An overview of treatment options for COVID-19

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ABSTRACT
Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) which emerged in Wuhan initially as pneumonia of unknown origin in December 2019, later spread to whole world and became pandemic on 11th March, 2020. Many drugs have been proposed but are backed without clinical evidence. Scientific bodies are in the row to discover a reliable vaccine and effective drugs against the novel coronavirus. Many antiviral and anti-parasitic drugs which were thought to have some effect on Coronavirus disease 2019 (COVID-19) have been tried during the crisis but none have shown concrete evidence of action. Randomized clinical trials on the repurposed drugs are now registered under clinical trial registry to look at the safety profile and efficacy of the drugs to be used against SARS-CoV-2. Many meta-analyses are being conducted worldwide to frame evidence for the fight against this novel coronavirus. We are providing below a review of various drugs that have been tried for treatment of COVID-19 as well as different clinical trials which are underway.

Keywords: Antivirals, Convalescent plasma therapy, COVID-19, Immunosuppressant, Mesenchymal cell

INTRODUCTION
The 2020 novel coronavirus named as Corona virus disease-19 (COVID-19) emerged in China in late December causing severe respiratory infection in humans and was declared as a pandemic by World Health Organization (WHO) on 11th March 2020. Initially considered as pneumonia of unknown etiology in China, it started spreading to Asian countries and then worldwide. According to WHO, there are 15,107,950 confirmed cases of COVID-19 and 6,19,817 deaths with United States of America leading amongst the countries followed by Brazil, India, Russia by June 22, 2020.1 The detection of SARS-CoV-2 is done by polymerase chain reaction test of samples obtained from throat and nasal swabs. The dynamics of the disease assessed using the reports of polymerase chain reaction (PCR) have raised serious concerns and urgent need for containing the pandemic. Given the magnitude of global health crisis, there is no effective prophylaxis or therapy, as of now, for the disease. We are providing below a review of various drugs that have been tried for treatment of COVID-19 as well as different clinical trials which are underway.

MOLECULAR MECHANISM FOR COVID-19 THERAPY
There are four genera of coronavirus named as α, β, δ and γ coronavirus. β- coronavirus has been further sub classified as A, B, C and D variety. So far, there have been seven coronavirus variants that causes human infection called human coronavirus (HCoVS). HCoV-229E and HCoV-NL63 belong to α- coronavirus, HCoV-OC43 and HCoV-HKU1 are β- coronavirus subtype A, severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 are β- coronavirus subtype B while middle...
east respiratory coronavirus (MERS-CoV) is a β-coronavirus C type. SARS-CoV-2 has spike proteins which has two subunits, S1 and S2. S1 subunit has receptor binding domain which utilizes human angiotensin converting enzyme 2 (ACE-2) receptor present on epithelial cells of oral mucosa and type-2 pneumocytes of lung parenchyma while S2 subunit mediates membrane fusion process of virion and target cell. Drugs targeting this fusion protein may cause effective inhibitory action on SARS-CoV-2. Soluble recombinant human ACE2 protein can also prove to be an effective therapeutic option.

After entering the cell, SARS-CoV-2 utilizes cellular serine protease enzyme transmembrane protease serine 2 (TMPRSS2) to confer the virion infectivity. Ribonucleic acid (RNA) polymerase and protease inhibitors also affect intracellular virion assembly. Drugs targeting these enzymes should be evaluated for possible action against the virus. The mature virion enters endosomes and initiates inflammatory pathways by interacting with toll like receptor. Drugs that change the pH of the endosome and thereby stop the inflammatory pathways are also helpful. The cytokine storm which results following virion entry to cell and thereby releases interleukins (ILs) by inflammatory pathway can also be targeted for management of COVID.

SEARCH METHOD

We searched PubMed, Cochrane COVID-19 Study Register, LitCovid open database, World Health Organization (WHO) COVID-19 International Research Database, Centers for Disease Control and Prevention COVID-19 Research Article Database to identify studies published up to 20 May 2020. We also identified ongoing trials registered under ClinicalTrials.gov and WHO international clinical trial registry. Articles for this review were identified using filters to include clinical trials, randomized controlled trials, meta-analysis and systematic reviews. Only English language studies were identified and considered for this review. Further, relevant studies were identified through hand search of references of selected studies. We excluded case reports, studies involving other types of coronavirus, non-indexed studies and news reports. A total of 148 studies were identified after removing duplicates, and using the strategy outlined above, 99 studies relevant to this article were selected for review.

ANTIVIRAL THERAPY

Many of the antiviral drugs used for treatment of Human immunodeficiency virus (HIV-1) have been thought to be useful in treatment of SARS-CoV-2. Drugs that inhibit RNA polymerase and protease inhibitors are being tried in management of novel coronavirus. (Table 1) A randomized open labelled clinical trial done by Cao et al on 199 COVID-19 patients with lopinavir-ritonavir compared with standard therapy did not show significant reduction in viral RNA or mortality as opposed to standard therapy group. However, Chen et al found no death when treated with lopinavir-ritonavir but the sample size was very small to reach a conclusion. Two clinical trials are in phase 4 comparing the efficacy of lopinavir-ritonavir with other antivirals for novel coronavirus. Remdesivir is a nucleotide analogue which inhibits viral RNA polymerase that has been tried in both mild and severe COVID-19 patients. Grein et al found that compassionate use of remdesivir caused clinical improvement in 36 out of 53 SARS-CoV-2 patients (68%), mortality was 18% in patients on invasive ventilator and 5% without ventilator.

| Group | Drugs | Mechanism of action |
|-------|-------|---------------------|
| Viral protein synthesis inhibitor | Lopinavir/ritonavir | Protease inhibitor |
| Viral RNA polymerase inhibitor | Remdesivir | Adenosine nucleotide inhibitor |
| Viral entry inhibitors | Favipiravir | Guanosine nucleotide inhibitor |
| Viral replication inhibitor | Hydroxychloroquine | Increase endosomal pH |
| | Chloroquine | and inhibit viral entry to host cell |
| | Azithromycin | Inhibit IMP α/β1 importin of viral proteins and replication |
| | Ivermectin | Inhibit viral replication by its metabolite in vitro |
| | Nitazoxanide | |
| Viral particle release from host inhibitor | Oseltamivir | Neuraminidase inhibitor and inhibit viral particle release |

Table 1: Summary of drugs and mechanism of action for COVID-19.
oseltamivir is ineffective in reducing mortality and ventilator rates. Clinical trials are underway with Oseltamivir used along with chloroquine and favipiravir.

Arbidol, a fusion inhibitor which blocks entry of virus into host cell is approved for SARS. Clinical trials have been registered comparing arbidol with standard treatment for COVID-19 treatment. Three more trials are in the pipeline comparing efficacy of arbidol with oseltamivir, lopinavir-ritonavir and carrimycin. Favipiravir is an RNA dependent RNA polymerase inhibitor used for treatment of Ebola has been considered for treatment of SARS-Cov-2. Studies done on 80 patients of COVID-19 in China showed that favipiravir is more potent than lopinavir-ritonavir and had less side effects but the article has been withdrawn for unknown reason. In addition, patients with COVID-19 infection are being recruited for randomized trials to evaluate the efficacy of favipiravir versus hydroxychloroquine (NCT04373733) and favipiravir versus interferon-α (INF-α) (ChiCTR2000029600). A systematic review done by Yousefifard et al concluded that the beneficial effect of currently used antiviral agents for COVID-19 is not clear due to few published data and lack of randomized clinical trials. Further ongoing clinical trials may bring out effective and potent antiviral drugs with less adverse effects of COVID-19.

**ANTIPARASITIC THERAPY**

Chloroquine (CQ), an anti-malarial agent has also antiviral and anti-inflammatory properties and is believed to play an important role in the treatment of novel coronavirus. Chloroquine is a weak base and it interferes with the glycosylation of ACE2 receptors of SARS-CoV-2 by increasing the endosomal pH and thereby inhibiting viral entry into host cell. Chloroquine also prevents viral exit from host cell and release of inflammatory cytokines. The clinical effectiveness of CQ for COVID-19 came from China where Gao et al tried CQ on 100 COVID-19 patients at different sites in China using different study protocols. They reported reduction in the duration of illness, and improvement in COVID-19 pneumonia and appearances on chest imaging. No scientific data supporting these findings have been published and the evidence has therefore not been peer reviewed. A systematic review done by Andre et al suggested that CQ is effective in limiting SARS-CoV-2 replication in vitro but still more clinical trials is needed to mark its safety. Hydroxychloroquine (HCQ), a derivative of chloroquine with hydroxy moiety has similar action as CQ in inhibiting entry, transport and post entry event of SARS-CoV-2. However, HCQ was found to be more potent than CQ against SARS-CoV-2 in one study by Liu et al and adverse effects like retinal toxicity were also less compared to CQ. The first clinical trial of HCQ on COVID-19 was conducted by Chen et al. which was a randomized controlled trial on 30 patients. Their primary outcome was nasopharyngeal test result on day 7 and the result of the trial was discouraging as there was neither a difference in negative test result between control and study group nor there was reduction in duration of illness. The adverse events were more in the treatment group. A second trial on HCQ was done by Guetret et al on 36 COVID-19 patients which was an open label non-randomized controlled trial. The primary outcome was SARS-CoV-2 carriage at day 6, detected by PCR on nasopharyngeal swabs. Patients in the treatment group were significantly more likely to test negative for SARS-CoV-2 on day 6 than controls (70% versus 12.5% virologically cured, p<0.001). A systematic review and meta-analysis done by Sarma et al in which they included 7 studies with an objective to look at the virological cure found that treatment with HCQ resulted in fewer cases showing radiological progression of lung disease (Odds ratio (OR) 0.31, 0.11-0.9). However, there was no difference observed in virological cure (OR 2.37, 0.13-44.53), death or clinical worsening of disease (OR 1.37, 1.37-21.97) and safety (OR 2.19, 0.59-8.18), when compared to the control/ conventional treatment. Five studies reported either the safety or efficacy of HCQ + Azithromycin. An updated systematic review and meta-analysis on use of HCQ in COVID-19 patients by Singh et al suggested that there was no viral clearance with the use HCQ and in fact there was two fold increase in mortality in COVID-19 patients due to HCQ compared to control. However, clinical trials are on with HCQ to establish its efficacy in SARS-CoV-2 management. Ivermectin, a broad spectrum anti-parasitic drug has been found to be effective in inhibiting the interaction of HIV-1 integrase protein and importin heterodimer for nuclear import and HIV-1 replication. Ivermectin was found to inhibit nuclear transport in SARS-CoV-2 virus. Leon et al demonstrated that ivermectin has antiviral activity against novel coronavirus clinical isolate and can control viral replication within 24-48 hours in human body. Nitazoxanide another potent anti-parasitic drug also has antiviral activity by potentiating the interferon alpha and interferon beta production. It has been shown to be active against MERS CoV and other coronaviruses and has hence been suggested by few authors to be used synergistically with azithromycin.

**ANTIBIOTICS**

Macrolides besides their antibiotic effects is also found to have immunomodulatory and anti-inflammatory action. Clarithromycin and azithromycin had already been tried on SARS-CoV-2 patients and has been found to be effective in combination with HCQ. Multiple mechanisms have been proposed for the antiviral properties of macrolides like azithromycin which was used in few trials. Azithromycin is a weak base and accumulates intracellularly in endosomal vesicles thereby increasing pH levels and blocks viral replication. The acidic environment required for the uncoating of enveloped viruses such as influenza and human immunodeficiency virus (HIV) is also required for coronaviruses. The antiviral effects of azithromycin may also be mediated by a host interferon mediated antiviral responses. In SARS-CoV-2 patients, it is suggested that azithromycin may act by interfering with viral entry by interacting between the
SARS-CoV-2 spike protein and host receptor ACE2 protein. Many clinical trials are authorized to start up using various combination of azithromycin with other repurposed drugs in COVID-19 patients. Three important randomized trials of which two trials have started recruiting patients have been registered under clinical trial registry looking at efficacy of using azithromycin in combination with HCQ. Teicoplanin, a glycopeptide antibiotic used to treat bacterial infection was found to be active in vitro against SARS-CoV. It acts on the early step of the viral life cycle by inhibiting cleavage of the viral spike protein by cathepsin L and thereby preventing the release of genomic viral RNA and virus replication. A randomized controlled clinical trial looking at the efficacy of teicoplanin in coronavirus patient has been registered under WHO international clinical trial registry platform and patients are being recruited for the purpose (IRCT20161204031229N3).

**CONVALESCENT PLASMA THERAPY**

The plasma obtained from blood of patients infected with novel coronavirus and had recovered from the disease is called convalescent plasma. The plasma contains large amount of antibodies which can be injected to a newly infected person to combat the viral antigen. This decade old technique has been tried earlier in many diseases including SARS and MERS. A systematic review was conducted by Rajendran et al on clinical effectiveness of convalescent plasma therapy for treatment of COVID-19 patients. They included critically evaluated five studies with 27 patients and the outcome of interest was clinical effects, survival benefits, viral load, antibody titre status and adverse events. All patients had good clinical effects and survival benefit and the viral load decreased between day 1 and day 30. This warrants a multicentric trial in this pandemic to further evaluate convalescent plasma therapy in management of COVID-19. Nearly 74 clinical trials have been registered in the clinical trial registry among which the CONCOVD trial has started recruiting patients.

**ANTICOAGULATION THERAPY**

Heparin has antiviral properties and it inhibits viral attachment by causing conformational change in spike protein-1 of SARS-CoV-2. Tang et al in his study found that disseminated intravascular coagulation and elevated D-dimer level were independent predictors for mortality in a cohort of 449 COVID-19 patients. Low molecular weight heparin (LMWH) administered in COVID-19 patients were associated with lower level of IL-6 suggesting that it not only prevent thrombosis but also take part in reducing cytokine storm. Hence, it is justified to give heparin and LMWH as prophylaxis of venous thrombosis or as treatment where rapid respiratory deterioration is attributed to thromboembolism. A Chinese study of 81 patients and a Dutch study of 184 critically ill COVID-19 patient showed incidence of 25% and 31% of venous thromboembolism events respectively. Hence, WHO and Sciensano guidelines recommended the use of prophylactic LMWH or heparin against venous thromboembolism in critically ill COVID-19 patients. The International society on thrombosis and haemostasis recommended that all hospitalized COVID-19 patients should receive prophylactic LMWH. Two randomized clinical trial has been registered and are recruiting COVID-19 patients to obtain evidence about the benefit of anticoagulation therapy in these patients (NCT04362085, NCT04359277).

**IMMUNOSUPPRESSIVE THERAPY**

Cytokine storm refers to excessive and uninhibited release of pro-inflammatory cytokines. It is an important event that occurs once the viral infection cascade continues thereby releasing cytokines causing severe respiratory distress and organ damage with high inflammatory parameter in COVID-19 patients. Systemic corticosteroid: Glucocorticoids has been tried to suppress this cytokine storm in few trials. A meta-analysis done by Lu et al on use of systemic corticosteroid in COVID-19 patient showed that corticosteroid did not reduce the risk of mortality with (relative risk (RR) =2.0, CI-95%: 0.7-5.8), duration of pneumonia (weighted mean difference (WMD)=-1.0 day, 95%- CI: -2.9-0.9) and hospital stay (WMD=2.4days, 95%- CI: 1.4-3.4 days) in COVID-19 patients. Tobaigy et al in his systematic review found that the most common drug used in COVID-19 is corticosteroid and suggested that they are not recommended in guidelines. Dexamethasone, a synthetic anti-inflammatory drug however showed promising result from the RECOVERY TRIAL conducted in UK and hence low dose of dexamethasone was recommended by Horby et al from the preliminary report obtained from this trial. Interleukin-6 inhibitor (Tocilizumab): It is a humanized immunoglobulin that blocks IL-6 receptor. It has been used to block the cytokine storm in severe covid-19 patients. Two studies have been done using tocilizumab in severe COVID-19 patients. A case series published by Xu et al from China which included 21 patients with severe COVID-19 symptoms were given a trial of tocilizumab along with methylprednisolone. They observed that the was significant improvement in clinical symptoms and oxygen saturation. Another study done by Roumier et al in France using tocilizumab on 30 critically ill COVID-19 patients concluded that significantly reduced the requirement of mechanical ventilation compared to controls (weighted odds ratio (WOR)=0.42; 95% CI: 0.20-0.89; p=0.025) and reduced the risk of Intensive care unit (ICU) admission in those treated outside ICU (weighted OR=0.17; 95% CI: 0.06-0.48; p=0.001). However, there was no statistically significant difference in reduction of mortality after weighted analysis (OR=0.25; 95% CI: 0.05-0.95; p=0.04). Both studies were published in a preprint server without peer review. However, the current evidence is insufficient to support the use of tocilizumab outside clinical trials. A multicentric phase 2 clinical trial to treat COVID-19 patients with tocilizumab had already started enrolling the subjects (NCT04317092). Sirolimus: It is
an immunosuppressant used to prevent organ transplant rejection and treatment of lymphangioleiomyomatosis. It acts by inhibiting the mammalian target of rapamycin (mTOR) kinase which helps in viral replication. A randomized double-blind placebo-controlled trial (SCOPE) has been planned by University of Cincinnati to observe the effect of sirolimus in critically ill COVID-19 patients requiring respiratory support. Zhou et al using a network-based drug repurposing obtained from data of other coronavirus found sirolimus to be one of the potential drug that can be used for novel coronavirus management.\(^{47}\)

**Interferon beta 1b**

Type I IFNs (IFN-\(\alpha\) and IFN-\(\beta\)) are the major contributors in innate immunity serving as the first line of defence against viruses as well as linking innate to adaptive immunity. Both IFN-\(\alpha\) and IFN-\(\beta\) signal through a common receptor IFNAR that consists of IFNAR1 and IFNAR2 chains and binding to the receptor leads to the activation of JAK-STAT signalling pathway, which results in direct antiviral effects of type I IFNs and expression of interferon-inducible genes. An open label randomized phase 2 clinical trial conducted by Hung et al to look at the efficacy of interferon beta-1b on 127 COVID-19 positive patients admitted to six hospital in China. It was triple combination drug therapy trial that included in interferon beta-1b in combination with lopinavir-ritonavir and ribavirin compared to lopinavir-ritonavir alone. The primary outcome was time to SARS-CoV-2 RT PCR negativity and the secondary outcome was time to symptom resolution, duration of hospital stay, 30 day mortality and SOFA score 0. They found that in subgroup analysis there was a significant improvement in the triple combination group compared to control group.\(^{48}\) Six clinical trials with interferon beta-1b in combination with various drugs has been registered in the clinical trial registry. One has been completed while others are in the stage of recruitment.

**OTHER ADJUNCTIVE THERAPIES**

**Mesenchymal stem cells**

Mesenchymal stem cells have immunomodulatory functions and can reduce cytokine storm caused due to the SARS-CoV-2 virus. SARS-CoV2 virus targets the angiotensin-converting enzyme (ACE)-2 receptors through their spike proteins but bone marrow which produces mesenchymal cells lack ACE-2 receptors making them immune to the effects of the virus. Clinical study using mesenchymal stem cell therapy on severely ill COVID-19 patients has been tried in China as a pilot study. Leng et al. performed a clinical pilot trial of mesenchymal stem cell treatment on 7 critically ill COVID-19 patients. Three patients with severe illness served as controls. There was reversal of symptoms with no adverse effects in trial group with the biochemistry demonstrating increase in lymphocytes and decrease of cytokines.\(^{49}\) A clinical trial using mesenchymal stem cells in COVID-19 pneumonia has been registered and in the phase of recruitment (NCT04339660).\(^{50}\)

**Fluvoxamine**

Fluvoxamine is an anti-depressant drug used for treatment of obsessive-compulsive disorder. The drug was found to be effective in preventing sepsis in mice and hence being interpreted that it will prevent cytokine storm. A clinical trial by University School of Medicine in St Louis, Missouri has been recruiting COVID-19 patients to evaluate the effectiveness of fluvoxamine (STOP COVID Trial) (NCT04342663).\(^{51}\)

**Vitamin C**

It neutralizes free radicals and reverse cellular damage. Vitamin C not only inhibits reactive oxygen species production and cytokine storm syndrome but also involved in immune response to viral agents through lymphocytes and natural killer (NK) cells. China is conducting a clinical trial with high-dose IV vitamin C in severe COVID-19 patients and the results are still awaited (NCT04264533).\(^{52}\)

**Inhaled pulmonary vasodilators**

Inhaled pulmonary vasodilator therapy has been suggested in mechanically ventilated COVID-19 patients with severe hypoxemia not responding to maximum ventilatory support. Inhaled epoprostenol and inhaled nitric oxide are two common pulmonary vasodilators that have been used. Clinical trials evaluating the efficacy inhaled nitric oxide for treatment and prevention of COVID-19 patients are ongoing (NCT04305457, NCT04312243).\(^{53,54}\)

**Chinese herbal medications**

Chinese herbal medications were tried along with generic drugs in China during the pandemic and was found to be effective. This idea was drawn from the Cochrane systematic review which suggested the effectiveness of use of the herbal medication in SARS. A systematic review and meta-analysis done by Lin et al concluded that use of herbal medication along with western medications can reduce the symptoms.\(^{55}\)

**FUTURE PERSPECTIVES**

**Mycobacterium w**

A vaccine containing heat killed *Mycobacterium w* previously used as a immunomodulator for leprosy and has been tried in sepsis was administered to four severe COVID-19 patients and the result was found to be remarkable with clinical and radiological resolution as well as the need for ventilator was also deferred. A randomized clinical trial has been registered to evaluate the efficacy of this vaccine in COVID-19 pneumonia (NCT04347174).\(^{56}\)
Colchicine

Colchicine is a lipid-soluble alkaloid drug administered orally and has anti-inflammatory action. It is used in acute pericarditis as well as in various other conditions. In concern to COVID-19, majority of the patients suffer from acute respiratory distress syndrome (ARDS) and myocardial injury. This was from evidence obtained from study conducted in Wuhan, China on 150 patients in which 7% of deaths was attributed to myocarditis and 33% with myocarditis had adverse outcome. It has been shown in experimental models that inflammosome NLRPF3 is a major pathophysiological component for development of ARDS while in dry lab model the SARS-CoV-2 proteins such as viroporins E, 3a and 8A plays important role in viral replication. These viral proteins provoke inflammosome NLRPF3 and cause ARDS which can be inhibited by colchicine. The GRECCO-19 trial is recruiting patients and to evaluate the effect of colchicine in prevention of complication due to COVID-19 (ClinicalTrials.gov identifier: NCT04326790).

Vasoactive intestinal polypeptide

Vasoactive intestinal polypeptide (VIP) target the VAPC1 receptor of alveolar type II cells and prevent them from damage. It has been observed in animal models that VIP prevents from NMDA induced caspase-3 activation in lung, inhibits IL-6 and TNFα production and prevents pulmonary oedema. Synthetic form of VIP has been tried and found to be safe in treatment of sarcoid, pulmonary hypertension, ARDS and erectile dysfunction. A multi-center randomized placebo-controlled trial has been registered in clinical trial registry and patients with moderate or severe COVID-19 infection are being recruited for trial with intravenous synthetic VIP compared to standard treatment. The trial is in phase 2 and soon to be rolled to phase 3 (ClinicalTrials.gov Identifier: NCT04311697).

Monoclonal antibodies

Anti-spike S monoclonal antibodies which target the spike proteins at two sites are being tried in critically ill COVID-19 patients. It has been found to give promising results in treating hospitalized adult patients. A randomized placebo-controlled trial is the process of recruiting patients for evaluating the safety and efficacy of monoclonal antibodies (ClinicalTrials.gov Identifier: NCT04426695).

CONCLUSION

There is presently no definite treatment or prevention for COVID-19. Many drugs have been repurposed and are on clinical trials to evaluate the safety and efficacy in critically ill COVID-19 patients as well as for prophylaxis. Beside creating awareness about the global crisis about the virus, it is safe for policy makers and stake holders to follow expert opinion and draw conclusions based on evidence-based recommendations. While, WHO is awaiting the results of trials involving lopinavir-ritonavir and interferon beta 1b as well as effective vaccines, awareness of social distancing and maintaining hand hygiene seem to be the most important strategy against this virus for the time being.

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