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TREATMENT AND CLINICAL OUTCOME OF PATIENTS WITH CORONAVIRUS DISEASE

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ABSTRACT
The COVID-19 outbreak has brought our lives to a sudden and complete lockdown. While the numbers of confirmed cases and deaths still rise, people round the world are taking brave actions to mitigate transmission and save lives. Coronavirus disease 2019 (COVID-19) is an infectious disease caused by coronavirus-2 (SARS-CoV-2) that causes a severe acute respiratory syndrome, a characteristic hyper inflammatory response, vascular damage, micro-angiopathy, angiogenesis and widespread thrombosis. During this emergency period of the COVID-19 outbreak, clinical researchers are using and testing a spread of possible treatments. Combination treatment of low-dose systematic corticosteroids and anti-virals, anti- coagulants, use of statins, zinc , role of vitamin C, D and convalescent plasma have been encouraged as part of critical COVID-19 management. Vaccine-associated enhanced disease has been rarely encountered with existing vaccines or viral infection. Safe and effective vaccines are a game-changing tool: but for the foreseeable future we must continue wearing masks, cleaning our hands, ensuring good ventilation indoors, physically distancing and avoiding crowds. But it's not vaccines that will stop the pandemic, it's vaccination. We must all do our part to keep each other safe until this outbreak subsides and humanity are back to being greater than ever.

KEYWORDS: COVID-19, Outbreak, Treatment, Clinical Research, Vaccine.

INTRODUCTION
Coronaviruses belong to the Coronaviridae family in the Nidovirales order. Corona represents crown-like spikes on the outer surface of the virus; thus, it was named as a coronavirus. Coronaviruses are minute in size (65–125 nm in diameter) and contain a single-stranded RNA as a nucleic material, size ranging from 26 to 32kbs in length . These viruses were thought to infect only animals until the world witnessed a severe acute respiratory syndrome (SARS) outbreak caused by SARS-CoV, 2002 in Guangdong, China.[1] All coronaviruses contain specific genes in ORF1 downstream regions that encode proteins for viral replication, nucleocapsid and spikes formation.[2] The glycoprotein spikes on the outer surface of coronaviruses are responsible for the attachment and entry of the virus to host cells. The receptor-binding domain (RBD) is loosely attached among virus, therefore, the virus may infect multiple hosts.[3.4] SARS-coronavirus require angiotensin-converting enzyme 2 (ACE2) as a key receptor. The spike protein of SARS-CoV-2 contains a 3-D structure in the RBD region to maintain the van der Waals forces.[5] The 394 glutamine residue in the RBD region of SARS-CoV-2 is recognized by the critical lysine 31 residue on the human ACE2 receptor.[6]

Anti-Virals for SARS-CoV-2 infection
Lopinavir
Lopinavir is employed together with ritonavir for treatment and prevention of HIV infection. It is reported that lopinavir inhibited SARS-CoV-2 at a half-maximal effective concentration (EC50) - the level of drug that induces a response halfway between the baseline and maximum after a specified exposure time - of 26.36 μM[7], therapy was discontinued in some of the studies due to serious side effects including severe gastrointestinal disturbances , hypokalemia, and self-limited skin eruptions is seen in some of the reported studies.[8,9]

Remdesivir
Remdesivir is an NtRTI drug that's deserve a "solidarity" clinical test for COVID-19, consistent with WHO.[10] It acts as an RNA-dependent RNA polymerase (RdRp) inhibitor and its pharmacokinetics and characteristics are studied in SARS-CoV and MERS-CoV infections.[11] It alters functions of viral exonuclease and thanks to

disturbed proof reading, viral genomic RNA replication and production declines.[12] Since it can prevent viral replication and may be recommended for COVID-19 patients to stop the severity of disease progression.

Favipiravir

Favipiravir may be a prodrug and becomes a lively molecule called favipiravir ibufuranosyl-5′-triphosphate (T-705-RTP) upon administration.[13] It competes with guanine nucleosides during RNA viral replication by getting integrated with viral RNA, leading to selectively blocking the RdRp to arrest the synthesis of viral RNA.[14]

Barcitinib

Baricitinib is a Janus kinase (JAK) inhibitor with high potential to bind to and inhibit AAK1.[15] Hence baricitinib can be used to inhibit both viral entry as well as the inflammatory response associated with SARS-CoV-2 infection.[15] Therapeutic use of baricitinib is associated with the occurrence of neutropenia, lymphocytopenia, and viral reactivation.[16]

Ivermectin

The basis of ivermectin's broadspectrum antiviral activity appears to relate to the very fact that ivermectin binds to, and inhibits, the nuclear transport role of the host importin α (IMPα) protein.[17,18,19]

Role of Anti-coagulants

Several recent studies administered in quick succession have reported coagulopathy to be a standard complication of the novel coronavirus SARS-CoV-2.[20]

The nature of the coagulopathy seen in COVID-19 has been repeatedly characterised by elevated D-dimers and fibrin degradation products (FDP), mild thrombocytopaenia, and prolonged prothrombin time with pulmonary coagulation and fibrinolysis alleged to be influenced by, and correlate to, certain proinflammatory cytokines.[21,22-24] Viral injury, abnormal release of cytokines, and damage associated molecular patterns (DAMPs) are thought to induce localized microvascular inflammation.

Heparin has also been discussed favourably by Thachil.[25] This piece outlines the bidirectional relationship between the system and thrombin production whereby the inflammatory response could also be attenuated by the action of heparin inhibiting thrombin. They also outline heparin's innate ability to bind to inflammatory cytokines, disabling neutrophil chemotaxis, inhibiting the complement factor C5a, and sequestering acute-phase proteins.[26]

Another important consideration in reference to antithrombotic therapies is that the occurrence of drug interactions with antivirals utilized in COVID-19 in terms of their active metabolites and competition surely CYP450 enzymes.[27] LMWH should be considered altogether patients with COVID-19 requiring hospital admission.[28]

Rivaroxaban inhibits thrombin generation in blood and platelet-rich plasma.[29]

Convalescent plasma transfusion for the treatment of COVID-19

A private who is sick with infectious diseases and recovers has blood drawn and screened for particular microorganism neutralizing antibodies. Following identification of these with high titers of neutralizing antibody, convalescent plasma containing these neutralizing antibodies are often administered in individuals with specified clinical disease to scale back symptoms and mortality. Hence, convalescent plasma transfusion (CPT) has been the topic of accelerating attention, especially within the wake of large-scale epidemics.[30]

In addition, studies show convalescent plasma antibodies which will limit the virus reproduction within the acute phase of infection and help clear the virus, which is useful to the rapid recovery of the disease.[31]

Impact of Corticosteroids in Coronavirus Disease

Corticosteroids are the most immunomodulatory agent used for the clinical management of SARS; both benefits and poor outcomes are reported as a results of their use. the many role of the immune reaction within the pathogenesis of SARS-CoV-2, it became clear that immune modulation are going to be essential in its management.[32,33] A study of 107 patients treated with high-dose methylprednisolone (0.5–1 mg/kg prednisolone on day 3, followed by hydrocortisone 100 mg every 8 h plus methylprednisolone pulse 0.5 g intravenously for 3 additional days), 95 (89%) patients recovered from SARS.[32]

Dexamethasone are often beneficial in patients with COVID-19 due to its ability to inhibit the generation of cytokines and reduce their destructive effects. Therefore, it are often useful to counter the COVID-19-associated cytokine storm.[34] it's been demonstrated that short-term dexamethasone therapy can reduce the severity of inflammation by inhibiting the severe cytokine storm or the hyperinflammatory introduce patients with COVID-19 who develop pneumonia.[35]

Colchicine are often an honest therapeutic option due to several effects within the immunology system involved in SARS-CoV-2 infection.[36]

The infection of cells by coronaviruses involves the interaction of the cytoplasmic tail of the spike protein with cytoskeletal proteins (i.e., tubulin).[37] This interaction results in viral entry. Furthermore, microtubules are involved within the transport and assembly of spike proteins into virions during the

replication cycle.[38,39] The colchicine-tubulin complex may block viral entry and replication.[40]

The Role of Vitamin C in the Immune System

A meta-analysis has shown that administration of high doses of vitamin C at the onset of the cold decreased the duration of the cold and relieved the symptoms, like pain, fever, and chills.[41] After vitamin C treatment, the patients had decreased inflammatory markers, like ferritin and D-dimer, and a fraction of the sooner inspired oxygen requirements[42]

The study suggests that the antiviral effect of vitamin C might be mediated by radical formation or its binding to the virus or molecules involved in viral replication. Therefore, the antiviral effect of vitamin C could also be attributed to the assembly of antiviral cytokines (IFN-α/β), radical formation, or direct binding to the virus.[43]

The Role of Vitamin D in the Immune System

Vitamin D reduces the danger of viral infections. It improves the body's physical barrier by regulating the assembly of proteins for tight junctions[44], adherens junctions[45], and gap junctions[46], which may be disturbed by infection by microorganisms, including viruses.[47]

Severely ill patients with COVID-19 have a high level of pro-inflammatory cytokines, like IL-6, compared to patients with moderate symptoms.[48] The increased level of IL-6 in critically ill COVID-19 patients was associated with the detection of SARS-CoV-2 macromolecule in serum.[49] vitamin D can decrease the assembly of pro-inflammatory cytokines, like TNF-α, IL-6, IL-1β[67], IL-12, and IFN-γ.[50]

Use of Statins in Human Viral Infections

There also are some reports suggesting that statins might enhance ACE2, which could mitigate the invasion of SARS-CoV-2 through the ACE2 receptor.[51] of these results seem encouraging but got to be confirmed in further observational and interventional clinical studies.

Potential Impact of Zinc Supplementation on COVID-19

The very fact that deficiency disease is liable for 16% of all deep respiratory infections world-wide[52] it had been suggested that zinc can prevent fusion with the host membrane, decreases the viral polymerase function, impairs protein translation and processing, blocks viral particle release, and destabilizes the viral envelope.[53,54,55]

Other Drugs

Hydroxychloroquine (HCQ) alone or in combination with azithromycin (AZ) reduced viral load in coronavirus disease 2019 (COVID-19) patients.[56] multiple mechanisms have been proposed for the putative antiviral properties observed with AZ and HCQ. These are weak bases and preferentially accumulates intracellularly in endosomal vesicles and lysosomes, which could increase pH levels, and potentially block endocytosis and/or viral genetic shedding from lysosomes, thereby limiting viral replication.[57,58]

Interleukin-6 as a potential biomarker of COVID-19 progression

Cytokines are vital in regulating immunological and inflammatory responses. Among them, IL-6 is of major importance because of its pleiotropic effects.[59]

Tocilizumab and sarilumab are monoclonal antibodies that inhibit both membrane-bound and soluble interleukin-6 receptors and are used to treat inflammatory conditions, such as rheumatoid arthritis, as well as cytokine release syndrome after chimeric antigen receptor (CAR) T-cell therapy (tocilizumab).[60]

The neutralizing antispike monoclonal antibodies against SARS-CoV-2—bamlanivimab, casirivimab-imdevimab, and bamlanivimab-etesevimab—are available under separate emergency use authorizations (EUAs) by the US Food and Drug Administration (FDA) for early outpatient treatment of mild-to-moderate coronavirus-19 disease (COVID-19) in patients at increased risk of clinical progression and hospitalization.[61,62]

In a subsequent analysis of this ongoing clinical trial, the patients who received the combination of balmanivimab and etesevimab had significant reductions in viral load compared with those who received bamlanivimab monotherapy.[63] In an interim analysis of a phase 1 to 2 trial of 275 patients, the use of casirivimab and imdevimab was also associated with reduction in viral load, especially among patients with high initial viral load and negative SARS-CoV-2 serology.[64]

Vaccines for SARS-CoV-2

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are the most important counter measure to fight the coronavirus 2019 (Covid-19) pandemic. There is a strong consensus globally that a COVID-19 vaccine is likely the most effective approach to sustainably controlling the COVID-19 pandemic. From December 2020 through March 2021, the European Medicines Agency approved four vaccines on the basis of randomized, blinded, controlled trials: two messenger RNA–based vaccines — BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) — that encode the spike protein antigen of SARS-CoV-2, encapsulated in lipid nanoparticles; ChAdOx1 nCov-19 (AstraZeneca), a recombinant chimpanzee adenoviral vector encoding the spike glycoprotein of SARS-CoV-2; and Ad26.COV2.S (Johnson & Johnson/Janssen), a recombinant adenovirus type 26 vector encoding SARS-CoV-2 spike glycoprotein.[65]

a. BNT162b2, [66]is a lipid nanoparticle–formulated,[67] nucleoside-modified RNA (modRNA)[68] encoding the SARS-CoV-2 full-length spike.

b. Covaxin (BBV152) is India's first indigenous COVID-19 inactivated vaccine developed and manufactured by Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR) and the National Institute of Virology (NIV).[69] The recent findings indicate that Covaxin can effectively neutralize the recently emerged B 1.1.7 SARS-CoV-2 variant (UK variant).[70]

c. Covishield is the Indian version of the replication-deficient adenoviral vector vaccine developed by Oxford University and AstraZeneca (AZD1222, previously called ChAdOx1 nCoV-19 vaccine). It is manufactured by the Serum Institute of India (SII), the world's largest vaccine manufacturer and one of the leading exporters of vaccines. SII has also collaborated with Codagenix to manufacture COVI-VAC, a live-attenuated intranasal vaccine against COVID-19.[71]

d. [69]In addition to that, indigenously developed vaccine candidates such as ZyCoV-D (plasmid-based DNA vaccine), HGCO19 (mRNA vaccine) and Mynvax COVID-19 vaccine (RBD-based subunit vaccine) are also making significant progress in pre-clinical/clinical studies.[72]

CONCLUSION

Patients presenting with Symptoms are advised to take COVID 19 Test as soon as possible. Most of the mortality rates are in patients with late presentation.

There is also promising evidence of pharmacological treatment efficiency when treated early. Vaccination, Monoclonal Antibodies, Preventive measures are effective in prevention of Pneumonitis. Physicians of varied specialization along with the government must get updated information from the doctors who treated large number of COVID patients with evidence based clinical data.

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