A Review on Role of Anti-SARS-CoV-2 Monoclonal Antibodies in the Treatment of COVID-19

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons)

School of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.

2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

4. I have acknowledged all main sources of help.

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Approval

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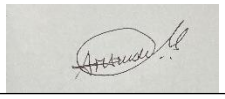

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Ethics Statement

This study does not involve any kind of animal and human trial.

Abstract

Traditional treatments and symptomatic care are still the only options for most patients as no therapeutic drug has been licensed for treating COVID-19 yet. Monoclonal antibodies generated from convalescent patients or humanized mice exposed to SARS-CoV-2 antigens were awarded emergency use authorization. An ongoing phase I, II, and III placebo-controlled trial is testing whether symptomatic adults can be treated safely and effectively. Casirivimab and imdevimab may have a therapeutic benefit in people who were seronegative when they received treatment. An IgG1 (Immunoglobulin G1) with an unaltered Fc region, Bamlanivimab was generated from the convalescent plasma of a COVID-19 patient. Patients with renal impairment, pregnancy, or breastfeeding status are not advised to alter their dosages. SARS-genomic CoV-2's organization is nearly identical to that of SARS-CoV, with the exception of a few genes for accessory proteins.

Keywords: Casirivimab, Imdevimab, Bamlanivimab, SARS-CoV-2, Immunoglobulin G1, Placebo-controlled trial.

Dedication

This project is dedicated to my parents, who have always been supportive

Acknowledgement

To begin with, I want to express my gratitude to Almighty Allah for providing me with the strength and dedication required to complete the project and overcome all of the problems that came with it. Without his mercy, the work would not have been possible.

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List of Acronyms

NCov-2	Noval Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
MER-CoV-2	Middle East Respiratory Syndrome Coronavirus 2
EUA	Emergency Use Authorization
MAbs	Monoclonal Antibodies
PEG	Polyethylene Glycol
IgG1	Immunoglobulin G1
EMA	European Medical Agency
MAC	Membrane Attack Complex
FcR	Fc Receptor
ADE	Antibody Dependent Enhancement
ACE	Angiotensin Converting Enzyme 2
RBD	Receptor Binding Domain
LALA	Leu234Ala/Leu235Ala
RT-PCR	Real Time Polymerase Chain Reaction
RCT	Randomized Control Trial
RDT	Rapid Antigen Detection Test
AD	Antigen Detection
NP	Nasopharyngeal
OP	Oropharyngeal

PEP	Pre-Expose Prophylaxis
RBD	Receptor Binding Domain
FDA	Food and Drug Administration

Chapter 1

Introduction

1.1. Background

A new coronavirus linked to severe acute respiratory syndrome (SARS-CoV-2) was reported early in December 2019, and since then, worldwide morbidity and mortality have continued to rise. There are also reports of re-infections as well (Tillett et al., 2021). There has been a huge amount of work to come up with an effective treatment for COVID-19, but no drug has been approved to handle COVID-19. Traditional treatments and symptomatic care are still the only options for most patients in many countries, even though multiple vaccines have been granted EUA in various nations. It has been proven yet again that we are powerless to combat this disease with our current treatments after the findings of the WHO solidarity trial (Pan et al., 2021). In addition to a reliable vaccine, new therapeutic methods are now an important requirement in the fight against this pandemic.

Viral infectious disorders have previously been successfully treated using immunotherapy, such as vaccines or antibody treatment, etc. There is a good chance that plasma or hyperimmune immunoglobulin from patients who have already been infected with influenza, SARS, MERS, and Ebola will help cut down on the viral load and subsequently reduce disease mortality (Winkler & Koepsell, 2015). In contrast, monoclonal antibodies (mAbs) work as a passive immunotherapy, so it is possible to cure particular diseases with monoclonal antibodies (mAbs). Since mAbs are identified from infected patients' blood or produced in the laboratory, they are significantly more specific, exact, and safe than standard convalescent plasma therapy (Wang et al., 2020). Though Covid-19 vaccine is invented, but it is not 100% effective still now. Because of this, the best way to fight this pandemic is to get a safer and more effective COVID-19 vaccine, however mAbs can help in places like care homes and areas where infection spreads quickly (Marovich et al., 2020).

1.2. The coronavirus disease 2019 (COVID-19)

There were cases of pneumonia in Wuhan, China, in December 2019. The new coronavirus SARS-CoV-2 was found to be the cause. COVID-19 is the medical term for the condition produced by a novel coronavirus (Wang et al., 2020). One of the largest families of viruses, the Coronaviruses (CoVs) have a wide range of phenotypical and genotypical variations. In the Orthocoronavirinae subfamily, CoVs are single-stranded positive-sense RNA enveloped viruses that can cause sickness in birds, mammals, as well as humans. In the virus genome, respectively structural and non-structural proteins are made, is around 27-32 kb in length. Structure proteins including membrane, envelope, nucleocapsid and spike proteins are critical to virus entrance and reproduction in the host cell, respectively. Two highly virulent zoonotic coronaviruses, SARS-CoV and MERS-CoV, have caused substantial outbreaks and mortality in a number of countries. After MERS-CoV and SARS-CoV, SARS-CoV-2 is the third extremely virulent human coronavirus infection to be discovered in the recent two decades. SARS-specific CoV-2's origins, animal reservoir, and enzootic transmission patterns are all unknown, despite the widespread belief that bats are to blame (Shanmugaraj et al., 2020).

COVID-19 symptoms have been described as moderate to life-threatening, depending on the individual. The symptoms, which include fever, cough, shortness of breath, and pneumonia, typically develop 2-14 days after virus exposure. Respiratory, hepatic, gastroenterological and neurological problems might lead to death in the more severe forms of the disease. Human-to-human transmission of COVID-19 is thought to occur by respiratory droplets or direct contact with infected individuals (Gralinski & Menachery, 2020). The virus has spread to more than 20 nations in a short time, and as of February 18, 2020, about 73,000 cases of COVID-19 infection and 1,870 deaths had been reported. COVID-19-related infections and deaths are increasing on a daily basis. In an effort to combat coronavirus infection, there have been significant efforts. An important part of the research has been devoted to discovering antiviral compounds that target the spike protein during viral entry, as well as their potential to stimulate the host immune system and elicit protective antibodies from those who are infected with the virus (Shanmugaraj et al., 2020).

1.3. Monoclonal antibody definition and production

B cells, a kind of lymphocyte, are the primary source of monoclonal antibodies. This cell type cannot be cultured for an extended period of time because of its limited capacity for growth in cell culture. This means that there are distinct ways to run and make cell lines depending on B cells. For immunodiagnostic reasons, monoclonal antibodies derived from mouse lymphocytes are most commonly utilized. Therapeutic antibodies against SARS-CoV-2 can be generated by using human cells, particularly those from convalescent patients, as COVID-19 patients (Henderson, 2020).

In order to make certain mouse monoclonal antibodies, the most common way to make them is to fuse splenic cells from mice that have been immunized with SARS-CoV-2 proteins as well as mouse myeloma cell lines with fusing media like Polyethylene glycol (PEG). For immunodiagnosis, mouse monoclonal antibodies are mainly employed (Tabll et al., 2021). Plasmids expressing human IgG1 heavy chain as well as Ig Kappa light chain are required for the development of recombinant therapeutic mAbs that could be used in the treatment of patients with autoimmune diseases. For efficient antibody production, the interleukine-2 signal sequence is included on both plasmids. They are then purified by using Protein-A affinity chromatography to remove the antibodies made in HEK-293T cells that aren't made in the same way as the original human antibodies (Wang et al., 2020).

1.4. The First Generation of Antibodies—Hurdles for Global Access

It has become clear that a mix of mAbs or broadly cross-reactive single mAb products are needed to respond to fast emerging SARS-CoV-2 variants of concern (VOCs). SARS-CoV-2 anti-neutralizing antibody solutions have been developed and certified for emergency use in a short period of time, however ensuring global access and uptake has proved difficult. First-generation mAb treatments require high doses supplied intravenously (IV), increasing production and delivery costs as well as the pressure on already overcrowded health care systems. We must overcome these challenges if mAbs are ever going to become accessible to patients with mild to moderate COVID-19 disease in outpatient clinics. MAb products can be beneficial in treating the early stages of infection if they are detected and linked to care quickly; regrettably, these systems are still lacking in resource-limited areas. In order to make these and other early-infection

treatments more widely available and effective, People who are infected with SARS-CoV-2 need to get better at getting early diagnoses and getting mAbs into their treatment options (*Monoclonal Antibodies For COVID-19 Are A Potentially Life-Saving Therapy: How Can We Make Them More Accessible? | Health Affairs*, n.d.).

Priority medicines, which have proved efficacy and safety in resource-constrained settings, need to be expedited through the adoption of collaborative regulatory approaches across national regulators. As an example of how this might operate, the Ebola vaccine Ervebo received conditional approval from the European Medicines Agency (EMA) and was approved for use in multiple African countries within a few months. World Health Organization (WHO), European Medicines Agency, Food and Drug Administration (FDA), Merck, African Vaccines Regulatory Forum, and several African governments worked together to speed up prequalification and coordinate regulatory review in affected countries (*Monoclonal Antibodies For COVID-19 Are A Potentially Life-Saving Therapy: How Can We Make Them More Accessible? | Health Affairs*, n.d.).

1.5. Aim

The aim of this review is to better understand how anti-SARS-CoV-2 monoclonal antibodies are being used in clinical studies to combat the pandemic and treat COVID-19.

1.6. Rationales of the study

The epidemic of novel coronavirus-2 (nCoV-2) has been called a pandemic and a global public health crisis by the WHO. People all over the world are working to fight it. It's a dynamic scenario that's always evolving (Dong et al., 2020). According to WHO, COVID-19 has been detected in 402,044,502 persons over the world, resulting in 5,770,023 deaths. To begin, the purpose for selecting this research was to gain a better understanding of nCoV-2 biology and the epidemiology of the novel coronavirus disease-19 (COVID-19).

Secondly, the virus's expected basic reproduction number is far higher than that of many other infectious diseases, potentially causing overcrowding in healthcare facilities, even in the most

developed countries. Around 20% of cases result in clinically significant and complex diseases. Adults over 60 years of age with co-morbid diseases are the most vulnerable group, with occasional sporadic incidences of serious illness in younger people (Hasan et al., 2020). In this article, the present COVID-19 situation in Bangladesh is described, along with some advice for how the country should tackle the pandemic. The present COVID-19 scenario has been articulated in this write-up, along with some proposals for how the world can battle this pandemic.

Chapter 2

Research Methodology

The first step in this review was to read an abundant number of academic literature on the topic. Detailed literature searches were conducted to gather all of the data that went into this review. This review paper's citation was done in Mendeley by Elsevier, as required. The following is a list of some of the many databases that were thoroughly searched for the current study-

- Research Gate
- PubMed
- Google Scholar
- Academic journals
- Chem-med
- Science direct

Chapter 3

Neutralizing monoclonal antibodies for the treatment of COVID-19

3.1. Neutralizing monoclonal antibodies

Neutralizing monoclonal antibodies (mAbs) that can be used in an emergency to treat COVID-19 were made by people who were healthy or by mice that had been exposed to antigens from the coronavirus 2 that causes severe acute respiratory syndrome (SARS-CoV-2). On the other hand, mABs can be created in a variety of ways, including from vaccinated persons. The paths indicated below converge throughout the selection and production stages for monoclonal antibodies (Taylor et al., 2021).

3.2. Mechanism of action of monoclonal antibodies for viral infection and antibody-dependent enhancement

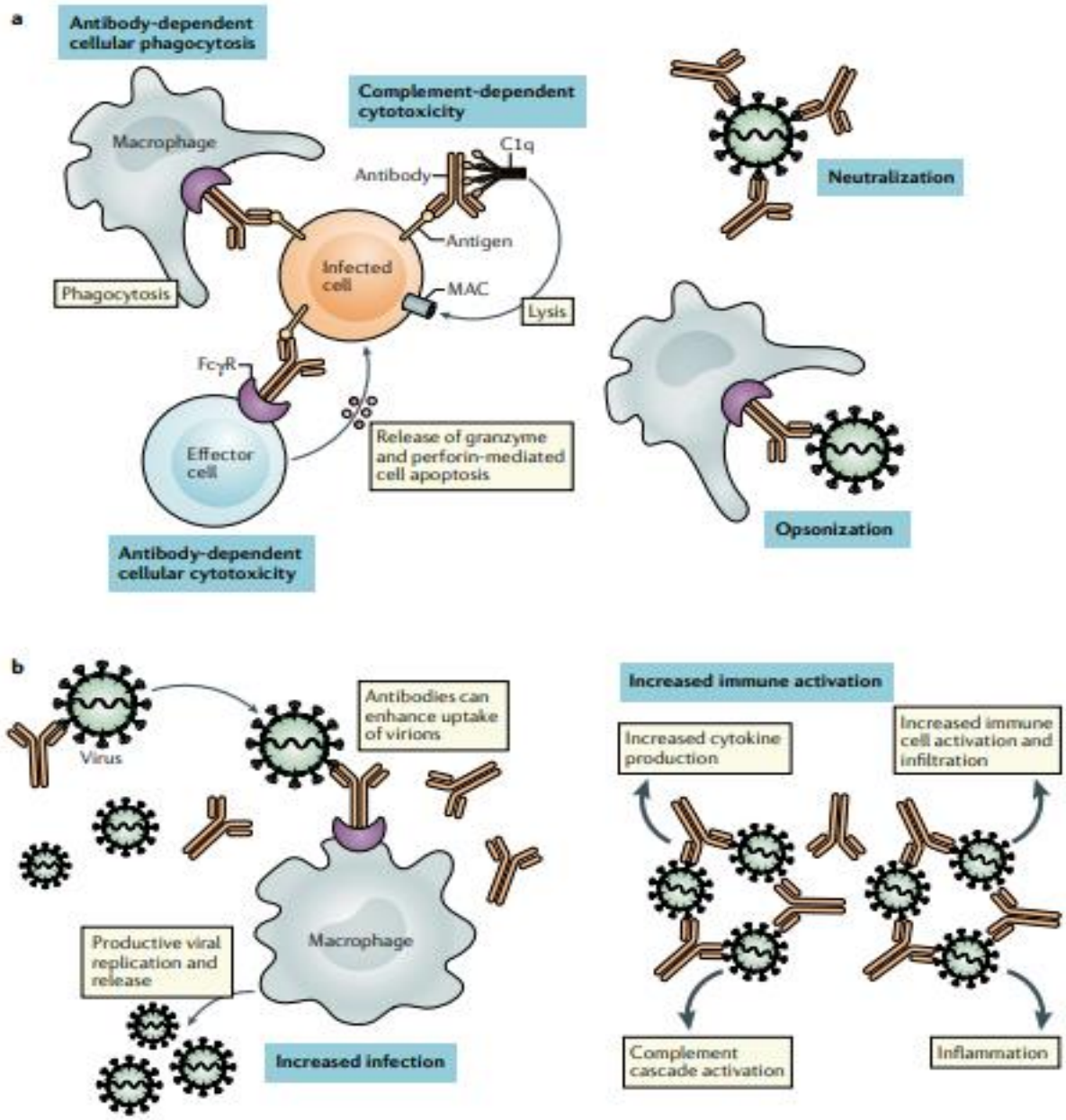

Figure 1: Mechanism of action and antibody-dependent enhancement of antiviral monoclonal antibodies (Taylor et al., 2021).

Monoclonal antibodies have a number of direct effects on viral pathogenesis (fig. 1; upper part). To start with, a neutralizing antibody can be attached to the virion. This can stop the virion from binding to and/or fusion with the cell. Additionally, Antibody binding makes virions and infected cells opsonized, which makes them easier for phagocytes to take. Monoclonal antibodies can help target cells die if viral proteins get into their membranes during viral egress. Complement fixation and activation of the membrane attack complex (MAC) or antibody-dependent cytotoxicity are two ways this can happen. Apoptosis or necrosis may occur as a result of these processes (Taylor et al., 2021).

Sometimes, opsonization of a virus might make it more dangerous because of a process called "antibody-dependent enhancement" (ADE) (fig. 1; bottom part). ADE can also be caused by one of the two ways. To start with, antibodies that are specific to a disease may help people get sick because they help viruses get into and grow in immune cells that have the Fc receptor (FcR). There are two ways that ADE can happen: First, the immune system can become more active because of Fc-mediated effects or because of the formation of immunological complexes (Lee et al., 2020).

Chapter 4

Monoclonal antibodies for COVID-19

SARS-CoV and SARS-CoV-2 include a significant antigenic epitope in the form of the S protein, which binds to the cell surface ACE2 receptor on respiratory, gastrointestinal, and endothelial cells to promote binding and fusion (Wan et al., 2020). Antibodies to the virus's S protein can prevent the virus from binding and merging with host cells. Recovered patient plasma or humanized murine technology have been used to create mAbs that specifically target the RBD of the S protein (Wu et al., 2020).

4.1. Neutralizing monoclonal antibodies inhibit target cell interaction of SARS-CoV-2

MAbs against anti-COVID-19 attack the RBD of the spike protein (S) of coronavirus 2 associated with severe acute respiratory syndrome (SARS-CoV2) (fig. 2). MAbs that target anti-RBD mAbs inhibit the S protein's interaction with ACE2 on host cells by blocking the binding of the protein to its corresponding receptor (ACE2) (fig. 2). In case of COVID-19, the FDA granted three mAb regimens to use. Dissociation constants K_D of 46 and 47 pM distinguish the binding of casirivimab and imdevimab to different RBD epitopes. S protein RBDs are targeted by imdevimab and casirivibb, respectively, from the front or lower-qeleft side, while the spike-like loop is targeted by casirivibb Bamlanivimab has a dissociation constant (K_D) of 71 pM for the dissociation of approximately 7 of the approximately 25 side chains discovered to make contact with ACE2 in its open and closed confirmations. Bamlanivimab and etesevimab both recognize separate but overlapping epitopes in the RBD of SARS-S CoV-2's protein. Etesevimab has a dissociation constant K_D of 6.55 nM for binding to the RBD in the up/active conformation; it has the LALA mutation in the Fc region, which results in no effector action (Taylor et al., 2021).

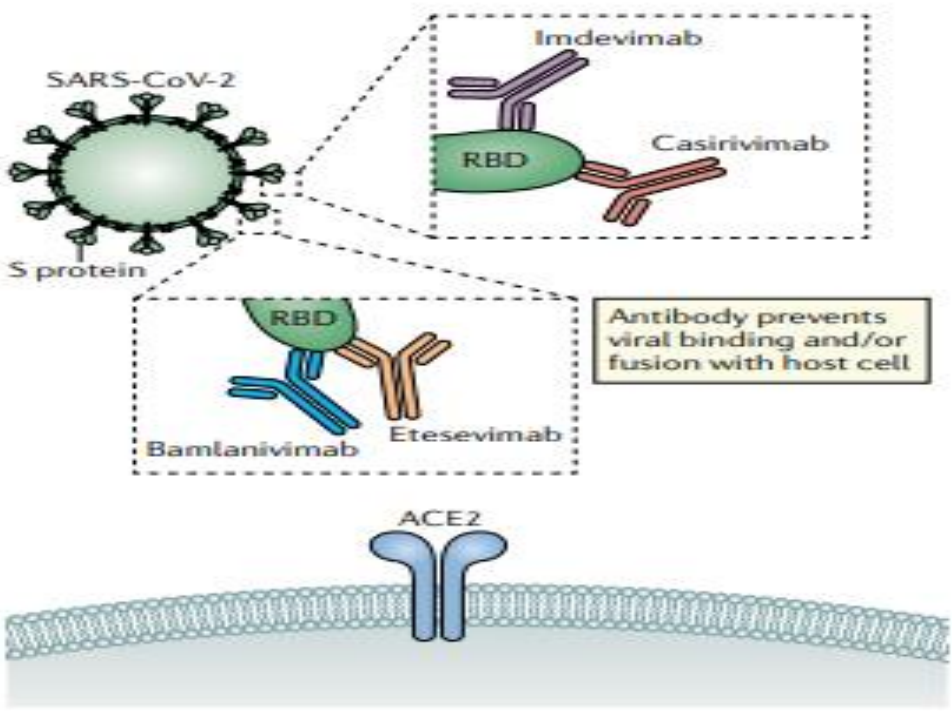

Figure 2: Neutralizing monoclonal antibodies inhibit SARS-CoV-2 target cell engagement (Taylor et al., 2021).

4.2. Treatment with REGN-COV2

REGN-COV2 consists of two highly effective neutralizing antibodies: casirivimab as well as imdeviab. They work together to make a powerful team. Antibodies from humanized mice and people who had COVID-19 were used to find these two mAbs. They were selected from a pool of around 200 neutralizing monoclonal antibodies derived from thousands of antibodies (Hansen et al., 2020). An antibody clings to the RBD in two places that are unique and don't touch each other (Baum et al., 2020). A change in the S protein of SAR-CoV-2 isn't likely to affect both antibodies at the same time, so they were paired together. After extensive laboratory testing, it was determined that this combination was capable of neutralizing all known S protein mutations (Baum et al., 2020). In the lab, the combination of casirivimab and imdevimab led to cytotoxicity and phagocytosis in virus-infected cells. On rhesus macaques and golden hamsters, this medication was evaluated, both of which had mild and severe illnesses, as a way to see how it worked (Baum

et al., 2020). Compared to a placebo, both casirivimab and imdeviab cut down on the number of viruses in the body and cut down on the number and severity of lung illnesses.

Casirivimab and imdevimab patients were less likely to have COVID-19-related medical visits, according to a key clinical end objective (2.8% for pooled doses versus 6.5% for placebo). In post-hoc investigations, individuals treated with casirivimab or imdevimab had fewer COVID-19-related hospitalizations and emergency department visits, compared to placebo-treated patients (2% vs 4%). Patients with a higher likelihood of progressing to severe COVID-19 or hospitalization saw the greatest absolute risk reduction from casirivimab and imdevimab compared to placebo (3% vs 9%). Regeneron's EUA for casirivimab and imdevimab in November 2020 in the United States was strengthened by these findings (Taylor et al., 2021).

4.3. Bamlanivimab Monotherapy

Bamlanivimab is an IgG1 antibody with an unaltered Fc region that is very good at neutralizing COVID-19. Plasma from a COVID-19 patient was used to make this antibody (Chen et al., 2021). With Bamlanivimab, the RBD of the S protein is filled, which means this antibody could be used as a single treatment. In the past, monotherapy with neutralizing mAbs (like MAb114 for Ebola) has been shown to be very good at getting rid of the virus (Mulangu et al., 2019). Bamlanivimab didn't work at concentrations as low as 100-fold lower than the dose needed for half of the response. It didn't work in primary human macrophages or immune cell lines that had been exposed to the SARS-CoV-2 virus. Rhesus macaques were given bamlanivimab 24 hours before they were given a virus to see if it worked as a preventative. As expected, the inoculation-induced drop in viral load and replication in the respiratory tract after treatment showed the medication's ability to fight infections (Jones et al., 2021).

People who had mild to moderate COVID-19 symptoms and a positive nasopharyngeal swab for SARS-CoV-2 were enrolled in the ongoing phase II/III BLAZE-1 study (NCT04427501). They received a single outpatient dose of bamlanivimab (700, 2,800, or 7,000 mg) or a placebo. An interim study was done on 452 patients who had reached day 11 after their infusion (median age 45–46; 13% are 65 or older; 88% are white, 6% black, and 68% are at high risk). This study looked at how well the patients were doing (e.g. elderly, obese or suffering from underlying chronic

medical issues). It was found out how long it took for the virus to be cleared by the body's own immune system and how quickly it was cleared when a neutralizing mAb was given. This led to a better clinical response (Chen et al., 2021). A new collaboration between home health research and nasopharyngeal swabs was used to find out how many viruses were in the blood after intravenous infusions. It started to drop on day 3 compared to baseline (−0.85 for placebo versus −1.35 for pooled bamlanivimab doses), and it kept going down on day 7 (−2.56 for placebo versus −2.90) and day 11 (−3.47 for placebo versus −3.70) after the treatment, which means that it worked. This risk was even greater for the elderly and those who were obese. Bamlanivimab's clinical effectiveness was shown by two secondary goals. People in the placebo group were hospitalized with COVID-19 at day 29, but only 1.6 percent of people in the bamlanivimab dosage pooled group were. In a post-hoc analysis, 15% of patients 65 years of age or older or with a BMI of 35 kg m-2 or more were hospitalized in the placebo group and 4% in the pooled bamlanivimab group, which was made up of both groups. For people who had risk factors, the absolute risk of being hospitalized went down more. Second, the bamlanivimab doses that were pooled worked better than placebo from day 2 to today. There is a good chance that bamlanivimab monotherapy will be approved for use in the US and Canada in November 2020 (Taylor et al., 2021).

4.4. Bamlanivimab and Etesevimab

This IgG1 with a modified Fc region, which has no effector activity, was examined in combination with etesevimab in other treatment groups of the BLAZE-1 experiment (Shi et al., 2020). When compared with a placebo on days 3–11, the viral load was significantly reduced with the combination of etesevimab and bamlanivimab (Gottlieb et al., 2021). Hospitalizations for COVID-19-related illnesses were reduced in persons treated with bamlanivimab and etesevimab compared to those who received placebo medication (5.8% for placebo reduced to 0.9% for bamlanivimab together with etesevimab). It was found that high-risk ambulatory patients who took both Bamlanivimab and Etesevimab had a 70% lower chance of dying from COVID-19-related causes when they took the drugs, which were given to 1,035 people in a placebo-controlled phase III study (7.0% for placebo reduced to 2.1% for bamlanivimab together with etesevimab). European Medicines Agency authorization for two new drugs was given in light of these findings (Gottlieb et al., 2021).

4.5. Sotrovimab

An unpublished study for sotrovimab also indicates a decrease in hospitalization and death. Sotrovimab or placebo were given to 583 non-hospitalized persons with risk indicators for severe disease or age above 55 years old in the study. 1% of the treatment group and 12.7% of the placebo group experienced a reduction in total hospitalizations and deaths. The placebo group was responsible for a single death in this research. This study's complete findings have not yet been published and cannot be examined at this time. EUA for sotrovimab is a single 500-mg intravenous dose (Brobst & Borger, 2021).

Chapter 5

5.1. Therapy with monoclonal antibodies for severe COVID-19 disease

Patients with severe COVID-19 are currently being studied for neutralizing mAbs. The REGN-COV2 hospitalized patient trial is currently enrolling patients with or without oxygen supplementation. Casirivimab and imdevimab medication may have a therapeutic benefit in people who were seronegative when they received treatment (Taylor et al., 2021). For patients with severe viral infection, rapid viral clearance alone is not sufficient, as indicated by prior studies looking at CPT or neutralizing mAbs (such as COVID-19). Other variables, including an overactive immune response, contribute significantly to the development of sickness in this patient population. In patients with severe disease, the etiology is primarily postviral or periviral, and clinical condition is uncoupled from viral load, although early illness seen in outpatients is almost certainly viral in nature (Taylor et al., 2021).

5.2. Monoclonal antibody therapy-related adverse effects.

COVID-19 monoclonal antibody therapy had the same risk of treatment-related side effects as a placebo. In RCTs, the most common side effects were vomiting, diarrhoea, dizziness, and nausea. On the other hand, patients who experienced an infusion-related reaction of grade 2 or higher within the first four days of treatment were given casirivimab and imdevimab instead of the usual placebo (Weinreich et al., 2021). One patient had bamlanivimab monotherapy, another received bamlanivimab and etesevimab combined, and a final patient received placebo in BLAZE-1's phase II section and experienced an infusion-related response. The majority of side effects occurred during infusion and were of a mild to moderate degree, with no apparent connection to dose. In vitro studies show that neutralizing mAbs have no effect on the ability of SARS-CoV-2 to infect immune cells. According to the existing clinical evidence, these treatments do not appear to boost immunological responses in a way that is consistent with ADE2. SARS-CoV-2 infection is treatable with both modified and modified plus unmodified mAbs, which suggests that ADE may have little effect on clinical results (Gottlieb et al., 2021).

5.3. The role of monoclonal antibodies in SARS-CoV-2 immunodetection

When it comes to detect SARS-CoV-2, monoclonal antibodies are crucial tools. Despite the fact that molecular biology is widely employed in the diagnosis of COVID-19, it cannot be used to evaluate the progress of COVID-19 or to identify previous infections and humoral immunity (Khalaf et al., 2020). Rapid and simple tests based on immunity have become increasingly popular as a result of the current diagnostic approaches' limitations. In term of diagnosing a disease, RT-PCR is one of the most reliable and accurate methods, but it can only tell you whether or not a patient has been infected with a certain virus at a given time. Immunological testing, on the other hand, have a number of advantages (rapid, sensitive, specific, safety reagents, qualitative or quantitative determination). Testing for SARS-CoV-2 antibody responses can distinguish between those who have been infected for a long time and those that have only recently been infected. COVID-19 epidemiology, vaccine development, and immune response all benefit from their presence. Immunoassays can also be used to measure an analyte's concentration using components of the immune response, such as an antigen (analyte) that reacts with an antibody (analyte) (Chen et al., 2021). When using enzyme-based immunoassays, monoclonal antibodies are used to find the antigen. There is a possibility that this antigen is present in bodily fluids (Oropharyngeal swab, saliva, sputum, blood, urine, stool). Monoclonal antibodies were recently employed in an immunological assay to identify SARS-CoV-2 proteins. Monoclonal antibodies against the SARS-CoV-2 virus can identify multiple forms of N protein or S protein as targets (S1, S2). SARS-CoV-2 nucleocapsid protein monoclonal antibodies may serve as a foundation for a quick antigen detection test in the near future (Tabll et al., 2021).

Currently, there are a number of immunoassay techniques that have been approved or are seeking approval, and their variety and inventiveness could enhance the number of ways in which infections can be detected in clinical specimens. Detection of SARS-CoV-2 antigens in biological samples, such as nasopharyngeal secretions, can be done quickly employing viral antigen-targeting techniques. A lot of work has been done to create these tests. SARS-CoV-2 antigen detection using rapid antigen assays has been proposed and is now the approach most frequently used (Tabll et al., 2021). It is possible for patients with high viral loads at the onset of infection to benefit from quick antigen detection (Weitzel et al., 2021).

A novel rapid antigen detection test (RDT) on transport medium can detect SARS-CoV-2 antigens in NP and OP swabs from suspected COVID-19 infections. An alternative to the real-time polymerase chain reaction (RT-PCR) is the SARS-CoV-2 antigen fluorescence immunochromatographic assay (Bioeasy Biotechnology Co., Shenzhen, China). 93.9% of the time, RDT assays are able to achieve both sensitivity and specificity. Antigen detection (AD) tests based on monoclonal antibodies are less time-consuming and less costly. One automated AD test (VITROS) was recently put up to the clinical performance of five different AD tests, including 4 rapid AD (RAD) tests (biotical, Pan-bio, Healgen, and Roche). Patients with larger viral loads can be identified with higher RT-PCR positivity rates because of the study's findings, which show that the RAD tests perform more modestly. Because of the sensitivity, some samples with high viral loads were missed, with a range of 93.1 to 96.6%. The sensitivity and specificity of the VITROS automated assay are both 100%. Hence, the VITROS assay is entirely matched with the RT-PCR, which may give an easier, faster, and cheaper way to the detection of SARS-CoV-2 contagious patients as compared to RAD testing (Favresse et al., 2021).

5.4. Monoclonal Antibody Therapy for COVID-19 in Children: Suggested Criteria

5.4.1. Monoclonal antibodies for post-exposure prophylaxis

On September 9th and September 16th, 2021, the FDA updated and expanded the EUAs for casirivimab/imdevimab and bamlanivimab/etesevimab to include post-exposure prophylaxis (PEP). At least 40 kg in a kid between the ages of 12 and 17 is required to be a candidate for PEP, as is an increased risk of severe COVID-19. Those who are eligible for PEP must additionally meet the following requirements:

- For example, those with immunocompromised conditions, particularly those taking immunosuppressive drugs, must not be fully vaccinated or anticipated to create an effective immune response to complete SARS-CoV-2 immunization (Minnesota Departement of Health, 2021).

- SARS-CoV-2 infection was acquired by close contact with a person infected with the virus, as defined by the CDC, or the individual must be at high risk of exposure to a person infected with the virus due to the presence of SARS-CoV-2 infection in other individuals at the same facility (for example, group homes, shelters, etc.). Bamlanivimab/etesevimab can be used for post-exposure prophylaxis in children younger than 12 years old on December 6th, 2021, when the EUA was expanded to encompass this age group. Casirivimab/imdevimab can be administered either intravenously or subcutaneously for pre-exposure prophylaxis (PEP). Only intravenous infusion of bamlanivimab/etesevimab has been approved; it is not permitted for subcutaneous administration. Pre-exposure prophylaxis (PEP) using monoclonal antibodies is not a substitute for vaccination, and it is not approved for this purpose (Minnesota Departement of Health, 2021).

5.4.2. Utilization of monoclonal antibodies in hospitalized patients

Each of the three monoclonal antibodies currently authorized for the treatment of COVID-19 is indicated for use in outpatients or patients who are hospitalized for reasons other than COVID-19 treatment.

COVID-19-infected patients aged 2 and older may be treated with bamlanivimab/etesevimab, however casirivimab/imdevimab and sotrovimab are not permitted. There are no approved treatments for COVID-19-related comorbidities that necessitate the use of one or more of these three monoclonal antibody therapies, regardless of the patient's age, regardless of whether or not the underlying comorbidity is COVID-19-related or not (Minnesota Departement of Health, 2021).

5.5. Dosing

5.5.1. Bamlanivimab-Etesevimab

- ✓ In accordance with the FDA's fact sheet, an IV infusion of 700 mg of bamlanivimab and 1400 mg of etesevimab over 60 minutes has been approved. When IV delivery isn't an option or would cause a delay in therapy, a subcutaneous injection can be used instead.
- ✓ Bamlanivimab-etesevimab should be administered within 10 days of the onset of symptoms.
- ✓ If a patient is pregnant or nursing, no dose changes should be made because of renal or hepatic impairment (Brobst & Borger, 2021).

5.5.2. Casirivimab-Imdevimab (REGEN-COV2)

- ✓ According to the FDA's data sheet, a single intravenous infusion of 600 mg casirivimab and 600 mg imdevimab administered over 60 minutes is the maximum dosage allowed. When intravenous delivery is unavailable or would delay treatment, subcutaneous injection is an option.
- ✓ Casirivimab-imdevimab should be administered within 10 days of the onset of symptoms.
- ✓ Patients with renal impairment, pregnancy, or breastfeeding status are not advised to alter their dosages (Brobst & Borger, 2021).

5.5.3. Sotrovimab

- ✓ According to the FDA fact page, a single intravenous infusion of 500 mg of sotrovimab administered over 30 minutes is the maximum dosage permitted. Subcutaneous administration of Sotrovimab is not permitted.
- ✓ Within 10 days after symptom onset, Sotrovimab should be administered.
- ✓ Patients with renal impairment, pregnancy, or breastfeeding status are not advised to make any dose modifications (Brobst & Borger, 2021).

5.6. High-risk conditions

- Owing one's age (for example, aged 65 years or older).
- Bamlanivimab/etesevimab is only available to children under 1 year of age at this time.
- When a person's body mass index (BMI) exceeds 25 kg/m2 (for adults) or 85th percentile for their age and gender (for children aged 12-17), they are considered obese or overweight.
- Pregnancy.
- Kidney disease that is both chronic and progressive.
- Diabetes.
- A sickness or treatment that suppresses the immune system.
- Hypertension or cardiovascular disease (including congenital heart disease)
- When it comes to long-term lung conditions such as respiratory illnesses such as COPD, asthma and interstitial lung disease, cystic fibrosis is among the most common.
- Patients with sickle cell disease.
- The presence of medically complex illnesses, such as neurological problems (such as cerebral palsy) (for example, genetic or metabolic syndromes and severe congenital abnormalities) (Minnesota Departement of Health, 2021).

5.7. Risk In Leukemia patients

A high risk of death and severe disease from COVID-19 exists in people with acute leukemia, both in adults and children (Meena et al., 2021). Patients with SARS-CoV-2-infected leukemia may also have a bad prognosis if treatment is delayed or halted, especially in severe forms of leukemia (Hurt & Wheatley, 2021).

In this case, the patient was complaining of a high fever, severe bone pain, and internal bleeding (petechiae and spontaneous ecchymosis). Mild non-regenerative normocytic anaemia (105 g/l) was found as was moderate thrombocytopenia (86 ×109/l) and normal neutrophil counts in the patient's blood. A tertiary care facility was then recommended for the patient (Avanzato et al., 2020). Large numbers of medium-sized blast cells with a high nucleocytoplasmic ratio and non-granular cytoplasm were seen in bone marrow aspirates. 10% of $CD19^{+}$, $cCD79a^{+}$, $cCD22^{+}$, and $CD10^{+}$

cells co-expressed monocytic markers in an unclear lineage leukemia (MPO, CD14, CD64, CD33). The complicated karyotype 46, XX, -10, -12, -17, -21, +4mar/46, XX was discovered through cytogenetic research. *BCR-ABL1, ETV6-RUNX1, TCF3-PBX1 and TCF3-HLF* fusions, *KMT2A* rearrangements, and chromosome 21 amplification were all shown to be negative by fluorescence in-situ hybridization investigation. A fusion of *AF15* and *ZNF384* was discovered using multiplex ligation-dependent probe amplification (Saultier et al., 2022).

Real-time polymerase chain reaction (RT-PCR) results showed that the patient was infected with SARSCoV-2 shortly after admission (RTPCR; multiplex TaqPath COVID-19; ThermoFisher Scientific, Waltham, MA, USA. There were no COVID-19 respiratory symptoms despite the patient's fever. The ground-glass opacity on the computed tomography (CT) scan was modest (Avanzato et al., 2020). Her sister and both parents tested positive for SARS-CoV-2, which suggests that the patient was infected with COVID-19 through family transmission. The patient's mother developed COVID-19 symptoms when she was pregnant.

The anti-SARS-CoV2 mAbs bamlanivimab and etesevimab were given to the patient in conjunction to lessen the chance of a severe form of COVID-19 (off-label) (off-label). Experts from the French drug authority (ANSM) and the manufacturer were engaged in making this determination (Eli Lilly). The patient was administered 700 mg of bamlanivimab (about 25 mg/kg) and 1,400 mg of etesevimab (about 50 mg/kg) the day after admission (adult doses). Corticosteroids were then started three days following the mAbs infusion, as the COVID-19 medicine was well tolerated. SARS-CoV-2 nucleocapsid antibodies were not identified, indicating that the patient had not acquired a natural immune response to the virus. (Abdul-Jawad et al., 2021). An extraordinarily high blood levels of anti-spike antibodies that were neutralizing after the injection (i.e., infused mAbs) were detected. There was no need to provide more mAbs because the antibodies were still high enough that they didn't need it. Within 10 days of the mAb injection, the virus had been eradicated, and no recurrence had been recorded over the course of the subsequent >10week follow-up (Hurt & Wheatley, 2021).

Induction chemotherapy included corticosteroids, vincristine, daunorubicin, pegaspargase, and triple intrathecal chemotherapy as per established protocols for acute lymphoblastic leukemia. In addition, a single dosage of rasburicase was administered to the patient to treat a minor form of tumour lysis syndrome associated with elevated levels of serum uric acid. During the period of 15-

42 days, aplastic angiogenesis was observed (neutrophil count nadir of 50/mm3). There were no serious issues. Immediately following the completion of induction chemotherapy, the patient was declared free of disease. Consolidation training was given to the patient (Avanzato et al., 2020).

Patients with hematological malignancies have a higher risk of viral evolution, viral clearance impairment, humoral response change, T-cell exhaustion, and prolonged virus release (Meena et al., 2021). Treatment for patients with COVID-19 acute lymphocytic leukemia must be postponed or interrupted, both of which increase the chance of developing a severe SARS-CoV-2 infection (Vijenthira et al., 2020)

A patient with high-risk leukemia may be able to tolerate mAbs for the treatment of SARS-CoV-2 infection, according to these findings. Induction therapy was completed without any delays or interruptions, and the patient was in complete remission at the end of the treatment. The combination of high-risk haematological malignancy and COVID19 may arise in places where COVID-19 is on the rise (Gallian et al., 2020).

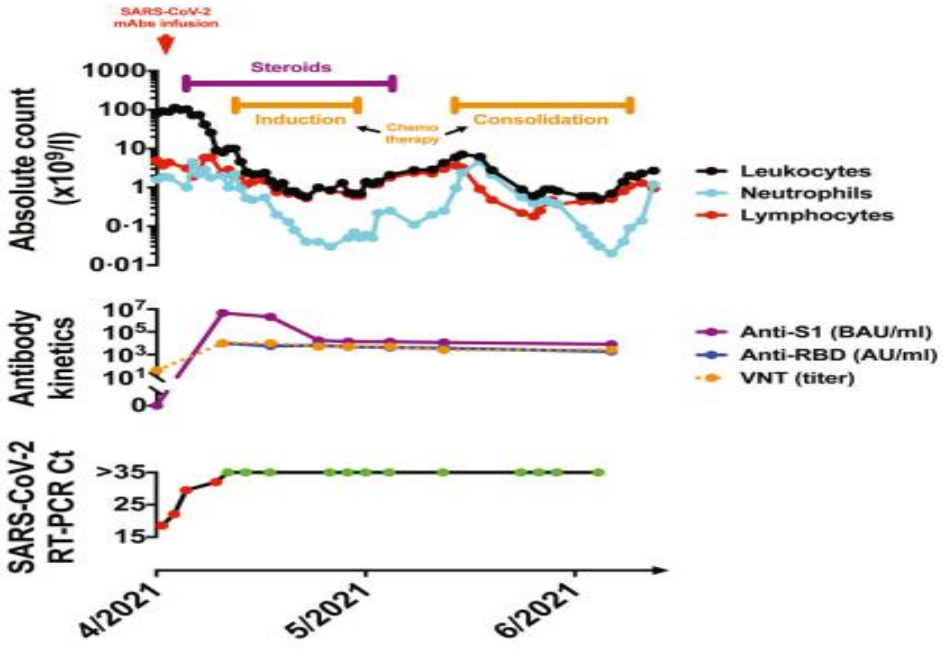

Figure 3: The evolution of the clinical, haematological, immunological, and viral parameters over the course of treatment (Saultier et al., 2022).

Time for the monoclonal antibodies to be injected: The red arrow shows when to do this. The timeline of when steroids and chemotherapy are given to people with leukemia is shown in purple

and orange (fig. 3; top part). A kit called Anti-SARS-CoV-2 QuantiVac (IgG) [Euroimmun, Lubeck, Germany] was used to (fig. 3; middle part) out how many anti-S1 antibodies there were in each ml of blood. In this case, an Access SARS-CoV-2 IgG II Reagent Kit [Beckman Coulter Brea, CA, USA (arbitrary units per ml)] was used to check for antibodies against RBD. Viral neutralizing titers were measured. Results for SARS-2 CoV-2 from samples of nasal mucus (multiplexed TaqPath COVID-19, ThermoFisher Scientific, USA) are shown (fig. 3; bottom part). Positive and negative tests are marked with red and green dots (Saultier et al., 2022).

Chapter 6

Challenges

The efficacy of monoclonal antibodies is challenging to prove in clinical trials. Since most people with an early infection recover, obtaining the clinical end points necessary to demonstrate a benefit over a placebo is challenging to do so successfully. Viral replication may not be as essential as inflammation and coagulopathy in patients with more severe disease, making it difficult to show improvement. Individuals with a high enough risk of infection must be found for monoclonal antibody prevention trials in order to establish that the treatment prevents symptoms of infection (Corey et al., 2020). This pandemic of COVID-19 will necessitate an adaptable clinical research infrastructure that can quickly provide monoclonal antibodies for persons or places at high risk of infection. Insufficient production of monoclonal antibodies is another concern. Existing commercial production capability is expected to produce millions of doses per year, however this will be decided by the required quantity and may differ for preventive and therapeutic purposes (Marovich et al., 2020).

There is a strong probability that vaccinations for COVID-19 may have the same effect on animal models of SARS and other animal coronaviruses. Target cells (Fc-bearing monocytes or macrophages) with increased viral entry and multiplication due to antibody-mediated mechanisms and virus-antibody immune complexes and the associated cytokine release are two potential disease enhancement methods to consider. As a result of the presence of sub-neutralizing antibodies or non-neutralizing antibodies, it is commonly defined as Fc-receptor-mediated increased disease (Graham, 2020).

Chapter 7

Conclusion

Finally, for SARS-CoV-2 and other infectious diseases, monoclonal antibodies are and will likely remain an important treatment option in the twenty-first century. Research should be aimed at enhancing monoclonal antibodies that are very effective, can be made for a fraction of the cost, and have a specific group of people who benefit from them (Deb et al., 2021).

COVID-19 pandemic's unexpected appearance and devastation spurred an international research endeavor to explore efficient methods of limiting viral propagation and reducing COVID-19 mortality (Wang et al., 2020). As of 10 a.m. CET on 3 March 2020, COVID-19 has expanded to 73 countries, territories, or places around the world and is accountable for 90,870 cases. Wuhan Huanan seafood market may not have been the sole source of the infection. It doesn't matter how you look at it, wildlife sales should be banned and wet markets should be emptied of their stock. Only a few genes encoding accessory proteins distinguish SARS-genomic CoV-2 from SARS-CoV in terms of genome organization. SARS-CoV-2 penetrates cells via the ACE2 receptor as a consequence. Droplets from coughing or sneezing or direct contact are the most common means of transmission between humans. The most common symptoms are a fever and a cough. An essential diagnostic tool, a chest computed tomography (CT) scan, can detect SARS-CoV-2 in samples taken from the upper and lower respiratory tracts. In terms of treatment, no specific medications exist for the infection, and various therapies are now being investigated in clinical trials with promising preliminary results (Ge et al., 2019). Tocilizumab, baricitinib, and dexamethasone have all been shown in clinical trials to reduce mortality in SARS-CoV-2 infected patients with hypoxia (data still under review). Some experiments with various immune-modulating drugs have been conducted or are now in progress to lessen tissue damage in the later phases of COVID-19, as well (Taylor et al., 2021).

References

Tillett, R. L., Sevinsky, J. R., Hartley, P. D., Kerwin, H., Crawford, N., Gorzalski, A., Laverdure, C., Verma, S. C., Rossetto, C. C., Jackson, D., Farrell, M. J., Van Hooser, S., & Pandori, M. (2021). Genomic evidence for reinfection with SARS-CoV-2: a case study. *The Lancet Infectious Diseases*, *21*(1), 52–58. https://doi.org/10.1016/S1473-3099(20)30764-7

Pan, K. Y., Kok, A. A. L., Eikelenboom, M., Horsfall, M., Jörg, F., Luteijn, R. A., Rhebergen, D., Oppen, P. van, Giltay, E. J., & Penninx, B. W. J. H. (2021). The mental health impact of the COVID-19 pandemic on people with and without depressive, anxiety, or obsessive-compulsive disorders: a longitudinal study of three Dutch case-control cohorts. *The Lancet Psychiatry*, *8*(2), 121–129. https://doi.org/10.1016/S2215-0366(20)30491-0

Winkler, A. M., & Koepsell, S. A. (2015). The use of convalescent plasma to treat emerging infectious diseases: focus on Ebola virus disease. *Current Opinion in Hematology*, *22*(6), 521–526. https://doi.org/10.1097/MOH.0000000000000191

Marovich, M., Mascola, J. R., & Cohen, M. S. (2020). Monoclonal Antibodies for Prevention and Treatment of COVID-19. *JAMA*, *324*(2), 131–132. https://doi.org/10.1001/JAMA.2020.10245

Shanmugaraj, B., Siriwattananon, K., Wangkanont, K., & Phoolcharoen, W. (2020). Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19). *Asian Pacific Journal of Allergy and Immunology*, *38*(1), 10–18. https://doi.org/10.12932/AP-200220-0773

Henderson, J. P. (2020). *The Journal of Clinical Investigation What are protective antibody responses to pandemic SARS-CoV-2? 130*. https://doi.org/10.1172/JCI143466

Monoclonal Antibodies For COVID-19 Are A Potentially Life-Saving Therapy: How Can We Make Them More Accessible? | Health Affairs. (n.d.). Retrieved January 14, 2022, from https://www.healthaffairs.org/do/10.1377/forefront.20210901.667955/full/

Taylor, P. C., Adams, A. C., Hufford, M. M., Torre, I. De, Winthrop, K., & Gottlieb, R. L. (2021). Neutralizing monoclonal antibodies for treatment of COVID-19. *Nature Reviews Immunology*, *21*(June). https://doi.org/10.1038/s41577-021-00542-x

Wan, Y., Shang, J., Graham, R., Baric, R. S., Li, F., & Wan, C. Y. (2020). *Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus*. https://doi.org/10.1128/JVI.00127-20

Wu, Y., Wang, F., Shen, C., Peng, W., Li, D., Zhao, C., Li, Z., Li, S., Bi, Y., Yang, Y., Gong, Y., Xiao, H., Fan, Z., Tan, S., Wu, G., Tan, W., Lu, X., Fan, C., Wang, Q., … Liu, L. (n.d.). *A noncompeting pair of human neutralizing antibodies block COVID-19 virus binding to its receptor ACE2*.

Jones, B. E., Brown-Augsburger, P. L., Corbett, K. S., Westendorf, K., Davies, J., Cujec, T. P., Wiethoff, C. M., Blackbourne, J. L., Heinz, B. A., Foster, D., Higgs, R. E., Balasubramaniam, D., Wang, L., Zhang, Y., Yang, E. S., Bidshahri, R., Kraft, L., Hwang, Y., Žentelis, S., … Falconer, E. (2021). The neutralizing antibody, LY-CoV555, protects against SARS-CoV-2 infection in nonhuman primates. In *Sci. Transl. Med* (Vol. 13). https://www.science.org

Baum, A., Fulton, B. O., Wloga, E., Copin, R., Pascal, K. E., Russo, V., Giordano, S., Lanza, K., Negron, N., Ni, M., Wei, Y., Atwal, G. S., Murphy, A. J., Stahl, N., Yancopoulos, G. D., & Kyratsous, C. A. (2020). Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. *Science (New York, N.Y.)*, *369*(6506), 1014–1018. https://doi.org/10.1126/SCIENCE.ABD0831

Hansen, J., Baum, A., Pascal, K. E., Russo, V., Giordano, S., Wloga, E., Fulton, B. O., Yan, Y., Koon, K., Patel, K., Chung, K. M., Hermann, A., Ullman, E., Cruz, J., Rafique, A., Huang, T., Fairhurst, J., Libertiny, C., Malbec, M., … Kyratsous, C. A. (2020). Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. *Science (New York, N.Y.)*, *369*(6506), 1010–1014. https://doi.org/10.1126/SCIENCE.ABD0827

Chen, P., Nirula, A., Heller, B., Gottlieb, R. L., Boscia, J., Morris, J., Huhn, G., Cardona, J., Mocherla, B., Stosor, V., Shawa, I., Adams, A. C., Van Naarden, J., Custer, K. L., Shen, L., Durante, M., Oakley, G., Schade, A. E., Sabo, J., … Skovronsky, D. M. (2021). SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. *New England Journal of Medicine*, *384*(3), 229–237. https://doi.org/10.1056/nejmoa2029849

Mulangu, S., Dodd, L. E., Davey, R. T., Tshiani Mbaya, O., Proschan, M., Mukadi, D., Lusakibanza Manzo, M., Nzolo, D., Tshomba Oloma, A., Ibanda, A., Ali, R., Coulibaly, S., Levine, A. C., Grais, R., Diaz, J., Lane, H. C., Muyembe-Tamfum, J.-J., & the PALM Writing Group. (2019). A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *New England Journal of Medicine*, *381*(24), 2293–2303. https://doi.org/10.1056/nejmoa1910993

Shi, R., Shan, C., Duan, X., Chen, Z., Liu, P., Song, J., Song, T., Bi, X., Han, C., Wu, L., Gao, G., Hu, X., Zhang, Y., Tong, Z., Huang, W., Liu, W. J., Wu, G., Zhang, B., Wang, L., … Yan, J. (2020). A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2. *Nature*, *584*(7819), 120–124. https://doi.org/10.1038/s41586-020-2381-y

Weinreich, D. M., Sivapalasingam, S., Norton, T., Ali, S., Gao, H., Bhore, R., Musser, B. J., Soo, Y., Rofail, D., Im, J., Perry, C., Pan, C., Hosain, R., Mahmood, A., Davis, J. D., Turner, K. C., Hooper, A. T., Hamilton, J. D., Baum, A., … Yancopoulos, G. D. (2021). REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. *New England Journal of Medicine*, *384*(3), 238–251. https://doi.org/10.1056/NEJMOA2035002/SUPPL_FILE/NEJMOA2035002_DATA-SHARING.PDF

Gottlieb, R. L., Nirula, A., Chen, P., Boscia, J., Heller, B., Morris, J., Huhn, G., Cardona, J., Mocherla, B., Stosor, V., Shawa, I., Kumar, P., Adams, A. C., Van Naarden, J., Custer, K. L., Durante, M., Oakley, G., Schade, A. E., Holzer, T. R., … Skovronsky, D. M. (2021). Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. *JAMA*, *325*(7), 632–644. https://doi.org/10.1001/JAMA.2021.0202

Khalaf, K., Papp, N., Chou, J. T. T., Hana, D., Mackiewicz, A., & Kaczmarek, M. (2020). SARS-CoV-2: Pathogenesis, and Advancements in Diagnostics and Treatment. *Frontiers in Immunology*, *11*, 570927. https://doi.org/10.3389/FIMMU.2020.570927

Chen, H., Zhang, X., Liu, W., Xue, M., Liao, C., Huang, Z., Hu, H., & Sun, B. (2021). The role of serum specific- SARS-CoV-2 antibody in COVID-19 patients. *International Immunopharmacology*, *91*, 107325. https://doi.org/10.1016/J.INTIMP.2020.107325

Favresse, J., Gillot, C., Oliveira, M., Cadrobbi, J., Elsen, M., Eucher, C., Laffineur, K., Rosseels, C., Van Eeckhoudt, S., Nicolas, J.-B., Morimont, L., Dogné, J.-M., & Douxfils, J. (2021). Clinical Medicine Head-to-Head Comparison of Rapid and Automated Antigen Detection Tests for the Diagnosis of SARS-CoV-2 Infection. *J. Clin. Med*, *10*, 265. https://doi.org/10.3390/jcm10020265

Weitzel, T., Legarraga, P., Iruretagoyena, M., Pizarro, G., Vollrath, V., Araos, R., Munita, J. M., & Porte, L. (2021). Comparative evaluation of four rapid SARS-CoV-2 antigen detection tests using universal transport medium. *Travel Medicine and Infectious Disease*, *39*. https://doi.org/10.1016/J.TMAID.2020.101942

Minnesota Departement of Health. (2021). *Suggested Criteria for Monoclonal Antibody Treatment of COVID-19 in Children*. 1–5.

Brobst, B., & Borger, J. (2021). Benefits And Risks Of Administering Monoclonal Antibody Therapy For Coronavirus (COVID-19). *StatPearls*. https://www.ncbi.nlm.nih.gov/books/NBK574507/

Meena, J. P., Kumar Gupta, A., Tanwar, P., Ram Jat, K., Mohan Pandey, R., & Seth, R. (2021). Clinical presentations and outcomes of children with cancer and COVID-19: A systematic review. *Pediatric Blood & Cancer*, *68*(6). https://doi.org/10.1002/PBC.29005

Avanzato, V. A., Matson, M. J., Seifert, S. N., Pryce, R., Williamson, B. N., Anzick, S. L., Barbian, K., Judson, S. D., Fischer, E. R., Martens, C., Bowden, T. A., de Wit, E., Riedo, F. X., & Munster, V. J. (2020). Case Study: Prolonged Infectious SARS-CoV-2 Shedding from an Asymptomatic Immunocompromised Individual with Cancer. *Cell*, *183*(7), 1901. https://doi.org/10.1016/J.CELL.2020.10.049

Abdul-Jawad, S., Baù, L., Alaguthurai, T., del Molino del Barrio, I., Laing, A. G., Hayday, T. S., Monin, L., Muñoz-Ruiz, M., McDonald, L., Francos Quijorna, I., McKenzie, D., Davis, R., Lorenc, A., Chan, J. N. E., Ryan, S., Bugallo-Blanco, E., Yorke, R., Kamdar, S., Fish, M., … Irshad, S. (2021). Acute Immune Signatures and Their Legacies in Severe Acute Respiratory Syndrome Coronavirus-2 Infected Cancer Patients. *Cancer Cell*, *39*(2), 257-275.e6. https://doi.org/10.1016/j.ccell.2021.01.001

Gallian, P., Pastorino, B., Morel, P., Chiaroni, J., Ninove, L., & de Lamballerie, X. (2020). Lower prevalence of antibodies neutralizing SARS-CoV-2 in group O French blood donors. *Antiviral Research*, *181*(July 2020), 104880. https://doi.org/10.1016/j.antiviral.2020.104880

Vijenthira, A., Gong, I. Y., Fox, T. A., Booth, S., Cook, G., Fattizzo, B., Martín-Moro, F., Razanamahery, J., Riches, J. C., Zwicker, J., Patell, R., Vekemans, M. C., Scarfò, L., Chatzikonstantinou, T., Yildiz, H., Lattenist, R., Mantzaris, I., Wood, W. A., & Hicks, L. K. (2020). Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood*, *136*(25), 2881. https://doi.org/10.1182/BLOOD.2020008824

Tabll, A. A., Shahein, Y. E., Omran, M. M., Elnakib, M. M., Ragheb, A. A., & Amer, K. E. (2021). A review of monoclonal antibodies in COVID-19: Role in immunotherapy, vaccine development and viral detection. *Human Antibodies*, *29*(3), 179–191. https://doi.org/10.3233/HAB-200441

WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. (n.d.). Retrieved February 11, 2022, from https://covid19.who.int/

Dong, E., Du, H., & Gardner, L. (2020). An interactive web-based dashboard to track COVID-19 in real time. *The Lancet. Infectious Diseases*, *20*(5), 533. https://doi.org/10.1016/S1473-3099(20)30120-1

Hasan, M. K., Hosen, M. J., Anwar, S., & Nasrullah, M. (2020). COVID-19 and Bangladesh: Challenges and How to Address Them. *Frontiers in Public Health | Www.Frontiersin.Org*, *1*, 154. https://doi.org/10.3389/fpubh.2020.00154

Baum, A., Baum, A., Ajithdoss, D., Copin, R., Zhou, A., Lanza, K., Negron, N., Ni, M., Wei, Y., Mohammadi, K., Musser, B., Atwal, G. S., Oyejide, A., Goez-gazi, Y., Dutton, J., Clemmons, E., Staples, H. M., Bartley, C., Klaffke, B., … Kyratsous, C. A. (2020). *REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters*. *2402*(October), 1–12.

Graham, B. S. (2020). Rapid COVID-19 vaccine development. *Science*, *368*(6494), 945–946. https://doi.org/10.1126/SCIENCE.ABB8923

Corey, L., Corey, B. L., Mascola, J. R., Fauci, A. S., & Collins, F. S. (2020). *A strategic approach to COVID-19 vaccine R & D*. *5312*(May).

Gralinski, L. E., & Menachery, V. D. (2020). Return of the coronavirus: 2019-nCoV. *Viruses*, *12*(2). https://doi.org/10.3390/V12020135

Lee, W. S., Wheatley, A. K., Kent, S. J., & Dekosky, B. J. (2020). SARS-CoV-2 vaccines and therapies. *Nature Microbiology*, *5*(October), 1185–1191. https://doi.org/10.1038/s41564-020-00789-5

Hurt, A. C., & Wheatley, A. K. (2021). Neutralizing Antibody Therapeutics for COVID-19. *Viruses*, *13*(4). https://doi.org/10.3390/V13040628

Deb, P., Molla, M. M. A., & Saif-Ur-Rahman, K. M. (2021). An update to monoclonal antibody as therapeutic option against COVID-19. *Biosafety and Health*, *3*(2), 87–91. https://doi.org/10.1016/j.bsheal.2021.02.001

Wang, C., Li, W., Drabek, D., Okba, N. M. A., van Haperen, R., Osterhaus, A. D. M. E., van Kuppeveld, F. J. M., Haagmans, B. L., Grosveld, F., & Bosch, B. J. (2020). A human monoclonal antibody blocking SARS-CoV-2 infection. *Nature Communications 2020 11:1*, *11*(1), 1–6. https://doi.org/10.1038/s41467-020-16256-y

Ge, H., Wang, X., Yuan, X., Xiao, G., Wang, C., Deng, T., Yuan, Q., & Xiao, X. (2019). *The epidemiology and clinical information about COVID-19*. https://doi.org/10.1007/s10096-020-03874-z