83640_Auto_EditedC.docx

WORD COUNT	2800	TIME SUBMITTED	24-APR-2023 01:50PM
		PAPER ID	99022949

Name of Journal: *World Journal of Respirology*

Manuscript NO: 83640

Manuscript Type: MINIREVIEWS

Monoclonal antibody for COVID-19: Unveiling the recipe of a new cocktail

Bajpai J *et al*. Monoclonal antibody for COVID-19

Jyoti Bajpai, Surya Kant, Ajay Kumar Verma, Akshyaya Pradhan

Abstract

The coronavirus disease 2019 (COVID-19) pandemic has had a tremendous adverse impact on the global health system, public sector, and social aspects. It is the worst pandemic of the century. However, COVID-19 management is a mystery in front of us, and authentic treatment is urgently needed. Various repurposed drugs, like ivermectin, remdesivir, tocilizumab, baricitinib, *etc.*, have been used to treat COVID-19, but no one was promising. Antibodies therapy and their combinations are emerging modalities for treating moderate COVID-19, and COVID-19 has shown its potential to reduce hospitalization. One antibody monotherapy, bamlanivimab, and two cocktails, casirivimab/imdevimab and bamlanivimab/esterivimab, have been acknowledged for emergency use authorization by the United States Food and Drug Administration for the treatment of mild COVID-19 at higher risk. The European Emergency has the same recommendation to use in COVID-19 patients without oxygen therapy. This brief review focuses on monoclonal antibodies and their combination cocktail therapy in managing COVID-19.

Key Words: SARS-CoV-2; Mild COVID-19; Antibodies; Risk factors

Bajpai J, Kant S, Verma AK, Pradhan A. Monoclonal antibody for COVID-19: Unveiling the recipe of a new cocktail. *World J Respirol* 2023; In press

Core Tip: The coronavirus disease 2019 (COVID-19) pandemic is a severe public health emergency that necessitates the rapid development of novel medicines and viral detection technologies. Monoclonal antibodies have become effective instruments for the treatment and detection of many diseases due to their high specificity and dependability. The receptor-binding domain of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein has become an important target for the creation of therapeutic antibodies because its exact structure is known and because it is essential for viral infection. The use of antibody cocktails is anticipated to be a key component of an efficient COVID-19 treatment plan because SARS-CoV-2 is an RNA virus with a high mutation rate, particularly when subjected to the selection pressure of aggressively applied preventive vaccinations and neutralising antibodies.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has placed a high burden on healthcare systems[1]. The first case of COVID-19 was reported on January 30, 2020. As of July 20, 2021, India has the highest number of COVID-19 instances, with more than 30 million[2]. The second wave of COVID-19 was much more dreadful and severe than the first. There was a shortage of drugs, oxygen, hospital beds, and vaccines. Some patients with COVID-19 will develop acute disease and multiorgan complications, but there are currently no proven therapeutics to prevent or reduce COVID-19 related hospitalizations, complications, or mortality. Various drugs are approved for hospitalized severe COVID-19 patients but only a few for mild COVID-19 patients who are not sick enough to be hospitalized[3]. Monoclonal antibodies (mAbs) are a new treatment for mild COVID-19 outpatients with high risk. Recently cocktail therapy has been approved for mild to moderate covid patients. Immunity to viral infection is a multi-arm response, comprising the innate response, which restricts viral replication and creates an antiviral state in the local tissue environment, and the adaptive response, in which virus-specific CD4+ T cells, CD8+ T cells, and antibodies produced by B cells control and clear the infection and generate immune memory. COVID-19 appears to evade or delay the innate immune response, and too long of a delayed adaptive immunity - either because of efficient viral evasion, diminished innate immunity in the patient, or both - leads to the inability to control infection and puts patients at increased risk for severe or even fatal COVID-19 disease[4].

Despite recent studies demonstrating immune responses to COVID-19 as far as eight months after symptom onset, much remains to be learned about post-infection immunity to COVID-19[5,6]. Immunity to seasonal human coronaviruses is usually of short duration, and reinfection has been documented in patients who have already been infected with COVID-19[7]. Moreover, some individuals might not benefit from vaccination, as the vaccine trials published to date have not shown 100% efficacy, and real-world experience has demonstrated breakthrough events[8,9]. Furthermore, large parts of the population still are not vaccinated primarily because of supply issues and, in part, because of vaccine

hesitancy. There is a pressing need for other therapy for COVID-19 patients. This article reviews currently approved cocktail therapy in the management of COVID-19.

WHAT ARE MABS?

mAbs are essential in protecting immunity against most viral diseases. mAbs are a single isotype with a defined specificity targeting high potency, a particular antigen *via* the antibody structure's antigen-binding fragment. As such, mAbs against COVID-19 has been derived from plasma donated by patients who recovered from COVID-19[10]. Polyclonal antibodies are usually defined as a mixture of diverse antibodies with mixed affinities for their targets. However, in the world of COVID-19 therapeutics, the term "polyclonal antibodies" is more descriptive of convalescent plasma with several antibody components[11]. An antibody is a protein molecule naturally developed by the immune response to infection. mAbs are designed in a laboratory and mimic the natural immune system in response to infection. They are created for a specific target of infectious particles. A mAb is produced by exposing white blood cells to a particular viral protein cloned to produce antibodies to treat several infections and cancers[12] mAbs bind to the spike (S) protein of the COVID-19 virus and stop the virus from binding on the angiotensin-converting enzyme II (ACE2) receptor of human cells and prevent its invasion and replication, too[13]. mAbs have been effective against new COVID-19 variants B.1.1.7. Even though more than 75 mAbs have been licensed by the United States Food and Drug Administration (FDA), only three are used to treat or prevent infectious diseases like anthrax, respiratory syncytial virus, and clostridium difficile, and two for ebola virus diseases. mAbs are intended for patients recently diagnosed with COVID-19 who are not very sick and have risk factors for severe infection[14-16]. This article focuses on mAbs with neutralizing activity against SARS-CoV-2, which work by targeting the receptor binding domain (RBD) of the viral S protein, thereby preventing viral attachment to the ACE2 receptor and preventing a critical step in viral entry and infection. Bamlanivimab is a recombinant, neutralizing human immunoglobulin G-1 (IgG1) mAb effective against the S protein of COVID-19. Etesevimab is a recombinant,

fully human monoclonal neutralizing antibody that binds to the surface S protein receptor-binding domain with high affinity and blocks the virus's binding to the ACE2 receptor of the host cell surface. Imdevimab and casirivimab are IgG1 that act against SARS-CoV-2 S protein. Thus, the antibody cocktail thwarts the attachment of the virus and its entry into the human cell.

MABS THERAPY-SCIENTIFIC PIECES OF EVIDENCE

Casirivimab (REGN10933) and imdevimab (REGN 10987) was developed by Regeneron F and Hoffmann-La Roche ltd pharmaceuticals and bamlanivimab and the cocktail of bamlanivimab and esterivimab was developed by Eli Lilly and AbCellera. The following studies or their scientific data will tell us how these mAbs are helpful in to fight against COVID-19 (Table 1).

BLAZE-1

The BLAZE 1 trial is a phase 2/3 trial that enrolled 452 ambulatory COVID-19 patients and was given in one of three doses bamlanivimab (LYCoV555) (700 mg, 2800 mg, 7000 mg) in intravenous (IV) infusion or placebo and assessed the quantitative virologic endpoints and clinical outcome[17]. The immediate result was the change in the viral load by day 11. For patients who received a 2800 mg (middle) antibody dose, viral load decreased by a factor of 3.4. The patients who received the 700 mg (lower) dose or the 7000 mg (higher) amount showed a more negligible difference from the placebo in the viral load change from baseline. In addition, bamlanivimab antibody therapy resulted in fewer hospitalization and or emergency room visits, 1.9% in 2800 mg treatment group compared to 6.3% in the placebo group.

ACTIVE-3

The ACTIVE -3 trial enrolled 314 (163 drug group and 151 placebo group) hospitalized COVID-19 patients without end organ failure[18]. All the patients were also on supportive care as background therapy, including an anti-viral drug and, when indicated,

supplemental oxygen and glucocorticoids. Bamlanivimab at a 7000 mg or placebo dose was administered as a single IV infusion over one hour. It showed that mAbs when administered with remdesivir, did not show efficacy among hospitalized COVID-19 patients without end-organ failure[19,20].

BLAZE-2

This randomized phase 3 clinical trial enrolled 966 residents and staff at a United States nursing facility with at least one confirmed COVID-19 index case and who were negative at baseline for COVID-19 infection and serology. The incidence of COVID-19 disease among those treated with antibody bamlanivimab *vs* placebo (8.5% *vs* 15.2% respectively) was lower[21].

Bamlanivimab monotherapy, compared with a placebo reduced the risk of COVID-19 in residents and staff of nursing facilities.

COCKTAIL THERAPY

Bamlanivimab and etesevimab

The BLAZE-1 phase 3 trial showed the cocktail of bamlanivimab and esterivimab, which was associated with a significant reduction in viral load than the placebo. In contrast, bamlanivimab monotherapy did not result in a substantial reduction. The cocktail was also shown to reduce the number of hospitalizations. The trial included 518 patients in the treatment arm who received a single infusion of bamlanivimab 2800 milligrams and etesevimab 2800 milligrams together, and 517 patients received a placebo[22]. The primary endpoint was COVID-19 related hospitalizations or death by any cause during 29 d of follow-up. Hospitalization or death occurred in 36 (7%) patients who received a placebo compared to 11 (2%) patients treated with bamlanivimab 2800 milligrams and etesevimab 2800 milligrams administered together, a 70% reduction. All ten deaths (2%) deaths occurred in the placebo group. Thus, all-cause death was significantly lower in the bamlanivimab 2800-milligram and etesevimab 2800-milligram group than the placebo

group. The United States FDA granted Emergency Use Authorization (EUA) for the 700 mg dose of bamlanivimab for ambulatory COVID-19 patients at high risk[23].

The EUA advice also population, despite uncertainties around the benefits of monotherapy[19]. The authorized dosage of 700 milligrams bamlanivimab and 1400 milligrams etesevimab administered together is based on analyses of available preclinical, clinical, and virologic data, as well as pharmacokinetic and pharmacodynamic modeling, which, in totality, support that the authorized dosage is expected to have a similar clinical and virologic effect to 2800 milligrams bamlanivimab and 2800 milligrams etesevimab administered together.

Casirivimab and imdevimab

REGN-COV-2

The mAbs casirivimab and imdevimab bind to the non-overlapping portion of the RBD. A phase 1/2/3 trial (NCT04425629) is taking place across several countries. The phase 3 trial results have been reported. The trial enrolled 4576 patients with one risk factor for severe COVID-19, and an IV infusion of 1200 mg or 2400 mg caserivimab/imdevimab *vs* placebo was given. The trial reached its primary outcome and depicted that the casirivimab and imdevimab cocktail significantly reduced the risk of hospitalization or death by 70% in the 1200 mg dose arm and 71% in the 2400 mg dose arm, both were significant compared with placebo[23]. In addition, the rest all secondary outcomes were also found, including a four-day reduction in the medium duration of symptoms *vs* placebo.

Interim data from the first 275 patients (phase 1/2 portion) revealed that the cocktail showed virological efficacy resulting in an overall reduction in viral load of 0.25 Log10 RNA copies/mL (95%CI: 0.60, 0.10) for the 2400 mg dose and a reduction of 0.56 Log10 RNA copies/mL (95%CI: 0.91, 0.21) for an 8000 mg dose (combined dose reduction was 0.41 Log10 RNA copies/mL, 95%CI: 0.71, 0.10) *vs* placebo at day 7.

No data on infectious virus titers or time to the cessation of viral shedding endpoints have been reported, similar to the situation with bamlanivimab or any mAb study. An

ongoing dose-ranging phase 2 companion trial in low-risk symptomatic or asymptomatic non-hospitalized patients with COVID-19 (NCT04666441) showed significant and comparable viral load reductions in casirivimab/imdevimab doses ranging from 300 mg to 2400 mg delivered *via* IV or subcutaneous (SC) route. The casirivimab/imdevimab cocktail has received EUA by the US FDA for the treatment of ambulatory patients with mild to moderate COVID-19 and a high risk of hospitalization, and the EUA has similarly recommended casirivimab/imdevimab for use in COVID-19 patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 (Figure 1). A trial showed that SC injection of antibody cocktail casirivimab and imdevimab reduced the risk of symptomatic COVID-19 infection by 81% in household contact with an infected person without COVID-19 antibodies. The trial was done by the National Institute of Allergy and Infectious Disease. The person treated with cocktail therapy with symptoms get relieved in 1 wk compared to 3 wk in placebo. FDA has given EUA for the use of casirivimab and imdevimab antibody combination for the treatment of mild to moderate COVID-19 in adults and in pediatrics age over 12 years and weight more than 40 kg who were at high risk for progressing severe disease/hospitalization. The trial showed that cocktail antibodies casirivimab and imdevimab have more effective when given as early as possible[24]. The Indian drug regulatory body- Central drugs Standards Control Organization has recently approved the cocktail regimen for use in the country in the fight against COVID-19. The drug, marketed by Cipla Inc. in India, is currently in vogue for clinical use[25]. Another contemporary mAb has been evaluated and is primarily targeted against the COVID-19 S protein. Sotrovimab, a mAb, also blocks the attachment and viral entry into the host cell. A phase 1/2/3 double-blind placebo-controlled trial enrolled 583 non-hospitalized mild to moderate COVID-19 adult patients.

Of these, 291 received sotrovimab, and the rest received a placebo within 5 d of symptoms. The primary endpoint was hospitalization or death through day 29. The result showed 21 (7%) patients were hospitalized or died in the placebo arm compared to 3 (1%) patients in the sotrovimab group. 85% reduction in hospitalization or death in the treatment group[26].

Sotrovimab showed activity against the current variants reported in the United Kingdom, South Africa, Brazil, California, New York, and India.

The EUA recommends the 500-milligram single IV dose of sotrovimab for non-hospitalized mild to moderate COVID 19[27].

WHICH GROUPS ARE SUITABLE FOR MAB?

Although mAb therapies have shown promise for treating non-hospitalized patients with mild to moderate COVID-19.

The EUA recommends that mAb treatment be given within 10 d of symptom onset or as early as 72 h of positive COVID-19 result. However, treatment should begin as early as possible to mitigate viral proliferation. In the REGN-COV2 study, the effect of REGN-COV2 on viral load was most pronounced among patients with a negative serum antibody test result at baseline. Furthermore, most trials administered mAb treatment within 3 d of a positive COVID-19 test result and a median of 3 to 4 d after symptom onset. Altogether, these studies suggest that early mAb treatment is more efficacious than the later treatment for COVID-19 patients. Indeed, by the time a patient reaches the lung injury phase of infection, it is too late for mAb treatment to be effective, as suggested by the results from the ACTIV-3 study (Figure 2).

Route, dose, and cost of mAb

A 600 mg of each or a combined 1200 mg of the cocktail has been approved for administration. This can be given either IV or SC. The administration of a total dose of cocktail antibody takes around half an hour. The patient should be kept on observation for one hour to check for any adverse effects. The price for a dose of 1200 mg cocktail (600 mg of caserivimab and 600 mg of imdevimab) is Rs 59750. This drug should be stored at 2-8 °C.

Efficacy and safety

The clinical efficacy and safety profiles do not differ between mAb monotherapy and cocktails. Yet, monotherapy *vs* combination therapy is particularly relevant given the emergence of variant strains from the United Kingdom, South Africa, Brazil, California, New York, and India. The results from one study suggested that a mAb cocktail, particularly one combining antibody that bind distinct and non-overlapping regions, can minimize mutational escape[28]. More importantly, viral mutations can reduce the effectiveness of mAb monotherapy. A recent preprint publication reported that bamlanivimab and casirivimab are abolished against the South African variant. Several variants have been labeled by the Centers for Disease Control and Prevention as "variants of concern" because the mutations they carry increase transmission, increase disease severity, and reduce the efficacy of mAb therapy and vaccinations.

CONCLUSION

There is growing evidence that mAb treatment is effective, safe, and well-tolerated. Patients should know that mAb treatment is available to all patients at a high cost in India and that mAb treatment should be started within 72 h of a positive COVID-19 test result to affect the clinical course of COVID-19. Further studies on mAb efficacy and safety in different patient populations (*e.g.*, young children, and pregnant women) are needed.

83640_Auto_EditedC.docx

ORIGINALITY REPORT

27%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.fda.gov Internet	90 words — 3%
2	img.medscape.com Internet	86 words — 3%
3	Mohammad Shane Alam, Farhana Riyaz Shah, Muntser Mohammad Fadoul Alhassen, Saif Elden B. Abdalla et al. "Therapeutic Implications of Monoclonal Antibody", Journal of Biosciences and Medicines, 2023 Crossref	62 words — 2%
4	www.pharmacytimes.com Internet	59 words — 2%
5	www.precisionvaccinations.com Internet	39 words — 1%
6	calhospital.org Internet	38 words — 1%
7	www.selectscience.net Internet	38 words — 1%
8	jamanetwork.com Internet	30 words — 1%
9	www.biospace.com Internet	

29 words — 1%

10	www.ncbi.nlm.nih.gov Internet	26 words — 1%
11	www.ema.europa.eu Internet	21 words — 1%
12	Debdoot Basu, Vivek P. Chavda, Anita A. Mehta. "Therapeutics for COVID-19 and post COVID-19 complications: An update", Current Research in Pharmacology and Drug Discovery, 2022 Crossref	20 words — 1%
13	www.medrxiv.org Internet	17 words — 1%
14	www.pubfacts.com Internet	17 words — 1%
15	"A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19", New England Journal of Medicine, 2020 Crossref	16 words — 1%
16	www.covid19.nh.gov Internet	16 words — 1%
17	www.news18.com Internet	16 words — 1%
18	chk.static.cigna.com Internet	15 words — 1%
19	pubmed.ncbi.nlm.nih.gov Internet	15 words — 1%

20	www.iavi.org Internet	14 words — < 1%
21	www.jstage.jst.go.jp Internet	14 words — < 1%
22	newdrugapprovals.org Internet	13 words — < 1%
23	www.drugtopics.com Internet	13 words — < 1%
24	Marco Tuccori, Irma Convertino, Sara Ferraro, Giulia Valdiserra, Emiliano Cappello, Elisabetta Fini, Daniele Focosi. "An overview of the preclinical discovery and development of bamlanivimab for the treatment of novel coronavirus infection (COVID-19): reasons for limited clinical use and lessons for the future", Expert Opinion on Drug Discovery, 2021 Crossref	12 words — < 1%
25	ijpras.com Internet	11 words — < 1%
26	www.genengnews.com Internet	11 words — < 1%
27	www.verywellhealth.com Internet	11 words — < 1%
28	Elnaz Khani, Sajad Khiali, Taher Entezari‐Maleki. "Potential COVID‐19 Therapeutic Agents and Vaccines: An Evidence‐Based Review", The Journal of Clinical Pharmacology, 2021 Crossref	10 words — < 1%

29	Hazael Ramiro Ceja-Gálvez, Francisco Israel Renteria-Flores, Ferdinando Nicoletti, Jorge Hernández-Bello et al. "Severe COVID-19: Drugs and Clinical Trials", Journal of Clinical Medicine, 2023 Crossref	10 words — < 1%
30	covid19-data.nist.gov Internet	10 words — < 1%
31	f6publishing.blob.core.windows.net Internet	10 words — < 1%
32	www.ashp.org Internet	10 words — < 1%

EXCLUDE QUOTES	OFF	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	OFF	EXCLUDE MATCHES	< 10 WORDS