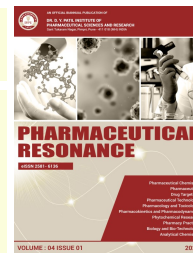




REVIEW ARTICLE

MONOCLONAL ANTIBODIES IN THE TREATMENT OF COVID-19: MYTHS AND FACTS



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ABSTRACT : In order to address COVID-19 pandemic there has been efforts to advance potent neutralizing mAbs against SARS-cov-2 as therapeutics. In this review we have summarized some of the leading mAbs currently in development and present the evidence supporting inhaled delivery of antiviral mAbs as an early intervention against COVID -19 that could prevent important pulmonary morbidities associated with the infection. Highly potent mNABs has great potential. To study SARS-CoV-2 antigenic drift under selective immune pressure by mNABs is important for the optimal implementation of mNABs for the therapeutic management of COVID-19. The use of monoclonal neutralizing antibodies (mNABs) is being actively sought as a viable intervention for the treatment of Severe Acute Respiratory Syndrome CoV-2 (SARS-CoV-2) infection and associated coronavirus disease 2019 (COVID-19) .

Keywords : SARS-CoV-2, COVID-19, Monoclonal antibodies, Treatment.

INTRODUCTION :

Due to their track record of safety in humans, target specificity (which reduces the risk of off-target effects), and ability to coordinate the immune defence in the fight against infection, monoclonal antibodies (mAbs) are one of the most promising classes of molecules among the various potential therapeutic intercessions. In the last two decades, numerous technological advancements have been produced. Makes mAbs to promptly respond to the COVID-19 pandemic in single cell screening and sequencing, as well as manufacturing. The pathophysiology of SARS-CoV-2, antibody protective roles in mucus, and some of the leading mAb under development for SARS-CoV-2 are all discussed in this paper. Then, by looking at the history of mAbs that have been developed and utilised to treat different diseases, ARIs in the past and used the information to identify areas where antiviral mAb efficacy for COVID-19

could be improved[1].

The US Food and Drug Administration (FDA) has issued separate emergency use authorizations (EUA) for bamlanivimab, casirivimab-imdevimab, and bamlanivimab-etesevimab, which are neutralising anti-spike monoclonal antibodies against SARS-CoV-2. They are available for early outpatient treatment of mild to moderate coronavirus-19 disease (COVID-19) in patients at increased risk of clinical progression [3,4]. However, due to the minimal efficacy revealed in clinical trials, healthcare practitioners are hesitant to prescribe these monoclonal antibodies and have not recommended their routine use. Furthermore, patients are unaware that these mAbs are available. Monoclonal antibody therapy have risen in popularity as a result of the spike, are administered intravenously, and they need that eligible patients leave their homes and undergo quarantine in order to get infusions at medical institutions. Long-term care centres and nursing homes that are able to deliver the medications can also provide the infusions. [2] The removal of the N-terminal region from monoclonal antibodies against the MERS coronavirus N protein improved antibody specificity for the virus and increased recombinant protein solubility[3]. Human monoclonal antibodies

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(mAbs) are the quickest to develop among the several therapeutic possibilities available[4]. Neutralizing antibodies (NAbs) are an important component of the host's adaptive immune response that are generated in response to viral infections after spontaneous infection or vaccination[5].

1.1 MECHANISM OF MONOCLONAL ANTIBODIES

The spike glycoprotein (S protein), a trimeric class I fusion protein that promotes virus entrance into host cells by binding to the human angiotensin-converting enzyme 2 (hACE2) and cellular heparan sulphate as receptors, neutralises SARS-CoV-2 infection. The S protein exists in two states: a metastable pre-fusion state and a stable post-fusion state. Each S protein monomer is made up of two unique units called S1 and S2. The receptor-binding domain (RBD) of the S1 subunit is important for interacting with hACE2 and heparan sulphate, which is present on host cell membranes, causing the S protein to destabilise in its pre-fusion state and transition into the post-fusion conformation. This event resulted in the viral particle entering the host cell, which therefore resulted in the commencement of infection [4]. The connection between the heterotrimeric Spike (S) glycoprotein and its functional receptor, the angiotensin converting enzyme, is required for a successful SARS-CoV-2 infection. enzyme 2 (ACE2), which is located on host cells that are vulnerable. The SARS-CoV-2 S protein's receptor-binding domain (RBD) is required for virus entrance into the host cell and has been identified as a major target for many of the currently known SARS-CoV-2 mNabs. The SARS-CoV-2 S protein is cleaved at the S1/S2 cleavage site by the host cell during viral entry. S1, which contains the RBD, and S2, which is responsible for the conformational change that causes the fusion of viral and host cell membranes, are separated by proteases. While the receptor binding motif, a sequence inside the RBD, determines SARS-CoV-2 S binding activity and contributes to infectivity, mutations within critical residues of the SARS-CoV-2 S cause infectivity. Infectivity may be enhanced by 2 S, which enhances S1/S2 cleavage. The epitopes on the S are the principal target of mAbs against SARS-CoV-2. While certain SARS-CoV-2-induced Abs preferentially bind to the S1 or S2 subunits of the S

protein, others bind to the RBD inside the S1 subunit with a high affinity[5]. Monoclonal antibodies are proteins that bind to one of the body's unique substances. This binding is quite adaptable, as it can imitate, inhibit, or create modifications to exact pathways, resulting in a successful therapeutic intervention with a very specific illness treatment [20]. Antibodies that can identify epitope regions from virus foreign particles can be passively immunized to decrease virus transmission proliferation and disease severity [7,20].

1.2 ADVANTAGES:

1. Among the several therapeutic interventions available, monoclonal antibodies (mAbs) are the quickest to create.
2. The extended industrial experience in designing and producing mAbs reduces the risks often associated with exploratory product technological development.
3. Finally, the remarkable technological advancement in this field has allowed for the reduction of traditional timescales, allowing for a 5–6 month timeframe from discovery to proof-of-concept trials.
4. The specificity of mAbs for viral antigens helps to their efficacy and safety, and it is likely that it reduces regulatory requirements prior to starting human research.
5. By mixing complementary pairs of mAbs, the risk of viral escape can be reduced.

1.3 DISADVANTAGES

1. The dose of mAbs employed in clinical trials against SARS-CoV-2 in the field of infectious diseases is large, ranging from 500 to 8,000 mgs.
2. Because of the large dosage of mAbs and the fact that they can only be delivered intravenously, this therapeutic intervention is exceedingly expensive and offered nearly only in high-income nations. Indeed, the expensive cost of this intervention has hampered the global availability of mAbs.
3. The risk of antibody-dependent enhancement (ADE) of disease, which is usually mediated by

the binding of the fragment crystallizable (Fc) region portion of the antibody to Fc gamma receptors (FcγRs) expressed by immune cells, is the second limit of mAbs in the field of infectious diseases[4].

1.4 SYSTEMIC VS. INHALED DELIVERY OF ANTIVIRAL MAB THERAPIES USING VIBRATING MESH NEBULIZERS

Antibodies are big (150 kDa for IgGs), hydrophilic molecules with a small volume of distribution and slow distribution kinetics out of the plasma, resulting in restricted passive transport of IgG from the circulation to mucosal surfaces. Despite the fact that secretory IgA and IgM can be directly released into airway secretions via a transcytosis process across epithelial cells[9,10]. In the lungs, IgG does not benefit from the same active mechanism. This makes getting enough IgG antibodies into the lungs to be effective extremely difficult, and it demands a very systemic high dose, with only a small fraction of the dose making it to the infection site[6]. Inhaled administration of anti-SARS-CoV-2 mAbs appears to be effective in preclinical investigations. Even when dosed at a significantly lower dose than IV administration, currently under clinical development is projected to achieve comparable efficacy[6].

Antiviral mAbs delivered directly into the airways have numerous key advantages over systemic delivery. One of them is inhaled mAbs, which are immediately available because they are administered into the airways to exert antiviral action and are deposited in the mucus secretions of the airways, which are the site of virus infection and transmission. The administration of mAb via the lungs appears to be particularly well suited to combating infection spread within the lungs. Inhaled mAb therapies are likely to be well tolerated due to the substantial amounts of endogenous IgG already present in airway mucus discharges. Finally, Fc-mucin interactions [11,12] were exploited. As a result, the viral antigens that cause pulmonary hyperinflammation are physically eliminated. Prior research has demonstrated that human mAbs administered directly into the lung are very potent, which is consistent with the aforementioned advantages of direct delivery into the lung as well as

the apical route of infection and propagation of these viruses. Inhaled mAb delivery necessitates a reliable delivery mechanism. Because VMNs can: 1) provide a high dose of mAb to the airways while keeping the overall volume relatively modest [14], and 2) achieve uniform dispersion throughout the airways [14,15], they are an appealing technique for the pulmonary administration of proteins and antibodies. Furthermore, unlike jet or ultrasonic nebulizers, which rely on heating elements, by utilizing a vibrating mesh to generate aerosols, protein breakdown is maintained to a minimum. Whereas traditional jet nebulizers possess only a ~ 10% delivery efficiency, the latest VMNs exceed 60% and avoid problems associated with hygroscopic growth and agglomeration of proteins - common challenges for dry powder formulations of proteins [6,16]

1.5 CHALLENGES IN MONOCLONAL ANTIBODY THERAPY

Although this technology shows encouraging results in neutralising infection, large-scale manufacturing of monoclonal antibodies, especially against emerging pathogens, is laborious, expensive, and time-consuming [20]. Sequences of monoclonal antibodies that are efficient against SARSCoV may be cloned and expressed in a variety of organisms, including mammals, yeasts, and plants [21]. Plant expression systems can be utilised to produce monoclonal antibodies in a short amount of time and at a low cost [22], which could be one of the most important benefits of epidemic conditions[7].

CONCLUSION

Pharmaceutical and biotech companies have been able to find lead mAb candidates and push them into Phase 1 studies in a matter of months, an outstanding success in advancing lifesaving medicines for the millions of SARS-CoV-2 patients. Combining these ultrapotent therapeutic mAb candidates with fast diagnostic advancements Potentially enables an early COVID-19 intervention that differs from traditional passive vaccination and systemic therapy. We feel that early inhalation mAb therapy is an additional mAb-based therapeutic modality that should be evaluated alongside systemic mAb-based medicines that have shown early clinical benefit. enabling for more effective therapies that minimise the course of

severe pulmonary sickness and hospitalisation while lowering the dose of mAb necessary, allowing for the treatment of more people Early intervention with direct nebulized mAb delivery could be a viable strategy beyond the present COVID-19 epidemic. In the future, a treatment approach for ARIs caused by commonly circulating infections or newly developing pathogens will be developed.

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