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Review Article

The New Outlook of Monoclonal Antibodies in Neutralizing Target Cells in COVID-19

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Abstract

Background: The deadly arrival of novel coronavirus (COVID-19) in late December 2019, caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) has emerged worldwide causing a pandemic. The World Health Organization (WHO) has proved ineffectiveness against existing medications this influenced the prompt identification of Monoclonal antibodies (mAbs) which plays a vital role as the prophylactic application that helps in developing new interventions.

Objectives: To study the effect of mAbs in high-risk individuals in treating COVID-19.

Methodology: The recent studies related to the aim of the review were undertaken through a literature search to analyze the importance of mAbs in combating SARS-CoV-2.

Results: In several countries even though vaccines have reached the Emergency Use Authorization (EUA) people still rely on traditional medications. Besides repurposed drugs, recently many mAbs targeting S-protein of SARS-CoV-2 have been signed up for clinical trials. Currently, no specific neutralizing mAbs have been reported for SARS-CoV-2 and it may take several years for such antibodies to be readily available. The development of mAbs for preventing the SARS-CoV 2 infection is challenged by the threat of antibody-dependent enhancement, antibody-resistant against SARS-CoV-2 variants, acute respiratory infections, clinical trials and risk assessment, and inexplicable. The clinical trial data proved that there is no life-threatening Adverse Drug Reactions (ADR) occurred during mAbs therapy for COVID-19 patients.

Conclusion: Establishing monoclonal antibodies will continue to be the best prophylactic application as it minimizes the risk of hospitalization in the high-risk individuals affected by SARS-CoV-2 infection.

Keywords: COVID-19, Monoclonal antibodies (mAbs), Emergency Use Authorization (EUA), Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2)

1. INTRODUCTION

Passive immunization

Passive immunization also called passive immunotherapy or passive immunity that allows the transfer of antibody-mediated immunity to high-risk individuals for preventing the patients from unresponsive state or treating life-threatening illnesses [1]. Maternal antibodies (MatAb) also known as the natural form of passive immunity are transferred to the fetus via the placental receptor (FcRn) cells at the time of pregnancy whereas, Artificial acquired passive immunity can be delivered through many different forms such as human or animal blood products, immunoglobulins (IG), and monoclonal antibodies (mAbs) [2]. The immunological intervention was developed many years back for treating diphtheria and tetanus, which was derived from the serum of actively immunized animals [3, 4]. At present, the artificial passive immunization includes mAbs or polyclonal antibodies (pAbs) which were established from both human and non-human blood samples. The pAbs extracted from the non-human origin were associated with an increased risk of 'serum sickness' where these risks can be minimized by effective convalescent plasma therapy (CPT) or mAbs isolated from the human subjects [5, 6].

Development of monoclonal antibodies

Monoclonal antibodies are molecules defined as the body's natural immune system enhancer were evolved from exposing a white blood cell (WBC) to the viral host cell target protein, which was later cloned and developed into antibodies for combating severe infections [7]. The mAbs were manufactured by operating the hybridoma technology, which was the first approved antibody for preventing kidney transplant rejection in 1986. Beyond binding to their targeted antigenic epitope mAbs produces multiple effects like the destruction of functional antigen and removal of cells and pathogens [8]. Even though mAbs are restricted to single epitope specificity it is superior to polyclonal antibodies with multiple epitope specificities because they can be manufactured from large-scale industries, with increased consistency [9, 10].

Monoclonal antibodies in COVID-19

In late December 2019, the emergence of the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) the causative agent for novel coronavirus (COVID-19) has built a worldwide crisis causing a pandemic. This influenced the immediate identification for preventing the SARS-CoV-2 infection. The mAbs are the key factor of protective immunity for most viral diseases which have the therapeutic potential and prophylactic applications that help to design new interventions and development. Nevertheless, attention has focused on the development of new antiviral agents, vaccines, and convalescent plasma infusions [11-13].

In many different countries even though several vaccines have reached the Emergency Use Authorization (EUA) people still rely on traditional medications and management for symptomatic relief. The recent World Health Organization (WHO) international clinical trial has proved our ineffectiveness against this pandemic with our existing medications [14]. Patients at the highest risk of hospitalization or death include certain comorbidities like obesity, diabetes mellitus, chronic pulmonary diseases, and chronic kidney disease [15]. So, to combat this SARS-CoV-2 infection highly effective therapeutic interventions are urgently needed for these high-risk individuals. The new data suggest that mAbs therapy is one of the best options which can reduce the risk of hospitalization in such patients [16, 17].

Immunotherapy in the form of vaccine or antibody therapy which is effective in the treatment of infectious diseases is also recommended from the proof and experience in treating other viral infections such as influenza, SARS, Middle Eastern Respiratory Syndrome (MERS), and Ebola [18, 19] However, mAbs called passive immunotherapy which is particular, accurate, and safe as their antibodies can be separated from the blood of the affected patients as well as can be organized in the laboratory when compared to conventional convalescent plasma therapy [20]. Whereas, the vaccine which is safe and effective against COVID-19 remains the leading choice to overcome this crisis. Monoclonal antibodies can be beneficial, specifically in surroundings such as care homes and places where the rapid spread of infection occurs and also for those who are unvaccinated or currently vaccinated high-risk patients [21].

This review aims to elucidate the inhibition of SARS-CoV-2 target cell engagement by neutralizing monoclonal antibodies and to analyze the effect of mAbs in high-risk individuals. It also discusses the possible challenges, clinical use, adverse drug reactions (ADRs), prevention, and future prospective.

2. METHODOLOGY

The related articles were collected through online literature searching in PubMed, Embase, and Cochrane Library by using the keywords as strategy tool according to different databases: ("coronavirus 2019" OR "SARS-CoV-2" OR " novel coronavirus" OR " clinical trials on mAbs" OR " neutralizing monoclonal antibodies") and (" prophylactic monoclonal antibodies" OR "role of monoclonal antibodies" OR " randomized control trials"). We also used websites like Food and Drug Administration (FDA) and Emergency Use Authorization (EUA) for further information and extracted related to the aim of the study from the identified articles.

3. RESULTS AND DISCUSSION

3.1 The cardinal steps involved in the pathogenesis of SARS-CoV-2 transmission:

The theorem explains the prevention of SARS-CoV-2 infection in humans based on evidence published in previous literature and clinical observations [22]. SARS-CoV-2 belongs to the genus Betacoronavirus and Coronaviridae family which is believed that it is originated from bats, palm civets, and raccoon dogs before being transmitted to humans, although the exact sources of the virus remain uncertain [23-25]. It is transmitted via nasal droplets or close contact with an infected person, surfaces, or objects and it is identified by several samples techniques including saliva, stool, and blood [26].

The viral genome encodes four important structural proteins which include spike (S), membrane (M), envelop (E), and nucleic capsid (N). Between them, the S protein plays a major key role in viral attachment and transmission of the infection [27, 28]. It has two domains in which S1 having the receptor-binding domain (RBD) where the Cov interacts first a region of 193 residues involved in binding to the Angiotensin converting enzyme- 2 receptor (ACE-2) that triggers into the host cell and S2 plays a vital role in viral host cell fusion [29]. So, it remains the main target for neutralizing antibodies and designing therapeutic agents and vaccines [30].

3.2 An overview reports of different types of monoclonal antibodies in the prevention of SARS-CoV-2 from recent findings:

The mAbs in the prevention of SARS-CoV-2 is an effective strategy as it can detect the specific epitope region from the foreign bodies of the virus and helps to reduce the virus multiplication and disease severity [31, 32]. Currently, no specific neutralizing mAbs have been reported for SARS-CoV-2 and it may take several years for such antibodies to be readily available for human use. Therefore, researchers are working on it passionately to develop such mAbs for the prophylactic or therapeutic agents to protect against COVID-19 [11]. The studies suggest that the recently established human neutralizing mAbs which was isolated from SARS-CoV (S230.15, m396, S109.8 or S227.14) and MERS-CoV (MERS-27, m336, MERS-GD27 or MCA1) include mAbs induced by the vaccines or infected individuals play a major role in blocking the viral proliferation by targeting the S1-RBD and interfering with the S2-mediated membrane fusion [33-35]. Since SARS-CoV-2 proteins have a high sequence identity closely related to SARS-CoV these similarities showed a better way for the researchers to reprofile their specific neutralizing mAbs to handle against SARS-CoV S protein or host angiotensin-converting enzyme 2 (ACE-2) receptors [36].

Besides repurposed drugs, recently many mAbs targeting S-protein of SARS-CoV-2 have been signed up for clinical trials such as casirivimab and imdevimab (REGN-COV2) is an antibody cocktail which has been developed to supply resistance against the SARS-CoV developed by Regeneron Pharmaceuticals and approved on November 21, 2020 by food and drug administration (FDA) for EUA [37]. United States (US) granted mAbs for EUA such as bamlanivimab (LY-CoV555) as monotherapy and LY-CoV555 together with etesevimab or REGN-COV2 as a combination therapy after concluding that disease continuance was steady in patients who received LY-CoV555 for treating non-hospitalized patients with mild-to-moderate COVID-19 [38, 16]. A recent study Covid-19 Monoclonal antibody Efficacy Trial-Intent to Care Early (COMET-ICE) finds that, Sotrovimab (VIR-7831) a designed human mAbs that neutralizes SARS-CoV-2 showed no safety signals and strongly supports the need for mild to moderate Covid-19 outpatients [39]. This review reports that most of the mAbs neutralize SARS-CoV-2 entry by inhibiting engagement of ACE2 by targeting the host cell virus.

3.3 Advantages, Challenges and Future prediction on the development of antibodies against SARS-CoV-2 viral infection:

The therapeutic use of mAbs has increased in recent years which has become the dominant force in dealing with infectious diseases, cancer, and autoimmune diseases. The mAbs may remain as an efficient prophylactic application against SARS-CoV-2 infection if the mechanism involved within the actual disease or protein molecules are documented compared to vaccines and drugs because they must have a deep understanding of the key factors which is involved in the SARS-CoV-2 transmission. At the same time, attention should be focussed on ''antibody-dependent enhancement'' (ADE) which is an unexpected event that may occur after the administration of vaccination or antibody therapies where the specific antibody production enhances rather than inhibiting the host viral infection [40-42].

ADE has two main functions both negative and positive. First, offending immune cells, proliferating the infection and activating harmful immunopathological agent's second, promoting antigen presentation and protective immune response. However, the negative role has become more challenging for the development of vaccines and antibody therapies. This is particularly true in the development of a vaccine has that relies on the genetic background whereas, for antibodies, it is easy to be isolated with few strategies like Fc engineering, and antibody cocktails may surpass or block ADE that remains as the major advantage [43, 44]. The mechanism of antibodies is to engage the immune system through binding to their constant domains to Fc gamma receptors on immune cells by doing so can enhance the immunity as well as exacerbate the coronavirus infections. Though this step may hinder the vaccine development this would not interfere in the clinical use of potent antibodies has that can be transformed and obstruct the Fc gamma receptor interactions and thus protects them against viral pathogens [45].

The experiments show that antibody-resistant against SARS-CoV-2 variants may reduce the efficacy of mAbs where antibody cocktail remains as the solution to this challenge. Currently, REGN-COV2 the mixture of two mAbs cocktails that targets only contrasting spike protein on the SARS-CoV-2 epitopes rather than that new approach must be focused on the mixture of both anti-virus and anti-host monoclonal antibodies that should target both the S protein as well as the membrane, proteins, envelop and nucleocapsid [46, 47].

Another global health challenge is acute respiratory infections (ARIs) in COVID-19 where poor clinical efficacy had resulted by using systemically dosed antiviral mAbs therapies. So the delayed initiation of mAbs into the respiratory tract had further increased the complications by allowing the viruses to proliferate and spread thus leading to inflammation until the inhibitory effect of the drug concentration reaches the specific site of action [48, 49]. In such cases, Inhaled delivery of mAb may be the effective strategy in limiting the spread of SARS-CoV 2 to the ocean level. Notably, all antiviral mAbs under clinical trials for COVID-19 are also administered systemically thereby limiting the efficacy of the drug [50].

A bibliometric study was recently conducted for better knowledge about the current trend on mAbs but there were around 4,435 studies related to the topic and the situation was very challenging for them to overtake the study entitled antibody against covid-19 even though, there are several tools like artificial intelligence (AI), bioinformatics, and the COVID-19 antibody therapeutics tracker yet the traditional way of writing the papers is the effective method for this problem [51, 52].

During clinical trials there are essential challenges to reveal the advantages of mAbs because the person with an initial stage of infection reclaim likewise, in the severely infected patient in whom coagulopathy and inflammation remain more dominant than viral progression so in such conditions the benefits need to be revealed at the end of the trial are not easily attained and it's very difficult for them to find the individual risk in preventing infection. Clinical research will need sufficient infrastructure for providing enough mAbs to the highly infected persons because large scale production of antibodies across several countries is high-priced, time-consuming, and rigorous even though, it is influenced by the dose required it may vary with treatment and prevention this will be the potential challenge near future [53, 54].

The evolution of mAbs for preventing the SARS-CoV 2 infection is challenged by the threat of antibody-dependent enhancement, antibody-resistant against SARS-CoV-2 variants, acute respiratory infections, clinical trials and risk assessment, and inexplicable where the development of mAbs should follow the WHO guidelines in both the clinical and non-clinical phases of study therefore, researchers have to go by many responsibilities for the upcoming preparation and before administering them in the clinical trial settings [55].

Yet safety measures such as vaccines are introduced to reduce the disease progression, challenges like contraindications to vaccines, vaccine hesitancy, and immunocompromised individuals had a high lack of medical need where mAbs remained has a potential critical therapeutic agent in ruling against Covid-19 pandemic [39]. Moreover, we trust that antibodies against COVID-19 will be the best prophylactic target in combating the pandemic in the future.

3.4 Adverse drug reactions associated with monoclonal antibodies in COVID-19:

The risk related to mAbs therapy for COVID-19 was compared to the placebo group in which most commonly noticed adverse drug reactions (ADR) in phase 2 randomized control trials (RCTs) in the LY-CoV555 group were diarrhea, nausea, dizziness, headache, and vomiting and no serious ADR was reported. The overall percentage of ADR in the treatment group was about 22.3% (69 of 309) whereas, in the placebo group it is 24.5% (35 of 143) in which the most frequently occurred was nausea (3.9%) in the intervention group and diarrhea (4.9) in the inactive group. Besides, mild infusion-related reactions like facial swelling, flushing, rash, and pruritus were observed for those patients antihistamine was administered to cure the symptoms [16].

Likewise, hypersensitivity reactions associated with the infusion administration was reported in another RCTs conducted by the experimenter among LY-CoV555 as monotherapy, bamlanivimab and etesevimab as combination therapy, and placebo therapy in which 9 cases were documented (6 in the monotherapy group, 2 in the combination group, and 1 in the placebo group) from this study they confirmed that most of the reactions were due to infusion administration and no changes in the vitals had been noted. The infusions were finished in all the cases [56].

Research's concluded that the percentage of hypersensitivity reactions related to infusion was similar in both REGN-COV2 as well as in the placebo group from the recent clinical trials conducted among antibody cocktails [57]. Therefore, from these clinical trial data, it is obvious that no life-threatening ADR occurred during mAbs therapy for COVID-19 patients

and no clear evidence that these therapies will result in increased immune reactions compatible with ADE.

4. CONCLUSION:

The devastating spread of the COVID-19 pandemic caused irreparable damage and has stimulated a speed-up program of international research to seek out the acceptable method to attenuate the spread of the virus and to reduce the morbidity and mortality rate associated with the virus. In such instance, researchers found mAbs as an effective treatment option that combines with other alternative medications with clinical utility plays a vital role in treatment settings and this encouraged several researchers to investigate further information regarding the mAbs therapy in clinical trials [58, 59].

In further clinical trials optimal dosage regimen and administration of antibodies based on the possible clinical factors, the advantage of mAbs as a prophylactic application in individuals at risk, the impact of mAbs on successive vaccination, and the duration of antibodies and its protection should be taken into consideration by the investigators for the better hold out. In conclusion, developing monoclonal antibodies will continue to be the best therapeutic prophylactic agents for combating SARS-CoV-2 infection as well as recovery from many other viral pathogens and efforts should be initiated for establishing mAbs that are highly beneficial in catastrophic pandemic near future.

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