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The Next Frontiers and Innovative Therapeutics Strategies for Treatment - Prophylaxis in the Most Vulnerable Patients with the New Variants of Sars-Cov-2 and Comorbility: A Literature Review at January 2025

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Abstract

Over four years have passed since the beginning of the most significant health challenge in the 21st century has been the Sars-Cov-2. The extensive research and the Global Cooperation response has been rapid and effective with the profound understanding of fundamental biological and molecular characteristic of Covid-19 and many therapeutic monoclonal antibodies and small molecules developed for clinical use.

The effectiveness of monoclonal antibodies has been questioned because the virus and its variants have changed over time. This technical note highlights the need to assess the antiviral activity of these antibodies against new variants and adapt treatment strategies accordingly.

Pre-exposure prophylaxis using the latest monoclonal antibodies is one complementary preventative therapy to reduce severity of breakthrough Sars-Cov-2 in vulnerable persons with severe immunocompromise due organ transplant, cancer, HIV or use of certain medications experience diminished Covid-19 vaccine immune response and remain at higher risk for severe Sars-Cov-2 outcomes ; across many studies, Monoclonal Antibodies Pre-Exposure is associated with a 60% to 80% reduction in severe COVID-19 outcomes.

Covid-19 variants evolution, however, leads to viral mutations that can evade Monoclonal Antibodies due to the selective nature of their binding sites. Several Monoclonal Antibodies that received FDA emergency use authorization for prevention of Sars-Cov-2 have since had this authorization revoked once circulating variants demonstrated immune evasion.

Keywords: SARS-CoV-2; Covid-19

Background

Over five years have passed since the beginning of the most significant health challenge in the 21st century has been the Sars-Cov-2. As of January 2025, monoclonal antibodies for treating immunocompromised patients with the Neus Variants of Sars-Cov-2 (especially those with comorbidities) have evolved significantly since the early pandemic stages. However, newer treatments may still be under investigation or regulatory review. The extensive research and the Global Cooperation response has been rapid and effective with the profound understanding of fundamental biological and molecular characteristic of Covid-19 and many therapeutic monoclonal antibodies and small molecules developed for clinical use [1].

The effectiveness of monoclonal antibodies has been questioned because the virus and its variants have changed over time. This

technical note highlights the need to assess the antiviral activity of these antibodies against new variants and adapt treatment strategies accordingly.

Pre-exposure prophylaxis using the latest monoclonal antibodies is one complementary preventative therapy to reduce severity of breakthrough Sars-Cov-2 in vulnerable persons with severe immunocompromise due organ transplant, cancer, HIV or use of certain medications experience diminished Covid-19 vaccine immune response and remain at higher risk for severe Sars-Cov-2 outcomes [2]; across many studies, Monoclonal Antibodies Pre-Exposure is associated with a 60% to 80% reduction in severe COVID-19 outcomes.

Covid-19 variants evolution, however, leads to viral mutations that can evade Monoclonal Antibodies due to the selective nature of their binding sites. Several Monoclonal Antibodies that received FDA emergency use authorization for prevention of Sars-Cov-2 have since had this authorization revoked once circulating variants demonstrated immune evasion [3].

Introduction

Sars-Cov-2 still represents a disproportionate risk for vulnerable patients, with infection often leading to serious and protracted illness. Vaccination against Sars-Cov-2 has reduced in the Word the burden Covid-19. The urgent need to find new therapeutic strategies to combat the Sars-Cov-2 pandemic led to the design of numerous anti-Covid 19 monoclonal antibody for Therapy and Pre-Exposure Prophylaxis for the Latest Variants [4]. The immunocompromised persons and those who cannot be vaccinated, remain at risk for severe Covid-19.

As the world deals with this evolving threat, the narrative extends to the realm of emerging variants, each displaying new mutations with implications that remain largely misunderstood. Notably, the JN.1 Omicron lineage is gaining global prevalence, and early findings suggest it stands among the immune-evading variants, a characteristic attributed to its mutation L455S. Moreover, the detrimental consequences of the novel emergence of SARS-CoV-2 lineages bear a particularly critical impact on immunocompromised individuals and older adults. Immunocompromised individuals face challenges such as suboptimal responses to COVID-19 vaccines, rendering them more susceptible to severe disease. Similarly, older adults have an increased risk of severe disease and the presence of comorbid conditions, find themselves at a heightened vulnerability to develop COVID-19 disease. Thus, recognizing these intricate factors is crucial for effectively tailoring public health strategies to protect these vulnerable populations. In this context, this review aims to describe, analyze, and discuss the current progress of the next-generation treatments encompassing the latest monoclonal antibodies for Pre-Exposure Therapy immunotherapeutic approaches and advanced therapies emerging as complements that will offer solutions to counter the disadvantages of the existing options.

Although Monoclonal Antibodies as Prophilaxis and Therapy report efficacy as between 50-85% [5-6], global access is currently largely inequitable. Preliminary outcomes show that these strategies target the virus and address the immunomodulatory responses associated with COVID-19. Furthermore, the capacity to promote tissue repair has been demonstrated, which can be particularly noteworthy for immunocompromised individuals who stand as vulnerable actors in the global landscape of coronavirus infections [7-9].

Monoclonal antibodies, which protect against disease irrespective of immune system status and provide rapid protection, are potential options for Covid-19 immunoprophylaxis. Some combinations of monoclonal antibodies are already in use through emergency or temporary authorization for pre-exposure or post-exposure prophylaxis against Covid-19 or treatment of mild-to-moderate disease.

The emerging next-generation treatments possess broader potential, offering protection against a wide range of variants and enhancing the ability to counter the impact of the constant evolution of the virus. On the one hand, in vitro studies have suggested reduced susceptibility of the latest variants to monoclonal antibodies, whereas clinical data still show benefits in reducing severe illness and mortality, indicating that laboratory results do not always mirror real-world outcomes. As a result, although resistance to monoclonal antibodies can develop over time, they could still have an important role in COVID-19 treatment, especially when used in combination, and ongoing research aims to identify effective antibodies against new variants. The main purpose of this literature Review is to highlight the possible strategies to optimize and protect current and future therapeutic options Pre-Exposure to treat the most vulnerable patients [10-11].

New Variants: "Almost a New Pandemic"

Because of the fast-evolving nature of COVID-19 treatments and the emergence of new variants, the landscape for monoclonal antibody therapies may have shifted. It is critical for healthcare providers to stay updated on the most current guidance from agencies like the FDA and the WHO, and to choose therapies based on the latest variant prevalence, individual health conditions, and treatment availability.

With the emergence of this new variants, the researchers realized that vaccination offered less protection and that a third dose was needed to immunize the population. While previous variants had fewer than ten mutations on the spike protein compared with the original strain, Omicron had more than thirty. It was almost as if a new pandemic had begun. What the researchers were less aware of was that Omicron had a significant ability to evade monoclonal

antibodies. This was demonstrated by several scientists in an article published in December 2021. In their research, the scientists showed that two thirds of the monoclonal antibodies used in clinical practice or currently under development lost all their antiviral activity against Omicron. The situation also became increasingly complex as several sub variants (BA.1, BA.2, etc.) emerged over the following weeks. So the scientists tried to determine whether the monoclonal antibodies were effective against the new strains that were co-circulating. In a study published in March 2022, they provided a number of answers. The casirivimab/imdevimab combination, which until then had offered a similar level of protection against severe forms of COVID-19 as vaccination, was no longer active against Omicron. The neutralizing activity of another antibody cocktail (tixagevimab/cilgavimab) was significantly reduced against BA.1 compared with the Delta variant, but its neutralizing activity was not reduced nearly as much against BA.2. This result, which showed that a monoclonal antibody could lose its neutralizing capability for a given variant before recovering it for a subsequent variant, emphasizes the importance of continuing with efficacy testing on all available antibodies (Figure 1).

The protective efficacy of monoclonal antibodies depends primarily, but not solely, on their neutralizing capability. Some monoclonal antibodies can also induce a key immune defense mechanism known as antibody-dependent cellular cytotoxicity (ADCC), which kills cells infected with SARS-CoV-2. In the case of COVID-19, natural killer (NK) cells in the immune system recognize the antibodies that bind to antigens on the surface of infected cells and then specifically lyse those cells. These antibodies are described as "polyfunctional." This characteristic is all the more interesting since the monoclonal antibodies with the highest neutralizing capability are not those that induce ADCC the most, as shown in a study published in December 2022. In short, to obtain protective antibody cocktails, it may be a good idea to include polyfunctional antibodies which combine a high neutralizing capability with a strong ability to induce immune defense mechanisms [12].

Key Variants of Concern in December 2024

Omicron Sublineages (XBB family)

XBB.1 and XBB.1.5: These sublineages of XBB have been circulating widely. XBB variants, including XBB.1 and its sublineages, continue to show high levels of immune escape, meaning they can evade immunity from previous infections or vaccinations to some extent. These variants have been associated with reinfections in individuals who had previously been exposed to COVID-19 or vaccinated.

XBB.2.75: This sublineage of XBB is also a major variant of concern, with continued reports of immune evasion and increased transmissibility compared to previous strains. The high number of mutations in the spike protein and other regions make this subvariant a key focus for both surveillance and vaccine updates [12,13].

BQ and BF Subvariants

BQ.1 and BQ.1.1: These are subvariants of Omicron that have demonstrated increased transmissibility and partial resistance to immunity from both previous infection and vaccines. They have been circulating in various regions and remain a concern due to their ability to evade neutralizing antibodies.

BF.7: Another important Omicron subvariant, which has been noted for its ability to potentially escape immunity, though vaccines still help protect against severe disease.

Monitoring of Emerging Variants

While Omicron remains the dominant lineage, there are always potential for new subvariants or entirely new variants to emerge, especially if mutations lead to more concerning traits, such as:

- Increased transmissibility.
- Higher resistance to immunity from vaccines or past infections.
- Potential to cause more severe disease.

Health authorities like the WHO, CDC, and other global and regional bodies continuously monitor for any significant changes in the virus's behavior. If new strains show signs of increased transmissibility or a higher risk of severe outcomes, they may be classified as Variants of Concern.

As of January 2025, monoclonal antibodies for COVID-19 treatment, particularly for immunocompromised patients and those with comorbidities, are still a key part of managing COVID-19 in high-risk groups. The emergence of new SARS-CoV-2 variants, especially Omicron subvariants, has impacted the effectiveness of some earlier treatments, and newer monoclonal antibody combinations are being investigated or deployed to counteract immune evasion and improve outcomes for vulnerable patients.

Latest Monoclonal Antibodies and Combinations (December 2024)

Evusheld (AstraZeneca):

- Components: Tixagevimab and Cilgavimab.
- Indication: Evusheld is still widely used for pre-exposure prophylaxis (PrEP) in immunocompromised individuals who are unable to mount an adequate immune response to vaccines. This includes people with conditions like cancer, autoimmune diseases, or those on immunosuppressive therapies.

- Effectiveness: Though Evusheld has shown some diminished effectiveness against certain Omicron subvariants (e.g., XBB and BQ/BF subvariants), it is still considered a cornerstone in protecting vulnerable populations. Efforts to modify or enhance its effectiveness are ongoing.

Bebtelovimab (Lilly):

- Indication: Bebtelovimab was used for treatment of mild to moderate COVID-19 in high-risk patients, including those who are immunocompromised, to prevent severe outcomes. However, due to the emergence of newer Omicron subvariants with mutations in the spike protein, Bebtelovimab has seen reduced effectiveness.
- Status: It is becoming less favored due to its reduced efficacy against Omicron subvariants, but it may still be used in some contexts where other options are unavailable.

Combination of Monoclonal Antibodies (Emerging Treatments):

- New combinations of monoclonal antibodies are being developed to provide broader protection against immune-evading variants. These combinations are designed to target multiple epitopes of the spike protein, reducing the chance of the virus escaping the therapy due to mutations. Examples include:
- Dual or Triple Antibody Combinations: Research is ongoing to combine multiple monoclonal antibodies that can bind to different parts of the spike protein or other regions of the virus. These could provide better protection against the current circulating Omicron subvariants.
- Bamlanivimab and Etesevimab (Eli Lilly): These were used as a combination treatment in the earlier stages of the pandemic but have shown limited effectiveness against recent Omicron variants, making them less commonly used today.

Long-Acting Antibodies for Prevention and Treatment:

- Long-Acting Monoclonal Antibodies (LAMAs): These therapies are being investigated to offer longer-lasting protection against SARS-CoV-2, which is particularly beneficial for those who cannot mount an effective immune response. The concept behind these therapies is to provide extended immunity, which may be crucial for immunocompromised individuals who cannot rely on vaccines alone.

Key Considerations for Immunocompromised Patients

Variant-Specific Efficacy: The effectiveness of monoclonal antibodies has varied based on the circulating variant of SARS-CoV-2. Omicron subvariants like XBB and BQ have shown the potential to evade some antibodies designed for earlier strains. As a result, new monoclonal antibodies or combinations are being developed to enhance neutralizing activity against these newer variants.

Therapeutic vs. Prophylactic Use: Some monoclonal antibodies, such as Evusheld, are used prophylactically (to prevent infection), while others, like Bebtelovimab, have been used to treat COVID-19 in the early stages of infection. The choice of therapy will depend on the patient's condition, the timing of infection, and the specific circulating variants [13].

Combination Therapies

In some cases, monoclonal antibodies are combined with antiviral medications (like Paxlovid) or other supportive therapies to improve outcomes in immunocompromised patients. These combinations may include:

- Monoclonal antibodies + Antiviral treatments (e.g., Paxlovid): This combination can reduce viral load and prevent progression to severe disease, especially in high-risk individuals.
- Monoclonal antibodies + Corticosteroids: For more severe cases, the combination of monoclonal antibodies with corticosteroids (which reduce inflammation) is sometimes used to manage severe COVID-19 infections.

Ongoing Research and Regulatory Approval

With the continuing evolution of SARS-CoV-2, pharmaceutical companies and researchers are focusing on:

- Broader spectrum monoclonal antibodies: These would bind to various parts of the virus's spike protein or other regions, reducing the likelihood of immune escape.
- Updated monoclonal antibodies tailored to emerging Omicron subvariants like XBB and BQ/BF, as these strains continue to circulate globally.

Patients Immunocompromised with comorbidity and Sars-Cov-2 (Emerging Treatments)

Individuals with immunosuppressed conditions, including people with primary immunodeficiency's and secondary immunodeficiencies, consisting of people with solid-organ transplants, metastatic cancers, hematologic malignancies, advanced or untreated HIV (human immunodeficiency virus) infection, those receiving cancer chemotherapy, and patients with autoimmune diseases receiving immunosuppressive biologics and medications. Patients in this heterogeneous group had a higher risk of COVID-19-related hospitalization, severe COVID-19, or death and tend to have higher risk for opportunistic infections. In addition, prolonged SARS-CoV-2 infection and persistent viral replication in ICP not only cause long duration of symptoms but also risk of

emergence of antiviral-resistant or vaccine-escaped variants, prolonging the pandemic [14-20].

Although COVID-19 treatment guidelines had been proposed to manage patients with different severities and clinical cohorts, a consensus on COVID-19 patients in ICP was lacking and the information was limited. Immunocompromised individuals are at higher risk of severe COVID-19 outcomes. Vaccination remains a critical preventive mea-sure for this vulnerable population. Although some may have a reduced response to vaccines, receiving the recommended doses can still provide some level of protection and potentially mitigate severe disease.

Given the potential for diminished vaccine response, immunocompromised individuals should be considered for booster doses based on local guidelines and emerging data. In cases of exposure to COVID-19, immunocompromised individuals may require specific isolation or quarantine measures, depending on their risk profile. The management of COVID-19 in ICP necessitates an individualized approach. Clinicians must carefully consider the patient's specific immunocompromised condition, medical history, and risk factors to determine the most appropriate treatment plan. In severe COVID-19 cases among ICP, antiviral therapies such as remdesivir may be considered.

The decision to use antiviral drugs should be based on clinical judgment and consultation with specialists from multidisciplinary areas. In severe COVID-19 cases with significant inflammatory responses, corticosteroids like dexamethasone may be used under close medical supervision. The use of CCP therapy in specific severe cases of COVID-19 among immunocompromised patients may be considered on a case-by-case basis early in the pandemic. Therapeutic recommendations for antiviral or immunomodulation therapy of adults with varying severities of COVID-19 are summarized in (Table 1).

Disease severity	Patient disposition	Recommendations
Nonhospitalized adults with mild to moderate COVID-19 who do not require supplemental oxygen	All patients	All patients should be offered symptom management. The Panel recommends against the use of dexamethasone or other systemic corticosteroids in the absence of another indication
	Patients who are at high risk of progressing to severe COVID-19b	Preferred therapies. Listed in order of preference: ritonavir-boosted nirmatrelvir (Paxlovid) Remdesivir Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate: molnupiravir
Hospitalized adults with COVID-19 but do not require oxygen supplementation	All patients	The Panel recommends against the use of dexamethasone or other systemic corticosteroids for the treatment of COVID-19
	Patients who are at high risk of progressing to severe COVID-19b	Remdesivir
Hospitalized adults with COVID-19 and requiring conventional oxygen	Patients who require minimal conventional oxygen	Remdesivir
	Most patients	Use dexamethasone plus remdesivir. If remdesivir cannot be obtained, use dexamethasone
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add oral baricitinib or intravenous tocilizumab to 1 of the options above
Hospitalized and requires HFNC oxygen or NIV	All patients	Dexamethasone should be administered to all patients. If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in order of preference): oral baricitinib intravenous tocilizumab Add remdesivir to 1 of the options above in certain patients

Hospitalized and requires MV or ECMO	All patients	Dexamethasone should be administered to all patients. If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in alphabetical order): oral baricitinib intravenous tocilizumab
Abbreviations: COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; MV, mechanical ventilation; NIV, noninvasive ventilation.		

Table 1: *Therapeutic recommendations for antiviral or immunomodulator therapies for adults with varying severities of COVID-19.*

Therapeutic mAb	**Use**	**mAb-resistant SARS-CoV-2 variants**	**Status**	**PDB ID**
Bebtelovimab	Treatment	Omicron: (BQ.1; BQ.1.1; BA.2; BA.2.12.1 and BA.5)	Not currently authorized by the FDA	7MMO]
Regdanvimab (CT-P59) (Regkirona)	Treatment	Gamma Delta Omicron: B.1.1.529	Paused by Omicron resistance	7CM4
Sotrovimab (S309)	Treatment	Delta Omicron	Strong recommendation against its use	7TN0
Amubarvimab (BrII-196), Romlusevimab (BRII-198)	Treatment	Omicron	Available in China	–
Bamlanivimab (LY-CoV555) and Etesevimab (CB6)	Treatment	Beta Gamma] Omicron]	Paused by Omicron resistance	7KMH 7F7E]
	Post-exposure prophylaxis			
REGEN-COV: [Casirivimab (REGN10933)/Imdevimab (REGN10987)]	Treatment	Omicron	Paused by Omicron resistance	6XDG [
	Post-exposure prophylaxis			6XDG 7ZJL
Evusheld [Cilgavimab (COV2-2130/tixagevimab (COV2-2196 [	Pre-exposure prophylaxis	Omicron	Not authorized for emergency use in the U.S	8D8Q 8D8R
aPDB ID. Protein Data Bank identification code.				

Table 2: *Anti-SARS-CoV-2 RBD therapeutic monoclonal antibodies.*

Table 3: *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. 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. PROVENT	Tixagevimab plus cilgavimab (AZD7442) Single 300-mg AZD7442 dose (two intramuscular injection, 150 mg each of tixagevimab and cilgavimab) AZD7442 (N = 3460) placebo (N = 1737)	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
Levin et al. 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. 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%)	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

Study	Regimen	Study population	Study period and/or variants of concern	Study design	Efficacy outcomes	Safety outcomes
					Median time of symptom resolution (casirivimab plus imdevimab (1.2 weeks) vs placebo (3.2 weeks) REGEN-COV reduced the 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. 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

Study	Regimen	Study population	Study period and/or variants of concern	Study design	Efficacy outcomes	Safety outcomes
Dougan et al.	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 three days after a laboratory diagnosis of severe SARS-CoV-2 infection	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 (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	Serious AEs occurred in 1.4% in the bamlanivimab-etesevimab group and in 1.0% patients in the placebo group
Gupta et al.	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	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

Study	Regimen	Study population	Study period and/or variants of concern	Study design	Efficacy outcomes	Safety outcomes
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.						

Study	**Regimen**	**Study population**	**Study period and/or variants of concern**	**Study design**	**Outcomes**
Tixagevimab plus cilgavimab					
Conte WL, 2022	Tixagevimab plus cilgavimab 150 mg (tixagevimab and cilgavimab) IM	Vaccinated MS patients exposed to B-cell depleters during vaccination	N.D.	Single-center cohort (N = 18) Study completed prior to US Food and Drug Administration's update to 300 mg each of tixagevimab and cilgavimab	Prior to AZD7442 mean antibody level was 12.38 U/ml, 66% of 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.	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	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	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 et al.	Tixagevimab plus cilgavimab (AZD7442)	Vaccinated KTR w/ no humoral response after ≥3 doses COVID-19 vaccine	December 28, 2021 to February 28, 2022 Omicron wave	Retrospective study of KTR (N = 430) Received AZD7442 (tixagevimab plus cilgavimab) 300 mg (N = 333) or did not (N = 97)	AZD7442 group significantly 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	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	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.	Tixagevimab plus cilgavimab	SOTR	December 28, 2021 to April 13, 2022 Omicron	Retrospective cohort comparing (N = 222) SOTR receiving tixagevimab plus cilgavimab for pre-exposure prophylaxis and (N = 222) vaccine matched SOTR who did not	Breakthrough infections: 11 (5%) of SOTR tixagevimab plus cilgavimab group vs 32 (14%) in 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	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	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	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	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	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.	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.	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.	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), Combination treatment with sotrovimab and remdesivir (N = 38)	Sotrovimab alone or in combination with remdesivir did not decrease in-hospital mortality compared to control groups. Mortality: 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.	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.	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	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	Tixagevimab plus cilgavimab and casirivimab plus imdevimab	Vaccinated KTR	December 23, 2021 to March 7, 2022 Omicron outbreak BA1 variant was predominant, until February 14, 2022, and then BA2 became predominant	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 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	113 (13.1%) got Omicron, 85 were symptomatic 21 patients hospitalized, eight ICU, and five died of COVID-19. End of 80 days, symptomatic 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	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	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.	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 Omicron BA.1 and BA.2	Retrospective cohort study in Wales Total participants, N = 7013 Untreated, N = 4973 Received sotrovamib, N = 1079, 52.9%; Molnupiravir, N = 359, 17.6%; Nirmatrelvir-Ritonavir, N = 602, 29.5%	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. 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	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	Casirivimab/imdevimab (1200/1200 mg) sotrivimab (500 mg)	Frail COVID-19 vaccinated/unvaccinated patients referred by primary care physicians for mAb treatment 78.1% vaccinated	From July 2021 to May 15, 2022 B.1.617.2 Omicron B.1.1	Prospective study N = 1026 60.2% received casirivamab/imdevimab and 39.8% sotrivimab	60-day overall mortality, 2.14% Mortality: casirivimab/imdevimab 12/618, 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 O2 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.

					sNo significant difference in type of side effects between two treatment regimens.

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.

Table 4: *Overview of real-world evidence of monoclonal antibodies as pre- and post-exposure prophylactics for COVID-19 in immunocompromised populations.*

Effectiveness of Monoclonal Antibody-based therapy Against Covid Variants (January 2025)

Monoclonal antibodies against the SARS-CoV-2 S protein act through mechanisms related to their structure. First, the antigen-binding fragments (Fab) prevent the virus from binding to the ACE2 receptors, and second, the Fc fragment can activate the complement system and bind to the Immunoglobulin Fc receptors (FcRs) on cytotoxic cells that can eliminate virus-infected cells through Ab-dependent cell-mediated cytotoxicity (ADCC). Unfortunately, some mAbs can bind to macrophage FcRs and induce a hyperinflammatory response resulting from Ab-dependent enhancement (ADE) of cytokine production.

The SARS-CoV-2 RBD has become the main target of mAbs because of its crucial role in virus entry into host cells (Table 2). Analysis of the structural relationship between RBD and anti-RBD NAbs has led to the classification of these antibodies according to structural features and mechanism of action. Class 1 NAbs, e.g., CT-P59 (regdanvimab), target the receptor binding motif (RBM). They recognize the RBD in the up conformation, thus blocking the interaction with the ACE2 receptor. Class 2 NAbs, e.g. LY-CoV1404 (bebtelovimab), target the ACE2 binding site of the RBD in both up and down conformations. Class 3 antibodies, e.g., S309 (sotrovimab), target the conserved core domain of the RBD without altering interactions with the ACE2 receptor. Class 4 antibodies, e.g., S2X259, target epitopes in both the RBM and the core domain of the RBD. Unfortunately, frequent mutations in the RBD have modified the epitopes recognized by mAbs, resulting in the emergence of viral variants resistant to mAbs. To address this issue, researchers are exploring other SRS-CoV-2 regions as potential targets for therapeutic mAbs.

Monoclonal Antibodies Aprovation as Prophylaxis-Therapy in the Elderly and Immonocompromised Sars-Cov-2 population at January 2025

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 [21]. 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 [22].

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 3).

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 [23].

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 4).

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

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. [24-28] (Figure 2).

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 [14,15]. 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 modeling 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). 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. The modelled 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).

Development of universal COVID-19 antibodies

A new human monoclonal antibody moves a step closer to a universal antibody cocktail that works against all strains of SARS-CoV-2. A consortium of scientists at Texas Biomedical Research Institute (Texas Biomed), the University of Alabama at Birmingham (UAB) and Columbia University have developed a promising new human monoclonal antibody that appears a step closer to a universal antibody cocktail that works against all strains of SARS-CoV-2.

This antibody worked against the original SARS-CoV-2 strain, Omicron and SARS-CoV, providing strong evidence that this antibody will continue to work against future strains, especially if paired with other antibodies. The newly designed antibody, called 1301B7, is a receptor binding domain antibody, meaning it targets a region of the spike protein responsible for enabling the virus to bind and enter a cell. By targeting this region, these antibodies are essentially stopping the virus before they can infect a cell.

The antibody binds to multiple positions within the receptor binding domain, which is thought to enable it to tolerate variations that occur in this domain as the virus continues to evolve. The precise nature of how the antibody binds to the

receptor binding domain was solved. The monoclonal antibody is designed based on antibodies the UAB team isolated from patients infected with the Omicron variant of SARS-CoV-2. The teams at Texas Biomed and Columbia University tested the antibody against several variants including the original SARS-CoV-2 isolated in China, Omicron JN.1 and SARS-CoV.

In 2022, the researchers described a monoclonal antibody targeting a different part of the spike called the stalk. The researchers plan to next study what happens when they combine the two antibodies together, attacking the virus from different angles and hopefully preventing it from escaping neutralization. A single antibody therapy is not going to work, so may have to try something similar to therapies being developed for other diseases like Ebola and HIV whereby two or three antibodies are combined to target different regions of the virus.

They are also interested in adapting the antibodies into a preventative vaccine. The Researchers are also trying to design vaccines that would be able to induce these types of antibodies so we don't have to update vaccines regularly. The consortium of scientists has filed a provisional invention patent for 1301B7 and is in the process of licensing it for commercialization.

Conclusion

COVID-19 still represents a significant and disproportionate risk for immunocompromised patients with comorbility, with infection often leading to serious and protracted illness. Infection-fighting antibodies directly to patients who often don’t respond adequately to vaccines, the data support that sipavibart has the potential to provide much-needed protection against COVID-19 in this highly vulnerable population. Immunocompromised patients currently have limited or no options for COVID-19 protection and continue to face a significant burden of disease, despite often being fully vaccinated. Sipavibart has the potential to prevent COVID-19 in the immunocompromised and we will now work with regulatory authorities globally to bring sipavibart to these vulnerable patients.

Studying the adaptation trajectory of SARS-CoV-2, it is crucial to anticipate possible future events rooted in the molecular mechanisms that underpin the evolutionary success of SARS-CoV-2 is essential. The potential role of advanced Treatment as Pre-Exposure Prophylaxis against SARS-CoV-2 has introduced it as a new platform to encourage the adaptation of emerging medical technologies for infectious diseases. The use of monoclonal antibodies for Pre-Exposure in these cohorts has the potential to provide long-term protection from both symptomatic and severe COVID-19 for these vulnerable groups.

In December 2024, the latest monoclonal antibody treatments for immunocompromised patients with comorbidities still include Evusheld for prevention, but the emergence of immune-evading Omicron subvariants has reduced the effectiveness of many monoclonal antibodies like Bebtelovimab. The focus is on combination therapies, long-acting monoclonal antibodies, and newer specific antibodies that can better target a wider range of variants. Additionally, antiviral treatments are often combined with monoclonal antibodies for a more comprehensive approach to reducing disease severity and preventing complications. 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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