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.

delay of breakthrough transmissions. However, it is possible that the small sample sizes after stratification by vaccination status reduced the power of the study to detect moderate delays. Inadequate effectiveness of vaccines in reducing the generation times of the alpha and delta variants, as shown in the study by Hart and colleagues,[7] suggests that quarantine practices for exposed close contacts should remain unchanged regardless of vaccination status.

The surging omicron variant (B.1.1.529) gained an additional growth rate advantage (2·0–3·5 times) according to the US Centers for Disease Control and Prevention (CDC), which might be explained by a combination of improved inherent transmissibility and immune escape. The observed shorter incubation period of the omicron variant (around 3 days) implies a further shortened generation interval.[10] Household studies with similar designs to the study by Hart and colleagues should be conducted to assess the transmissibility and generation interval of, and vaccine effectiveness against, omicron so that control policies can be amended in a timely manner if necessary.

We declare no competing interests.

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For the **US CDC modelling** see https://www.cdc.gov/coronavirus/2019-ncov/science/forecasting/mathematical-modeling-outbreak.html

CD24Fc: an emerging COVID-19 therapy

In *The Lancet Infectious Diseases,* James Welker and colleagues[1] report a randomised, double-blind, placebo-controlled, phase 3 study of intravenous CD24Fc (480 mg over 60 min on day 1) versus placebo in adults hospitalised with COVID-19 at nine medical centres in the USA. The primary endpoint was time to clinical improvement, defined as time elapsed between a baseline National Institute of Allergy and Infectious Diseases 8-point ordinal scale (NIAID-OS) score of 2–4 and a score of 5 or higher or hospital discharge.[2] Among all 234 participants who were randomly assigned to a treatment group (of whom 62% were male and 38% female, 47% were non-Hispanic White, and median age was 59 years [IQR 48–68]), time to clinical improvement was accelerated among participants who received CD24Fc (median 6·0 days) compared with those who received placebo (10·5 days) over the 28-day study period (hazard ratio [HR] 1·40, 95% CI 1·02–1·92).

The study was well designed, with near-complete protocol adherence and minimal loss to follow-up. However, the trial enrolled participants between April and September, 2020, and preceded landmark clinical trials of dexamethasone,[3] remdesivir,[4] and interleukin-6 (IL-6) receptor antagonists[5] in the treatment of severe COVID-19. As a result, CD24Fc infusion was compared with an outdated standard of care that included a combination of experimental corticosteroids, remdesivir, and convalescent plasma given at the discretion of the treating physician. Since the enrolment period ended, trials have shown that convalescent plasma was not associated with reduced time to clinical improvement,[6] and IL-6 receptor antagonists have emerged as an important part of the COVID-19 treatment framework.[5]

A key component of clinical trial design is ensuring the control group reflects the current standard of


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See **Articles** page 611

care. For example, when baricitinib was evaluated in a phase 3 clinical trial, the study showed that baricitinib plus remdesivir was superior to remdesivir alone in the treatment of severe COVID-19 infection.[7] Global collaborations have enabled accelerated clinical trial enrolment during the COVID-19 pandemic, which has resulted in a rapidly evolving standard of care that incorporates emerging effective therapies. Welker and colleagues effectively recorded background treatments and showed that, among participants who received the current standard daily dose of dexamethasone (6·0 mg; n=61 in the CD24Fc group, n=59 in the placebo group), time to clinical improvement was still accelerated in the CD24Fc group compared with the placebo group (HR 1·64, 95% CI 1·05–2·55). The trial findings show promise, but do not conclusively show that CD24Fc improves time to clinical improvement relative to the current COVID-19 treatment framework, consisting of dexamethasone, remdesivir, or IL-6 receptor antagonists, or a combination of these treatments.

The evolving use of background therapies during the enrolment period might also partially account for the weakened association that was observed after the prespecified interim analysis. In the interim analysis, after 146 time to clinical improvement events were accrued among 197 randomised participants, CD24Fc showed an improved clinical improvement rate compared with placebo (HR 1·61, 95% CI 1·16–2·23). After the interim analysis, the protocol was amended to allow inclusion of participants requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (NIAID-OS score of 2), and an additional 37 participants were enrolled. In the entire randomised population, CD24Fc was still associated with accelerated time to clinical improvement compared with placebo, but the magnitude of the association was slightly reduced.

The inclusion of participants with an NIAID-OS score of 2 after the interim analysis might account for the reduced strength of the association between CD24Fc and time to clinical improvement. Participants with an NIAID-OS score of 2 or 3 appeared to derive minimal benefit from CD24Fc treatment, although larger studies are required to evaluate the effectiveness of CD24Fc in subgroups defined by severity of illness. An alternative explanation is that evolving background therapies after the interim analysis led to reduced efficacy of CD24Fc therapy. An additional trial evaluating CD24Fc in combination with the current COVID-19 treatment framework would help elucidate whether CD24Fc improves time to clinical improvement over the current standard of care. Another explanation for the weakened association in the entire randomised population is that CD24Fc might be most effective in subgroups of patients with a heightened inflammatory response to COVID-19.

An observational study in patients with critical COVID-19 has identified two distinct subgroups using latent class analysis.[8] The hyperinflammatory phenotype had higher proinflammatory markers and showed improved overall survival after treatment with corticosteroids compared with patients who did not receive corticosteroids. By contrast, the hypoinflammatory phenotype had increased mortality after corticosteroid treatment. It is possible that CD24Fc, an anti-inflammatory therapy that suppresses production of inflammatory cytokines,[9] might be most effective in patients with a heightened inflammatory response. In general, identifying subphenotypes of critical illness might facilitate discovery of interventions that are most effective in specific subgroups with distinct biological characteristics.[10] However, the optimal methods for identifying subphenotypes in severe COVID-19 remain unknown and require further investigation.

CD24Fc has shown promise as a COVID-19 therapy with systemic effects that might persist against emerging viral variants. CD24Fc treatment accelerated time to clinical improvement compared with placebo in a diverse patient population and might represent an emerging addition to the COVID-19 treatment armamentarium.

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Time to knock monoclonal antibodies off the platform for patients hospitalised with COVID-19

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See **Articles** page 622

The research community has responded to the COVID-19 pandemic with innovative platform trials to address the need for rapid evaluation of novel agents using a common protocol, among them being RECOVERY,[1] ACTIV,[2] and Solidarity.[3] Despite several successes with anti-SARS-CoV-2 monoclonal antibodies (mAbs) for treatment of mild or moderate COVID-19 in ambulatory patients,[4,5] an effective SARS-CoV-2-specific treatment for patients with COVID-19 who are being treated in hospital (ie, hospitalised) has remained elusive.

The ACTIV-3 Therapeutics for Inpatients with COVID-19 (TICO) platform was developed to assess multiple candidate mAbs in individuals hospitalised with moderate or severe COVID-19 within 12 days of symptom onset. In *The Lancet Infectious Diseases*, the ACTIV-3 TICO Study Group[6] report the results of two neutralising mAb treatments (sotrovimab and BRII-196 plus BRII-198) that were provided in addition to standard of care, typically including remdesivir and corticosteroids, in a double-blind, randomised fashion, predominantly before the availability of SARS-CoV-2 vaccines, and were compared with a pooled placebo group. Enrolment into the trial was stopped early after a prespecified interim futility analysis in 536 participants in the modified intention-to-treat population found no improvement in odds of favourable pulmonary outcome scores on day 5 after infusion with either sotrovimab or BRII-196 plus BRII-198 compared with placebo. By day 90, no difference was seen in the primary endpoint of sustained clinical recovery with either sotrovimab or BRII-196 plus BRII-198 compared with placebo, and composite safety outcomes were similar across the three groups.

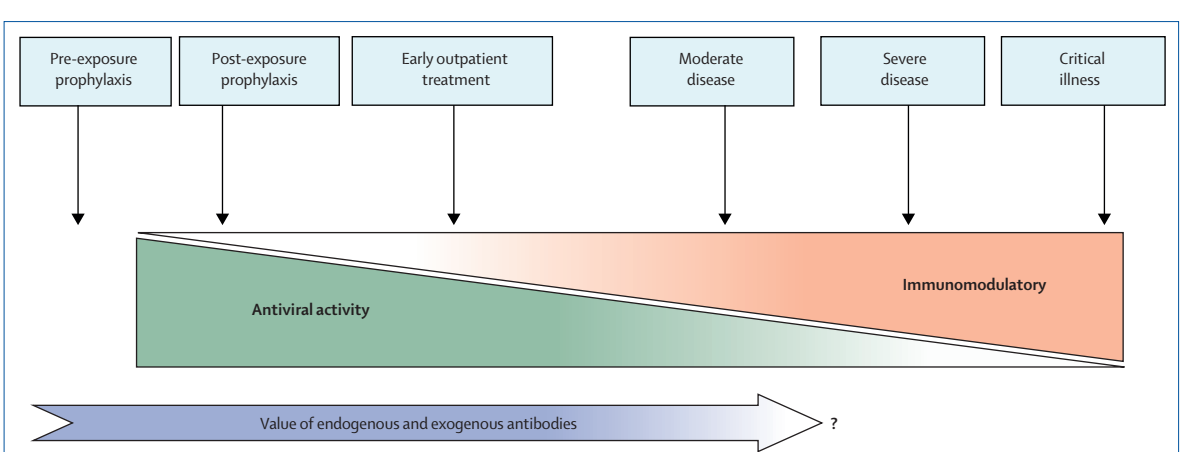

***Figure*: Role for anti-SARS-CoV-2 antibodies in the disease course of COVID-19**
As disease states progress from preinfection through to critical illness (blue boxes), the potential for antibodies to mitigate illness decreases (dark blue arrow) as pathology transitions from being virally mediated, where antiviral acting therapies are most effective (green triangle), to a hyper-inflammatory state best treated with immunomodulatory therapies (orange triangle).