International Journal of Contemporary Dental and Medical Reviews (2020), Article ID 030820, 7 Pages

REVIEW ARTICLE

A literature review of pandemic novel coronavirus disease 2019 and potential drugs treatment

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Received 28 April 2020;
Accepted 22 August 2020

doi: 10.15713/ins.ijcdmr.155

How to cite the article:
Hange VB, Devki SM. A literature review of pandemic novel coronavirus disease 2019 and potential drugs treatment. Int J Contemp Dent Med Rev vol.2020, Article ID: 030820, 2020. doi: 10.15713/ins.ijcdmr.155

Abstract

Background: Coronaviruses (CoVs) belong to a family that comes under the order "Nidovirales." Nidovirales order includes the viruses that use a nested set of mRNAs for their replication. CoV disease 2019 (COVID)-19 is a βCoV-2, CoV of the same subgenus as severe acute respiratory syndrome (SARS) virus, but in a different clad. The constitution of the receptor-binding gene region is very like to that of the SARS-CoV, and the virus has been demonstrated to utilize the same receptor, the angiotensin-converting enzyme 2, for entrance into respiratory cells. There are presently no drugs or vaccinations that are known to be successful for SARS-CoV-2 management or preventing the spread as per various major health officials. **Aim:** This review describes various drug treatment options available against COVID-19. It focuses on the use virology of SARS-COV2, potential drugs that can be utilized to treat COVID-19 infection, their dosages, advantages, side effects, and indications. **Conclusion:** As there are no definitive treatment modes accessible to cure SARS-COV2 infection to this date, drug repurposing can provide effective tool to combat against COVID-19 until definitive drugs or vaccines discovered to treat SARS-CoV2 infection. Various antiviral, antiparasitic, and antimalarial drugs, antibodies, Vitamin C, Vitamin D, melatonin hormone, etc., are effective to reduce viral load of COVID-19. **Clinical Significance:** Drug repurposing and previous or recent clinical experiences with CoV infection provide an efficient weapon to COVID-19 infection. They are effective in not only reducing viral load of COVID-19 infection but also minimize the symptoms related to SARS.

Keywords: Coronavirus disease 2019, Coronaviruses, Outbreak, Respiratory illness, Transmission, Infection control and management

Background

Coronaviruses (CoVs) are the predominant genus of Nidovirales-related viruses, comprising *Coronaviridae*, *Arteriviridae*, *Mesoniviridae,* and *Roniviridae* groups. CoV virion is circular with a diameter of nearly 125 nm. Its most conspicuous characteristic of CoV is the club-shaped spiked figures emerging from the coating of the virion. These spikes are a distinct peculiarity of the virion and lend them the expression of a solar corona contributing to the phrase CoV.[1] *Coronaviridae* covers a broad range of host and carriers, infecting many mammalian and avian species/subspecies, this may affect the upper respiratory, gastrointestinal, hepatic, and central nervous system through a number of diseases.[2]

Severe acute respiratory syndrome (SARS)-CoV, Class 2b-β CoV, was revealed as the potential culprit of the 2002–2003 epidemic of SARS throughout the Guangdong territory of China. In a cluster of extensively pathogenic respiratory infections in Saudi Arabia as well as other Middle East countries during 2012, the Middle East respiratory CoV syndrome (MERS-CoV) has been defined as the potential culprit of yet another novel human CoV.[3]

On December 31, 2019, the Wuhan Health Commission in the Republic of China's Hubei Province notified the National Health Commission, China Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO) of a series of 27 cases of unexplained etiological pneumonia. Leaks have been predominantly tracked to the Huanan Seafood Wholesale Market in Wuhan that trades fish and a myriad of livestock species comprising chickens, bats, marmots, and snakes.[4] By January 7, 2020, Chinese CDC officials had isolated SARS-CoV-2. On February 11, the WHO officially named the disease as the CoV disease 2019 (COVID-19).[5] The WHO also announced a global emergency on January 31 due to increasing concern about its rapid expansion and the disease became listed as a pandemic by March 11.[6]

According to the world's leading health authorities, there are currently no known medicines or vaccines is neither successful in reducing viral load of SARS-CoV-2 nor in preventing its spread. Within clinical trials and compassionate use guidelines, numerous different compounds are used relying on *in vitro* activity (against SARS-CoV-2 or associated viruses) and on constrained clinical knowledge. There was no proven efficacy for any drug therapy.[7] As of April 13, 2020, COVID-19 has been recognized in 196 countries, with a total of 1,876,707 laboratory-confirmed cases, 435,591 recovered, and 116,789 deaths. Till this date, 9352 laboratory-confirmed cases, 980 recovered, and 324 deaths were reported by Indian Council of Medical Research in India.

Literature Search

This narrative review discusses the relevant literature, including updated studies, case series, protective measure, treatment guidelines, and the implications for practice with respect to (novel CoV, nCoV) infection. We performed a literature search using ProQuest, Medline, PubMed, and Google Scholar search engines. The search terms used were COVID-19, CoV, outbreak, "respiratory illness," "transmission," and "infection control and management." A total of 150 articles were selected after citation screening and removing duplicates from search databases. Sixty-six articles then selected for inclusion based on full text publication after initial review. Forty-three articles were included from the searched articles on the basis of description of methods and content, hence, 23 articles which lack the given inclusion criteria were excluded from the study.

Discussion

Virology

CoVs belong to a family that comes under the order "Nidovirales." Nidovirales order includes the viruses that use a nested set of mRNAs for their replication. Further, the CoV subfamily has four genera (alpha, beta, gamma, and delta coronaviruses).

Beta-CoVs that carry the disease comprise HCoV-HKU1, HCoV-OC43, MERS-CoV syndrome, severe acute respiratory CoV syndrome (SARS-CoV), and SARS-CoV-2.[8] Genomic and phylogenic research has shown that COVID-19 is a βCoV-2, CoV of the same subgenus as SARS virus, but in a different clad. The constitution of the receptor-binding gene region is very like to that of the SARS-CoV, and the virus has been demonstrated to utilize the same receptor, the angiotensin-converting enzyme 2 (ACE2), for entrance into respiratory cells.[9] The another one-third of the genome contains four structural proteins (spike [S], envelope [E], membrane [M], nucleocapside [N], and some other helper proteins. The spike protein plays an important role in virus entry into the host. The spike protein are responsible for Initial interactions between the S1 domain and its host receptor (ACE2) in case of SARS-CoV and SARS-CoV-2.[10] The E protein is the smallest (8.4–12 kDa size) TM structural protein of CoV. The E protein plays a crucial role in the morphogenesis of viruses, notably during acquisition as well as egress. Maintenance of the shape of the viral envelope is the most important function of the M protein, and the M protein performs this job by interacting with other CoV proteins. M protein also takes part in the sensitization of the host by the virus.[11]

Formation and maintenance of the ribonucleoprotein complex are the most important functions of the N protein, it often controls viral RNA replication and transcription, and in host, it inhibits protein translation through EF1α-mediated action. Hemagglutinin-esterase is present in the envelope of CoV, more specifically among beta-coronaviridiae. The HE is a marker of CoV and influenza virus evolution.[12] E protein plays a crucial role in the assembling and release of viruses. In addition, the E proteins have several other roles, like the activation of the ion channel necessary for SARS-CoV pathogenesis, and presumably SARS-CoV-2. The presence of this furin-like cleavage region in SARS-CoV-2 promotes the priming of S proteins and may improve the performance of SARS-CoV-2 dissemination.[8,9]

Treatment and management

Drug repurposing is a feasible, quick, and expense effective approach that can solve the obstacles of the conventional *de novo* drug discovery and production by addressing various diseases and disorders. Drug repurposing is the method of finding new applications for existing or candidate drugs and is a successful drug development technique.[13]

As per the WHO, the CDC, and the Food and Drug Administration (FDA), there are presently no medicines or vaccinations that are believed to be likely to succeed for SARS-CoV-2 management or preventing the spread.[7] The only alternative available is to use wide spectrum antiviral drugs such as nucleoside analogs as well as human immunodeficiency virus (HIV) protease inhibitors that can attenuate viral infection before the actual antiviral is available.[14]

Pharmacological management of young, stable patients with minor symptoms and no inherent comorbid circumstances is usually not recommended.[7]

The People's Republic of China's National Health Commission has supported the use of chloroquine phosphate to treat COVID-19 patients, in its revised guidelines for the prevention, diagnosis, and treatment of pneumonia developed due to COVID-19 infection in the vast populous country (Gao *et al*., 2020; Lin and Li, 2020).[13]

Passive antibody transfer is one of the most effective and traditional tools used in most of the infectious outbreaks which is the use of serum of patients who just recovered from the active viral infection to treat patients who contract in future.[15] Monoclonal antibodies will be used in passive immunotherapy as powerful biotherapeutics to overpower the SARS-CoV-2and to control the harmful outcomes of COVID-19. Intravenous use of immunoglobulins can prove helpful in the therapy of SARS-CoV-2-induced pulmonary inflammation.[13]

Hormone – melatonin

Viruses trigger an eruption of reactive oxygen molecule and the cure is melatonin a renowned antioxidant. Melatonin prevents the programmed death of cells that coronaviruses cause, causing significant damage to the lungs. Coronavirus triggers lung inflammation through inflammasome activity and melatonin is known to avid this process. One of the most severe complications after COVID-19 is fibrosis of the lungs which can be prevented by melatonin administration.[16]

Melatonin is a bioactive agent with a variety of health booster activity (N-acetyl-5-methoxytryptamine); melatonin was in fact commonly used in sleep disorder diagnosis, respiratory diseases and viral delirium, and atherosclerosis. Melatonin does not have antiviral capacity, but it can indirectly exert antiviral effect through anti-inflammatory, anti-oxidation, and immunity boosting capacity.[17] During drug trials, melatonin is given in severely ill intensive care unit (ICU) patients in the dosages of 3 mg, 6 mg, and 10 mg through oral rote showed adequate safety compared with placebo. Interestingly, even though melatonin was administered to individuals for a month at a dosage of 1 g/d, there were no detrimental treatment observations.[18] Thus, melatonin can serve as a potential adjuvant treatment along with combination of the antiviral drugs lopinavir/ritonavir.

Protein – lactoferrin (Lf)

Lf is the highly conserved pleiotropic iron-binding transferrin of glycoprotein family, which is expressed and secreted by glandular cells and found in most body fluids. Lfs anti-inflammatory and immunomodulatory role appears to be capable of moderating the response of the host to pathogens and having dual capacity to activate the immune system to combat pathogenic infiltration while at the same time avoiding adverse immune and inflammatory responses.[19] Lf prone human pathogenic viruses known to be suppressed from Lf comprise DNA and RNA viruses: Cytomegaloviruses, herpes simplex viruses, HIV, rotaviruses, polioviruses, respiratory syncytial viruses, hepatitis B and C (HCV) viruses, parainfluenza viruses, alpha viruses, hanta viruses, human papilloma viruses, adenoviruses, enteroviruses 71, echoviruses 6, influenza A viruses, and Japanese viruses. Lf is a naturally produced and non-toxic glycoprotein tested against a wide array of viruses including SARS-CoV that is genetically similar to COVID-19-causing SARS-CoV-2.[20] Lf doses ranging from 100 mg to 4.5 g a day for various indications without apparent toxicities. Newer formulations of Lf including encapsulation and liposomalization have been explored.[21] Reportedly, zinc-saturated Lf has a much more potent antiviral activity. This is of particular relevance in COVID-19 as zinc supplementation has been proposed as a possible supplemental intervention for the disease.[22]

Passive antibody – COVID-19 convalescent plasma

Passive antibody transfer is one of the most efficient and conventional technique used in nearly all infectious outbreaks which utilizes of serum of patients who just recovered from the active viral infection to treat patients who contract in future. Patients recovering through active viral infections generate a polyclonal immune system response to varying SARS-CoV-2 antigens, thus counteracting active viral infections, and hence, convalescent phase plasma can be used as a therapeutic alternative.[15] Patients eligible under the emergency investigatory New Drug Applications: (I) Must have laboratory confirmed COVID-19. (II) Should have devastating or instantaneous life-threatening COVID-19 severe infection described as dyspnea, respiratory rate 30 breaths/min or elevated, blood oxygen saturation 93% or below, arterial oxygen partial pressure of less than 300 inspired oxygen ratio, and/or pulmonary infiltration of more than 50% in <24 to 48 h. (III) Life-threatening condition described as respiratory failure, septic shock, malfunction or failure of multiple organs. (IV) Must give informed consent.[7]

Neutralizing antibody: Tocilizumab

Tocilizumab is an interleukin-6 (IL-6) receptor-inhibiting monoclonal antibody. Tocilizumab inhibits IL-6-mediated signaling by competitively binding to both soluble and membrane-bound IL-6 receptors. IL-6 is a pro-inflammatory cytokine implicated in myriad physiological processes, such as the induction of T-cells, the initiation of immunoglobulin generation, stimulate hepatic acute-phase protein synthesis, and the multiply and differentiate hematopoietic precursors. IL-6 is produced by myriad types of cells comprising T- and B-cells, lymphocytes, monocytes, and fibroblasts.[23] Tocilizumab first became authorized by the FDA for the treatment of rheumatoid arthritis in 2010. It received FDA approval for severe or life-threatening chimeric antigen receptor T-associated cytokine release syndrome in 2017 due to its efficacy and safety profile.[13] Xu *et al*. retrospective assessment analyzed 21 patients in whom tocilizumab was incorporated to standard COVID-19 therapy. Early data postulate that tocilizumab may have therapeutic benefit as an adjunct treatment. Clinical symptoms, computed tomography opacity changes, lymphocyte percentage, and C-reactive protein levels all improved in these patients.[24] The prescribed dose is 4–8 mg/kg or 400 mg of the typical IV dose once and may be repeated in 12 h (not to reach a maximum dose of 800 mg). Possible complications are risk of GI perforation, risk of hepatotoxicity, caution in patients with thrombocytopenia and neutropenia, and infusion-related reactions.[7]

Antibiotics – teicoplanin

Teicoplanin, a glycopeptide antibiotic routinely used to treat bacterial infections, currently used in the treatment of Gram-positive bacterial infections, especially staphylococcal infections. It has usefulness against myriad viruses like those of Ebola virus, influenza virus, flavivirus, hepatitis C virus, and HIV and even coronavirus including MERS-CoV as well as SARS-CoV.[25] According to Zhou *et al*. in coronaviruses, teicoplanin works at the initial stage of the viral life cycle by impeding the low pH cleavage of the viral spike protein by cathepsin L in late

endosomes, prohibiting the emergence of genomic viral RNA and the progression of the virus replication process.[26]

Zhang *et al.* (2020) showed that teicoplanin has antiviral activity against SARS-CoV-2 in their study. The concentration of teicoplanin required to inhibit 50% of viruses (IC 50) *in vitro* was 1.66 μM, which is much lower than the concentration reached in human blood (8.78 μM for a daily dose of 400 mg).[27] Thus, teicoplanin may potential candidate for alternative drugs used against COVID-19.

Hormone – IgG

Immunoglobulin G has been prescribed as a treatment in critical patients with COVID-19. FcR plays a role in pulmonary inflammation; thus, blocking FcR activation will reduce inflammatory damage to COVID-19. Thus, intravenous use of immunoglobulins can prove efficient in the therapy of SARS-CoV-2-induced pulmonary inflammation.[28] The efficacy of IV IG could be better if the IgG antibodies were collected from cases improved from SARSCoV-2 infection, so as to elevate the possibility of inactivating the virus, this process is called as "convalescent immune plasma" therapy. Immunity-based therapy with specific IgG antibodies along with antiviral drugs can be an alternative therapy against COVID-19 disease until better choices such as vaccine are accessible.[9]

Nucleotide analog – remdesivir (GS-5734)

Remdesivir is a new nucleotide analog that has effect against SARS-CoV-2 *in vitro* and linked coronaviruses (including SARS and MERS-CoV) both *in vitro* and in animal studies. Remdesivir is an investigatory monophosphoramidate prodrug of an adenosine analog.[9] Remdesivir is a monophosphoramidate prodrug of remdesivir-triphosphate (RDV-TP), an analogous adenosine, which functions as an RNA-dependent polymerase inhibitor. Remdesivir-TP competes with adenosine-triphosphate for incorporation into nascent viral RNA chains. Once incorporated into the viral RNA at position i, RDV-TP terminates RNA synthesis at position i+3. Because RDV-TP does not cause immediate chain termination.[7]

Wang *et al. in vitro* study showed that remdesivir has significant activity against COVID-19 and a high genetic barrier to resistance. Remdesivir attains potent antiviral action toward SARS-CoV-2 clinical isolates; (Half-maximum effective concentration [EC50] = 0.77 mcgM, Half-cytotoxic concentration [CC50] >100 mcgM, selective index [SI] >129.87).[14]

The drug has a long intracellular half-life that allows for once daily dosing. The dosage being investigated for COVID-19 has been 200 mg intravenously (IV) on day 1 followed by 100 mg IV each day for up to 10 days, infused for more than 30–60 min.[29]

Antivirals – lopinavir; ritonavir

Lopinavir is indeed a protease antagonist of HIV-1 provided in a fixed-dose combination with ritonavir (LPV/r), a formidable CYP3A4 inhibitor which "augments" lopinavir concentrations. Lopinavir tends to suppress the primary SARS-CoV-1 protease, which prohibits viral replication.[29]

Lopinavir and ritonavir may bind to M_{pro}, a key enzyme for coronavirus replication. This may reduce CoV activity. Lopinavir; ritonavir in a dose of 400 mg/100 mg (2 capsules/tablets) by mouth twice a day for no more than 10 days is advised according to Chinese SARS-CoV-2 guidelines. In children's weighing 15–40 kg, the recommended dose is 10 mg/kg suspension by mouth twice daily as per to the United States guidelines.[30]

Safety concern regarding lopinavir, ritonavir has risk of cardiac arrhythmias (e.g., QT prolongation), caution in patients with hepatic disease or hepatitis, has myriad drug interactions. Cao *et al.* conducted comparative study of lopinavir; ritonavir used single agent or combined with either ribavirin or interferon (IFN)-α in mature patients hospitalized with severe COVID-19. There was a statistically significant difference in the time to clinical improvement between the two groups on day 14, but this result was not statistically significant on day 28. The morbidity at 28 days decreased by 5.8% and the duration of stay in the ICU minimized by 5 days with the lopinavir-ritonavir treatment.[31]

Vitamin D

Vitamin D is a steroid hormone which may be synthesized endogenously from the effect of UVB irradiation on skin or gained from exogenous dietary sources or supplements. Vitamin D is capable for reducing the immunity acquired and regenerating the endothelial lining. This may be desirable in decreasing the alveolar damage caused in ARDS.[32,33]

Systematic review and meta-analysis by Martineau *et al.* showed that level I findings (n = 11,321) revealed that Vitamin D supplementation has a 12% cumulative therapeutic benefit against bacterial and viral acute respiratory tract infection (adjusted OD = 0.88, p patients on a regular or weekly Vitamin D regimen relative to those consumed on a monthly Vitamin D bolus (adjusted OD = 0.81, P = 0.001).[32] Recommend intakes of Vitamin-D are 20 mg/day and 37.5–50 mg/day, respectively, for older adults as per the U.S. standards.[33]

Vitamin C

Vitamin C is well recognized for its antioxidant properties, which can harvest hazardous reactive oxygen species and thereby safeguard the cells as well as tissues of the body from oxidative damage and malfunction.[34] Vitamin C (L-ascorbic acid) has a defensive effect of high-dose intravenous Vitamin C (HDIVC) throughout ARDS-induced sepsis. Vitamin C enhances the conservation of the alveolar epithelial barrier and transcribes the protein channels (CFTR, aquaporin-5, ENaC, and Na+/K+ ATPase) to control alveolar fluid clearance.[33] Randomized trial involving Fowler *et al.*, 167 patients with sepsis-related ARDS demonstrated that 4-day administration of ~15 g/day of IV Vitamin C could reduce mortality in such patients.[35]

A randomized controlled trial (RCT) was performed at the Zhongnan Hospital (NCT04264533) on February 14, 2020, to assess the clinical effectiveness and protection of Vitamin C

in SARSCoV-2 viral pneumonia. They believe that Vitamin C injection can enhance the prognosis of serious acute respiratory tract infections. The treatment arm requires a 7-day infusion of 12 g Vitamin C (q12h) and the primary result tests ventilation-free days. The expected time for fulfillment is September 2020.[33]

NSAID

That coronaviruses of the acute respiratory syndrome SARS-CoV and SARS-CoV-2 bind to targeting cells by the 2-converting angiotensin enzyme (ACE 2), generated by lung, intestine, kidney, and blood vessel epithelial cells. Thus, the theory was raised that the management of diabetes and hypertension with ACE2 stimulant drugs raises the risk of severe and fatal COVID-19. Ibuprofen has been seen to upregulate ACE2 receptors and SARS-CoV-2 utilizes it to reach the cells where it amplifies.[36]

Acetaminophen is first-line antipyretic. Repeated prescriptions typically involve oral acetaminophen, 10–15 mg/kg, 4–6 times/day. There is no current evidence indicating that ibuprofen worsens the clinical course of COVID-1. The current standpoint of the WHO is to continue the use of ibuprofen as antipyretic agent.[9,33]

Corticosteroids

Corticosteroid medication for viral pneumonia is not suggested, but use has been taken into consideration in patients with refractory shock.[7]

The explanation behind all this strategy is that the corticosteroids extend the viral shedding cycle and sustain a widespread anti-inflammatory environment that minimizes ARDS occurrence, dyspnea, and severe pneumonia.[33]

The WHO/CDC advises them not be given in COVID-19 disease with pneumonia except for there are other indications (e.g., exacerbation of chronic obstructive pulmonary disease, asthma, etc.). Chinese guidelines also advocate short-term therapy with low-to-moderate dose steroids for ARDS complication of COVID-19 disease. Corticosteroids can be administered in a short period of time (3–7 days). The suggested dose of methylprednisolone should not surpass 1–2 mg/kg/day.[9]

Antiparasitic – ivermectin

Ivermectin is an FDA-approved broad-spectrum antiparasitic agent, shown to have antiviral activity against a broad range of viruses *in vitro*.[37]

A study by Leon *et al.* ivermectin has an antiviral effect toward clinical isolate SARS-CoV-2 *in vitro*, with a single dose capable of regulating viral replication across 24–48 h throughout the system. They hypothesize that this is likely through inhibiting IMPa/b1-mediated nuclear import of viral proteins. A single dose of ivermectin can reduce viral load in cell culture to ~5000- fold within 48 h. Ivermectin is FDA approved for parasite infections and therefore has the capacity for re purposing. Ivermectin is readily available, as it is included in the WHO model list of essential medicinal goods.[38]

Antiviral agents

Umifenovir, oseltamivir, arbidol, nitazoxanide

Arbidol, an effective antiviral against SARS-CoV in combination with antibiotics (moxifloxacin or levofloxacin, nemonoxacin, linezolid, azithromycin or amoxicillin), corticosteroids, and oxygen therapy has been used in COVID-19 therapy (Zhang *et al.*, 2020) arbidol available in Russia and China. Arbidol is given orally to adults at a dosage of 200 mg, 3 times a day. Treatment period is no greater than 10 days.[9,22]

Umifenovir is a non-nucleoside broad-spectrum antiviral licensed for influenza treatment and prophylaxis in Russia and China. Umifenovir is a membrane fusion inhibitor. Current regimens of umifenovir used in China include a PO dose of 200 mg TDS for a duration of 10 days.[39]

Neuraminidase inhibitors are known to reduce viral shredding in respiratory secretions and are used for prophylaxis against influenza. In a systematic review by Cochrane, Jefferson *et al.* found that oseltamivir declined symptomatic influenza by 55% and zanamivir by 61%.[40]

Huang *et al.* (2020) used antibiotics, methylprednisolone corticosteroid (40–120 mg/day), and oseltamivir (orally 75 mg twice daily) in COVID-19 patients along with oxygen support. Combination with oseltamivir and other anti-influenza medications may be required for coinfections with influenza A/B.[13]

Nitazoxanide has demonstrated potent *in vitro* activity against SARS CoV-2, with an EC50 at 48 h of 2.12 μM in Vero E6 cells. In comparison to coronaviruses, nitazoxanide demonstrates broad spectrum of antiviral behavior *in vitro* against influenza, respiratory syncytial virus, parainfluenza, rotavirus, and norovirus among several others. In an outpatient influenza study, a 600 mg oral dose of nitazoxanide BID has been strongly linked with a ~1-day improved performance in time to symptoms resolution compared to placebo ($p = 0.008$). In a study by Wang *et al.*, nitazoxanide was effective against SARS-CoV-2 *in vitro*.[29]

Antimalarial – chloroquine

Chloroquine is an well known antimalarial agent containing anti-inflammatory and immunomodulatory properties. In viruses, chloroquine can inhibit pH-dependent stages of replication. Furthermore, chloroquine's immunomodulation is dependent on the suppression of cytokines (IL-6 and TNF-α) production and dissemination. Moreover, experiments with monkey cell line (Vero E6) showed that chloroquine interferes with the receptor glycosylation and thereby affects the entry mechanism of SARS-CoV-2.[33]

Yao *et al.* demonstrated result of a study that chloroquine and hydroxychloroquine inhibit SARS-CoV-2 *in vitro* with hydroxychloroquine (EC50=0.72%μM) found to be more potent than chloroquine (EC50 = 5.47% μM) *in vitro*.[41]

These findings have supported the clinical use of chloroquine, at a dose of 500 mg by mouth twice daily, in numerous clinical

trials in China during this outbreak. An *in vivo* study by Gao *et al.* demonstrated that chloroquine phosphate is superior to control medication to control pneumonia exacerbation, enhance pulmonary imaging results, facilitate virus-negative conversion, and reduce the duration of disease. Severe adverse reactions to chloroquine phosphate were not noted in the aforementioned patients.[29]

Side effects and safety concerns include risk of cardiac arrhythmias (e.g., QT prolongation), risk of retinal damage, especially with long-term use, caution in patients with G6PD deficiency, caution in diabetics, and significant drug interactions.[7]

Antimalarial – hydroxychloroquine

Hydroxychloroquine is formed by addition of hydroxyl group to chloroquine. Comparatively better tolerance is responsible for its long term use in rheumatological disorders. Clinical safety profile is better than that of chloroquine and allows higher daily dose and has fewer concerns about drug-drug interactions.[29]

Mechanisms might include suppression of viral enzymes or processes such as those of viral DNA and RNA polymerase, glycosylation of viral proteins, aggregation of viruses, transportation of new virus particles, and release of viruses. Certain mechanisms might include cellular receptor inhibition of ACE2, surface acidification of the cell membrane hindering virus fusion, and cytokine release immunomodulation.[7]

Yao *et al.* suggested dosing PO hydroxychloroquine 400 mg BID for the 1st day and then 200 mg BID for the following 4 days from *in vitro* study. Gautret *et al.* recommended oral hydroxychloroquine sulfate 200 mg, 3 times/day during 10 days as per their *in vivo* study.[29,41]

Side effects and safety concerns include risk of cardiac arrhythmias, caution in patients with G6PD deficiency, risk of retinal damage, especially with long-term use, caution in diabetics, and significant drug interactions.[7,13,33]

IFN

IFN-α is a broad-spectrum antiviral that is usually used for the treatment of hepatitis. IFNs may stimulate inherent antiviral reactions and are anticipated to have *in vitro* activity against SARS-CoV-2, considering the previously known activity exhibited against MERS-CoV. Chinese guidelines recommend ribavirin 500 mg IV 2–3 times daily in combination with lopinavir/ritonavir or inhaled INF-α (5 million units nebulized twice daily) as one of the "standard treatment" options for COVID-19.[29]

IFN-α can decrease viral load during the early stage of COVID-19 disease and it can help to improve disease manifestations and curtail the course of infection; however, toxicities are substantial including severe cytopenias, hepatotoxicity (including fatality), neuropsychiatric events, and risk of developing fatal or life-threatening ischemia or infection.[9]

IFN-α nebulization: 200,000–400,000 IU/kg or 2–4 μg/kg in 2 ml of sterile water, twice daily for 5–7 days; OR IFN-α2b inhalation (puff): Dispensed to high-risk persons in close contact with presumed SARS-CoV-2-infected cases or those in the early phase with only upper airway expressions. Cases should be administered bilaterally 1–2 puffs in the nasal cavity, 8–10 puffs in the oropharynx, and 8000 IU per 1–2 h for each application, that is, 8–10 puffs/day for 5–7 days.[42]

Conclusion

The latest outbreak of COVID-19 was deemed a pandemic by the W.H.O. As of March 24, 2020, COVID-19, as of April 13, 2020, COVID-19 has been recognized in 196 countries, with a total of 1,876,707 laboratory-confirmed cases, 435,591 recovered, and 116,789 deaths. Till this date, 9352 laboratory-confirmed cases, 980 recovered, and 324 deaths were reported by Indian Council of Medical Research in India. Until now, no effective antiviral drug or vaccine has been identified for the treatment of COVID-19. Drug repurposing is a highly touted, quick, and price-effective method which can resolve the conventional *de novo* drug discovery and innovation obstacles of COVID-19. Passive antibody transfer is one of the most effective and traditional tools used in most of the infectious outbreaks which is the use of serum of patients who just recovered from the active viral infection to treat patients who contract in future. Passive antibody transfer has given encouraging results against latest outbreak of COVID-19. Wide spectrum antiviral drugs such as nucleoside analogs as well as HIV protease inhibitors shown to attenuate COVID-19 viral infection in various *in vitro* and *in vivo* study and are widely used until more definitive therapy or vaccine discovery against COVID-19. Drugs such as melatonin can serve as a potential supportive treatment along with combination of the antiviral drugs lopinavir/ritonavir, Lf has anti-inflammatory and immunomodulatory against COVID-19, and supplementation has been proposed. Vitamins C and D having antioxidant properties have been used as supportive treatment along with combination of the antiviral. We expect to see conclusive drug treatment and vaccine against COVID-19 in the anytime soon, until then prevention is the gold standard approach against the novel CoV.

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