

Review Article

A review on “monoclonal antibodies: effective treatment against COVID-19”

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ABSTRACT

Novel coronavirus disease caused by the SARS-CoV-19 virus enters the host cell through the S-spike protein by binding to ACE-2. In December 2019, an outbreak of coronavirus originated from Wuhan, China and by the end of 2020, it was recorded in almost every part of the world including Italy, Germany, Iran, Spain, and also United states. This led to a Pandemic which was declared by World Health Organization on 11th March 2020. SARS-CoV-19 causes mild to moderate illness which leads to acute respiratory syndrome, by causing infection in the nose, sinuses, or upper throat. It can also affect the upper or lower respiratory tract and has caused millions of cases and deaths. Many diagnostic tests have been authorized by the WHO including Direct and Indirect tests. Due to the increase in the number of covid 19 cases, many medications were introduced as per the demands like anti-malarial drugs, anti-viral drugs, antibiotics, anti-inflammatory drugs, steroids, biological agents, etc. The SARS-CoV-2 has a spike protein on its surface that aids in the virus's attachment to and entry into human cells. To attach to the protein of SARS-spike-CoV-2 and stop the virus from infecting human cells, many monoclonal antibodies like Casirivimab, imdevimab, Tocilizumab, Sarilumab, Itolizumab, Siltuximab have been created. As monoclonal antibodies prevent viruses from entering cells and continuing to proliferate, as well as lowering viral loads and lowering the frequency of hospital visits, they can be used as an alternative to conventional therapies. Hence monoclonal antibody treatment can be considered an effective alternative treatment for treating SARS-CoV-2.

Keywords: Coronavirus, Outbreak, Pandemic, Diagnostic tests, Medication, Monoclonal antibodies

INTRODUCTION

The novel Coronavirus is a disease caused by the SARS-CoV-19 virus. Coronavirus is an enveloped positive-stranded RNA virus with a crown-like structure over an electron.¹ The life cycle of coronavirus with the host cell is of five steps- attachment, penetration, biosynthesis, mutation, and release. Once the virus enters the host cell through S spike protein by binding to angiotensin-converting enzyme-2 [ACE-2] (attachment), the viruses enter the host cell via membrane fusion or endocytosis (penetration). After penetration, the viral contents of the virus enter the host cell, once viral contents are released the viral RNA enters the host nucleus where it gets replicated. Viral proteins are prepared by using viral

mRNA (biosynthesis). After biosynthesis, the new viral proteins are prepared (mutation) and released. SARS Coronavirus consists of four structural proteins; Spike (S), Membrane (M), Envelop (E), and Nucleocapsid (N). Spike (S) is made up of transmembrane trimetric glycoprotein protruding from the viral surface; there are two functional subunits which are the S1 subunit and the S2 subunit.^{2,3} The fusion of the viral and cellular membranes is promoted by the presence of (1) S1, which has an N Terminal Domain (NTD) and the Receptor-Binding Domain (RBD) in charge of binding to host-cell receptors, and (2) S2, which has a fusion peptide (FP), heptapeptide repeat sequences (HR1, HR2), a transmembrane domain (TM), and a cytoplasmic domain.⁴

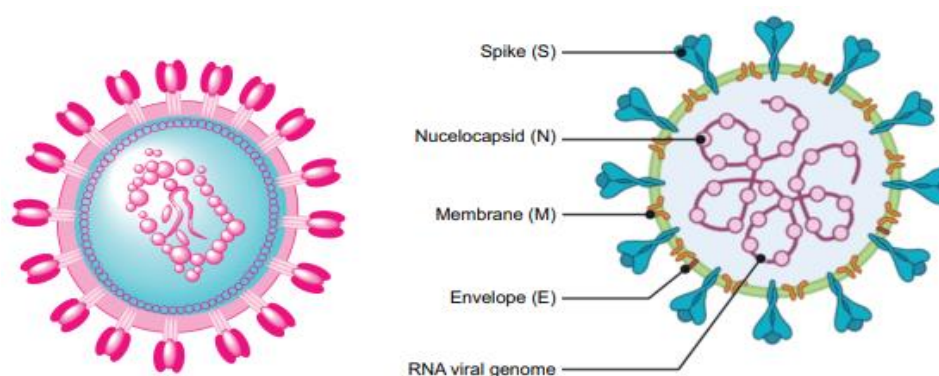


Figure 1: Severe acute respiratory syndrome coronavirus.⁵

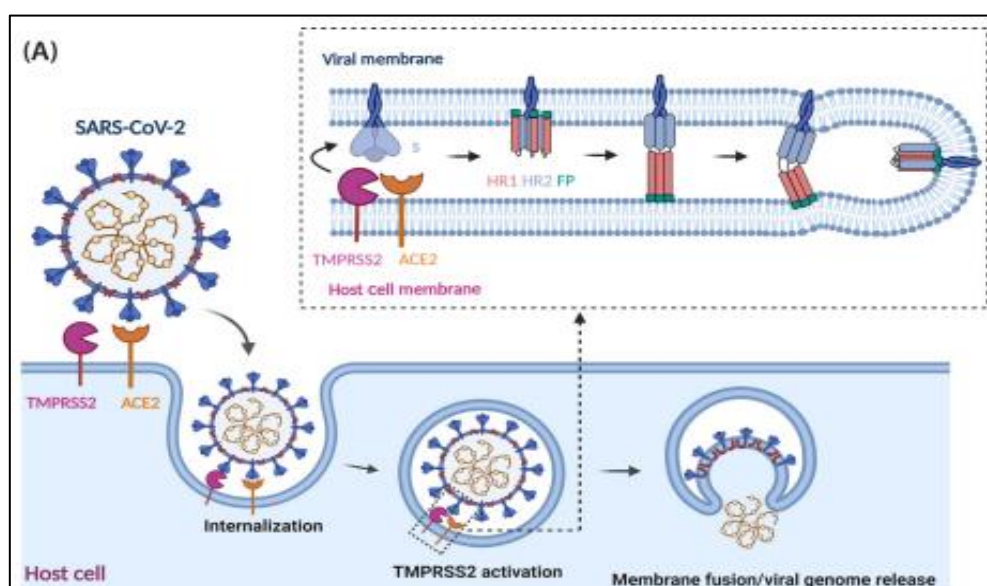


Figure 2: SARS-CoV-2 infection depends on the host cell receptor ACE2. Animated illustration of the spike protein attaching to the host cell's ACE2.⁷

The spike binds with angiotensin-converting enzyme-2 (ACE-2). After the binding of the virus to the host protein, the spike undergoes protease cleavage the distant S1 subunit helps the membrane-anchored S2 subunit to stabilize at the pre-fusion state. As ACE-2 is highly expressed in the apical site of lung epithelial cells in the alveolar space, heart, kidney, ileum, and bladder. Hence, these viruses can easily enter and destroy them. SARS-CoV-19 causes mild to moderate illness which leads to an acute respiratory syndrome, by causing infection in the nose, sinuses, or upper throat. It can affect the upper respiratory tract (nose, sinuses, and throat) or lower respiratory tract (windpipe and lungs). By 5th August 2022 coronavirus has led to around 580 million confirmed cases and around 6.4 million confirm deaths globally. From which around 244 million cases were found in Europe, around 171 million in the United States, around 59 million in South East Asia, around 73 million in Western Specific, around 22 million in East Mediterranean, and around 9 million in Africa are confirmed.⁶

The human protease TMPRSS2 activates the SARS-CoV-2 spike protein S after it binds to ACE2 via the receptor-binding domain (RBD). This action releases the fusion peptide's structural restraints, sets off a series of refolding events (such as the formation of the three-stranded coiled-coil), and promotes membrane fusion and viral genome release. The scale of the S protein, FP, HR1, HR2, ACE2, and TMPRSS2 is not shown.⁷

OUTBREAK

In 2002 and 2012 the two highly pathogenic coronaviruses with zoonotic origin severe acute respiratory syndrome coronavirus (SARS CoV-19) and Middle East respiratory syndrome coronavirus (MERS CoV) emerged in humans and caused fatal respiratory illness making emerging coronavirus a new public health concern in the twenty-first century. The first case of coronavirus was found in Wuhan, China in December 2019.⁸ It was reported by Dr. Li Wenliang, an Ophthalmologist in Wuhan China.⁹ Then between January

10 and January 15 of 2020, a family cluster was found in Shenzhen, a city in southern China that is 550 miles from Wuhan. This family of six had been to Wuhan, and between December 29 and January 4, 2020.⁹

Then it was further proliferated in various countries which directed toward the path of the pandemic. Initially, most of the cases were found in elderly people. Further, as the outbreak continued, the cases were observed among all age groups. However, it was studied and inferred that higher risk prevailed in people with various diseases like hypertension, diabetes mellitus, renal failure, cardiovascular disorders, and chronic liver diseases.¹ The outbreak started in China but due to the high virulence and transmittance of the virus, the infection proliferated all over the world. The transmission of covid through contaminated areas or fomites following the contact with nose, eyes, or mouth also takes place. The infection of the virus leads to various symptoms like high blood pressure, dry cough, runny nose, fatigue, hypoxia, and dyspnea. By the end of March 2020, a high frequency of cases of Covid-19 was recorded in Italy, Spain, France, Iran, Germany, and also United states. Further, the various variants of viruses like Alpha coronavirus, Beta coronavirus, Delta coronavirus, and Gama coronavirus were observed all over the world. The Genomic characterization has shown that bats and rodents are the probable gene source of AlphaCov and BetaCoV. However, on 11th March 2020, it was declared a Pandemic by World Health Organization.¹⁰

COVID-19 AS PANDEMIC

A pandemic is a disease outbreak that spreads across countries or continents, it is a situation where the disease growth is exponential. A pandemic of coronavirus disease caused by novel coronavirus acute respiratory syndrome coronavirus2 (SARS-CoV-2) has undertaken to cause high ailment and mortality across the globe. It has caused a global threat to health.^{11,12} The disease caused huge changes in the priorities of medical and surgical procedures. Covid-19 is a pandemic of unparalleled proportions in recent human history. Less than 18 months since the onset of the pandemic there were a total of two hundred million confirmed cases and four million deaths worldwide. There have also been effective efforts triggered toward effective and safe vaccines. The covid-19 pandemic has concerned the entire world. Spain and also Catalonia were among the most affected areas in the first month of the pandemic, which caused an unprecedented crisis in the social, economic, and also cultural fields. To terminate and halt the spread of covid-19 in Spain, a nationwide at-home lockdown was declared. Similar to other countries, the government of India has executed various restrictions on social life to slow down the spread of the coronavirus. This results in millions of people being isolated for a long duration. This uncommon circumstance has been linked to a rise in anxiety and sadness among the general public as well as

in more vulnerable communities, such as people who have had prior mental illnesses.¹³

A coronavirus pandemic is transitioning into its endemic phase. The disease outbreak is endemic when it is consistently present but limited to a particular region. Malaria, for example, is considered endemic in certain countries and regions. The objective of eradicating SARS-CoV-2 globally has been abandoned in favor of a transition to endemicity as many countries struggle with COVID-19's successive waves.¹⁴

DIAGNOSTIC TESTS USED FOR THE DETECTION OF COVID-19

Although 560 SARS-CoV-2 laboratory tests for the diagnosis of COVID-19 were available in the Foundation for Innovative New Diagnostics' database as of May 22, 2019, which is maintained by the WHO Collaborating Centre for Laboratory Strengthening and Diagnostic Technology Evaluation. These included 287 immunoassays and 273 molecular assays. There are 152 molecular assays and 211 immunoassays that are CE-marked for in-vitro diagnostic equipment, excluding those that are only intended for research usage. Currently, there are many detection kits used for SARS-CoV-19 which are approved by US Food and Drug Authorization's Emergency Use Authorization.¹⁵ They are as follows (1) Using nucleic acid amplification technique: Specific viral gene sections can be identified by real-time reverse transcriptase-polymerase chain reaction (RT-PCR): These are direct tests as they are designed to detect the virus and thereby reflect current infection. In this technique, the samples from a patient are taken, and then it is determined whether viral RNA is present or not. This is accomplished by the virus's genetic material, typically the Spike protein, N protein, or envelope, being captured and amplified. The RT-qPCR assay is utilized for the qualitative detection of the SARS-CoV-2 nucleic acid in viral testing. Swabs are typically collected from aspirates or washes of the lower respiratory tract, sputum, nasal passages, nasopharynx, or oropharynx. Positive assays show the presence of SARS-CoV-2 RNA and support the diagnosis when combined with the clinical presentation. Negative test findings must be interpreted in light of the clinical picture and epidemiological data as they do not rule out SARS-CoV-2 infection.¹ In contrast, the antibody test is an indirect test as they do not detect the virus; rather discovers established seroconversion to previous infection or ongoing infection.¹⁶ (2) Immunoglobulins Blood test: The immune system's production of antibodies in response to a viral infection (IgG and IgM testes): An antibody is a protein produced by the immune system in response to an antigen. Each antibody has sites that can bind only one specific type of antigen to remove it from the body. In this technique, the presence and concentration of IgG and IgM antibodies in blood, plasma, or serum are determined by antibody tests to check whether the body is fighting the pathogen.¹⁶ (3) Antigen testing by lateral flow assays: An antigen is a

substance that can stimulate the immune system and cause the development of antibodies to combat diseases, defending the body. These tests do not detect the virus but work by detecting the patient's immune antibody response to the virus. Several diagnostics businesses are working hard to develop these tests for SARS-CoV-2 since they can be made cheaply and completed rapidly. The capacity to determine whether patients are currently infected or have recovered from COVID-19, even if they were fully recovered and free of the virus months ago, is another

significant benefit of this kind of test. It is unable to differentiate between an ongoing infection and a former infection, though.¹⁶ (4) Direct test: The detection of SARS-CoV-2 involves the test for identification of the viral RNA by the Nucleic acid amplification test (NAAT). In areas with rapid community transmission, where there is a limited laboratory resource, the detection of RT-PCR of a single discriminatory target is considered sufficient.^{15,16}

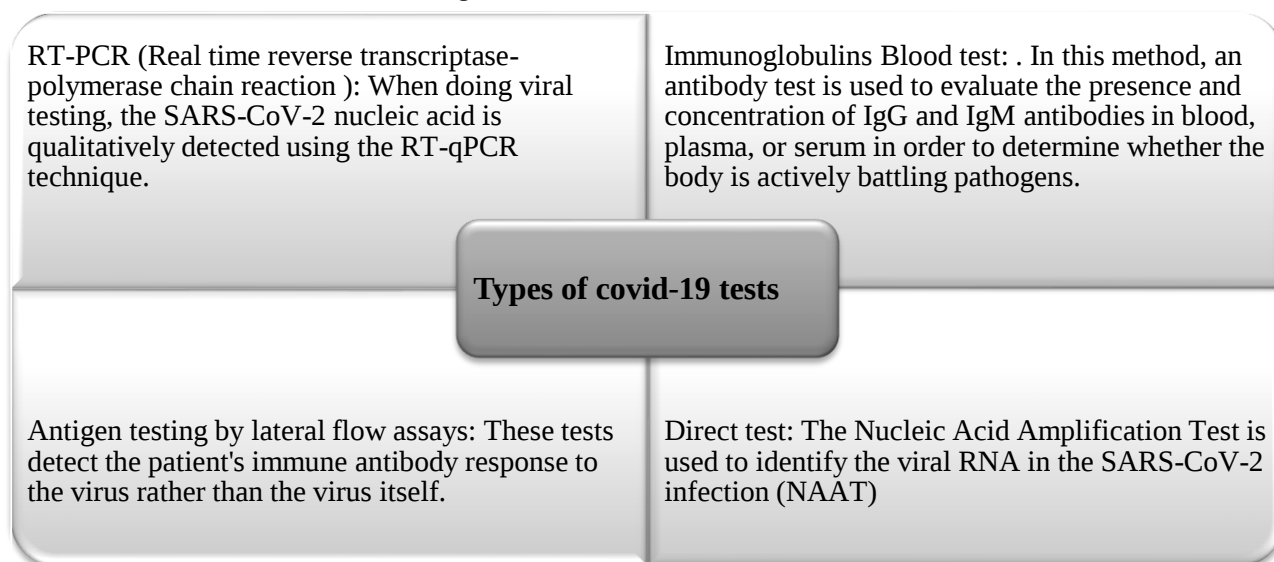


Figure 3: Overview of types of tests used to detect Covid-19.

Table 1: Overview of drugs and biological agents used to treat covid-19 and their mechanism.

S. no.	Name of drug	Mechanism
1.	Remdesivir	Remdesivir an antiviral drug acts by inhibiting RNA polymerase which metabolizes to an active C-adenosine nucleoside triphosphate analog which shows activity against coronavirus. The first case of covid was treated with Remdesivir in the United States. ¹⁷
2.	Ribavirin	Ribavirin a guanosine analog act against the mechanism of viruses, which include both direct and indirect mechanism but Ribavirin does not help in the reduction of negative viral conversion time. ¹⁷
3.	Favipiravir	Favipiravir is a prodrug of a purine nucleotide, an RNA polymerase inhibitor that inhibits viral replication and hence acts against SARS-CoV-2. Favipiravir shows a tolerable safety profile in terms of serious adverse effects as compared with other drugs, used for short-term treatment. ¹⁷
4.	Hydroxy-chloroquine	Hydroxychloroquine is a chloroquine analog. The in vitro studies showed the efficacy of hydroxychloroquine against SARS-CoV-19. Hydroxychloroquine showed anti-viral activity hence, it was able to reduce the replication of concentration-dependent replication of the virus. ¹⁷
5.	Azithromycin	Azithromycin is an antibiotic, which is a semisynthetic derivative of erythromycin. Azithromycin act by interrupting protein synthesis by binding to 50S ribosomal subunits of microorganisms. It was given to patients along with hydroxychloroquine and the patients were found to be clinically cured. ¹⁸
6.	Corticosteroid	Corticosteroids are majorly used to cure serious infections. However, studies show that SARS and MERS patients treated with corticosteroid show inconsistent results against SARS. ¹⁹
7.	Convalescent plasma	Convalescent plasma from recovered patients is given to patients on medication, when the convalescent plasma was given to SARS patients it was observed that the viral load was decreased one day after transfusion and the patients were cured. ²⁰

Building an indirect test for SARS-CoV-2

Serological testing: In contrast to NAAT Test, where as soon as the sequence is known, a diagnostic test can be built. The development of serological tests is quite different, with a significantly longer timeline to obtain a sturdy product that is suitable for routine deployment.¹⁵

Rapid serological test

For rapid detection of SARS-CoV-2 antibodies, POC immunoassays have also been developed. The primary advantage of this test is to obtain a diagnosis without sending samples to centralized laboratories. This enables the small laboratories to detect SARS-CoV-2 without any laboratory infrastructures by using only finger prick testing rather than blood draws.¹⁵

Clinical interpretation of the COVID-19 tests

The accuracy of the test and the estimated risk of COVID-19 before performing the test declare the interpretation of the test for SARS-CoV-2. A positive direct antigen test and specifically NAAT is more effective for current infection due to its high specificity but moderate sensitivity as compared to negative testing. The negative test needs to be interpreted with caution.¹⁵

MEDICATIONS

As the increase in the number of covid-19 cases, the demand for drugs to treat covid-19 increased all over the world and hence different medications like anti-malarial drugs, anti-viral drugs, antibiotics, anti-inflammatory drugs, steroids, biological agents, etc. were used to cure coronavirus.¹⁷

A few drugs that were tried for overcoming the infection are given in Table 1.

The COVID-19 pandemic has caused over 160 million illnesses and over 3 million fatalities worldwide as of May 2021. The disease's rapid spread has led to the rapid creation of numerous successful vaccinations, as well as intensive research for potential innovative treatments, including the reuse of current medications approved for other uses.²¹ Vaccines are the biologics that provide active adaptive immunity against several diseases and infections. Vaccines are introduced into the body via the mouth, injection, or nasal route to incite the immune system to battle foreign bodies. As many countries were in the run to pursue the new infectious disease caused by the coronavirus (COVID-19), vaccine generation and development have been accelerated to achieve immunity to the virus and stop transmission. The process of vaccine development is long and monotonous. The recent advances in COVID-19 vaccines have indicated that research innovations are cumulative on already existing knowledge. By mid-2021 more than 3 billion doses of COVID-19 vaccines were administered worldwide and 24% of the population had received at least the first dose of COVID-19 vaccines.¹⁴

COVID-19 VACCINES

Today COVID-19 vaccines have accelerated at an unbelievable speed. Currently, there are 184 vaccines in the predevelopment stage and 104 vaccines in the clinical stages of development. Recent data signs that there are 18 vaccines approved and in use around the world.²²

The covid-19 vaccines are categorized into four different types depending on platforms.

Table 2: Overview of vaccines depending upon their platforms.

S. no.	Name of vaccine	Mechanism
1.	Whole virus vaccines	This type of vaccine uses a weakened (attenuated) or inactivated form of severe acute respiratory syndrome coronavirus 2 to activate protective immunity. Live attenuated vaccines use a weakened form of the virus, which can grow and replicate but does not cause illness. Inactivated vaccines contain viruses whose genetic material has been demolished by heat, chemicals, or radiation, so they cannot infect cells and replicate but can still trigger an immune response. Existing live attenuated virus vaccines include measles, oral poliovirus, and yellow fever vaccines; and inactivated vaccines include inactivated polio and seasonal influenza vaccines. Currently, there are 16 inactivated and two live attenuated SARS-COV2 vaccines in development. ²²
2.	Protein based vaccines	Protein-based vaccines mainly contain two types that are subunit and virus-like particle vaccines. Protein subunit vaccines contain viral antigenic fragments developed by recombinant protein technique. These are easy to produce, safe, and well tolerated as compared to other viruses. There are currently five virus-like particle vaccines under development. The existing vaccine that uses this technology is the papillomavirus vaccine. ^{22,23}
3.	Viral vector vaccine	There are currently 16 non-replicating and two replicating viral vector SARS-CoV-2 vaccines in clinical development. Various viral vector SARS-CoV-2 vaccines have been approved by regulatory authorities around the world for emergency use. ^{22,23}
4.	Nucleic acid vaccines	This type of vaccine uses genetic directives, in the form of Deoxyribonucleic acid (DNA) or Ribonucleic acid (RNA) that prompts to immune response. There are currently at least 10 DNA and 18 RNA vaccines under development. ²²

Along with medicines and vaccines, few countries started using monoclonal antibodies to treat disease as US Food and Drug Administration (FDA) has approved mAbs for emergency use in early-stage, high-risk COVID-19 patients, and the latest findings are likely to justify the use of therapeutic antibodies in high-risk patients as standard of care.²⁴

An antibody is a protein that the immune system normally produces in response to infection. A monoclonal antibody is a laboratory-created molecule that mimics or enhances the body's natural immune system reaction to an intruder, such as cancer or infection.²⁵ Monoclonal antibodies are a versatile class of pharmaceuticals that have been employed successfully by the pharmaceutical industry to deliver an effective therapeutic intervention with a highly precise treatment against a specific disease. In recent years, many monoclonal antibodies against viruses have been produced, and some are currently in clinical trials.²⁶ The use of monoclonal antibodies in the prevention of infectious illnesses is a novel approach. Monoclonal antibodies are antibodies that are designed to

bind to a specific substance in the body. This binding is extremely adaptable, as it can imitate, inhibit, or create modifications to exact pathways, resulting in a highly successful therapeutic intervention with a very specific treatment for disorders.²⁷ Even though the US Food and Drug Administration has approved more than 75 monoclonal antibodies, only three are utilized to treat or prevent infectious diseases: respiratory syncytial virus, anthrax, and *Clostridioides difficile*. Two monoclonal antibody products have been demonstrated to be beneficial in lowering Ebola virus disease mortality, particularly when given early in the infection.²⁸

MONOCLONAL ANTIBODIES IN COVID-19

The COVID-19 pandemic has caused over 160 million illnesses and over 3 million fatalities worldwide as of May 2021. The disease's rapid spread has led to the rapid creation of numerous successful vaccinations, as well as intensive research for potential innovative treatments, including the reuse of current medications approved for other uses.²¹

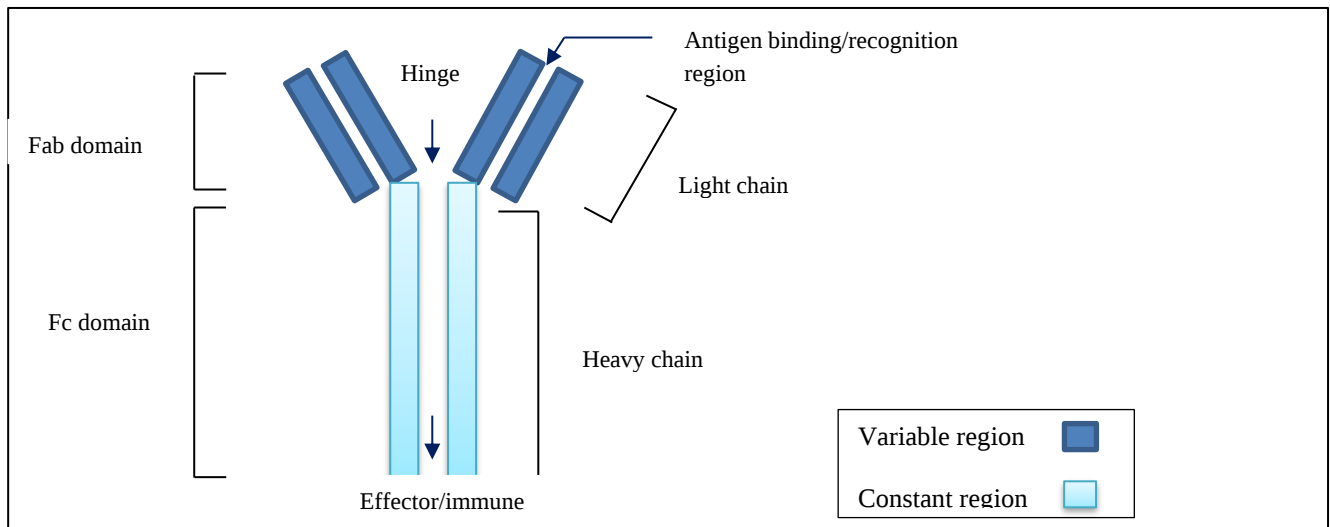


Figure 4: Structure of monoclonal antibody and its components.

Structure of monoclonal antibodies

These are Y-shaped antibodies with a molecular weight of approximately 150 kDa, monoclonal antibodies are composed of four peptide chains of which two are identical light(L) chains that weigh about 25 kDa each, and two are heavy (H) chains that weigh about 50 kDa each. The covalent bond present between heavy and light chains helps in stability between heavy and light chains which are present next to each other.²⁹

Classification of monoclonal antibodies based on their mode of action:

Based on their respective goals, the SARS-CoV-2-specific monoclonal antibodies can be divided into three groups: (1) Antibodies prevent virus attachment and entry

by either targeting the virus structure or host receptors. (2) Antibodies that prevent virus replication and transcription. (3) Antibodies that obstruct different immune response stages.³⁰

The action of monoclonal antibodies

A spike protein on the surface of the severe acute respiratory syndrome coronavirus2 (SARS-CoV-2) helps the virus bind to and enter human cells. Several monoclonal antibodies have been produced to bind to SARS-spike CoV-2's protein and prevent the virus from infecting human cells. An intravenous (IV) infusion of a monoclonal antibody may be given to COVID-19 patients in an emergency unit, an infusion center, or another outpatient environment (such as the patient's home or nursing home).²⁵ Numerous research organizations have identified monoclonal antibodies against SARS-CoV-2,

the causal agent of COVID-19 since its discovery (most often from the B cells of patients who have recently recovered from SARS-CoV-2 and in some cases from individuals who were infected with the severe acute respiratory syndrome coronavirus [SARS-CoV] in 2003). Monoclonal antibodies against SARS-CoV-2 have the potential to be utilized for both infection prevention and treatment. Several monoclonal antibodies against SARS-CoV-2 are expected to enter clinical trials in the summer of 2020. Patients with SARS-CoV-2 infection and varying degrees of illness will be treated in therapeutic trials to prevent disease development.²⁸

For the treatment of COVID-19, three neutralizing mAb regimens have been provided emergency use authorization. One is Casirivimab and Imdevimab which bind to different epitopes on the RBD, with KD values of 46 and 47 pM, respectively. Imdevimab attaches to the S protein RBD on the front or bottom left side, whereas Casirivimab binds to the spike-like loop on the top (overlapping with the ACE2-binding site). The other is Bamlanivimab which binds to an epitope on the RBD in both open and closed conformation, with a dissociation constant of 71 pM, encompassing 7 of the approximately 25 side chains that make contact with ACE2. And the third one is Bamlanivimab and Etesevimab which binds to different but overlapping epitopes in the RBD of SARS-CoV-2's protein. Etesevimab binds to the up/active conformation of the RBD with a dissociation constant of 6.45 nM; it has the LALA mutation in the Fc region, which results in null effector action. Most advanced research into the therapeutic use of neutralizing mAbs is confined to a small number of medicines under clinical development, some of which have already been approved for emergency use based on phase I/II and phase II evidence.²⁴

The US Food and Drug Administration (FDA) has previously approved some mAbs for emergency use in early-stage, high-risk COVID-19 patients. Six mAbs have been created and granted an Emergency Use Authorization (EUA) from regulatory agencies in the United States and South Korea in only 16 months, and several more are being examined in phase 3 clinical studies or are now pursuing a EUA.²¹

Monoclonal antibodies also reduce IgI and IgM as the high level of IgI and IgM indicates high severity in patients.³¹

Monoclonal antibodies used to treat SARS-CoV-19 are classified into two types Non-SARS-CoV-2 specific mAbs and SARS-CoV-2 specific mAbs. Non-SARS-CoV-2 mAbs are the mAbs that are now being used in hospitals to treat COVID-19 and target the virus's immune responses, which can impact the severity of the disease. Tocilizumab, Sarilumab, and Siltuximab were chosen as mAbs to treat COVID-19 patients with high IL-6 levels and other non-SARS-CoV-2 specific mAbs whose therapeutic targets are not IL-6/IL-6R are also in clinical trials, such as Bevacizumab, Clazakizumab, Eculizumab, Emapalumab, Gimsilumab, Itolizumab, Mavrilumab, Meplazumab, Nivolumab, Pembrolizumab, and others. SARS CoV-2 Specific mAbs are SARS-CoV-2 mAbs Isolated from Patients, Cross-Neutralizing mAbs for SARS-CoV and SARS-CoV-2 and mAbs that have been approved for emergency use.³⁰

Some of the Monoclonal antibodies used in covid-19 are given in Table 3.

Table 3: An overview of some monoclonal antibodies with their target site, route of administration, and outcome.³²

Drug Name	Route of Administration	Target site	Outcome
1. Tocilizumab	1. subcutaneous 2. Intravenous	Interleukin receptor	CRP dropped dramatically, but IL6 spikes at first and subsequently reduces. After one day CRP falls dramatically and fever returns to normal
2. Sarilumab	1. Subcutaneous 2. Intravenous	Interleukin receptor	Within 5 days, the CRP level decreases to a level that was generally below the upper normal range. CRP returned to baseline in 6 days versus 12 days in the control group.
3. Itolizumab	1. Intravenous	CD6 receptor	After one dose within 48 hours, the amount of circulating IL6 decreases.
4. Siltuximab	1. Subcutaneous 2. Intravenous	Interleukin-6	In comparison to Tocilizumab, IL6 normalization takes longer. CRP reduces in around 76% of patients and clinical improvement in around 33% of patients
5. Infliximab	1. Intravenous	TNF-alpha	TNF alpha normalizes, and IL6 and IL8 levels reduce.
6. Lenzilumab	1. Intravenous	Granulocyte-monocyte colony-stimulating factor	Clinical improvement in treated patients in 5 days compared to 12 days in non-treated controls; reduction in inflammatory myeloid cells in 2 days; improvement in CRP and inflammatory cytokines in 2 days.

MECHANISM OF MONOCLONAL ANTIBODIES FOR COVID-19

Granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL6), both generated by activated CD4⁺ T cells, are important components of the immunopathogenesis of SARS-CoV-2. A cascade of pro-inflammatory cytokines and chemokines, including GM-CSF and IL-6, are produced after SARS-CoV-2 attaches to alveolar epithelial cells, drawing in more monocytes and macrophages and creating a cytokine storm. More severe cases of inflammation were shown to have higher levels of IL-2, IL-6, IL-7, IL-10, IL-17, G-CSF, GM-CSF, IP-10, MCP1, MIP1A, TNF, IFN-, VEGF, CCL2, and other cytokines and chemokines. Patients with COVID-19 in various studies.³³

The RBD, which interacts with the target receptor angiotensin-converting enzyme 2, is the target of all mAbs approved or under development (ACE2). The majority of the mAbs recognize distinct epitopes that fully or partially overlap with the RBD's receptor-binding motif (RBM). Via targeting epitopes that coincide with the RBM, the mAbs prevent SARS-CoV-2 entrance by blocking ACE2 interaction. In some situations, mAbs binding to RBM might prematurely initiate fusogenic S conformational changes, which can result in the protein's deactivation, as the SARS-CoV-specific neutralizing mAb S230 has previously demonstrated.²¹

The mechanism of a few monoclonal antibodies is as follows:

ITOLIZUMAB

Itolizumab, an anti-CD6 monoclonal antibody (MAb), binds to human CD6's domain 1. It is an immunoglobulin G1 (IgG1) isotype antibody.³⁰

One of the postulated mechanisms for rapid epidemic development is a cytokine storm, in which IL-6 appears to be a significant mediator, and the severity of the disease is correlated with basal IL-6 levels. One dosage of itolizumab decreases baseline blood levels of IL-6 in severely and seriously sick COVID-19 patients and stabilizes baseline low levels in moderately and seriously ill older COVID-19 patients. Due to its generally benign profile, itolizumab could be an appealing option to lessen the negative effects of the cytokine storm in COVID-19 patients.³⁴

LY-CoV555

LY-CoV555 (also known as LY3819253), a powerful Antispike neutralizing monoclonal antibody that binds to the receptor-binding region of SARS-CoV-2 with great affinity, was generated from convalescent plasma recovered from a Covid-19 patient. A single IV dose of LY-CoV555 changes the baseline in the SARS-CoV-2 viral load at day 11 (± 4 days) after positive results on

testing and reduces the emergency department visits in hospitals and deaths.³⁵

SOTROVIMAB

COVID-19 patients who received sotrovimab had a lower probability of being admitted to the hospital or dying. Although its precise mode of action is uncertain, it seems to stop membrane fusion once the virus binds to the angiotensin-converting enzyme-2 receptor, blocking virus entry into the cell. It is only prescribed in the early stages of mild to moderate COVID-19 disease and is only given to patients over 12 years old who weigh at least 40 kg.³⁶

TOCILIZUMAB

TCZ is a humanized IgG1 mAb that blocks the signal provided by both soluble and membrane-bound IL-6 receptors.³⁰ TCZ reduces CRP drastically and IL6 first increases and then decreases subsequently.³²

SARILUMAB

Sarilumab is an IgG1 monoclonal antibody that suppresses IL-6-mediated signaling by targeting both soluble and membrane-bound IL-6 receptors (IL-6R).³⁰

SILTUXIMAB

Siltuximab is a chimeric human-murine monoclonal antibody that blocks the binding of human IL-6 to both soluble and membrane IL-6 receptors (IL-6R). Siltuximab is currently being studied in three clinical trials, with one completed.³⁰

REGN-CoV2

REGN-CoV2 is a combination of Casirivimab and imdevimab. REGN-CoV2 is given to the patient within 7 days of symptoms and 72 hours of a positive result. The reduction in the percentage of patients who had at least one Covid-19-related medically attended visit through day 29 is observed, as well as the viral load from day 1 to day 7 is decreased.³⁷

DATA OF CLINICAL TRIALS OF MONOCLONAL ANTIBODIES

The first monoclonal antibody used for the treatment of covid-19 was approved by the UK's Drug Regulator which was Ronapreve, a combination of casirivimab and imdevimab, for the treatment and prevention of acute covid-19 in adults. The treatment binds to two different sites on the SARS-CoV-2 spike protein, preventing it from infecting cells. The Medicines and Healthcare Products Regulatory Agency (MHRA) approved it after reviewing the available evidence. The government and NHS have yet to specify how the treatment would be implemented.³⁸ Bamlanivimab and casirivimab plus imdevimab's initial EUAs were based on modest data

from phase 2 clinical trials that suggested that, if administered early in the course of the disease, mAb therapy might reduce hospitalization, ED visits, or other medical visits in patients with mild to moderate COVID-19.³⁹ After a phase III trial found that casirivimab and imdevimab reduced hospital admission or death by 70% in high-risk non-admitted patients, Japan became the first country to license the medication in July. The medication can be given by injection or infusion and has been shown to shorten symptom duration by four days. The casirivimab and imdevimab as a combination was also evaluated as part of the UK's Recovery trial, which found that it lowered the risk of death in people admitted to hospitals with severe covid-19 who had not developed a natural antibody response to the virus. Since they aim to disrupt the SARS-CoV-2 spike protein's receptor-binding domain, they prevent the virus from attaching to and entering human cells. Ronapreve has been granted a license in the United States, India, Switzerland, and Canada, as well as by the European Union.³⁸

The other two humanized immunoglobulin G1 (IgG1) kappa-neutralizing antibodies, bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016), work against the receptor-binding domain of SARS-CoV-2 S glycoprotein to stop the virus from attaching to and entering human cells.⁴⁰

Pharmaceutical and academic laboratories are working on developing therapeutic antibodies against COVID-19 as quickly as possible, using practically every conceivable platform. Antibodies that target the virus itself or the hyperinflammatory consequences associated with illness progression are the focus of the research.⁷

RESULTS OF CLINICAL TRIALS

594 covid 19 patients with high risk were given mAbs Casirivimab/ Imdevimab and Bamlanivimab and they were compared with 5536 covid 19 patients who were not administered with mAbs as result was found that patients who were administered mAb had fewer emergency hospital visits than the patients who were not administered with mAbs.⁴¹

Also, when 577 covid patients were treated with Bamlanivimab Monotherapy no significant difference was observed when they were compared with patients treated with Placebo, but when Etesevimab was combined with Bamlanivimab and given to patients a significant decrease in SARS-CoV-2 viral load was observed.⁴²

CONCLUSION

As monoclonal antibodies prevent viruses from entering cells and continuing to proliferate, as well as lowering viral loads and lowering the frequency of hospital visits, they can be used as an alternative to conventional therapies. Hence monoclonal antibody treatment can be

considered an effective alternative treatment for treating SARS-CoV-2.

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