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EMERGING TREATMENT STRATEGIES FOR COVID-19 INFECTION

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ABSTRACT COVID 19 is an emerging infectious infection caused by the SARS CoV 2 virus. As of July 1, 2020, more than 10 million people worldwide have been infected with SARS CoV 2.The COVID-19 pandemic demands for the quick testing of novel therapeutic methods. The majority of COVID-19 patients have mild or moderate illness, while 5 to 10 % of patients have severe, life-threatening condition. Thus, the need for efficient and targeted antiviral treatment is critical. Supportive patient care is the current gold standard of care includes ventilation, oxygenation, and fluid management. Several clinical studies are currently ongoing to find the most effective therapy or combination against the condition, and patients are highly encouraged to participate in ongoing trials. Several antimalarials (chloroquine, hydroxychloroquine) and antivirals (remdesivir, favipiravir) have emerged as potential treatments for treating Covid-19 despite the fact that there are presently no therapeutic medicines that are directly active against SARS-CoV-2. In a randomized clinical study conducted by the United Kingdom, dexamethasone, a first-known steroid medication, decreased the death rate in COVID-19 patients and a life-saving treatment for very ill patients.The vast array of treatment approaches aims to identify the most effective strategy. This article's goal is to evaluate all the existing literature and discuss the therapeutic approaches that have been implemented to COVID-19 patients.

KEYWORDS : Covid, Management, Novel, Therapy.

INTRODUCTION:

SARS-CoV-2, a new form of coronavirus (COVID-19) that originated in Wuhan, China, has caused a worldwide catastrophe. The unusual circumstances of the Coronavirus Disease 2019 (COVID-19) pandemic have proven to be exceptionally difficult due to a lack of documented medicines and treatment standards. SARS CoV 2 infection appears to be less virulent than severe acute respiratory syndrome SARS and Middle East respiratory syndrome MERS in terms of morbidity and mortality. COVID-19 causes a wide range of symptoms in infected people, from asymptomatic or mild disease to serious illness with rapid deterioration and death.

As a result, patient care differs based on the intensity of the disease and the presence of underlying illnesses. Supportive care techniques like ventilation, oxygenation, and fluid management are still the standard care. Only in the context of randomized clinical trials established antivirals are safe and effective. Chloroquine, corticosteroids, favipiravir, monoclonal antibodies, convalescent plasma, hydroxychloroquine and vaccines are some of the therapies now being investigated. During the pandemic, nucleic acid vaccines have emerged as viable alternatives to traditional vaccination techniques, while research on specific antiviral therapies for treating SARS COVID-2 infection is underway. A huge number of treatment interventions are being conducted in order to determine the best effective regimen.

Pharmacological Therapies:

Remdesivir:

Remdesivir, an intravenous nucleoside analogue, blocks RNA-dependent RNA polymerase and prevents viral replication from having developed. Remdesivir is a phosphoramidate prodrug that, in contrast to other nucleotide analogues, has broad-spectrum activity against a variety of viruses, including those belonging to the families Filoviridae, Paramyxoviridae, Pneumoviridae, and Orthocoronavirinae (SARS-CoV and Middle East respiratory syndrome coronavirus [MERSCoV]).

Remdesivir is effective against SARS-CoV-2 infection, in-vitro experiment at nanomolar concentrations. Combination of remdesivir with medication to treat hepatitis C virus was 10 times more effective in suppressing SARS-CoV-2, according to a recent in vitro experiment. Remdesivir also had a therapeutic benefit in non-human primate trials, as evidenced by decreased viral load and lung damage.

Recent clinical trials are trying to evaluate the safety and efficacy of remdesivir in COVID-19. Statistics regarding the compassionate use of remdesivir were made available to the public on July 10, 2020. These results showed that remdesivir medication was associated with a significantly better clinical improvement and 62 % decreased risk of death when compared to standard of care. The comparative study's findings showed that by day 14, 74.4 % on remedesivir had recovered compared to 59 % of those receiving standard care. At day 14, the analysis's remdesivir-treated patients' death rate was 7.6%, compared to 12.5% for those who weren't taking it. A recent study shows that remdesivir helped to reduce mortality and that the median recovery time for hospitalised COVID-19 patients receiving placebo was 11 days as compared to 15 days.[1]

In hospitalised COVID-19 patients receiving remdesivir treatment, a recent meta-analysis study of randomised controlled trials found no statistically significant indication of decreased death.[2]The WHO advised against taking remdesivir on November 19, 2020. Remdesivir had little to no impact on hospitalised COVID-19 patients, according to the Solidarity Trial's findings in February 2021. Remdesivir cannot yet be recommended for routine usage, according to National Institutes of Health (NIH) COVID-19 therapy guidelines.[3]

Systemic Corticosteroids

Corticosteroids' ability to reduce inflammatory organ damage in viral pneumonias continues to remain controversial.[4]A biphasic pattern of SARSCoV-2 infection is frequently seen, with the initial viremic phase lasting 7–10 days, following a second inflammatory phase characterized by cytokine storm and respiratory failure, which occurred in around 20% of patients.[5]

It has been hypothesised that corticosteroids have an impact on pulmonary and systemic inflammation considering that host immune response plays a significant part in the pathophysiological effects of organ damage in viral pneumonias.Additionally, a prospective meta-analysis of seven randomised trials revealed that patients who received corticosteroids had shorter 28-day all-cause mortality than those who got standard care or a placebo.[6]

According to a single-center retrospective cohort research, hospitalised COVID-19 patients receiving steroids (n = 396) had a lower mortality rate than those who did not (n = 67), 13.9% vs.

23.9%.[7] As inflammatory lung complications are expected to have been more frequent within the first week from symptom onset, the benefit of dexamethasone was evident in patients being treated more than seven days after symptom onset. Based on these data, low-dose systemic steroids may be recommended for COVID-19 patients who are critically ill and who require supplemental oxygen.

Favipiravir:

Favipiravir, also marketed as Avigan or T-705, is an antiviral drug that was used in Japan in 2014 to treat influenza infection.[8]In 2014, the Ebola virus was also treated with favipiravir and it is a potent and specific inhibitor of viral RNA polymerase.

Favipiravir prevents SARS-CoV-2 infection in Vero cells, according to a study by Wang et al. (EC50: 61.88 M).[9] Favipiravir medication, as compared to the control arm, resulted in a shorter viral clearance period (4 vs. 11 days) and a considerable improvement rate in CT imaging (91.43 % vs. 62.22 %), as per recent medical research (N = 80) with mild to severe COVID-19 patients.[10] Additionally, a meta-analysis of 9 clinical research reveals that the favipiravir group significantly improved clinically when compared to the control group in terms of viral clearance rate, in need of oxygen therapy, ICU transfer, and reduced mortality.[11]

Monoclonal Antibodies:

A number of Clinical studies are now being conducted to evaluate SARS-CoV-2 monoclonal antibodies. These antibodies mostly belong to the IgG1 class, have a long half-life, and target certain viral spike areas. This suggests that might be given in a single infusion. However, the bioavailability is unclear in the tissues and organs that are impacted by it. Recombinant monoclonal antibody tocilizumab, also known as Actemra, was developed by Roche Pharmaceuticals. Rheumatoid arthritis is mostly treated with tocilizumab. It was developed as an IL-6 receptor blocker to prevent IL-6 from binding to its receptor, hence reducing cytokine release syndrome.In mild-to-moderate COVID-19 patients receiving sotrovimab (monotherapy) vs placebo, interim data from the Phase 3 COVID-19 Monoclonal antibody Efficacy Study-Intent to Care Early trial (n = 583) showed an 85% reduction in hospitalization or mortality.[12]

The REGEN-COV medication bind to several epitopes on the spike protein RBD of Corona virus. Within 28 days of receiving the REGEN-COV medication vs placebo in a randomised, double-blinded, placebo-controlled Phase 2 clinical study (n = 799), substantial reductions in the level of the virus and reduced medical visits were seen.[13]

The FDA has approved the use of Bamlanivimab, Etesevimab, and Sotrovimab for the management of mild to moderate COVID-19 patients who are not hospitalised.

Hydroxychloroquine

HCQ are antimalarial medications that are also authorized for the treatment of autoimmune conditions such systemic lupus erythematosus (SLE) and rheumatoid arthritis. HCQ have inhibitory effects on SARS-CoV-2 replication, according to preliminary in vitro testing.[14]However, SARS-CoV-2 infection model studies in hamsters and non-human primates[15] do not replicate such in vitro effects.On April 24 2020 the FDA published warnings about risk of arrhythmias while taking chloroquine or hydroxychloroquine for COVID 19 patients outside of a hospital setting or a research study.

As a consequence of mounting evidence to the contrary the FDA discontinued the use of chloroquine or hydroxychloroquine as an effective COVID 19 therapy on June 15 2020.

In a large observational study, conducted in New York, the researchers evaluated the clinical outcomes of COVID-19 hospitalized patients who either got or did not receive hydroxychloroquine. The first dosage of hydroxychloroquine was administered to the majority of the patients within 2 days of admission. The multivariable analysis did not show any differences between the two groups that were significant for intubation or mortality.[16]

Thromboprophylaxis And Fibrinolysis:

Compare to earlier viral pneumonias and acute respiratory distress syndromes, pulmonary embolism (PE) and venous thromboembolism (VTE) have emerged as the biggest concerns associated with severe SARS-CoV-2 infection. Approximately 25–27% of occurrences were reported. Low molecular weight heparin (LMWH) is the ideal therapy, and it should be avoided in cases of active bleeding, low platelet levels (less than 25×10^9/L), and low fibrinogen levels (less than 0.5 g/L).[17]

When creatinine clearance is < 30 mL/minute, unfractionated heparin or reduced-dose LMWH should be administered, and fondaparinux should be given to patients who have a history of heparin-induced thrombocytopenia.

The observed coagulopathy and evidence that links fibrin accumulation in the pulmonary vasculature provide the justification for fibrinolysis in critically sick SARSCOV- 2 infected patients. In one case study, three critically sick patients with ARDS who received alteplase followed by intravenous heparin had seen a temporary improvement in their PaO2/FiO2 (P/F) ratio. Defibrotide is one of the other fibrinolytics that is presently being studied, although safety concerns, such as haemorrhage, exits.[18]

Convalescent Plasma Therapy (CPT):

CPT is a passive immunisation method that uses plasma with a high antibody titer to treat infectious diseases. In concept, this method might halt the progression of the illness. For the management of Argentine hemorrhagic fever, CPT is regarded as standard of care.[19] A number of nonrandomized studies have also claimed effectiveness against SARS, MERS, H1N1 influenza, and Ebola.[20] Given the lack of a successful therapeutic approach against SARSCoV-2, CPT could be a critical element of the COVID-19 patient treatment regimen. Convalescent plasma has been the subject of several randomized studies for the treatment of hospitalized COVID-19 patients, but none of these studies have shown a beneficial effect on mortality [21, 22]. FDA has changed the policy to limit its use of high-titer convalescent plasma to patients who are hospitalized and have early disease stage COVID-19.[23]

Vaccines:

The process of developing a vaccine is complicated, lengthy, and expensive. In order to produce a license, there must be many participants, many procedures, checks, and data analysis. A revolutionary experimental RNA-based vaccination (mRNA-1273) that makes use of a section of the genetic code for the S protein was the first vaccine and its clinical trials started February 2020. Moderna Therapeutics a pharmaceutical firm already working on the SARS-CoV and MERS-CoV vaccines, is developing it. Based on past investigations, this allowed the clinical development to avoid certain animal testing.

Challenges In Vaccine Development:

Undoubtedly, there seems to be an urgent need for a vaccine to combat this epidemic. Unexpected immunopotentiation (eosinophilic infiltration) following whole virus vaccination and spike protein vaccination was one of the biggest barriers in the development of the SARS coronavirus vaccine in 2003.[24] Granulocytes known eosinophils have the capacity to cause immunopathology in conditions like bronchial asthma.[25]

Additional Novel Therapies:

Inhaled Nanobodies:

Camelid single-domain antibody fragments known as nanobodies are more economical than monoclonal antibodies and have certain biophysical characteristics, such as small dimension and stability, which makes them an effective pulmonary administration technique via aerosolization.[26] In comparison to a placebo, recent research showed that moderate dosages (0.2 mg/kg) of aerosolized inhaled Nanobody-21 (PiN-21) protected Syrian hamsters against weight loss caused on by infection and protected against mild to severe COVID-19 infection.[27] Further more trails are need for exploring whether such therapeutic advantages can be transferred in human clinical trials.

Mesenchymal Stem Cells:

Adult multipotent stem cells with immunomodulatory and immune-privileged potential are mesenchymal stem cells (MSCs). MSCs are immune to SARS-CoV-2 infection because they lack ACE2 receptors and TMPRSS2.[28] Compared to the placebo group, intravenous infusion of clinical-grade human MSC enhanced functional outcomes and recovery in a recent pilot study of 7 patients with COVID-19 pneumonia.[29]

CONCLUSION:

The COVID-19 pandemic has accelerated the development of vaccinations and treatment protocols at an unprecedented rate.

Developments in COVID-19 prevention and management will need scientific and clinical research, as well as clinical and public health interventions. Information on the effectiveness of specific treatments has become available as the SARS-CoV-2 epidemic progresses. Secure vaccination that is widely accessible is the primary means of stopping the transmission of the virus, notwithstanding the importance of the treatment approach to the condition. Making vaccinations accessible to individuals from all social classes, especially those from less developed countries, is the next obstacle we must overcome in order to stop the spread of SARS-CoV-2 illnesses.

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