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Evolving Impact of Latest Monoclonal Antibodies as Pre-Exposure and Treatment in Immunocompromised and Elderly Patients with New Variants of Sars-Cov-2. A Review of Knows and Unknowns at December 2024

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Abstract

The most significant health challenge in the 21st century has been the Sars-Cov-2. The Extensive research and the Global Cooperation have provided a profound understanding of the latest therapies, fundamental biological and molecular characteristics of SARS-CoV-2. Pre-exposure prophylaxis using monoclonal antibodies is one complementary preventative therapy to reduce severity of breakthrough Sars-Cov-2 in persons with severe immunocompromise due organ transplant, cancer, HIV or use of certain medications experience diminished SARS-CoV-2 vaccine immune response and remain at higher risk for severe COVID-19 outcomes; across many studies, Monoclonal Antibodies Pre-Exposure is associated with a 60% to 80% reduction in severe COVID-19 outcomes.

Covid-19 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.

This Review explain the Next –Generation of Pre-Exposure Prophylaxis, the recommendations for the Clinical Management for Persons with Risk factors for COVID-19, include obesity, older age, underlying medical conditions such as diabetes, inadequate vaccination, immunocompromised condition.

Keywords: SARS-CoV-2; Covid-19

Background

The most significant health challenge in the 21st century has been the Sars-Cov-2. The Extensive research and the Global Cooperation have provided a profound understanding of the lastest therapies, fundamental biological and molecular characteristics of SARS-CoV-2 [1].

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

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since had this authorization revoked once circulating variants demonstrated immune evasion [3]. This Review explain the Next –Generation of Pre-Exposure Prophylaxis, the recommendations for the Clinical Mamagement for Persons with Risk factors for COVID-19 , include obesity, older age, underlying medical conditions such as diabetes, inadequate vaccination, immunocompromised condition.

Introduction

COVID-19 still represents a significant and disproportionate risk for immunocompromised 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 [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 lastest 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 preexposure or postexposure 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. The main purpose of this leterature 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].

Omicron Variant: "Almost a new Pandemic"

With the emergence of this variant, 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 subvariants (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].

Lastest Monoclonal Antibodies for Pre-Exposure Prophylaxis in Patients for the most vulnerable persons at June 2024

Pemivibart (Pemgarda): The FDA issued an emergency use authorization (EUA) for pemivibart (Pemgarda) opens in a new tab or window as COVID-19 pre-exposure prophylaxis in immunocompromised individuals who are unlikely to mount a sufficient immune response following vaccination. A long-acting monoclonal antibody, pemivibart is specifically authorized for people ages 12 years and older (and weighing 40 kg or more) with moderate-to-severe immune compromise either because of a medical condition or due to immunosuppressant medications. Pemivibart is given as a single intravenous infusion and is not for use as post-exposure prophylaxis or in people currently infected with SARS-CoV-2.

The EUA was based on immunobridging data involving other human monoclonal antibodies against SARS-CoV-2 demonstrating that pemivibart may be effective for COVID prevention. Serum neutralizing antibody titers of Pemgarda were consistent with the titer levels associated with efficacy in prior clinical trials of adintrevimab and certain other monoclonal antibody products.

According to the EUA, individuals who would qualify for the antibody include those undergoing active treatment for cancer (including those receiving CAR T-cell therapy or stem cell transplant); patients with hematologic malignancies associated with poor responses to COVID vaccines regardless of their treatment status; solid-organ transplant recipients; those with moderate-or-severe primary immunodeficiency; people with advanced or untreated HIV; and those on high-dose corticosteroids, B-cell depleting agents, and other immunosuppressants.

No long-acting monoclonal antibody has been available for preventing COVID infection in individuals with moderate-to-severe immune compromise since the agency pulled the EUA opens in a new tab or window for tixagevimab-cilgavimab (Evusheld) in January 2023 -- the move followed data showing the combination was unlikely to be sufficiently active against circulating SARS-CoV-2 variants. At the time, the CDC recommended opens in a new tab or window that immunocompromised individuals receive the latest COVID booster (if they had not already), wear a well-fitting high-quality mask in public, maintain distance in crowded areas, and improve indoor ventilation.

Pemivibart is administered at a dose of 4,500 mg over a 60-minute infusion, with repeat dosing every 3 months recommended if ongoing protection is needed. FDA cautioned that anaphylaxis occurred in 0.6% of clinical trial participants who received pemivibart. Therefore, patients should be monitored for 2 hours after the infusion is finished, and pemivibart should be administered in settings where health providers have immediate access to medications to reverse severe allergic reactions and can alert EMS if necessary. Other potential side effects noted in the labelingopens in a new tab or window include infusion-related reactions, fatigue, nausea, and headache [13].

SUPERNOVA Phase III trial of sipavibart long-acting antibody met primary endpoints in preventing COVID-19 in immunocompromised patient population

SUPERNOVA is a large Phase III global trial providing the only efficacy data in immunocompromised patients, demonstrating the potential benefit of a COVID-19 antibody against recent SARS-CoV-2 variants. Immunocompromised patients include those with blood cancer, organ transplant recipients, patients with end-stage renal disease requiring dialysis, patients receiving B-cell depleting therapy within the past year, and those taking immunosuppressive medications. Despite accounting for approximately 4% of the population, immunocompromised patients make up about 25% of COVID-19 hospitalisations, ICU admissions, and deaths, even after multiple doses of COVID-19 vaccines [14].

The trial met both dual primary endpoints; the first one being the relative risk reduction of symptomatic COVID-19 caused by any SARS-CoV-2 variant and the second being the relative risk reduction of infections caused by SARS-CoV-2 variants not containing the F456L mutation. SUPERNOVA demonstrated the potential benefit of sipavibart in an evolving variant landscape in which COVID-19 cases captured over the course of the trial were caused by several different SARS-CoV-2 variants.

Primary efficacy endpoints. The first evaluated the efficacy of sipavibart against any confirmed SARS-CoV-2 positive symptomatic illness occurring post dose prior to day 181 caused by any variant (i.e., all cases regardless of if the variant has the F456L mutation or not, which sipavibart is not expected to neutralise). The second dual primary efficacy analysis was conducted using only the confirmed COVID-19 cases in the trial where the variant causing the COVID-19 cases did not have the F456L mutation, referred to as a “matched” variant analysis.

Participants were individuals 12 years of age and over who would benefit from prevention with the investigational LAAB, defined as having increased risk for inadequate response to active immunisation (predicted poor responders to vaccines or intolerant of vaccine). Participants at the time of screening had a negative point-of-care SARS-CoV-2 serology test. Participants will be followed for 15 months, with SARS-CoV-2 neutralising antibodies assessed at one, three and six months.

All participants in the trial had an immunocompromising condition and/or were on immunosuppressive treatments, which put them at risk to mount an inadequate immune response to vaccination and at high risk of developing severe COVID-19. This included patients with hematologic malignancies, solid organ transplant recipients, hematopoietic stem cell transplants, end stage kidney disease/dialysis and being within one year of receipt of B cell depleting therapy, among others. Across the treatment groups, demographic and baseline characteristics were generally well balanced.

Positive high-level results from the SUPERNOVA Phase III COVID-19 pre-exposure prophylaxis (prevention) trial showed AstraZeneca's sipavibart (formerly AZD3152), an investigational long-acting antibody (LAAB), demonstrated a statistically significant reduction in the incidence of symptomatic COVID 19 compared to control (tixagevimab/cilgavimab or placebo) in an immunocompromised patient population.

COVID-19 still represents a significant and disproportionate risk for immunocompromised patients, 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 [15,16].

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.

Sipavibart was well tolerated in the trial and preliminary analyses show adverse events were balanced between the control and sipavibart arms. The data will be presented at a forthcoming medical meeting. AstraZeneca is in dialogue with regulatory authorities on potential authorisation or approval pathways [17-19].

Sipavibart

Sipavibart (formerly AZD3152) is an investigational long-acting monoclonal antibody (LAAB) against COVID-19. Sipavibart was designed to provide broad and potent coverage across Omicron and ancestral viral variants by neutralising spike protein interaction with the host receptor ACE2.

Sipavibart was derived from B-cells donated by convalescent patients after SARS-CoV-2 infection. Sipavibart has been engineered using the same antibody scaffold as Evusheld and was optimized with the same half-life extension and reduced Fc effector function and complement C1q binding platform. The reduced Fc effector function aims to minimise the risk of antibody-dependent enhancement of disease - a phenomenon in which virus-specific antibodies promote, rather than inhibit, infection and/or disease. Sipavibart was licensed by AstraZeneca in May 2022 from RQ Biotechnology [20].

Patients Immunocompromysed and Sars-Cov-2

Individuals with immunosuppressed conditions, including people with primary immunodeficiencies 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 heterogenous 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 notonly cause long duration of symptoms but also risk of emergence of antiviral-resistant or vaccine-escaped variants, prolonging the pandemic.

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, corticoste-roids 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 immunomodulator therapy of adults with varying severities of COVID-19 are summarized in (Table 1).

Figure 1: *3D visualization of mutations in the spike protein of the Omicron variant. Mutations are indicated in red.*

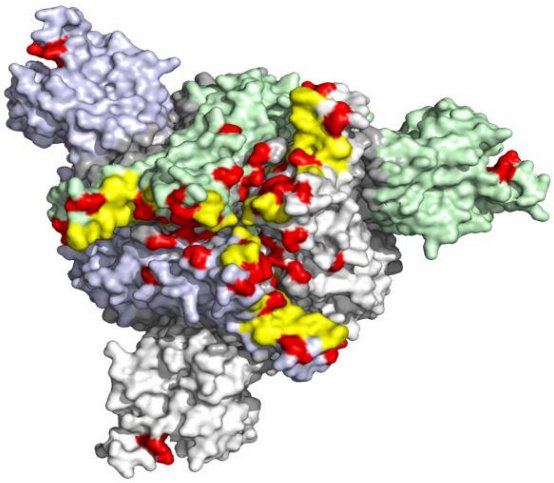

Figure 2: *Reported protection and antibody concentration from RCTs of monoclonal antibodies in preventing. COVID-19.*

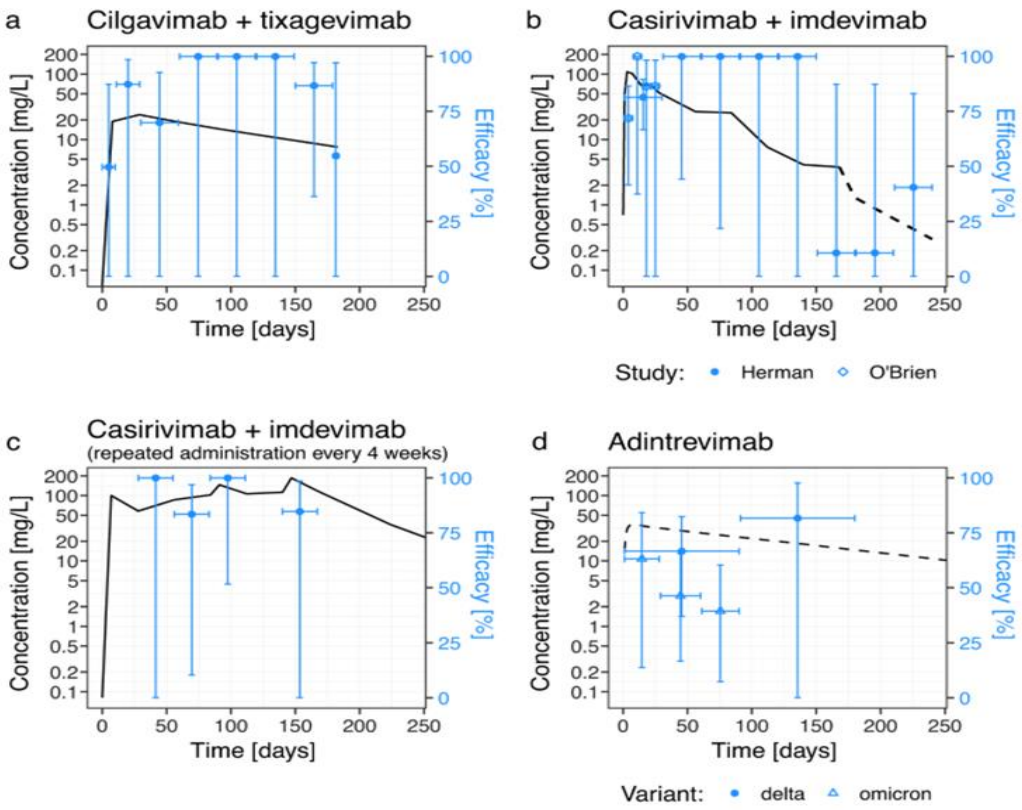

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Table 1: *Therapeutic recommendations for antiviral or immunomodulator therapies for adults with varying severities of COVID-19.*

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

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

Therapeutic mAb	Use	mAb-resistant SARS-CoV-2 variants	Status	PDB ID

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

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%) 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.	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
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

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

Table 4: *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 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	Antineutrophil cytoplasmic antibody vasculitis patients	December 2021 to June 2022	Retrospective study 21 (100%) vaccinated, 95% had a booster	COVID-19 infection: 1 (4.7%), 122 days after Tixagevimab plus cilgavimab (300 mg).

	mg tixagevimab-300 mg cilgavimab), and 300 mg (150 mg tixagevimab-150 mg cilgavimab)			20 (95%) received Evusheld and one (4.7%) received tixagevimab- cilgavimab	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	Ambulatory patients, 11 immunocompromised individuals—SOTRs	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

	Single IV infusion of tixagevimab plus cilgavimab (300 mg/300 mg)	that were infected w/ BA.2 subvariant			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	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

				patients); 89 patients received other mAbs	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. No significant difference in type of side effects between two treatment regimens.

Effectiveness of Monoclonal Antibody-based therapy Against Covid Variants (June 2024)

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 Ederly and Immonocompromised Sars-Cov-2 population at June 2024

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 favorable 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).

SARS-CoV-2 variants of concern as of 26 June 2024

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.

Variant classification serves as an important communication tool for alerting EU/EEA countries about the emergence of SARS-CoV-2 variants with concerning properties likely to impact the epidemiological situation in the EU/EEA.

ECDC utilises three categories of variant classification to communicate increasing levels of concern about a new or emerging SARS-CoV-2 variant: variant under monitoring (VUM), variant of interest (VOI) and variant of concern (VOC). Classification criteria and recommended Member state actions are available here: ECDC variant classification criteria and recommended Member State actions.

New evidence is regularly assessed on variants detected through epidemic intelligence, genomic horizon scanning, 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.

Variant surveillance data, including the distribution of VOC and VOI variant proportions in the EU/EEA, is presented as part of the European Respiratory Virus Surveillance Summary (ERVISS).

Description of the tables

Category: variant of concern (VOC), variant of interest (VOI), or variant under monitoring (VUM).

WHO label: As of 31st May 2021, WHO proposed labels for global SARS-CoV-2 variants of concern and variants of interest to be used alongside the scientific nomenclature in communications about variants to the public. This list includes variants on whose 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. 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.

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. [24-27] (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. a 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 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). 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).

Conclusion

COVID-19 still represents a significant and disproportionate risk for immunocompromised patients, 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. 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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