Review Article

Neutralizing Monoclonal Antibody: New Member of Therapeutic Armamentarium Against COVID-19

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Abstract:

Many targeted treatment methods have focused on SARS-CoV-2's spike protein, along with neutralizing monoclonal antibodies (mAbs), which are recombinant proteins, may be employed as a kind of passive immunotherapy to reduce pathogenicity. While vaccines are still the best way to prevent COVID-19 infection, mAbs are an effective treatment for those who have already been infected, as well as having the potential to prevent infection in those who have already been exposed to SARS-CoV-2, which can be especially beneficial to certain high-risk groups. Due to the limited initial availability of these new treatments, it is essential to consider their larger potential and create methods for their optimal deployment in clinical practice. The objectives of this review is to answer the most commonly asked clinical questions from HCPs and patients about the target population, dose, interactions with other medicines and vaccines, duration of immunity, and variants.

Keywords: Neutralizing Monoclonal antibody (mAb), COVID-19 treatment, Antiviral therapy

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Introduction:

The rapid onset and catastrophic spread of COVID-19 pandemic has sparked an intensive program of international research to find effective strategies to restrict infection transmission and minimize COVID-19-related morbidity and mortality[1]. To address COVID-19, a number of prophylactic and therapeutic medications are being developed or repurposed. Monoclonal antibodies (mAbs) are a new category of antiviral therapeutic that can attach to and 'neutralize' the virus in infected patients. They represents a new era in infectious disease prevention, overcoming many of the shortcomings of serum treatment and intravenous immunoglobulin preparations in terms of specificity, purity, minimal risk of blood-borne pathogen contamination, and safety[2].

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Neutralizing mAbs are recombinant proteins generated from convalescent patients' B cells or humanized mice. Antibodies with the required specificity and affinity for binding virus and inhibiting entrance of the virus can be identified through high-throughput screening of these B cells, eliminating the pathologies associated with productive infection. These mAbs are referred to as 'neutralizing,' and they can be utilized as a form of passive immunotherapy to reduce virulence. In this brief review, we present the incremental learnings from mAb studies and answers the most common questions Health Care Professionals (HCPs) and patients have about the intended population, dosage, interactions with other medicines and vaccine, duration of protection, and new variants. This is a narrative review instead of a systematic review, and the goal is to give HCPs a comprehensive understanding of function of neutralizing mAbs within the range of possible COVID-19 therapies, highlighting the relative benefit that these medicines can bring for patients and clinicians as well as clinical practical aspects of prescribing mAb in the perspective of vaccines and mutants. This article is based on previously published studies and

does not include any new human or animal investigations undertaken by any of the authors. Though vaccinations are still the greatest way to prevent COVID-19, mAbs might help some susceptible groups before or after exposure to SARS-CoV-2, such as high-risk individuals who yet to be vaccinated or who have just been immunized. The antiviral activity demonstrated with neutralizing mAb therapy highlights the necessity of early intervention to help mitigate the virus's catastrophic impact in these and other high-risk individuals.

Mechanism of action of mAbs: The S protein, which promotes target cell attachment and fusion when it interacts the cell-surface angiotensin-converting enzyme 2 (ACE2) receptor, which is present in the respiratory system, vascular endothelium and alimentary tract, is the major antigenic epitope on SARS-CoV and SARS-CoV-2[5,6]. Antibodies designed against S protein can thereby block the virus's ability to attach and fuse with the target host cell. Neutralizing mAbs targeting the RBD of the S protein have been developed using humanized murine technology or convalescent plasma from recovered patients[7].

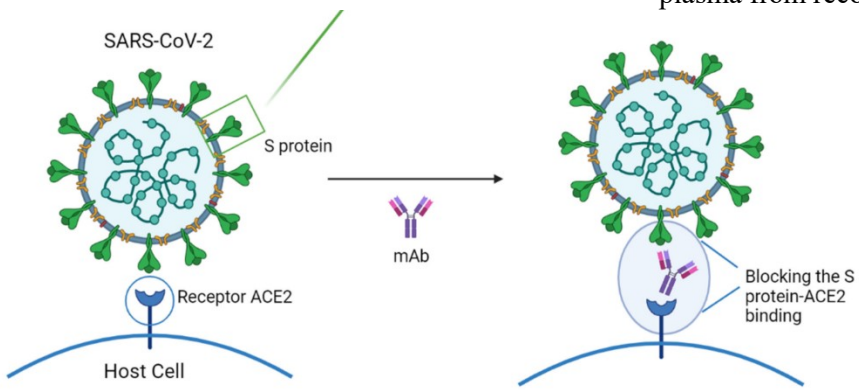

Fig-1: Mechanism of action of mAb by blocking the SARS-Cov-2 S protein and human ACE2 receptor binding. Reprinted with permission from reference[8].

Neutralizing monoclonal antibodies for COVID-19

Bamlanivimab: Bamlanvimab (LY-CoV555), obtained from convalescent plasma of a COVID-19 patient, is a potent neutralizing mAb that target SARS-CoV2-2 spike protein. Thefirst therapeutic trial of mAb for treating COVID-19 initiated on 28.5.2020 with bamlanivimab (NCT04411628)[9].

In BLAZE-1, a randomized, placebo controlled phase 2 study, ambulatory adults with mild to moderate COVID -19 was given a single IV infusion of one of 3 doses of bamlanivimab (700, 2800 or 7000 mg), within 3 days of positive SARS-CoV-2 test. 452 patients, median age 45–46 years, 88 percent white, 6% black, and 68% at high risk (for example elderly, obese or had multiple chronic comorbidities) were included in a pre-planned interim study. Patients experienced depletion in viral load (mean 3.81) at 11th day when all three bamlanivimab dosages were combined, which was equivalent to placebo. The average time to symptom remission in the bamlanivimab arm was 5 days, compared to 8 days in the placebo groups. The rate of hospitalization or emergency room visits was 1.6 percent compared to 6.3 percent for the placebo. The incidence was 4% for patients with minimum one risk factor for severe COVID-19 against 15% for placebo[10].

Interestingly, only 2800 mg (medium dosage) group showed reduction of viral load at 11th day tht is statistically significant when compared to placebo, while higher dose (7000 mg) did not. On 9th November 2020, the FDA granted Bamlanivimab an emergency use authorization (EUA) for newly diagnosed COVID-19 patient's treatment, who are at risk of developing severe illness[11].

Bamlanivimab with Etesevimab:

The BLAZE-1 study's final analysis incorporate a fourth treatment arm which employed a 2800 mg/2800 mg mixture of bamlanivimab and etesevimab. When compared to placebo, bamlanivimab and etesevimab significantly reduced viral load (proportion of patients with persistently high viral load and mean changes from baseline) from 3rd to 11th day. Patients who received bamlanivimab or etesevimab had reduced COVID-19-related admission in hospital than those who received placebo (5.8% for placebo reduced to 0.9% in bamlanivimab with etesevimab).

Phase III data of 1035 subjects randomized 1:1 to placebo or bamlanivimab and etesevimab in high-risk ambulatory patients (including 12–17 years patients with specific risk factors and 18 years or older having specific adult risk factors), treatment with bamlanivimab and etesevimab showed 70% reduction in COVID-19 associated hospitalization and death compared to placebo (7.0% for placebo reduced to 2.1% in bamlanivimab with etesevimab)[12]. A supplementary EUA for bamlanivimab and etesevimab has been issued based on these findings[13].

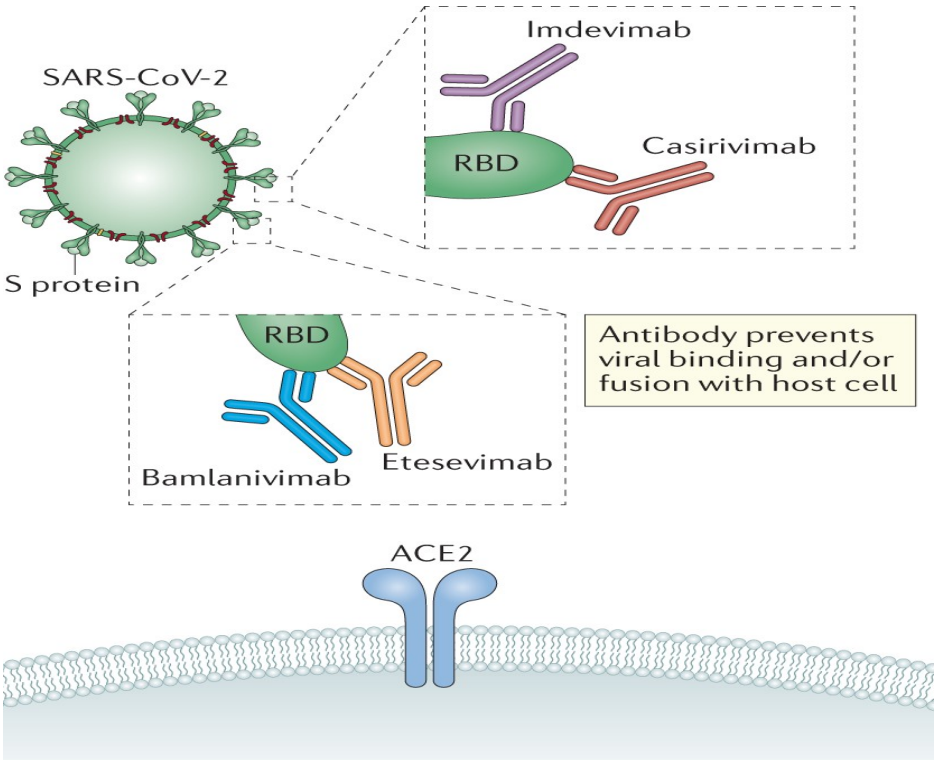

Fig-2: Schematic depiction of the potential mechanism of mAbs in COVID-19 infection. Reprinted with permission from reference[17]. Reproduction permission was obtained from Rights Link. Abbreviations: ACE2, angiotensinconverting enzyme 2; COVID-19, coronavirus disease 2019; mAb, monoclonal antibody; RBD, receptor binding domain; S, spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Casirivimab and imdevimab bind distinct epitopes on the RBD-Imdevimab binds the S protein RBD from the front or lower-left side, while casirivimab targets the spike-like loop from the top direction (overlapping with the ACE2-binding site). Bamlanivimab binds an epitope on the RBD in both its open confirmation and its closed confirmation. Bamlanivimab and etesevimab bind to distinct, but overlapping, epitopes within the RBD of the S protein of SARS-CoV-2. Etesevimab binds the up/active conformation of the RBD.

REGEN-CoV (Casirivimab and imdevimab):

REGN-COV2 combines two powerful neutralizing mAbs, casirivimab and imdevimab, both of which are IgG1 mAbs. These two mAbs were selected from a pool of >200 neutralizing mAbs discovered during the first isolation of thousands of antibodies. They were developed in parallel using humanized mice and serum from COVID-19 patients[14]. On the RBD, the antibodies bind to two separate and non-overlapping locations[15]. The reason for this antibody cocktail is that a of S protein of SAR-CoV-2 is unlikely to render both antibodies ineffective at the same time. In vitro, a combination of casirivimab and imdevimab induced antibody-mediated cytotoxicity with cellular phagocytosis in virus infected cells. This product was evaluated on SARS-CoV-2-infected rhesus macaques and golden hamsters, which were used as models for mild and severe illness, respectively[16]. Both models showed that prophylactic and therapeutic therapy with casirivimab and imdevimab reduced viral load while also lowering the incidence and severity of lung illness when compared to a placebo[8].

A phase I/II/III placebo-controlled trial (NCT04425629) is looking into the safety and efficacy of casirivimab and imdevimab, intravenous single dose — 2,400 mg (n = 266, interim), 8,000 mg (n = 267, interim), or matching placebo (n = 266) — for symptomatic adults who haven't been admitted in hospitalin 3 days of a positive active SARS-COV-2 diagnosis (and within 7 days of the first symptoms). The combination has been demonstrated to decrease viral load, especially in individuals with higher viral loads who were seronegative during diagnosis. COVID-19-related medical visits were less common in persons treated with casirivimab and imdevimab (2.8% in treatment group versus 6.5% in placebo group). In post hoc studies, patients treated with casirivimab and imdevimab had a lower rate of COVID-19 associated hospitalizations or emergency department visits than those treated with placebo (2% vs 4%). When compared to placebo, the absolute risk reduction for casirivimab and imdevimab was higher in individuals at high risk of severe COVID-19 progression and/or hospitalization (3% vs 9%)[15]. Overall, these findings supported Regeneron's casirivimab and imdevimab cocktail receiving an EUA in November 2020 in the United States[17].

Sotrovimab:

Sotrovimab, previously VIR-7831, is a human monoclonal antibody that neutralizes SARS-CoV-2 and SARS-CoV, the virus that caused the SARS outbreak two decades ago. In reality, Sotroivimab was first isolated from a SARS survivor. Sotrovimab interacts to a conserved epitope on SARS-CoV-2's spike protein. Although the precise method of action is uncertain, it appears to inhibit membrane fusion when the virus attaches to the human ACE2 receptor[18].

A planned interim analysis of the COvid-19 Monoclonal antibody Effectiveness Trial-Intent to Care Early (COMET-ICE) trial looked at the efficacy and safety of sotrovimab therapy in high-risk, ambulatory individuals with mild/moderate Covid-19 disease. The primary efficacy objective was reached in this study, which comprised an intent-to-treat population of 583 individuals (sotrovimab, 291; placebo, 292). With three (1%) patients advancing to the main endpoint in the sotrovimab group vs 21 (7%) patients in the placebo group, the risk of Covid-19 progression was significantly decreased by 85 percent (97.24 percent confidence range, 44 percent to 96 percent; P = 0.002). All five patients admitted to critical care, one of whom died on day 29, got placebo[19].

Recommendations for use of mAb:

COVID-19–positive outpatients with symptom onset within 10 days after infusion and concomitant illness conditions with a high risk of poor outcomes are eligible for mAb treatments. The treatments are not approved for hospitalized patients requiring oxygen supplementation or who have a COVID-19-associated increase in baseline oxygen therapy[20,21].

FDA criteria for emergency use authorization of mAbs:

Patients must fulfill all of the following:[13,15]

1. SARS-CoV-2 test positive and duration of symptom ≤ 10 days
2. No need of hospitalization or oxygen supplementation or no change in baseline oxygen therapy
3. Fulfill the listed below patient criteria

- Age 65 years or more
- Age 55 years or more AND minimum 1 of the mentioned severity risk factors
  - A. Cardiovascular disease
  - B. HTN
  - C. COPD or any chronic respiratory disease
- Age 18 or more and minimum 1 of the criteria below
  - A. BMI ≥ 35 kg/m2
  - B. CKD
  - C. DM
  - D. Now on immunosuppressive drugs
  - E. Immunosuppressive illness
- Patients 12 to 17 years old AND weight 40 kg or more AND minimum 1 of the criteria given below:
  - A. BMI 85th percentile or higher for age and gender based on CDC growth chart
  - B. Sickle cell disease
  - C. Cardiac disease (Congenital or acquired)
  - D. Cerebral palsy and other developmental neurological disease
  - E. Medical-associated technical dependencylike positive-pressure ventilation (not associated to COVID-19), gastrostomy or tracheostomy
  - F. Asthma or other chronic airway diseases requiring daily medication for control

mAb in severe COVID-19:

ACTIV-3: This Phase 3 RCT (n = 326, 1:1 randomization) found that adding bamlanivimab to standard of treatment (usually containing remdesivir) had no extra clinical benefit in hospitalized patients[22].

RECOVERY: Several potential therapies were compared to standard care in patients hospitalized with COVID-19 in this randomized, controlled, open-label platform study. Patients who were eligible and have given consent, randomly allocated (1:1) to either normal standard of treatment (usual care group) or usual standard of care with a single intravenous dose of REGEN-COV 8g (casirivimab 4g with imdevimab 4g) (REGEN-COV group). The primary outcome was 28-day death, which was measured first in patients who did not have detectable antibodies to SARS-CoV-2 at the time of randomization (seronegative) and later in the entire population.

3153 (32%) seronegative patients, 5272 (54%) seropositive patients, and 1360 (14%) patients with unclear baseline antibody status were randomly assigned to receive usual treatment with REGEN-COV or standard care alone. In the main efficacy group of seronegative patients, 396 (24%) of 1633 REGEN-COV patients and 451 (30%) of 1520 patients receiving standard treatment died after 28 days (rate ratio 0.80; 95% CI 0.70-0.91; p=0.0010).

In a study of all randomly assigned patients (regardless of initial antibody status), 944 (20%) of 4839 REGEN-COV patients and 1026 (21%) of 4946 REGEN-COV patients died after 28 days (rate ratio 0.94; 95% CI 0.86-1.03; p=0.17). There was a significant difference in the proportionate impact of REGEN-COV on mortality between seropositive and seronegative patients (p value for heterogeneity = 0.001)[23].

Adverse effectsof monoclonal antibody therapies:

Therapy-related adverse effects related with mAb treatment of COVID-19 were equivalent to those associated with placebo. In RCTs, the most common adverse effects were nausea, diarrhoea, dizziness, headache, and vomiting(10,12,24). Within 4 days of receiving casirivimab and imdevimab, 1% of patients experienced a grade 2 or higher infusion-associated response (comparable to 1 percent reported for placebo treatment)[24]. Nine individuals had an infusion-related reaction in the phase II section of BLAZE-1 (1.9% (6/309) in bamlanivimab monotherapy, 1.8% (2/112) in bamlanivimab and etesevimab combined, and 0.6 percent (1/156) with placebo). The majority of responses occurred during infusion and were moderate in intensity and unrelated to the dosage. Based on the clinical data available till now, there is no confirmed evidence that these treatments result in increased immune responses consistent with ADE[8].

Challenges for mAb:

Owing to the rapid evolution of viral infections, the risk of developing drug resistance is a hazard for any antiviral therapy. If mutations in the targeted epitope decrease or abolish antibody binding, mAbs are vulnerable to the development of viral resistance.

Several SARS-CoV-2 variants of special concern have been found and are currently spreading across the world. In the fall of 2020, a variation known as 'B.1.1.7'(Alpha) with a significant number of mutations was discovered in the United Kingdom. A variation known as B.1.351(Beta) was discovered in South Africa. B.1.351 was discovered in early October 2020 and has several mutations with B.1.1.7. A variation known as P.1(Gamma) was discovered in Brazil, and it has a series of additional mutations that may impact its capacity to be identified by first-generation neutralizing monoclonal antibodies and immune responses elicited by first-generation vaccines[25]. Both bamlanivimab and etesevimab were shown to have reduced binding to the Beta (South African origin, B1.351) and Gamma (Brazilian origin, P.1, B.1.1.28) variants. Due to resistance in multiple important viral strains, Emergency Use Authorization for monotherapy with the mAb Bamlanivimab (LY-CoV555) was cancelled[26]. Another variant B.1.617(Delta) identified in India on October 2020. Some anti-RBD mAbs, such as bamlanivimab, were unable to neutralize the Delta variant, and these antibodies had poor binding to the spike protein[27].

This hazard can be minimized by utilizing a mix of non-overlapping epitope-binding mAbs(14). Despite the fact that spike glycoprotein mutations in some variants (e.g. B.1.351 [beta] and B.1.617 [delta]) have been linked to a reduction in casivirimab neutralisation activity, the combination of casirivimab and imdevimab retains potency against these variants due to imdevimab's inhibitory activity[28]. Notably, the combination of bamlanivimab with etesevimab maintains efficacy against both the Alpha version (B.1.1.7) and the rapidly spreading Delta variant (Indian origin, B.1.617)[29].

Meanwhile, it's essential to keep an eye on resistance patterns in order to spot variants that are resistant to both components and It will be necessary for physicians to review the most recent factsheet.

Clinical Use of mAb in COVID-19:

Timing: When administered early in the course of SARS-CoV-2 infection, mAb reduce viral load and improve clinical outcomes in patients with mild-to-moderate COVID-19 infection[10]. Although full clinical trial findings are still awaited, top-line and interim results from many studies show that the treatments might be used as prophylactic in at-risk individuals who have recently been exposed to SARS-CoV-2[30,31].

Patient selection: Individuals with persistently higher viral loads are more likely to have medically attended visits, emergency department visits, or hospitalization, according to early data, and this impact is especially evident in patients with pre-existing risk factors for disease development[15]. Early evaluation of viral loads may be useful in determining who within the 'lower-risk' population could benefit from neutralizing mAbs. The therapeutic benefit of neutralizing mAb treatment appears to be greater

in patients who are seronegative during diagnosis, according to RCT evidence. Measuring viral load and serology together would enable for selective deployment for individuals with no other known risk indicators while also allowing for early supply to the high-risk group. Another method to categorize candidates for neutralizing mAbs is to choose individuals who are likely to have weak antiviral responses (for example, the elderly or immunocompromised), or to use experimental techniques to identify patients with poor T cell and/or B cell performance (such as by serology or flow cytometry). In terms of the latter, there is a paucity of published information on humoral immune responses dynamics and their relationship to clinical outcomes[8].

Cocomitant use of medication or vaccine with mAb: Concomitant medication usage with bamlanivimab and etesevimab is not prohibited in the EUA since these mAbs are not excreted by the kidneys or processed by cytochrome P450 enzymes, thus interactions with other medicines are unlikely. Data on the safety and effectiveness of mAbs in patients of renal failure and those on hemodialysis is few, and the majority of what is available is based on case studies. There are currently no data on the efficacy and safety of giving a SARS-CoV-2 vaccine, or any other vaccine, before or after receiving bamlanivimab and etesevimab for the treatment of mild-to-moderate COVID-19. Antibody treatment has the potential to reduce the endogenous immune response to SARS-CoV-2, making patients more vulnerable to reinfection[13].

Prior receipt of a SARS-CoV-2 vaccine should not impact COVID-19 treatment decisions or the timing of such therapies in partially and completely vaccinated individuals who develop COVID-19. As a precaution, the CDC recommends deferring immunization for 90 days after antibody therapy until further evidence becomes available. The reason for a 90-day deferral is based on assumptions rather than clinical research, such as the anticipated half-life of such treatments and the assumption that reinfection is unusual for 90 days after first infection[33].

Summary and Conclusion:

Many studies with various immune-modulating therapies have been done or are now underway in order to reduce the tissue damage associated with COVID-19's latter phases. However, there have been few unambiguous results so far. As extensive vaccination efforts gather momentum and society gets closer to terminating the COVID-19 pandemic and achieving herd immunity, neutralizing monoclonal antibodies remain essential therapeutic choices for high-risk patient groups. Early clinical trial results that are encouraging warrant additional research into neutralizing mAbs to find the best dosage protocol. Unanswered questions about this novel therapeutic approach have compelled a research agenda; we need to figure out which at-risk people would benefit from neutralizing mAbs, how long these mAbs provide protection, and whether mAb therapy has any impact on subsequent vaccination. On the basis of viral load, serology, and other possible clinical variables, it will also be necessary to decide the best time to provide neutralizing mAbs.

The development of biomarkers for response and the long-term benefit of mAb is currently in progress. Real-world trials, such as OPTIMISE-C19, will be crucial in determining the long-term efficacy of monoclonal antibodies in preventing hospitalizations and mortality in subgroups of high-risk patients, as well as symptom relief [34].

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