# ***Review Article***

## *MONOCLONAL ANTIBODIES: USAGE IN THE TREATMENT OF COVID-19 INFECTION*


***Abstract***

*Since the COVID-19 emergence in December 2019, significant efforts are being made in the hunt for appropriate medical interventions. This forces scientists to produce or discover traditional curative medications, preventive vaccinations, or passive immunological techniques as quickly as possible. Therapeutic monoclonal antibodies (mAbs) have drawn a lot of interest throughout this context. COVID-19 approved Emergency Use Authorization (EUA) medications for the outpatient treatment of mild to moderate symptoms for many monoclonal antibodies (mAbs) aimed against the Receptor binding domain of the S protein of the coronavirus 2 (SARS-CoV-2). We investigated the feasibility of monoclonal antibodies for the diagnosis and treatment of COVID-19 infection in this review. Human monoclonal antibodies targeted SARS-CoV-2 viral protein domains, especially the spike protein area, and hyper-immune plasma from recovered COVID-19 patients are also included in this review. In summary, monoclonal antibodies are the promising remedies that could be used to regulate the SARS-CoV-2 (COVID-19 infection causal agent) through immunotherapy, vaccine development, and viral screening.*



***Key words***-

*Monoclonal antibodies, SARS-CoV-2, vaccine development, immunotherapy, COVID-19.*


### *1. Introduction*

*COVID-19 is a pandemic disease caused by SARS-COV-2 i.e., severe acute respiratory syndrome-2 or coronavirus. The first COVID case is reported at 'Wuhan' which is present in China, in December 2019. Coronavirus has since spread over the globe [1]. More than 279 million illnesses and over 5.3 million fatalities have resulted from the COVID-19 pandemic and several treatments are present based on the stages of infection. SARS-CoV-2 is a positive-stranded RNA virus with an envelope and it is a member of the Beta coronavirus family. Coronaviruses have the most complex and massive genome of any RNA virus. Both structural and non-structural proteins are encoded by the viral genome. The SARS-CoV-2 virus's spike (S) protein projects through the viral envelope. One of the most important structures that permits the SARS-CoV-2 virus to enter host cells is the S protein, which is a homotrimeric glycoprotein [2].*

*Based on our present understanding of COVID-19 pathophysiology, antiviral medicines such as Remdesivir and neutralising antibodies will be most effective in the early stages of the disease i.e., 9 days following the commencement of symptoms at the most and this results in reduced mortality rate. In the later phases, it is the inflammatory response that causes damage, thus medications that reduce inflammation, such as dexamethasone and tocilizumab, are employed [3]. When it comes to immunomodulatory medicines like steroids and tocilizumab, the timing of treatment is crucial. The global spread of COVID-19 necessitates an immediate search for coronavirus illness prevention and therapy [4,5].*

*Mainly people's attention was concentrated on the development of vaccines, novel antiviral medicines, and plasma infusions during the time, but monoclonal antibodies received less attention, despite the fact that neutralising antibodies are essential components of protective immunity against most viral infections. Neutralizing monoclonal antibodies are used to make vaccines and have a wide range of therapeutic and preventative benefits [6]. Many research organisations have concentrated on monoclonal antibodies since the causal agent of COVID-19 was discovered as SARS-CoV-2.*

## *2. Materials and methods*

### *Monoclonal antibodies*

*Definition-*

*Monoclonal antibodies (mAb) are mostly made from convalescent patients' B-cell lymphocytes or humanised mice. These can serve as a means of passive immunotherapy. Monoclonal antibody therapy also called as monoclonal antibody infusion treatment is used to treat COVID-19.*

*The main aim of this therapy is to prevent or reduce the hospitalizations, reduce the viral loads, reduce the symptom severity. This is an effective therapy but not a replacement for vaccination. So, the people have to get the vaccination to break the virus chain of transmission [7].*

### *2.1 Anti-SARS-CoV-2 therapeutic monoclonal antibodies*

*The spike (S), envelope (E), membrane (M), and nucleocapsid (N) are the 4 major structural proteins, and also non-structural, auxiliary proteins, are all encoded by the SARS-CoV-2 genome. S1 and S2 are two main components of the spike protein that regulates the host cell adhesion and penetration. S1 binds to angiotensin-converting enzyme 2 (ACE2) on the host cell via its receptor-binding domain (RBD), which causes S2 to undergo a shape change which ultimately leads to virus-host cell membrane adhesion and viral penetration. [8]*

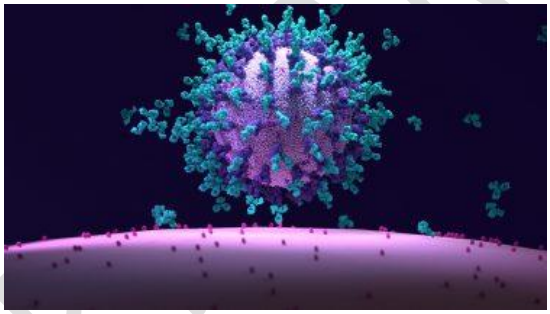

*Fig-1 mAbs bound to SARS-CoV-2 spike protein and neutralises the virus*

*Anti-SARS-CoV-2 monoclonal antibodies (mAbs) that aim the spike protein have been found to help in the management of SARS-CoV-2 infection clinically. After a probable SARS-CoV-2 contact in a residential environment, some anti-SARS-CoV-2 mAbs have been proven to be successful for post-exposure prophylaxis (PEP) [9] and also in providing specialist care and home care facilities during the SARS-CoV-2 breakouts [10]. When administered before as pre-exposure prophylaxis, several anti-SARS-CoV-2 mAbs were reported to significantly diminish the chances of infection. [11]*

*Many pharma companies, including Celltrion, AstraZeneca, and Regeneron, are in favour for the development of monoclonal antibodies for the diagnosis and treatment of COVID-19. The FDA granted monoclonal antibodies from Regeneron and Eli Lilly during the Delta variant strain of virus, which got a lot of attention. Despite the fact that even more than 70 monoclonal antibodies are in various phases of development, the Food and Drug Administration (FDA) has granted three anti-SARS-CoV-2 monoclonal antibodies Emergency Use Authorization (EUA) for the therapies of mild to moderate COVID-19 infection in non-hospitalized individuals with SARS-CoV-2 infection which is confirmed by research laboratories. These monoclonal antibodies are usually prescribed for the patients who are at a high risk of developing a condition that will require hospitalisation. Bamlanivimab (like a monotherapy), a combination of Bamlanivimab and Etesevimab or Casirivimab and Imdevimab as a combination therapy, and Sotrovimab are the monoclonal antibodies that have*

*received EUA [12]. Some SARS-CoV-2 variants with specific mutations have significantly lowered susceptibility to a majority of the approved anti-SARS-CoV-2 mAbs in preclinical development [13]. There are two monoclonal antibodies that have been proven to be beneficial in lowering Ebola virus disease deaths, especially when treated early in the infection [14], among them one is three-monoclonal antibody mixture, whereas the other one is a single monoclonal antibody.*

***2.1.1 Bamlanivimab –***

*On November 9, 2020, the FDA granted Bamlanivimab as an Emergency Use Authorization (EUA) for the management of mild to moderate COVID-19 in adults i.e; elderly people and certain paediatric patients. It's the first monoclonal antibody to be officially granted by the FDA for the diagnosis of COVID-19. It should be given in the form of single infusion of 700mg of Bamlanivimab. It is specifically developed to block SARS-CoV-2 spike protein from attaching to and entering host cells via the ACE-2 (Angiotensin converting enzyme-2) receptor. Bamlanivimab monotherapy does not show any significant advantages in terms of viral load reduction. As a result, the FDA terminated the EUA for Bamlanivimab monotherapy on April 16, 2021, stating a growth in the number of SARS-CoV-2 variants resistant to this therapy [15].*

***2.1.2 Casirivimab and Imdevimab combination –***

*The R10933-10987-COV-2067 research of Phase III trial, includes individuals with mild to moderate COVID-19 infection, provided scientific information for the usage of Casirivimab and Imdevimab [16]. On November 21, 2020, the combo of Casirivimab and Imdevimab monoclonal antibodies gained emergency use authorisation and it gets distributed together as a cocktail under the brand name of REGEN-CoV. These antibodies are recombinant monoclonal antibodies that bind to non - overlapped epitopes of the SARS-CoV-2 spike protein RBD [15]. This combination combines 600 mg of Casirivimab with 600 mg of Imdevimab, which is given as an Intravenous (iv) infusion or injections under the skin. If an IV infusion is not accessible or would create a postponement in the treatment, four subcutaneous injections can be used instead (2.5 ml per injection) [17]. The distribution of Casirivimab with Imdevimab in the US has been suspended due to diminished susceptibility of Omicron strain to Casirivimab and Imdevimab, individuals with Omicron virus infection are unlikely to benefit from this treatment plan.[18]*

*The clinical studies are evaluating the efficacy of REIGN-COV2 in minimizing the symptoms of COVID-19 infection in teenagers (over than 12yrs old), those who are residential connections of SARSCoV-2 positive persons, as well as in lowering SARS-CoV-2 VL in children's (of less than 18 years) [19,20]. Next it compares the efficacy of REIGN-COV2 against placebo in terms of both survival and the need for mechanical ventilation in less-flow oxygen patients in the hospital [20]. People who undergone treatment with the cocktail were not hospitalised as a reason of COVID-19, after the observation of 41 days [21].*

*Clinical trials demonstrate that Regeneron's combinational monoclonal antibody minimizes COVID-19-related patients' hospitalisation and mortality by roughly 70% in high-risk individuals and when these monoclonal antibodies are given to the persons who came in contact with the infected persons, it reduces the chance of acquiring a symptomatic illness by 80%. People those who had no antibodies to SARS-CoV-2 at beginning of the study showed the greatest clinical benefit. [22]*

***2.1.3 Bamlanivimab and Etesevimab combination –***

*The combination of Bamlanivimab and Etesevimab is used to target various epitopes of the SARS-CoV-2 spike glycoprotein. On February 9, 2021, the FDA granted this combination an EUA for the management of mild to moderate COVID-19 in children and adolescents who are not hospitalised. Bamlanivimab and Etesevimab are kappa neutralization antibodies that work against the SARS-CoV-2 S glycoprotein's receptor binding region to block virus adherence and its entry into human cells [23].*

*In areas where the cumulative frequency of SARS-CoV-2 mutations is low, a combination dose of Bamlanivimab of 700mg and Etesevimab of 1400mg was given as an Iv drip. COVID-19 vaccination must not be given to these people for up to 3 months following the infusion, according to official recommendations [15]. A phase I randomised, placebo-controlled and double-blind clinical trial was recently conducted to assess the safety, acceptability, pharmacokinetics (ADME parameters) and pharmacodynamics (how drug does to the body) of COVID-19 in 24 hospitalised patients. The obtained results were shown as the reduction of risk by 70% in COVID-19 related hospitalizations who received Bamlanivimab and Etesevimab versus placebo [24]. The distribution of Bamlanivimab with Etesevimab in the US has been suspended due to diminished susceptibility of Omicron strain to Bamlanivimab and Etesevimab in both the Gamma and Beta forms, individuals with Omicron virus infection are unlikely to benefit from this treatment plan [25]. The product's marketing has been re-established all across United States due to the total frequency of the Gamma and Beta types is less than 5%.*

***Table 1 – Information on currently authorised (EUA) monoclonal antibodies administration and its side effects.***

| ***Authorised Monoclonal antibodies (EUA)*** | ***Administration*** | ***Side effects*** |
|---|---|---|
| *Bamlanivimab* | *Adults: 700 mg of Bamlanivimab should be given as soon as feasible following a positive SARS CoV 2 analysis results, but no later than 10 days of the first appearance of indications.* | *Nausea, Diarrhoea, Dizziness, Headache, Itching, Vomiting.* |
| *Bamlanivimab and Etesevimab combination* | *Adults: After a confirmed SARS CoV 2 analysis results, 700 mg of Bamlanivimab and 1400 mg of Etesevimab should be administered as quickly as possible.* | *Nausea, Diarrhoea Dizziness, Headache, Itching, Vomiting.* |
| *Casirivimab and Imdevimab combination* | *1200 mg of Casirivimab and 1200 mg of Imdevimab in a single continuous infusion is the standard dose (intravenous infusion). Casirivimab and Imdevimab must be given together at all times.* | *Fever, Chills, itchy rash skin, abdominal pain, redness of face.* |
| *Sotrovimab* | *In elders and children's (aged 12 and over and weighed minimum 40 kg) should take 500 mg each day. Before use, Sotrovimab should be diluted. Sotrovimab should indeed be given as a 30-minute IV infusion. Patients must be closely observed for approximately 60 minutes after* | *Headache, Pneumonia, Dyspnoea, Nausea, Diarrhoea.* |

| | | |
|---|---|---|
| | *the infusion.* | |

*The US FDA [26] and the European Medicines Agency in Europe [27,28] proposed some recommendations for the use of combinational monoclonal antibodies such as Casirivimab and Imdevimab (REGN-COV2) and Bamlanivimab and Etesevimab and in outpatients who may not require oxygen therapy and who have been at elevated risk for serious COVID-19 progression.*

***2.1.4 Sotrovimab –***

*Sotrovimab is one of the monoclonal antibodies which is currently available for the COVID-19 therapy. This mAb was first discovered in a victim of SARS-CoV infection in 2003. It interacts to an epitope in the spike protein's RBD that is shared by SARS-CoV and SARS-CoV-2[29]. It obtained emergency use authorization (EUA) from the FDA on May 26, 2021. It is given as a single intravenous (iv) infusion of 500 mg of Sotrovimab that last for 30 minutes, where Sotrovimab for intramuscular injection is currently under the phase III clinical trial. Sotrovimab is a drug which is used in the treatment of mild to moderate COVID-19 virus infection in those patients who are at a significant risk of developing the disease and its use is currently limited to the outpatients. Sotrovimab 500 mg IV in 291 subjects or placebo in 292 subjects were given to a total of 583 subjects. The primary outcome was the percentage of people who were hospitalised for 2 days or died from any reason by Day 29. Endpoint events occurred in 3 of 291 participants (1%) in the Sotrovimab arm and 21 of 292 participants (7%) in the placebo arm, tends to result in a 6 percent absolute decline in hospitalizations or death relating with Sotrovimab and an 85 percent relative decrease in hospitalizations or fatality associated with placebo [17,30].*

***2.2 Monoclonal antibodies infusion criteria –***

*A list of particular things that keep the individuals at more risk for clinical advancement is included in the FDA EUAs for anti-SARS-CoV-2 mAbs. The FDA updated the EUAs on May 14, 2021, to widen these conditions [31,32]. The FDA allow these authorised drugs to be used in individuals diagnosed for a reason apart from COVID-19, since they have mild to moderate COVID-19 and having a chance of risk of developing severe disease. [33,34]*

- *The use of monoclonal antibodies for an individual is dependent on an individual risk and benefit assessment.*
- *These monoclonal antibodies are being used to treat mild to moderate corona virus disease in patients who have been hospitalised for a purpose besides COVID-19 or who meet the EUA requirements for outpatient therapy.*
- *Anti-SARS-CoV-2 monoclonal antibodies are not yet being used to treat severe COVID-19 in those patients who are hospitalised.*
- *These are not recommended for COVID-19 patients who require oxygen therapy (having breathing problem).*
- *Treatment with monoclonal antibodies should begin as early as possible after a positive outcome on a SARS-CoV-2 antigen test or nucleic acid amplification test (NAAT) and also within 10 days of the onset of symptoms.*

- *Timing is critical for monoclonal antibodies treatment. If they are given at early stage, the more effective they are at treating or preventing COVID-19. After ten days of onset of symptoms, monoclonal antibodies must not be given.*
- *During the IV infusion or SQ injections, after infusion or injections, the patient should be examined for at least 60 mins.*
- *For up to 3 months that after infusion, these people must not get COVID-19 vaccination, according to current recommendations. Current CDC guidelines recommends to wait 90 days after obtaining the first dose of vaccine before receiving the second dosage because monoclonal antibody therapy may interfere with vaccine-induced immune responses.*
- *Patients who might have a considerable interaction with those who have COVID 19 disease and aren't fully vaccinated, and who are vaccinated but have a poor immune system response to vaccination due to an immunocompromising condition or medication usage are eligible for the therapy.[35]*

***2.3 High-risk conditions –***

*For all patients older than 12 years in each Emergency Use Authorization, high risk is characterized as meeting at least one of these criteria -*

*• Getting older (for instance, if you're 65yrs or older).*

*• Obese or becoming overweight (people with only a BMI i.e.; Body mass index larger than or equal to 25 kg/m², as determined by CDC standard criteria and children of aged between 12 and 17 with a BMI roughly equivalent to the 85th percentile of their demographic characteristics like age, gender).*

*• Pregnant women.*

*• Renal disease is a condition that damages the kidneys on a long-term basis.*

*• Increase in glucose levels i.e., Diabetes mellitus.*

*• The term "immunosuppressive condition" refers to a condition or treatment that suppresses the immune system.*

*• High blood pressure or cardiac disease (includes congenital heart abnormalities).*

*• Lung disorders that are chronic (example Chronic obstructive pulmonary disease, severe asthmatic problem, interstitial lungs disorder, cystic fibrosis (CF), and pulmonary hypertension - type of high blood pressure that affects the arteries in the lungs).*

*• Haemoglobin S disease (type of an anaemia).*

*• Nervous disorders (like cerebral palsy) or any other medically challenging situations (Hereditary disorders, severe congenital abnormalities).*

*• Dependence on medicinal technology (like tracheostomy, gastrostomy, or positive pressure ventilation).*

*Infants under the age of 12 months. [36 – 39]*

*It's worth noting that having numerous high-risk conditions enhances the chances of acquiring severe COVID-19 infection.*

***2.4 Mechanism of action of Monoclonal antibodies (mAbs) –***

*SARS-CoV-2 neutralising mAbs are primarily directed against the membrane spike glycoprotein that facilitates entry of pathogens into human host. If virus is unable to enter cells, it will not be able to replicate and spread throughout the body. This protein is the target of almost all monoclonal antibodies. The viral spike makes contact with the angiotensin converting enzyme 2 (ACE 2) receptor, which is located on a various cell causes the viral infection, but neutralising monoclonal antibodies prevent this step. Although knowledge of the viral spike protein's epitopes is expanding, previous experience of other human viral diseases has facilitated quick progress in determining the spike protein's atomic arrangement. [40]*

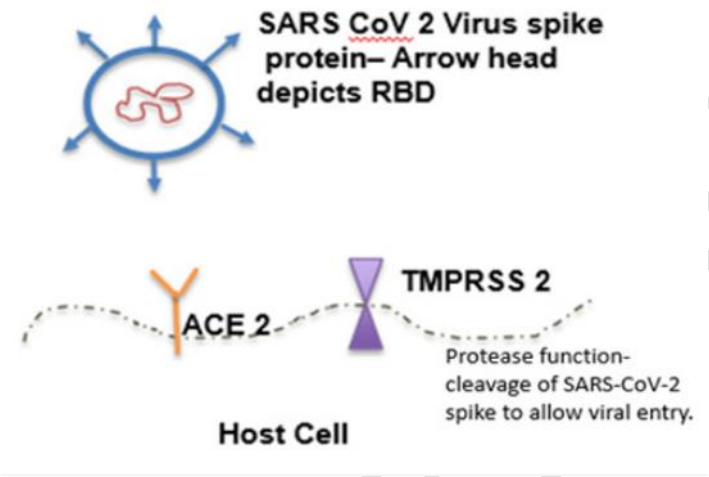


*Fig-2*: It shows interaction of SARS CoV2 virus with the host cell.

*In this image broken line indicates cell membrane with ACE2 receptors and TMPRSS2 protease which are essential for virus to enter host cell. A monoclonal antibody attach to the spike protein on virus, hence blocks the virus interaction with host cell.*

*Majority of monoclonal antibodies discovered so far selectively targets the spike protein's receptor-binding region, which permits corona virus to interact with ACE 2 receptor [41,42]. Neutralizing antibodies are likely to target additional areas of the spike protein as well. Based on recent SARS-CoV and Middle East respiratory sickness coronavirus information (MERS-CoV), potency is a key characteristic that is typically used to characterise neutralising monoclonal antibodies. It can be used to choose monoclonal antibodies with clinical potential. [43]*

***2.5. Production of Monoclonal antibodies -***

*Monoclonal antibodies are the ones made exclusively by lymphocytes called B cells, such cells are unable to grow for a long period of time in a cultured cell. As a result, numerous techniques were developed for running and producing them in stable cell lines, including protocols based on B cells. When these cells come from mouse lymphocytes, the resulting murine monoclonal antibodies are mostly employed for immunotherapeutic purposes. When human cells, particularly those from convalescent patients, are used as corona virus patients. Human neutralised monoclonal antibodies produced as a result are considered as effective antibodies against severe acute respiratory syndrome. [44]*

*Traditional process for producing mouse monoclonal antibodies involves fusing splenic cells from immunised mice (for example, immunisation with SARS-CoV-2 proteins) utilizing fusing media like Polyethylene glycol (PEG), particular mouse monoclonal antibodies were produced using mouse myeloma cell lines, followed by cell cloning as well as subcloning. The majority of the mouse monoclonal antibodies produced were indeed employed in immunotherapy. [45,46]*

*The cloning of cDNAs, encoding the numerous sections of the heavy and light chains onto production plasmids carrying the human IgG1 heavy chain and Ig kappa light chain constant regions, is required for creation of potential therapeutic recombinant human monoclonal antibodies. The interleukin-2 signal sequence is included on both plasmids, allowing for effective recombinant antibody secretion. After transfection with sets of IgG1 heavy and light chain expression plasmids, recombinant human antibodies are generated in HEK-293T cells and extracted using protein-A affinity chromatography. [47]*

*In 1975, in order to create significant amounts of homogeneous monoclonal antibodies, the hybridoma technology was introduced. Producing mouse monoclonal antibodies against specific SARS surface epitopes from the spike protein using traditional hybridoma technology; then separating the RNA and conducting humanization and chimeric human monoclonal antibodies using the same hybrid cell line that generates the unique mouse monoclonal antibodies. Human monoclonal antibody 47D11 was created using this approach. In Vero cell culture, the antibody showed neutralisation of shared epitopes from SARS-CoV and SARS-CoV-2 viruses. [47]*

***2.6 FDA Expansion for Authorization of Two Monoclonal Antibodies for Treatment of COVID-19 in younger paediatrics (including Newborns)-***

*Bamlanivimab and Etesevimab emergency use authorisation (EUA) was modified by the US FDA (Food and Drug Administration) which is priorly authorised for paediatrics of 12 years and for elders of minimum 40 kgs weight, includes Bamlanivimab and Etesevimab are used together to treat mild to moderate COVID-19 in all smaller paediatrics, includes the new-borns who have tested positive with COVID. This change also allows Bamlanivimab and Etesevimab to be used combined as a post prophylactic for COVID prevention in all paediatric patients, including Newborns, who had a more chance of COVID-19 infection, which could result a hospitalisation or death.*

*In February, the FDA first approved Bamlanivimab and Etesevimab for the therapy of mild-to-moderate COVID-19 in elders and paediatrics (who are having 12 years or older and a weight of minimum 40 kg) with positive corona virus testing and those having more chances of progression to serious COVID-19 infection which may leading to hospitalisation. In September, the FDA approved its use for COVID-19 post prophylaxis in elders and small children's of having 12 years age and more than that, weight of minimum 40 kg and who are having more chances of developing COVID-19 infection, which can lead to hospitalisation or death. [48]*

***3. Results***

***3.1 COVID-19 prevention using Monoclonal antibodies -***

*The epidemic of COVID-19 necessitates the development of an efficient vaccine. Despite the fact that vaccine development often requires years and may even decades, concerted attempts for screening the multiple COVID-19 vaccines at the same time are intended to cut the time to 12 to 18 months [49]. A patient's decision to employ anti-SARS-CoV-2 mAbs should indeed be based on a personalized risk-benefit analysis [17]. For patients who cannot take the vaccine or need more urgent protection before or after exposure, monoclonal antibodies offer an alternative to vaccination in the treatment of corona virus infection. Passive infusion of monoclonal antibodies as a pre- or post-exposure prophylactic could provide immediate protection that lasts weeks or months. Even if a vaccination is available, it takes weeks to build an adequate immune response. As a result, monoclonal antibodies against SARS-CoV-2 can be employed simultaneously for prevention and therapy of infection. MAbs should be preserved for the persons who are at a major chance of having a severe COVID-19 illness, such as the obese, getting older or those who have more glucose levels i.e., diabetes, pulmonary disorders, cancer [50]. Although mortality rates may not appear to be consistently higher*

*throughout the studies, the frequency of occurrence of COVID-19 infection is higher in SOT individuals when compared to a people with more chances of respiratory failure. [51-56]*

***3.2 Adverse effects –***

*An allergic reaction is one of the possible side effects of monoclonal antibody therapy. These reactions usually occur during or immediately after the infusion, and your healthcare provider will monitor for any signs of an allergic reaction. Patients who have had anti-SARS-CoV-2 monoclonal antibodies are reported to have hypersensitivity, including anaphylaxis and infusion-related events. There have also been reports of hives or itching, rashes, diarrhoea, dizziness and pruritis [17,32,57]. There are also some other adverse effects, such as -*

- *Fever and/or chills*
- *Nausea*
- *Headache*
- *Breathing problems*
- *Hypotension*
- *Lips, cheeks, and throat swelling*
- *Wheezing, Muscle pains [35]*

*Clinical study participants those who have injected Casirivimab and Imdevimab combination via Sub cutaneous route experienced injection site reactions such as ecchymosis and erythema.*

***4. Conclusion –***

*Despite the fact that monoclonal antibodies manufacturing is a time consuming and costly, they have been viewed as a promising therapy option for COVID-19 since the outbreak began. Monoclonal antibodies have proven to be successful and easy to administer in the treatment of a variety of diseases over the last three decades. Monoclonal antibodies are a crucial component of COVID-19 therapies, and they're making their way into therapy guidelines. These compounds have significant advantages for usage against the corona virus infection because they are developed from COVID-19 affected persons, who are in remission. Currently, over than 70 monoclonal antibodies are now being developed in animal or human trials, which could allow for fast production in the event of a pandemic. Vaccines are well recognized for providing extended time protective action only after a few days or weeks of use. Monoclonal antibodies might be an excellent addition to vaccinations, particularly in the event of an epidemic, because they provide immediate relief that can remain for weeks or even months after administration. This would also aid with the management of sick patients and the prevention of infection in children's and the elderly people.*

***5. References -***


1. *https://covid19.who.int/*
2. *Masters PS, Perlman S (2013) Coronaviridae. In: Knipe DM, Howley PM, Cohen JI, et al (Eds), Fields Virology, (6th edn), Lippincott Williams & Wilkins, a Wolters Kluwer business, Philadelphia 2: 825.*
3. *R.M. Mehta, S. Bansal, S. Bysani, H. Kalpakam, A shorter symptom onset to remdesivir treatment (SORT) interval is associated with a lower mortality in moderate-to-severe COVID-19: A real-world analysis, Int J Infect Dis 106 (2021) 71–77, https://doi.org/10.1016/j.ijid.2021.02.092.*
4. *Mongardon N, Piagnerelli M, Grimaldi D, Perrot B, Lascarrou JB; COVADIS study group investigators. Impact of late administration of corticosteroids in COVID-19 ARDS. Intensive Care Med. 2021 Jan;47(1):110-112. doi: 10.1007/s00134-020- 06311-z. Epub 2020 Nov 6. PMID: 33156381; PMCID: PMC7645397.*

5. *J. Liu, S. Zhang, X. Dong, Z. Li, Q. Xu, H. Feng, J. Cai, S. Huang, J. Guo, L. Zhang, Y. Chen, W. Zhu, H. Du, Y. Liu, T. Wang, L. Chen, Z. Wen, D. Annane, J. Qu, D. Chen, Corticosteroid treatment in severe COVID-19 patients with acute respiratory distress syndrome, J Clin Invest. 130 (12) (2020 Dec 1) 6417–6428, https://doi.org/10.1172/JCI140617. PMID: 33141117; PMCID: PMC7685724.*
6. *Marston HD, Paules CI, Fauci AS. Monoclonal antibodies for emerging infectious diseases—borrowing from history. N Engl J Med. 2018;378(16):1469-1472.*
7. *Katie McCallum, (2021, August 20), What is Monoclonal Antibody Therapy and Who is Eligible to Receive it? Houston Methodist leading medicine, https://www.houstonmethodist.org/blog/articles/2021/jan/what-is-monoclonal-antibody-therapy-and-who-is-eligible-to-receive-it/.*

8. *Jiang S, Hillyer C, Du L. Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses. Trends Immunol. 2020;41(5):355-359.*

9. *O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV antibody combination to prevent COVID-19. N Engl J Med. 2021;385(13):1184-1195.*
10. *Cohen MS, Nirula A, Mulligan MJ, et al. Effect of bamlanivimab vs placebo on incidence of COVID-19 among residents and staff of skilled nursing and assisted living facilities: a randomized clinical trial. JAMA. 2021;326(1):46-55.*
11. *Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Evusheld (tixagevimab co-packaged with cilgavimab). 2021.*
12. *National Center for Advancing Translational Sciences. SARS-CoV-2 variants & therapeutics: therapeutic activity explorer. 2022.*
13. *Centers for Disease Control and Prevention. SARS-CoV-2 variant classifications and definitions. 2021.*

14. *Mulangu S, Dodd LE, Davey RT Jr, et al; PALM Writing Group. A randomized controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019;381(24):2293-2303. doi:10.1056/ NEJMoa1910993.*

15. *Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, et al. (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.*

16. *https://investor.regeneron.com/news-releases/news-release-details/phase-3-trial-shows-regen-covtm-casirivimab-imdevimab-antibody.*

17. *Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of sotrovimab. 2021.*
18. *Public Health Emergency. REGEN-COV. 2022.*
19. *COVID-19 Study Assessing the Efficacy and Safety of Anti-Spike SARS CoV-2 Monoclonal Antibodies for Prevention of SARS CoV-2 Infection Asymptomatic in Healthy Adults and Adolescents Who Are Household Contacts to an Individual with a Positive SARS-CoV-2 RT-PCR Assay - Full Text View - ClinicalTrials.gov n.d.*

20. *Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Adult and Pediatric Patients With COVID-19 - Full Text View - ClinicalTrials.gov n.d.*

21. *A. Dhand, S.A. Lobo, K. Wolfe, N. Feola, L. Lee, R. Nog, et al., CasirivimabImdevimab for Treatment of COVID-19 in Solid Organ Transplant Recipients: an Early Experience, Transplantation (2021), https://doi.org/10.1097/ TP.0000000000003737.*

22. *D.M. Weinreich, S. Sivapalasingam, T. Norton, S. Ali, H. Gao, R. Bhore, et al., REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19, N Engl J Med 384 (2021) 238–251, https://doi.org/10.1056/NEJMoa2035002.*

23. *M. Tuccori, S. Ferraro, I. Convertino, E. Cappello, G. Valdiserra, C. Blandizzi, et al., Anti-SARS-CoV-2 neutralizing monoclonal antibodies: clinical pipeline, MAbs 12 (2020), https://doi.org/10.1080/19420862.2020.1854149.*

24. *A Study of LY3819253 (LY-CoV555) in Participants Hospitalized for COVID-19 - Full Text View - ClinicalTrials.gov n.d.*
25. *Public Health Emergency. Bamlanivimab/etesevimab. 2022.* Available at: https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab-etesevimab/Pages/default.aspx. Accessed January 24, 2022.
26. *Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19 | FDA n.d. https://www.fda.gov/news-events/pressannouncements/coronavirus-covid-19-update-fda-authorizes-monoclonalantibodies-treatment-covid-19-0 (accessed April 29, 2.*

27. *EMA issues advice on use of REGN-COV2 antibody combination (casirivimab / imdevimab) | European Medicines Agency n.d. https://www.ema.europa.eu/en/ news/ema-issues-advice-use-regn-cov2-antibody-combination-casirivimabimdevimab (accessed April 29, 2021).*

28. *EMA issues advice on use of antibody combination (bamlanivimab / etesevimab) | European Medicines Agency n.d. https://www.ema.europa.eu/en/news/emaissues-advice-use-antibody-combination-bamlanivimab-etesevimab (accessed April 29, 2021).*

29. *Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of sotrovimab. 2021.*
30. *Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med. 2021;385(21):1941-1950.*
31. *Food and Drug Administration. Fact sheet for health care providers: emergency use authorization (EUA) of bamlanivimab and etesevimab. 2021.*
32. *Food and Drug Administration. Fact sheet for health care providers: emergency use authorization (EUA) of REGEN-COV®(casirivimab and imdevimab). 2021.*
33. *Food and Drug Administration. Frequently asked questions on the emergency use authorization of casirivimab + imdevimab. 2020. Available at: https://www.fda.gov/media/143894/download.*
34. *Food and Drug Administration. Frequently asked questions on the emergency use authorization of bamlanivimab and etesevimab. 2021.*
35. *Katie McCallum, (2021, August 20), What is Monoclonal Antibody Therapy and Who is Eligible to Receive it? Houston Methodist leading medicine, https://www.houstonmethodist.org/blog/articles/2021/jan/what-is-monoclonal-antibody-therapy-and-who-is-eligible-to-receive-it/*

36. *Kim L, Garg S, O'Halloran A, et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET). Clin Infect Dis. 2021;72(9):e206-e214.*
37. *Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55(5).*
38. *Zhang Y, Luo W, Li Q, et al. Risk factors for death among the first 80,543 COVID-19 cases in China: relationships between age, underlying disease, case severity, and region. Clin Infect Dis. 2021.*
39. *Zhang Y, Luo W, Li Q, et al. Risk factors for death among the first 80,543 COVID-19 cases in China: relationships between age, underlying disease, case severity, and region. Clin Infect Dis. 2021.*
40. *Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-1263.*
41. *Ju B, Zhang Q, Ge X, et al. Potent human neutralizing antibodies elicited by SARS-CoV-2 infection. bioRxiv. Preprint posted online March 26, 2020. doi:10.1101/2020.03.21.990770.*
42. *Pinto D, Park YJ, Beltramello M, et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. Nature. Published May 18, 2020. doi:10.1038/s41586-020-2349-y.*

43. *Wang L, Shi W, Chappell JD, et al. Importance of neutralizing monoclonal antibodies targeting multiple antigenic sites on the Middle East respiratory syndrome coronavirus spike glycoprotein to avoid neutralization escape.J Virol. 2018;92(10):e02002-e02017. doi:10.1128/JVI. 02002-17.*

44. J.P. Henderson, What are protective antibody responses to pandemic SARS-CoV-2? J. Clin. Invest 130(12) (2020), 6232– 6234.

45. A. Tabll, A.T. Abbas, S. El-Kafrawy and A. Wahid, Monoclonal antibodies: principles and applications of immmunodiagnosis and immunotherapy for hepatitis C virus, World J. Hepatol 7(22) (2015), 2369–2383.
46. C.A. Abdel Malak, T.H. Abelhafez, A.A. Tabll, M.M. Mashaly, R. El Shenawy, Y.S. El-Abd, M.H. Shaker and M.K. El-Awady, Neutralizing activity and safety of human monoclonal antibodies against hepatitis C virus, Hum Antibodies 26(3) (2017), 127–134.

47. C. Wang, W. Li, D. Drabek, N.M.A. Okba, R. van Haperen, A.D.M.E. Osterhaus et al., A human monoclonal antibody blocking SARS-CoV-2 infection, Nat. Commun 11(1) (2020), 2251.
48. Food and Drug Administration, FDA Expands Authorization of Two Monoclonal Antibodies for Treatment and Post-Exposure Prevention of COVID-19 to Younger Pediatric Patients, Including Newborns, 2021, December 03.
49. Corey L, Mascola JR, Fauci AS, Collins FS. A strategic approach to COVID-19 vaccine R&D. Science. 2020;368(6494):948-950. doi:10.1126/ science.abc5312.
50. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020:1–10. 10.1001/ jamainternmed.2020.0994.

51. S. Trapani, L. Masiero, F. Puoti, M.C. Rota, M. Del Manso, L. Lombardini, et al., Incidence and outcome of SARS-CoV-2 infection on solid organ transplantation recipients: A nationwide population-based study, Am J Transplant 21 (2020) 2509–2521, https://doi.org/10.1111/ajt.16428.

52. M.R. Pereira, S. Mohan, D.J. Cohen, S.A. Husain, G.K. Dube, L.E. Ratner, et al., COVID-19 in solid organ transplant recipients: Initial report from the US epicenter, Am J Transplant 20 (2020) 1800–1808, https://doi.org/10.1111/ajt.15941.

53. M. Fernandez-Ruiz, ´ A. Andr´es, C. Loinaz, J.F. Delgado, F. Lopez-Medrano, ´ R. San Juan, et al., COVID-19 in solid organ transplant recipients: A single-center case series from Spain, Am J Transplant 20 (2020) 1849–1858, https://doi.org/ 10.1111/ajt.15929.

54. Linares L, Cofan F, Diekmann F, Herrera S, Marcos MA, Castel MA, et al. A propensity score-matched analysis of mortality in solid organ transplant patients with COVID-19 compared to non-solid organ transplant patients. PLoS One 2021; 16. 10.1371/journal.pone.0247251.

55. Z.S. Chaudhry, J.D. Williams, A. Vahia, R. Fadel, T. Parraga Acosta, R. Prashar, et al., Clinical characteristics and outcomes of COVID-19 in solid organ transplant recipients: A cohort study, Am J Transplant 20 (2020) 3051–3060, https://doi.org/ 10.1111/ajt.16188.

56. S.G. Yi, A.W. Rogers, A. Saharia, M. Aoun, R. Faour, M. Abdelrahim, et al., Early experience with COVID-19 and solid organ transplantation at a US high-volume transplant center, Transplantation (2020) 2208–2214, https://doi.org/10.1097/ TP.0000000000003339.

57. Food and Drug Administration. Frequently asked questions on the emergency use authorization of sotrovimab. 2021, https://www.fda.gov/media/149535/download.