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Treatment Methods and Vaccine Alternatives of COVID–19

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ABSTRACT

COVID-19, which is triggered by the new SARS-CoV-2 virus, is the main reason of mortality in the whole world. This virus outbreak has clearly demonstrated that it is a pandemic.

The global COVID-19 outbreak has galvanized whole scientific community to join forces in the fight against this viral threat. Scientists and huge pharmaceutical companies are working around the clock to discover a cure. This project consists of two parts: first, testing current medications against the COVID-19 onslaughts and second, developing, testing, and manufacturing a harmless and efficacious vaccination as a long-term solution for the pandemic.

At the end of October 2020 COVID-19 had approximately 39000000 cases around the world with almost 1100000 deaths around the globe.

Fever, cough, sore throat, anosmia, difficulty breathing and myalgia are some of the symptoms. There is evidence of immune cells migrating to damaged organs, resulting in overproduction of proinflammatory cytokines that help in the illness process and make the immune system a key component in the COVID-19 infection illness process.

The first clinical trials for Hydroxychloroquine (HCQ), a promising medication, have been halted. The FDA then approved the use of recovered COVID-19 individuals with the same blood group's convalescent serum as a therapeutic option.

Research is going on a number of possible vaccine candidates containing monoclonal antibody as method of eradicating this viral spread.

The motive of this article is to review the recent pharmacological therapies under trial and the various vaccine candidates in development to stop this global pandemic.

Key words: COVID-19, Vaccine candidates, Therapeutic drugs

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INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-coV-2) is an enveloped RNA virus which causes the global pandemic of COVID-19.

It was originally detected in Wuhan, China, in December 2019 and subsequently spread throughout the world, resulting in a global pandemic. It's the third pandemic to be caused by a new coronavirus. First one happened in Hong Kong in 2000's and symptoms included fever, cough, and myalgia six days after infection. The lung was the principal organ affected, with CT evidence of consolidation 7 to 10 days after infection, which later converted into pulmonary infiltrates.

Symptoms: Fever, cough, myalgia, arthralgia, anosmia, lethargy, ageusia, headache, increased sputum production and other symptoms are common in COVID-19 individuals. Approximately 20% of patients are asymptomatic.

LITERATURE REVIEW

Radiological findings

On a CT scan of the chest, common radiological findings include bilateral pulmonary infiltrates and bilateral ground glass opacities in subsegmental areas of consolidation that proceed to solid areas of mass later.

Laboratory findings

- Leucopenia, lymphopenia and hypoalbuminemia are the maximum informed abnormal lab trials with COVID-19.
- There are high levels of cytokines and inflammatory markers like ERS, CRP and D-dimer [1].
- A number of laboratory indications have been demonstrated to suggest severe disease. One difference is that patients who needed extreme care and/or mechanical ventilation had a greater Neutrophil to

Lymphocyte Ratio (NLR) than those who had a mild illness.

Histopathological findings

- In COVID-19 patients with moderate to severe disease, immunophenotyping of bronchoalveolar cells revealed that both M_2 and M_1 like macrophages and elevated cytokines of inflammation.
- Direct evaluation of substances released by cells of immune system and chemoattractant cytokines in plasma revealed greater amount of IL1, IL7, IL10, ifn, tnf, cxcl10, IL-1, IL8, IL9, ccl4, ccl2, ccl3, ccl8, cxcl2 and cxcl8 were enhanced [2].
- IL-6 and TNF levels were observed to be high in spleen as well as lymph node specimens in addition to serum levels, suggesting that IL-6 may emulate in causing decreased lymphocyte count in unadorned COVID-19 cases.

Disease course

- A fever, which can last up to 12 days after infection, is one of the first symptoms to occur.
- Dyspnea and cough can occur quickly and last for a long period of time; in one research, cough continued in 45% of survivors after they'd been discharged from the hospital.
- Around the ninth day, the first non-virus related symptoms, such as sepsis, appear. More serious lung infections, such as ARDS and CRS, usually develop in the 2^{nd} week of infection and might necessitate voluntary ventilation.
- Acute heart and renal damage might also manifest within 10-20 days.
- Those aged above 45, particularly those with numerous prior severe medical issues, were recognized as the key "at risk" demographic in February 2020, when COVID-19 swept across the United States.
- COVID-19 patients might have longstanding harmful effects, including diabetes induction, despite recovery and release from the hospital, according to recent results.
- Furthermore, post-recovery cerebral microstructural changes contribute to common complaints of extended anosmia, "brain fog," or trouble with numerous reasoning tasks [3].

Rationale

- This review article focuses mainly on the various vaccine candidates and therapeutic strategies out there in the field of testing and research in order to defeat this pandemic.
- The main reason for doing this review article is to collect the various data available from various sources on types of vaccine candidates and therapeutic strategies that have been and are still being tested and to present it in a systemic way so that people can gather the required information easily and effectively.

DISCUSSION

Vaccine candidates

Non-replicating Viral Vectors (NRVV): The most prevalent viral vectors for non-replicating SARS-CoV-2 are adenoviruses. They are rendered ineffective for replication by deleting their E1 gene.

They create a huge amount of cytokines and chemokines when they attack target cells, which boosts immunogenicity. Adenovirus type 5 was used by CanSino Biologics and the Beijing Institute of Biotechnology to create a vaccine (Ad5). The efficacy of this vaccination has been shown to be enhanced when given intranasal rather than intramuscularly. A vaccine containing the full S protein has been produced by Oxford University and AstraZeneca [4]. Non-replicating Viral Vector (NNRV) vaccines have proven to be protective and persuade immunogenic responses in clinical experiments utilising two methods. This is performed in two ways: first, cell-mediated immunity is triggered and second, anti-spike antibodies against spike proteins are generated.

Messenger RNA vaccine candidates: Protein vaccines cost more and take longer to produce than nucleic acid vaccines. Because m-RNA vaccines degrade quickly, their stability and ability to appropriately translate once within the host cell are critical for COVID-19 protection. By eliminating the double-stranded RNA and integrating it into lipid nanoparticles, these issues have been solved [5]. The NIAID's and Moderna's m-RNA -1,2,7,3, as well as Pfizer's and BioNTech, are among the most popular m RNA vaccines. To sustain immunogenicity for a longer period of time, both of them require booster doses.

Some of these vaccines are: BNT162b2, CVnCoV, BNT162b1 and mRNA-1273.

Self-amplifying messenger RNA vaccine Types: Compared to a non-replicating m-RNA vaccine, these vaccines have a better likelihood of triggering a significant immunological response. Self-amplifying RNA builds implanted in numerous types of adjuvant nanoparticles are used in these. Some of these vaccines are: LION/repRNA-CoV-2S, LNP-n CoVS aRNA and ARCT-021.

DNA vaccine types: There are various benefits of a DNA based vaccine over the others which includes the following:

- Additional steadiness of a DNA molecule as equated to a RNA molecule.
- A single DNA molecule can make a massive number of RNA molecules which in turn increases the antigen's immunogenic exposure.
- Increased thermal stability of a DNA molecule means that the refrigeration requirements of a DNA based vaccine is less.
- Some of these vaccines are: gx-19, nCoV Vaccine, ino-4800, ag0301-COVID-19 and ag0302-COVID-19.

Inactivated whole-virus vaccine types: These vaccines have proven to be the most effective in previous pandemics, but their longer manufacturing time puts

them at a disadvantage in the COVID-19 pandemic. Vero cell lines are employed to propagate the SARS-CoV-2 virion variants employed in this vaccine. The viral particle is inactivated with beta-propiolactone before being adsorbed onto an adjuvant (aluminium hydroxide) [6]. Antiviral resistance growth is being studied in current trials at 14 as well as 28 days following getting vaccinated, with varying timing and dosages of booster vaccine, together with a comparison of two booster doses.

Some of these vaccines are BBV152A/B, CoronaVac/ PiCoVacc, bbibp-CorV, Inactivated SARS-CoV-2 Vaccine, bbv152A/B and Inactivated COVID-19 vaccine.

Protein subunit vaccine types: A recombinant spike protein is used in this type of vaccination. Because peptides are relatively unstable, they must be packed in lipid nanoparticles that are organised into an adjuvant to improve their uptake by the host's immune system. Side effects included injection site redness and swelling, arthralgia, lethargy, headache, myalgia, nausea and malaise.

Pharmacological therapies

Remdesivir: It is a wide-spectrum anti-viral drug that has proven to be effective against RNA viruses like Ebola by competitively blocking ATP foe integration into RNA polymerase dependent on RNA [7]. RNA dependent RNA-polymerases (RDRP) aren't able to continue outside the addition of it, thus causing the cessation of chain elongation. It has a unique process of acting against a large range of RNA viruses [8]. A large number of medical experiments are going on to evaluate the drug's efficacy and ability to treat the COVID-19 infection.

According to Beigel, et al. this drug successfully decreased the recovery time in people hospitalized with SARS-CoV-2 infection from fifteen to ten days on average [9].

The medicine label recommends a five day treatment for mild-medium infections and ten-day term in spartan diseases needing mechanical breathing in patients who are of twelve and older and weight at least forty kg.

Tocilizumab: It is completely humanized recombinant monoclonal antibody that operates on both soluble and membrane bound interleukin 6 receptors. In medical practice, applied for treatment of rheumatoid arthritis in adults and systemic juvenile idiopathic arthritis in children. Because higher IL-6 quantities have linked to a higher risk of death in COVID-19 patients, several researchers are interested in using tocilizumab to treat COVID patients. Tocilizumab has been shown to ameliorate oxygen consumption of the body and reduce inflammatory biomarkers in COVID-19 patients who are hospitalized [10]. There has been recently reported a fall of 12% in mortality of patients following the use of tocilizumab.

Fostamatinib: COVID-19 has been shown to be linked with an increased circulating levels of mucin1 (MUC1). Mucin 1 illustrates on the surface of the respiratory lumen; overaction of this protein and increased mucus building has been proven to prolong infections and increase the mortality from respiratory diseases [11]. It's a Spleen Tyrosine Kinase (SYK) inhibitor. Several immunological mechanisms involving SYK have been linked to the over-inflammatory response expressed by anti-Severe Acute Respiratory Syndrome-CoV-2-Spike IgG [12].

R406, is an dynamic part of this drug, has been proven to inhibit SYK, suggesting its effectiveness in controlling COVID-19 illness [13,14].

Chloroquine/Hydroxychloroquine (CQ/HCQ): These medications raise endosomal pH, decreasing viral entrance into the cellular cytoplasm and preventing acidification. Chloroquine prevents SARS-CoV infection and binding by inhibiting glycosylation of the cellular ACE-2 receptor.

Following research and clinical trial data, however, give unclear evidence of these medications' effectiveness against COVID-19.

Corticosteroids: Because COVID-19 has a severe inflammatory effect on the lungs, corticosteroids with anti-inflammatory properties appear to be a better option. The recovery experiment, found that dexamethasone decreased mortality in patients on ventilation support, but not in those who did not get any ventilatory support [15]. Additional research suggests that decreased dose and short-course chemotherapy inhibits the COVID-19 inflammatory pathway.

Janus kinase Pathway Inhibitors (JAKi): The presence of chemicals acting in inflammation and chemo attractant cytokines in COVID-19 patients suggests that the Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathway has been activated. Ruxolitinib was the first JAK inhibitor to be authorized. Patients report that the medicine is well tolerated and has few side effects.

According to a recent retrospective study, this drug characteristically decreased COVID-19 inflammatory levels, with persistent medical enhancement in COVID-19 patients with proof of CRS.

Other FDA approved JAK inhibitors, such as Tofacitinib and Baracitinib, are now being tested in COVID-19 patients, with some proof that combining JAK inhibitors combined with help of Remdesivir might shorten the retrieval time period in patients admitted in hospital.

Melatonin: Melatonin plays a role as an antioxidant, reducing oxidative tension and vascular penetrability [16]. Melatonin reduces vascular penetrability and inhibits Calmodulin, an important protein for ACE-2 action, which helps to relieve respiratory pain. Melatonin has been suggested for use against SARS-CoV-2 infection because it indirectly aims numerous cellular targets of SARS-CoV-2, including the angiotensin converting enzyme 2 [17].

Anticoagulant Therapy: Many studies have found elevated D-dimer, fibrin/fibrinogen degradation products

and SARS-CoV-2 infection-associated disorders of coagulation and bleeding.

Non fractioned or decreased molecular weight heparins (enoxaparin) are suggested for the prevention or treatment of thromboembolism, DIC and sepsis related coagulopathy. Infected patients with SARS-CoV-2 have yet to face any bleeding. If such a situation arises, normal coagulopathy and bleeding control procedures must be abided.

Heparin treatment must be checked on a regular basis for Activated Partial Thromboplastin Time (APTT) and anti-factor Xa levels, since an OD can cause bleeding [18,19].

Additional novel therapies

Complement inhibitors: Complement plays an important role in killing the phagocytic cells and clearing out the infection from our body. Its dysregulation can lead to thrombosis, systemic inflammation and a coagulation pathway, thrombosis plays an important. It plays a significant part in COVID-19 pathology and is a key discovery in COVID-19 related lung illness [20]. Eculizumab, a monoclonal antibody that targets C5 protein convertase and has now shown to be helpful in boosting COVID-19 recovery, was one of the first medications to be evaluated [21].

The complement C3 antagonist medication AMY-101, which is based on compstatin, has also looked promising. A minor set of COVID-19 patients received Conestat alfa (a human recombinant C1 esterase) which yielded defervescence occurs almost immediately, inflammatory indicators improve and oxygen needs stabilize or decrease [22].

Convalescent Plasma (CP): The plasma obtained from treated COVID-19 patients has organically manufactured antibodies that might provide temporary safeguard to counter the disease's severe outcomes when injected into at-risk people. In spite of the difficulties presented by this new and quickly scattering viral illness, unprecedented levels of scientific collaboration and involvement have occurred around the world, which will surely aid as a model for upcoming pandemic comebacks [23]. The total rate of blood transfusion response was 1% the most prevalent adverse effects were heart related in nature and were considered to be caused by COVID-19 clinical illness other than CP treatment.

Anti-SARS-CoV-2 antibody cocktails: Antibodies against the SARS-CoV-2 spike glycoprotein in artificial anti-SARS-CoV-2 antibody mixtures are extremely enhanced precise anti bodies which attach to the infective particle and inhibit cellular entrance. To prevent the viral mutation, a mixture of various spike protein types is usually given concurrently.

Single-Domain Antibodies (SDAb): Camelids are a common source of heavy chain antibodies. Their lack of a variable region allows them to be smaller than traditional antibodies while maintaining increased constancy and affinity for each similar epitope. So, the separation of camelid derived Single Domain anti-body (SDAb) is accepted an original capable treatment option. The treatment method is based on virus neutralizing activity, similar to monoclonal antibodies. As a result, SARS-CoV-2 primarily targets RBD, preventing it from binding to the ACE-2 receptor. H11, a SDAb with increased affliation, neutralising activity and a KD of 1 M, was discovered [24,25].

Hyperbaric Oxygen Therapy (HBOT): The patient breathes 100% oxygen at 1-1.5 times ambient pressure in the hyperbaric chamber. When the pressure rises, the amount of dissolved oxygen in the plasma and tissues rises as well. HBOT has the potential to treat the hallmarks of serious COVID-19 disease, such as progressive hypoxia and pulmonary inflammation.

Ultra-high oxygen levels may have many antiviral effects, including raising the development of viricidal free oxygen radicals, up regulating Hypoxic Inducible Factor (HIF), which stimulates the production of antiviral peptides like defending, cathelicidins and lowering proinflammatory cytokines like IL-6, which trigger cytokine storm.

HBOT was first accepted for COVID treatment in Wuhan, China. Five patients were treated with HBOT for acute respiratory illness, two of whom had critical disease and three of whom had severe disease. Awaiting intubation, identified as increased oxygen requirements with falling saturation and extreme tachypnoea, was the primary criterion for HBOT. All five patients experienced fast resolution of increased breathing rate and correction of decreased oxygen levels.

CONCLUSION

Scientists have been working tirelessly since the discovery of SARS-CoV-2 to develop both short-term therapies and a long-term vaccine strategy to minimize morbidity and mortality due to COVID-19 Despite tremendous progress and encouraging findings from vaccine candidate trials, a number of challenges remain, including logistical constraints associated with mass manufacturing and delivery of millions or billions of doses to the global population. Unfortunately, some kind of vaccines, like the mRNAs, are specifically labile at normal room temperature and might need freezers, which aren't generally available in countryside clinics as well as hospitals distant from research organizations; vaccine types not requiring refrigeration might be a more realistic alternative in these situations. In spite of the problems faced by this unique and quickly scattering viral contamination, the whole world has witnessed unimaginable heights of scientific collaboration and engagement, which without hesitation will aid as an example for upcoming pandemic comebacks.

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