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**Review Article**

# Monoclonal antibodies in COVID-19 management: a scoping review

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## ABSTRACT

Coronavirus disease 2019 (COVID-19) was declared as pandemic on March 11th 2020 by the world health organization (WHO). Vaccination is for preventing COVID-19 morbidity but when people are infected, treatment is required and even after one and half years the effective cure is yet to be discovered. In this context monoclonal antibodies (mAbs) are promising innovative therapeutic agents in controlling COVID-19 infection. Researchers have found more than 50 mAbs against COVID-19 and they are at different stages of development. Scientists are pacing the research on mAbs. mAbs are innovative therapeutic agents in this context a scoping narrative review was done. At present we have evidences from numerous randomized controlled trials (RCT) on mAbs in effective control of respiratory and coagulation related complications due to COVID-19 infection. Many have got emergency use approval and few of which were withdrawn due to absence of enough evidences or adverse reactions. Examples are bamlanivimab, etesevimab, casirivimab and imdevimab. Other than these many investigational (mAbs) are under scrutiny. With the current evidences the article will give an insight to new and repurposed mAbs which are still under investigation in the management of COVID-19 infections.

**Keywords**: COVID-19, Bamlanivimab, Etesevimab, Casirivimab, Imdevimab, mAbs

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared as pandemic on March 11th 2020 by the world health organization (WHO) mainly because of its speed of transmission. Till July 2021, there have been 194 million COVID-19 confirmed cases, 4 million deaths, and around 3 billion people have been vaccinated against it. Vaccination is for preventing COVID-19 morbidity but when people are infected, treatment is required and even after one and half years the effective cure is yet to be discovered.[1] In this context mAbs are promising innovative therapeutic agents in controlling COVID-19 infection.[2,3] Researchers have found more than 50 mAbs against COVID-19 and they are at different stages of development.

In the pathogenesis of COVID-19, the early phase of disease is attributed to viral replication of SARS-CoV-2 and later phase is due to tissue damages caused by the dysregulated immune/inflammatory responses. So, during the initial phase of disease, administration of antiviral therapy is found to be highly effective whereas in the later phase, administration of immunosuppressive or anti-inflammatory agents are found to be beneficial.[4] SARS-CoV-2 activates both the innate and adaptive immune system. Uncontrolled innate response and inadequate adaptive immune response activation, bring extensive tissue damages resulting in multiple organ failure.[4] There are numerous complex mechanisms that contribute to the disease progression, of which immunopathology is the hallmark of the disease.[5,6] The proposed pathophysiological mechanisms that underlie COVID-19 infection are viral entry into the host cell producing

cytopathic effects followed by down regulation of angiotensin converting enzyme2 (ACE-2) enzyme and bradykinin resulting in a state of 'cytokine storm', autoimmunity and hypercoagulation.[7]

## MONOCLONAL ANTIBODY THERAPY

From previous evidences and experiences of treating viral infections like severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and Ebola, monoclonal antibody therapy has become a novel way to prevent COVID-19 infection. Antibodies are B cells produced in the human body following an infection which have many targets to keep the infection under control. Having them as base, researchers developed mAbs which have a single but specific predetermined target unlike polyclonal antibodies present in convalescent plasma. mAbs are produced from pathogen-specific B cells found in humans who recovered following infection and also from animals like mice (by immunizing them to have a genetically modified humanized immune system).[8] After identification of B cells, the genes of heavy and light chain components are studied and these genes are expressed to produce mAbs that have a specific target.[8]

The different proteins of SARS-CoV-2 genome can be grouped into structured, unstructured and accessory proteins. The four major proteins of structured proteins are used as targets for developing mAbs and these are spike (S), envelope (E), membrane (M) and nucleocapsid (N). Spike protein is further divided into $S_1$ for attachment and $S_2$ for invasion. $S_1$ attaches to ACE2 of the human host cell which brings about a conformational change in $S_2$ and leads to fusion which is followed by entry of virus into the host cell. This receptor binding domain (RBD) is the target for mAbs.[9] These mAbs can bind to and neutralize the virus, so that we can consider them as a novel class of antiviral drugs.

The COVID-19 treatment guidelines by US food and drug administration (FDA), recommend one of the following anti-COVID-19 mAbs, to treat patients with mild to moderate COVID-19 infection who are at high risk of clinical progression to severe COVID-19 as defined by the emergency use authorization (EUA) criteria.[10] These are bamlanivimab as a monotherapy and bamlanivimab with etesevimab or casirivimab with imdevimab as a combination therapy.

This scoping review was done by performing literature search using PubMed, Google scholar, Medscape, drug bank, official websites of WHO, NIH, FDA, IDSA and relevant reports of clinical trials conducted on investigational and repurposed mAbs which include randomized controlled clinical trials (RCT), case reports, case series and meta-analysis through 2020 and 2021. Search terms included are "COVID-19", "cytokine-storm", "mAbs", "immunomodulators", "bamlanivimab", "etesevimab", "casirivimab", "imdevimab", "crizanlizumab" and "ravulizumab". The available information about this will be presented as narrative review in this paper.

### *Bamlanivimab*

Bamlanivimab is a recombinant human IgG1 neutralising mAb isolated from convalescent plasma obtained from patients with COVID-19, and it was developed by AbCellera biologics and Eli Lilly. This mAb binds to the receptor-binding domain of the spike protein of SARS-CoV-2 and thereby preventing the attachment of spike protein to ACE2.[8,11] Bamlanivimab was approved as a monotherapy on November 2020 based on the interim analysis of RCT on mild to moderate COVID -19 infected patients who were at high risk of progression to severe disease.[8] But due to concern for a sustained increase in variants of SARS-CoV-2 which shows resistance to Bamlanivimab monotherapy on March 24, 2021, the U.S. department of health and human services issued a notice to stop the distribution of Bamlanivimab as monotherapy.[8]

### *Etesevimab*

Etesevimab is also a neutralising IgG1 mAb, isolated from convalescent plasma of COVID-19 patients, binding to the receptor binding domain of spike protein of SARS-CoV-2 to different but overlapping epitope.[10]

### *Bamlanivimab and etesevimab combination*

Bamlanivimab and Etesevimab are neutralizing IgG1 mAbs that bind to distinct but overlapping epitope of the receptor binding domain (RBD) of Spike protein. Both are new drugs under investigation and not given currently for any other indication.[10,12] Etesevimab on binding to a different epitope neutralizes resistant variants with those having mutations to the epitope bound by bamlanivimab. Combining these two neutralizing antibodies may enhance viral load reduction and reduce resistant variants.[13]

In the 2/3 phase of an RCT (ClinicalTrials.gov Identifier: NCT04427501) with 577 patients, no significant difference in change was found in viral load with 3 different doses of bamlanivimab monotherapy compared with placebo. But during the treatment with a combination of bamlanivimab and etesevimab a significant decrease in SARS-CoV-2 log viral load was found at day 11when compared with placebo (between-group difference, –0.57 [95% CI, -1.00 to -0.14], p=0.01).[13] US FDA issued an EUA on February 2021, for combination therapy with bamlanivimab and etesevimab in hospitalized patients of >12 years of age and weighing more than 40 kg and at high risk for progressing to severe disease and/or hospitalization.[10,12] This was mainly based on data from BLAZE-1 and BLAZE-4 trials.[10] The advised dosage is bamlanivimab 700 mg and etesevimab 1,400 mg in combination. But E484K mutations have less susceptibility to bamlanivimab.[10] In regions where SARS-CoV-2 variants are seen like B.1.526, casirivimab and imdevimab are used. But on June 2021 distribution of

bamlanivimab/etesevimab alone or in combination is paused on a national basis by public health emergency of the U.S. The reason is due to the upward trend of the combined frequencies of P.1/ Gamma variant that was first identified in Brazil and B.1.351/Beta variant first identified in South Africa throughout the U.S and centers for disease control and prevention (CDC) found out that the above combination mAbs therapy has no role on these variants.[14]

### *Casirivimab and imdevimab (REGEN-COV)*

REGEN-COV or antibody cocktail is a combination of casirivimab (REGN10933) and Imdevimab (REGN10987). These are human IgG1 mAbs that target the receptor binding domain of the spike protein of SARS-CoV-2. Advantage of using this combination is to prevent mutational escape.[15-17] They are used in treatment of mild to moderate COVID-19 in adults and paediatric patients (12 years or more weighing at least 40kg). It was developed by the American biotechnology company regeneron pharmaceuticals. US-FDA granted EUA of REGEN-COV for the treatment of mild to moderate COVID infected patients who are at risk for progressing to severe COVID-19 on November 2020, and its use is also associated with worse clinical outcome patients requiring high flow oxygen or mechanical ventilation. The EUA for this combination is based on a randomized double blind, placebo controlled clinical trial that was conducted in 799 non hospitalized adults who have mild to moderate COVID symptoms. Out of these participants 266 received 2400 mg (1:1) casirivimab and imdevimab, 267 received 8000 mg casirivimab and imdevimab and 266 received placebo. The primary endpoint was time weighted average change in viral load from baseline. They found that there is more reduction of viral load in patients treated with this combination than placebo, and hospitalization and emergency room visits occurred in only 3% as compared to placebo where it is 9%.[15-17] Possible side effects of casirivimab and imdevimab include: anaphylaxis and infusion-related reactions, fever, chills, hives, itching and flushing.

### *Sotrovimab*

Sotrovimab is a recombinant engineered human IgG1 monoclonal antibody that targets the highly conserved epitope on the spike protein receptor binding domain of SARS-CoV-2 and thereby blocking the virus attachment and entry into human cells. It is an investigational monoclonal antibody with activity against SARS-CoV-2.[18] It is used for the treatment of mild to moderate COVID-19 in adults and paediatric patients (12 years or more weighing at least 40 kg) who are at risk of progressing to severe disease and it has not shown any benefits in patients who is hospitalized and requiring high flow oxygen or mechanical ventilation and it may even produce worse clinical outcome in such patients.[18] US-FDA issued EUA for Sotrovimab therapy on May 2021 based on VIR-7831 for the early treatment of COVID -19 in Outpatients study (COMET-ICE). In this preplanner interim analysis, which included an intent-to-treat population of 583 patients (sotrovimab-291; placebo-292), the primary efficacy endpoint was met. The risk of COVID-19 progression was significantly reduced by 85% (95% confidence interval, 44% to 96%; p=0.002) with a total of three (1%) patients progressing to the primary endpoint in the sotrovimab group versus 21 (7%) patients in the placebo group. All five patients admitted to intensive care, including one who died by day 29, received placebo.[18] Safety was assessed in 868 patients (sotrovimab, 430; placebo, 438). Adverse events were reported by 17% and 19% of patients receiving sotrovimab and placebo, respectively; serious adverse events were less common with sotrovimab (2%) versus placebo (6%). The study conclusion was sotrovimab reduced progression of COVID-19 in patients with mild/moderate disease, was well tolerated, and no safety signals were identified.[19-21]

## OTHER INVESTIGATIONAL MONOCLONAL ANTIBODIES

### *Sarilumab*

Sarilumab is a monoclonal IgG1 antibody directed against interleukin 6 (IL-6) receptor alpha, which inhibits the IL-6 mediated inflammation cascade. It is FDA approved in 2017 for use in treatment of moderate to severe Rheumatoid arthritis in combination with methotrexate.[22,23] A meta-analysis with data from 23 clinical trials showed that patients with severe COVID-19 infection had high concentration of IL-6 in comparison with that of those mild COVID-19 infection. There was a direct correlation between high IL-6 levels and covid related mortalities.[24]

Sarilumab inhibits both membrane bound and soluble IL-6 receptor forms. Thereby with the hypothesis that Sarilumab may act potentially by suppressing inflammation cascade reaction in both pulmonary epithelial and immune cells, sarilumab was administered in patients with severe COVID-19 infection to reduce pulmonary complications.[24]

Following administration of sarilumab in a placebo-controlled trial (60-day, multinational, 45 hospitals, and 420 patients) to patients with severe COVID-19 infection and to those who were receiving critical care no benefit was observed and failed to meet primary endpoint in phase 3 of clinical trial.[24,25]

### *Otilimab*

Otilimab is a neutralising monoclonal antibody against granulocyte macrophage colony stimulating factor (GM-CSF) under investigation for severe pulmonary complications in COVID-19. By blocking the interaction of GM-CSF with receptors, otilimab mitigates inflammation and is under investigation for rheumatoid arthritis (phase 3).[26,27]

In May 2020 OSCAR (Otilimab in severe COVID-19 related disease) trial, a placebo-controlled trial, conducted in two parts with primary end point of proportion of subjects alive and free of lung failure after 28 days.[26,27] And the data received showed treatment difference with benefits to patients above 70 years but not of statistical significance. With the benefits of clinical improvement in a subgroup of high-risk population, OSCAR study was amended to expand the cohort study to confirm the potential benefits.[27,28]

***Lenzilumab***

It is an anti-human GM-CSF monoclonal antibody developed by humanigen, given for hospitalized hypoxic COVID infected patients who were not on invasive mechanical ventilation. It binds with GM-CSF/CSF2 and thereby prevents hyperinflammatory immune response or cytokine storm (CS) which is responsible for respiratory failure, ARDS and death in COVID infected patients.

Cytokine storm is characterized by GM-CSF mediated activation and trafficking of myeloid cells, increase in inflammatory chemokines like MCP-1, IL-8, IP-10, cytokines like IL-6, IL-1 and other markers of systemic inflammation like CRP, D-dimer and ferritin which leads to fever, hypotension, coagulopathy, respiratory failure, ARDS and death in COVID infected patients. Lenzilumab was originally designed for the treatment of CMML (Chronic myelomonocytic leukaemia) and JMML (Juvenile myelomonocytic leukaemia).[29]

In LIVE-AIR, phase 3 randomized, double-blind, placebo-controlled study, 520 COVID infected patients who are >18 years with $SpO_2$ ≤94% but not requiring invasive mechanical ventilation were included also included patients with comorbidities like diabetes (53.4%), CKD (14%), CAD (13.6%) patients taking other medications for COVID like corticosteroids (93.7%), remdesivir (72.4%) or both (69.1%). Among these 261 received lenzilumab (three intravenous infusions 8 hours apart) and 259 received placebo. Patients were followed up on day 28 following treatment. They concluded that lenzilumab has significantly improved SWOV (survival without ventilation) in hospitalized, hypoxic COVID-19 patients. Patients<85 years with CRP<150 mg/L had the greatest benefit from Lenzilumab, survival improved by 54% when compared to placebo. Adverse events were similar in both the study groups. Death rate is 15.6% in patients treated with lenzilumab as compared to placebo where it is 22.1%.[30,31]

***Crizanlizumab***

Crizanlizumab is a monoclonal antibody developed by Novartis, sold under the brand name Adakveo targeted towards p-selectin. It was originally designed as an effective drug to prevent Vaso occlusive crisis in patients with sickle cell anaemia. P-selectins are present on the surface of vascular endothelial cells.[32]

In severe COVID-19, hyper inflammatory and hyper thrombotic state due to viral injury to vascular endothelium, release of Von-Willebrand factor and p-selectin leads to thrombosis and inflammation, it binds with p-selectin and thereby blocking leucocyte and platelet adherence to the vessel wall and hence it can be used in COVID-19 vasculopathy.

In a phase 2 randomized double-blind placebo-controlled study to assess the safety and efficacy of crizanlizumab in COVID infected patients, 50 hospitalized COVID infected patients with age more than 18 years were included. The primary outcome of this study is measured by assessing the level of soluble p-selectin level (ng/ml) 3 days after randomization or hospital discharge whichever is earlier. Secondary outcome measured by assessing the level of p-selectin after 7 and 14 days of randomization and also levels of CRP, VWF, D-dimer after 3, 7 and 14 days of randomization, time to hospital discharge are measured and also by assessing clinical status of the patient.[32]

It is available as a 10 mg/ml vial. Commonly used for reducing Vaso occlusive crisis in sickle cell disease patients who are more than 16 years of age and main side effects are nausea, arthralgia, back pain and pyrexia. Animal studies show foetal harm may occur if administered to a pregnant woman. It can be used only if benefits justify the potential risk to the foetus.[33]

***Ravulizumab***

Ravulizumab is a humanized monoclonal antibody complement inhibitor, sold under the brand name ultomiris. It is the first and the only long acting C5 complement inhibitor. It is a drug designed for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) and atypical uremic syndrome. It is long acting and it is designed by some target modifications of eculizumab. Frequent dosing schedule and short half-life was the major limitation of eculizumab. Ravulizumab was designed to address these limitations in PNH therapy.

Two changes were made to the antibody of eculizumab, one to facilitate eculizumab-C5 dissociation in endosome by substituting two amino acid residues with histidine which changes the antibody's binding kinetics to C5, so antibody and C5 continue to dissociate at PH 7.4 and PH 6. Two to enhance the antibody's affinity towards the neonatal Fc receptor, 2 amino acid substitutions were made to the Fc binding portion of antibody. This alteration with 4 amino acids generates a new antibody ravulizumab with longer half-life (3-4 times).[34, 35]

***Leronlimab***

Leronlimab belongs to a group of HIV drugs called CCR5 antagonists. CCR5 is expressed predominantly on T cells but also found on macrophages, dendritic cells, and eosinophils to mediate chemotaxis in response to its cognate ligands that include CCL5

(RANTES), CCL3 (MIP-1α), and CCL4 (MIP-1β). These ligands are integral in the recruitment of these immune cells to inflammatory sites. The immunopathogenesis of COVID-19 likely involves the excessive influx of immune cells into the lungs. This monoclonal antibody can recognize chemokine receptor type 5 (CCR5). It is an investigational drug under development by CytoDyn, Inc (CytoDyn).

Two separate clinical trials were conducted by CytoDyn on leronlimab regarding COVID-19 treatment. CD10-small trial with 86 patients, to study the effect of Leronlimab on mild to moderate COVID-19 disease and CD12-A large trial 394 patients, to know the effect of leronlimab on severe respiratory symptoms of COVID-19. And they concluded that, the data of both CD-10 and CD-12 do not support clinical benefit for considering leronlimab for COVID-19 treatment.[36-38]

## CONCLUSION

Amidst COVID pandemic, despite not having any known cure, researchers are still working on repurposed drugs, and pacing the research of innovation therapeutic agents like mAbs anticipating that, the world will be back to normal soon and there won't be a necessity to fit ourselves to the so called 'new normal'. Distribution of bamlanivimab and etesevimab together and etesevimab alone is paused until further notice from FDA. Alternative monoclonal antibody therapies REGEN-COV and sotrovimab are authorized for same use instead of bamlanivimab and etesevimab. We have many mAbs (new and repurposed), which are still under investigation in the management of COVID-19 infections.

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