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Review Article

The Potentials of Monoclonal Antibodies as a COVID-19 Intervention Tool

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Abstract

Summary: COVID-19 has been ravaging the world since late December, 2019 and it is not slowing down as the global cumulative counts of confirmed cases and fatalities continue to rise every day. Currently, there is no established cure. Monoclonal antibodies (mAbs) are the major therapeutic agents for passive immunotherapy in the fight against viral infection. They are increasingly being recognized as a promising class of drugs to combat the novel coronavirus. Besides their therapeutic potentials, infectious disease experts are hopeful that they may also provide short-term protection and could serve as important components of the COVID-19 pandemic response until vaccines become accessible globally. Since the outbreak assumed a global proportion, several biotechnology companies across the globe are developing monoclonal antibodies with the hope it will become an intervention tool in combating the pandemic. Different randomized, placebo-controlled, double-blind clinical trials are currently enrolling healthy individuals at clinical trial sites in the United States of America and elsewhere. In addition to assessing their safety, the trials are seeking to establish whether mAbs can prevent infection in susceptible individuals or ameliorate disease symptoms in those already infected. This review takes a look at the available literatures on the role of monoclonal antibodies as an intervention tool for combating the COVID-19 pandemic.

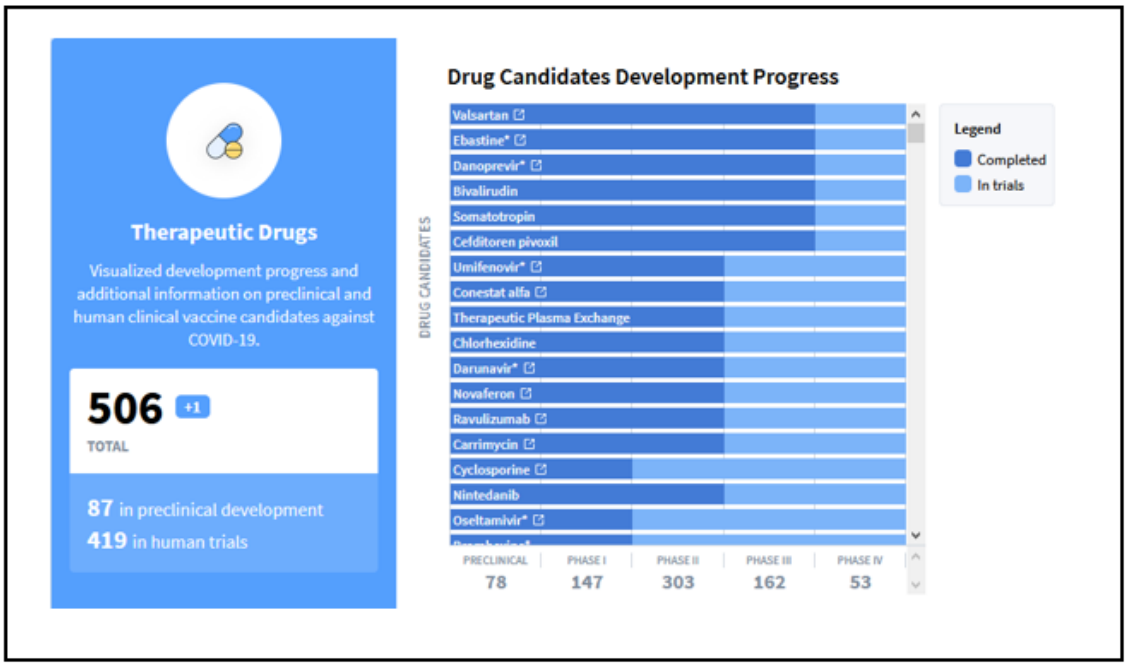
Keywords: COVID 19, SARS-CoV-2, Monoclonal antibodies, Prophylactics, Therapeutics.

INTRODUCTION

The Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), the etiologic agent of the Coronavirus Disease-2019 (COVID-19) has been of global public health concern since December, 2019[1]. Infection has been associated with the development of variable levels of antibodies with neutralizing activity. According to Gaebler *et al.*,[2] titres of IgM and IgG antibodies against the receptor-binding domain (RBD) of the spike protein of the virus decrease significantly over a period of 6.2 months with IgA being less affected. Simultaneously, neutralizing activity in plasma decreases by five-fold in pseudo type virus assays. By contrast, the number of RBD-specific memory B cells remains unchanged after infection. Memory B cells were additionally shown to show being turnover once this era, and therefore the antibodies that they express have greater somatic hypermutation, resistance to RBD mutations and increased potency, indicative of continued progression of the humoral response.

Furthermore, cases of re-infection have been reported in several countries.[3,4] Interestingly, individuals who recovered from the primary infection have been shown to have persistent high levels of virus-specific IgG antibodies in their serum. It is however unclear if these antibodies possess the ability to neutralize the virus or perhaps to protect against re-infection. Nonetheless, a direct association between disease severity and circulating IgG levels following primary infection has been documented.[5,6]

The persistent rise in the number of cases has necessitated the urgent need to develop both preventive and therapeutic tools to combat the pandemic. Despite its high infectivity, there is no validated curative therapy for the disease as of now.[7] The current management approach is basically palliative and symptomatic care which is geared towards maintaining vital signs, oxygen saturation as well as blood pressure; relieving pain and treating complications, such as secondary infections or organs failure. Although, anti-malarial drugs such as chloroquine and hydroxyl-chloroquine are currently used for the treatment of severe COVID-19 cases in some countries, there are a lot of conflicting opinions regarding their efficacy, optimal therapeutic dose and risk-benefit ratio among other consideration.[8] what is more, variety of prospective gold normal therapies (such as Remdesivir, Lopinavir/Ritonavir, antiviral agent beta-1a, Cyclosporine, Valsartan, Ebastine, Danoprevir, etc.) are undergoing clinical trials to determine their safety and effectiveness.[9,10] Currently, there is a total of 506 candidate drugs under investigation; 87 in preclinical development and 419 in human trials (Figure 1). Remdesivir particularly has been shown to be of questionable effectiveness and associated with important adverse effects like elevated liver enzymes, headaches, nauseas and rash. Meanwhile its concomitant use with hydroxychloroquine is discouraged.[11,12]



Source: https://biorender.com/covid-vaccine-tracker

Figure-1: COVID-19 Drug Candidates Development Progress

Convalescent plasma therapy (CPT and monoclonal antibody therapy (MAP) are few of the various therapeutic approaches presently being investigated. Shen *et al.*[13] and Pawar *et al.*[14] showed that CPT is also of huge profit within the treatment of critically unwell COVID-19 patients, because it considerably reduced infectious agent load in patients receiving it. However, there are a unit risks related to this kind of medical care as indicated by Casadevall and Pirofski.[15] These include serum disease which is associated with transfusion transmissible infections (TTIs); as well as antibody-dependent enhancement of infection which describes the phenomenon in which antibodies to one strain of coronavirus could enhance infection to another.

Infectious disease experts have expressed optimism on the potential benefits of identifying monoclonal antibodies to specific viral epitopes which could serve in viral neutralization. Neutralizing antibodies, whether natural or monoclonal, recognize and bind specific proteins on virion surface, thus preventing attachment to host cell and initiation of infection cycle.[16] Monoclonal antibodies (mAbs) targeting exposed sites on viral surface proteins are increasingly being recognized viruses.[17] One main advantage of mAbs is that the shortness of amount throughout at intervals that it may be developed, so creating it advantageous within the case of COVID-19 pandemic.[18] throughout the viral haemorrhagic fever happening of 2014, mAbs were initial wont to combat the virus as recommended by World Health Organization (WHO) and its development was speedy compared to therapy agents and vaccine.[19] The purpose of this review is therefore to examine available literatures on the role of monoclonal antibodies as an intervention tool for combating the COVID-19 pandemic.

DISCUSSION

Monoclonal antibodies as a COVID-19 Intervention tool

The COVID-19 pandemic has impacted the entire world so greatly since its advent in late December, 2019. As of March 25, 2021, the novel Coronavirus has unfold to 215 countries and territories, with 125,234,087 total confirmed cases and a couple of,749,397 total deaths globally.[20] The seemingly unending global health catastrophe associated with the pandemic has inspired great urgency in the global search for preventive and therapeutic interventions for the disease. Being viral in nature, attention has been majorly centered on development or discovery of new antiviral agents and immunotherapy.Vaccine development and convalescent plasma infusion have received more attention over the last one year with little or no focus on monoclonal antibodies.

Monoclonal antibodies (mAb) area unit monospecific antibodies. They are produced by identical plasma cells originating from a single progenitor parent cell thus binding to the same antigenic epitope and with monovalent affinity, whereas polyclonal antibodies are produced by different clones of plasma cells and bind to different antigenic epitopes. Given almost any substance, it is possible to produce monoclonal antibodies that specifically bind to it; which can then serve to detect or purify that substance. This has become an invaluable tool in biomedical science and biotechnology. For many years ago, researchers have had problems with serological diagnosis of infectious diseases in the sense that the antibodies generated then were polyclonal. Such antibodies have low sensitivity, specificity and avidity. It was after 1816, when Milstein and Kholler discovered “MONOCLONAL ANTIBODIES” from myeloma cells that significant progress was made in its application. The mAbs obtained from their experiment were observed to be advantageous in the sense that they have a higher sensitivity, specificity and avidity. Other advantages include: homogeneity and consistency, absence of lot-to-lot variation in reactivity and reduced risk of infectious diseases.[21,22,23]

being antibodies (mAbs) area unit terribly specific and versatile, and by this reason have found nice connectedness in therapy and diagnostic techniques.[20,21] presently, humanized mAbs instead of murine mAbs area unit typically used because the therapy for human diseases. The development of monoclonal antibodies has consistently opened doors to new approaches of handling human challenges especially in prevention of diseases. Based on their specificity, they bind to specific targets thus mimicking, blocking or causing changes that enact precise mechanism thus providing an effective therapeutic intervention.[24] It has been established that neutralizing antibodies are a critical component of the adaptive immune response against most viral infection. This gives hope to the promising potentials of monoclonal antibodies in the treatment and management of COVID-19. Antibodies are produced in a complex form that can bind with several antigenic epitopes. These can be individually isolated, so one can know which antibodies made by a convalescent individual really have virus-neutralizing capacity. The portion of the antibody that recognizes the virus can be engineered into a manufacturing platform to make monoclonal antibodies. Monoclonal antibodies may therefore be considered to provide short-term protection from SARS-CoV-2 and serve as important components of the COVID-19 pandemic response.[16]

Neutralizing monoclonal antibodies to SARS-CoV-1 have been reported to have potentials for both therapeutic and prophylactic applications and may guide the vaccine design and development.[25] The role of neutralizing antibodies as an important part of the adaptational response to most infectious agent infections stems from the pathophysiology of infectious agent infections. Monoclonal antibodies are used as an efficient therapy technique for clinical treatment and prevention of infectious diseases and are therefore proposed for COVID-19 diagnosis and treatment. Viral infection requires an interaction between viral surface protein and the surface of host’s cell or tissue.[26,27] In the case of SARS-CoV-2, interactions between the receptor binding domain on spike protein of the virus and angiotensin converting enzyme 2 (ACE-2) receptors on the surface of numerous human cells are critical in establishing an infection.

Neutralizing being antibodies targeted to those binding sites have the potential to dam the interaction and ultimately inhibit attachment, the terribly start in virus-host cell interactions, so subsiding infectious agent entry into the infections like viral hemorrhagic fever, MERS, SARS; has been found to scale back the morbidity cell.[28]

Some strategies being employed through the use of monoclonal antibodies include:

- Neutralization of SARS-CoV-2-CTD-ACE-2 interaction by monoclonal antibodies
- Blocking ACE with anti-ACE2 monoclonal Antibodies
- Inhibiting proteases by monoclonal antibodies
- Blocking of cytokine storm especially by anti-interleukin 6.[28]

From previous available research, the use high-titre serum for the treatment of viral infections such as Ebola, MERS, SARS; has been found to reduce the mortality rate.[29-33] This lends support to the findings of Walker *et al.*[34] that passive protection antibodies that detects epitope region from foreign particles of the virus might cut back virus proliferation and illness severity. Since SARS-CoV-1 and SARS-CoV-2 are rumored to be connected, researchers have thus suggested the employment of respiratory illness antiviral being antibodies within the treatment of COVID-19 patients. Majority of SARS antiviral monoclonal antibodies have been discovered to identify the S1 fragment of SARS-CoV-1[30] and Receptor Binding Domain (RBD) in the subunit S1 has been proposed as the most important target for SARS-CoV-2 as monoclonal antibodies can hinder and block the association between RBD and its ACE2 receptor.[31] Most monoclonal antibodies signal the epitopes in subunit S2 of SARS-CoV-1 which suggest that other mechanisms may play a role in neutralization.[35,36] The combination of monoclonal antibodies targeting S-proteins in SARS-CoV-1 detects different epitopes both *in vitro* and *in vivo*. This can be potentially effective at the viral level; for example, CR3022 alone did not show neutralization, but a mixture of CR3022 and CR3014 showed neutralization.[37]

A good understanding of the molecular mechanism of action of any infection or disease is pivotal to the successful applications and design of approach for monoclonal antibody intervention. Prior knowledge of other human coronaviruses has expedited the understanding of the molecular structure of the SARS-CoV-2 spike proteins. At present, it is known that there is about a 77.5% similarity within the primary organic compound sequence of spike proteins between SARS-CoV-2 and SARS-CoV-1[38], disposition credit to the sturdy relationship between SARS-CoV-1 and SARS-CoV-2. Although, differences exist at some regions (at the C-terminus residues of the RBD) of both viruses, sequence analyses of the spike macromolecule have shown that each viruses area unit similar. Also, the life cycle and pathogenicity of both viruses are alike and thus suggesting similar pathogenicity. Consequently, since the specific antibodies against SARS-CoV-1 targets its receptor binding sites and were also effective in neutralizing its activity as well as inhibiting its binding, it can therefore be expected that specific antibodies against SARS-CoV-2 may also be effective in preventing its receptor binding too.[26,39,40,41]

Furthermore, SARS-CoV-2 shares the ACE-2 receptor with SARS-CoV-1, while MERS uses the DPP4 receptor. Studies even showed that the RBD in SARS-CoV-2 'S' protein bound strongly to human and bat angiotensin-converting enzyme 2 (ACE-2) receptors than SARS-CoV RBD. This indicates that SARS-CoV-2 uses ACE2 as its receptor. Similar to other human coronaviruses, SARS-CoV-2 is made up of two groups of proteins; the structural and non-structural proteins. The structural protein which is of most relevance to the subject of discussion is further grouped as spike proteins (S), membrane proteins (M), envelop proteins (E) and nucleic capsid protein (N). The spike protein (the receptor binding domain) which has been noted for its indispensable role in interaction with ACE2 on the human cell surface is cleaved by proteases into S1 and S2 subunits. The S1 monetary unit is any divided into a C-terminal domain (CTD) Associate in Nursingd an N-terminal domain (NTD) each of which might operate as a receptor binding entity. SARS-CoV and MERS-CoV utilize the S1 CTD to recognize receptor binding domain (RBD).[39,42,43]

Sui *et al.*[26] had earlier reported that an anti-S1 human monoclonal antibody 80R with a nanomolar affinity potently neutralizes SARS-CoV-1 infection by binding to the conformational epitope (amino acid residues 426-492) on S1 fragment of SARS-CoV-1 and efficiently inhibits the interaction of S1 subunit protein with cellular receptor ACE2. If the antibodies will neutralize SARS-CoV-1, there's a powerful indication that very same might occur with SARS-CoV-2 based on the level of similarities in the amino acid sequence of both viruses. Furthermore, a study on the structural details at the binding interface reveals that residue substitution in the SARS-CoV-2-CTD slightly strengthen the interactions resulting in about a four-fold increase in affinity for receptor binding than SARS-RBD.[38] This may account for the higher infectivity of SARS-CoV-2 compared to SARS-CoV-1. Present knowledge suggests that monoclonal antibodies can effectively block the SARS-CoV-2-CTD-ACE2 interactions even though most of the monoclonal antibodies targets against its other counterparts (human coronaviruses which includes SARS-CoV-1 and MERS-CoV) have not

successfully blocked infection despite their binding to the SARS-CoV-1, suggesting that there is an antigenic variation between them.

A couple of monoclonal antibodies have proven to bind to SARS-RBD and SARS-CoV-S but not to SARS-CoV-2. They include B30A38, A50A1A1, and C31A12.[29,37] This suggests that most monoclonal antibodies available at present are not effective against SARS-CoV-2, but those from convalescent plasma may be used as template for the production of monoclonal antibodies using hybridoma technology. Further studies have reported some human neutralizing antibody block SARS-CoV-2. Some of these antibodies include B38, H4 and 47D11. Others such as CR3022 have however not shown the ability to neutralize SARS-CoV-2 except when combined with CR3014[44]. The 47D11 antibody was discovered by Wang and his team[39] using ELISA cross- reactivity approach. This group of scientists assessed antibody-containing supernatant obtained from immunized transgenic H2L2 mice. In their experiment, 47D11 was found to bind to SARS-CoV-2 and SARS-CoV-1, and to potently block the virus' infection of Vero cells (a type of cell line). The chimeric 47D11 H2L2 antibody was reformatted and expressed as a fully human IgG1 isotope antibody for further study. Using ELISA, 47D11 was shown to target the S1B receptor-binding domain (RBD) of SARS-S and SARS2-S and prevent the binding of S protein to the human-ACE2 receptor. The study also showed that 47D11 neutralizes SARS-CoV-1 and SARS-CoV-2 through a yet unknown mechanism that is different from 86 receptor binding interference. The research report declared that the 47D11 binds a conserved epitope on the spike receptor-binding domain and cross-neutralized SARS-CoV-2. The cross-reactive nature of 47D11 shows that the antibody is more possible to target the conserved core structure of the S1B receptor binding domain. Hence these neutralizing antibodies can reduce the course of virus action in the host or defend an uninfected host that is exposed to the virus.[30]

Wu and his team also reported another four promising monoclonal antibodies (B5, B38, H2, and H4) collected from a convalescent patient. They discovered that all the antibodies bound to SARS-CoV-2 receptor-binding domain (RBD), but not to SARS-CoV-1 RBD. Evaluation of the ability of each antibody to block RBD and ACE binding showed that B38 and H4 fully competed with ACE2 for binding to RBD, whereas B5 displayed partial competition, while H2 did not compete with ACE2 for RBD binding.[44]

Furthermore, a number of monoclonal antibodies that have been designed to manage COVID-19 include Tocilizumab (TCZ) and Sarilumab. SARS-CoV-2 is known to induce a dose-dependent production of interleukin-6 (IL-6) from bronchial epithelial cells[45,46] Excessive IL-6 induces cytokine storm which activates the coagulation pathway and vascular endothelial cells, while inhibiting myocardial function. Cytokine storm has been reported to be responsible for some of the most severe complications of COVID-19. Tocilizumab blocks the IL-6 receptors thus hindering the resultant effect of the cytokine storm. It has been approved by the FDA for the treatment of severe or life-threatening cytokine release syndrome caused by CAR T-cell therapy (an innovative immunotherapy against leukaemia). The major setback in the use of TCZ is the associated immunosuppressive effect. This poses a significant risk of infection that could be harmful in patients with severe COVID-19 pneumonia.[12,47] Similarly, Sarilumab targets the IL-6 receptor. Its setback however is rheumatoid arthritis indications which can nevertheless can still be managed with some JAK-inhibitors such as Anakinra and Barcitinib.

In another study at Monoclonal Antibody Discovery (MAD) Lab, Fondazione Toscana Life Sciences, Siena, Italy reported that mAbs are likely to become one of the first available therapy for COVID-19 patients. Preliminary evidences showed that administration of plasma from infected people improves the outcome of patients with severe disease, therefore it is highly possible that a therapeutic and/or prophylactic mAb-based intervention can be highly effective.[48]

Furthermore, vaccination strategies inducing neutralizing antibodies have shown to protect non-human primates from infection.[49] These results further stress the importance of mAbs as an intervention tool to counterattack SARS-CoV-2 infection and to constrain its spread. In the experiment, it was addressed whether mAbs recognizing SARS-CoV-2 can be recovered from memory B cells of people who survived COVID-19, and whether some of them would be able to neutralize the virus. Data showed that SARS-CoV-2 specific mAbs can be successfully isolated from most convalescent donors even if the frequency of S-protein specific memory B cells is highly variable among them. In addition, approximately 28% of isolated mAbs were able to inhibit the binding of the S-protein to the receptor(s) on Vero E6 cells. The work of Wan *et al*.[49] also showed that a fraction of the isolated mAbs (N=17) were able to effectively neutralize SARS-CoV-2 with high potency when tested *in vitro*. These data suggested that the method they implemented allows them to successfully retrieve mAbs with potent neutralizing activity against SARS-CoV-2.

Also, while studying a cohort of 175 COVID-19 recovered patients with mild symptoms, SARS-CoV-2-specific neutralizing antibodies (NAbs) were detected at the convalescent phase of infection from day 10-15 after the onset of the

disease and remained thereafter. This is in spite of variable titers of NAbs found in different patients. Plasma NAbs titers in elderly and middle-age patients were significantly higher. Plasma C-reactive protein (CRP) levels were positively correlated with NAbs titer. The NAbs titer negatively correlated with the lymphocyte counts of patients at the time of admission; it could suggest that other immune responses, including T cells or cytokines, may contribute to the recovery of these patients. One of the important practical results of this study was the highly variable levels of NAbs in COVID-19 patients. It could indicate that convalescent plasma and serum from recovered donors should be titrated before use in passive antibody therapy; an easy task that can be performed using the PsV neutralization assay [44]. According to Evan *et al.*[50] convalescent plasma or serum with neutralizing antibody titer of >1:640 should be used for treating patients with severe COVID-19 cases, hence the need for titration before commencing therapy for better clinical outcome.

Future Focus of COVID-19 Monoclonal antibodies

presently, there is no established cure to combat COVID-19 and the current management of the patients is based on symptoms and supportive care. Monoclonal antibodies can be employed not only as the immunotherapy, but also for producing vaccines against COVID-19[51] Developing safe and potent monoclonal antibodies might change the landscape of the pandemic. Although Tia *et al.*[52] had earlier reported that the RBD of SARS-CoV-2 differs largely from the SARS-CoV-1 at the C-terminal residue; this contradicts previously reported studies and implied that monoclonal antibodies specific for SARS-CoV-1 may not be effective in neutralizing SARS-Cov-2. However, based on the other similarities between the two viruses, there is still a strong indication that SARS-Cov-2 specific monoclonal antibodies, when produced, will have a neutralizing effect on the virus and may be a strong therapeutic agent in combating the infection.[15]

The present literature about the potential role of monoclonal antibodies provides an insight and basis for use as passive antibody therapy against SARS-CoV-2. But, the side effect of using antibodies to prevent and protect against pulmonary SARS-CoV-2 should be considered with care.[53] Furthermore, understanding the action and mechanisms of neutralizing monoclonal antibodies performance will provide valuable implications for antibodies in treatment of COVID-19 in the near future.[54] Hopefully, monoclonal antibodies found to be highly effective against SARS-CoV-2 will be cloned and expressed in appropriate vector such as mammals, yeasts or plants. Expression system in plants can be used for the rapid production of monoclonal antibodies within a short time and at a very low cost, so as to make it available for COVID-19 patients[31]

Furthermore, infectious disease experts and biotechnology companies are optimistic that monoclonal antibodies may provide short-term protection from SARS-CoV-2 and could serve as a major pharmaceutical breakthrough pending the availability of vaccines. Since the outbreak assumed a global dimension, up to twenty-one (21) biotechnology companies across the globe have commenced the process of developing monoclonal antibodies, and are optimistic that it will become an intervention tool in combating the pandemic.[16] Two 'Phase 3, randomized, placebo-controlled, double-blind clinical trials' on the efficacy of experimental monoclonal antibodies (mAbs) in preventing infection by SARS-CoV-2 have also enrolled healthy adults at clinical trial sites in the United States of America. Many of the trial sites and study investigators are part of the COVID-19 Prevention Network (CoVPN) recently established by the National Institute of Allergy and Infectious Diseases (NIAID), one of the National Institutes of Health.[55]

One trial is being conducted jointly by NIAID and trial sponsor Regeneron Pharmaceuticals of Tarrytown, New York. The trial will evaluate Regeneron's investigational double mAb combination, *REGN-COV-2*, which is designed to bind to two points on the SARS-CoV-2 spike protein and prevent it from entering healthy cells. The trial is enrolling approximately 2,000 asymptomatic adults who are household contacts of persons with COVID-19. Participants must have been in close contact (typically due to residing at the same address) with the infected person in a 96-hour window preceding administration of either *REGN-CoV-2* or placebo. In addition to assessing safety, the trial also

Seeks to establish whether the trial drug can prevent infection in susceptible individuals or ameliorate disease symptoms in those already infected. The efficacy assessment will be a one-month period following administration of REGN-COV-2 or placebo. All trial participants will be followed for safety for seven months after efficacy assessment period ends.

A second randomized trial sponsored by Eli Lilly and Company of Indianapolis, Indiana, and implemented in collaboration with NIAID, evaluated the efficacy and safety potentials of LY-CoV555 compared to placebo, over an 8-week period. LY-CoV555 (also known as bamlanivima) is an investigational monoclonal antibody (mAb) isolated from a recovered COVID-19 patient by scientists at AbCellera (Vancouver, British Columbia, Canada) and the NIAID Vaccine Research Center, and developed by Eli Lilly and Company. The trial is a part of the ACTIV-2 master protocol which

started in August, 2020. It was designed to assess whether LY-CoV555 can prevent SARS-CoV-2 infection among people at high risk of exposure due to residing or working in skilled nursing or assisted living facilities. It was also designed to evaluate its efficacy in preventing symptoms of a given severity in those already infected[16]. The trial which was designed to enroll about 2,400 participants, was however, closed to new enrollees on October 26, 2020, after the independent Data and Safety Monitoring Board (DSMB) reviewed the data of 326 enrollees from stage 1 of the trial and made their recommendation known to the investigators. Although LY-CoV555 did not provide clinical benefit or accelerate clinical improvement (time to hospital discharge, sustained recovery and back at home for 14 days) compared to placebo at day 5 using the ordinal scale among hospitalized COVID-19 patients having no end-stage organ failure studied in this trial; in November, 2020, LY-CoV555 was granted an Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration (FDA) as the virus continue to escalate with more rising cases and deaths recorded in the country. The U.S. FDA however, authorized LY-CoV555 for use only in non-hospitalized adolescents and adults with mild to moderate COVID-19 symptoms who are at elevated risk of progressing to severe COVID-19 disease pending the other outcome of other trials[56,57]

Meanwhile, another two randomized, controlled Phase 3 clinical trials sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health have commenced evaluating VIR-7831, BRII-196 and BRII-198 for their efficacy and safety in the treatment of patients hospitalized with moderate COVID-19. The trials are part of the ACTIV-3 master protocol, which has an adaptive design allowing investigators to add new sub-studies of additional investigational agents. One sub-study is evaluating VIR-7831, a monoclonal antibody developed through a partnership between Vir Biotechnology, Inc. (San Francisco) and GlaxoSmithKline plc (Brentford, United Kingdom). The other sub-study is evaluating the combination of BRII-196 and BRII-198 (synthetic versions of antibodies produced naturally by humans) manufactured by Brii Biosciences (Beijing, North Carolina and Durham). At the outset, investigators will enroll approximately 450 volunteers who have been hospitalized with mild to moderate COVID-19 with fewer than 13 days of symptoms. After five days, the participants' symptoms will be evaluated on a seven-point ordinal scale ranging from being able to undertake usual personal activities with minimal or no symptoms, to death. If an antibody appears to be effective and safe, each sub-study will enroll an additional 700 people. Half of the enrollees (350) will be assigned to receive the intervention, while the other half (350) will receive the placebo. The new group of volunteers may include those with more severe illness. The primary endpoint of the trial is the participants' sustained recovery for 14 days after release from the hospital[16,57] While these trials are ongoing, there is need for comparisons, which is why it's good to have an organization like the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) to bring all important stake-holders together, making sure everyone is using the same endpoints and the same laboratory measures. It is also very important to devise and perfect a separate master protocol for outpatients and inpatients.

While significant progress is being made in exploring the potentials of mAbs as a COVID-19 intervention tool, some experts argued that polyclonal antibodies (pAbs) would be a better option since it may be able to grapple with the virus better considering the spherical confirmation of the virus, unlike the Ebola virus with a "flat" type of conformation. Whether potential agonist sites would be left open for contact or not, requires further investigation. To this end, in August, 2020, the National Institute of Health (NIH) commenced a Phase 2/3 trial to evaluate a new fully-human polyclonal antibody therapeutic (SAB-185) targeted to SARS-CoV-2 among non-hospitalized people with mild or moderate cases of COVID-19. The polyclonal antibody therapeutic was developed from the SAB's platform (SAB Biotherapeutics, Inc., Sioux Falls, South Dakota). This biotechnology platform uses genetically engineered cattle to produce fully-human antibodies. The primary objective of the Phase 3 trial is to determine if the SAB therapy prevents either hospitalization or death by 28 days after study entry. SAB-185 had demonstrated neutralization of live SARS-CoV-2 at titers higher than convalescent plasma in previous pre-clinical studies[58] the outcome of this Phase 2/3 trial is still being awaited.

CONCLUSION

The Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) can be effectively and therapeutically neutralized via monoclonal antibodies (mAbs). They are a promising entity to combat the virus and appear to be able to provide short-term protection for highly susceptible and compromised individuals. This has become a global health and commercial priority and as such more efforts and resources should be invested in evaluating its therapeutic/ prophylactic potentials. It is also very important and essential to isolate the antibodies raised by the different strains of SARS-CoV-2 in all countries currently affected. The isolated antibodies should be engineered into a manufacturing platform to make

monoclonal antibodies in large scale as they may serve as an immediate strategy for emergency COVID-19 prophylaxis and therapy, while alternative and more time-consuming development of vaccines and new drugs are underway. If this is successful, SARS-CoV-2 neutralizing antibodies may be used to prevent infection in people exposed to SARS-CoV-2, such as healthcare workers caring for suspected and confirmed COVID-19 patients, and may also be used for early treatment of infected individuals to prevent the onset of serious COVID-19 and to reduce the chance of spreading the virus to exposed individuals. To this end, other already existing platforms should be leveraged on in order to enhance the rapid production of mAbs that are affordable and distributable especially in the developing countries with very fragile health system, and while Scientists continue to explore the therapeutic potentials of monoclonal antibodies as an intervention, more work is required in learning and understanding the potential risks (side effect/adverse reaction) associated with their usage before they are deplored for immunotherapy, including dosage, duration of administration, and others clinical factors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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