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Upgrade on Monoclonal Antibodies as Prophylaxis-Therapy in the Elderly and Immunocompromised Sars-Cov-2 Population. A Review

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Abstract

COVID-19 is highly transmissible with potentially serious health outcomes, underscoring the need for effective prevention and treatment strategies. Vaccines are highly effective at preventing COVID-19 for the general population; however, efficacy is often impaired in immunocompromised patients given insufficient response to initial exposure and/or memory for secondary exposures. Risk factors for COVID-19 include older age, obesity, underlying medical conditions such as diabetes, inadequate vaccination, and/or being immunocompromised. People living with immunocompromising conditions including but not limited to active treatment for solid tumor and hematologic malignancies, solid organ transplant recipients, or people living with human immunodeficiency virus, even with appropriate vaccination, are at a greater risk for adverse outcomes from COVID-19 including hospitalization, time in the intensive care unit (ICU), and mechanical ventilation. Consequently, therapeutic monoclonal antibodies (mabs), developed rapidly as a part of the global response to COVID-19, have been crucial. Nevertheless, the evolving VOCs have reduced the effectiveness of current abs, necessitating the development of new ones effective against various sarbeco viruses. This Mini review explain the importance of Prophylaxis, Therapy with Monoclonal Antibodies as The First Major Therapeutic Opportunity to change the Clinical History in the Sars-Cov-2 Variants Era for elderly and immunocompromised persons.

Keywords: Combination Therapy; Monoclonal Antibodies, Sars-Cov-2; Early Treatment

Background

COVID-19 is highly transmissible with potentially serious health outcomes, underscoring the need for effective prevention and treatment strategies. Vaccines are highly effective at preventing COVID-19 for the general population; however, efficacy is often impaired in immunocompromised patients given insufficient response to initial exposure and/or memory for secondary exposures. Risk factors for COVID-19 include older age, obesity, underlying medical conditions such as diabetes, inadequate vaccination, and/or being immunocompromised [1]. People living with immunocompromising conditions including but not limited to active treatment for solid tumour and hematologic malignancies, solid organ transplant recipients, or people living with human immunodeficiency virus, even with appropriate vaccination, are at a greater risk for adverse outcomes from COVID-19 including hospitalization, time in the intensive care unit (ICU), and mechanical ventilation [2]. Consequently, therapeutic monoclonal antibodies (mAbs), developed rapidly as a part of the global response to COVID-19, have been crucial. Nevertheless, the evolving VOCs have reduced the effectiveness of current mAbs, necessitating the development of new ones effective against various sarbecoviruses. This mini review explain the importance of Prophylaxis, Therapy with Monoclonal Antibodies as The First Major Therapeutic Opportunity to change the Clinical History in the Sars-Cov-2 Variants Era for elderly and immunocompromised persons.

Introduction

Vaccination in elderly and in many immune-compromised persons is less effective where immunogenicity and clinical data show considerably impaired responses to vaccination. Thus Monoclonal antibodies targeting the anti-SARS-CoV-2 spike (S) protein are prescribed in high-income countries to prevent severe disease in at-risk patients. Although studies report efficacy as between 50–85% [3-4]. Global access is currently largely inequitable. Multivariate omicron (B.1.1.529) and sub variant (BA.2 followed by BA.4 and BA.5) dominance has challenged the treatment landscape for mild-to-moderate disease, introducing considerable certainty on the efficacy of monoclonal antibodies [5-7] and leading to changes to initial recommendations for some of them. Contemporaneously, oral, direct-acting antivirals with a reported efficacy ranging from 30% (molnupiravir) to 89–90% (nirmatrelvir/ritonavir) have recently received conditional or emergency approval in some countries and been recommended in international guidelines such as the World Health Organization guidelines [8-9]. S-217622, also known as ensitrelvir, a 3CL protease inhibitor that has been shown to significantly reduce the infectious viral load, is currently in phase 3 trials and waiting for emergency approval in Japan and should be submitted soon in China. The main purpose of this opinion paper is to highlight the possible strategies to optimize and protect current and future therapeutic options to treat the most vulnerable patients. [10].

Monoclonal Antibodies Aprovation as Prophylaxis-Therapy in the Ederly and Immonocompromised Sars-Cov-2 population at October 2023

Currently, most mAbs are ineffective at providing an immune response to Omicron strains post BA.2. Recently, the US Food and Drug Administration and provinces in Canada have found tixagevimab plus cilgavimab ineffective against Omicron variants [11]. Similar decisions in the US have been made previously for bamlanivimab monotherapy, which was revoked in April 2021 because of low efficacy against newer COVID-19 variants [12]. In the context of increasing prevalence of resistant SARS-CoV-2 subvariants, the decision to administer tixagevimab plus cilgavimab, or any other mAbs to a given patient should be based on regional prevalence of resistant variants, individual patient risks, available resources, and logistics. Further, patients who receive mAbs as a prophylactic for COVID-19 should continue taking precautions, including proper hand hygiene, physical distancing, and mask wearing to avoid exposure (Table 1). Although mAbs demonstrated effectiveness, concerns have been raised regarding the potential for creating spike protein resistance-associated viral mutations, particularly in immunocompromised patients. A study conducted from January to February 2022 investigated whether resistance-associated mutations developed after treatment with sotrovimab in high-risk patients. Out of the high-risk patients, specimens were collected at three time points from 14 of the 18 patients (78%). Genomic analysis revealed that all 18 (100%) patients were infected with the Omicron variant; 17 with BA.1 (94%) and one with BA.2 (6%). Ten patients (56%) developed receptor-binding domain mutations at spike position E340 or P337 within 3-31 days after treatment. The researchers identified six mutations in the spike protein S: E340K/A/V/D/G/Q and three in S: P337L/R/S. Mutations increased over time, exceeding 50% between days 5 and 28. Patients with mutations had significantly delayed time to viral clearance

(mean, 32 [SD, 8.1] days vs 19.6 [SD, 11.1] days for those without mutations; HR, 0.11 [95% CI, 0.02-0.60]). No S: E340 or S: P337 mutations were found in the Omicron variant from sequences in the general population. The four patients with the sotrovimab resistance-associated S: E340K mutation were immunocompromised [13]. Evidence of how Fc-dependent antibody functions may impact infection consequences within immunocompromised populations is still limited, requiring a more robust framework for evaluation.

Sotrovimab is one of the few mabs that demonstrated retained favourable clinical outcomes against the Omicron variant and as such it is crucial to understand Fc-mediated effects in order to evaluate and improve application of antibody therapy. The Omicron variant presents a heightened risk to patients that are immunocompromised due to their inability to mount a sufficient antibody response, even when they are vaccinated and/or have previous COVID-19 infections. This reality places immunocompromised patients at risk of death and hospitalization due to increased likelihood of high viral load and their difficulty in eliminating the virus. There is a continued need for research supporting multiple COVID-19 prophylaxis. The medical and scientific community can best serve their immunocompromised patients by updating their understanding of COVID-19 prophylaxis and its utility in supporting immunocompromised patients. Moreover, there is an urgent need for new randomized controlled trials in vaccinated, immunocompromised subjects, during current strains of COVID-19 to support the development of more effective mAbs [Table 2]. Cowan J., Amson A., et al. Monoclonal antibodies as Covid-19 prophylaxis therapy in immunocompromised patient populations. International Journal of Infectiuos Diseases Vol.134:P228-238, (2023). AE, adverse event; ARD, absolute risk difference; CI, confidence interval; RCT, randomized control trial; RRD, relative risk difference; RRR, relative risk reduction; RR, relative risk. Amson A., et al. Monoclonal antibodies as Covid-19 prophylaxis therapy in immunocompromised patient populations. International Journal of Infectious Diseases Vol.134:P228-238, (2023). AE, adverse event; aOR, adjusted OR; BAU, binding antibody unit; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; IM, intramuscular; IQR, interquartile range; IV, intravenous; KTR, kidney transplant recipients; mAb, monoclonal antibody; MS, multiple sclerosis; NP, nasopharyngeal; OR, odds ratio; RRR, relative risk ration; SOTR, solid organ transplant recipients.

ECDC Variant Classification Criteria and Recommendations at October 2023

New evidence is regularly assessed on variants detected through epidemic intelligence, rules-based genomic variant screening, or other scientific sources. If a decision is made to add, remove, or change the category for any variant, the tables are updated to reflect this change. The tables are regularly sent for consultation to ECDC and WHO Regional Office for Europe's joint virus characterisation working group.

Description of the Tables

Category

Variant of concern (VOC), variant of interest (VOI), or variant under monitoring ($VU^{M)}$.

WHO label

As of 31st May 2021, WHO proposed labels for global SARS-CoV-2 variants of concern and variants of interest (link is external) to be used alongside the scientific nomenclature in communications about variants to the public. This list includes variants on WHO's global list of VOC and VOI, and is updated as WHO's list changes

Lineage and additional mutations

The variant designation specified by one or more Pango lineages and any additional characteristic spike protein changes. An alternate description may be used if the variant is not easy to describe using this nomenclature. For updated information on Pango lineages and definition of lineages and for instructions on how to suggest new lineages, visit the Pango lineages website (link is external). Each lineage in then table is linked to the respective lineage page on the Pango lineages website

Country first detected

Only present if there is moderate confidence in the evidence relating to the first country of detection.

Spike mutations of interest

Not all spike protein amino acid changes are included – this is not a full reference for assignment of the variants. It includes changes to spike protein residues 319-541 (receptor binding domain) and 613-705 (the S1 part of the

S1/S2 junction and a small stretch on the S2 side), and any additional unusual changes specific to the variant.

Year and month first detected

As reported in the GISAID EpiCoV database. This can be adjusted backwards in time if new retrospective detections are made.

Evidence

Concerning properties in three different categories:

- Transmissibility
- Immunity
- Infection severity

Each category is annotated as increased, reduced, similar, unclear, or no evidence depending on the currently available evidence. Increased or reduced means that there is evidence demonstrating that the property is different enough for the variant compared to previously circulating variants that it is likely to have an impact on the epidemiological situation in the EU/EEA. Similar means that there is evidence that demonstrates that the property is not different enough for this variant compared to previously circulating variants that it is unlikely to have an impact. Unclear means that the current evidence is preliminary or contradictory enough to make the assessment uncertain. No evidence means that no evidence has yet been evaluated for this category. The evidence is further annotated with v or m to indicate whether the evidence is available for the variant itself (v) or for mutations associated with the variant (m).

Transmission in the EU/EEA

Categorised as dominant, community, outbreak(s), and sporadic/travel. The categories are qualitative, and the assessment is based on surveillance data collected in TESSy, GISAID EpiCoV data, epidemic intelligence data, and direct communications with the affected countries.

Variants of Concern (VOC)

As of 3 March 2023, ECDC has de-escalated BA.2, BA.4 and BA.5 from its list of SARS-CoV-2 variants of concern (VOC), as these parental lineages are no longer circulating. ECDC will continue to categorise and report on specific SARS-CoV-2 sub-lineages in circulation that are relevant to the epidemiological situation.

There are currently no SARS-CoV-2 variants meeting the VOC criteria.

Variants of interest (VOI)

X: including its sub-lineages (BN, CH and others). Omicron-Omicron Recombinants XBF and XBK that share the same spike as BA.2.75 are monitored under BA.2.75 lineages

Y: W152R, F157L, I210V, G257S, D339H, G446S, N460K, Q493 (reversion)

A: Monitoring an umbrella of SARS-CoV-2 lineages that have similar Spike protein profiles and characterised by a specific set of mutations (S: Q183E, S: F486P and S: F490S). For the full list of lineages, please look at the table here.

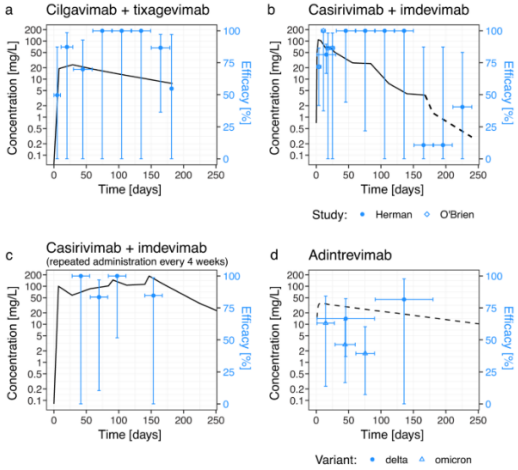

Figure 1: *Reported protection and antibody concentration from RCTs of monoclonal antibodies in preventing COVID-19.*

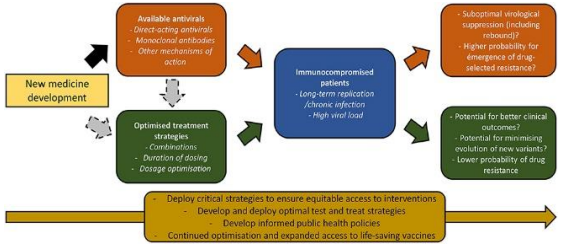

Figure 2: *Potential impact of SARS-CoV-2 antiviral drugs optimization in protecting available antivirals in the shifting landscape of new variants.*

B: Monitoring an umbrella of SARS-CoV-2 lineages that have similar Spike protein profiles and characterised by a specific set of mutations (S: F456L, S:

Q183E, S: F486P and S: F490S). For the full list of lineages, please look at the table here.

All sub-lineages of the listed lineages are also included in the variant

Variants under Monitoring

Reported protection and antibody concentration from RCTs of monoclonal antibodies in preventing COVID-19

Stadler et al. [14] searched MEDLINE, PubMed, Embase, and the Cochrane COVID-19 Study Register for randomized placebo-controlled trials of SARS-CoV-2-specific monoclonal antibodies (mAbs) used as pre-exposure and peri-exposure prophylaxis for COVID-19. They was included only studies where both protection from symptomatic infection and pharmacokinetic information of the monoclonal antibody were provided within the same study. They was identified six eligible studies assessing monoclonal antibodies as pre-exposure and peri-exposure prophylaxis for COVID-. The antibodies used in these studies were casirivimab/imdevimab (three studies), bamlanivimab, cilgavimab/tixagevimab, and adintrevimab. Omicron variants were the dominant circulating variants. One study assessed protection in two time periods; firstly in a pre-Omicron period when the Delta variant was the dominant circulating variant, and separately later when Omicron variants BA.1 and BA.1.1 were the dominant variants13. The overall efficacies against pre-Omicron variants in the included studies ranged from 68.6% to 92.4%. Stadler et al.was identified a trend for lower efficacies with increasing time since administration and against the escaped variant, the latter being reported previously by Schmidt et al. [15] (Figure. 1). Stadler,E.et al. Monoclonal antibody levels and protection from COVID-19. Nature Communications volume 14: 4545 (2023).The efficacy at each time interval is shown in blue (points indicate observed efficacy, horizontal error bars indicate time interval and vertical error bars represent 95% CIs of efficacy). The antibody concentration is shown in black. an Antibody concentration (n = 1776 individuals) and efficacy data (n = 5172 individuals) for cilgavimab/tixagevimab was extracted from Levin et al.13 b Single administration of casirivimab/imdevimab data are a combination of data from O'Brien et al.14 and Herman et al.15 who report on the same clinical trial over different follow-up intervals. Efficacy data were reported weekly over the first four weeks in O'Brien et al. (diamonds) (n = 1505), and monthly for eight months in Herman et al. (circles) (n = 1683). Antibody concentration data was reported up to day 168 in O'Brien et al. (solid line, b n = 12), and modelling of the pharmacokinetic profile of the antibody concentration, reported in Herman et al., was used to inform the antibody concentration between 168 and 240 days (dashed line, b). C Isa ET al.16 reported efficacy (n = 969) and in vivo concentration after repeated administration of 1.2 g of casirivimab/imdevimab every 4 weeks (n = 723). Hence, the antibody concentration did not decline as in the other studies. D The modeled concentration of adintrevimab after a single administration was extracted from the study by Schmidt ET al.12. The efficacy of adintrevimab was reported both when the delta variant was dominant (circles) (n = 1267) and when Omicron variants BA.1 and BA.1.1 were dominant (triangles) (n = 378).

Protecting Emerging Treatment Options

Several crucial issues warrant urgent attention to optimize the use of these emerging treatment options e (Figure 2). First, as proven to be transformational for HIV, rapid, affordable access to early antiviral treatment to slow the tide of new variants is critical to effective "test-and-treat" strategies to protect the most fragile patients and avoid a severe and/or persistent infection. After more than 2 years of pandemic, progress has been slow [17] and public health attention has recently been attracted by the low-profile agreement during the) in Geneva in May 2022. Together with vaccination, early diagnosis and treatment have the ability to reduce disease worsening, to reduce transmission and to constrain variability in viral sequences. Figure 2. Potential impact of SARS-CoV-2 antiviral drugs optimization in protecting available antivirals in the shifting landscape of new variants. Second, although the combined effect of omicron and increasing vaccine deployment in some regions has shifted the demand response from hospital to outpatient care, considerable uncertainty exists about who is now at risk for severe omicron disease [18]. While the risk/benefit ratio across at-risk subpopulations has unquestionably changed in vaccinated populations, gains made can only be preserved if those at highest risk are rapidly diagnosed and receive treatment in less than one week. Third, high levels of antiviral efficacy will be critically important, especially in immunocompromised patients who are grossly underrepresented in registration trials [19]. Causes of immunosuppression are diverse (including organ/stem cell transplants, cancer, immunosuppressive medications or uncontrolled HIV) and these patients represent a significant proportion of the population, e.g., 7 million adults in the USA [20] , but also in low- and middle-income countries due to the high prevalence of uncontrolled HIV. Overall, the mortality risk with omicron is still unclear, but protection of those who cannot be effectively vaccinated or protected by a prior SARS-CoV-2 infection remains imperative. Importantly, in

regions where HIV is highly prevalent, there is a clear need and opportunity to reinforce HIV epidemic control by prompt diagnosis and sustained viral suppression with antiretroviral, key factors to also enable the control of SARS COV-2 spread in this group.

Although there are many other causes for variant emergence (host jump or adaptation, vaccine exposure, to name the most frequent), data confirm that immunocompromised patients with long-term SARS-CoV-2 replication are particularly susceptible to resistance and transmissible variant emergence. The emergence of resistance mutation thus impacting treatment efficacy is more likely if a patient has been exposed to specific antiviral drugs. In addition, it remains unclear if the small percent rebound occurrence (2%) observed with nirmatrelvir/r in the EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) trial, performed in the delta variant era, is underestimating a risk that would be particularly of concern in patients harbouring an impaired immune system and in the omicron era. In one recent case series, one out of 7 patients who had a virologist rebound also had an immunosuppressing condition. Another recent case series revealed that all three patients with viral rebound were highly immunocompromised. This potentially raises concerns about the need of longer antiviral courses, especially in these patients. Preclinical data have clearly demonstrated that virological efficacy is higher for combinations of existing antiviral drugs than single agents. To achieve the goal of changing the treatment guidelines in SARS-CoV-2-infected immunocompromised individuals, independent and academic clinical trials for drug combinations should be considered as an urgent, unmet research priority. Today, collaboration with industry to allow early access to antiviral drugs to be combined has been an objective still to be achieved. Certain potent monoclonal antibodies, such as bebtelovimab, cannot even be accessed for research or for routine care outside of the USA [21].

Early Treatment Optimization

Treatment optimization has been truly transformational for other viral diseases [e.g., HIV/hepatitis C virus and was only achieved when antiviral drug combinations became the mainstay. With few drugs currently available, the opportunity must be seized prior to the emergence of resistance to drugs deployed widely as monotherapies. Combinations of polymerase inhibitors and polymerase/protease inhibitors have proven highly successful for other viruses and in animal models for SARS-CoV-2. Thus, as drugs that are appropriate to combine are available, there is no good reason not to study them clinically. In addition to the opportunities that combinations present for a more potent antiviral response (individual benefit), there can be no doubt that the rate at which resistance emerges will also be reduced (public health benefit). Higher potency will result in a lower variability in sequences through a lower degree of replication. In addition, the probability of the occurrence of multiple mutations to drive resistance to multiple antivirals simultaneously is much lower than for a single agent. This is particularly the case where concentrations achieved are close to the therapeutic efficacy threshold or in the case of low compliance. It is incumbent upon the international research community and the pharmaceutical industry to pool knowledge and provide the critical information that the World Health Organization and country-level authorities so urgently require, as well as early diagnosis and increased access to vaccines and antiviral therapy. The resistance risk for existing drugs has been woefully understudied throughout development, making it extremely challenging to rationalize during policy development. Looking beyond efficacy, drug combinations will unquestionably reduce the rate at which resistance and new variants impacting treatment options emerge and could be made available and accessible to those in need if timely efforts are made. In conclusion, we call for combination therapies to be tested in adequately powered clinical trials in the target population of immunocompromised patients, both in wealthy and in low-income countries where HIV-driven immunosuppression is prevalent. If higher efficacy is confirmed, the diversity of possible combinations will enable the tailoring of therapeutic options to individual patient needs (e.g., avoiding drug-drug interactions in transplant patients) as well as their specific regional context (e.g., oral-only combinations).

Does their use as a prophylactic or treatment potentially affect natural long-term immunity?

Considering the large doses used and the relative half-life of antibodies (~3 weeks for IgG molecules), there is a pertinent consideration whether the presence of circulating neutralizing mAbs could impact active immunity, whether through memory from infection or vaccination. From the collective clinical data with MAb114, REGN-EB3 and palivizumab, the general benefits and risks associated with neutralizing mAbs are similar to those observed with traditional passive immunization against infectious agents. The agents themselves are relatively tolerable for patients, efficacious during the early onset of disease symptoms and in certain cases as a prophylactic, but with limited efficacy once infections are severe. The distinctions between these therapies are largely logistical; CPT is

more rapidly implemented during an emerging pandemic when few therapeutic options are yet available, while neutralizing mAbs take time to discover and it takes time for regulatory approval for their use to be obtained as well as to scale up manufacturing capacity. The use and promise of passive immunization during the coronavirus outbreaks of the twenty-first century (that is, with SARS-CoV, Middle East respiratory syndrome-related coronavirus and SARS-CoV-2) have re-emphasized these past lessons while also highlighting additional insights, as we discuss next [22]. Fortunatly today, the process to mass-produce recombinant mAbs has become scalable to meet demand and is cost-competitive with other treatments. Neutralizing mAbs overcome limitations intrinsic (for example, the risk of blood-borne diseases, time to development of detectable high-affinity antibodies and risk of low antibody titres, as well as variable epitope specificity. Furthermore, a high titre of neutralizing antibodies — which current evidence indicates is necessary for the efficacy— is inherent with neutralizing mAbs. As of April 2021, at least 20 neutralizing mAb therapies were being tested in late-stage clinical trials or had already been approved for use in nine infectious diseases, including RSV infection and Ebola.

Association with Several SARS-CoV-2 Neutralizing Monoclonal Antibodies Therapies with Adverse Outcomes of COVID-19

Elsewhere in JAMA Network Open, Ambrose et al. [23-25]. evaluated the association of several SARS-CoV-2 neutralizing mAb therapies with adverse outcomes of COVID-19 in subpopulations at high risk of poor outcomes and across multiple variant epochs. A population of 167 183 patients met study inclusion criteria, of whom 25 241 (15.1%) received mAb treatment. All patients were nonhospitalized, had a EUA-defined risk factor for progression to severe disease, and received no other outpatient therapy for COVID-19. From November 2020 through January 2022, mAb treatment was associated with reductions in the odds of hospitalization of almost 50% and the odds of emergency department visits by 24% compared with no mAb treatment. The odds of 30-day all-cause death were reduced by 86% (OR, 0.14; 95% CI, 0.10-0.20). After adjusting for confounders, the number needed to treat (NNT) to prevent the composite outcome of hospitalization or death at 30 days was 42. This association was observed against a backdrop of remarkable safety, with only 0.2% of patients experiencing any kind of adverse event.The association of mAb therapy with improved outcomes was not uniform across all SARS-CoV-2 variants or across all patients. Patients who were unvaccinated or immunocompromised benefited the most from mAb therapy. The NNT to prevent 1 hospitalization at 14 days was 35 in the unvaccinated group and 17 in the immunocompromised group compared with 60 in the fully vaccinated group. In addition, the authors found that the mAb treatment effect size increased incrementally among patients with greater probability of poor outcomes (ie, those with multiple or more severe comorbidities). It is unclear whether any patient in the study received tixagevimab-cilgavimab for prevention of COVID-19; however, this long-acting mAb combination was granted EUA in early December 2021 and was not widely distributed until February 2022. Therefore, it is unlikely that its use substantially overlapped with the study period. Regardless, the authors' findings are consistent with most other studies of COVID-19 therapies wherein patients who were seronegative at baseline were more likely to progress to severe disease and benefit from treatment. For immunocompromised individuals, the safety and efficacy of mAbs are especially notable because many of these patients have drug interactions or contraindications to other recommended outpatient COVID-19 therapies.5 unfortunately, at the time of publication, there are no mAb therapies available for the treatment or prevention of COVID-19. All EUAs were revoked or paused due to the emergence of substantial in vitro drug resistance among currently circulating SARS-CoV-2 variants.

The question of whether in vitro potency directly correlates with clinical efficacy remains unanswered. In the absence of clinical data, regulatory bodies had to make decisions to offer or withdraw therapies relying on laboratory data alone. For example, the EUAs for both bamlanivimab-etesevimab and casirivimab-imdevimab were revoked on January 26, 2022, due to inability to neutralize Omicron variants. Intriguingly, Ambrose et al4 found that casirivimab-imdevimab was associated with decreases in 14-day hospitalization (OR, 0.05; 95% CI, 0.01-0.42) in a small sample of 115 patients infected with sequence-confirmed Omicron BA.1 despite the significantly reduced in vitro neutralizing ability of this mAb against this variant. Only 7.6% of patients received sotrovimab (which was expected to retain in vitro neutralization against early Omicron variants) despite approximately 25% of the patients being diagnosed in the Omicron era. When the Omicron-era analysis was limited to patients who received sotrovimab, the treatment was associated with significant reductions in the odds of death within 30 days (bamlanivimab-etesevimab and casirivimab-imdevimab were not).What should clinicians and researchers do with these results, which describe 14 months of safe and effective therapy that is no longer

available? Monoclonal antibodies provide important lessons that inform our future research and practice. First is the salient reminder to evaluate both the relative and absolute treatment effects when allocating scarce health care resources and/or determining the economic value of any given treatment. For instance, while the relative odds of 14-day hospitalization were exactly 49% lower in both unvaccinated and fully vaccinated groups, the NNT was notably smaller and more impactful in the unvaccinated group (NNTs of 35 vs 60, respectively).

Table 1: *Overview of randomized control trials of monoclonal antibodies as pre- and post-exposure prophylaxis for COVID-19 in immunocompromised populations.*

Study	Regimen	Study population	Study period and/or variants of concern	Study design	Efficacy outcomes	Safety outcomes
Preventative studies						
Cohen et al. [10] BLAZE	Bamlanivimab Single IV infusion of Bamlanivimab 4200 mg (N = 588) or placebo (N = 587)	Unvaccinated residents and staff of 74 skilled nursing and assisted living facilities in the US w/ at least one confirmed SARS-CoV-2 index case	August 2 to November 20, 2020	RCT double-blind, placebo-controlled, single-dose phase III trial	Bamlanivimab reduced incidence of COVID-19 vs placebo (8.5% vs 15.2%; *P* <0.001; ARD, -6.6% [95% CI, -10.7 to -2.6])	AEs: 20.1% (bamlanivimab) vs 18.9% (placebo) Most common AEs: urinary tract infection (2% bamlanivimab vs 2.4% placebo); hypertension (1.2% bamlanivimab vs 1.7% placebo) Five deaths in placebo arm
Levin et al. [11] PROVENT	Tixagevimab plus cilgavimab (AZD7442) Single 300-mg AZD7442 dose (two intramuscular injection, 150 mg each of tixagevimab and cilgavimab)	Unvaccinated adults without prior SARS-CoV-2 infection	Nov 2020 to May 2021	2:1 RCT, double-blind, placebo-controlled, phase III trial	AZD7442 reduced risk of symptomatic COVID-19 by 77% (95% CI 46.0, 90.0) vs placebo (*P* <0.001). Incidence of infection = 0.2%	AEs: 35% (AZD7442); 34% (placebo). One case of severe/critical COVID-19; and two COVID-19-related deaths w/ placebo arm

	AZD7442 (N = 3460) placebo (N = 1737)					
Levin et al. [12] STORM CHASER	Tixagevimab plus cilgavimab (AZD7442) 1121 participants (AZD7442, single 300 mg dose, N = 749; placebo, N = 372)	Participants ≥18 with potential exposure within 8 days to a symptomatic or asymptomatic individual with confirmed SARS-CoV-2 and who were at risk of developing COVID-19 Nine (0.8%) were on immune-suppressive treatment	December 02, 2020 and March 19, 2021	RCT, phase III, double-blind, placebo-controlled, multi-center study	Symptomatic COVID-19 occurred in 23/749 (3.1%) and 17/372 (4.6%) (AZD7442 and placebo, respectively) (RRR, 33.3%; 95% CI, -25.9 to 64.7; *P* = 0.21)	AEs: 162/749 (21.6%) and 111/372 (29.8%) (AZD7442 and placebo, respectively), mostly mild/moderate No deaths related to the study intervention
O'Brien et al. [13] REGEN-COV	Casirivimab plus imdevimab Patients randomized 1:1 to 1200 mg subcutaneous injection casirivimab and imdevimab (N = 753) or placebo (N = 752)	Unvaccinated, asymptomatic, healthy adolescents and adults who were contacts of a person w/ SARS-CoV-2 w/ no prior positive SARS-CoV-2 reverse transcription-polymerase chain reaction test or positive SARS CoV-2 serology test before screening	January 28 to March 11, 2021	Two-part RCT, double-blind, placebo-controlled, phase III 112 sites in US, Romania, Moldova	SARS-CoV-2 developed in 11/753 (1.5%) in casirivimab plus imdevimab group vs 59/752 (7.8%) in placebo (RRR [1 minus the relative risk], 81.4%; *P* <0.001) Casirivimab plus imdevimab prevented symptomatic/asymptomatic infections (RRR, 66.4%) Median time of symptom resolution (casirivimab plus imdevimab (1.2 weeks) vs placebo (3.2 weeks) REGEN-COV reduced the	20.2% participants in the REGEN-COV group and 29.0% in placebo group had at least one AE, and 16.0% and 16.5%, respectively, had non-COVID-19 AEs

					duration of symptomatic disease and the duration of a high viral load During the 8-month assessment period there were zero hospitalizations for COVID-19 in the REGEN-COV group and 6 in the placebo group No dose-limiting toxic effects of casirivimab plus imdevimab.	
Treatment studies						
Montgomery et al. [12] TACKLE	Tixagevimab plus cilgavimab	Non-hospitalized, unvaccinated ≥18 w/ COVID-19	January to July 2021	RCT, double-blind, placebo-controlled, phase 3 910 patients randomly (1:1) assigned to tixagevimab + cilgavimab (600 mg, N = 456) or placebo (N = 454) within 7 days of symptoms 95 sites in US, Latin America, Europe, Japan	Severe COVID-19/death: 4% (18/407) for tixagevimab plus cilgavimab vs 9% (37/415) for placebo (RRR 50.5%) COVID-19 deaths: tixagevimab plus cilgavimab (N = 3) placebo (N = 6)	AEs: mild to moderate (29%) tixagevimab plus cilgavimab group vs 36% w/ placebo
Dougan et al. [14]	Bamlanivimab plus etesevimab Single IV dose of either a combination agent (2800 mg of bamlanivimab and 2800 mg of etesevimab, administered together, N = 518) or placebo (N = 517) within	Ambulatory patients w/ mild or moderate COVID-19 and at high risk for progression to severe disease Vaccinated participants were allowed in the study	September 04, 2020 to December 08, 2020	RCT, double-blind, placebo-controlled, phase III	By day 29, 11/518 patients (2.1%) in bamlanivimab-etesevimab arm had a COVID-19-related hospitalization or death from any cause, vs 36/517 (7.0%) placebo arm (ARD, -4.8% points; 95% CI, -7.4 to -2.3; RRD, 70%; *P* <0.001) At day 7, greater reduction from baseline in the log viral load observed among bamlanivimab plus etesevimab vs placebo arm	Serious AEs occurred in 1.4% in the bamlanivimab-etesevimab group and in 1.0% patients in the placebo group

	three days after a laboratory diagnosis of severe SARS-CoV-2 infection				(difference from placebo in the change from baseline, -1.20; 95% CI, -1.46 to -0.94; *P* <0.001) No deaths w/ bamlanivimab-etesevimab vs 10 in the placebo	
Gupta et al. [15]	Sotrovimab 583 patients (291 sotrovimab; 292 placebo) Single IV infusion of sotrovimab (500 mg)	Non-hospitalized unvaccinated patients w/ symptomatic COVID-19 w/ at least one risk factor for disease progression.	August 27, 2020 to March 04, 2021	RCT, double-blind, placebo-controlled, phase III, multicenter trial	Three (1%) sotrovimab vs 21 (7%) placebo, had disease progression leading to hospitalization or death (RRR, 85%; 97.24% CI, 44 to 96; *P* = 0.002). Intensive care unit: (five placebo) including one who died by day 29	AEs: 17% sotrovimab and 19% placebo. Serious AEs less common w/ sotrovimab than w/ placebo (2% vs 6%)
Recovery Collaborative Group RECOVERY [16]	Casirivimab and imdevimab Usual standard of care alone (N = 4946) or usual care plus casirivimab and imdevimab (4 g each; N = 4839) administered together IV	Any patient aged at least 12 admitted to hospital w/ clinically suspected or laboratory-confirmed SARS-CoV-2 infection 812 (8%) patients were known to have received at least one dose of a SARS-CoV-2 vaccine.	September 18, 2020 to May 22, 2021	RCT, open-label platform trial comparing possible treatments w/ usual care in patients admitted to hospital w/ COVID-19	Seronegative: 396/1633 (24%) casirivimab and imdevimab vs 452/1520 (30%) usual care died within 28 days (RR: 0.79, 95% CI 0.69-0.91; *P* = 0.0009) Randomly assigned: 943/4839 (19%) casirivimab and imdevimab vs 1029/4946 (21%) usual care died within 28 days (RR 0.94, 95% CI 0.86-1.02; *P* = 0.14)	Serious AEs reported in seven (<1%) participants were believed to be related to treatment w/ casirivimab and imdevimab

Table 2: *Overview of real-world evidence of monoclonal antibodies as pre- and post-exposure prophylactics for COVID-19 in immunocompromised populations.*

Study	Regimen	Study population	Study period and/or variants of concern	Study design	Outcomes
Tixagevimab plus cilgavimab					
Conte WL, 2022	Tixagevimab plus cilgavimab	Vaccinated MS patients exposed to B-cell depleters	N.D.	Single-center cohort (N = 18)	Prior to AZD7442 mean antibody level was 12.38 U/ml, 66% of

[17]	150 mg (tixagevimab and cilgavimab) IM	during vaccination		Study completed prior to US Food and Drug Administration's update to 300 mg each of tixagevimab and cilgavimab	patients had undetectable antibody levels (<0.8 U/ml). Two weeks post-AZD7442, all patients had antibody levels >250 U/ml, which were significantly higher than pre-AZD4772 levels (P = 0.001)
Stuver et al. [18]	Tixagevimab plus cilgavimab (AZD7442) AZD7442 initially as 150 mg. Patients subsequently received either a second 150 mg dose or 300 mg in those without prior treatment	Adult vaccinated patients w/ hematologic malignancies	Late 2021, before Omicron (B.1.1.529)	Prospective observational study	Five patients (second 150 mg dose) and five patients (300 mg dose) achieved significantly higher neutralization of Omicron (P = 0.003) vs single 150 mg. 9/10 patients achieved neutralizing capacity above the positive cut-off value. Two (3.8%) patients who received a single 150 mg dose developed COVID-19.
Benotmane I, et al., 2022 [19]	Tixagevimab plus cilgavimab IM gluteal injections of 150 mg tixagevimab and 150 mg cilgavimab	Vaccinated KTR	December 2021 Omicron variants BA.1, BA.1.1, and BA.2	Case series of 416 KTR	39 (9.4%) developed COVID-19; 14 (35.9%) were hospitalized; three (7.7%) transferred to ICU; and two (5.1%) died. Omicron variants BA.1, BA.1.1, and BA.2 responsible for five, nine, and one of cases, respectively. Serum viral neutralizing activity against BA.1 negative among 12 tested patients.
Benotmane I, et al., 2022 [20]	Tixagevimab plus cilgavimab Tixagevimab (150 mg) plus cilgavimab (150 mg) for preexposure prophylaxis	Vaccinated KTR	Omicron BA.2 wave	Single-center cohort of KTR (N = 98)	Anti-SARS-CoV-2 antibody titers peaked 30 days after AZD7442, then declined significantly at 4-5 months. 74% patients had antibody titers <2500 BAU/ml after median of 117 days.
Kaminski	Tixagevimab plus	Vaccinated KTR w/ no	December 28,	Retrospective study of KTR	AZD7442 group significantly

et al. [21]	cilgavimab (AZD7442)	humoral response after ≥3 doses COVID-19 vaccine	2021 to February 28, 2022 Omicron wave	(N = 430) Received AZD7442 (tixagevimab plus cilgavimab) 300 mg (N = 333) or did not (N = 97)	lower risk of symptomatic COVID-19 (12.3% vs 43.3%) (*P* < 0.001), hospitalizations (1.2% vs 11.3%) (*P* < 0.001), or ICU (0.3% vs 2%) (*P* <0.001) vs non-AZD7442 group. Deaths: (0.3% AZD7442 vs 2% non-AZD7442) from COVID-19 acute respiratory distress syndrome (HR, 0.076; 95% CI, 0.005-1.161; *P* = 0.066).
Nguyen Y, et al, 2022 [22]	Tixagevimab plus cilgavimab Patients received tixagevimab plus cilgavimab 150/150 mg IM	Immunocompromised vaccinated individuals	December 28, 2021 to March 31, 2022	Observational multicenter cohort study Immune-compromised individuals (N = 1112) w/ no humoral responses after ≥3 doses of COVID-19 vaccine	88% had mild to moderate COVID-19, 4% died. Almost no individuals receiving early treatment progressed to moderate-to-severe COVID-19. COVID-19 incidence rate lower in study population than general population during the study period.
Kertes J., et al., 2022 [23]	Tixagevimab plus cilgavimab (AZD7442) 825 administered AZD7442, 4299 ICIs not administered AZD7442	Immunocompromised vaccinated individuals	December 2021 to April 2022. Fifth Omicron-dominated wave of COVID-19	Retrospective observational study Evaluation of AZD7442, SARS-CoV-2, and severe disease (hospitalization and all-cause mortality) among selected immune-compromised individuals	COVID-19 infections: 29 (3.5%) treated w/ AZD7442 vs 308 (7.2%) non-AZD7442 (*P* < 0.001). Hospitalizations: one (0.1%) AZD7442 vs 27 (0.6%) in non-AZD7442 group (*P* = 0.07). Deaths: zero AZD7442 group vs 40 (0.9%) in non-AZD7442 group (*P* = 0.005). AZD7442 group 92% less likely to be hospitalized/die than non-AZD7442 group (OR: 0.08, 95% CI: 0.01-0.54).
Al Jurdi et al. [24]	Tixagevimab plus cilgavimab	SOTR	December 28, 2021 to April 13, 2022 Omicron	Retrospective cohort comparing (N = 222) SOTR receiving tixagevimab plus cilgavimab for	Breakthrough infections: 11 (5%) of SOTR tixagevimab plus cilgavimab group vs 32 (14%) in

				pre-exposure prophylaxis and (N = 222) vaccine matched SOTR who did not	control (*P* <0.001). 150-150 mg vs 300 mg higher incidence of breakthrough infections (*P* = 0.025). Safety outcomes: nine (4%) in treated SOTRs; nausea, vomiting, or diarrhea (N = 4, 1.8%), headache (N = 3, 1.4%), and abdominal pain (N = 2, 0.9%). One (0.5%) experienced mild heart failure exacerbation, and one (0.5%) developed new atrial fibrillation requiring cardioversion.
Aqeel F and Geetha D, 2022 [25]	Tixagevimab plus cilgavimab 600 mg Evusheld (300 mg tixagevimab-300 mg cilgavimab), and 300 mg (150 mg tixagevimab-150 mg cilgavimab)	Antineutrophil cytoplasmic antibody vasculitis patients	December 2021 to June 2022	Retrospective study 21 (100%) vaccinated, 95% had a booster 20 (95%) received Evusheld and one (4.7%) received tixagevimab- cilgavimab	COVID-19 infection: 1 (4.7%), 122 days after Tixagevimab plus cilgavimab (300 mg). Nine patients received rituximab after Tixagevimab plus cilgavimab. Breakthrough COVID-19: 3 (15%) in 600 mg group. Mean (± SD) time to COVID-19 onset: Tixagevimab plus cilgavimab 98.6 (± 36.5) days; rituximab use to Tixagevimab plus cilgavimab 141 (± 64) days. All infections were mild and did not require hospitalization.
Karaba AH, et al., 2022 [26]	Tixagevimab plus cilgavimab 300 + 300 mg tixagevimab plus cilgavimab (either single dose or two 150 + 150 mg doses)	Vaccinated SOTR	January 10, 2022 to April 4, 2022 Omicron BA.1 and BA.2	Prospective observational cohort submitted pre- and post-injection samples	Vaccine strain neutralization increased from 46-100% post-tixagevimab plus cilgavimab (*P* <0.001). BA.1 neutralization was low (8-16% of participants post-

					tixagevimab plus cilgavimab, *P* = 0.06). BA.2 neutralization increased from 7-72% of participants post-tixagevimab plus cilgavimab (*P* < 0.001).
Kleiboeker HL, et al., 2022 [27]	Tixagevimab plus cilgavimab	SOTR	January 11, 2022 to May 1, 2022	SOT recipients were screened for receipt of tixagevimab/cilgavimab w/subsequent new onset of myalgia Patients were excluded if another cause of myalgia was identified	76.7% RRR (*P* <0.001) of symptomatic COVID-19, improved to 82.8% at extended follow-up 35.3% reported 1+ mild-to-moderate AE; injection-site reaction was most common. Four experienced musculoskeletal and connective tissue disorders. Three cases of significant myalgia after receiving tixagevimab plus cilgavimab.
Young-Xu Y., et al., 2022 [28]	Tixagevimab plus cilgavimab	Veterans ≥18 as of January 01, 2022, receiving VA healthcare, 92% immune-compromised; predominately vaccinated	January 23, 2022 to April 30, 2022 Omicron and Delta	Retrospective cohort study w/ propensity matching and difference-in-difference analyses 1733 recipients of tixagevimab/cilgavimab and 6354 control patients who were immunocompromised or otherwise at high risk	Compared to propensity-matched controls, tixagevimab plus cilgavimab-treated patients had a lower incidence of: SARS-CoV-2 infection (HR 0.34; 95% CI, 0.13-0.87); COVID-19 hospitalization (HR 0.13; 95% CI, 0.02-0.99); and All-cause mortality (HR 0.36; 95% CI, 0.18-0.73).
Vellas C., et al., 2022 [29]	Tixagevimab plus cilgavimab Single IV infusion of tixagevimab plus cilgavimab (300 mg/300 mg)	Ambulatory patients, 11 immunocompromised individuals—SOTRs that were infected w/ BA.2 subvariant	March to May 2022	18 NP samples from those given a single IV infusion of tixagevimab plus cilgavimab	Median SARS-CoV-2 NP virus load decreased from 5.8 (IQR, 5.3-6.5) log10 copies/ml before infusion to 4.5 (IQR, 3.8-5.7) log10 copies/ml 7 days post-infusion (*P* = 0.04). Resistance-associated mutations in spike protein (positions 444, 346 and 452) in 8/11 (73%), 7-14 days post-infusion.

					Decreased virus load (1.3 log10 copies /ml) observed 7 days after tixagevimab plus cilgavimab, compared to 10 untreated immunocompromised Alpha-infected patients (2.5 log10 copies/ml).
Sotrovimab					
Calderón-Parra et al. [30]	Sotrovimab	Presence of any immune-compromising condition	October 2021 to December 2021 Predominantly Delta	Retrospective multicenter cohort including immune-compromised hospitalized patients (N = 32) w/ severe COVID-19 treated w/ sotrovimab	Seven (21.9%) respiratory progression: 12.5% died; 9.4% required mechanical ventilation Anti-spike antibodies undetectable in 91%, 20/22 w/ available serology at baseline testing. Patients treated within the first 14 days of symptoms had lower progression rate: 12.0% vs 57.1%, *P* = 0.029. Safety Outcomes: No AE attributed to sotrovimab.
Aggarwal et al. [31]	Sotrovimab	Non-hospitalized adult patients with SARS-CoV-2 Omicron variant infection	From December 26, 2021 to March 10, 2022 Omicron BA.1 or BA.1.1	Observational cohort study Patients who were untreated (N = 3663) or who were treated with sotrovimab (N = 1542)	Sotrovimab did not reduce odds of 28-day hospitalization 39 (2.5%) vs 116 (3.2%) aOR, 0.82; 95% CI: 0.55-1.19 or mortality (0.1% vs 0.2%; aOR, 0.62; 95% CI: 0.07-2.78). Observed treatment OR was higher during Omicron than during Delta (OR 0.85 vs 0.39, respectively; *P* = 0.053).
Woo et al. [32]	Sotrovimab	Hospitalized COVID-19 patients at risk of disease progression	Between December 2021 and June 2022 Omicron BA.1, BA.2, BA.4/5	Retrospective cohort study, N = 1254 Received sotrovimab alone (N = 147),	Sotrovimab alone or in combination with remdesivir did not decrease in-hospital mortality compared to control groups. Mortality:

				Combination treatment with sotrovimab and remdesivir (N = 38)	Normal ward sotrovimab (6.7% [N = 4] vs 2.8% [N = 10]; *P* = 0.11); Sotrovimab and remdesivir (4.5% [N = 1] vs 3.0% [N = 4]; *P* = 0.72). ICU: Sotrovimab (41.4% [N = 36] vs 27.6% [N = 24]; *P* = 0.09); Sotrovimab and remdesivir (31.2% [N = 5] vs 32.3% [N = 31]; *P* = 0.91).
Other regimens					
Bruel et al. [33]	Bamlanivimab, etesevimab, casirivimab, sotrovimab, adintrevimab, regdanvimab and tixagevimab	Immunocompromised	Measured serum against: Delta, Omicron; Breakthrough infections: Omicron	Study compared the sensitivity of Delta and Omicron BA.1 and BA.2 neutralization by nine therapeutic monoclonal antibodies	Seven mAbs (bamlanivimab, etesevimab, casirivimab, sotrovimab, adintrevimab, regdanvimab and tixagevimab) were inactive against BA.2. Two mAbs (imdevimab and cilgavimab) showed IC50 of 693 ng/ml and 9 ng/ml against BA.2. Tixagevimab plus cilgavimab was not more efficient than cilgavimab alone.
Bruel et al. [33]	Cilgavimab, tixagevimab, bebtelovimab, sotrovimab, casirivimab, and imdevimab	Vaccinated immune-compromised individuals	Delta, BA.2, BA.4, and BA.5	Analyzed 121 sera from 40 immunocompromised individuals up to 6 months after imdevimab+ casirivimab or cilgavimab+ tixagevimab	The IC50 of 4/6 mAbs (sotrovimab, tixagevimab, casirivimab, and imdevimab) higher for BA.4/BA.5 vs Delta Sotrovimab was 15-/17-fold less potent against BA.4 and BA.5 vs Delta. Imdevimab more potent than sotrovimab against BA.4 and BA.5 (IC50 of 265 and 996 ng/mL for BA.4 and 208 and 1088 ng/mL for BA.5). Cilgavimab and bebtelovimab

					no/minimal changes w/ Delta; remained highly potent against BA.4 and BA.5. BA.2 vs BA.4/BA.5 slightly improved neutralization by imdevimab (4.2- and 5.3-fold) and sotrovimab (9- and 8.3-fold) compared to other mAbs Cilgavimab+ tixagevimab and imdevimab+ casirivimab displayed a drop in potency compared w/ Delta, which was less marked for cilgavimab+ tixagevimab (BA.4: 10.4-fold and BA.5: 9-fold) vs imdevimab+ casirivimab (BA.4: 330-fold and BA.5: 350-fold).
Lafont E, et al., 2022 [34]	Remdesivir, Sotrovimab, Tixagevimab plus cilgavimab, and Casirivimab plus imdevimab	Immunocompromised w/ laboratory-confirmed COVID-19	December 2021 and March 2022	Single-centre retrospective case series of 67 immunocompromised patients w/COVID-19 Targeted treatment; IV remdesivir (N = 22), sotrovimab (N = 16), tixagevimab plus cilgavimab (N = 13) and casirivimab plus imdevimab (N =1), no treatment (N = 10).	No treatment group (N=10) (15%) presented severe COVID-19 and 2 (3%) died from Omicron COVID-19. Death rate significantly lower in treated patients (N = 0 [0%] vs N = 2 [20%]); *P* = 0.034]. 6/15 patients on tixagevimab plus cilgavimab, received an additional curative treatment. None died from COVID-19. Safety outcomes: No severe AEs reported.
Bertrand D, et al., 2022 [35]	Tixagevimab plus cilgavimab and casirivimab plus imdevimab	Vaccinated KTR	December 23, 2021 to March 7, 2022 Omicron outbreak	Outcomes based on immunization status (all subjects previously vaccinated w/ three or more messenger RNA doses; Group II and III considered ‘unprotected’ based on antibodies below 264	113 (13.1%) got Omicron, 85 were symptomatic 21 patients hospitalized, eight ICU, and five died of COVID-19. End of 80 days, symptomatic

			BA1 variant was predominant, until February 14, 2022, and then BA2 became predominant	BAU/ml at least 1 month after last injection): Group I: vaccine-induced immunization, (N = 288); Group II: passive immunization w/ tixagevimab plus cilgavimab, (N = 412) (vaccinated). Group III: insufficient immunization (N = 160), 62 received casirivimab-imdevimab	infection, hospitalization, ICU, and COVID-19 death significantly higher in group III vs group II (8 vs 103). Group II had outcomes like group I, but significantly fewer infections (both severe and non-severe), compared to unprotected KTRs.
Woopen C, et al., 2022 [36]	Casirivimab plus imdevimab, sotrovimab, and tixagevimab plus cilgavmab	Vaccinated MS patients	February to June 2022 Omicron	Six patients on treatment w/ sphingosine-1-phosphate receptor modulators who failed to develop antibodies and T-cells after three doses	One got asymptomatic COVID-19 Sotrovimab, vs casirivmab plus imdevimab, and tixagevimab demonstrated best neutralizing capacity. Safety outcomes: No severe AEs recorded
Lombardi AV, et al., 2023 [37]	Tixagevimab plus cilgavimab, Casirivimab plus imdevimab, Bamlanivimab plus Etesevimab, and sotrovimab	Immunocompromised patients w/ COVID-19 diagnosis	August 28 to October 15, 2022 Omicron BA.4 and BA.5	Two groups given early treatment (tixagevimab plus cilgavimab vs other mAbs) compared for hospitalization/ mortality within 14 days from administration Early treatment w/ tixagevimab plus cilgavimab (19 immunocompromised patients); 89 patients received other mAbs	One patient (5.3%) tixagevimab plus cilgavimab admitted to emergency room within first 14 days of treatment and died; three patients (3.4%) from mAbs group admitted and one patient (1.1%) died. COVID-19 negative status 14 days since treatment: 36/89 (40.4%) other mAbs and 5/19 (26.3%) tixagevimab plus cilgavimab group (P = 0.088).
Evans et al. [38]	Molnupiravir, Nirmatrelvir-Ritonavir, and sotrovimab	Adult vaccinated patients with COVID-19 at higher risk of hospitalization and death	Between December 16, 2021 and April 22, 2022	Retrospective cohort study in Wales Total participants, N = 7013	628 (9.0%) total hospitalizations or deaths within 28 days of positive test, 84 (4.1%) in treated and 544 (10.9%) in untreated participants.

			Omicron BA.1 and BA.2	Untreated, N = 4973 Received sotrovamib, N = 1079, 52.9%; Molnupiravir, N = 359, 17.6%; Nirmatrelvir-Ritonavir, N = 602, 29.5%	Lower risk of hospitalization or death within 28 days in treated participants compared to untreated. Estimated HR, 35%; 95% CI: 18-49% lower in treated than untreated after adjusting for confounders. Event rates were 3.9% (14/359); adjusted HR, 0.49; 95% CI: 0.29-0.83 for molnupiravir, 2.8% (17/602); adjusted HR, 0.59; 95% CI: 0.36-0.97 for nirmatrelvir-ritonavir, and 4.9% (53/1079); adjusted HR, 0.73; 95% CI: 0.55-0.98 for sotrovimab. No indication of superiority of one treatment over another.
Sridhara S, et al., 2023 [39]	Bebtelovimab	Adult COVID-19 high-risk patients	Between 4/5/2022 and 8/1/2022 BA.2, BA.2.12.1, and BA.5	Observational retrospective cohort study COVID-19 infected patients who received bebtelovimab (N = 1,091) compared to propensity score matched control (N = 1,091)	All-cause hospitalizations in bebtelovimab cohort (2.2%; 95% CI, 1.4-3.3%) vs (2.5%; 95% CI, 1.6-3.6%); *P* = 0.77. All-cause mortality in bebtelovimab cohort 0% (95% CI, 0-0%) vs 0.3% (95% CI, 0.1-0.8%); *P* = 0.25. Bebtelovimab use lacked efficacy in patients with BA.2, BA.2.12.1, and BA.5. Bebtelovimab use not associated with lower hazards of composite outcome (HR 0.75; 95% CI, 0.43-1.31, P = 0.31).
Nevola R, et al., 2023 [40]	Casirivimab/imdevimab (1200/1200 mg) sotrivimab (500 mg)	Frail COVID-19 vaccinated/unvaccinated patients referred by primary care physicians for mAb treatment	From July 2021 to May 15, 2022 B.1.617.2	Prospective study N = 1026 60.2% received	60-day overall mortality, 2.14% Mortality: casirivimab/imdevimab 12/618,

		78.1% vaccinated	Omicron B.1.1	casirivamab/imdevimab and 39.8% sotrivimab	1.94%, sotrovimab 10/437, 2.28%; *P* = 0.582. No significant difference between two regimens in need for hospitalization (*P* = 0.345) and reduction in nasopharyngeal swab negative days (*P* = 0.999). A significantly lower need for O_2 administration observed in sotrovimab group (*P* < 0.005). Safety outcomes: Mild, short-lived side effects in 11/618 (1.18%) patients in casirivimab-imdevimab group, 8/408 (1.96%) patients in sotrovimab group. No significant difference in type of side effects between two treatment regimens.

Variants of Interest (VOI)

WHO label	**Lineage + additional mutations**	**Country first detected (community)**	**Spike mutations of interest**	**Year and month first detected**	**Impact on transmissibility**	**Impact on immunity**	**Impact on severity**	**Transmission in EU/EEA**
Omicron	BA.2.75 (x)	India	(y)	May 2022	Unclear (1)	Similar to Baseline (2-4)	No evidence	Community
Omicron	XBB.1.5-like (a)	United States	N460K, S486P, F490S	n/a	Baseline (5, 6)	Baseline (v) (5, 7)	Baseline (8)	Community
Omicron	XBB.1.5-like + F456L (b) (e.g. **EG.5, FL.1.5.1, XBB.1.16.6**,	n/a	**F456L**, N460K, S486P, F490S	n/a	Similar to Baseline	Increased (9)	Similar to Baseline	Community

	and **FE.1**)							

Variants under monitoring

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Transmission in EU/EEA
Omicron	XBB.1.16	n/a	E180V, T478R, F486P	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	BA.2.86	n/a	I332V, D339H, R403K, V445H, G446S, N450D, L452W, N481K, 483del, E484K, F486P	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	DV.7.1	n/a	K444T, L452R, L455F	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	XBB.1.5-like + L455F + F456L (b)	n/a	**L455F**, **F456L**, N460K, S486P, F490S	n/a	No evidence	No evidence	No evidence	Detected (a)

The second lesson is that the magnitude of a treatment's effectiveness may change over time if the disease evolves. As Ambrose et al. astutely comment, if severe disease and death decrease substantially between initial and later cases, treatments will have reduced effectiveness in preventing the same outcomes. For example, sotrovimab was associated with significant decreases in the odds of death within 30 days, but its NNT had increased to 666 by the Omicron era. Third, effective treatments are only effective if they can be readily administered to patients. Early in the pandemic, the outpatient infrastructure of US health care systems was not prepared or equipped to operationalize the rapid administration of intravenous infusions to highly contagious patients after diagnosis. Establishing processes to deliver mAb treatment was challenging, but the reward was great. Future investment in these therapies is even more important now that the infrastructure is in place to deliver them. Fourth, mAb therapies highlighted the importance of rapid diagnostic and/or point-of-care testing. Patients with symptoms needed quick access to SARS-CoV-2 testing with rapid turnaround times. Because real-time variant sequencing was not available in the clinical setting, clinicians had to make challenging decisions about whether to continue providing mAbs for treatment based on forecasting per geographic region. With point-of-care precision testing, more treatments could have been administered for longer periods, which is particularly important during times of scarce resources. While ethical allocation of scarce resources is challenging on many levels, it does bring into focus the fifth important lesson of mAb therapy: using risk-stratification strategies to optimize patient outcomes. These data from Ambrose et al further confirm that not all risk of COVID-19 progression is equal. Understanding this risk, ideally to the point of knowing patient-specific baseline immunity, would facilitate precision medicine and would be the gold standard for deploying optimal, equitable, and value-based care. Ambrose and colleagues found that mAb therapy allowed us to consistently keep patients out of the hospital and alive. Acknowledging that mAb development and implementation seems like a constant race against the clock, scientists and manufacturers will

need incentives to produce safe and effective therapies that are at risk of becoming obsolete. Authorizations for use of these therapies should focus on the patients most likely to benefit. Systematic efforts should continue to focus on both clinical and implementation science to capture clinical practice results as expeditiously as possible, which will allow us to effectively adapt to an ever-changing landscape

Effectiveness of monoclonal antibodies against covid variants

The FDA has provisionally approved the following for the treatment and/or prevention of COVID-19:

Monoclonal antibodies that target the sars-cov-2 spike protein

- Casirivimab plus imdevimab (RONAPREVE)
- Regdanvimab (REGKIRONA)
- Sotrovimab (XEVUDY)
- Tixagevimab and cilgavimab (EVUSHELD)

Immune modulating monoclonal antibodies

- Tocilizumab (ACTEMRA)

Non monoclonal antibody antiviral agents used in the treatment of COVID 19

- Nirmatrelvir-ritonavir (PAXLOVID)
- Molnupiravir (LAGEVRIO)
- Remdesivir (VEKLURY)

Monoclonal antibodies targeting the SARS-CoV-2 spike protein had shown clinical benefits against COVID-19 caused by variants predominant during the earlier stages of the pandemic. These antibodies are designed to neutralise the virus by binding to the spike protein on its surface. However, emerging data show that anti-spike protein monoclonal antibodies demonstrate a significant decrease in their in-vitro neutralising activities against many newer circulating SARS-CoV-2 variants, particularly Omicron and its sub variants. While there are few published clinical trials on the effectiveness of these monoclonal antibodies against clinical disease caused by these newer variants, it is expected that these mAbs will not provide clinical benefit in those people infected with the newer variants. The activity of the monoclonal antibody tocilizumab is not reduced against variants as this antibody does not target the virus but acts as a modulator of the immune response. Non monoclonal antibody antiviral treatments such as nirmatrelvir/ritonavir (PAXLOVID), molnupiravir (LAGEVRIO) and remdesivir (VEKLURY), which have different mechanisms of action, are likely to retain their activity against the emerging strains. In the word, the situation continues to evolve, with the epidemiology of circulating variants changing regularly. The characteristics of the circulating SARS-CoV-2 viruses should be considered when prescribing monoclonal antibodies for prevention or treatment of COVID-19. Healthcare professionals will need to consider alternative treatments as appropriate. At this stage, the regulatory status of the products remain unchanged in the word. The FDA and its counterparts will continue to monitor the efficacy and safety of all COVID-19 medicines. Potential updates to the Product Information for individual monoclonal antibodies will be published (if required) as they become available.

Conclusion

Vaccination has provided a high level of population immunity to COVID-19. However, there remain a number of subgroups in which vaccination is either not possible or ineffective (largely due to immunodeficiency).The use of monoclonal antibodies for prophylaxis in these cohorts has the potential to provide long-term protection from both symptomatic and severe COVID-19 for these vulnerable groups. However, the frequent observation of novel SARS-CoV-2 variants that escape antibody recognition has raised significant challenges in predicting monoclonal antibody protection against new variants. Several studies have investigated the efficacy of monoclonal antibodies as pre- and post-prophylaxis for COVID-19. Historical evidence is promising; however, new variants of concern are proving challenging for currently available regimens.

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