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Review on Monoclonal Antibodies for SARS-CoV-2 (COVID-19) Therapy

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ABSTRACT

Covid-19 virus outbreak which began in December 2019 continues to affect the world with new reported cases everyday and emerging variants. Since the pandemic began, significant endeavors from all sectors were undertaken in the hunt for appropriate treatments. Extensive research has been done on currently available medications, and novel treatments are also being developed. Therapeutic monoclonal antibodies (mAbs) which are antibodies designed to mimic the immune system's natural response have been verified to treat various diseases for years and became one of the potential remedies in Coronavirus disease therapy. SARS-CoV-2 on its exterior has spike glycoproteins that assist the virus in invading the cells of the human body. Many monoclonal antibodies were produced to attach to these spike proteins and prevent it from infecting and replicating in human cells. Also, because of the antigen specificity and overall efficacy of mAbs, it has an advantage over other types of Covid infection treatment since it is designed to target a specific section of the infectious process. This article aims to evaluate and highlight the significant value of monoclonal antibodies as one of the potential therapies against COVID-19. Moreover, to emphasize the mAb therapeutic agents made available on the market, as to why they are beneficial, among others. The researchers also believed that there is a need to have more in-depth knowledge and study on this approach to focus on how mAb potentially helps alleviate the disturbing Covid-19 infection.

*Keywords:*Covid 19 Treatment; SARS-CoV-2; Antiviral; Monoclonal Antibodies; Clinical trials

Introduction

With the disturbing Coronavirus infection that emerged in Wuhan, China in the year 2019 of December brought by the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a lot of individuals have been affected worldwide due to its rapid and unexpected spread, resulting in over a million deaths [1] The incident given by this outbreak devastatingly caused an alarming issue for the public considering that most of the wellness (physical, mental, emotional, and spiritual aspect) of human life has been damaged and most specifically led to a major problem for public health [2]. In response to this global emergency, efforts are being made by many researchers and scientists to find drug therapies and therapeutic agents to combat the infection [3]. Torrente-López [4]stated that included in these therapeutic drugs evaluated for the cure of COVID-19 are hydroxychloroquine, chloroquine, antibodies, antivirals, corticosteroids, and convalescent plasma. In addition, there are found strategies that are capable of helping fight coronavirus infection known as passive immunotherapy, which have two ways to consider. First, through convalescent plasma therapy (CPT) which are natural antibodies, and second is through polyclonal antibodies (pAbs) or monoclonal antibodies (mAbs) which are antibodies that are known to be biotechnologically designed. Basically, among these two strategies, it has been reported that the use of mAbs is potentially suitable as the most innovative treatment for COVID-19, which helps the infected patients to block SARS-CoV-2 [5].

As to the overview, Monoclonal Antibodies displayed a significant role in the spectrum of pharmacologic and biologic activities for many years. It is mainly defined as an antibody that is derived by cell division from a single ancestral cell and a molecule that is laboratory man-made produced and highly designed to restore, enhance and mimic the natural immune system from attacking cells against foreign or abnormal pathogens found in the body such as bacteria, viruses, cancers, and even infections [6]. In addition, since the introduction of this antibody starting in the year 1975 up to the present, there have been various key advantages produced in which they are clinically well-specific in targeting the intended focus cell and have a high degree of sensitivity, which makes them a versatile instrument for science and research [7].

Beyond the clinical intervention for over the years, monoclonal antibodies serve as an essential component and have been proven clinically safe for the therapy and diagnosis of different individual disorders like cancer as the common, inflammatory, autoimmune disorders, cardiovascular diseases, allergies, osteoporosis, ophthalmic problems and even infectious diseases such as the very rampant example virus we have nowadays that has disturbingly caused a significant issue globally known as the Coronavirus (COVID-19) [8]. They work by targeting one specific antigen and by

exposing white blood cells (WBC) to that particular antigen and use this as the basis to produce many identical cells, making a lot of identical copies of the monoclonal antibody [9]. Also, it assists the body of the person to combat the infection and eventually lower the viral quantity, known as the "viral load". And thus, they are clinically known to be one of the powerful defense mechanisms against unfamiliar molecules [9].

With the devastating shift that COVID-19 has brought across the globe, resulting in a pandemic, it can be seen that people are suffering due to its increasing number of cases. As a result of this outbreak, many scientists and researchers continue to work on developing and finding treatments for the novel virus, which includes those found in mAbs [10]. These monoclonal antibody treatments are primarily not new for healthcare providers since they have been used and tested already for other viral infections such as Ebola and HIV [10][11]. And now, as the search for a response to COVID-19 continues, there are several existing studies reporting that mAbs produce different approaches for the cure of the said viral infection, which has the potential to control and give both therapeutic and prophylactic efficacy. With the support given by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) around the world, they help to evaluate mAbs for use as a potential treatment for the existing viral infection [9]. According to the FDA, based on the experimental clinical trials conducted, mAbs have been reported to be significant in treating the virus because it has the ability to fight off harmful antigens [12]. Furthermore, most of these monoclonal antibodies specifically attach to the SARS-CoV-2 spike glycoproteins that help to prevent the infection from invading the cells of the human body [13] thus, preventing the risk of further hospitalization and severe complications [12].

Methods

Articles regarding mAbs concerning COVID-19 therapies were sought and downloaded for this peer review from publically available resources such as Google Scholar, PubMed, Research Gate, World Health Organization, and Covid-19 Update Sites/News. This peer review includes articles that were considered relevant to the topic and were published in a timely and substantial manner. There were no specific article format criteria. Therefore any relevant literature, including clinical trials, comprehensive reviews, editorials, and perspectives with topics within the scope of the study were considered.

mAbs: How does it work in general?

Monoclonal antibodies (mAbs) are a kind of antibody generated by identical B cell clones in response to a specific antigen. Several characteristics of mAbs are the same, including protein sequence, antigen-binding site area, binding affinity for targets, and downstream functional effects [14]. Monoclonal antibodies have four classifications and these are murine, chimeric, humanized, and human. Murine mAb was the first monoclonal antibody that was discovered and produced. Mice's lymphocytes are obtained and combined with myeloma cells in order to form murine mAb. [15]. These murine mAbs are identified with names ending in -omab (eg. blinatumomab, capromab, muromonab). The next kind of mAb is ChimericmAbs, which employ murine antigen but have human heavy and light chains. Genetic engineering was used to create chimeric mAbs, which are around 65 percent human and 35 percent murine [15]. Name that ends in -ximab (eg. cetuximab, infliximab, rituximab) are used to identify chimeric mAbs. Third is Humanized mAbs, which are created by integrating the murine hypervariable portions of the light and heavy chains into a human antibody framework [15]. Names that ends in -zumab (eg. alemtuzumab, bevacizumab, trastuzumab) are used to identify humanized mAbs. Finally, Animals having human Ig genes are used to create human mAbs. In transgenes, animal Ig genes are required for recombination of human antibodies [15]. Names that end in -umab (eg. alemtuzumab, daratumumab, denosumab) are used to identify human mAbs. In addition, monoclonal antibodies function in many different mechanisms including, directly targeting, retargeting cellular immunity, delivering cytotoxic compounds, and altering host response [16].

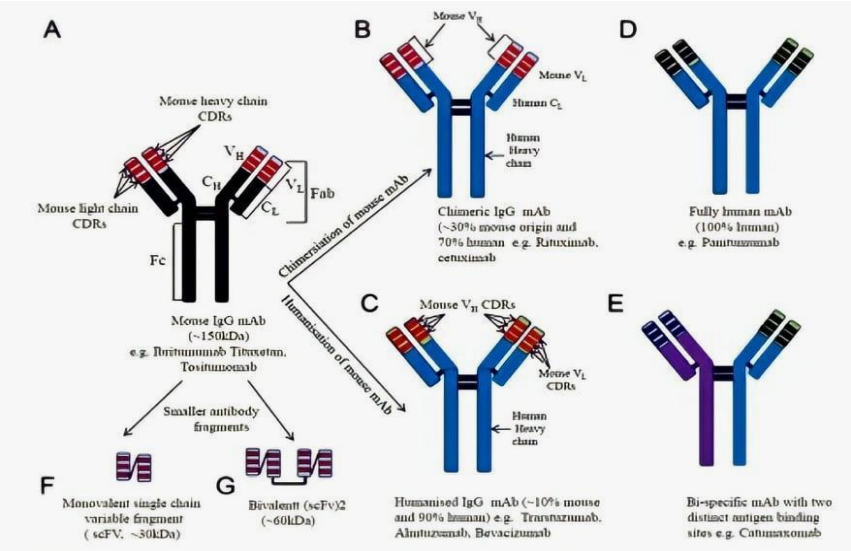

Figure 1. Structure of monoclonal antibody [15]

*Targeting the cancer cell***.** Monoclonal antibody-based treatments that target the malignant cells stimulate its effect through different mechanisms including direct targeting, ADCC, and cell death. MAb-based treatment that mediates its effect through explicit signaling binds to the surface receptors on malignant cells, which triggers the signaling cascade that results in a death signal [16]. This effect is mediated by receptor agonist activity, which occurs when an antibody attaches to and activates the surface receptors of malignant cells, resulting in cell death. This action can also be mediated by receptor antagonists by preventing dimerization, downstream signaling, and kinase activation, resulting in decreased proliferation and death [15]. Antibody-dependent cellular cytotoxicity is another way MAbs work (ADCC). As a result of their engagement with immune cells, opsonized cells or foreign substances are lysed, inducing ADCC. Any immune cell capable of secreting cytotoxic proteins or chemicals might induce ADCC. The three principal cell types that catalyze ADCC are natural killer cells. Monocytes, and neutrophils [17]. A number of these effector cells contain FcR, a protein receptor that recognizes an antibody's epitope. As a result, when FcRs bind to a target cell, it interacts withimmunoreceptor tyrosine-based activation motifs (ITAMS), which activates effector cells and triggers ADCC [18]. MAbs also mediate their effect via complement-mediated lysis, which activates various processes that aid in the clearance of a specific antigen. When IgG1 or IgG3 activates the complement cascade, a sequence of events occurs, culminating in the production of the membrane assault complex (MAC), which creates a hole in the targeted cell's membrane. Through the breakdown of the target cell's membrane, this MAC-mediated, immune cell-independent mechanism kills the target cell [17]. In addition, monoclonal antibodies that bind to antigen via the Fv region also activate the complement system, leading to apoptosis. These antigen and complement complexes are placed on the membrane of the target cell, creating an attack complex that breaks through the membrane [18].

Altering host response. Monoclonal antibody based treatments that modify the host response are the inhibition of angiogenesis and the change of T cell responsiveness. The vascular endothelial growth factor regulates the angiogenic processes such as blood clotting, progression of cancer, and arthritis [19]. The VEGF is a key factor in the formation of blood vessels as it stimulates cellular growth [20]. Bevacizumab, an anti-human VEGF antibody, has been created to prevent angiogenesis by inhibiting VEGF's ability to promote the formation of intratumoral blood vessels. This effect prevents the malignant cell from receiving nutrition and oxygen from the newly formed blood cells [18]. Moreover, checkpoint blockade mAb is a monoclonal antibody that interferes with inhibitory signals that prohibit T cell activation. These mAb keeps T cells activated and increases T-cells mediated lysis. CTLA4, otherwise called CD152, is a T-cell receptor that is produced by activated T cells [18]. CTLA4 and other negative T cell activation regulators are involved in the body's T cell response regulation. Tempering T cell response is necessary to enhance T cell response and avoid autoimmunity when it comes to efficiently developing and sustaining anti-tumor T cell responses [18].

Delivering cytotoxic moieties.Radioimmunotherapy and antibody-drug conjugates are Monoclonal antibody-based treatments that work by delivering cytotoxic compounds to the malignant cells. Radioimmunotherapy involves injecting a radioisotope-labeled monoclonal antibody (mAb) intravenously (IV) or intratumorally. In Radioimmunotherapy, radionuclides are delivered directly to the malignant cells, where they cause double-strand DNA cell death [21]. In addition, antibody-drug conjugates are able to optimize the targeting capacity of monoclonal antibodies by connecting them to cell-killing agents. These ADCs are a novel type of biopharmaceutical drugs made up of an antibody connected to a physiologically active medication or cytotoxic substance through a chemical linker. The targeted agents combine antibodies' unique and very sensitive targeting characteristics, which allow for sensitive differentiation between healthy and cancerous tissues, with cytotoxic chemicals' cell-killing power [22].

*Retargeting T Cells.*Bispecific antibodies can bind to target cells while activating cytotoxic cell receptors such as T cells and natural killer cells. [23]. ThismAb-type is made up of two distinct mAbs that allow it to bind to two separate antigens simultaneously. The protein that is located on cancer cells is one target, whereas the other is the protein present on immune cells. The cancer and the immune cells are used together in this combination in the hopes of eliciting a stronger immunological response and the death of cancer cells [15]. Furthermore, CAR T cells have been produced and altered to respond to antigen-producing target cells, and a variable area of a mAb is connected to a T cell activation motif in CAR T cells. Both the bispecific antibodies and chimeric antigen receptor T cells are intended to retarget many T cells to malignant cells without requiring the T cell receptor to identify target antigen activities [18]

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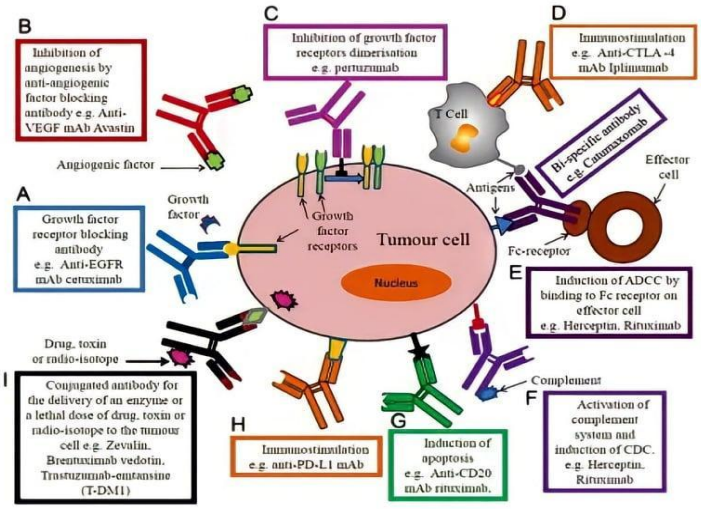

Figure 2. Mechanism of action of monoclonal antibody [15]

How does it work on COVID-19?

Mechanism of Action and Pharmacokinetics of mAb

For vaccines for Covid-19, they work by preventing the virus from spreading to people who are not yet infected and gives a chance of fighting off the virus or having the virus not express its effects [24]. Monoclonal antibodies on the other hand is a bit similar but also different as it works like antibodies that the body makes to fight off the virus like an example of Regeneron where they designed the mAb to specifically target the spike protein of the virus wherein when the mAb has attach itself to spike unit of the virus, it will then prevent Covid 19 virus by refraining it from entering the cells of the host. If it's unable to enter the cells then replication would not happen and there will be no spreading throughout the inside the body [25] [26]. But when a person is infected already, vaccines should not be used since its purpose is to prepare the body of someone who is not infected with the virus. This is one of the differences in using mAb since it can be used for people diagnosed with Covid which prevents severe symptoms. If a person was exposed to the virus, mAbs can fend it off and lessen the gravity of the symptoms [27].

The virus has four major structural units, one of them being the spike protein or the S subunit is the target of most mAbs. The spike protein is further subdivided to S1 and S2, the two S subunits have the function of host cell attachment and invasion. The help of the binding domain from the virus' receptor, S1 attaches to angiotensin-converting enzyme (ACE) 2 receptors [28] [29]. Preliminarily discussed the example of Regeneron monoclonal antibodies and how it binds to the spike protein or viral spikes of Covid-19 and inhibit the virus' ability to attach to the cell's surface of receptors or by choosing the targeting of the cell receptors (e.g ACE 2 receptors). This will make the binding sites of cells of the host unavailable for the virus. They also act as immunosuppressive agents on how it prevents people from experiencing the severe symptoms of Covid, which limits immune-mediated damage and reduces morbidity and mortality [12].

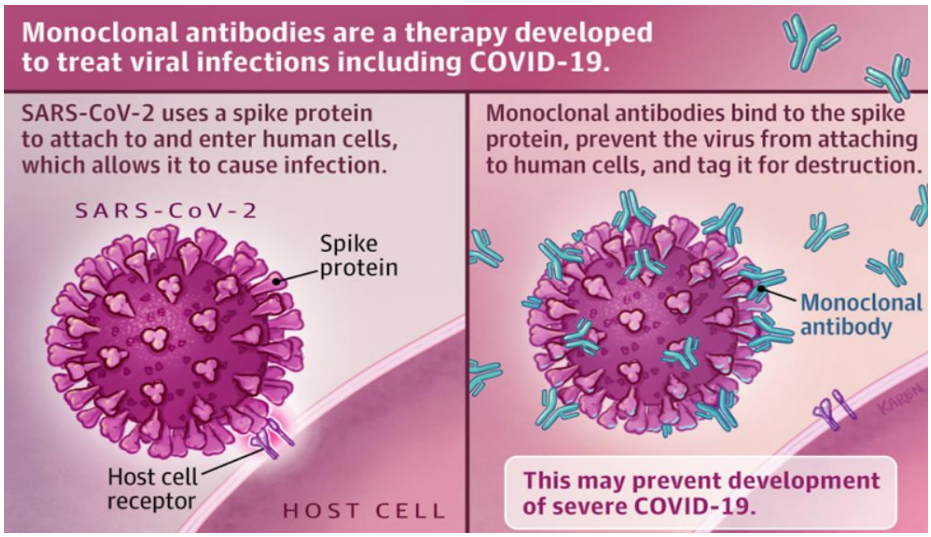

Figure 3. Mechanism of action of mAb against Covid-19 [6]

The SARS-CoV and SARS-CoV-2 S protein subunits contain an amino acid sequence of 77%, and its S2 subunit contains 89.8% sequence identity. This has helped in the repurposing of neutralizing mAbs targeting SARS-CoV-2 and its host ACE-2 receptors.[28] Currently, a number of counteracting SARS-CoV-2 mAbs are assessed within clinical trials. These antibodies such as IgG1 have a long half-life which indicated that a single infusion is enough as treatment for infected SARS-CoV-2 patients. However, passively infused IgG still has unknown bioavailability in affected tissues, specifically the lungs. mABs target specific spike regions of the virus and some products will be incorporating combinations of mABs to target different viral spike proteins [30].

Examples and Comparison of Therapeutic mAbs for Covid-19

A mAb that was authorized by FDA was Casirivimab (IgG1-kappa) and Imdevimab (IgG1-lambda) are recombinant human monoclonal antibodies, which are taken together by intravenous route of infusion to treat a level mild to moderate SARS-CoV-2 for patients within the criteria of a weight of at least 40 kg, aged 12 years old and above [31]. These mAbs target the Covid-19 spike protein then binds to the non-overlapping epitopes, which results in blockade or prevention of attaching or entering of the virus in the human ACE2 receptor [31][32]. This combination may cause serious hypersensitivity, and may also include anaphylaxis. Hypotension, throat irritation, bronchospasms, nausea, angioedema, headache, and rashes are some of the infusion-related reactions [32]. Moreover, this combination is unsuitable for hospitalized patients and in need of baseline oxygen flow increase because of SARS-CoV-2 [32].

Another monoclonal antibody that was recently authorized by FDA wereBamlanivimab and Etesevimab which are mAbs that aim at the spike subunits of the virus. This drawbacks SARS-CoV-2 in attaching itself and entering inside ACE2 receptor and in the host's body aside from targeting virus' spike proteins, they also bind to other epitopes that are overlapping of the S-protein's receptor-binding domain (RBD) [33][34]. These mAbs are used in treating mild to moderate Covid-19 patients ranging from years of 12 and above and having a weight of 40 kg. This was also authorized as a treatment for patients who have certain chronic medical conditions with an age of 65 years old. The aforementioned drugs are not authorized to be administered as monotherapy; thus, it must be administered in combination, with a ratio of 1 Bamlanivimab (20ml), and 2 Etesevimab (20 ml), which will then be diluted in sterile prefilled infusion bag, and/or Polyethylene (PE)-lined PVC or Polyvinyl chloride (PVC) [34].

In the study of Siemieniuk et al (2021) [35], they evaluated the effectiveness and safeness of antibodies for COVID-19. According to their results mAbs showed better effectiveness in patients with no severe disease compared to patients with severe disease. It was also stated that only casivirimab-imdevimab has a resulting effect of moderate certainty. Moreover, the result of the review also did not identify any evidence of antibodies having an

effect on the results in patients who have severe or critical conditions. But, antiviral monoclonal antibodies were found to have a possibility to reduce the rate of mortality in patients having no detectable antibodies for Covid-19 spike protein.

Dosage of mAbs for Coronavirus Disease (COVID-19)

The dosing procedure that can be attained to match the antigen by allowing the high doses or adjusting the quantity of the antigen formulated on the pharmacokinetic limiting factors. The preferred dose of mAbs used to cure infectious disease varies between 500 mg to 8000 mg based on clinical trials which obtained against Covid-19 virus is much higher [29]. Frequently, monoclonal antibodies are based on body size to reduce the analogical variation in drug addiction [36]. Although, mAbs intend to target the substantial therapeutic window and can contribute to minor pharmacokinetic variables of the body size. Based on the analysis, the dosing regimens for mAbs were assessed through body weight-based and body weight-independent [37]. The dosing of clinical development can be regulated based on the bodyweight outcome on safeness, pharmacokinetics, and effectiveness of advanced clinical study. Some drugs could treat severe COVID-19 infection such as convalescent plasma, interleukin-6 inhibitors, Remdesivir, mAbs, steroids, immunoglobulin (Ig), or antiviral drugs [37]. A study gathered by Alabama Public Health Department [38], there are three monoclonal antibodies available in treating patients having mild to moderate symptoms covered by EUA. A mAb drug that has been approved against the known variants and virus that compromised by Regeneron's Covid-19 or REGEN-COV consists of Imdevimab and Casirivimab, a type of treatment that helps to reduce the risk of developing symptomatic COVID-19 infection, which attach to epitopes that overlap the RBD spike of the virus by inhibiting its binding to ACE 2 receptor in the human body [39].

The panel recommendation based on the provided guidelines of Covid-19 therapy using the mAbs products includes: for adults and pediatric patients, the ideal single dose for IV mixture
is 1,200 mg [39].

Imdevimab and Casirivimab dosage:
Imdevimab and Casirivimab contain 600 mg, taken once daily for patients who were determined positive through an intravenous infusion administration or subcutaneous injections (SQ). A 600 mg single dose every four weeks is the prophylaxis dosing, depending on the duration of the exposure. 20 to 50 minutes is the minimum IV infusion, depending on the sodium chloride used [39].

Bamlanivimab and Etesevimab dosage:
People having mild to moderate symptoms, a combination of the two drugs Bamlanivimab contains 700 mg and Etesevimab also contains 1,400 mg intended to be given in children and not hospitalized persons through an intravenous infusion which merges the frequency of resistant variants is low. The patient and the capacity of sodium chloride used from 21 to 70 minutes determine the minimal infusion [39].

Recently, the FDA provided information regarding these anti-SARS-CoV-2 mAb products and recommends lower dosage of Casirivimab and Imdevimab to from 1,200 of Casirivimab and Imdevimab reduce to 600 mg. It is approved for IV and SQ injection; meanwhile the IV administration is not suitable and could affect the medication [38]. The subcutaneous injection contains four injections with 2.5 mL per injection and intended to administer in four different parts, including the thigh, abdomen, or humerus, and waistline area should be avoided. On the other hand, Sotrovimab which patients receive 500 mg intravenously within 30 minutes for patients who are highly at risk [38].

Side effects of mAbs in general

An adverse effect occurs when the treatment goes beyond the target effect and may cause undesired effect. Some results associated with the use of mAbs are due to the interactions between the antigen-antibody through the cells and tissues [40]. The mAbs have specific target and specific class adverse effects. A significant adverse event of class-specific which determines that monoclonal antibody is distinguished through the foreign natural resistance. Due to the machinery that begins the new peptide fragments present in IgG that may identify as foreign, even 100 percent human proteins are totally immunogenic. [41]. On the other hand, target-specific indicates undesirable effects that interfere with the normal activity of the human cell that increase the contamination exposure [42]. Considering the side effects and condition of mAbs, various advances and modifications to the monoclonal antibodies seemed to be developed. Even numerous mAbs are well tolerated and innovative, but hard to guarantee that each mAbs is definitely safe [39]. Common effect of monoclonal antibodies when first being given to the patient is an allergic reaction due to the proteins contained by the antibodies. It also includes cytokine release syndrome (fever, weariness, vomiting and nausea, diarrhea, rashes, and hypotension), as well as capillary leak syndrome where wheezing, hypotension and pulmonary edema are observed, perhaps this can noticed in mAbs that blocks interleukins, CD20 and especially CD3 receptors [8]. Some examples of monoclonal antibodies related to antigens are Bevacizumab that causes blood clots, hypertension, hemorrhage and cetuximab which induce dangerous rashes to few persons [8].

There are mAbs that are tolerated enough along with the latest and high-quality mAbs. Some challenges guaranteed absolute safety in using every new stock of antibodies. Even the administration of mAbs results in the risk of immunologic response including acute anaphylaxis, type III hypersensitivity reaction and some antibodies [41]. Moreover, countless adverse effects present in monoclonal antibodies, such as contamination, malignancy, autoimmunity, and heart disease. Furthermore, mAbs have a variety of side effects linked to their particular targets, such as microbes and malignancies, immunological illness including the adverse events in specific organs similar to cardiomyopathy. FDA abstained from authorizing monoclonal antibodies to patients: who are confined, require supplementary oxygen and require an increased flow rate of oxygen that is caused by Covid-19 [42]. Patients acquiring anti-SARS-CoV-2 mAbs may undergo anaphylaxis and other related infusion responses. Clinical study participants who received Casirivimab and Imdevimab via Subcutaneous administration experienced injection site responses such as ecchymosis and erythema. [37].

Potential risks of monoclonal antibody

Some potential risks that other patients might encounter are either an allergic or non-allergic infusion. These reactions are triggered by the antibodies activation, although they manifest in a variety of ways. Although the infusion-related symptoms looked to be remarkable, itching, dyspnea and a drop in blood pressure are all possible side effects. However, obtaining any IV medicationcan go together with discomfort, pain or injury around the site [30].

Discussion

The Covid-19 disease is spreading fast over the world, and neutralizing antibodies could be used to treat this disease. mAbs are believed to reduce the amount of virus by limiting it to enter the cells and linking to the spike protein that prevents it from attaching to the cell's exterior. In addition, mAbs can also be used as an immunosuppressive medication, lowering morbidity and mortality by decreasing immune-mediated damage [45]. Early infection phase, pulmonary phase, and hyper-inflammation phase are the three stages of COVID-19 progression. In the early infection phase, infection happens shortly after inoculation and before the onset of sickness. After an incubation period, SARS-CoV-2 infects mucous membranes, specifically the nasal and oral-pharyngeal portion, causing upper respiratory illness. Mild symptoms have been observed including fever, dry cough, and tiredness. The virus attaches to target cells through ACE-2 and primes S proteins by activating the transmembrane serine protease 2. The epithelial cells of the colon, blood arteries, lung, and kidney contain ACE-2. The main therapeutic objective at this phase is symptomatic relief. Patients who are able to confine the virus in this stage of illness have a high rate of recovery. In the pulmonary phase, SARS-CoV-2 proliferation and localized lung inflammation has been observed. Pneumonia with cough, fever, and hypoxemia are the most prevalent clinical signs reported in individuals at this stage. The chest imaging reveals ground-glass opacities or infiltrates that are diffused in the bilateral lung fields. Increased lymphocytopenia is revealed by blood testing. Inflammation indicators could be normal or slightly increased. Lastly, in the hyper-inflammation phase, the virus is still multiplying and destroying tissues in organs that express ACE-2, particularly, lungs. The quantity of regulatory, helper, and suppressor T cells decreases dramatically. In catastrophic COVID-19 patients, the most likely cause of death is cytokine storms followed by ARDS, which generates a substantial rise in cytokines in these severe cases [46].

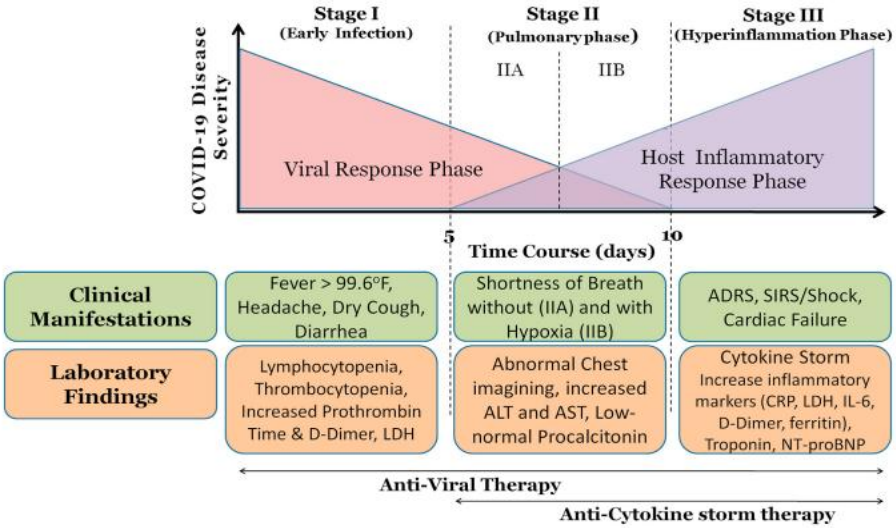

Figure 4. Disease advancement Phases of COVID-19 [46]

The immune system normally produces proteins to combat invading viruses or other infections and mAbs are lab-made replicas of these proteins. Monoclonal or natural neutralizing antibodies may attach to sections of viruses that they employ to cling to and enter cells, stopping the infection cycle from continuing. Mabs could also provide short-term protection against the virus and could be crucial attributes of the pandemic strategy while vaccines are developed [25].

Extensive research has been done on currently available medications, and novel treatments are also being developed. In recent years, mAbs have enabled qualitative and quantitative breakthroughs in therapy approaches for diseases on a well-targeted cell, including contagious diseases and COVID-19.MAbs have revolutionized the realm of passive immunization, allowing us to provide specific antibody responses against highly conserved SARS-CoV-2 epitopes as well as get novel medications in record speed [30]. There have been numerous efforts to find viable treatments. Numerous clinical studies are ongoing to examine the effectiveness and safeness of several monoclonal antibodies for the COVID-19 interventions, including some that are already used in hospitals and others that are still being evaluated [30]. Over ten medicinal mAbs for COVID have been developed in just one year, with another ten mAbs in various stages of clinical development. Despite the fact that mAb production takes time and money, especially for new infections, it was still regarded as a feasible therapy approach for COVID-19 since the outbreak began, and various clinical investigations on both SARS-CoV-2 and nonspecific mAbs are currently in progress. [47].

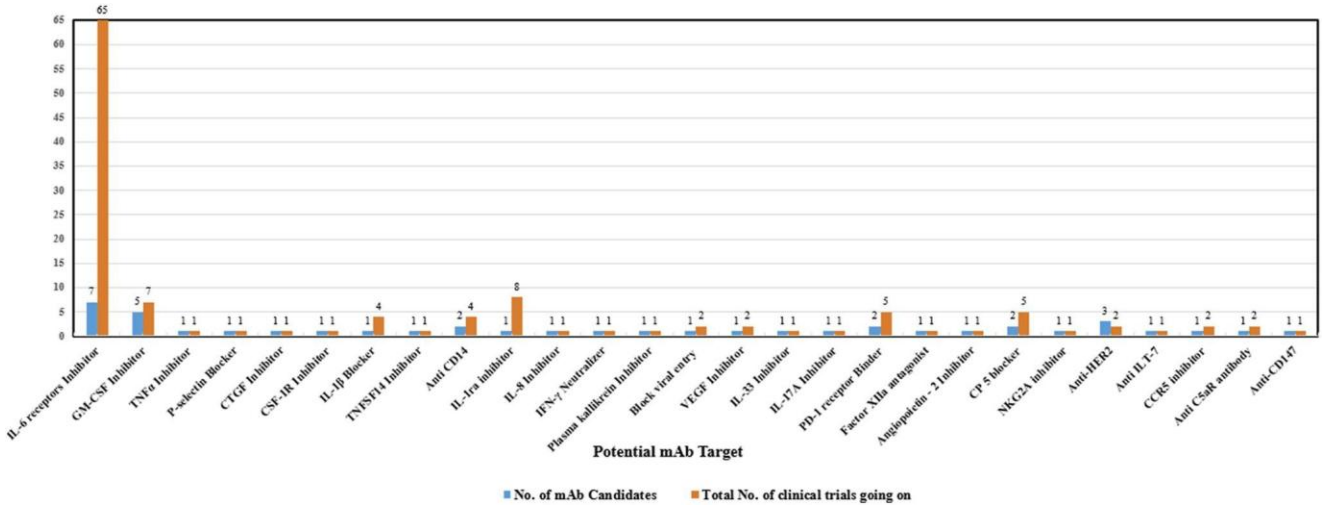

Figure 5. Current clinical trials and potential mabs for Covid-19 at various biological targets [46]

For mAbs repurposing of ARDS therapy in COVID-19 infected persons, 125 clinical studies have been submitted worldwide. Despite the fact that multiple mAbs targeting various cytokines are being tested in clinical trials that were shown in (Figure 5), it is clear that there is still a long way to go [46]. Tocilizumab, sirukumab, sarilumab, siltuximab, levilimab, clazakizumab, and olokizumab are the candidates for IL-6 inhibitors, and the majority of mAb are in clinical trials for treating individuals with mild and serious COVID-19 [48]. In Covid patients, the most widely distributed pro-inflammatory cytokines is IL-6. Tocilizumab, sarilumab, and siltuximab were chosen as the mAbs for patients with elevated levels of IL-6 and many clinical studies are presently being tested for effectiveness, which has yet to be confirmed [46]. In Covid positive patients, their levels of IL-6 appear to be linked to inflammation, respiratory failure, the requirement for intubation, and mortality [49]. As a result of the research, it's thought to be a prognosticator in SARS-CoV-2 patients. It is a tiny glycoprotein with anti- and pro-inflammatory effects. Classic signaling is responsible for IL-6's anti-inflammatory capabilities, while trans-signaling is a crucial regulator of its proinflammatory qualities. Tocilizumab is the subject of the most clinical trials out of the potential therapeutic mAb and suitable treatment of choice among all IL-6 inhibitors for severely ill COVID-19 patients with terrifying cytokine storm symptoms (Figure 6) [46].

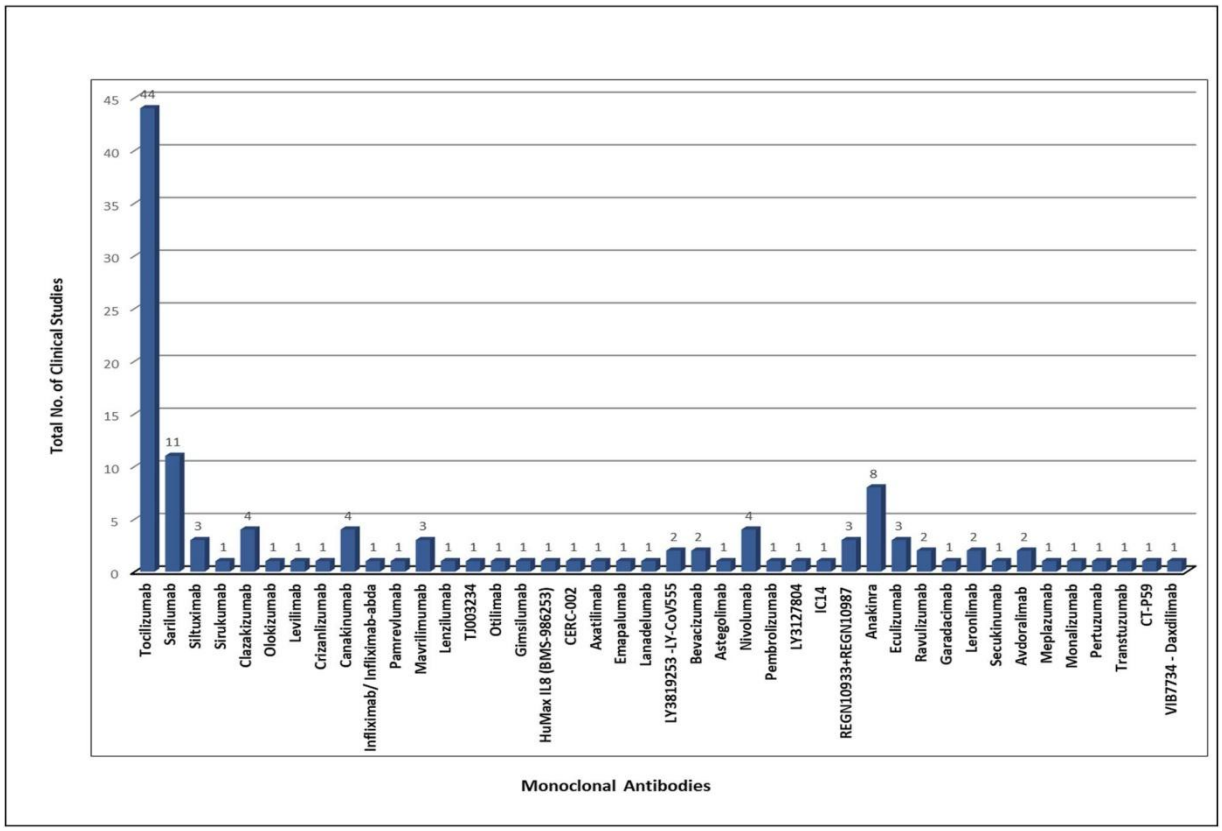

Figure 6. In progress mAb clinical trials or Covid-19 therapy [46]

FDA approved Anti-SARS-CoV-2 mAbs for emergency use

Anti-SARS-CoV2 mAbs have been suggested by the COVID-19 Treatment Guidelines Panel for the treatment of COVID-19 symptoms and post-exposure prophylaxis of infected persons at high risk of progression. Treatment should begin as soon as feasible after a positive result on an nucleic acid amplification test (NAAT) or antigen test. Anti-SARS-CoV-2 mAbs are particularly effective as a therapeutic or preventative treatment for COVID-19 infection in patients at high risk [47]. Three mAb products were granted EUAs for COVID-19 therapy in non-hospitalized patients with SARS-CoV-2 infection who are at risk of developing the serious disease and requiring hospitalization. FDA approval is not implied by the issuance ofan EUA. These are the products:

- Bamlanivimab and etesevimab bind to interrelated surface proteins in the protein RBD of the SARS-spike CoV-2. This is legal in adults, and it is legal in children of all ages, even babies and newborns.
- Recombinant human mAbscasirivimab and imdevimab attach to the SARS-CoV-2 spike protein RBD's non-overlapping epitopes.
- Sotrovimab binds to an antigen shared in the RBD's spike protein [50].

In contrast to FDA approval, an EUA is solely based on empirical evidence. When used for the treatment of COVID-19 in the permitted population, the potential advantages of the medications that have received an EUA surpass the potential dangers [13].

Assessment of COVID-19 Patients Treated with Monoclonal Antibody Therapy

Covid-19 is still causing death and morbidity. According to Cooper et al., patients with SARS-COV-2 from November 20, 2020 to May 30, 2021, 4328 are satisfied for mAb treatment with bamlanivimab or a combination of bamlanivimab-etesevimab or casirivimab-imdevimab. [51]. The variables age, BMI, race, illnesses, percentile of median wage by postal code, and positive polymerase chain reaction date were used to determine the closest propensity score between the no treatment and treatment groups. A total of almost 15,000 SARS-CoV-2 positives were considered for the study, however 2,404 of them were ruled out (Figure 7). During the trial period, 4,048 patients were treated with mAb treatment, with 2879 COVID-19 individuals in both cohorts due to propensity score matching.) 60 (48–69 was the respondents' median age (IQR), with 45.1 percent of them being male. It was discovered that the fast mAb infusion resulted in considerably lower hospital admission and mortality rates. People 65 and older with a BMI of less than 35 kg/m2 showed the most improvement. The findings are backed up by clinical investigations and other published information on the effectiveness of initial passive immunotherapy for COVID-19 infection. The number of patients who had serious COVID-19 conditions and required admission was considerably reduced after therapy with the combination medications bamlanivimab-etesevimab, or casirivimab-imdevimab, or bamlanivimab alone [51].

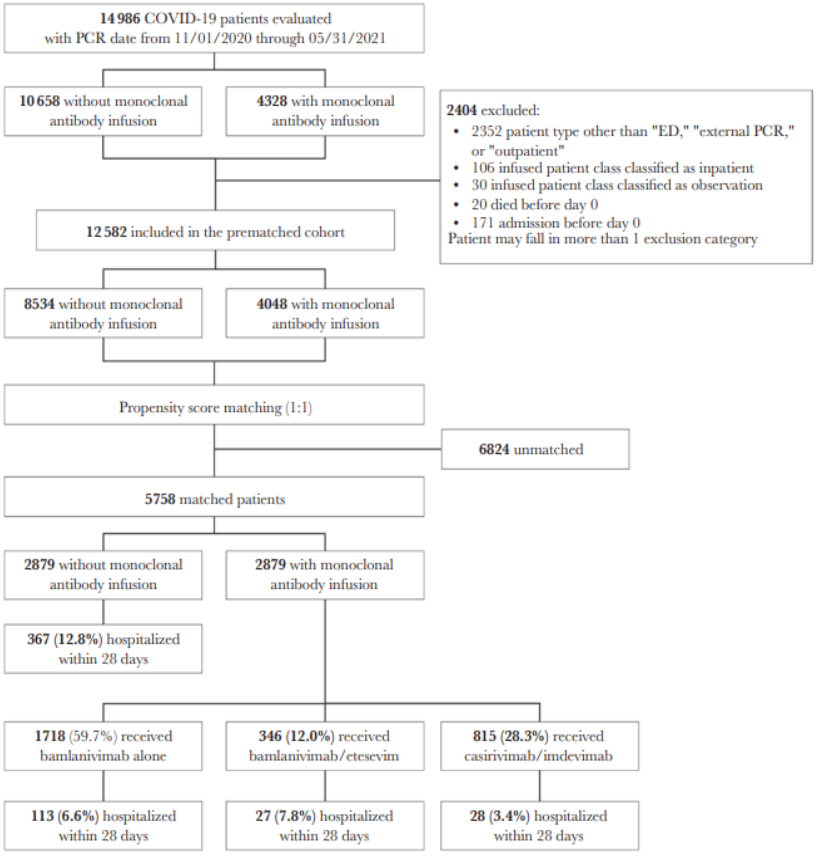

Figure 7. Flow Chart of Study Population therapy with or without Monoclonal Antibodies [51]

Conclusion

The Covid-19 Pandemic which began its unexpected spread in December 2019, has left people around the world fearing for their lives and locked themselves inside their homes. The abrupt changes made in all aspects of life, from the economy, education, religion, and international affairs, has pushed all sectors worldwide to collaborate in finding solutions to combat and lessen the spread of infection. In a year, scientists and researchers have done studies and undergone clinical trials to test possible remedies and as of date, many vaccines have been manufactured and are administered to over three billion in the world; however, its effectiveness and safety are still in question because of the short time it was made. The continuous search for remedies has opened a potential for Monoclonal Antibodies as a promising therapy in fighting the infection of SARS-CoV-2 and eventually ending this pandemic. MAbs can be quickly customized and tailored with the newly emerging variants which will allow for dynamic modification to combat new surges of SARS-Cov-2 variant-driven outbreaks. Therapeutic MAbs can also be developed to bind to the Covid-19 virus spike glycoproteins and inhibit invasion of the human cells which prevents the infection from happening. With its potential of being a prevention and a cure for Covid-19, MAbs can work wonders in eradicating this pandemic.

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Disclosure of conflict of interest

No conflict of interest from the authors.

References

[1] MornesePinna S, Lupia T, Scabini S, Vita D, Benedetto I, Gaviraghi A, Colasanto I, Varese A, Cattel F, De Rosa F, Corcione S. Monoclonal antibodies for the treatment of COVID-19 patients: An umbrella to overcome the storm. Elsevier. 2021;101:108200. Available from https://doi.org/10.1016/j.intimp.2021.108200

[2] Sheek-Hussein M, Abu-Zidan FM, Stip E. Disaster management of the psychological impact of the COVID-19 pandemic. International Journal of Emergency Medicine. 2021;14(1):19. Available from: http://dx.doi.org/10.1186/s12245-021-00342-z

[3] Clemente-Suárez VJ, Dalamitros AA, Beltran-Velasco AI, Mielgo-Ayuso J, Tornero-Aguilera JF. Social and psychophysiological consequences of the COVID-19 pandemic: An extensive literature review. Front Psychol. 2020;11:580225. Available from https://www.frontiersin.org/articles/10.3389/fpsyg.2020.580225/full

[4] Torrente-López A, Hermosilla J, Navas N, Cuadros-Rodríguez L, Cabeza J, Salmerón-García, A. The Relevance of Monoclonal Antibodies in the Treatment of COVID-19. MDPI. 2021;9(6):557. Available from https://www.mdpi.com/2076-393X/9/6/557/htm

[5] Kumar S, Chandele A, Sharma A. Current status of therapeutic monoclonal antibodies against SARS-CoV-2. PLoS Pathogens. 2021;17(9):e1009885. Available from: http://dx.doi.org/10.1371/journal.ppat.1009885

[6] Lloyd E, Gandhi T, Petty L. Patient Information: Monoclonal Antibodies for COVID-19. JAMA. 2021;325(10):1015. Available from https://jamanetwork.com/journals/jama/fullarticle/2776307?fbclid=IwAR3EZJItvAF3wW1mLs11EeVXcPoRQg2hAwBF40HdV6_XUe_eJXXBCSbRpBI

[7] Parray HA, Shukla S, Samal S, Shrivastava T, Ahmed S, Sharma C, et al. Hybridoma technology a versatile method for isolation of monoclonal antibodies, its applicability across species, limitations, advancement and future perspectives. IntImmunopharmacol. Elsevier. 2020;85(106639):106639. Available from: http://dx.doi.org/10.1016/j.intimp.2020.106639

[8] Lu, R.-M., Hwang, Y.-C., Liu, I.-J., Lee, C.-C., Tsai, H.-Z., Li, H.-J., & Wu, H.-C. (2020). Development of therapeutic antibodies for the treatment of diseases. *Journal of Biomedical Science*, *27*(1), 1. https://doi.org/10.1186/s12929-019-0592-z

[9] Jeong M. *Monoclonal antibodies for COVID-19: What do we know so far?*. Medical News Today. 2021. Available from https://www.medicalnewstoday.com/articles/monoclonal-antibodies-for-covid-19-what-do-we-know-so-far

[10] Qiu, X., &Kobinger, G. P. (2014). Antibody therapy for Ebola: is the tide turning around? *Human Vaccines &Immunotherapeutics*, *10*(4), 964–967. https://doi.org/10.4161/hv.27813

[11] Salazar G, Zhang N, Fu T, An Z. Antibody therapies for the prevention and treatment of viralinfections. National Center for Biotechnology Information. 2019;35(5):150927. Available from https://pubmed.ncbi.nlm.nih.gov/31488319/

[12] Rainwater-Lovett, K., Redd, J. T., Stewart, M. A., Calles, N. E., Cluff, T., Fang, M., Panaggio, M. J., Lambrou, A. S., Thornhill, J. K., Bradburne, C., Imbriale, S., Freeman, J. D., Anderson, M., &Kadlec, R. P. (2021). Real-world effect of monoclonal antibody treatment in COVID-19 patients in a diverse population in the United States. *Open Forum Infectious Diseases*, *8*(8), ofab398. https://doi.org/10.1093/ofid/ofab398

[13] NIH. Anti-SARS-CoV-2 Monoclonal Antibodies. 2019. Available from https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/

[14] Sadeghalvad M, Rezaei N. Introduction on Monoclonal Antibodies. IntechOpen. 2021. DOI: 10.5772/intechopen.98378

[15] Bayer V. An Overview of Monoclonal Antibodies. National Center for Biotechnology Information. 2019;35(5):150927. Available from https://pubmed.ncbi.nlm.nih.gov/31488319/

[16] Weiner G.J. Monoclonal antibody mechanisms of action in cancer. National Center for Biotechnology Information. 2007;39(1-3):271-278. Available from https://pubmed.ncbi.nlm.nih.gov/17917071/

[17] ScienceDirect. Monoclonal antibody targets and mechanisms of action. Woodhead Publishing Series in Biomedicine. 2012:163-595,459-595. Available from doi:10.1533/9781908818096.163

[18] Weiner G.J. Building better monoclonal antibody-based therapeutics. Nature Reviews Cancer. 2015;15(6):361-370. Available from https://www.nature.com/articles/nrc3930

[19] Adair TH, Montani JP. Overview of angiogenesis. Morgan & Claypool Life Sciences.NCBI 2010. Available from https://www.ncbi.nlm.nih.gov/books/NBK53238/

[20] Hicklin DJ, Witte L, Zhu Z, Liao F, Wu Y, Li Y, Bohlen P. Monoclonal antibody strategies to block angiogenesis. Drug Discovery Today. 2001;6(10):517-528. Available from https://www.sciencedirect.com/science/article/abs/pii/S1359644601017597

[21] Zaheer J, Kim H, Lee Y, Kim J, Lim S. Combination Radioimmunotherapy Strategies for Solid Tumors. National Center for Biotechnology Information. 2019;20(22):5579. Available from https://pubmed.ncbi.nlm.nih.gov/31717302/

[22] ADC Review. What are Antibody-drug Conjugates. 2019. Available from https://www.adcreview.com/the-review/antibody-drug-conjugates/what-are-antibody-drug-conjugates/

[23] Segal DM, Weiner GJ, Weiner LM. Bispecific antibodies in cancer therapy. Current opinion in immunology. PubMed. 1999;11:558–562. DOI: 10.1016/s0952-7915(99)00015-1

[24] CDC. Understanding how COVID-19 vaccines work. Cdc.gov. 2021. Available from https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/how-they-work.html

[25] Coffey D. Monoclonal antibodies vs. vaccines vs. COVID-19: What to know.. 2021. Available from https://www.webmd.com/vaccines/covid-19-vaccine/news/20210826/monoclonal-antibodies-vs-vaccines-vs-covid-19.

[26] Cohen, M. S. Monoclonal antibodies to disrupt progression of early covid-19 infection. New England Journal of Medicine. 2021;384(3):289-291. Available from https://www.nejm.org/doi/10.1056/NEJMe2034495

[27] Rubin R. Monoclonal antibodies for COVID-19 preexposure prophylaxis can't come fast enough for some people. JAMA . 2021;326(19):1895–7. doi:10.1001/jama.2021.19534

[28] Deb P, Molla MMA, Saif-Ur-Rahman KM. An update to monoclonal antibody as therapeutic option against COVID-19. Biosafety and health. 2021;3(2):87–91. Available from https://doi.org/10.1016/j.bsheal.2021.02.001

[29] Andreano E., et.al. Extremely potent human monoclonal antibodies from COVID-19 convalescent patients. 2021;184(7):1821-1835. Available from https://doi.org/10.1016/j.cell.2021.02.035

[30] Marovich M, Mascola JR, Cohen MS. Monoclonal antibodies for prevention and treatment of COVID-19. JAMA. 2020;324(2):131–2. Available from https://jamanetwork.com/journals/jama/article-abstract/2767383

[31] FDA. Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19. 2020. Available from https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19

[32] Medscape. Casirivimab/Imdevimab (Investigational). n.d. Available from https://reference.medscape.com/drug/regen-cov-casirivimab-imdevimab-4000144#4

[33] Office of the Commissioner. Coronavirus (COVID-19) update: FDA authorizes monoclonal antibodies for treatment of COVID-19. Fda.gov. 2021. Available from https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19-0

[34] Elsevier. Drug Monograph. Bamlanivimab;Etesevimab [Internet]. Elsevier.health. Available from https://elsevier.health/en-US/preview/etesevimab#mechanism-of-action

[35] Siemieniuk, R. et al. Antibody and cellular therapies for treatment of covid-19: a living systematic review and network meta-analysis. BMJ. 2021. Available from https://www.bmj.com/content/bmj/374/bmj.n2231.full.pdf

[36] Levêque D, Wisniewski S, Jehl F. Pharmacokinetics of therapeutic monoclonal antibodies used in oncology. Review. Anticancer Research. 2005;25(3c):2327–43. Available from: https://ar.iiarjournals.org/content/anticanres/25/3C/2327.full.pdf

[37] Bai S, Jorga K, Xin Y, Jin D, Zheng Y, Damico-Beyer L. A., Dresser M. J et.al. A guide to rational dosing of monoclonal antibodies. Clinical pharmacokinetics. ClinPharmacokinet 51,2012;119–135. DOI:https://doi.org/10.2165/11596370-000000000-00000

[38] Alabama Public Health. *Monoclonal Antibody COVID-19 Treatment for Non-hospitalized patients*. 2021. Available from https://www.alabamapublichealth.gov/covid19/assets/cov-antibody-treatment.pdf

[39] Anti-SARS-CoV-2 monoclonal antibodies. NIH. 2021. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/

[40] Dillman, R. O. (1999). Infusion reactions associated with the therapeutic use of monoclonal antibodies in the treatment of malignancy. Cancer and Metastasis Reviews, 18(4), 465-471. Available from https://link.springer.com/article/10.1023/A:1006341717398

[41] Castelli MS, McGonigle P, Hornby PJ. The pharmacology and therapeutic applications of monoclonal antibodies. Pharmacol Res Perspect. NCBI PMC. 2019;7(6):e00535. doi: 10.1002/prp2.535

[42] Cowden J, Parker S. K. Monoclonal antibodies: production, uses and side effects. *The Pediatric infectious disease journal*. 2006;*25*(6):553-555.

Available from
https://journals.lww.com/pidj/FullText/2006/06000/Monoclonal_Antibodies__Production,_Uses_and_Side.16.aspx

[43] Hansel TT, Kropshofer H, Singer T, Mitchell J.A, George A.J.T. The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov. 2010;9(4):325–38. Available from https://www.nature.com/articles/nrd3003

[44] COVID-19 Monoclonal Antibody Therapy. Hawaii Pacific Health. 2021. Available from https://www.hawaiipacifichealth.org/wilcox/covid-19-monoclonal-antibody-therapy/

[45] Teissier E, Penin F, PécheurE-I. Targeting cell entry of enveloped viruses as an antiviral strategy. Molecules. NCBI PMC. [2010];16(1):221–50. Available from:
https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC6259279/

[46] Patel S, Saxena B, Mehta P. Recent updates in the clinical trials of therapeutic monoclonal antibodies targeting cytokine storm for the management of covid-19. Heliyon Journal. Available from https://doi.org/10.1016/j.heliyon.2021.e06158

[47] Lopez A, Hermosilla J, Navas N, Rodríguez L, Cabeza J, Garcia A. The relevance of monoclonal in the treatment of covid-19. MDPI. 2021. Available from
https://www.mdpi.com/2076-393X/9/6/557/htm#B42-vaccines-09-00557

[48] Karkhur S, Hasanreisoglu M, Vigil E, Halim MS, Hassan M, Plaza C, et al. Interleukin-6 inhibition in the management of non-infectious uveitis and beyond. J OphJournal of Ophthalmic Inflammation and Infection. 2019;9(1):17. DOI:10.1186/s12348-019-0182-y

[49] Palanques-Pastor T, López-Briz E, Poveda Andrés JL. Involvement of interleukin 6 in SARS-CoV-2 infection: siltuximab as a therapeutic option against COVID-19. European Journal of Hospital Pharmacy. BMJ. 2020 ;27(5):297–8. Available from: https://ejhp.bmj.com/content/27/5/297

[50] Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Anti-SARS-CoV-2 antibody products. Nih.gov. 2021. Available from: https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_111.pdf

[51] Cooper MH, Christensen PA, Salazar E, Perez KK, Graviss EA, Nguyen D, et al. Real-world assessment of 2,879 COVID-19 patients treated with monoclonal antibody therapy: A propensity score-matched cohort study. Open Forum Infectious Diseases. 2021;8(11). Available from: https://academic.oup.com/ofid/article/8/11/ofab512/6384727