INTRODUCTION

Viruses continue to emerge and pose a challenge to Public Health. Human health, animal health, and the state of ecosystems are inextricably linked. About 70–80% of emerging and re-emerging infections are of zoonotic origin.[1] Population growth, climate change, increasing urbanization, and international travel have increased the emergence of respiratory pathogens.[1] On December 31, 2019, many pneumonia cases of unknown etiology were reported in the city of Wuhan in China. Novel coronavirus (2019-nCoV) was identified as the agent causing this pneumonia on January 7, 2020. The outbreak was declared a Public Health Emergency of International Concern on January 30, 2020. The WHO has now characterized the outbreak as a global pandemic. A nCoV is a new strain that has not been previously identified in humans. The main route of transmission is through respiratory droplets or close contact with an infected person, including through fomites. Contact transmission includes contact with oral, nasal, and mucous membranes of the eye.[2] Highest viral loads were detected within 3 days after symptom onset, with higher viral loads detected in the nose than in the throat, especially in the early stage of illness. Viral loads peaked between 6 and 12 days after symptom onset and were highest in those most severely ill.[3] The most common symptoms of COVID-19 are fever, tiredness, and dry cough. Some patients may have aches and pains, nasal congestion, runny nose, sore throat, or diarrhea. Some people become infected but do not develop any symptoms and do not feel unwell. Among the COVID 19 patients, 80% do not need hospitalization, 20% require hospitalization, and among these, only 5% need ventilators.[4] As of June 1, 2020, there have been more than 6 million reported cases and 379,044 deaths in more than 216 countries. The world is carrying out two concurrent wars against coronavirus: On the one hand, it is trying to slow down or stop the spread of the disease and, on the other hand, is trying to find out effective treatments. At present, more than 300 active trials are underway. The majority of the trials aim to repurpose the commonly used medications such as anti-malarial, anti-influenza, anti-HIV combinations, and antibacterial, immunomodulators.[5] In this article, we discuss some of the drugs that showed promising results based on their compassionate use against COVID 19.

MATERIALS AND METHODS

A literature search was performed using PubMed and Google scholar websites, and we accessed published literature, newspaper articles, and other internet resources. Our study included articles published between February 1, 2020 (1st case in India was reported on January 30) and June 1, 2020.

Various Treatments under Trial for COVID-19

Mycobacterium w

Mycobacterium w was developed as an immunomodulator for leprosy which acts through the toll-like receptor pathway
and enhances T cell responses. Indian Pharmaceutical major Cadila at Ahmedabad in Gujarat, along with Council for Scientific and Industrial Research (CSIR) in India, has successfully tested *Mycobacterium w* (heat-killed *Mycobacterium Indicus Pranii*). The safety trial of this drug was completed in the 1st week of May 2020, but its actual trial is ongoing among 40 patients in PGIMER, AIIMS Delhi, and AIIMS Bhopal in India to analyze the use of Mw as an adjunct to the treatment of critically ill COVID 19 patients. In the multi-center trial conducted in PGIMER, it was found that Mw reduces the mortality in ICU patients with severe sepsis and reduces the cytokine storm seen in COVID 19 patients.[6]

**Ivermectin + Doxycycline**

Dr Tarek Alam from Bangladesh conducted a trial using ivermectin (anti-parasitic drug) + Doxycycline (antibiotic), among 60 COVID 19 patients in Bangladesh Medical College and found an astounding success with this combination. All of them recovered within 4 days.[7] A study conducted in the University of Melbourne and Monash University by Caly et al., which was published in the Journal “Antiviral Research” in March 2020 suggested that a single treatment of ivermectin was able to effect a 5000-fold reduction in the viral RNA in ivermectin-treated patients compared to control subjects, indicating that ivermectin treatment resulted in the effective loss of essentially all viral material by 48 h in cell culture.[8] Sodhi et al. from the University of British Columbia in Canada observed that the nCoV depends on the matrix metalloproteinases for survival, cell infiltration, and replication. Tetracyclines, which are highly lipophilic drugs, inhibit matrix metalloproteinases, which reduces the viral load.[9]

**Favipiravir**

Favipiravir is an anti-viral agent that selectively inhibits RNA-dependent RNA polymerase of RNA viruses. The new strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is also a positive sense single-stranded RNA virus. Favipiravir has shown anti-viral activities against several RNA viruses such as Arenaviruses, Bunyaviruses, and Filoviruses. Hence, these unique anti-viral profiles will make favipiravir a potential drug for specifically untreatable RNA viral infections, including COVID-19. Favipiravir was first approved for the treatment of influenza in Japan in 2014. Favipiravir is under trial in many countries to treat COVID-19. The CSIR in India has received approval from the Drug Controller General of India for clinical trials of favipiravir – an antiviral drug that can stop the viral replication in infected cells.[10] In a non-randomized study in China in March 2020, a comparison of two treatment regimens was done. It was found that those who took favipiravir along with inhaled interferon cleared the virus in an average of 4 days compared with 11 days in the control group (lopinavir/ritonavir). The results of this study have not been published in a peer-reviewed journal to date.[10]

Now a Mumbai based company in India is conducting phase three trials and expecting trial results by July or August. Favipiravir is being tested in many countries against COVID-19 and results are awaited.

**Remdesivir**

Remdesivir (GS-5734) was developed to treat Ebola disease during the outbreak caused by RNA virus. It is a broad-spectrum antiviral that is being currently tested in various countries as a potential treatment for COVID-19. It has shown promising results in animal models for treating SARS-CoV-2 that causes COVID-19 infection. It was observed that the drug has antiviral activity in vitro against pathogens that cause MERS and SARS, which are coronaviruses and structurally similar to SARS-CoV-2 that causes COVID-19, an RNA virus.[11] It is an experimental drug and is not yet licensed or approved anywhere for the use of any condition. It was found in a study that remdesivir targets polymerase, making the virus difficult to spread. The trial, known as Adaptive COVID-19 treatment trial or ACTT, demonstrated that remdesivir accelerates the recovery from patients with advanced COVID-19 with lung involvement. National Institute of Allergy and Infectious Disease in the USA stated that patients who took remdesivir had 30% fast time to recovery than those who received placebo.[12] Gilead Sciences a US-based company has released the results of the phase three trial of this drug on June 1, 2020. They conducted an open-label study and evaluated 5-day and 10-day courses of the investigational antiviral remdesivir plus standard of care versus standard of care alone. In this study, hospitalized patients with confirmed COVID-19 infection and evidence of pneumonia without reduced oxygen levels were randomized (1:1:1) to receive open-label remdesivir for 5 or 10 days or standard care alone. They assessed the clinical status by a seven-point ordinal score on day 11, ranging from hospital discharge to increasing levels of oxygen and ventilatory support to death. The study stated that patients in the 5-day treatment group were 65% more likely to have clinical improvement on day 11 compared with those in the standard of care group, which was statistically significant. The improvement in clinical status within the 10-day treatment course of remdesivir versus standard care was also favorable, but it was not statistically significant. Remdesivir is currently approved in Japan as a treatment for patients infected with SARS-CoV-2. Outside Japan, this drug is an investigational drug. It is authorized for use under an Emergency Use Authorization only for the treatment of patients with suspected or laboratory-confirmed SARS-CoV-2 infection. In clinical studies with this drug, infusion-related reactions and liver transaminase elevations have been observed. They also stated that it is possible that Gilead may make a strategic decision to discontinue the development of remdesivir or that FDA and other regulatory agencies may not approve remdesivir, which may have significant limitations on its use.[13] However, in a
study published in the Journal “Lancet” done by Wang et al. in China in March 2020 showed that remdesivir was not associated with statistically significant clinical benefits.[13]

**Chloroquine and Hydroxychloroquine**

Hydroxychloroquine or chloroquine, often in combination with a second-generation macrolide, is being widely used for the treatment of COVID-19, despite no conclusive evidence of their benefit. Although, generally safe when used for approved indications such as autoimmune disease or malaria, the safety, and benefit of these treatment regimens are poorly evaluated in COVID-19. Hydroxychloroquine and chloroquine (used with or without a macrolide) are widely advocated for the treatment of COVID-19 based on *in vitro* evidence of an antiviral effect against SARS-CoV-2. Their use is based on small uncontrolled studies and in the absence of evidence from randomized controlled trials. On March 28, 2020, the FDA issued an emergency use authorization for these drugs in patients if clinical trial access was unavailable. Other countries, such as China, have issued guidelines allowing for the use of chloroquine in COVID-19. Several countries have been stockpiling the drugs, and shortages of them for approved indications, such as for autoimmune disease and rheumatoid arthritis, have been encountered. In a study published in the Journal “Lancet” by Mehra et al. in May 2020, which was based on hospital registry data (96,000 hospital registries) it was found that the use of a regimen containing hydroxychloroquine or chloroquine (with or without a macrolide) was associated with no evidence of benefit, but instead was associated with an increase in the risk of ventricular arrhythmias and a greater hazard for in-hospital death with COVID-19. These findings suggest that these drug regimens should not be used outside of clinical trials, and urgent confirmation from randomized clinical trials is needed. In this study, it was given that the use of the drug increased the risk of death by 34% and increased the risk of serious heart disease by 137%.[14] However, this Lancet study was based on hospital registry data, not a randomized controlled trial. Based on this study, the WHO announced a temporary suspension of the clinical trial of hydroxychloroquine, which has been used for the treatment of COVID-19 patients.[15] However, Indian Council of Medical Research (ICMR) announced on May 27 that it will be continuing the use of hydroxychloroquine as prophylaxis for COVID-19 disease. The council found that the drug is very effective, and it is having side effects for prophylaxis consumption. Taking into consideration the biological plausibility, *in vitro* data, and safety level of the drug, the ICMR had recommended it for empiric use under strict medical supervision.[16] Case–control and observational studies were conducted in AIIMS, ICMR, and also in three public hospitals in Delhi in India. Although randomized trials of the drug were not conducted, the ICMR observed that it may be working and without major side effects except nausea, vomiting, and palpitations occasionally. As per the Indian Pharmacopoeia Commission, results of all people taking HCQ are being monitored.[16]

**Lopinavir–Ritonavir**

Lopinavir–Ritonavir an anti-HIV drug combination is also under trial in many countries for COVID-19. The Indian Council of Medical Research has suggested lopinavir/ritonavir combination therapy for laboratory-confirmed COVID-19 patients based on the observational studies of clinical benefit among patients with SARS-CoV and MERS-CoV, as well as the docking studies conducted by the National Institute of Virology, Pune in India. The Indian Regulatory Authority, Central Drugs Standard Control Organization, has accorded approval for restricted public health emergency use of this treatment protocol. The initial treatment protocol was for administering the combination treatment to all laboratory-confirmed patients. However, the first three laboratory-confirmed patients from Kerala (in India) had mild symptoms of diagnosis and had a stable course of illness. Hence, lopinavir/ritonavir treatment was not administered in these patients. It is, however, crucial to initiate the treatment before the patient develops features of severe illness. In view of this, the treatment protocol was subsequently amended to include additional criteria of severity as well as organ damage for initiating the combination treatment. The inclusion criteria also include high-risk group patients associated with a higher risk of mortality (age >60 years, hypertension, diabetes mellitus, renal failure, chronic lung disease, and immunocompromised persons) for initiating the combination therapy. This treatment protocol has a limitation. The combination treatment is approved for emergency public health use, only among laboratory-confirmed patients with a moderate degree of severity and not designed as a controlled clinical trial. However, the treatment outcomes among the first few cases would be useful in providing guidance about the clinical management of COVID-19 cases in the future.[17] If found useful in managing initial COVID-19 infected patients, further evaluation using a randomized control trial design is warranted to guide future therapeutic use of this combination. A study published by Hung et al. in the Journal “Lancet” in May 2020 stated that a treatment involving a combination of the drugs interferon beta-1b, plus antiviral combination lopinavir-ritonavir, and ribavirin is better at reducing the viral load than lopinavir-ritonavir alone.[18]

**Interferon**

Interferons are a group of signaling proteins made and released by the host cells in response to the presence of several viruses. Commercially available interferons are human interferons manufactured using recombinant DNA technology. A Researcher Dr Eleanor Fish quoted that “Rather than developing virus-specific anti-viral for each new virus outbreak, we should consider interferons as the “first responders” in terms of treatment.”[19] Interferon provided...
therapeutic benefit during the SARS outbreak of 2002 and 2003. Researchers have found that interferon-alpha2b can help speed up the recovery of COVID-19 patients. A study published in the Journal “Frontiers of Immunology” by Zhou et al. in China stated that treatment with interferon α2b may significantly accelerate virus clearance and reduce levels of inflammatory proteins in COVID-19 patients. Treatment with this drug has been used clinically for many years, and it has significantly reduced the duration of detectable virus in the upper respiratory tract on an average by about 7 days. It also reduced blood levels of interleukin (IL)-6, C-reactive protein (CRP), and inflammatory proteins found in COVID-19 patients. Randomized clinical trial is the next important step for evaluating this drug. Now ICMR has approved interferon for clinical trials against COVID-19 patients, which is being tried in the state of Kerala in India.

Neutralizing Antibodies

The neutralizing antibody is an antibody that defends a cell from a pathogen or infectious particle by neutralizing any effect it has biologically and makes the pathogen no longer infectious. The Council of Scientific and Industrial Research (CSIR) in India has approved a multinational project on May 9, 2020, to develop human monoclonal antibodies (hmAbs) that can neutralize coronavirus in patients. This project was to generate hmAbs to SARS-CoV-2 from the convalescent phase of COVID-19 patients and select high affinity and neutralizing antibodies. The project also aimed to understand the future adaptation of the virus and generate hmAbs clones that can neutralize the mutated virus so that it could be readily used for combating future SARS-CoV infections. Chinese scientist Sunney Xie who is the director of Beijing Advanced Innovation Centre for Genomics said that when they injected neutralizing antibodies into infected mice, after 5 days, the viral load reduced by a factor of 2500. The drug uses neutralizing antibodies produced by the human immune system to prevent the virus from infecting cells for which they isolated the blood of 60 recovered patients. These neutralized antibodies can become a specialized drug that would stop the pandemic.

Another study done in China by Dai et al., who published his study in the Journal “Science” in April 2020, stated the probable effectiveness of two small molecule drug candidates named 11a and 11b which could block the SARS-CoV-2 M protease enzyme (which the virus uses to make copies of itself). The molecules could stop the virus from replicating in monkey cells and it was found safe for administration in rats and beagles. For both drugs, further studies must be conducted. Scientists have also tested the effectiveness of therapies involving the use of antibodies that can bind to some parts of the virus and block their entry into host cells. Furthermore, in a study published in the Journal “Cell” stated that antibodies derived from the immune system of the South American mammal called Llamas which belong to the same category of mammals as camels, produces antibodies that bind to the key protein on the nCoV. Clinical trials need to be done to prove this. Another research team from University of Washington in US found that a combination of antibodies, including the patient who recovered from the 2002 to 2003 SARS pandemic virus infection, can effectively block the nCoV. One of the molecules S309 showed strong neutralizing activity against SARS-CoV-2. They also stated that adding an S309 antibody in combination with another less potent antibody targets different site on the virus. These results are yet to be validated in human trials.

Plasma Therapy

Convalescent plasma therapy has been around for more than 100 years and was used during the flu pandemic in 1918. The use of convalescent plasma is not a new concept. The therapeutic potential of convalescent sera has been well recognized and was used to stem outbreaks of viral diseases such as polio, measles, and mumps. Based on the prior experience and existing evidence in treating other viral infections, the early administration of convalescent plasma or hyper-immune immunoglobulin from patients containing significant antibody titers is likely to reduce the viral load and disease mortality. Over the past two decades, this therapy was successfully used in the treatment of SARS-CoV-1, H5N1 avian influenza, and H1N1 influenza wherein the transfusion of convalescent plasma was found to be both effective and safe. In 2014, the use of convalescent plasma collected from patients who had recovered from Ebola virus disease was recommended by the WHO as an empirical treatment during the outbreaks. COVID-19 convalescent plasma is currently being studied as a therapy for COVID-19 patients. Preliminary data from China and other countries suggest some potential promise and further study is needed to determine its efficacy. The US FDA is accepting emergency Investigational New Drug Applications for the use of plasma from recovered patients to treat people who are critically ill with COVID-19. One of the effective passive therapeutic approaches during an outbreak of any infectious disease is the passive antibody therapy from convalescent patients sera who have recovered from the infection. This can be used for the treatment of patients who contract the infection in future. This type of passive therapy is simple but potentially a very effective tool for developing immediate immune responses under critical conditions. In case of the current COVID-19 pandemic (SARS-CoV-2), the patients with resolved SARS-CoV-2 viral infection will develop significant serum antibody response (IgG) to different viral epitopes of the SARS-CoV-2 virus and some of these developed antibody responses in the host system will be likely to have the potential to neutralize the virus. The high level of antibody titers produced by the host-immune system against the SARS-CoV-2 virus significantly reduces the chances of getting reinfected. A case series described administration of plasma from donors who had completely recovered from COVID-19 to five patients with...
severe COVID-19 on mechanical ventilation and persistently high viral titers despite investigational antiviral treatment. The patients had decreased nasopharyngeal viral load, decreased disease severity score, and improved oxygenation by 12 days after transfusion, but these findings do not establish a causal effect. Finding appropriate donors and establishing testing to confirm neutralizing activity of plasma may be logistical challenges.

**WHO’s “Solidarity Trial”**

The WHO is conducting an International Clinical trial to find an effective treatment for COVID-19. This trial will compare four treatment options against the standard of care, to assess the effectiveness against COVID-19. Remdesivir, lopinavir/ritonavir, lopinavir/ritonavir with interferon beta-1a, and hydroxychloroquine had been initially selected as treatment options. Following new evidence on the safety and efficacy of hydroxychloroquine as a treatment for hospitalized COVID-19 patients, enrollment for this drug was temporarily suspended on May 24, 2020. Over 100 countries have expressed an interest in participating in the trial and the WHO is actively supporting more than 60 of them. To date, over 400 hospitals in 35 countries are actively recruiting patients and nearly 3500 patients have been enrolled from 17 countries.[32]

**MISCELLANEOUS**

**Oseltamivir**

A neuraminidase inhibitor used for the treatment of influenza has no documented effect against SARS-CoV-2. COVID-19 outbreak occurred during the influenza season, so the patients were empirically given oseltamivir until they found the cause of COVID-19 as SARS-CoV-2.[33] Many clinical trials included oseltamivir in the comparison group but not as therapeutic option.[34]

**Umifenovir**

An antiviral agent which effectively inhibits the fusion of virus with host cells. This drug is used in Russia and China for the treatment of influenza and based on the in vitro data, now this drug is under trial for COVID-19. A study by Wang et al. published in the Journal of “Clinical Infectious Disease” stated that a non-randomized study was conducted on 67 patients with COVID-19 and it showed that the treatment with Umifenovir for 9 days lowered the mortality rates and ensured high discharge rates compared with those who did not receive the drug.[35] In India, phase three trial has been started in Mumbai by a company named Glenmark Pharmaceuticals for the combination of two antiviral drugs favipiravir and Umifenovir in COVID-19 patients. The study will involve 156 hospitalized patients who have moderate symptoms of COVID – 19.[36]

**Itolizumab**

Drug used for Biocon’s psoriasis is now being tested in India in the cities Mumbai and Delhi for moderate cases of COVID 19.[37]

**Disulfiram**

It is used to treat alcoholism. It was used in SARS and MERS outbreaks and helps to produce an immune response. It is yet to be studied if the drug is effective against COVID-19.[37]

**Sarilumab (Kevzara)**

A monoclonal antibody does not attack the nCoV but instead inhibits an abnormal immune response called “cytokine storm.” However, a small study was conducted in china which showed no benefit to the patients.[37]

**CONCLUSION**

A plethora of treatment modalities are being conceptualized, but we found that the most promising results were observed with remdesivir, followed by triple combination of lopinavir-ritonavir, interferon beta-1b, and ribavirin and then with hydroxychloroquine but there are many unanswered questions. Neutralizing antibodies are also a promising option. Although many trials are ongoing for COVID-19, at present the best strategy to overcome this pandemic is by the time tested concept of prevention: By maintaining Social Distancing, Proper hand hygiene, Cough Etiquette and the use of masks.

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