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Review Article

Monoclonal Antibodies as Drugs for Covid-19 and Public Health Impacts: A Review

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Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a pandemic that blew and ravaged across the various global continents, starting in 2019. Over 71.4 million people have been infected globally, with more than 1.6 million deaths. It is sad to opine that in the United States, over 16 million infections have been recorded with over 290,000 lives lost to the pandemic. The risks have been high in high density cities, communities, among those aged above 65 years and persons with co-morbid clinical conditions. Where population is high, it provided easier means for spread and containment has been most tasking in such cities.

The burden inflicted on man has been huge across families, homes and small-medium-large scale firms. As such, the search for curative drugs and vaccines started. Funds support have come from various sources in the direction of preventive measures (use of face and nose masks, lockdowns with palliative support for some citizens, social distancing and hand washing among others), drugs (attempted use of non-immunotherapeutic and now use of immuno-therapeutic monoclonal antibody drugs) and vaccines. The first monoclonal antibody was approved by the United State Food and Drug Administration Department (US FDA) in 1986. Present monoclonal antibody drugs (mAbs) have proved effective with fewer side effects due to their high level of specificity.

With over 75 mAbs approved by the US FDA and engaged against several stubborn ailments, design and development of mAbs against COVID-19 have now followed for treatment of stubborn diseases. The mechanisms of action of majority of these immune-therapeutic antibodies used to treat COVID-19 patients has been by their being used to target the receptor binding protein domain (RBD) of SARSCoV-2 and block it from binding on to the receptor Angiotensin-converting enzyme (ACE) on the human body cell, to prevent entry of SARCoV-2 virus into the human cell and halt its commencement of life in the human cells and associated pathologies.

For instance, the monoclonal antibody drug named Bamlanivimab and later Casirivumab-Imdemivab mAbs combination drug, both approved under Emergency use authorization (EUA) by United States Food and Drug Administration (FDA), have been used to successfully treat COVID-19 patients in mild to moderate clinical conditions not requiring oxygen therapy with good level of success. Recently, a neutralizing antibody named AR-711 was found to clear signs of SARS-CoV-2 infection in hamsters even when it was administered at what was considered to be low levels. There are other clinical trials ongoing with other developed mAb products against COVID-19 by other leading drug research and production firms and institutional researchers but mostly from the developed nations.

These mAb drugs help check progression of infection, associated pathology in mild to moderately ill COVID-19 patients, keep patients in stable conditions to help reduce the rate of hospitalization, reducing the number of frontline workers put at risk and who are needed to manage COVID-19 patients, in Health care systems (including that of the United States), many of which are currently overstretched at this period of COVID-19 pandemic.

Now that some level of support from curative and preventive medicine are coming in through first set of vaccines breakthrough with EUA back up, by leading Pharmaceutical and Biotechnology firms and institutions in The United States and Europe (with over 90% vaccine efficacy and good safety levels and in one about 70% efficacy as reported from outcome of Phase three clinical trials), these therapeutic vaccines can now support urgent emerging responses with antibody clinical treatment. This will now couple ongoing preventive measures for an integrated Public health fight back against the dreaded SARS-CoV-2 virus and burden from its COVID-19 handbag disease.

Keywords: *Monoclonal; Antibody; Neutralizing; ACE Receptor; RBD Protein; Preventive; Public Health*

Introduction

Coronavirus disease-19 (COVID-19) is a pandemic that blew across the earth in 2019 and ravaged through various continents with cascade of turbulent high transmission waves. Its causative agent is the deadly sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The picture at the moment is not yet encouraging in terms of respite for man. As at December 2020, over 70 million were infected with SARS-CoV-2 worldwide with more than 1,700,000 deaths [1,2]. In America alone, it is sad to note opine that over 1.2 million infections have been recorded with over 240,000 lives lost to the pandemic. The risks have been highest in cities and communities with high population densities. Containment has been most tasking in such cities where population density is high, as provided easier means for spread.

The novel coronavirus (later named SARS-CoV-2) detected in 2019 is closely related genetically to the SARS-CoV-1 virus. SARS first emerged in late 2002 in China [1,3].

About 8 in every 10 people with COVID-19 will likely have mild symptoms, around 1 in every six people will likely become severely ill and need hospital care, while scientific modeling suggests that 1 in 100 people who get COVID-19 [4].

Many are bed ridden, many have lost parents guardians and children, homes (families) have been broken, companies, institutions, small, medium and large scale industries negatively affected or closed down, while some have lost their businesses and means of livelihood, as a result of this species of coronavirus which as mutated to produce strains. As such, the search for curative drugs and vaccines started, with funds pumped in by pharmaceutical and biotechnology firms, governments and philanthropists in the direction of drugs and vaccines, alongside the funds streamed into preventive measures to produce face and nose masks, ventilators for hospitals hyperbaric-oxygen therapy, build more temporary health care centres and add more hospital beds, employ more medical personnel, train front-line medical staff who face the toughest risks of infection and death and support individuals, families, businesses in the wake of lock-downs added as part of steps to break transmission routes for the spread of coronavirus.

Antibodies are protein based bio-molecules that are synthesized by our immune system. They function as part of the antibody mediated immune system, and often in synergy with the cell mediated immune system. Antibodies are umbrella name under which we have monoclonal antibodies. One of the major ways in which antibodies function is by binding to their specific targets foreign agents or foreign molecules or deranged body cells called cancer cells in the body such as pathogens, of which coronaviruses are part of them. The binding help trigger further actions in the body that lead to destruction of such pathogens or deranged body cells.

Antibodies are used as pre-exposure prophylaxis and post-exposure therapy against COVID-19 [5]. Monoclonal antibody based drugs are a class of drugs that have supported our avenues for treating ailments and preventing them. They have been used to tackle diseases of the immune system, cancer and the doors are now opening for their immunotherapeutic use against infectious diseases [6]. Monoclonal antibodies are naturally produced by the body's immune system [7,8] as part of its defensive lines of action against diseases and scientists have developed a means of creating them in the laboratory [9] and mass producing them in pharmaceutical and biotechnology firms.

Monoclonal antibodies have singular activity against pre-determined target while convalescent plasma consists of polyclonal antibodies in serum derived from patients who are convalescing from an infection [10]. As such, antibody therapy could be a bridge treatment to some coronavirus vaccines [11] as they have proved for some other communicable and non-communicable diseases.

Monoclonal antibodies help where vaccines cannot be used or don't work, such as in elderly old ones and those with co-morbid conditions who may not elicit enough level of protective response after they may have been vaccinated. Now, antibodies can be designed to switch-off hyper-immune responses responsible for cytokine storm [6] associated with the pathological manifestations in COVID-19 patients. Invariably, this helps to decelerate and halt progression of infection.

Significance of mAbs as drugs and Justification of narrative insight review

Monoclonal antibodies used in Cancer immunotherapy have saved millions of lives globally over the last few years. For instance, the mAb Herceptin has been a game changer against Breast cancer and multiple cancer [5].

The best selling drugs in the pharmaceutical market over the past five years has been mAbs, and 8 of the top 10 best selling drugs world-wide where biologics of which mAbs are components [9].

As previously highlighted, mAbs have provided a bridge treatment and prophylaxis when the world stood in suspense to await development of possibly successfully developed COVID-19 vaccines.

Convalescent plasma from the blood of donors who have recovered from COVID-19 have been found to contain antibodies that suppress the virus, progression of its infection and associated pathology such as inflammation and organ damages [12].

Technically, mAbs have been found to neutralize SARS-CoV-2 virus by blocking its ability to gain entry into human body cells to establish habitation and infection. As such, mAbs might prove life saving interventions in people who cannot respond with robust immunity against the virus. This can prove helpful to adults above 65 years and those with existing co-morbid clinical conditions.

Until a large percentage of a population has immunity to an infectious disease such as immunity acquired through a vaccine, there will still be reliance on other complimentary disease treatment management methods such as those involving use of mAb immunotherapy, anti-virals, antimicrobials, and preventive measures put in place. The resultant of not engaging other treatment management methods will be pandemic that remains threatening to the global community. These vulnerable people at most risk of infection can only get protection by herd immunity when majority of the population gain immunity either through vaccination or protective natural immunity. This is an immunological concept with clinical applications. Monoclonal antibodies have been designed to treat some the dreaded diseases such as Ebola and Tuberculosis [9].

Objectives of the Study

The objectives of this study are to:

- Do a review based exposition on the potentials of monoclonal antibodies in supporting management of COVID-19 in patients.
- Discuss the significance of monoclonal antibodies in reducing burden of COVID-19 disease.
- Highlight the supportive role of antibodies to vaccines and vice versa in therapy against COVID-19.

Bottle necks with mAbs as drugs for COVID-19

Obviously, availability of mAb will hinge on rate at which large quantities of the drugs can be produced the price based on cost of production by pharmaceutical firms.

In designing them, the concept of antibody dependent enhancement (ADE) must be put in consideration and antibody engineering techniques developed to prevent this from happening.

Monoclonal antibodies are more complex and more expensive to produce and most poor countries may be priced out; compared to most other types of drugs [11].

The main marketing and sales focus has inevitably been in high income countries, and as such mAbs are more common in the United States, Canada and Western European nations where prices of commodities are fairly more stable, the average daily income and purchasing power higher are significantly higher. It is worth noting that mAbs have been difficult for generic drug manufacturers to reproduce the exact replicas.

Suggestions to address these bottlenecks in mAbs as drugs for COVID-19

Further research by Biotechnology firms that would reduce costs of mining data and genetic banks for candidate proteins for mAbs, the design of such mAb drugs, development and production of mAb drugs; support by Federal and State/Provincial governments to either subsidize thee prices or financial inducement to actual firms that developed these mAb drugs which would encourage them to partner with other Pharmaceutical firms who would produce them at cheaper prices; the use of Biosimilar products to reduce cost of production; support by philanthropists to give out free mAb drugs to individuals confirmed to be poor to afford these drugs and those in critical health conditions who do not have enough to purchase them, creation of standard online app that helps build credible network and partnerships between patients, patients-clinicians, clinicians, and patient-philanthropists and philanthropist-mAb drug manufacturers, for supporting patients' care, and more importantly those cases needing urgent mAb drugs support to overcome their dire health challenges where conventional drugs have not worked and engagement of second brand of same product.

Monoclonal antibodies designed and deployed to treat cancer have saved multitudes of lives over the past few decades.

Mode of action of monoclonal antibody drugs

The mechanisms of action of majority of therapeutic antibodies used to treat ad manage COVID-19 patients has been by their being used to target the receptor binding protein RBD domain protein of SARS-CoV-2 which normally binds on to the ACE receptor on the human body cells to gain entry into the human cell and establish metabolic life, sustained and progressing infection.

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Monoclonal antibody treatment mimics the body's natural immune response and targets foreign agents and pathogens in the body.

Recently, a neutralizing antibody named AR-711 was found to clear signs of SARSCoV-2 infection in hamsters even when it was administered at what was considered to be low levels [13].

Vaccine science has enabled the recovery of RBD protein specific B-cells from COVID-19 patients via isolation techniques, to pave way for production of antibodies having neutralizing capacities on SARS-CoV-2. As such, monoclonal antibodies have been engineered into useful clinical tool. This is now evident in its positive engagement in clinical research [14]. There are now various technologies in antibody immunotherapy against COVID-19 of which now embraces breath-taking discoveries in use of emerging nanobody and sybody technologies. Nanobodies and sybodies [15] have their individual impressive attributes just as normal antibodies, monoclonal antibodies, multiclonal antibodies and recombinant monoclonal antibodies.

The therapeutic signatures offered by mAbs should be encouraged and improved upon where necessary, and adventures into synergistic product development and engagement with other antibody based drugs like nanobodies (promising single domain tiny antibodies with attributes of specificity like mAb alongside and added qualities of stability that allows aerosolized administration, high penetrating capacity of these nanobodies), sybodies (synthetical nanobodies designed based on elucidative structure of nanobody- target complexes

with qualities of swift selection of against any target protein within very few working days that can be less than 15 days which is faster than that of nanobodies and monoclonal antibodies), recombinant human antibody hyper-immune therapy technique and other forms of nano-technologies that may likely emerge in future should be explored as appropriate and workable in the involved technologies.

Monoclonal antibody drugs for emergency treatment of COVID-19 patients approved by some governments

Bamlanivimab mAb drug and recently Casirivumab-Imdemivab mAb combination drug, both received approvals by the United States Food and Drug Administration Department [16,17]. They have both being used to prevent the deadly and invasive coronavirus from invading cells. These two sets of mAb drugs are both monoclonal antibody based and designed drugs which help to manage and check progression into severe form of infection and associated pathology in mild to moderately ill COVID-19 patients. Invariably, they help to keep patients in stable conditions that tend to reduce the rate of hospitalization of COVID-19 patients in Healthcare systems [11,16], which are currently being overstretched in this period of COVID-19 pandemic, during both the first and second wave of transmissions of infection. These liquid form antibodies that are intravenously administered take 2 or more hours for infusion to be completed.

Some monoclonal antibody drugs on approval list of United States Food and Drug Administration of the United States

Typical mAbs drugs therapeutically used by clinicians against specific ailments and on approval list of the United States Food and Drug Administration of the United States includes Abciximab (with brand name Reopro), Alefacept (Amevive), Alemtuzumab (Campath), Infectra (Remicadel), Natalizumab (Tysabri), Olaratumab (Lartruro), Peubrolizumab (Keytruda) and Basiliximab (Simulect) [4]. Monoclonal antibodies have been used to treat clinical conditions such as Rheumatriod Arthritis, Systemic Lupus Erythromatosus, Cancer and Transplant rejection. There are currently over 75 mAbs on FDA list of approved mAbs and have come in handy in supporting difficult cases where conventional drugs have met stiff blocks from certain clinical condition [18].

Monoclonal antibodies, from bench-side to bedside: Translational immunotherapy

Success in convalescent plasma research on our laboratory bench sides inspire development and engagement of monoclonal antibodies with clinical usage on patients while success in monoclonal antibody research guide design and development of preventive or therapeutic vaccines. Monoclonal antibody targets and inhibits action of a receptor involved in development of a clinical condition being treated, such as developed mAb already existing for treating cancer.

Monoclonal antibodies for SARS-CoV-2 targets and interferes with the action of a chemical receptor known to be involved in the condition being treated. In cancer, one of the ways mAb work is by being used to block a receptor that cancer cells use for preventing the Immune system from destroying the cancer cell, which allows their immune system to recognize cancer cells and destroy them [18].

However, the precise time required for these antibodies to establish required level of action and clearances of the viral load is yet to be ascertained. The therapeutic effects of these antibodies have been confirmed from treatments on high profile personalities who got infected with symptomatic expressions of COVID-19, such as one of the most recent United States Presidents. Cytokine storm which contributes to pathology of Covid-19 can now be halted with antibodies designed to shut down hyper-immune responses, thus making it halt progression of malaria [6].

They have side effects varying from simple common effects like cold, fever and headache among others [18]. The administration of mAbs is with caution as some have capacity to interfere with administered live vaccines and vice versa (including attenuated vaccines), as these side effects manifest when patients receive vaccination while being on treatment with mAbs. Patients are normally urged to complete all immunizations before receiving mAbs treatment [4]. For instance, Casirivimab and Imdevimab mAb drug combination used on C0VID-19 patients specifically attack the spike protein of Sarscov-2 and block this virus from engaging successful binding on it, a precursor event that leads to entry of virus into human cells during infection [4].

Majority of mAb drugs licensed by the US FDA are used to treat non-infectious diseases [5]. Though monoclonal antibodies have side effects, the newer ones are being designed to have fewer side effects. Antibody as drugs has added to the frontiers of options for chemotherapy [7,19] as biologics, as cell therapy kicks off to add to this pool of options for managing and treating diseases [20] in what is now called smart cell therapeutics of the future.

Public health implications of monoclonal antibody drugs to treat COVID-19 disease

Until herd immunity is reached, the most vulnerable groups in our communities and cities who cannot get vaccinations will not be protected against COVID-19. Herd immunity can only be reached when majority of the population gain immunity, such as through vaccination or by natural immunity. Monoclonal antibody designed drugs like Casirivimab-Imdemivab [6] and Bamlanivimab [17] helps manage and check progression of infection and related pathogenesis in mild to moderately ill COVID-19 patients. Invariably, they help to patients in stable conditions that reduce the rate of hospitalization or emergency visits in patients at high risk for disease progression to severe form of COVID-19 patients within 28 days after treatment in children of 12 years and older and even adults above 65 years [4]. This helps cushion the huge pressure and burden on Healthcare systems that are currently being overstretched in this period of COVID-19 pandemic. Added impact are in area of reducing the number of frontline workers required to attend to COVID-19, thus lowering chances of increased exposure of more frontline workers to the daunting risks. Many front line workers, including clinicians, Nurses, Paramedics and other Emergency health workers have been unfortunately lost in this pandemic. Obviously, this would add to burdens in families, communities and some organizations world-wide.

As such, the development and use of antibody drugs, such as monoclonal neutralizing antibodies is a welcomed positive omen on public health and of health promotional value, in the face of a devastating pandemic COVID-19 scourge. The recent vaccine breakthroughs coming in, will couple the bridge prophylactic and therapeutic treatment that mAbs have offered clinicians, nurses and trained emergency health workers, and synergize with ongoing preventive measures for an integrated Public health actions to stem down and check SARS-CoV-2 and its COVID-19 disease burden. These COVID-19 mAb drugs listed here received EUA approvals from FDA to help bridge the need for emergency treatment options while studies continues on their safety and efficacy, even as the earliest set of successful COVID-19 vaccines produced by Pfizer-BioN Tech, Moderna received emergency use authorizations EUA approvals from US FDA; and the vaccine developed by Oxford University-Astra Zeneca team also got emergency use approval in the United Kingdom in the wave of the urgency, to save some more lives, as remaining tests on them are done alongside. However, the emergence of variant strains of SARS-COV-2 has increased the tests to be done on all these vaccines and determine efficacies under the new conditions we find ourselves in this pandemic.

The risks have been unfortunately high in high density cities as experienced in major cities in New York, California and New Jersey in the United States, some high density cities in Western European countries. Where high counts of people are closer together and it provided easier means for spread and controls more difficult. The battle is still on both preventively and for effective, safe and functional drugs and vaccines to strongly buffer and support preventive measures put in place by most nations and institutions globally, with huge negative impacts on individual and national economies, alongside very possible socio-psychological effects.

Multitudes of lives have been lost with huge burdens on family and community health as a result of infections, morbidity and mortality due to this SARSCoV-2 species of coronavirus [1]. The species of SARS-COV-2 has been recorded from molecular diagnostics to have mutated into variant strain [21,22]; and variant strains have emerged in United Kingdom, United States, South Africa and Nigeria among other nations. This capacity for mutation has been confirmed from various genomic studies on SARS-CoV-2 and its predecessor SARS-CoV-1. The implications are been studied and just emerging. Our Public health authorities are now on their toes to monitor the extents and spectrum of mutations and pattern of spreads of such mutant strains. This will help against future outbreaks that we must pre-empt, watch and be prepared against. This is a vital principle in emergency management in Public health responses.

The main preventive measures applied with global outlook have been isolation of infected persons for treatment and management against transmission to others, quarantine of persons who travel from a country to another or from a state to another, use of face-mouth and nose masks, use of alcohol based hand sanitizers, contact restrictions and lockdowns that curtailed activities involving travels, work and businesses. Invariably, these measures have altered the psycho-social environment in deeply affected countries and carried along with it potential to put pressure on mental health of children and adolescents [23], neither are adults speared [24]. In a difficult situation like this, there are sacrifices to be made to cope and possibly surmount the pandemic on the long run. These are part of the challenges and public health burden, albeit, pool of its effects.

Its added impact is reducing the number of frontline workers against COVID-19 who would need to be absorbed periodically and in increasing number, thus lowering chances of increased exposure of more frontline workers to the huge risk of taking care of COVID-19 patients.

When persons infected with SARS-CoV-2 who are in quarantined and isolation centres receive the approved antibody treatments, it would help reduce chances of transmission of SARS-CoV-2 virus to uninfected persons, especially those categorized to be as high risk groups.

Conclusion

As COVID-19 is shaping into a phase of new waves of high rates of infections in the United States and many parts of Europe, and uncertainties as to when the waves will seize, our responses will require dynamics and flexibility that gives room for bridge treatment uses of mAbs, especially to most vulnerable groups. Monoclonal antibodies provide emergency bridge treatment not only against non-infectious diseases for which they are mostly designed, and now development of mAb drugs against infectious diseases is picking up and those for COVID-19 have not been an exception. This is good news, as our treatment options increases and support the potentials offered by antivirals, anti-microbials, hyperbaric oxygen support of critically hospitalized patients. Monoclonal antibody drugs are stepping in and filling bridge treatment gaps, alongside vaccines that are streaming in as added clinical therapy options.

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