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Viewpoint on monoclonal antibody therapy: Advances in COVID-19 treatment

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Abstract
Background: With the number of Coronavirus Disease 2019 (COVID-19) cases on the rise around the world, monoclonal antibodies (mAb) remain a feasible treatment option for COVID-19 disease and associated complications, particularly in the elderly. Monoclonal antibodies are antibodies generated mainly from B cells-lymphocytes. The need to treat the emerging SARS-CoV-2 virus, which has caused the current global health crisis, has shifted the focus to the development of monoclonal antibody-based passive immunotherapy in order to provide a rapid response.
Summary: SARS-CoV-2, a novel human coronavirus, emerged in Wuhan, China, causing a worldwide respiratory disease epidemic (COVID-19). Vaccines and targeted therapeutics for treatment of this disease are currently lacking.SARS-CoV-2 (and SARS-CoV) are neutralised by a human monoclonal antibody in cell culture. Researchers are attempting to find antibodies-based treatments that will block and/or kill the coronavirus in people who are infected. The virus's genetic and structural resemblance to the severe acute respiratory syndrome coronavirus (SARS-CoV) presented the possibility of learning more about the disease aetiology at first. Researchers have published reports of specific monoclonal antibodies against COVID-19 (B38, H4, and 47D 11) and are hopeful that this strategy will be successful. The human 47D11 antibody binds to cells expressing the full-length spike proteins of SARS-CoV and SARS-CoV-2.
Conclusion: Neutralizing monoclonal antibodies to SARS-CoV-2 have the potential for both therapeutic and prophylactic applications, and can help to guide vaccine design and development. Coronavirus-neutralizing antibodies primarily target the trimeric spike (S) glycoproteins on the viral surface that mediate entry into host cells. This review systematize some of the most promising mAbs currently under clinical trials or are approved as an early COVID-19 intervention that could avert serious pulmonary morbidities. The monoclonal antibodies are the potential counter measures that may control SARS-CoV-2, which causes COVID-19 disease, through immunotherapy and vaccine development, as well as viral detection. More than 50 monoclonal antibody-related clinical trials are currently underway in various countries around the world, with a handful reaching completion of the third and fourth phases.

Keywords: Neutralizing antibodies, clinical trials, mechanisms, COVID-19

1. Introduction
A new coronavirus disease (COVID-19), also known as Severe Acute Respiratory Syndrome CoronaVirus-2 (SARSCoV-2), emerged in Wuhan, China, at the end of 2019 [1]. Coronaviruses are encased positive sense RNA viruses that range in size from 60 nm to 140 nm and have spike-like projections on their surface that give them a crown-like appearance under an electron microscope; hence the name coronavirus [2]. CoVs' envelope spike (S) protein is a trimeric type-1 integral membrane protein and class-1 fusion protein that contains three copies of an N-terminal subunit (S1) that facilitates receptor attachment and three copies of a C-terminal subunit (S2) that mediates virus-cell membrane fusion. The S1 subunit has four domains (A-D), with A (N-terminal) and B (receptor binding domain or RBD) being the most immunologically important [3].
The virus that causes coronavirus disease 19 (COVID-19) is a highly transmittable and pathogenic viral infection and mainly transmitted through contact with respiratory droplets rather than through the air. Covid-19 can be spread by close contact with small droplets released from infected individual's upper respiratory tract secretions [4], e.g. sneezing, common cold or coughing from the nose and mouth. The virus can also be transferred through surface contamination, which occurs when these droplets land on things and surfaces around the person and another individual contacts these objects or surfaces, then touches their eyes, nose, or mouth, causing them to acquire this virus.

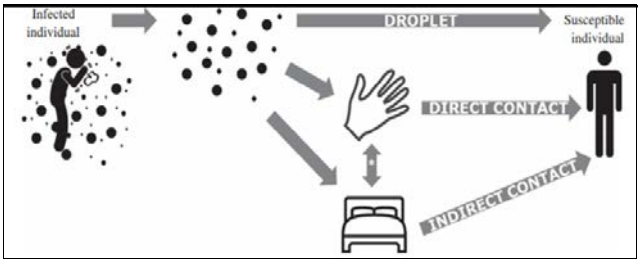

Fig 1: Transmission of coronavirus (direct or indirect contact)

Main text

2. Current treatment available for coronavirus disease

Allopathic treatment: Main therapeutic drugs which are available for treatment are

Lopinavir-Ritonavir (LPV-RTV): LPV-RTV is a protease inhibitor that can be used to treat a variety of treatments. Patients with COVID-19 who were given LPV-RTV had a higher risk of bradycardia. For more than 24 hours, the heart rate was found to be less than 60 beats per minute. Bradycardia was resolved in the patients when the LPV-RTV dose was reduced or stopped [5].

Remdesivir: RDV is another antiviral drug that can change to its active form. It causes to obscure the RNA polymerase, and eventually, prevents its replication. Side effects such as nausea and respiratory problems were observed in these patients [6].

Favipiravir: Favipiravir is a type of RNA-dependent RNA polymerase (RdRp) inhibitor. Favipiravir has also demonstrated activity against positive-strand RNA viruses such as noro- and flaviviruses. Therefore, favipiravir may have potential antiviral action on SARS-CoV-2, which is an RNA virus. The most common adverse effects of favipiravir are diarrhoea, raised liver enzymes, hyperuricemia, and QT prolongation [7].

Ayurvedic treatment: Ashwagandha (Aqueous extract of Withania somnifera IP) or its powder can be given. One need to intake 500 mg extract or 1-3 gram powder twice daily with warm water for 15 days or one month or as directed by Ayurveda physician in addition to Ashwagandha many other herbs were also given such as Guduchi Ghana vati and Chyawanprasha for supportive treatment but there is no conclusive evidence yet of the efficacy of specific Ayurvedic herbs, formulations or treatment protocols for COVID-19, it appears quite reasonable and plausible that Ayurveda can provide supportive care for patients diagnosed with COVID-19 [8].

Homeopathic treatment: There are a variety of homoeopathic medicines available for COVID-19 infection patients. For the treatment of corona disease, some studies recommend Arsenic Album, Pulsatilla, Silicia, Nitrum Muriaticum, Phosphorus, Calcarea Carbonicum, Hyper Sulphur, Lachesis, Nux Vomica, Sulphur, and a variety of other herbs. It's important to note that there's no clinical evidence that Arsenic is an effective treatment. However homoeopathy medication show no reasonable mechanism of action. Furthermore, some stated that proposing a trial for a serious pandemic is irresponsible [9].

Despite the fact that some vaccinations and therapeutic drugs have received Emergency Use Administration in various countries, the majority of people in most countries continue to rely on traditional medications and symptomatic treatment of the condition. The recent underwhelming results of the World Health Organization (WHO) solidarity trial have once again demonstrated our helplessness to combat this disease with our current treatments. Current treatments have numerous drawbacks, some of which can be addressed by monoclonal antibodies.

3. Monoclonal antibody for Covid

Immunotherapy, in the form of vaccines or antibody therapy, has previously been shown to be beneficial against viral infectious illnesses. Intervention using recovered patient plasma or hyper immune immunoglobulin from patients who had previously been infected with influenza, SARS, MERS, or Ebola, which includes a sufficient amount of antibody, is likely to lower viral load and, as a result, disease mortality [10]. Monoclonal antibodies (mAbs), on the other hand, are a type of passive immunotherapy that can give an effective therapeutic intervention against a specific disease. Furthermore, in comparison to standard convalescent plasma therapy, mAbs are significantly more specific, accurate, and safe because these antibodies may be extracted from infected patients' blood or synthesized in the lab. In preventing infectious diseases, the use of monoclonal antibodies is a novel outlook. Monoclonal antibodies are antibodies that are designed to bind to a solitary substance in the body. The binding is very adaptable and can imitate, stop or modify accurate mechanisms and offer very particular treatments for diseases for efficient treatments [11].

3.1 What are monoclonal antibodies and how do they work?

Monoclonal antibodies are a class of medicines that have transformed the way we prevent and treat diseases, as most medications are, they are not chemical compounds. They are based on natural antibodies – proteins that the body makes to prevent diseases but they are made in the laboratory and generated massively in the manufacturing plants [11].

Antibodies are proteins produced by our immune system and are one of the primary ways the body defends itself against disease. They function by attaching to their specific targets, such as viruses, bacteria, or malignant cells, and rendering them harmless. They either inhibit the target's action or flag it as foreign so that other sections of our immune system can clear the 'invaders' away. Monoclonal antibodies function in the same way. They bind to their specific target while causing no harm to anything else in their path. This target is not always a 'foreign intruder,' such as a virus [11].

Antibodies can be created to attach to certain molecules in the body, for example, to suppress the immune response when it overreacts; this occurrence is known as a cytokine storm, and it has been observed in some Covid-19 patients.

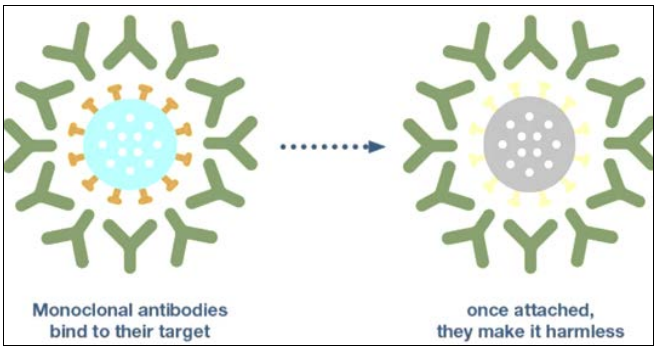

Fig 2: Working of Monoclonal antibodies

Mechanism of Monoclonal Antibodies

The mAbs are likely to aid in viral load reduction by interfering with virus entry into a cell by binding to viral spikes and thus inhibiting virus attachment to cell surface receptors, or by targeting host cell receptors or coreceptors, thereby rendering host cell binding sites unavailable for SARS-CoV-2. They can also act as immunosuppressive agents, minimising immune-mediated damage. Monoclonal antibodies act by a variety of ways, which are outlined below.

- **The antiviral MAbs target for Spike Protein**

SARS-CoV-2 enters the body and stimulates the innate immune response first, followed by the adaptive immune response after a few days. According to immunological responses, the clinical phases of SARS-CoV-2 infection are the viremia phase, the acute phase, and the chronic phase (also known as pneumonia phase as well as the healing period. The S proteins of SARS-CoV and SARS-CoV-2, two related viruses, exhibit approximately 77 percent amino-acid sequence identity, with approximately 89.8 percent sequence identity in S2 subunits [12]. These commonalities have aided researchers in repurposing neutralising mAbs directed against SARS-CoV S protein or host angiotensin-converting enzyme 2 (ACE-2) receptors for SARS-CoV-2, while various investigations have revealed a variety of differences about how these neutralising antibodies act. Several similar antibodies are now being developed for SARS-CoV-2, including 2B2, 1A9, 4B12, and 1G10, S309 [13].

- **Antibodies regulating immune microenvironment**

In the case of SARS-CoV-2, granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL6), both produced by activated CD4+ T cells, play a key role in Immuno-pathogenesis. 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 were found to be elevated in more severe COVID-19 patients in a number of investigations [14, 15]. Although the exact characteristics of the cytokine storm in COVID-19 are still uncertain, anti-cytokine mAbs could be critical in the event of severe COVID.

- **Human neutralizing antibodies**

47D11: Wang *et al*. found this antibody by evaluating antibody-containing supernatant produced from vaccinated transgenic H2L2 mice using an ELISA-(cross) reactivity method. 47D11 was discovered to attach to SARS-CoV-2 and SARS-CoV, and to effectively prevent the virus from infecting Vero cells. For additional research, the chimeric 47D11 H2L2 antibody was reformatted and produced as a completely human IgG1 isotope antibody. Using an ELISA assay, it was discovered that 47D11 targets the S1B receptor-binding domain (RBD) of SARS-S and SARS2-S, inhibiting S protein binding to the human-ACE2 receptor [16].

B38, H4: The report on four human-origin monoclonal antibodies (B5, B38, H2, and H4) from a convalescent patient showed that all four antibodies bound to SARS-CoV-2 receptor-binding domain (RBD), but not to SARS-CoV RBD [17].

4. Current status of mAbs in clinical trials

Several innovative humanised or bioengineered mAbs targeting different regions of the S-protein of SARS-CoV-2 are now in clinical testing. One such mAbs cocktail therapy consists of casirivimab and imdevimab (REGN-COV2), which bind to non-overlapping epitopes of the SARS-CoV-2 spike protein RBD and thereby block virus binding to the human ACE2 receptor, has been developed by Regeneron Pharmaceuticals and approved for EUA by the FDA [18]. Eli Lilly's mAbs LY-CoV555 was the first to enter a clinical trial to treat COVID-19. It is a human IgG1 antibody that targets the spike protein, which is produced from human B cells from convalescent patients. At all doses tested, it was well tolerated, with no major drug-related severe adverse events (SAEs) documented to date. A number of companies (e.g., Eli Lilly and Celltrion) have advanced or are advancing a single mAbs for COVID-19, while others are pursuing a combination of two mAbs (e.g. Regeneron). A key distinction between single mAbs vs. mAbs cocktail is the risk of viral escape with mutations such as N439K and Y453F [19].

Studies with a replicating VSV-SARS-CoV-2-S virus have shown that multiple independent viral escape mutants can be readily generated to each of the individual antibodies tested [20]. Tocilizumab (phase 4), sarilumab (phase 3) and siltuximab (phase 3) are among the IL-6 inhibitors now being studied in clinical studies in a variety of patient groups. Tocilizumab exhibited immediate improvement in the clinical outcomes of severe and critical patients, demonstrating that it is an effective treatment for lowering mortality [21]. Several other international clinical trials (phase 4/2) are currently underway, involving patients admitted to the intensive care unit with severe acute respiratory failure. Adult patients hospitalised with COVID-19 disease (8 mg/kg up to a total dose of 800 mg) and COVID-19 disease (8 mg/kg up to a total dose of 800 mg) were either diagnosed with moderate or severe pneumonia necessitating no mechanical ventilation or critical pneumonia requiring mechanical ventilation. In addition to the above mAbs there are now few more mAbs being tested in different phases of clinical trials, such as Canakinumab (Anti IL-1β), CPT-006 and AK119 (Anti CD73), Garadacimab/ CSL312 (F. XIIa antagonist), Pamrevlumab (mAb against connective tissue growth factor), Bevacizumab (Anti VEGF), Cizanlizumab (Anti P-selectin), Ravulizumab (Anti C5) and Emapalumab (IFNɣ antagonist) and Anakinra (IL-1 antagonist) combination therapy.

5. MAbs approved for therapy

Casirivimab plus imdevimab, these are recombinant human monoclonal antibodies that bind to non-overlapping epitopes of the spike protein RBD of SARS-CoV-2 [22].

Sotrovimab is a monoclonal antibody and was originally identified in 2003 from a SARS-CoV survivor. It targets an epitope in the RBD of the spike protein that is conserved between SARS-CoV and SARS-CoV-2 [22].

Bamlanivimab: It is approved drug in European Medicines agency and the US Food and Drug Administration (FDA) granted an emergency use authorization (EUA) for Bamlanivimab, an experimental monoclonal antibody therapy for the treatment of mild-to-moderate COVID-19 in adults and children. Monoclonal antibodies are laboratory-made proteins that mimic the immune system's ability to

fight off harmful antigens such as viruses. Bamlanivimab is a monoclonal antibody that is specifically directed against the spike protein of SARS-CoV-2, designed to block the virus' attachment and entry into human cells. Bamlanivimab is approved for individuals aged 12 and above who have tested positive for SARS-CoV-2 virus and weigh at least 40 kgs (88 pounds) and are at high risk of developing severe COVID-19 and/or requiring hospitalization. This covers people over the age of 65 and those with certain chronic medical conditions. For instance, combination of Bamlanivimab with etesevimab or Bamlanivimab monotherapy showed similar efficacy on clinical endpoints, while combination therapy appeared to be more efficacious on virological endpoints [18].

Bamlanivimab and etesevimab: A single intravenous infusion of Bamlanivimab and etesevimab delivered simultaneously significantly reduced COVID-19-related hospitalizations and death during 29 days of follow-up in a clinical trial of individuals with COVID-19 at high risk for disease progression compared to placebo. The safety and efficacy of this investigational medication in the treatment of COVID-19 are now being assessed [18].

Regdanvimab: Regdanvimab received a conditional marketing authorization by South Korea's drug safety agency. This approval was based on the first part of a global phase 2/3 trial showing that progression rates to severe COVID-19 were reduced by 54% for patients with mild-to-moderate symptoms and 68% for patients aged 50 years and older.

6. Approaches for overcoming previous setbacks

6.1 Advancing more potent mAb

MAbs are poorly distributed from the systemic circulation into the lung, with barely 1% of intravenously dosed mAb reaching lung tissue [23]. Improving the neutralisation potency (i.e. IC50) of the mAb is an obvious strategy to raise the likelihood of efficacy; assuming the same quantity of mAb can reach the lung, a more potent mAb will more effectively suppress viral reproduction locally in the lung than a less potent mAb.

6.2 Earlier initiation of mAb treatment

COVID-19 patients are hospitalised due to morbidities linked with SARS-CoV-2 infection-induced inflammation, rather than the presence of the virus itself. From our perspective, giving antiviral mAb to hospitalized patients with Lower Respiratory Tract infections. Indeed, it is doubtful that antiviral mAb alone can swiftly decrease the inflammation in late stages of infection when provided after the virus reaches this terminal hyper inflammatory phase. Earlier treatment also suggests lower viral titers in the lung when mAb therapy is initiated, making virus spread easier to stop and enabling more time for the infused mAb to reach the lung before the viruses may disseminate into the Lower Respiratory tract. As a result, the optimal antiviral medication should be commenced early in the course of illness, as soon as infection can be clinically identified, in order to minimise the associated pulmonary morbidities associated with deep lung infections.

6.3 Direct pulmonary delivery

The failures of systemically dosed antiviral mAb for ARIs is particularly notable, since nearly all antiviral mAbs currently under clinical development for COVID-19 are also administered systemically. Methods that can deliver greater quantities of mAb to where the viruses are concentrated more quickly are anticipated to be more effective in limiting SARS-CoV-2 propagation to the deep lung. Inhaled delivery of mAb offers a number of distinct advantages over systemic mAb delivery. In an RSV challenge cotton rat model, intranasal dosing of neutralising mAb lowered the quantity of mAb required by orders of magnitude; 4 g/kg IVIG supplied by i.p injection was required to obtain the same degree of protection as 0.025 g/kg delivered by intranasal deposition [24]. In other animal models, topical administration of neutralising mAbs into the lungs significantly inhibited viral multiplication. Another advantage with inhaled delivery of mAb is the time it takes to reach local Cmax. When mAb is inhaled, the maximal concentration of the substance in local lung tissues occurs immediately after inhalation.

7. Challenges in monoclonal antibody

In clinical trials, establishing the benefits of monoclonal antibodies poses significant obstacles. Because most patients recover from an early infection, achieving the clinical endpoints required to establish a benefit over placebo is difficult. In individuals with more severe disease, where inflammation and coagulopathy may be more important than viral replication, it may be more difficult to demonstrate benefit. Finding individuals at high enough risk (i.e., a high enough attack rate) to demonstrate prevention of symptomatic infection is difficult in monoclonal antibody preventive trials. As the COVID-19 pandemic spreads around the world, the clinical research infrastructure will need to be able to quickly deliver monoclonal antibodies to individuals or facilities at high risk of infection. Another potential stumbling block is the ability to manufacture enough monoclonal antibodies. Although the dose required will influence this and may differ for prevention and treatment, current commercial production capacity is expected to be able to manufacture millions of doses each year.

8. Future prospective for monoclonal antibody

Any mAb must meet strict guidelines specified by the World Health Organisation (WWHO). In each situation, the tests should be conducted both as non-clinical (in-vitro and in-vivo models) and clinical. The main focus of these investigations is pharmacokinetics (PK), Pharmacodynamics (PD), and safety and leads to pivotal clinical trials when they are completed. Antibodies work through a range of techniques from blocking the receptor to immune induced processes. However, precautions were required to take account of the effects of antibodies to defend against pulmonary SARS-CoV while a number of patients dying showed significant neutralising antibody responses and lung inflammation that could result from immediate fatal lung injury. It is expected, in the near future, that we will be able to comprehend the processes used to neutralise the efficiency of monoclonal antibody treatment. To summarize, monoclonal antibodies are useful as post-exposure prophylaxis to avoid serious diseases or complications, as indicated by research on plasma therapy against COVID-19.

9. Conclusions

Antibodies that neutralise viruses play a vital role in the protection and recovery from many viral illnesses. Over the next few months, several monoclonal antibody products will be evaluated in clinical trials to see if they can reduce or change SARS-CoV-2 infection. Furthermore, a medicine

that reliably inhibited COVID-19 progression would considerably alleviate the fears and ambiguity surrounding SARS-CoV-2 infection and provide clinicians with a therapeutic tool that they must have for their patients. Monoclonal antibodies' therapeutic or prophylactic efficacy would be a significant step forward in the COVID-19 pandemic's management.

List of Abbreviations

COVID-19-Coronavirus
WHO-World Health Organization
PK-Pharmacokinetics
PD-Pharmacodynamics
IL-Interleukins
MERS-Middle east respiratory syndrome
SARS-Severe acute respiratory syndrome
MAbs-Monoclonal antibodies

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