio RA. Lancet Infect Dis 2021.](image-url)
CoV-2 antibodies to have a significant impact on the course of COVID-19 is probably confined to the earlier phase of the infection when symptoms are mild and caused by the virus (see Figure 1). In severe infection, when significant lung damage has occurred, the pathophysiology is driven by a hyperinflammatory response due to macrophage activation, altered T cell function and a cytokine storm. At this stage, treatment is directed at cytokines that have a key role in propagating the immune response, rather than targeting the virus itself.

Neutralising antibodies
Convalescent plasma, or hyperimmune immunoglobulin from plasma, was a readily accessible source of neutralising antibodies that offered hope for hospitalised patients with severe COVID-19. However, a living systematic review of 13 trials involving 41,880 treated patients with moderate to severe COVID-19, updated in May 2021, showed that convalescent plasma does not reduce 28-day mortality or the need for mechanical ventilation, and has little to no impact on clinical improvement compared with placebo or standard care. There is also little evidence of efficacy in people with asymptomatic or mild COVID-19. It is not clear why antibodies from patients do not significantly protect other people but inconsistencies in plasma neutralising activity or variable activity against different strains of the virus are possible factors.

Monoclonal antibodies against SARS-CoV-2
Natural antibodies are used as sources from which to derive monoclonal antibodies that can be targeted at specific sites on the SARS-CoV-2 virus spike protein, which mediates viral entry into cells. Clinical trials of these agents have been analysed in a second living systematic review. Six randomised trials involving a total of 17,495 adults were included, four involving non-hospitalised people with mild symptoms and two involving hospital patients with moderate to severe COVID-19. The reviewers concluded in September 2021 that the available evidence was insufficient to draw meaningful conclusions regarding treatment with SARS-CoV-2 neutralising monoclonal antibodies. That review identified a total of 36 ongoing trials that should improve the evidence base over the next few years. Several monoclonal antibodies, either as single agents or in combination, have now reached phase 2 or phase 3 trials for the prevention or treatment of COVID-19. Two monoclonal antibodies that offer hope for hospitalised COVID-19 patients aged 12 and older who are not in hospital and are thought to be at high risk of progression to severe COVID-19 (see Table 1). A list of people who are high risk and have priority for neutralising monoclonal antibodies is provided in NHS England’s Interim Clinical Commissioning Policy. NICE also recommends casirivimab/imdevimab – have now been licensed in the UK. NICE recommends these monoclonal antibodies for people aged 12 years and older who are not in hospital and are thought to be at high risk of progression to severe COVID-19 (see Table 1). A list of people who are high risk and have priority for neutralising monoclonal antibodies is provided in NHS England’s Interim Clinical Commissioning Policy. NICE also recommends casirivimab/imdevimab for hospitalised COVID-19 patients aged 12 and older who are seronegative.

Tixagevimab/cilgavimab
The monoclonal antibodies against SARS-CoV-2 have been engineered from natural neutralising antibodies and some have undergone structural modification to enhance their activity. For example, AstraZeneca’s tixagevimab/cilgavimab (Evusheld) combines two monoclonal antibodies that have been modified to increase their elimination half-lives and reduce binding to the Fc receptor (lowering the risk of antibody-enhanced disease) and complement C1q. One phase 3 trial (not published at the time of writing) showed that Evusheld reduced the risk of symptomatic infection in unvaccinated people by 83% compared with placebo. In a second trial, it reduced the risk of severe disease or death by 88% compared with placebo in people in mild to moderate COVID-19 when given within three days of symptom onset. Evusheld has been shown to retain neutralising activity against the Omicron variant. It has been approved in the USA for emergency use for pre-exposure prophylaxis of people with immunosuppression and is under review by the European Medicines Agency. Ronapreve is a combination of casirivimab and imdevimab, which target different but overlapping components of the virus spike protein. It has a conditional marketing authorisation for the prophylaxis and treatment of acute COVID-19 and was the first monoclonal antibody product to be approved for this indication by the MHRA. The indication is not limited by age, though there is no experience of its use in patients aged under 12 years. The recommended dose is 600mg casirivimab and 600mg imdevimab, given by IV infusion or subcutaneous injection. Patients who need ongoing prevention (eg because they are immunosuppressed) should receive 300mg casirivimab and 300mg imdevimab every four weeks following the initial full dose. The Summary of Product Characteristics for Ronapreve states that the antibodies bind to spike protein sites that are used as immunogens in COVID-19 vaccines; it is therefore possible that it may interfere with the immune response to vaccination. Ronapreve is among the treatment options recommended by NICE (see Table 1).

An interim analysis of a phase 3 trial involving 275 non-hospitalised adults (median age 44 years, range 34–54 years) who had tested positive for COVID-19 within 72 hours of randomisation showed that a single infusion of Ronapreve significantly reduced viral load and lowered the COVID-19-related medical attendance rate within 29 days (3% with Ronapreve vs 6% with placebo). In those who were confirmed seronegative at baseline, the corresponding figures were 6% and 15%. Approximately 40% of this study population were obese. Participants had been randomised to receive either 2.4g or 8.0g total dose of monoclonal antibody therapy; the reduction in viral load was greater with the higher dose but clinical outcomes were similar.

In a second phase 3 trial, participants (≥12 years of age) were enrolled within 96 hours of a household contact receiving a diagnosis of COVID-19 and randomised to treatment with Ronapreve 1.2g total dose or placebo by subcutaneous injection. Ronapreve significantly reduced the rate of symptomatic COVID-19 infection (1.5% vs 7.8% with placebo) after 28 days, a relative risk reduction of 81%, and reduced symptomatic and asymptomatic infec-
| Pharmacological Treatment Options | Recommended | Conditionally recommended | Not recommended | Research only |
|----------------------------------|-------------|--------------------------|-----------------|---------------|
| Corticosteroids (dexamethasone, or if this cannot be used, either hydrocortisone or prednisolone) | Offer to people with COVID-19 who need supplemental oxygen to meet their prescribed oxygen saturation levels or have a level of hypoxia that needs supplemental oxygen but who are unable to have it | Do not routinely use corticosteroids to treat COVID-19 in people who do not need supplemental oxygen, unless there is another medical indication to do so |  |  |
| Casirivimab and imdevimab | Offer to people aged 12 and over hospitalised because of COVID-19 who have no detectable SARS-CoV-2 antibodies (seronegative) | Do not offer to people aged 12 and over hospitalised because of COVID-19 who have detectable SARS-CoV-2 antibodies (seropositive), or whose serostatus is unknown |  |  |
| Remdesivir | Consider for up to 5 days for COVID-19 pneumonia in adults, and young people 12 years and over weighing 40kg or more, in hospital and needing low-flow supplemental oxygen | Do not use for COVID-19 pneumonia in adults, young people and children in hospital and on high-flow nasal oxygen, continuous positive airway pressure, non-invasive mechanical ventilation or invasive mechanical ventilation, except as part of a clinical trial |  |  |
| Tocilizumab | Offer to: adults in hospital with COVID-19 if all the following apply: they are having or have completed a course of corticosteroids such as dexamethasone (unless they cannot have them); they have not had another IL-6 inhibitor; there is no evidence of a bacterial or viral infection that might be worsened by tocilizumab And they: need supplemental oxygen and have a C-reactive protein level of 75mg/L or more, or are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive or invasive mechanical ventilation | Considers in children and young people who have severe COVID-19 or paediatric inflammatory multisystem syndrome only if they are 1 year and over, and only in the context of a clinical trial |  |  |

Table 1. Summary of NICE recommendations on pharmacological treatment options for COVID-19 (as of 7 February 2022)
Antibody therapies for COVID-19

Symptoms resolved more quickly in Ronapreve recipients who developed symptomatic infection (median 1.2 weeks vs 3.2 weeks with placebo) and the duration of high viral load was 0.4 and 1.3 weeks respectively. Around 30% of patients had at least one risk factor for severe infection and about a third were obese.

**Sotrovimab**
The second monoclonal antibody therapy specifically approved for COVID-19 in the UK is sotrovimab (Xevudy). It has a conditional marketing authorisation for the treatment of symptomatic adults and adolescents (aged ≥12 years and weighing ≥40kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe infection. Treatment is administered as a single IV infusion of 500mg within five days of symptom onset.

Efficacy was demonstrated in the phase 3 COMET-ICE trial, in which 583 non-hospitalised patients with symptomatic COVID-19 and at least one risk fac-

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**Table 1.** Summary of NICE recommendations on pharmacological treatment options for COVID-191 (as of 7 February 2022, continued)
Bamlanivimab and etesevimab treatment reduced viral load and, within 29 days, reduced hospital admission or death by 70% (2.1% vs 7.0% with placebo). Despite these positive findings, manufacturer Lilly withdrew bamlanivimab/etesevimab from the European Medicines Agency’s fast-track approval process. The company stated the regulatory procedures would require the production of new batches of antibodies that were not needed to meet the anticipated demand for supply.

**Limitations**

This highlights the limitations of antibodies that target the virus: they have so far been shown to be effective only in the early phase of infection, in people who are relatively well. Only a small percentage of such a population would require hospital admission but many people would receive treatment, which needs to be administered by injection or infusion. In the trial of bamlanivimab/etesevimab, the 4.8% absolute risk reduction translates to a number needed to treat of 21 to prevent one admission or death compared with placebo. Antibody therapy is well tolerated but, with effective oral antiviral drugs such as molnupiravir and nirmatrelvir/ritonavir (Paxlovid) now available for people with mild COVID-19 who have risk factors for severe disease, the potential market for antibodies may be smaller than it once seemed. However, experience in managing COVID-19 and evidence for the wide range of treatment options for mild to moderate and severe disease are evolving rapidly.

A further concern is whether monoclonal antibodies will retain sufficient efficacy against SARS-CoV-2 variants with significant mutations of the spike protein. Most trials were carried out in 2020 and 2021, when the Alpha and Delta variants were predominant; at the moment, little has been published about their activity against the Omicron variant (though that may be less likely to cause severe disease). The mechanism of action of oral antivirals does not depend on antigen recognition and they may therefore be less susceptible to new variants.

One potential option avoids the cost of intravenous administration: DZIF-10c, a monoclonal antibody shown to prevent SARS-CoV-2 infection in a mouse model after intranasal administration, is now in a phase 1 trial in volunteers (ClinicalTrials.gov Identifier: NCT04631705).

**Summary**

There are many biological and small-molecule drugs under investigation for the prevention and treatment of COVID-19. Monoclonal antibodies against SARS-CoV-2 have been developed from natural isolates and engineered to target the virus spike protein. Most trials have shown they are effective in reducing the risk of hospital admission and severe disease in people with mild to moderate COVID-19. Two monoclonal antibody products have now been recommended by NICE for people at high risk of progression to severe COVID-19 but who have not been admitted to hospital. This overlaps with the patient group for whom oral antiviral therapy (molnupiravir or Paxlovid) has now been licensed, but NICE guidance is still awaited on this.

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