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A Review of Updates on Vaccines and Treatment Options for Covid-19

Abstract

The novel Coronavirus known as Covid 19 or SARS-CoV-2, is a newly discovered virus responsible for the huge global pandemic infecting the human race at a deadly pace. This is an RNA enveloped virus that targets the human respiratory system severely while damaging other major systems. Covid 19 pandemic is similar to the severe acute respiratory syndrome related coronavirus (SARS-CoV) endemic and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), but this one is spreading at a fire-speed. The outbreak was known as pneumonia in the beginning; however, it became a threat later on, owing to its high contagion rate. The origin of this virus was sought to be from the seafood wholesale market, very popular in the city of Wuhan. This review has been put together to overview the disease, its etiology, clinical features and treatment methods. The focal point of this review is to highlight the current management of this disease.

Key Words: Covid-19, SARS-CoV-2, Treatment Methods, Current Management

Introduction

The infamous Severe Acute Respiratory Syndrome Coronavirus is relative to the SARS-CoV and MERS-CoV. After the rapid spread of what seemed like pneumonia- in the capital city of the province Hubei, Wuhan - a virus was identified in early January 2020 ([Hassan et al., 2020](#)). The virus did not give away after infecting and killing thousands of people in China. Rather moved out of there to infect Italy, the USA and Europe at a rapid rate ([Pascarella et al., 2020](#)).

The SARS-CoV-2 enrages a high infective alert worldwide as it is highly contagious and affects the respiratory system, and causes enteric infections. It gives rise to symptoms that are similar to that of flu, including fever, coughing and fatigue. This disease was named “*coronavirus disease 2019*” by the World Health Organization and was declared a pandemic ([Pascarella et al., 2020](#)). SARS-CoV-2 is responsible

for causing Acute Distress Syndrome (ARDS) and results in multi-organ failures. These severe outcomes of being infected by coronavirus results in acute respiratory failure; thus, death is the fate of the patient. This is more liable in elderly individuals and people with multi-morbidities as this population is at high risk. Such individuals, when infected, are prone to dyspnea and radiological signs ([Hassan et al., 2020](#)). The summary of this disease, its clinical aspects, and proposed treatment management is the main feature of this writing.

Method

Online databases were used to carry out a systematic literature review of clinical aspects and treatment management of the coronavirus disease. The articles reviewed were recovered from Google scholar, PubMed and Medline, the key terms of which were

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“COVID-19”, SARS-CoV-2” and “coronavirus”. The scientific publications from 2019 -2020 were kept under consideration. It was made sure to include only those publications can have focused on the clinical features and treatment methods for coronavirus. Any publication that may be missed has been identified via screening of all reference lists.

The articles worthy of inclusion are available for full-text review. The publications chosen were in English only.

Covid-19 Clinical Aspects

When a person becomes infected with SARS-CoV-2, the virus not only enters and damage the lungs but also enters various parts of the body via the blood. The common symptoms include fever, fatigue, loss of taste and smell, sneezing, diarrhea, with some other non-specific symptoms. All this happens during incubation and the early stage of the disease. The incubation period of SARS-CoV-2 is 14 days. During the first seven days, the virus enters vital organs of the body and most abundantly into the tissues having ACE-2 receptors (Li, Lu and Zhang, 2020) (Khuroo, 2020), where SARS-CoV-2 basically attaches and replicates quickly, which then leads to the production of ‘cytokine storm’ with the beginning of symptoms.

During the next seven days, the virus attacks the body, and the immune system becomes weak because defending cells of the body are significantly reduced, which were at the normal level during the first seven days, but with the considerable increase in the virus, the body becomes weak, and abrasions caused by the virus in lungs become worse which is indicated by the significant changes seen from Chest CT scan (Li, Lu and Zhang, 2020).

Updates on Vaccine Development

RNA Vaccine

RNA vaccines are new generation vaccines- instead of antigen, they contain mRNA. When they are injected into the body, they encode an antigen which is then recognized by our immune system and produces antibodies. Recently, the development of a vaccine is measured on the basis of effectiveness and immunogenicity (Petsch et al., 2012, Pardi et al., 2017). In order to increase the production of antigens inside the body, a non-toxic and more workable RNA vector is developed (Pardi et al., 2015). To know about the immunostimulatory spectrum of mRNA, we can make complexes of mRNA with various carrier molecules, introducing improved nucleosides and by taking out in-vitro transcribed mRNA from the

mixture (Fotin-Mleczeck et al., 2011, Rettig et al., 2010). These vaccines can be degraded by nucleases enzyme inside the body, so these are made by special in-vivo and in-vitro techniques to prevent their degradation. When they reach the cytoplasm, the translation starts and make the required antigen. This mRNA property is suitable for vaccine and protein replacement therapies (Pardi, Hogan, Porter and Weissman, 2018). Among them is the BNT162b1 codon-optimized mRNA vaccine developed by Pifizer-Nbiotech. It is delivered as a lipid nanoparticle. The phase 1/2 clinical trials result in shows increased RBD-IgG antibodies geometric mean concentration titer is **8 to 46.3 times** titer of convalescent serum, which is more than SARS-CoV-2 titer antibodies which is **1.8 to 2.8 times** convalescent serum. No adverse effects were reported. Immune responses and safety do not persist for long, and two doses of vaccine are required (Mulligan et al., 2020). Some studies also show that after the first dose, its efficacy is 52%, while after the second dose, 95% (Polack et al., 2020, Tanne, 2020, Polack et al., 2020). Phase 3 trials also show their efficacy above 90% with the two-dose schedule.

Viral Vectored Vaccine

These are very effective in gene transduction and boosting immune response. They deliver the genes to targeted cells (Ura, Okuda and Shimada, 2014). They induce cellular and humoral immunity and have greater potential to stimulate cytotoxic T-Cells, which eliminate virus-infected cells (Le, Kuriki, Phan and Taylor, 2019). Among them is, Ad5-nCov developed by CanSino biologics, Beijing Institute of Biotechnology. It is a recombinant, replication-defective adenovirus type 5. It contains recombinant spike proteins of SARS-CoV-2, which it expresses on its surface. It is formed by cloning a full-length gene of S-protein along with plasminogen activator, devoid of E1 and E3 and was developed by Admax system from microbic biosystem. It is the first vaccine to reach phase II trials (Draft landscape of COVID-19 candidate vaccines, 2021). Phase I trials started on March 16 to March 27, and data showed that it led to an increase in the number of antibodies within 14 days of vaccination and were maximum at day 28 after vaccination. CD4 T cell and CD8 T cell responses also reach a peak 14 days after vaccination (Zhu et al., 2020). Phase II will be conducted among people age 18 and 60. The antibody response will be tested at 0,14, 28 days and six months after vaccination (A Phase II Clinical Trial to Evaluate the

Recombinant Vaccine for COVID-19 (Adenovirus Vector) - Full-Text View - [ClinicalTrials.gov, 2021](#).

Repurposing of Vaccines

Along with all the initiatives are taken by many pharmaceutical industries globally in favour of producing a vaccine for coronavirus, research and development also has taken a direction towards benefitting from the already ‘in-use viral vaccines like BCG (Bacillus Calmette-Guerin), which is an anti-tuberculosis vaccine, MMR (Measles-Mumps-Rubella) vaccine and OPV (Oral Polio Vaccine). There are some non-specific effects of these vaccines that provide protection against certain diseases ([Pollard, Finn and Curtis, 2017](#)). If this research works out in our favour, then humankind will definitely acquire a feasible solution to this pandemic and that too, quite speedy. It will also save a lot of resources and money.

Murdoch Children’s Research Institute has funded the study for the repurposing of BCG vaccine in collaboration with Royal Children’s Hospital that can help protect the healthcare workers from Covid-19. As of October 22, 2020, the vaccine is in recruiting status. It is a freeze-dried powder, live attenuated strain of *Mycobacterium Bovis* (BCG), Danish strain 1331 (BCG Vaccination to Protect Healthcare Workers Against COVID-19 - Full-Text View - [ClinicalTrials.gov, 2021](#)). The trial designs are quite comprehensive. The potential effect of the BCG vaccine is underway and will provide evident results after these phase III trials. Several studies have shown promising prospect towards the off-label use of BCG vaccine against Covid-19. In accordance with these studies, the countries that have had a routine BCG immunization program were hit less severely by this global disease. The death toll was not as significant as those that were not following this regimen. There is still a need for confirmation of data regarding this, and WHO was not in favour of BCG for Covid-19 as of May 7, 2020 (BCG Vaccination for Healthcare Workers in COVID-19 Pandemic - Full-Text View - [ClinicalTrials.gov, 2021](#)).

Another study sponsored by Kasr El Aini Hospital suggests the use of MMR vaccine for the prevention of this highly contagious SARS-CoV-2. The study revealed an affirmative wing in prevention against Covid-19, as the highest titers of neutralizing antibodies, were induced in the mice that were susceptible to the measles virus when this vaccination was used (Measles Vaccine in HCW - Full-Text View - [ClinicalTrials.gov, 2021](#)). It also suggested that the mortality rate among children

below the age of 9 is extremely low comparatively due to the immunization routine of MMR vaccine in children. But as of December 22, 2020, its recruiting status had been suspended on account of the failure of subject recruitment.

In an analogous manner, OPV has been taken into consideration for repurposing, but the evidence is still not affirmed to support this stance. Research is still progressing in this direction, but however, if this shows promising results, OPV has a greater safety margin than BCG ([Chumakov et al., 2020](#)). BCG can cause adverse reactions, but OPV has a less complicated profile in terms of side effects. Along with that, it would also ease down the economic and production burden that is a major concern in establishing new vaccines because already over 1 billion OPV are produced and utilized across 140 countries annually ([Chumakov et al., 2020](#)).

Updates on Treatment Options for Covid-19

Antivirals

Remdesivir

Remdesivir is an intravenous prodrug of an adenosine analogue that is used in the treatment of a large number of viral diseases. It was produced during the “Ebola” outbreak but could not produce favourable results and is now approved by FDA to treat Covid-19. It inhibits replication of virus by targeting the transcription enzyme, i.e., RNA replicase (RdRP) and cause termination of the transcription process. Some scientists conducted a study on the MERS covid-19 animal model that suggested a reduction in viral load in lung tissue by the use of Remdesivir ([Sheahan et al., 2020](#)). Another study on Remdesivir conducted on hospitalized covid-19 patients showed a shortening of recovery time and reduction in mortality rate due to covid-19 ([Beigel et al., 2020](#)). A recent report suggested that one of the potential antivirals that could be used to fight Covid-19 is Remdesivir ([Wang et al., 2020](#)).

Favipiravir

Favipiravir is an oral antiviral that works by inhibiting RNA polymerase that is responsible for viral replication. It proved to be an efficacious drug for the treatment of the “Ebola” virus ([Oestereich et al., 2014](#)). In April, a study conducted on mechanically ventilated inpatients showed that Favipiravir could somewhat reduce the number of inflammatory

mediators in the respiratory tract ([Yamamura et al., 2020](#)). In May, clinical trials of phase 2 and phase 3 were conducted in hospitalized patients who had moderate symptoms of covid-19 showed that Favipiravir showed viral clearance within 4-5 days in most of the randomized patients. Also, it proved to be a safe and efficacious drug, thus making it the approved oral drug to treat patients with moderate to mild covid-19 symptoms ([Ivashchenko et al., 2020](#)). A study conducted in inpatients in ICU in June 2020 showed that favipiravir is a safe drug for short term use and showed improvement in patients with covid-19 ([Yilmaz, Güner and Altuntas, 2020](#)).

Stem Cell Therapy

“Stem cell therapy” utilizes stem cells to cure and prevent various diseases because they have the unique potential to differentiate into specialized cells and helps in the repair process. Covid-19 patients represent symptoms of “Pneumonia”, which worsen, and the patient gets a more severe disease, i.e., “Acute Respiratory Distress Syndrome” (ARDS) that is the most common reason for death among covid-19 patients ([Gibson, Qin and Puah, 2020](#)). Till now, no treatment available that could completely treat ARDS. The current care standards to save a person from dying is to force oxygen into his lungs by putting him on a ventilator just to keep him alive ([Gibson, Qin and Puah, 2020](#)). A study was performed in Beijing YouAn from January 23 to January 31, 2020, in which MSCs were transplanted in 7 covid-19 patients with symptoms of pneumonia. Results of this study showed the disappearance of symptoms of the disease in patients, and no allergic reactions, hypersensitivity reactions or any other secondary infections were reported ([Leng et al., 2020](#)). A study conducted on the ARDS animal model made use of Multistem, a stem cell by Athersys Inc., to treat ARDS. This study demonstrated improvement in oxygenation, reduce lung inflammation and production of damaging pro-inflammatory cytokines ([Bellingan et al., 2019](#)).

Non-Steroidal Anti-Inflammatory Drugs

If NSAIDs like diclofenac and ibuprofen etc., are used over a long time, then they can lead to serious complications like high blood pressure, which turns into “heart attack, stroke, or heart failure”. NSAIDs also cause nephrotoxicity, which Covid-19 patients are more likely to suffer with and this situation becomes exaggerated by fever and dehydration

([Little, 2020](#)). ARDS, the leading symptom of Covid-19 attack, is also linked with “heart attack and strokes” as they may worsen the situation of a person suffering from ARDS. Recent studies propose that the use of NSAIDs is linked with some serious complications like pneumonia, painful pus-filled inflammation of tonsils and spread of infections to other sites. To support the use of NSAIDs against COVID-19, there is no strong evidence, but it is only recommended for occasional use, for example, relief of musculoskeletal pain ([Little, 2020](#)).

Those people who are taking aspirin for preventing “cardiovascular diseases” from getting worse can continue its use as at high doses, it exerts anti-inflammatory effects, which can be having benefits against Covid-19 and reduces the worsening of “cardiovascular diseases” that are associated with ARDS. However, its regular use is not recommended as a first-line treatment against Covid-19 ([Little, 2020](#)).

Anti-Malarial Drugs (Chloroquine and Hydro Chloroquine)

Both the drugs produce anti-viral and anti-inflammatory effects. Being anti-viral, these increase the pH inside the cell, causing the destruction of organelles that survive in acidic pH like endosomes, Golgi bodies and lysosomes. It also prevents virus entry ([Khuroo, 2020](#)), replication and spread as all these events occur at low pH. Mutations in viral stains also get reduced because post-translational changes in the glycoproteins of the viral envelope are affected with increased pH in the endoplasmic reticulum and Golgi bodies ([Khuroo, 2020](#)) (Li, Lu and Zhang, 2020). Chloroquine intervenes with the glycosylation of SARS-Cov 2, thereby preventing infections caused by the virus ([Khuroo, 2020](#)). Being anti-inflammatory inaction causes a reduction in the production of ‘cytokine storm’. The decrease in the production of cytokines relieves the COVID-19 patient from severe conditions like acute respiratory distress syndrome that even leads to the death of the patient. Hence, reduction of cytokine production is the main reason for its recommendation in COVID-19. Its dose is recommended according to the weight of the patient ([Khuroo, 2020](#)). However, there is still a dispute over the use of Chloroquine and Hydro Chloroquine against COVID-19 as both these drugs cause serious side effects at high doses and show drug-drug interactions, which are dangerous for patients already having a weak immune system (Li, Lu and Zhang, 2020).

Monoclonal Antibodies

Currently, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic is sweeping the globe, which has created crisis all around the world. Due to a huge spike in deaths and cases throughout the world, the need for immediate treatment as well as prevention of this virus became the need of the day. Most of the attention and priority is given to the development of vaccines, convalescent plasma infusions, and new antiviral agents, but despite the fact that neutralising antibodies are an important constituent of protective immunity against many of the viral diseases, comparatively 'Monoclonal Antibodies' are given less attention. The neutralizing process of monoclonal antibodies into SARS-CoV-2 may aid in the design and production of vaccines which has the potential for both prophylactic and therapeutic applications ([Marovich, Mascola and Cohen, 2020](#)).

Moreover, to treat and avoid diseases that cause infection, such as "clostridioides difficile", "anthrax", and "respiratory syncytial virus", only three monoclonal antibodies are used out of 75. After some research and experiment, if used during the early stages, two different monoclonal antibodies have been effective against the Ebola virus while reducing the possibilities of mortality ([Mulangu et al., 2019](#)). However, the patients who have acquired SARS-CoV-2 disease's treatment with different grades of illness to impede the progression of the disease would be included in therapeutic trials, and a single infusion would be sufficient, keeping in mind its long half-life. When the advanced age or comorbidity is not present, most SARS-CoV-2 patients won't require any treatment and will be recovered on their own, but the recovery time will vary, reinforcing the necessity to research monoclonal antibodies which are most likely to earn any sort of benefit from early therapy with monoclonal antibodies in the patient's body.

The tissues which are affected by the disease are passively infused by the unidentified bioavailability of IgG, particularly the lungs, being the major targets of SARS-CoV-2 infection, which is a possible drawback of monoclonal antibodies for the treatment of COVID-19. ([Marovich, Mascola and Cohen, 2020](#)). The viral diversity's effect is another factor, so monitoring for the development of resistant viral mutations beneath the selective pressure of treatment with monoclonal antibodies will result in much significance. However, during prevention or recovery from several viral diseases, neutralising antibodies play a significant role. An important advancement in the managing

process of the Covid 19 pandemic will be the establishment of the prophylactic or therapeutic potency of monoclonal antibodies.

On the other hand, convalescent plasma has the ability to provide an immediate and successful treatment choice which came into account while testing current drugs and developing new specific vaccines and treatment, and with experience, it shows that convalescent plasma also contains neutralizing antibodies. In this process, the convalescent plasma or blood is obtained from COVID-19 patients that have been recovered. The recovery of the patient was characterised for at least three days as an afebrile status, relief of respiratory symptoms, the two consecutive tests of SARS-CoV-2 nucleic acid RT-PCR should be negative, and after at least three weeks of the onset of the disease. The donors are required to be "anti-HIV, HBV, as well as HCV seronegative also anti-SARS-CoV-2 seropositive ([Ye et al., 2020](#)). As a routine plasma donation examination, by a real-time PCR, the convalescent plasma was also checked and certified as residual SARS-CoV-2 free.

As soon as the plasma is available, the eligible patients obtain the ABO-compatible convalescent plasma's transfusion. However, recently ABO-compatible convalescent plasma transfusion's one cycle (200 ml per cycle) at least was given to patients ([Ye et al., 2020](#)). Over a duration of 30 minutes, each transfusion was administered.

Conclusion

Covid-19 has become a global pandemic, and new cases and deaths due to covid-19 are reported with every passing day. Scientists are in search of treatment for this global pandemic. Based on studies by some scientists, many drugs are proved to be effective in treating covid-19 but are still under clinical trials. Also, scientists are working hard to develop a vaccine that could eradicate the corona virus from this world. RNA vaccine and viral vectored vaccines have been prepared and are proved to be efficacious during clinical trials. But still, these are under consideration, and clinical trials are being conducted before these drugs could be made available to all. In addition to these, some already available vaccines are being tested if they could be repurposed and used against this pandemic. Moreover, some organizations also have the idea to use stem cells for treating covid-19. Plasma therapy is also being considered. It is thought that the plasma of an infected individual who is cured now can be donated to the serious covid-19

patient and can be lifesaving as it contains antibodies against the coronavirus. But we still need to defeat covid-19 and find its cure as we do not have any

reliable and fully effective treatment option for covid-19. We hope that scientists will find a better and most suitable treatment of covid-19.

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