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Review Article

Investigational Drugs for the COVID 19 Pandemic – A Concise Review

Reena Sherin Parveen[1], Shreya Hegde[1], Veena Nayak[1*]

[1]*Department of Pharmacology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal , Karnataka, -576104, India.*

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Abstract

The present year saw the emergence of a pandemic Corona Virus Disease of 2019 (COVID 19). The unpreparedness for the pandemic and lack of drugs/vaccine against this virus has led to a high mortality rate across the world. In the process, a number of drugs have been tried against the corona virus including antivirals like remdesivir, lopinavir-ritonavir, and favipiravir, monoclonal antibodies like tocilizumab and sarilumab and antimalarial drugs like chloroquine and hydroxychloroquine. At the present time, none of these drugs have reported efficacy against the virus. Here we present a review of all these drugs, their proposed mechanism of action against the corona virus and their status in clinical trials.

Introduction

Since 2002, the world has witnessed the occurrence of three coronaviruses namely, the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East respiratory syndrome related Coronavirus (MERS-CoV) and the SARS-CoV-2, a new human pathogen being the causative agent of COVID-19. In December 2019, SARS-CoV-2 arose in Wuhan, China, and this novel coronavirus (2019-nCoV), was identified as the causative agent.[1] Ever since this virus has had a significant impact on health, morbidity and mortality rates, health services and economy of the people all over the globe.

The disease spectrum of COVID-19, varies in severity, ranging from asymptomatic carrier state to mild respiratory tract infection to fatal pneumonia. Furthermore, SARS-CoV-2 can spread within the family, community and hospitals, and has turned into a public health emergency of international concern (PHEIC), declared by the World Health Organization (WHO) on 30 January 2020.[2] Confirmed cases of COVID-19 have been reported in 56 countries and territories with the global number of confirmed cases being 2,83,31,121, including 9,13,015 deaths as of August 25, 2020, according to the WHO.[3]

Drug Targets on the Novel Corona Virus (CoV)

The seven major targets are (spike protein (S), envelop protein (E), membrane protein (M), protease, nucleocapsid protein (N), hemagglutinin esterase (HE), and helicase against which drugs are being designed. There are sixteen nonstructural proteins (NSPs) that are required for the formation of replicase transcriptase complex which are also being considered as drug targets.

CoV mechanism of infection: CoV attaches to the target cells with the help of the spike protein (S). The receptor for it is the angiotensin-converting enzyme 2 (ACE2) on the host cell. The enveloped virus can enter directly or via internalisation by endocytosis. Then the genome of the virus is released into the cytoplasm of the host cell by various lysosomal enzymes. The viral genome enters the ribosomes and endosomes. ORF1a and ORF1b genes produce polypeptides which take command over host ribosomes and synthesizes 16 NSPs which have an important role in replication and transcription. Once the structural proteins and mature virions are formed, they are then released from the infected cell through exocytosis.[4] There have been no drugs, vaccines or monoclonal antibodies which have been approved for the treatment of human infections due to coronaviruses. Here we present a review of drugs which have been used to date against this pandemic and we have included all experimental medications for COVID19 that are stated in WHO, Infectious diseases society of America (IDSA), National Institutes of Health (NIH) and National Institute for Health and Care Excellence (NICE) guidelines.

Hydroxychloroquine

Hydroxychloroquine(HCQ) is an aminoquinoline which is less toxic and more soluble than chloroquine.

HCQ raises the endosomal pH and hinders the glycosylation of the cellular receptor of SARS-CoV and thus blocks viral infection. It also exerts its antiviral effect via a modulating effect on the activated immune cells. It also has an additional action through downregulation of the expression of Toll-like receptors (TLRs) and reduction in interleukin-6 production.[5] The risk of retinal toxicity is less with HCQ when compared to chloroquine due to decreased permeability to the blood-retinal barrier and rapid clearance from the pigment cells of the retina as it has an additional hydroxyl group.[6]

In a study conducted by Gautret et al. in Marseille, France,

*Corresponding Author: Veena Nayak, E-mail: veena.nayak@manipal.edu

it was shown that HCQ by itself, and also the combination of HCQ along with azithromycin, when administered for three to six days, was greatly effective in the clearance of nasopharyngeal carriage of the virus in test subjects affected with COVID-19 when compared to control.[7]

In an observational study conducted at a large medical centre in New York City involving hospital-admitted COVID-19 patients, the outcomes were compared among those who received HCQ with those who did not, and it was found that there was no significant association between HCQ use and the composite end point of intubation or death.[8]

A comparative retrospective cohort study evaluating the clinical outcomes of COVID-19 patients hospitalized at the Henry Ford Health System (HFHS) in Southeast Michigan demonstrated that in a strictly monitored protocol-driven in-hospital setting, treatment with HCQ alone and HCQ + azithromycin was associated with a significant reduction in mortality among patients hospitalized with COVID-19.[9]

A case-control study was conducted in India to identify the factors associated with SARS-CoV-2 infection among health care professionals in the country. The study reported that the consumption of four or more maintenance doses of HCQ was associated with a significant decline in the risk of SARS-CoV-2 infection among the study participants. It is stressed that the protective effects of the drug are seen with the intake of four or more maintenance doses of HCQ. The National Task Force for COVID-19 in India recommended once a week maintenance dose for seven weeks (400 mg once weekly), following the loading dose (400 mg twice a day). The multivariate model in the study indicates HCQ prophylaxis should be taken in tandem with personal protective equipment (PPE) use.[10]

A randomized, double-blind, placebo-controlled trial was conducted across the United States and certain parts of Canada to test HCQ as a post-exposure prophylaxis for COVID-19. Adults who had either high-risk to moderate-risk of occupational or household exposure to individuals with confirmed COVID-19 were enrolled in the study. The study results revealed that HCQ when used as post-exposure prophylaxis (administered within 4 days of exposure) did not prevent illness compatible with Covid-19 or confirmed infection.[11]

Food and Drug Administration (FDA) reviewed the safety issues of HCQ and chloroquine to treat hospitalized COVID-19 patients for events of serious heart rhythm problems and other safety issues including blood and lymph system disorders, kidney and liver injuries. Based on this report, FDA cautioned against the administration of HCQ and chloroquine for COVID 19 patients outside the hospital setting or clinical trial due to the risk of heart rhythm problems on July 1, 2020.[12]

The Indian Council of Medical Research (ICMR), has recommended chemoprophylaxis with HCQ for all asymptomatic healthcare workers involved in containment and treatment of COVID-19, and asymptomatic healthcare workers employed in non-COVID hospitals/non-COVID areas of COVID hospitals/blocks, asymptomatic frontline workers, such as surveillance workers deployed in containment zones and paramilitary/police personnel involved in COVID-19 related activities and for asymptomatic household contacts of confirmed cases. Electrocardiography (ECG) should be monitored before the prophylactic regimen and during the prophylaxis and the drug should be given under medical supervision with administration of informed consent. HCQ would be taken 400mg twice a day on Day 1 and 400 mg once weekly for the next 3 weeks for household contacts and 7 weeks for asymptomatic healthcare workers and front line workers. This was revised on 23rd May 2020 to expand its indication. The experts further recommended for its use beyond 8 weeks on weekly dosage with strict monitoring of clinical and ECG parameters which would also ensure that the therapy is given under supervision.[13]

Remdesivir

It (GS-5734) is an antiviral drug with a broad spectrum of activity, produced by Gilead Science Inc. in the year 2017 as a treatment option for Ebola virus contagion. This is an experimental drug that has not yet received approval by the FDA.

Remdesivir is a nucleotide analogue prodrug that inhibits RNA-dependent RNA polymerase(RdRp). It metabolizes into its active form which exerts its action by escaping proofreading by the viral exonuclease thus leading to a reduction in the production of RNA.[14] A randomized double-blind clinical trial including 308 hospitalized patients diagnosed with mild or moderate COVID-19 were administered parenteral remdesivir as 200mg loading dose on the first day followed by 100mg intravenous once daily for a period of 9 days. The study aimed to assess the safety and efficacy of the drug.[15] Another phase 3 placebo-controlled clinical trial is being done in 452 hospitalized adult patients to evaluate the efficacy and safety of parenteral remdesivir in severe respiratory infection due to COVID-19.[16]

Compassionate treatment with parenteral remdesivir was provided to the first case of COVID-19 in Washington, USA, on the seventh day of hospitalisation for the progression of pneumonia. The patient's condition remarkably improved with no evident adverse effects.[17]

In a cohort study conducted on hospitalized severe COVID patients, remdesivir showed clinical improvement in 36 of 53 patients.[18]

The Drug Controller General of India (DCGI) approved remdesivir lyophilised powder for emergency use in patients hospitalised with severe COVID-19.

ICMR, has been considering the use of remdesivir, an antiviral drug that has shown improvement in COVID-19 patients in formal clinical trials. Currently, remdesivir is allowed for emergency/compassionate use in treating severely-ill Covid-19 patients and it is likely to be part of the revised protocol.[19]

Favipiravir

It is an antiviral agent that selectively and potently inhibits viral RNA-dependent RNA polymerase (RdRp).[20] The drug is active against a broad range of RNA viruses.

It was approved for the treatment for novel or re-emerging influenza viruses in 2014 in Japan.[21]

Favipiravir is a prodrug that undergoes intracellular phosphoribosylation by certain cellular enzymes like hypoxanthine-guanine phosphoribosyltransferase (HGPRT) to an active form, favipiravir-RTP (favipiravir ribofuranosyl-5'-triphosphate).[22] Favipiravir-RTP is recognized as a substrate by RdRp of the RNA virus. On being incorporated to the viral RNA, it acts as a chain terminator and prevents RNA elongation.[23]

A highly conserved lysine residue of RdRp plays a key role in the broad spectrum antiviral activity of favipiravir against positive-sense single-stranded RNA viruses.[24]

Several trials to assess the safety and efficacy of favipiravir as a single agent and also in combination with protease inhibitors in COVID-19 patients are in progress. In March 2020, favipiravir was claimed by the National Medical Products Administration of China to have demonstrated efficacy with minimal side effect.[25]

An open-labeled comparative controlled study was conducted in Shenzhen, China which showed faster viral clearance and better chest imaging changes in comparison with lopinavir/ritonavir in COVID-19 patients. The dose given in this study was 1600 mg twice daily on Day 1 and 600 mg twice daily orally on Days 2–14.[26]

An open-label, randomized, multi-center clinical trial was conducted by Glenmark pharmaceuticals to compare the safety and efficacy of favipiravir plus standard supportive care and standard supportive care alone in mild-moderate COVID-19 patients. A faster viral clearance and improvement in clinical symptoms were seen with favipiravir-treated group. [27]

The FDA has granted clearance to Appili Therapeutics to expand its phase II study to assess the safety and efficacy of favipiravir in controlling outbreaks following exposure to COVID-19 in long-term care (LTC) facilities. This study intends to explore the prophylactic potential of favipiravir.[28]

The adverse effects reported for favipiravir include an increase in uric acid levels, mild diarrhoea, elevated transaminases and reduced neutrophil count.[29]

Lopinavir-Ritonavir

Lopinavir is a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor. It also has an *in vitro* inhibitory activity against SARS-CoV, the virus causing SARS in humans.[30] Ritonavir is combined with lopinavir to increase its plasma half-life by the inhibition of cytochrome P450.

Lopinavir/Ritonavir inhibit HIV type 1 aspartate protease enzyme. This enzyme is involved in the production of structural proteins and enzymes of the virus from the large viral polyprotein synthesized inside the infected cell. The drug binds to the active site of aspartate protease enzyme thereby preventing the formation of functional viral proteins.[31] SARS-CoV-2 is a single-stranded RNA beta-coronavirus. The processing of viral RNA inside the host cell is carried out by the enzyme, 3-chymotrypsin-like protease ($3CL^{pro}$). Though the binding site in the corona virus protease structurally varies from the HIV protease, *in vitro* studies have shown lopinavir exhibiting antiviral activity against SARS-CoV-2.[32]

Several trials are being conducted to test the efficacy of lopinavir/ritonavir in patients of COVID-19. In a study conducted in hospitalized adult patients with severe COVID-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care in terms of time to clinical improvement and mortality.[33]

The commonly tried dosage regimens in the ongoing trials are 400 mg/100mg or 200 mg/ 50 mg of oral lopinavir/ ritonavir, given twice daily orally for 14 days. It is contraindicated in porphyria and should be cautiously used in patients with haemophilia, pancreatitis and cardiac conduction disorders.

A randomized, controlled, open-label trial involving hospitalized adult patients with severe COVID-19 was conducted in China. The patients were assigned in a 1:1 ratio to receive either lopinavir–ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone. The study failed to show any improvement with lopinavir-ritonavir beyond standard care.[34]

One of the largest clinical trials conducted on the potential COVID-19 treatment options, the RECOVERY Trial (Randomised Evaluation of COVID-19 therapy) concluded that lopinavir-ritonavir failed to provide any mortality benefit over standard care. Hence randomization was discontinued to lopinavir-ritonavir treatment arm.[35]

The Solidarity clinical trial was launched by the WHO and other partners in the wake of COVID-19 to find an effective treatment for the disease. The International Steering committee analyzed the data from the interim trial results and concluded that lopinavir-ritonavir showed little or no benefit when compared to standard of care in hospitalized COVID-19 patients. This led to the discontinuation of patient recruitment to the lopinavir-ritonavir treatment arm in the above trial.[36]

The adverse effects reported for lopinavir/ritonavir include gastrointestinal disturbances diarrhoea, abdominal pain, nausea, dyslipidaemia, diabetes mellitus and pancreatitis.[37]

Tocilizumab

It is a recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that competitively inhibits the binding of interleukin-6 (IL-6) to its receptor (IL-6R).[38] It is approved for use in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, giant cell arthritis and cytokine release syndrome.[39]

Patients of COVID-19 are found to have increased plasma concentrations of inflammatory cytokines like

tumor necrosis factor alpha(TNFα), interleukin 2,7 and 10, granulocyte -colony stimulating factor(G-CSF) and monocytes chemoattractant protein 1 alpha indicating a cytokine storm. It is believed that the pathogenic T cells and inflammatory monocytes with high IL-6 secretion may enter the pulmonary circulation and incite an inflammatory storm in severe/ critical COVID-19 patients.[40] Tocilizumab, by blocking the IL-6 receptors prevents the IL-6 signal transduction to inflammatory mediators and thus calms the cytokine storm.[41] Treatment with tocilizumab was included in the diagnosis and treatment program of COVID-19 (7th trial version, released on 3rd March 2020) by the National Health Commission of China. It is advised for use only in patients with extensive bilateral lung lesions opacity or critical patients with elevated laboratory detected IL-6 levels.

Further large scale, multicentre clinical trials are underway to get clear evidence on the safety and efficacy of the drug. (ClinicalTrials.gov Identifier: NCT04317092, NCT04335071, NCT04310228). Tocilizumab is administered through intravenous infusion wherein the first dose to be given is 4-8 mg/kg, diluted in 100 ml with 0.9% normal saline, the infusion time not less than 60 minutes. If required a repeat administration of the above dose may be done after 12 hours. A single dose should not exceed 800mg and not more than two doses should be administered.[42] An observational, retrospective cohort study conducted on adults with severe COVID-19 pneumonia in tertiary health centres of Italy concluded that both intravenous and subcutaneous tocilizumab administration is likely to reduce the risk of invasive mechanical ventilation or death.[43] In another retrospective cohort study on a small group of hypoxic COVID-19 patients, tocilizumab was associated with a significantly shorter duration of vasopressor support.[44] Both the above mentioned studies stressed the need for further clinical trials to validate their findings.

The CHIC study, prospectively investigated whether an intensive course of glucocorticoids with or without tocilizumab for patients with severe COVID-19 associated with cytokine storm syndrome showed faster clinical improvement, decreased mortality and reduced likelihood of mechanical ventilation. The study involved a comparison of these patients with a historic cohort of age- and sex-matched COVID-19 patients with cytokine storm syndrome who were given standard supportive care. The patients on glucocorticoids with or without tocilizumab were found to be more likely to attain the primary and secondary outcomes than the controls.[45]

Roche announced the results of its phase III COVACTA trial which was a randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of intravenous tocilizumab added to standard of care in hospitalised adult patients with severe COVID-19 associated with pneumonia compared to placebo plus standard of care. The primary and secondary endpoints included assessment of clinical status, mortality, need for mechanical ventilation and intensive care unit (ICU) variables at the end of four weeks. The study failed to meet the primary and key secondary endpoints.[46] Several phase II and III studies with tocilizumab (MARIPOSA, REMDACTA and EMPACTA trials) are underway.

The adverse effects reported with toclizumab include injection site reactions, upper respiratory tract infections, headache and diarrhoea.[42] It is contraindicated in patients with known hypersensitivity to tocilizumab or its excipients, diagnosed with tuberculosis and other active infections.

Sarilumab

It is a human monoclonal antibody against IL-6 signalling originally approved for the treatment of moderate rheumatoid arthritis.

IL-6 is also responsible for life-threatening inflammatory response that causes acute respiratory distress syndrome (ARDS) in patients who are critically ill due to COVID-19.[47] It is a pleiotropic cytokine produced by different cell types like macrophages, fibroblasts, etc. during sepsis and organ injuries. IL-6 induces acute phase response leading to leucocyte recruitment and infiltration and it is a poor prognostic marker in patients with acute lung injury.[48]

In multisite clinical trials enrolling COVID -19 patients, sarilumab was administered intravenously in different doses. In a preliminary case series from China, Sarilumab has reduced the requirement of supplemental oxygen in 15 patients and reduced temperature out of the 20 patients. China has updated its guidelines and added sarilumab for the treatment of critical patients with COVID 19.[47] The safety and efficacy details of this drug is not yet available. The adverse effects reported when used for rheumatoid arthritis were mild upper respiratory tract infections, injection site reactions, neutropenia and elevated liver enzymes.[49]

Arbidol Hydrochloride (Umifenovir)

Arbidol acts as an entry inhibitor against influenza viruses as well as arboviruses which has been approved in Russia and China.[50]

The main target of arbidol is hemagglutinin (HA) which is the major glycoprotein present on the surface of the influenza virus. After endocytosis, the drug inhibits the fusion of the influenza viral membrane with the endosome.[50]

Arbidol was compared with favipiravir in a randomized clinical trial and the latter was shown to be superior in treatment outcome in 240 COVID-19 positive patients.[51] A recent meta-analysis concluded that umifenovir is safe, however the data on efficacy in COVID -19 is limited. The meta-analysis concluded that umifenovir could not improve patient-important outcomes in COVID-19.[52]

Anakinra

Anakinra is a recombinant human Interleukin (IL)-1 receptor antagonist usually employed for the treatment of

rheumatoid arthritis and cryopyrin-associated periodic syndromes.[53] The mechanism of action is by inhibition of IL-1α and IL-1β which are the pro-inflammatory cytokines.[54]

In a case-series report in which anakinra was used in nine patients with moderate to severe COVID-19 pneumonia, the drug was well tolerated. Anakinra improved C reactive protein (CRP) by day 11 and resolved the changes in computerised tomography (CT) scan of chest as well. All the nine patients with COVID 19 survived with anakinra.[55] There was a significant improvement in pulmonary function and it also minimized the need for use of vasopressors. In a retrospective cohort study conducted by Cavalli g. et al. in Italy on 29 COVID-19 patients with moderate-to-severe ARDS, along with hyper inflammation, it was shown that additional treatment with parenteral anakinra was safe and it reduced serum levels of CRP and progressively improved the respiratory function in 72% of the patients.[56]

In a meta-analysis review done by Hong D. et al. for assessment of the safety and efficacy of anakinra, it was observed that the drug was well tolerated and the main adverse event among patients who were treated with anakinra was skin rash.[57]

Baricitinib - Janus Kinase Inhibitor

These agents inhibit the Janus kinase (JAK)-signal transducer and activator of transcription (JAK-STAT) pathway and are assumed to be useful in the management and treatment of severely ill patients infected with COVID-19.[58]

Majority of the viruses enter the cells through a process of endocytosis which is receptor-mediated. Disrupting one of the regulators of endocytosis, the AP2-associated protein kinase 1 (AAK1) by the JAK inhibitor can interrupt the virus entry into cells and also interfere with the assembly of virus particles intracellularly.[59] Baricitinib is a JAK1 and JAK2 inhibitor that is shown to possess a dual effect including viral entry reduction and decline in viral inflammation in COVID-19 patients via AAK1 inhibition. Due to its high affinity and relative safety profile baricitinib was suggested as a potential candidate in the management of patients with COVID-19. When administered as a once-daily dose of 2 mg or 4 mg, sufficient plasma concentration could be attained for inhibition.[60] It has low plasma protein binding and minimal enzyme interaction which makes it appropriate to be included in combination therapies with directly acting antiviral agents like remdesivir and others.[61]

In an open-label study including 12 patients diagnosed with moderate COVID-19 pneumonia in Italy, a combination therapy of baricitinib with lopinavir/ritonavir administered in such patients showed a noteworthy clinical improvement along with laboratory parameters.[62] Among these patients, none of them needed an ICU support.

The use of baricitinib has shown an increase in thromboembolic events including deep vein thrombosis and pulmonary embolism which is important, as the COVID-19 patients have a possibility of developing such events.[63]

Other adverse effects such as anaemia, increase in creatine kinase levels have been associated with baricitinib therapy. Risk of re-activation of latent infections such as tuberculosis and hepatitis B is also seen in infected patients.[64]

Corticosteroids

Corticosteroids could play a role in the advanced disease stage by suppression of lung inflammation owing to their potent action as an anti-inflammatory agent and antifibrotic properties.[65]

Corticosteroids in low doses downregulate the transcription of pro-inflammatory cytokines, thereby preventing a prolonged cytokine response. Corticosteroids also hasten the resolution of pulmonary and systemic inflammation in COVID-19 patients with pneumonia.[66] They may also aid improvement in the immune response that has been dysregulated due to the associated complication such as sepsis.[67] Corticosteroids can raise the blood pressure in patients with hypotension.[68]

In the RECOVERY trial, low-dose dexamethasone administered for 10 days was shown to decrease mortality among severe COVID-19 patients with respiratory complications.[69] Presently, systemic corticosteroids are not recommended for routine use in the management of viral pneumonia by the WHO, unless they are specified for another purpose, such as exacerbation of chronic obstructive pulmonary disease or bronchial asthma or patients with refractory septic shock.[70] In a study done by Wang et al., 46 patients diagnosed with severe COVID-19 pneumonia with acute respiratory failure, who were treated with intravenous methylprednisolone showed improvement in clinical parameters in 26 of them.[71] A study done by Wu et al. demonstrated that methylprednisolone treatment in ARDS patients with coronavirus infection reduced the death rate.[72] Higher dose methylprednisolone for the management of cytokine storm is recommended as follows: 60–125 mg every 6 hours for a maximum of 3 days, and dose tapering following this based on CRP levels.[73]

Some studies like Wang et al. have reported ineffective outcomes in COVID-19 patients treated with glucocorticoids, indicating that the benefit of corticosteroid use is outweighed by its adverse effects.[74] Due to lack of evidence corticosteroid use has not been supported by the WHO, as mentioned in their interim guidelines for the management of viral pneumonia and ARDS in suspected COVID-19 patients.[75]

The use of glucocorticoids may inhibit immune response, reduce pathogen clearance and increase the chances of viral replication in COVID-19 patients. In a study done by Russell et al., clinical evidence was not sufficient to support corticosteroid use for the management of COVID-19 patients with lung injury.[65]

Azithromycin

Azithromycin is a macrolide antibiotic with immunomodulatory and antiviral properties has a role in the treatment

of patients with COVID-19.[76]

The immunomodulatory action of azithromycin is exerted on the intracellularly located mitogen-activated protein kinase (MAPK) and inhibition of the nuclear factor-kappa B (NF-κB) pathway along with its effect on extracellular signal-regulated kinases 1/2 (ERK1/2). This mechanism influences cellular functions such as cell proliferation and inflammatory cytokine production thus aiding in controlling the cytokine storm occurring in COVID-19 patients.[77] The *in vitro* antiviral activity of azithromycin in the early phase of infection included blocking the internalization into the host cells and inactivation of the viral endocytic activity which contributed towards decreasing viral replication.[78] It is shown that azithromycin has anti-inflammatory effects in both acute and resolution phases of the viral infection. It decreases the production of pro-inflammatory cytokines including IL-8, IL-6, TNF alpha, and MMPs in the acute phase and increases the inflammation-related oxidative stress and neutrophil apoptosis in the resolution phase.[79]

Not much data is available to suggest the positive effect of azithromycin when administered along with chloroquine or HCQ in the management of ARDS patients affected with SARS-CoV-2 infection.

In a retrospective study conducted by Rosenberg et al. on 1438 hospitalized COVID-19 patients, 735 patients were treated with a combination of HCQ and azithromycin and no significant differences were seen in the in-hospital mortality among those who were treated with the combination compared to the patients who received monotherapy with either drug.[80] A non-randomized open-label clinical trial done in China on SARS-CoV-2 infected patients demonstrated a synergistic effect of HCQ and azithromycin combination therapy via a reduction in the levels of SARS-CoV-2 RNA in the upper respiratory tract specimens, without any comments regarding clinical benefits of such treatment.[81] Another observational study conducted on SARS-CoV-2 hospitalized patients in China, treated with the combination of HCQ and azithromycin neither showed evidence of any clinical benefit nor demonstrated rapid clearance of viral RNA.[82]

Both HCQ and azithromycin can cause corrected QT (QTc) prolongation, further leading to fatal arrhythmias. Caution should be exercised in such patients and also those with hepatic or renal dysfunction.[83]

Ivermectin

Ivermectin is a broad spectrum FDA approved anti-parasitic and antiviral drug which has shown its efficacy in the treatment of COVID-19 as a second line drug. An *in vitro* study conducted to demonstrate ivermectin effect on SARS-CoV-2 showed inhibition of viral replication.[84]

The mechanism of ivermectin against SARS-CoV-2 is not clearly known and probably could be similar to the mechanism by which it exerts antiviral activity against other viruses. The viral integrase protein and importin (IMP) α/β1 heterodimer are known to increase viral infection by nuclear import process which is inhibited by ivermectin.[84,85]

Ivermectin when administered at lower doses were shown to decrease the viral load thus providing an advantage to the immune system through developing an antiviral response against infection caused by SARS-CoV-2.[86] However, a pharmacokinetic simulation process studied by Schmith et al. showed that the inhibitory concentration of ivermectin needed for an effective antiviral activity against SARS-CoV-2 was higher than the maximum concentration attained in the plasma by the approved dose. Thus ivermectin seems to have partial benefit in the management of COVID-19.[87]

Further clinical trials are needed to establish the safety and efficacy in COVID-19 infected patients.

The main drawback of ivermectin is its cytotoxic potential that limits the clinical utility. Modification of the pharmacokinetic properties by alteration of the vehicles utilized in the formulations can significantly improve the systemic concentration of this drug.[88]

Vitamin C

The antimicrobial and immunomodulatory properties of the micronutrient and dietary supplement vitamin C are well recognized to reduce the possibility of infections, mostly in high concentrations.[89]

Vitamin C inhibits activation of the pro-inflammatory transcription factor, nuclear factor kappa-B (NFκB) which provides immune support through the genetic regulation of various inflammatory mediators.[90] In the host defence cells, vitamin C regulates the redox-signal transduction of cytokines and probably controls inflammatory responses by inhibiting the granulocyte macrophage colony stimulating factor (GM-CSF) signalling pathway.[91] A study conducted by Chen et al. showed that vitamin C inhibits oxidative stress further halting the cytokine storm progression thereby improving immunity in the host.[92] Vitamin C also has a positive effect in the bronchial epithelium of humans by the process of oxidative damage repair through modulation of both inflammatory expression and generation of reactive oxygen species (ROS).[93] Vitamin C has demonstrated antiviral activity *in vitro* through inhibition of the process of replication in different viruses including influenza A virus.[94]

In a randomized controlled trial conducted on 167 patients diagnosed with sepsis-related ARDS, approximately 15 g/day of intravenous vitamin C was administered for a period of 4 days which may have been a reason for decreased mortality in such patients.[95] In another study conducted in China on 50 patients with moderate to severe COVID-19, an improvement in the oxygenation index was seen following the administration of high-dose intravenous vitamin C with complete recovery.[96] Further, patients are being recruited for prospective randomized controlled trials in which high dose intravenous vitamin C will be administered for the management of COVID-19, expecting an improvement in the pulmonary function in such patients along with a reduction in mortality.[97] Due

to insufficient evidence against COVID-19 virus, the recommendations for the intake of vitamin C are limited.

Vitamin D

The micronutrient vitamin D has shown to interfere with viral replication exhibiting antiviral activity along with immunomodulatory action and anti-inflammatory property.[98] Vitamin D reduces the pro-inflammatory cytokine concentration, enhances anti-inflammatory cytokine concentration, improves cellular innate immunity and decreases the rate of viral replication by inducing antimicrobial peptides such as cathelicidins and defensins. These peptides disturb the invading pathogen cell membranes and also counteract the endotoxin activity thereby reducing lung inflammation and the occurrence of pneumonia.[99] Vitamin D can also decrease the production of pro-inflammatory Th1 cytokines including TNFα and interferon γ(IFN γ).[100] Macrophages have shown to diminish the pro-inflammatory cytokine expression and raise the anti-inflammatory cytokine expression on administration of micronutrient vitamin D thus decreasing the risk of infection.[101]

A reduction in hospital-related infections was observed when vitamin D supplements were administered in such patients in order to increase the serum 25-hydroxy vitamin D (25(OH)D) concentration.[102] A recent review has proposed that the risk and severity of infection with COVID-19 can be decreased by administering 50,000-IU capsules of vitamin D in loading doses of 200,000–300,000 IU.[103] An observational study which explored the association between serum concentrations of 25(OH)D and the risk of developing acute respiratory tract infections (ARTIs) in healthy adults, showed that 25(OH)D concentrations of 38 ng/mL or more were significantly associated with a twofold reduction in ARTIs along with a striking decrease in the percentage of days ill.[104] Also, a study done on SARS-CoV-2 positive patients in Switzerland demonstrated a significant reduction in 25(OH)D levels.[105] Thus, the hypothesis that vitamin D micronutrient supplementation can lead to decreased incidence in COVID-19 needs to be probed in clinical trials in order to regulate the dose of drug administered in accordance with serum 25(OH)D concentrations along with safety concerns.

Zinc

Zinc supplementation is hypothesized to play a role in the prophylaxis and treatment of COVID-19.[106] It is known to enhance the antiviral immune response through various mechanisms as demonstrated by certain *in-vitro* and *ex-vivo* studies.[107,108] In an *in-vitro* study conducted by te Velthuis et al. it was demonstrated that zinc exhibited direct inhibitory action on RNA-dependent RNA-polymerase activity which implied direct inhibition of SARS-CoV-2 replication.[108] Zinc plays an important role in cell-mediated immunity, regulates the function and proliferation of neutrophils, macrophages, natural killer cells and lymphocytes and controls the production of cytokines by the immune cells. Zinc has also shown to provide protection against ROS effects that are produced during the inflammatory processes.[109] Several studies on COVID-19 patients are being conducted to assess if zinc administration along with standard antiviral therapy is associated with favourable clinical outcomes. (ClinicalTrials.gov Identifier: NCT04370782, NCT04335084, NCT04342728, NCT04446104).

The recommended daily allowance for healthy adults is usually around 15–30 mg of elemental zinc and long-term high-dose zinc can lead to adverse effects such as decreased levels of high-density lipoprotein cholesterol, copper deficiency and anaemia.[110]

Table 1 summarized common drugs and their mechanism for COVID-19.

Anticoagulants in COVID-19

There is a rising concern regarding the occurrence of hypercoagulability in individuals with COVID-19.[111] The exact mechanism behind this association is yet to be elucidated. The WHO recommends the prophylactic use of low molecular weight heparin (if available) or unfractionated heparin to reduce the incidence of thromboembolic events in hospitalized adults and adolescents with severe COVID-19.[112] The NIH COVID-19 treatment guidelines recommend prophylaxis for venous thromboembolism in hospitalized adult COVID-19 patients unless contraindicated. In COVID-19 patients who experience a thromboembolic event or in whom there is high suspicion, therapeutic anticoagulation is recommended as per the standard of care followed in non-COVID 19 cases. Patients who are managed on an outpatient basis shouldn't be started on specific drugs for either prophylaxis or at therapeutic doses.[113] There is insufficient evidence on the incidence of thromboembolism and the outcomes of different antithrombotic therapies in COVID-19 patients. With the emergence of more data in this regard, we can expect standardized protocols to be in place for the management of hypercoagulability in COVID-19.

Convalescent Plasma Therapy

Convalescent plasma which is obtained from recovered patients with viral infections has been employed as a final approach to increase the survival rate of various influenza virus affected patients without the appearance of serious adverse events.

The probable therapeutic action of convalescent plasma seems to be through suppression of viremia by the immunoglobulin antibodies present in them.[114,115]

Shen et al. observed clinical improvement and reduced viral loads in five laboratory-confirmed critically ill COVID-19 hospitalized patients with ARDS in whom convalescent plasma obtained from recovered patients was transfused.[116]

The USA FDA has approved convalescent plasma therapy for patients with severe COVID-19 infections. The Indian Council of Medical Research (ICMR) has been conducting trials on convalescent plasma therapy for COVID patients.

Table 1. list of common drugs and their mechanism for COVID-19. viral replication and nascent viral synthesis

Drug	Mechanism of action
Hydroxychloroquine	-Raises the endosomal pH, prevents endocytosis; inhibits glycosylation of cellular receptor of SARS-CoV (ACE2), thereby preventing viral entry downregulation of the expression of Toll-like receptors (TLRs) and reduction in IL-6 production
Remdesivir	-Inhibits RNA-dependent RNA polymerase and prevents viral replication and nascent viral synthesis
Favipiravir	-Favipiravir-RTP (favipiravir ribofuranosyl-5'-triphosphate), a substrate by RdRp of the RNA virus, gets incorporated to the viral RNA and acts as a chain terminator and prevents RNA elongation
Lopinavir-ritonavir	-Binds to the active site of aspartate protease enzyme thereby prevents the formation of functional viral proteins
Tocilizumab	-Blocks the IL-6 receptors, prevents the IL-6 signal transduction to inflammatory mediators and calms the cytokine storm
Sarilumab	-Human monoclonal antibody against IL-6 which is responsible for inducing the acute phase response by recruiting leucocytes
Arbidol	-Binds to the hemagglutinin (HA) on the surface of the virus and inhibits the fusion of the influenza viral membrane with the endosome.
Anakinra	-Recombinant human IL-1 receptor antagonist which inhibits the actions of IL-1α and IL-1β which are the pro-inflammatory cytokines
Baricitinib	-A Janus kinase inhibitor, disrupts the regulators of endocytosis, the AP2-associated protein kinase 1 (AAK1) and prevents viral entry
Corticosteroids	-Downregulate the transcription of pro-inflammatory cytokines, thereby preventing a prolonged cytokine response
Azithromycin	-Influences cellular functions such as cell proliferation and inflammatory cytokine production by influencing MAPK, NF-κB, ERK1/2.
Ivermectin	-Inhibits the viral integrase protein and importin (IMP) α/β1 heterodimer which increase viral infection
Vitamin C	-Inhibits pro-inflammatory transcription factors, NFκB -Regulates the redox-signal transduction of cytokines -Controls inflammatory responses by inhibiting the GM-CSF signalling pathway -Inhibits oxidative stress further stopping the progression to cytokine storm
Vitamin D	-Reduces the pro-inflammatory cytokine including TNFα and IFN γ. -Decreases the rate of viral replication by inducing cathelicidins and defensins.
Zinc	-Inhibits RNA-dependent RNA-polymerase and thereby inhibits SARS-CoV-2 replication. -Regulates the function and proliferation of neutrophils, macrophages, natural killer cells and lymphocytes and controls the production of cytokines by the immune cells -Provides protection against ROS effects of the virus

Conclusion

As of now, there is no specific recommended treatment for COVID-19 due to insufficient evidence. The management strategy for COVID-19 as suggested by WHO mainly consists of prevention of infection, early case detection and prompt monitoring and adequate supportive care.[117] There are antivirals that have been proven to be effective as per currently available data. However, the status of the drugs being tried for this infection is undergoing drastic changes following reports from different parts of the world. Many clinical trials are in progress with the hope to find a suitable treatment option for this fast-spreading ailment. Only time will uncover a solution to overcome this pandemic.

Conflict of Interest

The authors declare they have no conflict of interest.

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