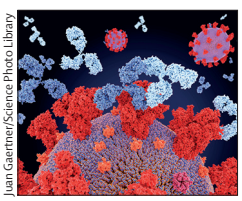
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Monoclonals for patients hospitalised with COVID-19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Monoclonal antibodies that neutralise SARS-CoV-2 have consistently reduced hospitalisation or death in outpatients with mild to moderate COVID-19.[1–3] Conversely, results of randomised trials in patients who are hospitalised are mixed.[4–8] In *The Lancet Respiratory Medicine*, Thomas L Holland and colleagues present results of the ACTIV-3 trial comparing intravenous tixagevimab–cilgavimab with placebo for patients hospitalised with COVID-19.[8] Although tixagevimab–cilgavimab did not improve the primary outcome of time to sustained recovery (rate ratio [RR] 1·08 [95% CI 0·97–1·20]; p=0·21), it was associated with improved 28-day (6% *vs* 9%; p=0·02) and 90-day (9% *vs* 12%; p=0·03) mortality.

This study represents the third trial in which intravenous monoclonal antibody treatment was associated with decreased mortality in some patients who are hospitalised. The RECOVERY trial compared casirivimab–imdevimab with standard care in 9785 patients hospitalised with COVID-19.[4] Although treatment was not associated with a 28-day mortality benefit in the overall cohort (RR 0·94 [95% CI 0·86–1·03]), mortality was lower in patients who were seronegative at the time of enrolment (RR 0·80 [0·70–0·91]).[4] In the company-sponsored trial of 1223 patients who were hospitalised, casirivimab–imdevimab treatment was associated with a significant reduction in 28-day mortality (relative risk reduction [RRR] 35·9% [95% CI 7·3–55·7]), most predominately observed in the seronegative subgroup (RRR 55·6% (24·2–74]).[5]

Conversely, three monoclonal antibodies (bamlanivimab, sotrovimab, BRII-196/BRII-198) previously evaluated in the ACTIV-3 platform failed the early futility analysis, which assessed pulmonary function at day 5 by means of a seven-category ordinal scale.[6–7] Enrolment was subsequently terminated, limiting the number of participants receiving each intervention to less than 200. It is noteworthy that neither the primary outcome of time to sustained recovery nor pulmonary function at day 5 (odds ratio 1·08 (95% CI 0·89–1·30) was improved with tixagevimab–cilgavimab.[8] However, tixagevimab–cilgavimab passed the early futility analysis and was permitted to continue enrolment. Therefore, it is unknown whether these failed monoclonal antibodies would have shown a mortality benefit in a larger trial despite no effect on the ordinal outcome scales, as was the case with tixagevimab–cilgavimab.

The effect of various therapies evaluated for COVID-19 on ordinal outcome scales has been inconsistent, and these scales have plagued findings of pandemic trials for several reasons. First, each step on the scale is not necessarily of equivalent clinical significance. Second, multiple non-clinical and non-COVID-19-related factors can influence recovery, depending on how recovery is defined. Finally, an intervention might halt progression of the disease course to more severe illness (a clinically important endpoint) yet fail to hasten symptom resolution or return to baseline functional status. Therefore, when evaluating COVID-19 therapeutics in patients hospitalised with severe disease, it might be more prudent to power studies to assess the objective and more important endpoint of mortality. ACTIV-3 illustrates this point. This trial was powered on the basis of a failed primary outcome of improvement in time to sustained recovery, and it was only by coincidence that the mortality rate in patients receiving placebo was high enough to show a benefit with tixagevimab–cilgavimab. If the Data Safety Monitoring Board had not made the decision midway through the study to allow enrolment of patients on high-flow nasal cannula or had the more severe delta variant not emerged—both of which significantly increased mortality rates beyond what was anticipated at the onset of the study—it is likely that this study would have concluded no benefit to tixagevimab–cilgavimab.

The question now facing clinicians is whether the results of this trial should lead to the recommendation of intravenous tixagevimab–cilgavimab therapy for patients who are hospitalised. This is challenging to answer for several reasons, relating to the dynamic nature of both the virus and the host. To first consider the virus, the in vitro activity of tixagevimab–cilgavimab, like other monoclonal antibodies, varies with emerging SARS-CoV-2 variants. It is unclear whether changes in in vitro potency are clinically meaningful and how those changes affect efficacy. Ideally, each monoclonal antibody would be studied clinically against each SARS-CoV-2 variant. However, this is not feasible, which makes application of these results to present and future variants difficult.

	Seronegative		p value	Seropositive		p value
	Monoclonal	Placebo		Monoclonal	Placebo	
Casirivimab–imdevimab	396/1633 (24%)	451/1520 (30%)	0·0010	411/2636 (16%)	383/2636 (15%)	0·30*
Casirivimab–imdevimab	24/360 (7%)	24/160 (15%)	0·0047*	26/369 (7%)	18/201 (9%)	0·42*
Tixagevimab–cilgavimab	15/307 (5%)	30/337 (9%)	0·059	22/380 (6%)	27/339 (8%)	0·29

Data are n/N (%); n is event rate; N is population in the study. *Calculated by authors of this commentary; not provided in manuscript.

Table: **28-day mortality rates by serostatus**

Furthermore, even if the relative efficacy shown in these trials is consistent across variants, the absolute benefit of therapy will change as mortality associated with SARS-CoV-2 changes. It is not appropriate to extrapolate the magnitude of a mortality benefit in a predominantly delta variant landscape to the current disease course of an omicron-subvariant-infected patient, especially when the former variant was associated with significantly worse outcomes.[9]

To consider the host, 73% of patients in this study were unvaccinated, and the mortality benefit observed with monoclonal antibodies in patients who are hospitalised appears limited to patients who are seronegative (table). Indeed, in ACTIV-3, 28-day mortality was identical (13%) in the tixagevimab–cilgavimab and placebo groups in the subset of patients who were vaccinated.[8] With up to five vaccine doses now recommended, and the decreased risk of death in those vaccinated,[10] the efficacy of tixagevimab–cilgavimab in these patients is unclear. Furthermore, nearly all unvaccinated patients have now been previously infected with SARS-CoV-2. The presence of infection-derived immunity further limits the seronegative population in which monoclonal antibodies have shown benefit. These factors collectively underscore the challenges of developing and evaluating monoclonal antibody therapies in the face of a rapidly mutating virus and evolving host population.

Should we use intravenous tixagevimab–cilgavimab in patients who are hospitalised? It might be reasonable to consider therapy in patients either known to be seronegative or severely immunocompromised and unlikely to respond robustly to vaccination. Although it might be enticing to expand tixagevimab–cilgavimab use beyond these populations, it is not supported by the evidence and future studies are needed to ascertain the role of monoclonal antibodies in a population that is no longer immune-naive.

Importantly, these same limitations and questions hold true for other antiviral agents used in both the inpatient and outpatient setting for COVID-19. The authors and study teams of ACTIV-3 and all previous trials should be applauded for their impressive work to establish the benefit of various therapies during a rapidly evolving pandemic landscape. Their work has saved countless lives to date. However, new trials adequately powered to current event rates within the emerging variant and immunity landscape are needed to establish whether there is a benefit to any antiviral or immunomodulatory therapy for patients with COVID-19.

JMP discloses serving as a consultant to Merck, Shionogi, and Roche. EKM discloses serving as a consultant to Shionogi and is the Director of infectious diseases improvement and clinical research innovation at UPMC. In this role, EKM oversaw clinical trials involving use of sotrovimab (donated by GSK) and evaluation of tixagevimab–cilgavimab in outpatients (funded by AstraZeneca). She does not receive salary support or funding for her involvement in these trials.

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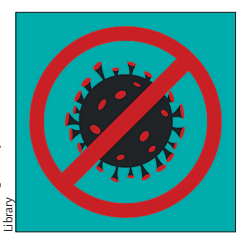
Early treatment to prevent progression of SARS-CoV-2 infection



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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