Mini-Review

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Opportunities and challenges to the use of neutralizing monoclonal antibody therapies for COVID-19

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SUMMARY The coronavirus disease 2019 (COVID-19) pandemic has resulted in a substantial global public healthcare crisis, leading to the urgent need for effective therapeutic strategies. Neutralizing antibodies (nAbs) are a potential treatment for COVID-19. This article provides a brief overview of the targets and development of nAbs against COVID-19, and it examines the efficacy of nAbs as part of both outpatient and inpatient treatments based on emerging clinical trial data. Assessment of several promising candidates in clinical trials highlights the potential of nAbs to be an effective therapeutic to treat COVID-19 in outpatient settings. Nevertheless, the efficacy of nAbs treatment for hospitalized patients varies. In addition, this review identifies challenges to ending the COVID-19 pandemic, including concerns over nAbs development and clinical use. Resistant variants significantly threaten the availability of nAb-based therapeutics. This review also discusses other approaches that may improve the clinical benefit of neutralizing mAbs.

Keywords SARS-CoV-2, COVID-19, neutralizing antibody, monoclonal antibody, clinical therapy

1. Introduction

A novel coronavirus, SARS-CoV-2, caused the global coronavirus disease 2019 (COVID-19) pandemic. COVID-19 results in substantial levels of morbidity and mortality, though a considerable proportion of the infected have only mild to moderate symptoms (*1-3*). The COVID-19 pandemic poses a massive threat to worldwide health along with widespread economic disruption, necessitating the urgent development of novel antivirals and effective therapeutic options to alleviate the disease's adverse outcomes.

Given these circumstances, broad-spectrum antivirals (remdesivir, lopinavir/ritonavir, *etc*.) and immune-modulators (tocilizumab and dexamethasone, *etc*.) were initially investigated and found to have varying degrees of efficacy (*4-8*). Hopes were raised by convalescent plasma therapy, *i.e*. use of blood from recovered patients, but its efficacy had been generally proved disappointing due to the lack of standardized doses and a consistent titer of active neutralizing antibodies (nAbs) (*9,10*). That said, the use of monoclonal antibodies (mAbs) offers a new avenue for the treatment of infectious diseases. nAbs are created to exclusively bind to the special epitope regions of a virus that are indispensable to its cellular entry, infectivity, and replication to decrease these events (*11,12*). Neutralizing mAbs serve as potent alternative to most of the current treatments for viral infections. The outstanding efficacy of nAbs against aggressive fatal viruses, like Ebola virus and respiratory syncytial virus (RSV) (*13,14*), substantiate the great potential of nAbs to serve as COVID-19 therapies.

2. Targets of SARS-CoV-2 neutralizing mAbs

The surface spike glycoprotein (S protein) on SARS-CoV-2 is a rational target for nAb-based therapies, as it facilitates virus entry into host cells *via* interaction with the cellular angiotensin-converting enzyme 2 (ACE2) receptor (*15,16*). The S protein contains two subunits. Its S1 subunit has an N terminal domain (NTD) and receptor-binding domain (RBD) (*15*). Components of the S2 subunit promote viral fusion (*17*). Due to its crucial role in facilitating direct viral contact with the ACE2 receptor, the RBD is the major target for nAbs to block SARS-CoV-2 from entering human cells (*15*). The NTD in the S1 subunit or S2 subunit of SARS-CoV-2 could likely serve as a potential target for nAb as well, but the mechanisms are unclear (*18-21*).

A point worth noting, however, is that the structure of the S protein fluctuates dynamically in that it has

two conformations: a closed state and an open state. In the closed ("down") conformation, the three RBDs are inaccessible, which sterically hinders binding (*22,23*). In contrast, an RBD that is necessary for SARS-CoV-2 fusion is exposed in the open ("up") state. (*22,24*). This character of the S protein poses a challenge to the development of mAbs that may bind to an RBD but fail to neutralize SARS-CoV-2 *in vitro*. The dynamic conformation of the S protein might also directly give rise to generation of infectivity-enhancing antibodies in patients with severe COVID-19. Most recently, researchers found that some anti-NTD mAbs from patients with COVID-19 were able to induce the RBD to transition into the "up" conformation to enhance the binding affinity of the S protein to ACE2 and increase the infectivity of SARS-CoV-2. Structural results indicated that almost all of the infectivity-enhancing mAbs bound to NTD in a similar manner (*25*), implying the imperative need to elucidate the complicated etiology of COVID-19.

3. Clinical development of and concerns regarding SARS-CoV-2 neutralizing mAbs

To date, a range of technologies has been adopted to elicit anti-SARS-CoV-2 nAbs. Most of the promising nAb candidates for COVID-19 therapy are generated by screening enriched B cells from the peripheral blood of convalescent patients (*20,26,27*). Similarly, phagedisplay mediated bio-panning or genetically humanized mice immunized with SARS-CoV-2 to produce fully human nAbs have been used to identify the best candidates (*27-29*).Some approaches to improve availability and pharmacological properties have been used during the development of nAbs against SARS-CoV-2. VIR-7831, an anti-SARS-CoV-2 nAbs from a convalescent patient who recovered from SARS, was engineered with mutations and modification of the Fc region of immunoglobulin G (IgG) as well as the neonatal Fc receptor (FcRn), to increase its affinity, extend the antibody half-life, and enhance lung bio-availability (*30*).

There are concerns about immune enhancement of nAbs against COVID-19. Some viral infections, including SARS and MERS, exhibit antibody-dependent enhancement (ADE) (*31,32*). ADE can activate or enhance various categories of processes, such as antibody-mediated boosting of viral entry and replication, complement activation, and cytokine release (*33-36*). The Fc domain could be modulated to attenuate interactions between nAbs and cellular Fc receptors, and thus, to minimize ADE-related events. A typical example is the evolution of AZD7442, a cocktail of two nAbs for treatment of COVID-19 (*37*). Similarly, point mutations (at positions 234 and 235) were introduced into the Fc regions of etesevimab (JS016) to reduce the risk of ADE phenomenon (*38,39*).

4. The clinical utility of SARS-CoV-2 neutralizing mAbs

The excellent pre-clinical evidence has given rise to accumulated clinical trials of anti-SARS-CoV-2 mAbs so far, but a limited number of nAbs have progressed to phase 3 trials for COVID-19 therapies (Table 1).

There are detailed data on the efficacy of bamlanivimab and bamlanivimab/etesevimab and casirivimab/imdevimab cocktails as therapies for ambulatory patients with COVID-19 from Phase 3 trials. The single nAb bamlanivimab (also known as LY-CoV555 or LY3819253) and a bamlanivimab/etesevimab cocktail (designated as LY-CoV016 or LY3832479), derived from convalescent patients by targeting the RBD, were developed by Eli Lilly and AbCellera (*40,41*). Bamlanivimab was well tolerated at a wide-range of doses without serious severe adverse events (AEs) (*41*). Administration of bamlanivimab resulted in fewer patients requiring hospitalization and a significant decrease in the viral load in patients receiving the 2800-mg dose (medium dose) in comparison to a placebo, but, surprisingly, did not have that effect at 7000 mg (a higher dose) (*42*). This might involve the "prozone effect". Thus, the US Food and Drug Administration (FDA) issued emergency use authorization (EUA) for bamlanivimab to treat patients with mild to moderate COVID-19, including those hospitalized (*43*). Further viral load and pharmacodynamic/pharmacokinetic data revealed a marked decrease in the log10 viral load on d 11 in the group receiving a bamlanivimab/etesevimab cocktail (bamlanivimab 700 mg and etesevimab 1400 mg), and this decrease was more obvious than that in the group receiving bamlanivimab mono-therapy (*41*). In a Phase 3 trial, the cocktail decreased the risk of hospitalization (by 70%) and death (0 *vs*. 10) in patients with COVID-19 (*44*). Based on the clinic trial data, the FDA granted an EUA temporarily authorizing administration of the cocktail to treat patients with mild to moderate COVID-19 who were at risk of developing severe COVID-19; the cocktail's safety and efficacy continue to be investigated in hospitalized patients (*45*).

Regeneron collaborated with F. Hoffmann-La Roche to develop a novel nAbs- casirivimab and imdevimab cocktail (REGN10987 and REGN10933) to treat COVID-19 (*46*). This cocktail for ambulatory patients reduced the viral load in patients (a 10-fold reduction, on average) in different countries compared to that in patients receiving a placebo. It also markedly reduced the risk of hospitalization by 70% (1200 mg) and 71% (2400 mg) (*47*). Both doses were well tolerated without severe SAEs (*48*). The cocktail has been issued an EUA by the FDA for ambulatory patients (*49*). A similar authorization was issued by the European Medicines Agency, which recommended it for patients who are at risk of developing severe COVID-19 (*50,51*).

Hospitalized patients with COVID-19 are a

Table 1. Neutralizing mAb-based therapeutics for COVID-19 in clinical trials[a]

Neutralizing antibody	Monotherapy or Cocktail	Sponsor	nAb Source	Phase
LY-CoV555	Monotherapy	AbCellera/Eli Lilly	Convalescent plasma	Phase 2/3
LY-CoV016 (JS016)	Monotherapy	Junshi Biosciences/Institute of Microbiology/Eli Lilly	Recombinant	Phase 2
LY-CoV555 + LY-CoV016	Cocktail	AbCellera/Eli, Lilly/Junshi Biosciences	Convalescent plasma/Recombinant	Phase 3
REGN10933 + REGN10987	Cocktail	Regeneron/F. Hoffmann-La Roche Ltd.	Convalescent plasma/humanized mice	Phase 1/2/3
BGB DXP593	Monotherapy	BeiGene/Singlomics Biopharmaceuticals	Convalescent plasma	Phase 2
CT-P59	Monotherapy	Celltrion	Convalescent plasma	Phase 2/3
TY027	Monotherapy	Tychan Pte. Ltd.	Engineered	Phase 3
BRII-196+ BRII-198	Cocktail	Brii Bio/TSB Therapeutics	Convalescent plasma	Phase 3
VIR-7831	Monotherapy	Vir Biotechnology, Inc. GlaxoSmithKline	Convalescent plasma	Phase 3
SCTA01	Monotherapy	Sinocelltech Ltd.	Recombinant	Phase 2/3
HLX70	Monotherapy	Hengenix Biotech, Inc.	Convalescent plasma	Phase 1
STI-1499	Monotherapy	Sorrento/Mount Sinai Health System	Convalescent plasma	Phase 1
MW33	Monotherapy	Mabwell (Shanghai), Bioscience Co., Ltd.	Convalescent plasma	Phase 2
SI-F019	Monotherapy	Sichuan Baili Pharmaceutical Co., Ltd.	Recombinant	Phase 1
HFB30132A	Monotherapy	HiFiBiO Therapeutics	Recombinant	Phase 1
ADM03820	Cocktail	Ology Bioservices	Convalescent plasma/Recombinant	Phase 1
APN-01	Monotherapy	Aperion Biologics	Recombinant	Phase 2

[a]Data in Table 1 are from the World Health Organization (International Clinical Trials Registry Platform (ICTRP) (who.int)) and National Institutes of Health (*https://clinicaltrials.gov/*) databases and drug company webpages to cite clinical trials investigating of antiviral mAbs as treatments for COVID-19.

difficult-to-treat population since they have extremely poor outcomes and significant critical care needs (*52,53*). In Phase 2-3 trials, bamlanivimab failed to provide a clinical benefit in hospitalized patients (*54*). Like bamlanivimab, a casirivimab/imdevimab cocktail did not significantly reduce the risk of death, but the RECOVERY trial is ongoing. Several other neutralizing nAbs, including VIR-7831, a BRII-196/BRII-198 cocktail, and SCTA01 (a humanized recombinant anti-SARS-CoV-2 mAb), are going to be assessed in hospitalized patients with COVID-19 (*55*).

5. The challenges of SARS-CoV-2 neutralizing mAbs in clinical settings

Substantial challenges have hampered clinical trials on and use of nAbs to treat SARS-CoV-2. Cost/access is one hurdle, as is large-scale manufacturing and storage. Since most people with an early infection recover, specifying a clinical endpoint with which to gauge the benefit relative to a placebo is difficult. Likewise, inflammation and coagulopathy may pose a more serious threat than viral replication in patients with severe disease, so determining the benefit of nAbs in that cohort is difficult.

There are also concerns about the route of administration in clinical settings. Administration *via* IV infusion (*e.g*., bamlanivimab and the bamlanivimab/etesevimab and casirivimab/imdevimab cocktails) is difficult in a community setting while far easier in a hospital. Clearly, oral administration would have an edge in an outpatient setting and limit damage to respiratory epithelial cells, thus prompting efforts to optimize routes of administration (*56*). Another aspect is the timing of nAb administration. Some deaths due to COVID-19 in the later stages are reported to be driven by infection-related inflammation stimulated by innate mediators, *e.g*. IL-6 (*57,58*). Thus, early intervention with nAbs seems to be necessary when considering the delayed initiation of mAbs dose before the effective inhibitory concentration is reached in the lung.

An underlying limitation of nAbs for treatment of COVID-19 is the unknown bio-availability of passively infused IgG in tissues affected by the disease, and especially the lungs. Some patients are likely to experience either a nonallergic infusion-related reaction or an allergic infusion-related reaction. Infusion-related reactions could facilitate effector functions, including complement-dependent cytotoxicity (CDC), opsonization, the classical complement cascade, and antibody-dependent cellular cytotoxicity (ADCC), to cause a series of symptoms such as itching and hypotension (*59-61*).

Another priority consideration is the effect of variants that directly make available therapeutics substantially reduced. The general approach is to use nAb cocktails instead of monotherapy, since the nAbs

in a cocktail bind to distinct epitopes corresponding to the diversity of the S protein, thus decreasing treatment-emergent resistant variants (*46*). Another method is to select nAbs that target conserved epitopes indispensable for viral function, *e.g*., VIR-7831 (*62*). Thus, comprehensive and continued monitoring of SARS-CoV-2 variants should remain a priority.

6. Conclusion

Hundreds of neutralizing mAbs in pre-clinical studies as COVID-19 therapies have emerged. Evaluation of several promising candidates in clinical trials suggests that nAbs could serve as an effective therapeutic intervention for SARS-CoV-2 in ambulatory patients. Nevertheless, there are substantial challenges. The efficacy of nAb therapies for hospitalized patients with COVID-19 varies, highlighting the concern about anti-SARS-CoV-2 nAbs treatment in patients who already have severe symptoms. In addition, resistant variants threat the availability of nAb-based therapeutics. Therefore, the importance should be attached on the development of nAbs with improved availability and increased efficacy. Moreover, anti-SARS-CoV-2 nAbs therapies are likely to shed light on development of alternative interventions to treat other acute respiratory infections.

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