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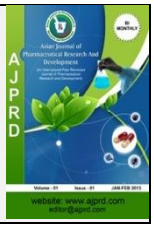

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Review Article

Covid-19: A Pharmacotherapeutic Perspective

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A B S T R A C T

Introduction: COVID-19 disease has been difficult to tackle owing to the lack of typical therapeutic options. Many antivirals, antimalarial, and biologics are being carefully evaluated for treatment. This literature analysis aims to shed light to the ongoing studies concerning treatment possibilities for COVID-19 and assist as a reserve for health experts.

Objectives: This literature review was done to underline the efficacy and safety of existing treatment alternatives for COVID-19 and the cautious use of non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

Methods: PubMed, Medline, Embase and SCOPUS were meticulously browsed utilizing an amalgamation of the keywords "COVID 19," "SARS-CoV-2," and "treatment." All categories of articles together with clinical guidelines, case-studies and systematic reviews were assessed.

Conclusions: Treatments that unswervingly target SARS-CoV-2 are not present so far; however, several antivirals (Remdesivir) and antimalarials (Hydroxychloroquine) have appeared as valuable treatment possibilities. Remdesivir and convalescent plasma may be expected to play a beneficial role in serious patients with respiratory failure. Interleukin-6 (IL-6) antagonists could also be utilized in patients who progress and display evidence of cytokine release syndrome. Corticosteroids need to be avoided lest there is a gripping indication for their usage. Available evidence for prevention and treatment of COVID-19 must be utilized till recognized treatments are derived into reality.

Keywords: Coronavirus, Wuhan Virus, Sars-Cov-2, Convalescent Plasma, Covid 19

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INTRODUCTION

SARS-CoV-2 is an exceedingly transmissible ailment that disperses from person to person employing respiratory droplets. The incubation period mounts to 2-14 days (median 5 days). Illness ranges from symptomless to severe disease. As of 12 December 2020: 68,567,527 cases and 1,563,130 deaths have been reported globally (WHO). Nearly every patient complains of cough, shortness of breath, fever, chills, headache, sore throat, muscle pain and loss of taste or smell. Laboratory investigation is compulsory as clinical judgment alone cannot accurately predict COVID-19 diagnosis. Acute infection can be detected by identifying viral RNA fragments.[1] COVID-19 is a pneumonia-like illness that was first recognized in Wuhan, China. A novel coronavirus SARS-CoV-2,set off the acute respiratory illness, which is similar to the Severe Acute Respiratory Syndrome (SARS) virus.[2] The order Nidovirales consists of coronaviruses which are grouped into four genera namely alpha, beta, delta, and gamma, of which alpha and beta coronaviruses are proclaimed to cause infection in humans. SARS-CoV-2 is a member of *Coronaviridae* family, *Betacoronavirus* genus and *Sarbecovirus*subgenus.The span of Coronaviruses is 60-140 nanometers and possess crown-like halo around them. Positive-sense single-stranded, lipid enveloped RNA viruses (+ssRNA viruses) with helical

capsids transmit this disease to a variety of hosts including humans, bats, other mammals and birds. Two beta coronaviruses have contributed to the SARS worldwide outbreak in 2002-2003 with 8,096 cases and 774 deaths reported, and Middle East respiratory syndrome coronavirus (MERS-CoV), responsible for 2,102 cases and 780 deaths in the 2012 MERS outbreak.[3]

The access of the SARS coronavirus into cells begins by binding of its spike envelope glycoprotein (S) to a receptor, ACE2 (Angiotensin-converting enzyme 2). ACE2 is concerned with the control of blood pressure and is expressed by cells of the heart, lungs, kidneys and intestines. Spike (S) glycoproteins of coronaviruses facilitate binding to host cells followed by membrane fusion. ACE2 is the chief focus for neutralizing antibodies and create the characteristic corona of large, distinctive spikes in the viral envelopes. The entry of the SARS Coronavirus into cells can be subdued by antibodies that attach the S glycoprotein and avert its attachment to ACE2. Numerous symptoms related to COVID-19 are produced by the patient's immune system and not the virus itself.[4]

Epidemiology of COVID-19

According to primary studies, 49–66% of patients had the contact history of Wuhan South China Seafood Wholesale Market, where poultry, bats, marmots and other wild animals were being sold. The outbreak of COVID-19 in Wuhan is speculated to be connected with wild animals. According to WHO, the environmental samples taken from the seafood market in Wuhan were tested positive for SARS-CoV-2, but the precise animals linked with the virus have not been yet recognized. Previous studies show that the bats, the host of more than 30 coronaviruses, maybe the origin of COVID-19. The bats are the natural reservoir of SARS-CoV and MERS-CoV which spread to a human through the palm civets and Arabian camels, respectively.[4]

Clinical manifestations

The clinical symptoms of SARS-CoV-2-infected patients range from mild non-specific symptoms to severe pneumonia with organ function impairment. The most common symptoms at the onset of illness are fever (77-98%), cough (59-81%), fatigue (38-69%), dyspnoea (3-55%), myalgia (11-35%), sputum production (28-56%) and headache (6-33%). Sore throat, rhinorrhea, chest pain, hemoptysis, conjunctival congestion, diarrhoea, nausea, and vomiting are less frequently reported. Symptoms such as throat pain, dyspnoea, dizziness, abdominal pain and anorexia are more expected in patients with severe illness.[5]

Laboratory investigations

Patients hospitalized with COVID-19 show noticeable lymphopenia, prolonged prothrombin time, raised lactate dehydrogenase, increased CRP, increased ESR and elevated D-dimer levels. These laboratory aberrations are comparable to the SARS-CoV and MERS-CoV infections. Bilateral patchy shadows and ground-glass opacities are seen on the radiological investigation of the chest. Ideal clinical samples for corroborating the laboratory confirmation of a suspected case include nasopharyngeal and oropharyngeal swabs collected using Dacron swabs, expectorated sputum, BAL fluid, endotracheal aspirate and tissue. The clinical sample must be collected in a sterile container with normal saline which shields the sample.[6]

The WHO endorses that the culture of the virus must be accomplished in a BSL-3 laboratory and the RT-PCR be done in a BSL-2 laboratory. While supervising specimens of SARS-COV-2, one must confirm that neither the sample nor the healthcare employee is contaminated to curtail any risks and to warrant precision of diagnosis.[7]

SARS-COV-2 is isolated in cell lines and confirmed by RT-PCR. After a negative result in acute-phase serum sample, the seroconversion of the disease is seen by uncovering of antibodies in convalescent-phase serum, or a four-fold rise in antibody titres between the acute and convalescent phases.[8]

Management and Vaccination

One likely approach for treating SARS-CoV-2 is to regulate the host's immune system. Excessive inflammation complements the most severe cases of COVID-19. Hyperactive (uncontrolled) immune responses can precedent to Cytokine Storm Syndrome, Acute Respiratory Distress Syndrome and eventual organ failure. Diminishing the inflammation assists in keeping the lungs and other organs functioning properly during viral infection.

Chloroquine and hydroxychloroquine lessen autophagy (self-regulated obliteration of host cells), affect Toll-like receptor (TLR) signalling and lessen cytokine production. Inflammation is limited and immune reactions are not as much severe. Evidence suggests that chloroquine and hydroxychloroquine may also affect the glycosylation of SARS-CoV-2 cellular receptors and thwart virus/cell fusion by raising endosomal pH. Both of these drugs are currently FDA permitted for the treatment of malaria, rheumatoid arthritis and lupus and have unveiled in vitro action against SARS-CoV and SARS-CoV-2.

A preliminary trial concerning 36 COVID-19 patients in France presented reassuring results. Six patients in the study were asymptomatic, 22 showed symptoms of upper respiratory tract infections and 8 displayed symptoms of lower respiratory tract infections. 20 were treated with hydroxychloroquine (600 mg daily, in a hospital setting). The virus was no longer demonstrable within six days in 70% of samples taken from patients who received treatment. In contrast, only 12.5% of patients who did not receive the hydroxychloroquine treatment had cleared the virus. A trial involving 100 patients in China described that chloroquine was effective at diminishing pneumonia and shortening the interval of the disease.[9]

Another probable strategy for treating SARS-CoV-2 is to avert replication of the virus. If the viral genome isn't copied, the virus can't replicate, and the infection will be cleared. Remdesivir is a broad-spectrum antiviral drug that impedes RNA-dependent RNA polymerase, the virus-encoded enzyme accountable for replication of SARS-CoV-2's genetic code.Blocking an enzyme essential for RNA replication stops the virus from making its copies and permits the body to mount an effective response to eradicating it. Remdesivir possesses strong antiviral action in vitro and efficacy in animal models of coronavirus disease 2019.

SARS-CoV-2 can be treated by attacking the virus directly. Blocking a virus's ability to recognize, attach to or enter host cells will prevent infection altogether. In many cases, this is attained through the creation of antibodies. Antibodies are naturally formed during exposure and recovery from infections.Monoclonal antibodies denote the chief class of biotherapeutics for passive immunotherapy to fight against viral infection. The therapeutic potential of monoclonal antibodies has been well documented in the treatment of many diseases. Instituting the therapeutic or prophylactic efficacy of monoclonal antibodies would be a major development in the control of the COVID-19 pandemic. Based on the existing evidence and earlier understanding in the treatment of other viral infections such as influenza, SARS, MERS, and Ebola, early prescribing of stimulant plasma or immunoglobulin overuse in patients with significant antibody titers can lead to a drop in the mortality rate. The outcomes of the new studies are very hopeful. The researchers proposed neutralizing antibodies that block COVID-19. B38, H4, 47D11 are new antibodies that have shown outstanding results in neutralizing the novel coronavirus infection.[10]

Plasma therapy, including neutralizing monoclonal antibodies, is one of the treatment approaches which have been explored in several studies with promising results. Evaluation of computed tomography (CT) scan of patients with acute infection has revealed that the viral load declined within a few days of treatment with plasma infusion, while the clinical ailment of the patients also displayed improvement.[11]

The source of the outbreak, the intermediate host, treatment regimen and tools for prompt diagnosis remain abstruse. Vaccine trials have commenced all over the world. The infectious disease threats of our era are far from over, and if these are to be checked with lesser scales of harm to human life and economy, investments need to be done in building up people-centric health systems, which anticipate and avert feedback loops motivated by the weight of human melancholy. Meanwhile no effective vaccine or drug has been established to treat and fight the COVID-19 yet, the current tactic for management concentrates on supportive care. Passive antibody therapy could be a technique to limit the advancement of the COVID-19 pandemic. The existing facts about neutralizing antibodies offer beneficial evidence for passive antibody therapy and vaccine development against SARS-CoV-2. Treatment options include oxygen therapy, antiviral agents, antibacterial agents, immunoglobulins, anticoagulants and corticosteroids.[12]

Hydroxychloroquine and chloroquine

Hydroxychloroquine and chloroquine are broadly used antimalarial drugs that stimulate immunomodulatory properties and are accordingly likewise used to cure autoimmune conditions (eg, systemic lupus erythematosus, rheumatoid arthritis). These drugs have added antiviral activity as they inhibit heme polymerase enzyme.

Alkalinization of the phagolysosome inhibits the pH-dependent steps of viral replication. Wang et al stated that chloroquine efficiently impedes SARS-CoV-2 in vitro. Hydroxychloroquine was instituted to be more effective than chloroquine in vitro. FDA determined that hydroxychloroquine is not likely to be effective in treating COVID-19.

Dosing regimen:

- Hydroxychloroquine Loading dose 400 mg PO BID, then, 200 mg BID for 4 days
- High-dose Hydroxychloroquine 600 mg PO BID for 10 days
- Low-dose Hydroxychloroquine 450 mg BID for 1 day, then 450 mg OD for 4 days

Most commonly co-administered drugs are ceftriaxone, azithromycin and oseltamivir. These drugs may help in controlling cytokine release syndrome in critically ill patients.[12]

Non-hospitalized patients with early COVID-19: Hydroxychloroquine has no role in improving outcomes when administered to outpatient adults with early COVID-19. Chloroquine phosphate 500 mg (300 mg base) given twice in a day in tablet form for ten days may be taken into consideration in patients with COVID-19 pneumonia. Hydroxychloroquine plays no role in reducing the rate of infection when used by individuals at high risk for exposure, such as high-risk healthcare workers, first responders, and individuals who share a home with a COVID-19–positive patient.[13]

Risk of QT prolongation with potential drugs for COVID 19: Chloroquine, hydroxychloroquine, and azithromycin each carry the warning of QT prolongation. There is an increased risk of cardiac death. Additional risk factors that may further increase the risk of QT prolongation are mentioned in Table 1. Chloroquine and hydroxychloroquine obstruct the potassium channel, specifically KCNH2-encoded HERG/Kv11.1. QTc can be increased by greater than 40 ms using combination of azithromycin and hydroxychloroquine. QTc may increase to more than 500 ms, which is considered a high risk for arrhythmia. Development of acute renal failure is a strong predictor of extreme QTc prolongation. Clinicians should carefully monitor QTc and concomitant medication usage if considering using hydroxychloroquine. An increased 30-day risk of cardiovascular mortality, chest pain/angina, and heart failure occurs with the addition of azithromycin to hydroxychloroquine.[14]

Lopinavir/ritonavir

Lopinavir/ritonavir or other HIV protease inhibitors, due to their unflattering pharmacodynamics have not established a clinical advantage in patients with COVID-19. There is a menace for severe cutaneous reactions, QT prolongation, and the expected drug interactions owing to CYP3A inhibition. Lopinavir/ritonavir [400 mg/100 mg 12 hourly], ribavirin [400 mg 12 hourly], interferon beta1b [8 million IU x 3 doses every 48 hours]. This triple therapy regimen for 14 days showed some benefit.[15-21]

Remdesivir

Remdesivir is a nucleotide analog prodrug and a broad-spectrum antiviral agent . Remdesivir inhibits replication of human coronaviruses in tissue cultures. [22]

10-day Dosing regimen:

- Day 1: 200 mg IV loading dose is infused over 30-120 min
- Days 2-10: 100 mg IV maintenance dose per day

Coadministration of remdesivir is not suggested together with chloroquine or hydroxychloroquine. In vitro data suggested that chloroquine had an antagonistic effect on the intracellular metabolic activation and antiviral action of remdesivir. Madsen et al., 2020 presented a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults who were hospitalized with Covid-19 and had indication of lower respiratory tract infection. The patients were arbitrarily allocated to accept either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. Remdesivir was better than placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and suffering from lower respiratory tract infection.[23-27]

Nitazoxanide

Nitazoxanide extended-release tablets (NT-300; Romark Laboratories) impede replication of a extensive variety of respiratory viruses in cell cultures, as well as SARS-CoV-2.[28] Several anti-flu drugs such as oseltamivir have been used for the treatment of COVID-19 patients.[29] Favipiravir demonstrated efficacy against SARS-CoV-2 in vitro.[30,31] Broad-spectrum antiviral Umifenovir can improve the discharging rate and decrease the mortality rate of COVID-19 patients[32]. Alpha-interferon (5 million units by aerosol inhalation twice per day) has shown efficacy for treating COVID 19.[33]

Ivermectin

An antiparasitic drug Ivermectin exhibited in vitro decrease of viral RNA in SARS-CoV-2 clinical isolate. The SARS-CoV-2 inhibitory concentrations for ivermectin are unattainable in humans. Ivermectin leads to neurotoxicity in patients with a hyperinflammatory state related to COVID-19. Drug interactions with potent CYP3A4 inhibitors (eg, ritonavir) warrant vigilant use of coadministered drugs. Ivermectin plasma levels with significant activity against COVID-19 would not be reached without theoretically causing harm to the patient.[34-37]

Azithromycin

Azithromycin exhibited a synergistic antiviral effect against SARS-CoV-2 when merged with Hydroxychloroquine both in vitro and in clinical situation. Azithromycin interferes with the entry of virus into cells and up-regulates the assembly of type I and III interferons (especially interferon-λ and interferon-β).MDA5 and RIG-I genes are implicated in virus recognition. The immunomodulation activity of azithromycin is the foundation of its usage against inflammatory manifestations resulting in interstitial lung disease.

Azithromycin inhibits several cytokines (IL-1β, IL-6, IL-8, IL-10, IL-12, and IFN-α) involved in COVID-19 severe respiratory syndrome. Azithromycin and Hydroxychloroquine both decrease the production of major inflammatory cytokines such as IL-1 and IL-6. Dose: 500 mg once, then 250 mg PO daily for 4 days.[38-45]

Corticosteroidsare usually used in severe acute respiratory syndrome (e.g., methylprednisolone 1 mg/Kg/day). Glucocorticoid usage in patients with early C-reactive protein (CRP) levels of 20 mg/dL or more is linked with drastically diminished danger of mortality or mechanical ventilation. The RECOVERY trial postulated that treatment with dexamethasone at a dosage of 6 mg once daily for up to 10 days slashes 28-day mortality rates in patients with Covid-19 who are getting respiratory support.[46-50]

COVID-19 patients have a higher incidence of venous thromboembolism and anticoagulant therapy is associated with reduced ICU mortality hence thromboprophylaxis is recommended. Known case of thrombophilia or thrombosis should be treated with enoxaparin 1 mg/kg twice daily subcutaneously. Aspirin 325 mg orally should be administered daily.[51-54]

PUL-042 (Pulmotech, MD Anderson Cancer Center, and Texas A&M) is a solution for nebulization with immunostimulating activity (ongoing Phase 3 trial). It comprises two toll-like receptor (TLR) ligands: Pam2CSK4 acetate (Pam2), a TLR2/6 agonist, and the TLR9 agonist oligodeoxynucleotide M362. PUL-042 attaches to TLRs on lung epithelial cells and induces the epithelial cells to produce peptides and reactive oxygen species (ROS) against pathogens in the lungs, including bacteria, fungi, and viruses.[55]

Investigational Vaccines in phase 3 clinical testing

Various areas explored for the search of an ideal vaccine against COVID 19, include inactivated virus vaccines, recombinant viral vaccines, subunit vaccine, DNA vaccines and attenuated vaccines. mRNA-1273 (Moderna Inc), mRNA vaccine BNT162b2 (BioNTech and Pfizer) and AZD1222 (AstraZeneca) are being studied for COVID 19.[56-58]

Investigational Antibody Therapies

Stone et al., 2020 conducted a randomized, double-blind, placebo-controlled trial using Tocilizumab. Patients with established severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were arbitrarily allocated in a 2:1 ratio to obtain standard care plus a single dose of either tocilizumab (8 mg/kg) or placebo. Patients who took tocilizumab had limited disease as compared to the placebo group. Tocilizumab was not effective in preventing intubation or death in moderately ill hospitalized patients.[59, 60]

COVI-SHIELD (Sorrento Therapeutics), AZD7442 (AstraZeneca), REGN-COV2 Anti-Viral Antibody Cocktail (Regeneron) and LY-Cov555 (Eli Lilly and AbCellera) have also been investigated for COVID-19. The patients who received LY-CoV555 had infrequent hospitalizations and a lesser symptom load than those who received placebo, with the most noticeable effects observed in high-risk cohort.[61-65]

Investigational Immunotherapies

Pegylated IFNs already exist and have a harmless profile in humans. Other formulations like Efineptakin alfa (NT-17;

NeoImmuneTech, Inc), Immune globulin IV (Octagam 10%; Octapharma), Peginterferon lambda (Eiger Biopharmaceuticals; Stanford University) and LY3127804 (Eli Lilly Co) are under development.[66-68]

Investigational Drugs for ARDS/Cytokine Release

The most severe presentation of COVID-19 is characterized by a hyperinflammatory state attributed to the massive pro-inflammatory cytokine release, also called the cytokine storm. Numerous anti-inflammatory/immunosuppressive agents are being appraised by continuing clinical trials; yet, at present there is insufficient evidence for their efficacy and safety in COVID-19 treatment. Neurokinin-1 (NK-1) receptor antagonists (Aprepitant and Tradipitant), Colony-stimulating factors (Sargramostim, Gimsilumab and Mavrilimumab), Mesenchymal stem cells, PLX-PAD (Pluristem Therapeutics) and Phosphodiesterase inhibitors (Apremilast and Ibudilast) are being explored for treatment of COVID-19.[69-74]

Ongoing phase 2 trials

Several Phase 2 trials are also being conducted including Decitabine (Nucleic Acid Synthesis Inhibitor), Infliximab (TNFα inhibitor) and Duvelisib (Inhibitor of phosphatidylinositol 3-kinase: PI3K). Convalescent plasma therapy, Hyperbaric oxygen therapy as well as Hyperimmune plasma therapy has been tried for treatment of COVID 19.[75-77]

The Solidarity trial compared treatment possibilities against standard of care to evaluate their comparative utility against COVID-19. WHO issued interim outcomes on 15th October 2020. Remdesivir, Hydroxychloroquine, Lopinavir/Ritonavir and Interferon had little or no outcome advantage on global mortality, commencement of ventilation and length of hospital stay in hospitalized patients. So far, only corticosteroids have demonstrated effectiveness against severe and critical COVID-19.[78]Grant et al., 2020 suggested that people at risk of COVID-19 should consider taking 10,000 IU/day of vitamin D3 for a few weeks followed by 5000 IU/day to elevate serum 25(OH)D concentrations. The goal should be to raise 25(OH)D concentrations above 40-60 ng/mL (100-150 nmol/L).[80] Treatments that directly target SARS-CoV-2 have not been discovered so far; however, several drugs have appeared as valuable treatment possibilities. Available data for prevention and treatment of COVID-19 must be used.

FDA approvals for treatment of COVID-19

Remdesivir (brand name Veklury)is an antiviral drug approved by FDA on October 22, 2020, for the treatment of hospitalized COVID-19 patients more than or equal to 12 years of age.Bamlanivimab (LY-CoV555) is a recombinant, neutralizing human IgG1 monoclonal antibody (mAb) targeting the spike protein of SARS-CoV-2.FDA authorized its use on November 9, 2020 for the treatment of recently diagnosed COVID-19.Casirivimab and Imdevimab (REGN-COV2) is a combination of two monoclonal antibodies which block the infectivity of the SARS-CoV-2 virus. On November 21, 2020 this combination was approved for the treatment of mild to moderate COVID-19.[81]

Table 1: Risk factors which intensify the risk of prolongation of QT interval[79]

Modifiable risk factors	Nonmodifiable risk factors
Duration of treatment	Acute Coronary Syndrome
QT-prolonging drugs co-administration	Renal Failure
Hypocalcemia	Congenital Long QT syndrome
Hypokalemia	Hypoglycemia
Hypomagnesemia	Female sex
	Age ≥65 years

CONCLUSION

COVID-19 is ensuing a trajectory that is difficult to prognosticate.Hydroxychloroquine or chloroquine have been widely adopted worldwide for the treatment of SARS-CoV-2 pneumonia. However, this treatment was based on retrospective, non-randomized controlled studies.Even though gold standard treatment for COVID-19 has not yet been found, large RCTs will assist finding definitive COVID-19 therapy and offer a scientific groundon the basis of which treatment decisions can be made.

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