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Monoclonal antibodies for the treatment of COVID-19 patients: An umbrella to overcome the storm?

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**ABSTRACT**

The world is facing up the most considerable vaccination effort in history to end the Coronavirus disease 2019 (COVID-19) pandemic. Several monoclonal antibodies (mAbs) direct against the Receptor binding domain of the S protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) received an Emergency Use Authorization for outpatient management of mild to moderate manifestation from COVID-19. MAbs could prevent the transmission SARS-CoV-2 infection and protect individuals from progression to severe disease. Under the pressure of different treatment strategies, SARS-CoV-2 has been demonstrated to select for different sets of mutations named “variants” that could impair the effectiveness of mAbs by modifying target epitopes. We provide an overview of both completed and unpublished, or ongoing clinical trials of mAbs used and review state of art in order to describe clinical options, possible indications, and the place in therapy for these agents in the treatment of COVID-19 with a particular focus on anti-spike agents. Then, we reassume the current evidence on mutations of the SARS-CoV-2 that might confer resistance to neutralization by multiple mAbs.

**1. Introduction**

The coronavirus disease 2019 (COVID-19) pandemic has resulted in more than 4.7 million deaths globally and nearly 227 million cases, representing a global challenge that demands pressing prevention and treatment research. Two processes are involved in COVID-19 pathogenesis: in the first phase of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the damage is induced by the virus entering the host cell through the binding of the S spike protein to ACE-2 receptors and starting to replicate [1]. In the second phase of the infection, the disease is driven by an exaggerated inflammatory response [2]. Several treatments are indicated according to the different stages of the infection.

Remdesivir (RDV) has shown clear clinical benefit if administered early during the viral stage of the disease, resulting in reduced mortality rate in patients who received RDV administration at most 9 days after the onset of symptoms [3]. The timing of therapy is also pivotal for immunomodulatory drugs, such as steroids and tocilizumab since they are employed to manage the hyper inflammation stage associated with acute respiratory distress syndrome (ARDS) [4,5].

Data from the RECOVERY trial have shown that dexamethasone improves the outcome of 4 weeks mortality in hospitalized convalescents with oxygen or mechanical ventilation. In contrast, it had no apparent effect on patients who were not receiving respiratory support [6]. The NIH panel recommends against the use of corticosteroids in individuals who do not necessitate supplemental oxygen and in outpatients with mild to moderate symptoms because there are insufficient data to support this decision; in addition, corticosteroids may lead to serious adverse effects (e.g., hyperglycemia, neuropsychiatric symptoms, secondary infections) [7]. Similarly, tocilizumab is indicated in combination with dexamethasone in recently hospitalized patients exhibiting rapid respiratory decompensation and significantly increasing inflammation markers [8].

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Another treatment still under evaluation is convalescent plasma from donors who have been cured of COVID-19. Early treatment with plasma could increase the patient’s immune response and lower the risk of disease progression. The use of convalescent plasma has lately been associated with improved outcomes in patients with defective immunity after chemo-immunotherapy or with hematologic malignancy in healthcare settings. However, the efficacy of convalescent plasma has not yet been clear, as other trials did not find significant differences in clinical status and mortality among patients treated with plasma from donors who had recovered from SARS-CoV-2 infection and patients treated with placebo.

Treatments mentioned earlier are recommended for hospitalized patients with hypoxemia, and no standard therapies were available for outpatients who do not require supplemental oxygen.

Promising drugs that have emerged are monoclonal antibodies (mAbs), mainly aiming at the trimeric spike (S) glycoprotein on the viral surface that mediates entry into host cells. The FDA, in United States [11] and the EMA, in European countries [12,13] have issued advice for the use of two combinations of monoclonal antibodies, casirivimab and imdevimab (REGN-COV2) and bamlanivimab and etesevimab in outpatients who are not needing supplemental oxygen and who are at high risk of progressing severe COVID-19.

In this review, we provide an overview of what is currently known about the efficacy and safety of mAbs in COVID-19 patients and provide a new perspective on their potential applications.

2. Material and methods

To rapidly summarize the emerging evidence on the use of new mAb with activity against the S proteins of SARS-CoV-2, all publication types, including peer-reviewed manuscripts, were included in this narrative review. Publications were identified primarily through a search including the following Key search terms: casirivimab and imdevimab OR bamlanivimab and etesevimab OR mAb OR antibody treatment OR COVID-19 OR SARS-CoV-2 from January 01, 2020, to September 15, 2021. PubMed, Scopus, Google Scholar, and ClinicalTrials.gov were used for this purpose. An overview of the clinical trials addressing this topic was performed by searching on ClinicalTrials.gov using the following condition “SARS-CoV-2, COVID-19”. Studies published in non-English languages were excluded. This search was limited to review articles focused on monoclonal antibodies with specific activity against SARS-CoV-2. Articles focusing on mAb used in the treatment of COVID-19 but without specific activity against SARS-CoV-2 were excluded. All authors reviewed every step of the manuscript.

3. Results

3.1. Monoclonal antibodies anti-SARS-CoV-2

3.1.1. Casirivimab and imdevimab

Casirivimab (REGN10933) and imdevimab (REGN1098) are two noncompeting, neutralizing human IgG1 antibodies that target the receptor-binding domain of the SARS-CoV-2 spike protein, thus blocking the attachment and entry of SARS-CoV-2 into human cells. Based on the result of the trial of Weinreich et al., the FDA and EMA have issued Emergency Use Authorization (EUA) for the “cocktail” of casirivimab 1200 mg and imdevimab 1200 mg (REGN-COV2) for outpatients with mild or moderate COVID-19 who do not need oxygen supplementation and who are at high risk of progressing to severe disease [12-14]. This study suggested that a single intravenous dose of REGN-COV2 (1200 mg + 1200 mg or 4000 mg + 4000 mg) reduced SARS-CoV-2 viral load (VL), COVID-19 hospitalization days or medical visits when administered within seven days from the onset of symptoms compared to placebo. Patients were treated with a median of 3 days after SARS-CoV-2 infection confirmation. The median time to symptom improvement was five days for the interventional arm then 11 days for the placebo arm. Of note, patients with no initial antibodies for SARS-CoV-2 demonstrated the most significant clinical benefit [14]. The incidence of serious adverse Preliminary data from REGN-COV 2069 [15] trial suggested that a subcutaneous administration casirivimab and imdevimab lowered the risk of symptomatic COVID-19 infection by over 80% SARS-CoV-2 negative individuals household contact with COVID-19 infected individuals. The risk of progression to symptomatic infection was also reduced by 31% in asymptomatic SARS-CoV-2 positive individuals. The [15] and [16] trials are assessing the efficacy of REIGN-COV2, respectively, in preventing symptomatic COVID-19 infection in adolescents (greater than 12y) who are a household contact of SARS-CoV-2 positive individuals and in reducing SARS-CoV-2 VL in pediatric setting (~18y). The latter trial [16] investigates the efficacy of REIGN-COV2 vs placebo in terms of survival and need of mechanical ventilation in hospitalized individuals who require low-flow oxygen. Dhand et al. reported promising results in 25 solid organ transplant (SOT) patients treated with REIGN-COV2. After a median of 41 days of follow up, none of the patients treated with the cocktail was hospitalized due to COVID-19 [17].

3.1.2. Bamlanivimab and etesevimab

Bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016) are two humanised immunoglobulin G1 (IgG1) kappa neutralising antibodies that act against the receptor-binding domain of SARS-CoV-2 S glycoprotein to prevent the virus from attaching to and entering human cells [18]. Bamlanivimab and etesevimab are co-administered with synergistic intent to target different epitopes of the SARS-CoV-2 spike glycoprotein [18]. The FDA [11] and EMA [13] have issued a EUA for the combined use of these antibodies to treat mild to moderate coronavirus disease 2019 (COVID-19) in adults and children who are not hospitalised. In an animal model, Jones et al. [19] found that prophylactic bamlanivimab reduced viral replication in the upper and lower respiratory tracts. Recently, a phase I randomized, placebo-controlled, double-blind clinical study was commenced to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous bamlanivimab in 24 hospitalised patients with COVID-19 (NCT04411628) (Table 1).

The primary and secondary outcomes included the area under the concentration–time and the VL change from the baseline to day 29; however, definitive results are not yet available [20]. In an interim analysis, Chen [21] and then Gottlieb et al. [22] presented data from the BLAZE-1 study. In this study 577 patients were randomized and allocated to three arms to receive one of the following: a single infusion of bamlanivimab (at doses of 700 mg [n = 101], 2800 mg [n = 107] or 7000 mg [n = 101]); a combination treatment of 2800 mg bamlanivimab plus 2800 mg etesevimab (n = 112) or a placebo (n = 156). 533 (92.4%) completed the efficacy evaluation period. The combination therapy of bamlanivimab and etesevimab significantly reduced VL at days 3, 7 and 11. An exploratory analysis showed that fewer patients in the intervention arm had persistently high VL at day 7 compared to the placebo arm (3.0% vs 20.8%, p < 0.0001). Moreover, no emergent putative resistant variants have been found in convalescents treated with combination therapy. The improvement of symptoms at day 11 remained significant in the combination therapy (p = 0.009). The rate of COVID-19-related hospitalizations and emergency room visits decreased in patients treated with the combination therapy (0.9%) vs the placebo (5.8%). The relative risk reduction was 84.5% in the combination arm compared to the placebo arm (p = 0.049) similar to bamlanivimab monotherapy. Treatment-emergent side effects were comparable to the placebo for both bamlanivimab monotherapy and combination therapy, and no drug-related serious adverse events have been reported. The ongoing BLAZE-2 [23] phase III trial, which is scheduled to enroll 2,400 patients, and a placebo-controlled phase II/III in outpatients (ACTIV-2, [24]) aims to assess the efficacy of bamlanivimab in preventing SARS-CoV-2 infection in an assisted living facility and outpatients tested positive for COVID-19, respectively. Then, the study will evaluate
Table 1
Studies, interventions and results regarding monoclonal antibodies for SARS-CoV-2 infection in use and under investigation.

| Study | Interventions | Results |
|-------|---------------|---------|
| **Casirivimab and Imdevimab** | • Casirivimab and Imdevimab SC or IM  
• Placebo SC or IM  
• Casirivimab and Imdevimab high dose IV  
• Casirivimab and Imdevimab low dose IV  
• Placebo IV | Active, not recruiting  
Recruiting |
| NCT04452318A Phase III, Randomized, Double-Blind, Placebo-Controlled |  
Cohort 1 (On Low-Flow Oxygen):  
• Casirivimab + Imdevimab  
• Placebo | Recruiting |
| A Phase I/Phase II/Phase III, Randomized, Placebo-Controlled Study | Cohort 1A (With COVID-19 symptoms but not requiring supplemental O2):  
• Casirivimab + Imdevimab  
• Placebo |  |
| NCT04425629 | Cohort 2 (High O2 No Mechanical Ventilation):  
• Casirivimab + Imdevimab  
• Placebo |  |
| A Phase I/Phase II/Phase III, Randomized, Placebo-Controlled Study | Cohort 3 (On Mechanical Ventilation):  
• Casirivimab + Imdevimab  
• Placebo |  |
| NCT04426695 |  |
| Bamlanivimab | • Bamlanivimab IV  
• Placebo | Completed |
| NCT04411628 Phase I, Randomized, Placebo-Controlled, Double-Blind |  |
| NCT04427501 |  |
| Bamlanivimab and etesevimab | • Bamlanivimab and Etesevimab SC  
• Bamlanivimab IV  
• Placebo  
Part 1:  
• Bamlanivimab IV  
• Placebo IV  
Part 2 (prevention):  
• Bamlanivimab IV  
• Bamlanivimab + etesevimab IV  
• Placebo IV | Recruiting |
| NCT04497987 Phase III Randomized, Double-Blind, Placebo-Controlled | Part 2 (treatment):  
• Bamlanivimab IV  
• Bamlanivimab + etesevimab IV  
Part 3:  
• Bamlanivimab IV  
• Bamlanivimab + etesevimab IV  
• Bamlanivimab7000 mg or 700 mg (Phase II) 700 mg (Phase III) IV  
• 1000 mg (BRII-196)/1000 mg (BRII-198) IV  
• 300 mg AZD7442 (150 mg AZD8895 + 150 mg AZD1061) IV  
• Placebo IV;  
• SNG001 1.3 mL inhalation Vs. placebo inhalation  
• AZD7442 IM (2 separate doses of 300 mg AZD8895 then 300 mg AZD1061)  
• placebo IM  
• Camostat 200 mg OS Vs Placebo;  
• CL5-LS + CL44-LS SC  
• Placebo SC  
• SAB-185 low or high dose  
• Bamlanivimab plus Standard of Care (remdesivir)  
• VIR-7831 plus Standard of Care (remdesivir)  
• BRII-196/BRII-198 plus Standard of Care (remdesivir)  
• AZD7442 plus Standard of Care (remdesivir)  
• Placebo plus Standard of Care  
• Bamlanivimab + Etesevimab IV  
• Bamlanivimab IV  
• Placebo IV  
• Bamlanivimab + VIR-7831 VS LY-CoV1404 IV  
• Bamlanivimab + etesevimab + LY-CoV1404 IV  
• CT-P59  
• Placebo | Recruiting |
| NCT04501978 Multicenter, Randomized, Blinded Controlled |  |
| NCT04571249 Phase II, Randomized, Double-blind, Placebo-Controlled |  |
| NCT04634409 |  |
| CT-P59 | • CT-P59  
• Placebo | Active, not recruiting |
| Study ID | Study Interventions | Results |
|---------|---------------------|---------|
| NCT04593641 | Pilot Phase I, Randomized, Double-blind, Placebo-controlled | CT-P59 Recruiting |
| NCT04602000 | Phase II/III, Randomized, Placebo-controlled, Double-blind | Placebo |
| VIR-7831 | NCT04545060 | Phase II/III, Randomized, Multi-center, Double-blind, Placebo-controlled |
| NCT04602000 | VIR-7831 IV | Placebo Active, not recruiting |
| TY027 | NCT04649515 | Phase 3 Multi-Site, Randomized, Placebo-Controlled, Double-Blind |
| NCT04429529 | TY027 0.5mg/kg or 5 mg/kg or 10 mg/kg or 20 mg/kg or 30 mg/kg IV | Placebo |
| NCT04545060 | VIR-7831 IV | Placebo Recruiting |
| NCT04551898 | TY027 1500 mg or 2000 mg IV | Placebo |
| AZD7442 | NCT04625972 | Phase III Randomized, Double-blind, Placebo-controlled, Multi-center |
| NCT04625725 | AZD7442 300 mg IM | Placebo Active, not recruiting |
| BRII 198 | NCT04479644 | Phase I Double-blind, Placebo-controlled |
| NCT046473394 | BRII 198 dose lv 1 | Placebo Recruiting |
| BRII 196 | NCT04479631 | Phase I Randomized, Single-blind, Placebo-controlled |
| NCT04507256 | BRII 198 dose lv 3 | Placebo |
| SCTA01 | NCT04483375 | Phase I Randomized, Double-blind, Placebo-controlled |
| NCT04644185 | SCTA01 | Placebo Completed |
| MW33 | NCT04533048 | Phase I MW33 injection |
| NCT04627584 | MW33 injection-1200 mg or 2400 mgMV33 | Placebo Recruiting |
| DXP593 | NCT04532294 | Phase I Randomized, Double-blind, Placebo-controlled |
| NCT04551898 | Dose level A: BGB-DXP593 10 mg/kg IV | Placebo |
| COVI-AMG | NCT04734860 | Group 1A (uninfected): COVI-AMG 40 mg or 100 mg or 200 mg |
| DZIF-10c | NCT04631705 | Placebo |
| BI767551 | NCT04822701 | Group 1B (infected): DZIF-10c mid dose inhaled |
| MW33 | NCT04533048 | Group 1C (uninfected): DZIF-10c high dose inhaled |
| NCT04627584 | Group 2A (infected): DZIF-10c low dose inhaled |
| NCT04627584 | Group 2B (infected): DZIF-10c mid dose inhaled |
| NCT04627584 | Group 2C (infected): DZIF-10c high dose inhaled |
| NCT04551898 | Group 2D (infected): randomized 1:1:1:1 to receive DZIF-10c by inhalation and infusion or DZIF-10c by inhalation and placebo by infusion or placebo by inhalation and infusion | Recruiting |
| DZIF-10c | NCT04631666 | Group 1A (uninfected): DZIF-10c 2.5 mg/kg IV |
| Phase II | Group 1B (infected): DZIF-10c 10 mg/kg IV |
| Phase II | Group 1C (uninfected): DZIF-10c 40 mg/kg IV |
| Phase II | Group 1D (uninfected): DZIF-10c 60 mg/kg IV |
| Phase II | Group 2A (infected): DZIF-10c 40 mg/kg IV |
| Phase II | Group 2B (infected): DZIF-10c 60 mg/kg IV |
| Phase II | Group 2C (infected): DZIF-10c 80 mg/kg IV |
| Phase II | Group 2D (infected): DZIF-10c 100 mg/kg IV |

(continued on next page)
multiple drugs, including bamlanivimab in the prevention of spreading and progression of SARS-CoV-2 infection [24]. Lastly, Lundgren et al. presented data from the ACTIV-3 study [25], a phase III trial that investigated the effectiveness and safety of bamlanivimab vs remdesivir in hospitalised convalescents. No significant differences in safety outcomes between the groups were found. However, enrolment had been prematurely terminated due to the absence of clinical improvement regardless of the severity of the disease.

### 3.1.3. Other monoclonal antibodies

A large amount of other monoclonal antibodies is currently under investigation (Table 1). CT-P59 has received emergency use authorization in South Korea (NCT04525079, NCT04593641, NCT04602000), and VIR-7831 has received EUA to FDA (NCT04545060, NCT04501978). [25–29].

Phase III trials are ongoing on monoclonal antibodies such as AZD7442 (NCT04625972, NCT04723394, NCT04625725), BRII 198 (NCT04479644, NCT04501978), BRII 196 (NCT04479631, NCT04501978), SCTA01, (NCT04483375, NCT04644185) [30–36].
Of interest, TY027 is a fully engineered human IgG1 whose preliminary data from the phase 1 trial (NCT04429529) showed safety and tolerability up to 20 mg/kg. In phase III trials, a total of 1,305 COVID-19 patients are scheduled to be enrolled [37]. The first 15 patients will be randomized 1:1:1 to be given either (i) a single dose of 1,500 mg TY027, (ii) 2,000 mg TY027 or (iii) Placebo for initial safety assessment. Subsequently, patients will be randomized 1:1 to receive either a single fixed dose of 2,000 mg TY027 or Placebo (N = 645 per group). All individuals will be admitted to the hospital for up to one-week post-dosing and followed up on Days 14 and 28. Moreover, phase II trials are ongoing on MW33 (NCT045330348, NCT04627584), DXP593 (NCT04532294, NCT04551898), COVI-AMG (NCT04734860), DZIF-10c (phase II/III NCT04631705, NCT04631666, NCT04822701) [38–44]. Indeed, phase I trials are ongoing on COR-101 (phase I/II NCT04674566), XLX70 (NCT04561076), DXP604 (NCT04669262), ADM03820 (NCT04592549), HFB30132A (NCT04590430), ABBV-47D11 (NCT04644120), C144-LS and C-135-LS (NCT04700163), ADG20 (phase I/II/III NCT04805671) [45–52].

AZD7442 is a combination of two mAbs (AZD8895 and AZD1061) currently investigated in one phase I (NCT04507256) and three safety and efficacy phase III studies vs placebo (NCT04625972; NCT04723394; NCT04625725) [30–32,53]. Aminoacidic replacements have been introduced into the ab to prolong their half-lives and their potential benefit and decrease Fc effector function and the potential antibody-dependent disease enhancement. In vitro data showed that both human monoclonal antibodies COV2-2196 and COV2-21301, combined under the name of AZD7442, have neutralizing activity against SARS-CoV-2 strain with mutation of concern including E484K, N501Y, and D614G, demonstrating theoretical activity in preventing escape from emerging variant viruses [54].

Recruiting phase III studies to date is a randomized, double-blind, placebo-controlled, multicenter study to assess safety and efficiency in post-exposure prophylaxis of COVID-19 in adults (STORM CHASER; NCT04625972) [32], a randomized, double-blind, placebo-controlled, multicenter study to determine the safety and efficacy of AZD7442 for the treatment of COVID-19 in non-hospitalised adults (TACKLE; NCT04723394) [31] and a randomized, double-blind, placebo-controlled, multicenter study to determine the safety and efficacy of AZD7442 for pre-exposure prophylaxis of COVID-19 (PROVENT; NCT04625725) [30]. Participating individuals will be randomly distributed in a 2:1 ratio to receive a single dose of either 300 mg of AZD7442 or saline placebo on day 1. Primary outcomes will be the SARS-CoV-2 RT PCR positive symptomatic illness rate within a period of time of 183 days.

Moreover, ACTIV-2 (NCT04518410) phase II and III trials are evaluating both infused and non-infused agents among AZD7442 (IM or iv), bamlanivimab, BRII-196/BRII-198, inhaled SNG001, camostat or placebo for outpatients, whereas ACTIV-3 (TICO; NCT04501978) is evaluating in a randomized controlled double-blind phase III trial safety and efficacy of multiple investigational agents among soc, LY3819253, VIR-7831, BRII-196/BRII-198, ADG42 or placebo for inpatients [24–25]. VIR-7831 is a fully human anti-SARS-CoV-2 dual-action mAbs derived from a parent antibody (S309) isolated from memory B cells of a 2003 SARS-CoV-2 infected patient [55]. The engineered ‘LS’ mutation in the Fc region has prolonged serum half-life and potentially enhanced distribution to the respiratory mucosa [55]. In vitro studies showed neutralising activity against wild-type SARS-CoV-2 as well as psudotyped virus encoding spike protein from the B.1.1.7 English, B.1.351 South African and P.1 Brazilian variants, binding an epitope that does not overlap with mutational sites and it is highly conserved among the current variants, showing a high barrier to resistance in vitro and in vivo [55]. To date, COMET-ICE (phase III) and COMET-PEAK (phase II) trials are ongoing. VIR-7831 has been included in the BLAZE-4 and previously cited ACTIV-3 trials [56]. The COMET-ICE trial (NCT04545060) is a randomized, multicentre, double-blind, placebo-controlled study to assess the safety and efficacy of 500 mg of VIR-7831 given once intravenously for the early treatment of COVID-19 outpatients [26]. An interim analysis on 583 patients demonstrated a significantly reduced 29-days hospitalization or death hospitalisation in patients receiving VIR-7831 compared to placebo [25]. Based on these results, has been submitted a EUA application to the FDA and the request for authorisation of VIR-7831 usage in other Countries [57].

The COMET-PEAK trial (NCT047799879) is a phase II, a multi-centre, randomized, double-blind, parallel-group, phase II study assessing whether VIR-7831 produced by different processes (gen1 vs gen2) was overlapping in terms of pharmacokinetics and safety in outpatient with mild to moderate COVID-19 [57–58].

The BLAZE-4 trial (NCT04634409) is a randomized, double-blind, placebo-controlled, phase 2 study that acted to assess the efficiency, safety, and pharmacokinetics of the administration of Bamlanivimab (700 mg) in monotherapy and in combination with Etesevimab or VIR-7831 compared to placebo to assess the proportion of patients with SARS-CoV-2 VL greater than 5.27 ng/ml at Day 7 [59–60]. Other two phase III trials have not started yet, COMET-TAIL and COMET-STAR, to assess if IM-administered VIR-7831 can lower the rate of hospitalization and fatality induce by COVID-19 and prevent symptomatic infection in an uninfected patient, respectively [57].

CT-P59 is a monoclonal antibody reformulated to a fully human immunoglobulin (IgG1) which binds the receptor-binding domain (RBD) of the spike protein of the virus to inhibit its interaction with the ACE2 receptor and to block the entrance of the virus in cells [18]. Preliminary data suggest the efficacy of CT-P59, against various SARS-CoV-2 isolates in vitro, including the D614G spike protein variant without antibody-dependent enhancement effect [61]. After positive interim results in phase I, randomized, double-blind, placebo-controlled trial (NCT04525079), CT-P59, its efficacy in individuals with mild to moderate symptoms of COVID-19 is currently under investigation [28,62]. A phase II/III randomized, double-blind, placebo-controlled, parallel-group trial (NCT04590430) [26]. The primary outcome is to assess the treatment efficacy from baseline to Day 14 and 28, measuring the proportion of negative patients, the time needed to negativization and to achieve clinical recovery, and the percentage of hospitalization or death among enrolled patients [26].

Last but not least, a study recently published [63] evaluated intranasal administration in mice of an IgM engineered antibody, IgM-14. So far most neutralizing monoclonal antibodies were IgG1 isotype and were administered intravenously; nevertheless, IgG antibodies have low mucosal penetration. IgM antibodies are usually the first line in the defence of mucous tissues. IgG-14 administered intranasally in a single dose showed persistently high levels in the nasal cavity of mice, while blood and other tissues had minimal antibody exposure [63]. The intranasal delivery of IgM-14 or other sprayed monoclonal antibodies could allow highly effective protection; so it has to be considered as a useful resource in alternative to intravenous administration of other monoclonal antibodies already approved for clinical use. In addition, IgM-14 has shown broad coverage of P1 (Gamma) and B.1.351 (Beta) mouse-adapted variants, with higher efficacy than the intranasally administered corresponding IgG-14 [63].

3.2. Emergence of resistance

Under the pressure of natural immunity and treatment with mAbs, SARS-CoV-2 has the potential to select viral variants with reduced susceptibility to mAbs and vaccines [64].

Of the different viral mutants, including those isolated in Brazil (P.1), the UK (B.1.1.7) and South Africa (B.1.351), the B.1.351 and P.1 variants have shown complete resistance to bamlanivimab and reduced susceptibility to casirivimab [65]. However, VIR-7831 has retained the ability to bind with some SARS-CoV-2 variants, including B.1.351 [56].

In the US, viral variants harbouring E484K and L452R substitutions with reduced susceptibility to bamlanivimab have been described and account for 20% in some regions. For this reason, the FDA revoked the
EUA for bamlanivimab monotherapy, but the combination of bamlanivimab and etesevimab remains available [66]. Imdevimab retains activity against some variants, and its association with casirivimab retains sufficient potency to neutralise even novel variants of SARS-CoV-2 [65,67]. Of concern, the emerging B.1.617.2 (delta) variant was resistant to Bamlanivimab and demonstrated reduced susceptibility to sera from convalescent patients or 3-fold reduced susceptibility to sera from patients vaccinated with BNT162b2 [68]. Another group has demonstrated that using a single antibody to directly spike proteins was associated with the development of variants with reduced susceptibility but not in the presence of ≥ 2 antibodies targeting different viral epitopes [69,70]. In synthesis, while single mAb demonstrated reduced or very low activity against different viral variants such as B.1.351, B.1.1.28, B.1.617.1, and B.1.526, combining two mAbs targeting different viral epitopes seems to reduce the probability of selecting escape mutants with retained antiviral activity [23,71].

On the basis of emerging variants data, on April 16, 2021 the FDA has revoked the approval of the use of bamlanivimab alone; later, FDA gave its authorization for the use of bamlanivimab and etesevimab in combination and according to the most recent studies these MAbs, if administered together maintain activity against Alpha variant (B.1.1.7) and Delta variant (B.1.617.2), while their binding to the Beta (B.1.351) and Gamma (P.1) variants has decreased. [72] In the update no. 658, AIFA extended its authorization for the use of casirivimab/imdevimab in adult patients hospitalized for COVID-19 requiring low flow oxygen therapy, according to preliminary data that show clinical benefit in this particular category of individuals [73]. At the time we write this review, the cocktail of casirivimab and imdevimab has maintained activity

Table 2
Currently authorized mAbs: way of administration, dosage, exclusion criteria, side effects and role against variants.

| Authorization | Administration | Exclusion criteria | Side effects | Activity Against Variants |
|--------------|----------------|--------------------|--------------|--------------------------|
| Bamlanivimab (Eli-Lilly) | Infusion solutionAdults: 700 mg bamlanivimab given as early as possible after a positive SARS-CoV-2 test result, and in any case within 10 days of testing. Onset of symptoms. | Patients hospitalized for COVID – 19 patients that receive oxygen therapy for COVID – 19 patients who need, due to COVID – 19, an increase in the flow of chronic oxygen therapy already in place due to pre-existing co-morbidities. | Nausea, Diarrhoea, Dizziness, Headache, Itching, Vomiting | Activity: |
| | | | | Impaired |
| Bamlanivimab and etesevimab (Eli-Lilly) | Infusion solutionAdults: 700 mg bamlanivimab + 1400 mg etesevimab given as early as possible after a positive SARS-CoV-2 test result, and in any case within 10 days of testing. Onset of symptoms. | Patients hospitalized for COVID – 19 patients that receive oxygen therapy for COVID – 19 patients who need, due to COVID – 19, an increase in the flow of chronic oxygen therapy already in place due to pre-existing co-morbidities. | Nausea, Diarrhoea, Dizziness, Headache, Itching, Vomiting | Activity: |
| | | | | Impaired |
| Casirivimab and imdevimab (Regeneron/Roche) | Infusion solutionThe recommended dose is 1200 mg casirivimab and 1200 mg imdevimab administered in a single infusion (intravenous infusion). | Patients on high flow oxygen therapy and / or mechanical ventilation. | Fever, Chills and chills, itchy rash, itchy skin, abdominal pain, reddening of the face | Activity: |
| | | | | Retained |
| Sotrovimab (GlaxoSmithKline) | Infusion solutionThe recommended dose in adults and adolescents (aged 12 years and over and weighing at least 40 kg) is 500 mg. Sotrovimab must be diluted prior to administration. | | Covid-19 pneumonia, Headache, Pneumonia, Dyspnoea, Nausea, Diarrhoea | Activity: |
| | | | | Retained |
| | | | | Impaired |
| Regdanvimab (CT-P59) (Celtrion Healthcare) | Infusion solutionThe recommended dosage of regdanvimab is a single intravenous (IV) infusion of 40 mg/kg. Treatment should be initiated as soon as possible after diagnosis, and not later than 7 days after the onset of symptoms. | | Neutropenia, Hypertriglyceridaemia | Activity: |
| | | | | Not Available |
4. Discussion

After over a year of the COVID-19 pandemic, morbidity and mortality resulting from severe SARS-CoV-2 infection remain high [76]. Therapeutic approaches are based on antiviral drugs or immunomodulating medications. Of this latter group, there is currently a colossal global attempt to develop and rapidly distribute effective vaccines against SARS-CoV-2. But billions of doses are required for a global vaccination campaign [77].

Meanwhile, attention has been focused on monoclonal antibodies capable of blocking the interaction between viral proteins and human cells. The primary aim of SARS-CoV-2 monoclonal antibodies is surface spike glycoproteins, the key elements that get the virus into the target cells [78] (Table 2).

In severely and critically ill SARS-CoV-2 infected patients there is often a dysregulated immune response, usually referred as cytokine release storm (CRS), characterized by high levels of inflammatory markers, like C-reactive proteins, Interleukin-6, ferritin and lactate dehydrogenase. Published data suggest that the administration of mAbs that lower the levels of cytokine, reducing the risk of CRS, could lead to a clinical benefit, reducing mortality from COVID-19 [79–80].

Clinically, the combination of casirivimab and imdevimab or bamlanivimab and etesevimab reduced the hospitalization rate and emergency department admissions in patients with a mild infection, and risk factors for severe manifestation from COVID-19 [23,81] (Figs. 1 and 2). [17,22] Following these results, the FDA and EMA released a EUA for both the combination of casirivimab and imdevimab and bamlanivimab and etesevimab reduced the hospitalization rate and emergency department admissions in patients with a mild infection, and risk factors for severe manifestation from COVID-19 [23,81] (Figs. 1 and 2). [17,22] Following these results, the FDA and EMA released a EUA for both the combination of casirivimab and imdevimab and bamlanivimab and etesevimab for mild symptomatic adults with COVID-19 who are not in need of additional oxygen but are at high risk of becoming severely ill. However, monoclonal antibodies are expected to work better in the early infective phase of SARS-CoV-2 infection, whereas the late phases are driven by immune dysregulation responsible to severe manifestation in critical patients [82,83]. Therefore, the “umbrella” provided by mAb is not likely to cover every individual with mild disease, so its use should...
be prioritised. mAbs should be reserved for individuals at high risk of developing a serious COVID-19 illness, such as people who are obese and elderly or have diabetes, chronic lung diseases and cancer [84]. Early administration might be recommended for household contacts of COVID-19 infected individuals, particularly when the aforementioned comorbidities are present. The results of the study NCT04452318 will clarify the issue.

The incidence of COVID-19 infection is higher in SOT patients compared to other groups with high rates of respiratory failure although mortality rates don’t appear constantly higher among studies [85-90]. One study suggested that casirivimab and idecmivm can prevent hospitalization among SOT recipients with mild and moderate COVID-19 [18]. Based on small and relatively heterogeneous groups, mAbs could prevent acute respiratory failure in SOT patients can safely be applied in this population [91].

Preliminary data from drugmaker suggest that REIGN-COV-2 is effective as a prophylaxis for household contacts of COVID-19 positive individuals by reducing the rate of symptomatic infection by 81% after subcutaneous administration [92], although the effective duration of the protection is not known. This finding could be particularly interesting for people with a poor serological response to vaccination, such as the elderly or patients with haematological malignancy as a complementary or alternative intervention [93-94]. Moreover, subcutaneous administration is more suitable than IV administration because of greater patient acceptance and easier administration, and it could be widely administered through territory ambulatory services. Recently, Avalon Globocare (US) and a company led by the University of Helsinki and Eastern Finland, and more recently a group of scientists in Australia have been working on a nasal-spray vaccine for COVID-19 [95-96]. In a mice model, the administration of intranasal mAbs (DZIF-10c) has been demonstrated to reduce the VL of SARS-CoV-2 and inflammation in the lungs, including variants of concern [97]. Ideally, even a early administration of aerosolized mAb in asymptomatic COVID-19 people could provide a high concentration of medicine on the respiratory mucosa, which could prevent the subsequent development of respiratory symptoms and pneumonia. The goal of the early administration of mAbs includes reductions in hospitalization, ICU admission and death rates, reducing the current tremendous pressure on hospitals and could be a suitable option in case of variants of concern with reduced susceptibility to vaccines.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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