Use of Neutralizing Monoclonal Antibodies and Its Outcome Measures in COVID-19 Patients

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Use of Neutralizing Monoclonal Antibodies and Its Outcome Measures in COVID-19 Patients

Moniruddin Chowdhury[1,2], Syeda Humayra[2], Taha Sulayman[3], Keichiro Mihara[4], P.K. Rajesh[1]

Abstract

Neutralizing monoclonal antibodies (mAbs) can stimulate protective immunity. Hence their rapid identification and characterization are incorporated into clinical practice to provide effective treatment and prophylaxis during the COVID-19 pandemic. Previously, mAbs have been effectively used in several other viral infections, including Ebola, influenza, HIV, RSV, Zika virus, and MERS-CoV. Currently, the utilization of mAbs appears to have favorable clinical outcomes in patients with mild-moderate SARS-CoV-2 infection, particularly individuals at high risk of hospitalization and progression to severe COVID-19. However, most of the interim results on anti-SARS-CoV-2 mAbs are based on ongoing clinical trial data; thereby, several questions revolve around this novel therapy, including its long-term implication, application, and feasibility. Although, the use of neutralizing mAbs may assist in alleviating the critical burden on healthcare settings and minimizing hospital stay due to severe progression of the COVID-19 symptoms especially among those with poor immune responses to vaccination, elderly, and/or vaccine-refractory individuals. Nonetheless, there is a broader need to explore these - novel therapies for their effective use in clinical practice and to improve patient-related outcomes.

Keywords: Monoclonal antibodies, mAb, anti-SARS-CoV-2, COVID-19, prophylaxis, outcome

Significance | The use of monoclonal antibodies in Covid-19.

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Introduction

Worldwide, the Coronavirus disease 2019 (COVID-19) outbreak due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global public health crisis and an urgency for effective, preventive and therapeutic life-saving measures (Marovich et al., 2020). This novel β-coronavirus has infected over 134 million individuals and killed approximately 2.9 million globally (Valdez-Cruz et al., 2021).

Several prophylactic and therapeutic strategies are being considered and designed during this pandemic to combat SARS-CoV-2 (Taylor et al., 2021). Based on the increasing needs in the healthcare system, more focus has been directed toward developing potent antiviral agents, convalescent plasma infusions, and vaccines. Neutralizing monoclonal antibodies (mAbs) to SARS-CoV-2 can stimulate protective immunity (Marovich et al., 2020). Hence, their rapid identification and characterization are incorporated in clinical practice to provide effective treatment and prophylaxis (Valdez-Cruz et al., 2021). Some clinically developed and currently used mAbs in treating COVID-19 have been listed (Table 1).

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Review Highlights

- Various preventative and treatment plans have been assessed and developed to tackle the Coronavirus Disease 2019 (COVID-19), including the use of Neutralizing Monoclonal Antibodies (mAbs)

- COVID-19 patients can be treated with antibodies using various mechanisms depending on the diversity and affinity of the SARS-CoV-2

- Previously, mAbs have been widely used for other viral infections such as Ebola, influenza, HIV, RSV, Zika virus, and MERS-CoV

- The mAbs may be more useful therapeutically or preventatively in elderly patients, individuals showing weak immune response and vaccine-resistance

- Since most of the preliminary findings of anti-SARS-CoV-2 mAbs are based on data from ongoing clinical trials, it may give rise to potential uncertainties surrounding this innovative therapy, including its long-term implications, applicability, and feasibility

SARS-CoV-2 Antibodies

Antibodies are naturally produced proteins released by the immune system in response to specific infections. Monoclonal antibodies are laboratory-developed proteins designed to mimic or enhance the body's natural immune system to fight against targeted pathogens such as viruses (Lloyd et al., 2021). These recombinant proteins can bind to and 'neutralize' the virus in COVID-19-positive patients, thus, serving as front-line antiviral agents amidst the pandemic (Lloyd et al., 2021).

SARS-CoV-2 infected patients can be treated with antibodies using various mechanisms. Convalescent plasma (CP) extracted from recovered COVID-19 individuals consists of polyclonal antibodies with varying diversity and affinity to the SARS-CoV-2 infection (Scourfield et al., 2021). Neutralizing mAbs can be derived by isolating the memory B cells of convalescent patients with high-neutralization capacity or immunized animals and screening of antibody mRNA (Taylor et al., 2021; Scourfield et al., 2021).

Based on their specific targets, COVID-19 therapeutic mAbs can be categorized into anti-virus and anti-host groups (Ning et al., 2021). Neutralizing responses to SARS-CoV-2 targets the receptor-binding domain (RBD) of the spike (S) glycoprotein, which is responsible for target receptor angiotensin-converting enzyme 2 (ACE2) interaction. Thus, steric hindrance of the RBD-ACE2 interaction via antibodies helps prevent infection by blocking the viral attachment or entry into human host's cells (Scourfield et al., 2021). Therefore, majority of the direct antiviral mAbs target the spike protein of SARS-CoV-2 as it mediates the virus entry, and affects the CP therapy which is dependent on the titre of neutralizing anti-spike antibodies (Ning et al., 2021). Host factors involved in the pathogenesis of COVID-19 or the life cycle of SARS-CoV-2 are also potent targets as it does not only exert antiviral and anti-inflammatory effects but also deals with the complications caused by SARS-CoV-2 infection (Ning et al., 2021).

Before the COVID-19 pandemic, mAbs were used for several other viral infections including Ebola, influenza, HIV, RSV, Zika virus, and MERS-CoV (Monoclonal antibodies, 2021). The mAbs are effectively used in antiviral interventions since they are specifically designed by exposing a white blood cell to a particular viral protein and cloned to produce a massive army of antibodies to target that unique virus (Lloyd et al., 2021). The U.S. Food and Drug Administration (FDA) has recently granted emergency use authorizations (EUA) for the application of neutralizing mAbs in COVID-19 patients with mild-to-moderate symptoms who do not require hospitalization (Taylor et al., 2021).

Tocilizumab, an anti-host monoclonal antibody that effectively targets the cytokine interleukin 6-receptor (IL-6R) has been the first monoclonal drug used for treating patients with severe COVID-19 (Ning et al., 2021; Zhou and Wei, 2020). The hyperactivation of IL-6 may play a major role in the pathophysiology of severe COVID-19 infection; hence, targeting the anti-inflammatory agents could provide additional treatment efficacy (Gupta and Leaf, 2021). Findings from the clinical trials indicate reduced hospital stays and improved clinical outcomes in patients treated with tocilizumab (Zhou and Wei, 2020).

On the other hand, bamlanivimab (also known as LY-CoV555 and LY3819253) is an anti-virus mAb that targets the RBD of the S protein of SARS-CoV-2. While, another neutralizing mAb called etesevimab binds to a different but overlapping epitope of the S protein RBD of SARS-CoV-2. Furthermore, casirivimab and imdevimab are recombinant human mAbs that bind to non-overlapping epitopes in the RBD of SARS-CoV-2 S protein (NIH, 2021).

Previous literature indicates that monotherapy of bamlanivimab in patients with mild-moderate COVID-19 curtailed mortality and hospitalization within 28 days (Bariola et al., 2021). When bamlanivimab, bamlanivimab together with etesevimab, and casirivimab with imdevimab are given early on in the course of SARS-CoV-2 infection, it decreases the viral load and shows favourable clinical outcomes based on data from the ongoing clinical trials (Taylor et al., 2021).

Another recent human mAb, approved for an early treatment option for COVID-19 is sotrovimab (GSK4182136 and VIR-7831). This genetically engineered anti-SARS-CoV-2 antibody has been derived from the cross-reactive S309 mAb, designed for an extended half-life and improved lung bio-distribution (Corti et al., 2021). It is expected to reduce the rate of hospitalization COVID-19 patients by effectively attaching to the spike protein of SARS-CoV-2, and diminishing the virus' entry into host cells (EMA, 2021).

Sotrovimab is currently being investigated in a Phase 1/2/3 randomized, double-blinded, placebo-controlled clinical trial among the SARS-CoV-2 infected, non-hospitalized patients presenting mild-to-moderate symptoms (The Antibody Society, 2021). Patients at an early-stage of COVID-19 with a higher risk of hospitalization (aged ≥55 years with pre-existing lung or cardiovascular disease) were intravenously administered a 0.5 g single dose of sotrovimab (Corti et al., 2021). The FDA EUA was granted based on the interim analysis on 583 COVID-19 patients who recently had onset of symptoms from the SARS-CoV-2 infection. Interestingly, it was deduced that hospitalization or death occurred in 3 (1%) patients treated with sotrovimab in comparison to 21 (7%) patients who received a placebo (The Antibody Society, 2021). The Phase III COMET-ICE trial involving adult outpatients with an increased risk of COVID-19 disease progression reported 85% reduction in hospitalization for over 24 hours and death in participants who received -

Table 1. Monoclonal antibodies used in the COVID-19 treatment

Authors	mAb(s)	Study name/ Developer company	Country(s)	Patient group	Target	Type of therapy/ Concomitant treatment	Clinical outcomes/ Findings	Status
Ning et al., 2021; Chen et al., 2021	Bamlanivimab (LY-CoV555)	BLAZE	United States	Aged 12 years and above patients at high risk of progressing to severe disease and/or hospitalization	Anti-virus (Spike protein)	Monotherapy by administering three doses (700 mg, 2800 mg, 7000 mg)	Overall reduced COVID-19 symptoms and related hospitalization frequency. However, the 2800 mg dosage appeared to be more effective in accelerating the natural decline in viral load	Approved under FDA's EUA
Lundgren et al., 2021		ACTIVE/TICO	United States	Adult hospitalized patients with COVID-19 and without end-organ failure		Combined therapy with remdesivir	It did not demonstrate efficacy when co-administered with anti-viral drug	
Ning et al., 2021; Gottlieb et al., 2021	Bamlanivimab and Etesevimab (LY-CoV555 and LY-CoV016)	BLAZE	United States	Non-hospitalized patients with mild-moderate COVID-19	Anti-virus (Spike protein)	Combination therapy of bamlanivimab and etesevimab	Combination therapy resulted in a reduction in SARS-CoV-2 log viral load but not with bamlanivimab monotherapy	EUA
Ning et al., 2021; 12)	Casirivimab and Imdevimab (REGN10933and REGN10987)	Regeneron pharmaceuticals	United States	Adults and paediatric patients (12 years or older and weighing at least 40 kg); pregnant women	Anti-virus (Spike protein)	Combination of casirivimab and imdevimab	REGN-COV-2 can greatly reduce virus load, limit weight loss, and alleviate pneumonia. Better results in patients whose immune response has not yet been initiated or those with high viral load at baseline	EUA
Gupta et al., 2021	Sotrovimab (VIR-7831)	COMET-ICE	United States, Canada, Brazil, and Spain	At-risk adults	Anti-virus (Spike protein)	Monotherapy	Progression of COVID-19 in patients with mild/moderate disease was reduced; it can be used as an early treatment option; well tolerated with less severe/ adverse events	EUA
Corti et al., 2021; Ryu et al., 2021	Regdanvimab (CT-P59)	Celltrion	South Korea	Mild-moderate COVID-19 cases who does not require oxygen therapy; elderly/ geriatric patients	Anti-virus (Spike protein)	Monotherapy	Significant reduction in COVID-19 related hospitalization or death by 72% for high-risk patients progressing to severe COVID-19, and 70% for all patients; shorter time for clinical recovery	Phase III
Rosas et al., 2021	Tocilizumab	Roche	Europe and North America	Adults with severe COVID-19 pneumonia	Anti-host (IL-6R)	Combination therapy with glucocorticoids, anti-viral drugs and convalescent plasma	It did not result in significantly better clinical status or lower mortality than placebo at 28 days	EUA
Abani et al., 2021		RECOVERY	United Kingdom	Adult hospitalized COVID-19 patients with hypoxia and systemic inflammation		Combined with corticosteroids	Tocilizumab improved survival and other clinical outcomes, regardless of the amount of respiratory support, and were additional to the benefits of systemic corticosteroids	
Reichert, 2021	Levilimab (BCD-089)	Biocad	Russia	Patients With Severe COVID-19	Anti-host (IL-6R)	In combination with standard therapy	Interim results demonstrate that levilimab therapy can significantly reduce mortality	Phase III
Diáz et al., 2020	Itolizumab	VICTORIA	Cuba	Elderly patients with moderate COVID-19	Anti-host (CD6)	Patients received itolizumab with standard treatment (lopinavir/ritonavir, chloroquine, prophylactic antibiotics, INF-α2B, and low-molecular-weight heparin)	Use of itolizumab in combination with other antivirals reduce COVID-19 worsening and mortality	EUA

- sotrovimab versus placebo (Pharmaceutical Techonology, 2021).

The anti-SARS-CoV-2 mAbs are contraindicated in severe COVID-19-related hospitalized patients requiring increased oxygen flow rate and/or chronic oxygen therapy due to any underlying non-COVID-19-related comorbidities. However, mAbs are permitted in patients with mild-moderate SARS-CoV-2 infection, particularly those at high risk of hospitalization and/or for progression to severe COVID-19 (FDA, 2021).

According to a research by the University of Pittsburgh Medical Center (UPMC), monoclonal antibodies helped mitigate the risk of mortality and hospitalization up to 60% when provided as an early therapeutic and prophylactic measure for the coronavirus infected patients (UPMC, 2021). Nevertheless, administering mAbs such as casirivimab and imdevimab to the hospitalized COVID-19 patients who require high flow oxygen or mechanical ventilation may lead to worse clinical outcomes (FDA, 2021).

There are also possible adverse reactions including both allergic or non-allergic infusion-related reactions. Itching, flushing, low blood pressure and shortness of breath are some of the rare infusion-related reactions. While soreness, pain, and bruising around the intravenous site are some potential side effects of administering IV medication (Chen et al., 2021). Diarrhoea and rash were major adverse events observed in patients treated with sotrovimab (Pharmaceutical Techonology, 2021).

The 'Coronavirus Treatment Acceleration Program' (CTAP) is on a constant surge to develop safely effective and novel therapies by utilizing every possible pathway to curb the viral effects and treat the COVID-19 infection FDA, 2021). Currently, more than 50 mAbs are being processed at different developmental stages against SARS-CoV-2, most of which are directed against the spike protein (Deb et al., 2021). It is necessary to investigate the neutralizing mAb treatment benefits on at-risk population, protection period of the mAbs, effect on subsequent vaccination, and optimum timing for mAb administration based on the serology, viral load and other clinical factors (Taylor et al., 2021).

As the number of infected cases are soaring globally at an alarming rate, several other factors related to the antiviral mAbs should also be considered. Due to increasing demands and limited medical resources, administration of mAbs might be difficult during the pandemic. Firstly, because these drugs are expensive, and secondly, the infusion must be carried out in specialized medical centres. There has also been mixed reporting regarding the benefits of mAbs among hospitalized patients with COVID-19, while many researchers anticipated that mAb treatment might work best during the early onset of infection rather than a late-stage with severe symptoms and complications (Nature, 2021). However, the human monoclonal antibody prevails as a viable therapeutic approach in most countries that are currently facing inadequate vaccine availability for their general population (Deb et al., 2021).

Furthermore, prophylactic or therapeutic use of the mAbs could have better utility among those with poor immune response to vaccination, elderly, and/or vaccine refractory individuals (Deb et al., 2021; Case et al., 2021). Due to emergence of mutated SARS-CoV-2 strains, modified mAb patterns and adjusted spike sequences of vaccines might have to be reformulated for effective immune protection from COVID-19 (Nature, 2021). The stability, production capacity, prevention of resistance, possible synergy in antibody combination, mechanism of neutralization, the role and optimization of Fc effector functions needs to be evaluated as more human mAbs are being tested and developed (Case et al., 2021).

Concluding Remarks and Future Perspectives

Several clinical trials are still underway to evaluate the efficacy, pharmacokinetics, safety, and tolerance of various mAbs (Jaworski, 2021). This indicates the limited body of scientific evidence or published data to support the clinical efficacies of these therapeutic agents, thus questioning the possible short and long-term implications of mAbs. Furthermore, developing multiple mAbs is associated with high-cost implications and is a leading barrier to their usage in therapeutic settings (Jaworski, 2021). It can be a potential drawback, so healthcare organizations should question how to address the affordability and economic burden revolving around using mAbs. The longevity of mAbs is another area of discussion occurring due to the advent of the SARS-CoV-2 variants of concern (VOC) with mutating spike protein near the binding epitope, leading to viral resistance (Razonable & Chen, 2022). According to preclinical research, COVID-19 treatment and prevention may benefit from combinations of powerful mAbs that target the SARS-CoV-2 receptor binding site as well as broad mAbs that target conserved areas of the viral spike (Jaworski, 2021). Therefore, collective efforts should focus on queries related to overcoming the issue of viral resistance and enhancing the use of cocktail mAbs for increased prophylaxis.

Since most of the interim results on anti-SARS-CoV-2 related mAbs are based on ongoing clinical trial data, several questions, as discussed above, revolve around this novel therapy, mostly involving its long-term implication, application, and feasibility. Although, the use of neutralizing mAbs may assist in alleviating the critical burden on healthcare settings, and minimizing hospital stay due to severe progression of COVID-19 symptoms. Nonetheless, there is a broader need for future studies to explore these novel therapies for their effective use in clinical practice and to improve patient-related outcomes.

Overview

Public health emergency response to massive infectious disease outbreaks such as the COVID-19 pandemic requires analytical and strategical approaches to prevent drastic fatalities and death. The preventive measure should focus on managing high-risk patients by providing them with passive immunity since they can be more susceptible to adverse events. The timely production of monoclonal antibodies has been a beneficial addition to the COVID-19 therapeutic toolkit and a clear illustration of how current technology may lead to identifying novel treatments for global protection.

Author Contributions

MC and SH developed the hypothedsis and concept. MC, SH, and TS survey literature. SH, TS, and MC prepared manuscript. MC, KM, and PKR review, validate, and supervise the study.

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Competing financial interests

The authors have no conflict of interest.

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