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REVIEW

Neutralizing monoclonal antibodies for the treatment and prophylaxis of SARS-CoV-2 infection

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SUMMARY

Neutralizing monoclonal antibody therapies against the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) play a significant role both in the prevention and treatment of the coronavirus disease 2019 (COVID-19).
In this review we discuss the monoclonal antibody therapies that have received preliminary authorization for use in COVID-19 patients by the U.S. Food and Drug Administration or the European Medicines Agency. We review here their mechanisms of action, their efficacy in prophylaxis and treatment, their indications for use, and the impact of SARS-CoV-2 variants of concern on their activity.

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INTRODUCTION

Although several effective vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed and over 6.5 billion vaccine doses have been administered globally (Ritchie et al., 2021), coronavirus disease 2019 (COVID-19) continues to cause infections, hospitalizations, and deaths worldwide (Coronavirus Resource Center, Johns Hopkins University, 2021). This is also fueled by the emergence of new viral variants, which are characterized by higher transmission rates, a more severe clinical course, and a possible indication of reduced vaccine effectiveness (Sheikh *et al*., 2021; Abdool Karim *et al*., 2021; Lopez *et al*., 2021). Therefore, the availability of medications that limit the progression of COVID-19 remains of critical importance, especially for the treatment and prophylaxis of high-risk patients.
One promising area of COVID-19 research is neutralizing monoclonal antibody (mAb) therapy. Currently, the only mAb therapies to receive preliminary authorization for use in patients with COVID-19 by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) are the combinations bamlanivimab-etesevimab and casirivimab-imdevimab, and the monotherapies with sotrovimab and regdanvimab (FDA Emergency use Authorization COVID Drugs, 2021; EMA COVID-19 Treatments, 2021).
In this review, we discuss the mechanisms of action and efficacy, both for prophylaxis and treatment, of these mAb therapies, as well as their indications for use and the impact of SARS-CoV-2 variants on their activity.

Key words:
SARS-CoV-2, COVID-19, monoclonal antibodies, Spike protein, Treatment, Prophylaxis.

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MECHANISMS OF ACTION

Monoclonal antibodies are isolated from a single B cell clone. Currently, the majority of neutralizing mAb are directed against the receptor-binding domain (RBD) of the spike (S) protein of SARS-CoV-2, and are derived from the convalescent plasma of recovered patients and, to a lesser degree, from humanized murine technology (Corti *et al*., 2021).
In particular, the mAb that bind the S protein are targeting its interaction with cellular angiotensin-converting enzyme 2 (ACE2) receptor, which enables viral entry and fusion in the host cells. ACE2 receptor is highly expressed by cells of the respiratory system, gastrointestinal tract, and the endothelium (Hoffmann *et al*., 2020). The S protein of SARS-CoV-2 consists of a signal peptide located at the N-terminus, an S1 subunit responsible for receptor binding, and an S2 subunit involved in membrane fusion (Xia *et al*., 2020). The S1 subunit contains the RBD, which binds the ACE2 receptor, and is therefore an im-

portant target for neutralizing antibodies. Antibodies directed against the S protein can prevent virus binding and fusion with the cellular targets, thereby inducing neutralization.

The function of mAb therapies may be also mediated by the recruitment of immune cells or serum complement by the Fc region of the antibody, a phenomenon known as Fc-mediated antibody effector functions (Corti *et al.*, 2019). These effector functions contribute to the elimination of virally infected host cells, as described in human immunodeficiency virus (HIV) and respiratory syncytial virus (Saunders, 2019; Forthal and Moog, 2009; van Erp *et al.*, 2019).

Finally, given that selective epitope binding to the target host cell is fundamental for their function, many mAb therapies are preferably used in combination according to their specificity. Different mAb bind to distinct epitopes on the RBD, without competing for antigen binding or functionality. Therefore, combining mAb therapies may broaden the coverage of different strains and increase the neutralization effect. This is especially important given that the use of a single mAb may led to the emergence of viral escape mutants, as demonstrated in HIV, SARS-CoV, and SARS-CoV-2 (Caskey *et al.*, 2017; ter Meulen *et al.*, 2006; Choudhary *et al.*, 2021).

USE OF NEUTRALIZING MONOCLONAL ANTIBIODIES FOR COVID-19 POST-EXPOSURE PROPHYLAXIS

The use of mAb therapy for post-exposure prophylaxis (PEP) might provide patients with immediate protection from SARS-CoV-2 infection. This would be especially impactful in health care facilities, nursing homes, and prisons, and among patients at high risk of clinical progression. In the context of the global burden of COVID-19 disease and the global distribution of COVID-19 vaccines, it is important to identify the population that would benefit from PEP with neutralizing mAb. For example, patients who are not fully vaccinated or who are not expected to mount an adequate immune response to full SARS-CoV-2 vaccination (e.g. patients with primary or secondary immune deficiencies) are potentially ideal candidates for PEP (Food and Drug Administration, 2021). In these vulnerable populations, the use of neutralizing mAb therapies as PEP agents may be beneficial to prevent infection, to limit the progression of the disease to a more severe stage, and to reduce the diffusion of the virus.

There have been three pivotal studies that evaluated the use of mAb therapies as PEP agents for SARS-CoV-2 infection.

The first was NCT04452318, a phase III prevention trial which demonstrated that subcutaneous injection of the neutralizing antibodies casirivimab with imdevimab (REGEN-COV; 600+600 mg) reduced the risk of symptomatic SARS-CoV-2 infections by more than 80% in asymptomatic household contacts of individuals with SARS-CoV-2 infection (O'Brien *et al.*, 2021). This trial enrolled 1,505 participants that were randomized in a 1:1 ratio to receive REGEN-COV or placebo. Overall, 11/753 (1.5%) participants in the REGEN-COV group versus 59/752 (7.8%) in placebo group developed a symptomatic SARS-CoV-2 infection (relative risk reduction, 81.4%; $p<0.001$). Within the first week after administration of REGEN-COV or placebo, 9/753 (1.2%) participants in the REGEN-COV group and 32/752 (4.3%) participants in the placebo group had symptomatic SARS-CoV-2 infection (relative risk reduction, 71.9%); in weeks 2 to 4, 2/753 (0.3%) and 27/752 (3.6%) had symptomatic SARS-CoV-2 infection, respectively (relative risk reduction, 92.6%). Moreover, in the REGEN-COV group compared to placebo, a faster viral clearance and a shorter duration of the symptoms (1.2 weeks vs 3.2 weeks, respectively) were observed among those who developed a symptomatic SARS-CoV-2 infection.

The second pivotal study was the BLAZE-2 trial (NCT04497987), which investigated the use of bamlanivimab as a PEP agent for SARS-CoV-2 infection both in monotherapy (part 1) and in combination with etesevimab (part 2), in a population of nursing home residents and staff (Cohen *et al.*, 2021). Results of part 1 (n = 966) demonstrated that bamlanivimab alone (4,200 mg administered intravenously) significantly reduced the incidence of COVID-19 by day 57 compared with placebo (8.5% vs 15.2%; odds ratio 0.43 (95% confidence interval (CI): 0.28, 0.68); $p<0.001$). The proportion of patients with adverse events was similar in the bamlanivimab and placebo group (20.1% vs 18.9%, respectively).

The third pivotal study was the Phase III PROVENT trial, which assessed the safety and efficacy of a single intramuscular 300 mg dose of AZD7442 compared to placebo for the prevention of COVID-19 (AstraZeneca, 2021). AZD7442 is a combination mAb therapy consisting of tixagevimab (AZD8895) and cilgavimab (AZD1061). The trial enrolled 5,197 participants who were randomized in a 2:1 ratio to receive AZD7442 (n=3,460) or placebo (n=1,737). AZD7442 reduced the 6-month risk of developing symptomatic COVID-19 by 77% (95% CI: 46-90%), compared to placebo

USE OF NEUTRALIZING MONOCLONAL ANTIBODIES FOR COVID-19 TREATMENT

Bamlanivimab-Etesevimab

The latest portion of the Phase III BLAZE-3 trial (Dougan *et al.*, 2021) enrolled a cohort of adult and adolescent (≥12 years of age) patients with mild or moderate COVID-19 who were at high risk for severe disease, in the outpatient setting. High risk patients

included those who were age ≥65 years, or with a body-mass index (BMI) ≥35 kg/m², or with medical conditions such as chronic kidney disease, diabetes mellitus, immunosuppression, cardiovascular disease, hypertension, and chronic respiratory disease. In total, 1,035 patients were randomly assigned in a 1:1 ratio to receive a single intravenous infusion of 2,800 mg bamlanivimab with 2,800 mg etesevimab, or placebo, within 3 days after laboratory diagnosis of SARS-CoV-2 infection. Primary outcome was proportion of patients who experienced COVID-19-related hospitalization or death from any cause, by day 29 (*Table 1*).

By day 29, 2.1% (11/518) of patients in the bamlanivimab - etesevimab group and 7.0% (36/517) in the placebo group had a COVID-19 - related hospitalization or death from any cause (absolute risk difference, -4.8%; 95% CI: -7.4, -2.3; relative risk difference, 70%; p<0.001). No deaths occurred in the bamlanivimab–etesevimab group; in the placebo group, 10 deaths occurred, 9 of which were reported as COVID-19-related by the investigators.

At day 7, a greater reduction from baseline in the $\log_{10}$ viral load was observed among patients who received bamlanivimab-etesevimab (difference from placebo in the change from baseline, -1.20; 95% CI: -1.46, -0.94; p<0.001). The combination of bamlanivimab–etesevimab was well-tolerated, with serious adverse events (SAEs) in 1.4% of the patients versus 1.0% in the placebo group. The proportion of

Table 1 - Main results of selected clinical trial for bamlanivimab-etesevimab (Dougan *et al*., 2021), casirivimab-imdevimab (Weinreich *et al*., 2021, RECOVERY Collaborative Group. 2021), regdanvimab (Ison *et al*., 2021) and sotrovimab (Gupta *et al*., 2021) for COVID-19 treatment.

	Treatment response (primary outcome)	*Treatment difference [experimental-comparator arm]:*	*Time to sustained resolution of symptoms*	*Treatment difference in time to symptoms resolution [experimental-comparator arm]:*	*Safety*
BAMLANIVIMAB-ETESEVIMAB (Dougan *et al*., 2021) **Median time from symptoms occurrence to randomization:** 4 (range 0-29) days **Primary outcome:** Overall clinical status of the patients, defined as COVID-19–related hospitalization (acute care for ≥24 hours) or death from any cause by day 29					
Bamlanivimab + etesevimab (2800+2800 mg IV) (n = 1035) **Compara tor arm**	2.1% (n = 11)	Absolute risk difference, –4.8% (95% CI: 7.4, –2.3); Relative risk difference 70%, p < 0.001	8 days (95% CI: 7, 8)	-1 day (p = 0.007)	Most common adverse events: Rash 1.2 % (n = 6) Nausea 1.0 % (n = 5) Dizziness 0.8 % (n = 4)
Placebo (n = 1035) **Comparator arm**	7.0% (n = 60)		9 days (95% CI: 8, 10)		Most common adverse events: Nausea 0.8 % (n = 4) Dizziness 0,6 % (n = 3) Rash 0.6 % (n = 3)
CASIRIVIMAB-IMDEVIMAB (Weinreich *et al*., 2021) **Median time from symptoms occurrence to randomization:** 3.0 (interquartile range 2-5) days. **Primary outcome:** Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29					
Casirimivab + imdevimab (1200+1200 mg IV) (n = 1355) **Experimental arm**	1.3% (n = 18)	Relative risk reduction 71.3% (95% CI: 51.7%, 82.9%; p<0.0001)	10 days	-4 days p<0.001	Any serious adverse events: 1.3% Any serious adverse events of special interest: <0.1%
Placebo (n = 1341) **Comparator arm**	4.6% (n = 62)		14 days		Any serious adverse events: 4.0% Any serious adverse events of special interest: 0.3%
CASIRIVIMAB-IMDEVIMAB (Weinreich *et al*., 2021) **Median time from symptoms occurrence to randomization:** 3.0 (interquartile range 2-5) days **Primary outcome:** Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29					
Casirimivab + imdevimab (600+600 mg IV) (n = 736) **Experimental arm**	1.0% (n = 7)	Relative risk reduction 70.4% (95% CI: 31.6%, 87.1%; p = 0.0024)	10 days	-4 days p < 0.001	Any serious adverse events: 1.1% Any serious adverse events of special interest: 0.1%
Placebo (n = 748) **Comparator arm**	3.2% (n = 24)		14 days		Any serious adverse events: 4.0% Any serious adverse events of special interest: 0.3%

CASIRIVIMAB-IMDEVIMAB (RECOVERY Collaborative Group. 2021) **Median time from symptoms occurrence to randomization:** 9 (interquartile range 6-12) days **Primary outcome:** 28-day all-cause mortality					
Casirimivab + imdevimab (4000+4000 mg IV) (n =1633 seronegative participants) **Experimental arm**	24% (n = 396)	Rate ratio 0.80 (95% CI: 0.70, 0.91; p=0.001)	NA	NA	Potential infusion reactions: fever (4%) sudden hypotension (4%) thrombotic events (2%)
Usual Care (n =1520 seronegative patients) **Comparator arm**	30% (n = 451)		NA		Potential infusion reactions: fever (3%), sudden hypotension (2%) thrombotic events (1%)
REGDANVIMAB (Ison *et al.*, 2021) **Time from symptoms occurrence to randomization:** All patients had symptom duration <7 days **Primary outcome:** Proportion of high-risk patients with clinical progression or death at day 28					
Regdanvimab (40 mg/kg IV) (n = 652) **Experimental arm**	3.1% (n = 14)	Absolute risk difference -8.0 (95% CI: -11.7; -4.5); p < 0.0001	9.27 (8.27-11.05) days	Clinical recovery ratio 1.58 (95% CI1.31; 1.90); p < 0.0001	Treatment related emergent adverse events: 6.7% (n = 44)
Placebo (n = 650) **Comparator arm**	11.2% (n = 48)		NR (12.35; NR)		Treatment related emergent adverse events: 7.1% (n = 46)
SOTROVIMAB (Gupta *et al.*, 2021) **Time from symptoms occurrence to randomization:** 59% of patients with a symptoms duration ≤3 days **Primary outcome:** Proportion of participants with hospitalization or death through Day 29					
Experimental arm Sotrovimab 500 mg IV (n = 528)	1.1% (n = 6)	Relative risk reduction 0.21 (95% CI: 0.09, 0.50; p<0.001)	NA	NA	Any adverse event 22% (n = 114) Any infusion-related adverse event 1% (n = 6) Any serious adverse event 2% (n = 11)
Comparator arm Placebo (n = 529)	5.7% (n = 30)		NA		Any adverse event 23% (n = 123) Any infusion-related adverse event 1% (n = 6) Any serious adverse event 6% (n = 32)

Abbreviations: IV: intravenous; CI: confidence interval; NA: not available; NR: not reached.

adverse events that occurred post-infusion was also similar in the two groups.

Casirivimab-Imdevimab for Outpatient Care

Previous Phase 1/2 data suggested that, in patients with COVID-19 in the outpatient setting, REGEN-COV (combination casirivimab-imdevimab) reduced the risk of hospitalization (Weinreich *et al.*, 2021). The Phase 3 portion of the REGEN-COV trial enrolled 4,057 COVID-19 patients with one or more risk factors for severe disease, in the outpatient setting (Weinreich *et al.*, 2021). Patients were randomized to a single intravenous dose of REGEN-COV or placebo and followed for 28 days. The pre-specified hierarchical analysis first compared a 2,400 mg dose of REGEN-COV (1,200 mg each of casirivimab and imdevimab) versus placebo, then compared a 1,200 mg dose (600 mg of each antibody) versus placebo. The primary endpoint was proportion of patients with one or more COVID-19-related hospitalizations or all-cause death through day 29.

Both the 2,400 mg and 1,200 mg doses of REGEN-COV significantly reduced COVID-19-related hospitalization or all-cause death compared to placebo (71.3% reduction [1.3% vs 4.6%; p<0.0001] and 70.4% reduction [1.0% vs 3.2%; p=0.0024], respectively). The median time to resolution of COVID-19 symptoms was shorter in both dose arms versus placebo (10 vs 14 days; p<0.0001). The safety profile of both doses was reassuring with SAEs that occurred more frequently in the placebo group (4.0%) than in the 1,200 mg (1.1%) and 2,400 mg (1.3%) groups. Grade ≥2 infusion-related reactions were infrequent (<0.3% in all groups).

Casirivimab-Imdevimab for Inpatient Care

The RECOVERY trial is an investigator-initiated, individually-randomized, controlled, open-label, plat-

form trial that evaluated the efficacy of different treatments in patients hospitalized with COVID-19 (RECOVERY Collaborative Group, 2021). For the evaluation of REGEN-COV, the enrolled patients were randomly allocated in a 1:1 ratio to either standard of care (usual care group) or standard of care plus a single intravenous infusion of REGEN-COV (4,000 mg casirivimab and 4,000 mg imdevimab; REGEN-COV group). The primary outcome was 28-day mortality assessed first among patients without detectable antibodies to SARS-CoV-2 at randomization (seronegative) and then in the overall population.

Overall, 9,785 patients were randomized to receive usual care plus REGEN-COV or usual care alone, including 3,153 (32%) seronegative patients, 5,272 (54%) seropositive patients, and 1,360 (14%) patients with unknown antibody status. In the primary efficacy population of seronegative patients (*Table 1*), 24% (396/1,633) of patients in the REGEN-COV group and 30% (451/1520) in the usual care group died within 28 days (rate ratio 0.80; 95% CI: 0.70, 0.91; p=0.001). In an analysis involving all randomized patients, 944/4,839 (20%) patients allocated to REGEN-COV and 1,026/4,946 (21%) patients allocated to usual care group died within 28 days (rate ratio 0.94; 95% CI: 0.86, 1.03; p=0.17). The frequency of fever (4% vs 3%), sudden hypotension (4% vs 2%), and thrombotic events (2% vs 1%) was marginally higher in the REGEN-COV group. Five serious adverse reactions that were potentially related to REGEN-COV were reported.

Regdanvimab

The efficacy of regdanvimab was investigated in a Phase II/III study of 1,300 adult patients with mild or moderate SARS-CoV-2 infection, without oxygen therapy demands, and with symptom duration 7 days or less (Ison *et al.*, 2021). Patients were randomized in a 1:1 ratio to regdanvimab (40 mg/kg) or placebo, both in addition to standard of care. The primary endpoint was the proportion of high-risk patients with clinical symptoms requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to day 28. In this context, high-risk patients were considered to be those with at least one of the following conditions: age >50 years, BMI >30 kg/m^2, chronic lung disease, chronic liver disease, chronic renal disease, diabetes, cardiovascular disease, or immunosuppression.

Up to day 28, COVID-19 progression was observed in 14/446 (3.1%) high-risk patients treated with regdanvimab versus 48/434 (11.1%) treated with placebo (risk difference -8.0% (-95% CI: 11.7; -4.5), reduction rate 72%, p<0.001). The efficacy of regdanvimab was maintained when all patients at all risk levels were included: 2.4% of patients treated with regdanvimab experienced disease progression compared to 8.0% of those treated with placebo (difference -5.9% (-8.5; -3.3), reduction rate 70%, p<0.001). Time to clinical recovery was shorter by at least 4.7 days in the regdanvimab group compared to the placebo group (p<0.001; *Table 1*). The safety profile was similar between groups, including infusion-related reactions (0.6% for regdanvimab vs 1.1% for placebo).

Sotrovimab

The efficacy of sotrovimab was investigated in a multicenter, double-blind, Phase 2/3 trial (part of the COMET-ICE trial) that enrolled patients with symptomatic mild-to-moderate COVID-19 in an outpatient setting (Gupta *et al.*, 2021). Participants were randomized 1:1 to an IV infusion of sotrovimab 500 mg or placebo and the primary outcome was proportion of participants with hospitalization or death through day 29.

Up to day 29, disease progression was observed in 6/528 (1.1%) patients in the sotrovimab group compared to 30/529 (5.7%) in the placebo group (*Table 1*). The risk of COVID-19 progression was significantly reduced among participants treated with sotrovimab versus placebo (adjusted relative risk reduction 79% (95% CI: 50%, 91%); p<0.001). The proportion of patients who experienced adverse events was similar between treatment arms (22% in the sotrovimab group vs 23% in the placebo group,) and SAEs were more common in the placebo arm (6% vs 2%); no SAEs were considered treatment-related. No deaths were reported in patients receiving sotrovimab, compared with four in patients receiving placebo.

IMPACT OF SARS-CoV-2 VARIANTS OF CONCERN ON SUSCEPTIBILITY TO ANTI-SARS-CoV-2 MONOCLONAL ANTIBODIES

Variants of concern (VOC) of SARS-CoV-2 are characterized by higher transmissibility, clinical severity, or impact on immunity. Four VOCs have been described: B.1.1.7 (also known as Alpha) first identified in the United Kingdom, B.1.351 (also known as Beta) first identified in South Africa, B.1.1.28 (also known as P.1 or Gamma) in Brazil, and B.1.617.2 (also known as Delta) in India (Center for Disease and Control Prevention, 2021) (*Table 2*). These VOC contain substitutions in the N-terminal domain and the receptor-binding motif of the RBD of the S protein, which facilitate increased transmissibility compared to original SARS-CoV-2 (Davies *et al.*, 2021; Pearson *et al.*, 2021; Sheikh *et al.*, 2021). Additionally, B.1.351 and B.1.1.28 have been associated with reduced treatment efficacy of mAb therapies, especially for the combination bamlanivimab-etesevimab (Wang *et al.*, 2021; Hoffmann *et al.*, 2021).

For VOC B.1.351, characterized by the presence of E484K and K417N mutations, previous studies have shown a marked reduction of in vitro susceptibili-

Table 2 - *SARS-CoV-2 Variants of Concern and Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies.*

WHO Label	Pango Lineage	Notable Mutations	Bamlanivimab Plus Etesevimab		Casirivimab plus Imdevimab		Regdanvimab		Sotrovimab	
			In vitro susceptibility	*Activity**	*In vitro susceptibility*	*Activity**	*In vitro susceptibility*	*Activity**	*In vitro susceptibility*	*Activity**
Alpha	B.1.1.7	N501Y	No change	Active	No change	Active	No change	Active	No change	Active
Beta	B.1.135	K417N, E484K, N501Y	Marked change[a]	Unlikely to be active	No change	Active	Marked change[c]	Likely to be active	No change	Active
Gamma	B.1.1.28	K417T, E484K, N501Y	Marked change[a]	Unlikely to be active	No change	Active	Marked change[c]	Likely to be active	No change	Active
Delta	B.1.167.2	L452R	Modest change[b]	Likely to be active	No change	Active	Marked change[c]	Likely to be active	No change	Active

*Anticipated clinical activity against the variant, based on in vitro studies or in vivo studies, when available.
[a]Marked change for casirivimab and no change for imdevimab. The combination of casirivimab plus imdevimab appears to retain activity.
[b]Modest change for the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not fully known.
[c]based on Ryu DK *et al.*, 2021.
Abbreviations; WHO: World Health Organization.
Adapted and modified by COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [05th October 2021].

ty to bamlanivimab, etesevimab, and casirivimab (Wang *et al.*, 2021). Sotrovimab and the combination casirivimab-imdevimab therapy maintains efficacy against B.1.351 variant, however (European Medicines Agency, 2021).

For VOC B.1.1.28, which involves E484K and K417T mutations, there is reduced or absent susceptibility to casirivimab, bamlanivimab, and etesevimab (Wang. *et al.*, 2021). However, imdevimab and sotrovimab have maintained their efficacy (European Medicines Agency, 2021). Although casirivimab activity was markedly reduced, the combination casirivimab-imdevimab therapy retained neutralization efficacy against the B.1.128 variant. The FDA no longer authorizes the use of bamlanivimab and etesivimab for COVID-19 treatment in U.S. states and territories in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5% (Food and Drug Administration, 2021).

First identified in India, the B.1.617.2 variant has been associated with a marked increase in transmissibility and with a more severe clinical course (Twohig *et al.*, 2021) and now is the dominant viral strain worldwide (Vaughan, 2021). It contains the L452R mutation, which is an escape mutation for bamlanivimab, thus there is a loss of antiviral activity of bamlanivimab against B.1.617.2 (Planas *et al.*, 2021). However, etesevimab remains active against B.1.617.2 and this finding results in only a modest decrease in viral susceptibility to the combination of bamlanivimab and etesevimab. Casirivimab, imdevimab, and sotrovimab appear to retain activity against the B.1.617.2 variant (COVID-19 Treatment Guidelines Panel, 2021).

Preliminary efficacy data on regdanvimab showed reduced in vitro susceptibility among B.1.351, B.1.1.28, and B.1.617.2 variants. However, therapeutic efficacy seems to be retained at a clinical dosage of 40 mg/kg (Ryu *et al.*, 2021; Ryu *et al.*, 2021).

REGULATORY STATUS

COVID-19 Treatment

Currently, remdesivir is the only antiviral treatment authorized by the FDA in October 2020 and EMA for use in adult and pediatric COVID-19 patients, being at least 12 years old and weighting at least 40 kilograms, requiring hospitalization. Among antivirals, molnupiravir, a ribonucleoside analogue, has proved to reduce the risk of hospitalization or death for adult patients with mild or moderate COVID-19 at the interim analysis in phase 3 MOVe-OUT trial (Merck. 2021). Its approval is on hold by the FDA,

Table 3 - *Italian Medicines Agency (AIFA). Clinical criteria for monoclonal antibody therapy of COVID-19 in the outpatient setting.*

Definition of high-risk COVID-19 patients (presence of at least one of the following):
BMI ≥30 kg/m² or BMI >95% percentile for age and gender
Chronic kidney disease, including those on dialysis
Type 1 or type 2 diabetes mellitus (HbA1c >9.0%, or >75 mmol/mol) or with associated chronic complications
Primary or secondary immune deficiencies
Age >65 years
Cerebrovascular diseases (including arterial hypertension with associated organ damage)
Chronic lung diseases (e.g. chronic obstructive pulmonary disease, asthma, pulmonary fibrosis)
Chronic liver diseases
Hemoglobinopathies
Neurodevelopmental disorders or neurodegenerative diseases

Abbreviations: Body mass index (BMI); glycated hemoglobin (HbA1c).

Table 4 - *Main ongoing studies on neutralizing monoclonal antibody therapies, for COVID-19 treatment, as reported in ClinicalTrials.gov (accessed on October 10th, 2021).*

ClinicalTrials.gov Identifier	*mAb tested*	*Recruitment Status*	*Phase*	*Population*	*Design*	*Enrollment (n)*	*Primary outcome*
NCT04771351	COVI-AMG	Recruiting	2	Adult patients with mild COVID-19	Randomized, double-blind, placebo-controlled, multi-center	500	Proportion of subjects who have remained out of the hospital or emergency room through day 29
NCT04900428	COVI-DROPS	Recruiting	2	Adults tested positive for COVID-19 and are either asymptomatic or have mild symptoms	Randomized, double-blind, placebo-controlled study	350	Viral load change from baseline to day 8
NCT04381936 RECOVERY	REGN-COV2	Recruiting	2/3	Children and adults hospitalized with suspected or certain SARS-CoV-2 infection	Randomized with factorial assignment, open label	45,000 (for all treatments tested)	All-cause mortality
NCT04501978	AZD7442	Recruiting	3	Hospitalized adult patients	Randomized, double-blind, placebo-controlled, multicenter, adaptive	1,000	Time from randomization to sustained recovery
NCT04634409	LY3819253 LY3832479 VIR-7831 LY3853113	Active, not recruiting	2	Adults with mild or moderate COVID-19, outpatient	Randomized, double-blind, placebo-controlled	1,782	Percentage of participants with SARS-CoV-2 viral load > 5.27 log10 at day 10
NCT04545060	VIR-7831	Not yet recruiting	2/3	Non-hospitalized adults at high risk of progression	Randomized, multi-center, double-blind, placebo-controlled	1,360	Proportion of participants who have progression of COVID-19 through day 29
NCT04644185	SCTA01	Recruiting	2/3	Hospitalized patients with severe COVID-19	Multicenter, adaptive, randomized, double-blinded, placebo-controlled	795	The clinical efficacy of SCTA01 through day 29, and time to clinical improvement (TTCI)
NCT04840459	Bamlanivimab/ Casirivimab/ Imdevimab	Recruiting	2	Patients with mild to moderate COVID-19, outpatient	Non-randomized	1,000	Number of patients with mild to moderate COVID-19 who are at high risk for progressing to severe COVID-19 and/ or hospitalization
NCT04709328	SCTA01	Not yet recruiting	2/3	High-risk outpatients with COVID-19	Adaptive, randomized, double-blinded, placebo-controlled	690	Proportion of participants who experience COVID-19-related hospitalization or death (all cause) up to day 29
NCT04683328	SCTA01	Not yet recruiting	2/3	Patients with severe COVID-19 admitted to high dependence or intensive care unit	Adaptive, randomized, double-blinded, placebo-controlled	560	All-cause mortality rate at day 29
NCT04790786	Bamlanivimab/ Casirivimab Imdevimab/ Bamlanivimab Etesevimab	Recruiting	3	Patients with COVID-19, outpatient	Adaptive platform	5,000	Alive and free from hospitalization, through day 28
NCT04545060	VIR-7831	Active, not recruiting	2/3	Patients with COVID-19, outpatient	Randomized, multi-center, double-blind, placebo-controlled	1,360	Proportion of participants who have progression of COVID-19 through day 29
NCT04649515	TY027	Recruiting	3	Patients with COVID-19	Multi-scenter, randomized, placebo controlled, double blind	1,305	Disease progression, defined as progression to score 4 and below on COVID-19 scale

Table 5 - *Main ongoing studies on neutralizing monoclonal antibody therapies, for COVID-19 prophylaxis, as reported in ClinicalTrials.gov (accessed on October 10th 2021).*

ClinicalTrials.gov Identifier	*mAb tested*	*Recruitment Status*	*Phase*	*Population*	*Type of prophylaxis*	*Design*	*Enrollment (n)*	*Primary outcome*
NCT04497987	Bamlanivimab LY3832479	Completed	3	Skilled nursing and assisted living facility residents and staff	Post-exposure	Randomized, double-blind, placebo-controlled	5,000	Percentage of participants with COVID-19 within 21 days of detection
NCT04625972	AZD7442 AZD8895 AZD1061	Active, not recruiting	3	Adults with potential exposure to SARS-CoV-2 infection	Post-exposure	Randomized, double-blind, placebo-controlled, multi-center	1,121	The incidence of the first case of SARS CoV-2 RT PCR positive symptomatic illness
NCT04625725	AZD7442 AZD8895 AZD1061	Active, not recruiting	3	Adults with potential exposure to SARS-CoV-2 infection	Pre-exposure	Randomized, double-blind, placebo-controlled, multi-center	5,198	The incidence of the first case of SARS CoV-2 RT PCR positive symptomatic illness
NCT04859517	ADG20	Recruiting	2/3	Adults at high risk of SARS-CoV-2 infection	Pre- and post-exposure	Randomized, double-blind, placebo-controlled	6,412	Proportion of participants with RT-PCR confirmed symptomatic COVID-19
NCT04452318	REGN10933 REGN10987	Completed	3	Household contacts to an individual with a positive SARS-CoV-2 RT-PCR assay	Post-exposure	Randomized, double-blind, placebo-controlled	3,750	Proportion of participants with symptomatic RT-PCR-confirmed SARS-CoV-2 infection

Abbreviations: monoclonal antibodies (mAb); real-time PCR (RT-PCR).

being of particular interest as it would be the first oral drug for COVID-19 treatment.

On the other hand, the role of convalescent plasma in COVID-19 treatment is still questioned, being approved by the FDA under an Emergency Use Authorization, given the lack of effective treatments. It was proven to beneficial in the early phase of infection (namely, less than 72 hours after symptom onset) on older, mildly-ill-infected patients on disease progression in a high-quality, multicenter, randomized, controlled trial (Libster *et al.*, 2021). In this study a dose-dependent effect according to the antibody titers was demonstrated; however, this relation has been questioned by different groups (Devos *et al.*, 2021; de Candia *et al.*, 2021) Moreover, little is known about seroreactivity in patients as a selection criterion for its administration. Other limits are the weak evidence of efficacy on hospitalized patients (Li *et al.*, 2021; Simonovich *et al.*, 2021; Agarwal *et al.*, 2021), the restricted window of administration and the difficult accessibility.

Still, high titer concentration convalescent plasma has been approved by the FDA only for the treatment of hospitalized patients with COVID-19 early in the disease course and to those hospitalized patients who have impaired humoral immunity and cannot produce an adequate antibody response (Food and Drug Administration. 2021).

Under this perspective, mAbs represent a more encouraging approach to providing passive immunity in the treatment of SARS-CoV-2 infection.

Presently, only the mAb combination therapies bamlanivimab-etesevimab and casirivimab-imdevimab, and the monotherapies sotrovimab and regdanvimab have received preliminary authorization, by the FDA or EMA, for use in patients with COVID-19 in the outpatient setting (FDA Emergency use Authorization COVID Drugs, 2021; EMA COVID-19 Treatments, 2021).

In addition, the Italian Medicines Agency (AIFA), has authorized the use of combined therapy casirivimab-imdevimab (4000 mg + 4000 mgin a single intravenous infusion) for the treatment of hospitalized COVID-19 patients who do not require high-flow oxygen therapy or mechanical ventilation (Agenzia Italiana del Farmaco, 2021).

In COVID-19 patients at high-risk of progression in the outpatient setting, the FDA, EMA and AIFA have preliminarily authorized the use of bamlanivimab-etesevimab (a single intravenous (IV) infusion of 700 mg bamlanivimab and 1,400 mg etesevimab), casirivimab-imdevimab (a single IV infusion with 1,200 mg each, in Europe, and a single IV infusion or subcutaneous injection with 600 mg each, in US) and sotrovimab (a single IV infusion of 500 mg)

(FDA Emergency Use Authorization COVID Drugs, 2021; EMA COVID-19 Treatments, 2021; Agenzia Italiana del Farmaco, 2021). The risk factors associated with a progression to severe COVID-19 may include: advanced age, overweight/obesity, cardiovascular disease, hypertension, chronic lung disease, diabetes, chronic kidney disease, liver disease, immunosuppression, and neurodevelopmental diseases (Agenzia Italiana del Farmaco, 2021).

The complete list of criteria indicated by AIFA for the prescription of monoclonal antibodies in the outpatient setting is reported in *Table 3*.

MAb therapies should be administered as soon as possible after testing positive for SARS-CoV-2 and must be prescribed within 10 days of symptom onset (Agenzia Italiana del Farmaco, 2021; Food and Drug Administration, 2021).

Post-Exposure Prophylaxis Against COVID-19

According with the results of the BLAZE-2 and NCT04452318 trials (Cohen, *et al*., 2021; O'Brien *et al*., 2021), the FDA approved an emergency use authorization (EUA) for both casirivimab-imdevimab and bamlanivimab-etesevimab as PEP for COVID-19 in adults and pediatric patients (≥12 years of age, weight ≥40 kg). To be eligible for PEP, these patients must meet several criteria. They must be at high risk for progression to severe COVID-19. They must be either not fully vaccinated, or not expected to mount an adequate immune response to full SARS-CoV-2 vaccination, such as in patients taking immune suppressants drugs. Finally, they must have been exposed to an individual infected with SARS-CoV-2, or be at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes or prisons) (Food and Drug Administration, 2021). More PEP authorizations may be forthcoming. AstraZeneca has submitted an EUA request to the FDA for AZD7442, for the prophylaxis of symptomatic COVID-19 based on data from the PROVENT study (AstraZeneca, 2021). There are several ongoing studies on neutralizing mAb therapy for the treatment and prophylaxis of COVID-19 (*Tables 4, 5*).

CONCLUSIONS

As COVID-19 continues to present a threat to global health, neutralizing mAb therapy may be a powerful tool for both the treatment and prevention of COVID-19. In this review, we reported the efficacy and safety data of the first neutralizing mAb therapies that have obtained preliminary authorization by the FDA or EMA. Many other mAb therapies are in the development pipeline and may represent future options for COVID-19 management. Due to their efficacy and safety, neutralizing mAb therapies are poised to revolutionize the treatment of not only COVID-19, but also other infectious diseases, in the coming years.

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