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The Pandemic of COVID-19, Virological Pathogenesis, Clinical Characteristics, and Pharmacological Treatment: A Review

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ABSTRACT

In ending December 2019, a number of cases having Novel Coronavirus-2019 pneumonia (SARS-CoV-2) in Wuhan China, becomes the concern of worldwide. Bats are the main origin of 2019-Novel Coronavirus and were transmitted to humans through yet unknown mediator in Wuhan, Hubei province in China. Till date near about 315,345,967reported cases, 5,510,174 deaths and 213 Countries, areas or territories are facing this problem. 2019-nCoV can progress to pneumonia and may cause acute respiratory distress syndrome (ARDS) with multi-organ dysfunction. Presently early diagnosis is done by the expression of the virus in respiratory secretions by molecular tests. Preventive measures at early can be home isolation of suspected persons and those with mild illnesses and strict infection control measures at hospitals that include contact and droplet precautions. In conclusion time alone will notify how 2019-nCoV will impact on the lives in whole world. Besides the limitations repositioning clinical trials are still in an attractive strategy and they may facilitate the discovery of novel group of medicine alone or combinations with other drugs for COVID-19 treatments but role of antiviral agents is yet to be established. In conclusion the time alone will tell how this deadly virus will impact lives in world and in India. Further in future such outbreaks of different categories of viruses, bacteria and pathogens of zoonotic origin are likely to continue. Different efforts should be made to plan comprehensive measures to prevent such future outbreaks of different viral & bacterial diseases without curbing this virus outbreak.

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Introduction

Coronavirus disease (COVID-19) comes under the communicable disease category and is caused by a newly discovered coronavirus (WHO). Previous human coronaviruses that have been reported to cause severe symptoms include the MERS-CoV that causes Middle East Respiratory Syndrome (MERS), SARS-CoV causes severe acute respiratory syndrome (SARS) and current recently epidemic 2019 Novel Coronavirus (2019-nCoV) that began in Wuhan China and spread round the world. These newly discovered viruses are belonging to the family Coronaviridae and are non-segmented enveloped positive-sense RNA viruses. The epidemics of β-coronaviruses, (SARS-CoV and MERS-CoV) have caused more than ten thousand cumulative cases in the past twodecades in the world [1]. These viruses are zoonotic pathogens, present in humans & various animals with a wide range of clinical features (asymptomatic, causing infections in respiratory, gastrointestinal, hepatic and neurologic systems) [3]. Just about ten years of SARS this time highly pathogenic CoV, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) has emerged in the Middle East countries [5]. In late December 2019, a new public health problem has emerged in the Huanan Seafood Market in Wuhan State of Hubei Province in China and gained the focus of global attention due to a its deadly face. Wuhan public health authorities on 1st January 2020, shut down the whole Market, because of its suspected link with this disease [6, 7]. China on 31th December 2019 reported a cluster of cases with pneumonia of unknown cause, attracting great attention nationally and worldwide [7]. On 30th January 2020, the WHO declared COVID-19 to be a Public Health Emergency of global concern and declared it as an epidemic [8].

Virology-Pathogenesis

According to the latest studies and review of literature, similar to SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), SARSCoV-2 is zoonotic, with Chinese horseshoe bats being the most probable origin and most likely the intermediate host are pangolins. Coronaviruses are prevalent in humans and several other vertebrates and cause respiratory, enteric, hepatic and neurologic diseases. Remarkably, the severe acute Respiratory

Syndrome Coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 have caused human epidemics. Comparison with the current virus shows several significant differences and similarities. Both MERSCoV and SARS-CoV have much higher case fatality ratese. Though the current SARSCoV-2 shares 79% of its genome with SARS-CoV, it appears to be much more transmissible [21, 22].

Till date among all RNA viruses the genome structure of Coronaviruses is best known, although the length of the CoV genome shows high variability for ORF1a/ORF1b and four structural proteins [23]. Spike Protein of the virus first interacts with sensitive human cells and genome encoding occurs after its entrance to the cell. This facilitates the expression of the genes that encode useful accessory proteins, which advance the adaptation of CoVs to their human host [23]. The genomic changes resulting from recombination, gene insertion, gene exchange, & deletion are frequently found among CoVs.

SARS-CoV and MERS-CoV that attach to the host cell respectively bind to cellular receptor angiotensin converting enzyme-2 (SARS-CoV associated) and cellular receptor of dipeptidyl peptidase-4 (MERS-CoV associated) [24]. After entering the cell, the viral RNA manifests itself in the cytoplasm. Genomic RNA is encapsulated polyadenylated which encodes various structural and non-structural polypeptide genes. These polyproteins are split by proteases that exhibit chymotrypsin-like activity [24]. The resulting complex drives (-) RNA production through both replication and transcription. Full-length (-) RNA copies of the genome are produced during replication, used as a template for full-length (+) RNA genomes [23]. During transcription, a subset of 7-9 sub-genomic RNAs, including those encoding all structural proteins are produced by discontinuous transcription. Viral nucleocapsids are combined from genomic RNA and R protein in the cytoplasm and then are budded into the lumen of the endoplasmic reticulum. Virions are then released from the infected cell through exocytosis. The released viruses can infect kidney cells, liver cells, intestines and T lymphocytes. They are infecting the lower respiratory tract as well, where they form the main symptoms and signs [24]. CDT lymphocytes were found to be remarkably lower in some patients with SARS-CoV infection. This virus can make the antiviral T-cell response irregular due to the stimulation of T-cell apoptosis which is cause of immune system collapse [25, 26].

Sources & Modes of Transmission

CoVs a large family of viruses, common in different animal species. In 1962 CoVs have been defined as a novel respiratory tract virus in the samples collected from the individuals having symptoms of respiratory tract infection [27]. Rarely animal CoVs can infect humans and as a result may spread among humans during epidemics such as MERS, SARS & COVID-19 [23-25]. However, more advanced virological and genetic studies have shown that bats are reservoir hosts of both SARS-CoV and MERS-CoV and before these viruses spread to humans, they use the other responsible animals as intermediate hosts [3]. Presence of wild animal trade in Huanan Seafoods Market where the first cases appeared supports the finding that the novel virus causing epidemics coincides with the CoV isolated in bats. [6, 21]. After the first outbreak, secondary cases began to be reported after approximately ten days. Moreover, while these new patients had no contact with the marketplace, confirmed that human to human transmission has started. In Wuhan many infection confirmed healthcare workers confirmed that human to human transmission occurs. The first non-Chinese case of the infection, which spread to the Chinese provinces and then to the Asian continent was reported from Thailand on 13th January, 2020. The case reported being a Chinese tourist who has traveled to Thailand and had no epidemiologic connection with the market place [26]. Other cases from oversea countries have continued to be reported, human-to-human transmission primarily occurs because of infected persons sneezing and respiratory droplets produced just as the spread of influenza and other respiratory pathogens. [27, 28]. However, cases, which were infected from an asymptomatic person in the prodrome period of COVID-19, were also reported. Sufficient data are not available till date on infectiousness of the disease and research is ongoing [13].

Clinical characteristics and Diagnosis

COVID-19 symptoms differ from individual to individual includes mild fever, cough (dry), sore throat, nasal congestion, malaise, headache, muscle pain, or malaise and may produce few or no symptoms in some infected persons. Though, in addition it can lead to severe illness and may be fatal. The COVID-19 may present with mild, moderate, or severe illness and in among severe clinical manifestations, there are severe pneumonia, ARDS, sepsis and septic shock [16, 17]. The clinical pictures of patients with COVID-19 and with sepsis are particularly serious, characterized by a wide range of signs and symptoms of multi-organ involvement. These signs and symptoms include respiratory manifestations such as severe dyspnea and hypoxemia, renal impairment with reduced urine output, tachycardia, altered mental status, and functional alterations of organs expressed as laboratory data of hyperbilirubinemia, acidosis, high lactate, coagulopathy, and thrombocytopenia [18, 19]. Common symptoms of COVID-19 are Cold- or flu-like symptoms usually set in from 2–4 days after a coronavirus infection and are typically mild. However, symptoms vary from person-to-person, and some forms of the virus can be fatal. Symptoms may include: sneezing, runny nose, fatigue cough, fever, sore throat, Exacerbated asthma.

The patients with underlying comorbidity exhibited a more severe clinical course, as expected by the experience gained from the previous epidemics [7]. As in SARS and MERS, the diagnosis of 2019 n-CoV infection is based on a history of detailed contact and travel and precise laboratory testing. The most common diagnostic methods are molecular methods as RT-PCR (reverse transcription) or real-time PCR. In particular, lower respiratory tract samples can offer significantly higher viral load and genome fraction than upper respiratory tract samples. These techniques are beneficial in terms of evaluating the results quickly, showing the genome structure and viral load. [37]. The sensitivity of antibody detection is generally lower than molecular methods and is mostly used in retrospective diagnosis.

The diagnosis of COVID-19 can be based on a combination of epidemiologic information, clinical symptoms, CT imaging findings and laboratory tests according to standards of either the WHO-2020 [7]. Since the outbreak of COVID-19, the diagnostic testing methods of the virus COVID-19 in human clinical specimens included, real-time RT-PCR, next-generation sequencing, Scanning electron microscopy (SEM) and cell culture [37]. The reason for delay in preventing and diagnosis the COVID-19 outbreak since the cell culture; PCR and SEM need more time to detect the virus in the COVID-19 samples [38]. The chest radiograph for a patient after 8 days of the diseases showed bilateral lung consolidation with relative peripheral sparing while was more extensive after 11 days [33]. It should be mentioned that a single negative RT-PCR test result from suspected patients does not exclude infection. Clinically, we should be alert of patients

with an epidemiologic history, COVID-19–related symptoms, and/or positive CT imaging results. So far, there has been no evidence from randomized controlled trials to recommend any specific anti-nCoV treatment, so the management of COVID-19 has been largely supportive (WHO 2020). Currently, the approach to COVID-19 is to control the source of infection; use infection prevention and control measures to lower the risk of transmission; and provide early diagnosis, isolation, and supportive care for affected patients [7].

So far, no antiviral therapy has been proved to be effective for the treatment of patients with COVID-19 infection. A couple of therapeutic interventions for coronavirus were investigated during the outbreak of SARS-CoV and MERSCoV [39, 40], and combination of ribavirin and interferon has been proved beneficial in patients with SARS-CoV or MERS-CoV infection [41, 42]. In addition, the potent efficacy of remdesivir [43] lopinavir and ritonavir [44], as well as intravenous immunoglobulin [47, 48] has been documented for MERS-CoV treatment. As previously reported, early administration of interferon protected mice from lethal MERS-CoV infection, while late administration of exogenous interferon promoted the pro-inflammatory cytokine response and inhibited the optimal virus-specific T cell response [47, 48].

Pharmacological Therapy

In general, there are few or no treatment options for viral diseases that occur suddenly [35]. Studies evaluating the antiviral activity of types I and II interferons have reported, interferon-beta (IFNb), as the most potent interferon, was reducing in- vitro MERS-CoV replication [26] According to a human MERSCoV case report from South Korea, the use of the combination of Lopinavir/Ritonavir (LPV/RTV) (Anti-HIV drugs), pegylated interferon and ribavirin provided a successful viral clearance [35]. For this purpose, a randomized control trial (MIRACLE Trial), that aimed to determine whether LPV/RTV-IFNb improved clinical results in MERS-CoV patients, was initiated in 2016 and 76 patients were enrolled [51]. Although another antiviral drug, remdesivir was used in the first case reported from the United States of America, seemed successful, controlled studies with more cases are needed [35].

Existing therapies

Pharmaceutical interventions for COVID-19 treatment include different drugs like human immunoglobulin, hydroxychloroquine, chloroquine, interferons, arbidol, oseltamivir, favipiravir, carrimycin, remdesivir, thalidomide, methylprednisolone, bevacizumab, vitamin C, pirfenidone, bromhexine, fingolimod, danoprevir, ritonavir, darunavir, xiyanping, cobicistat, lopinavir, and traditional Chinese medicines (TCM). We briefly introduced 21 different therapies based on reported literature.

Chloroquine and hydroxychloroquine

Hydroxychloroquine and chloroquine are two medications that have been used for many decades to treat malaria and autoimmune conditions like rheumatoid arthritis and lupus. These drugs are antimalarial and in past and current scenario they are used against human immunodeficiency virus (HIV), because it inhibits the virus entry into the host cells. Another antiviral mechanism of these drugs is related to the post-translation alteration of newly synthesized proteins by the inhibition of glycosylation [60]. In the treatment of acquired immune deficiency syndrome (AIDS) hydroxychloroquine is already being used in clinical trials [61]. Some studies suggest that they may also be helpful for treating hospitalized patients with mild cases of COVID-19. In a recent clinical trial of these drugs on COVID- 19 patients treatment, 100% of patients treated with hydroxychloroquine in combination with the macrolide antibiotic azithromycin were virologically cured as compared to hydroxychloroquine alone were only 57.1% COVID-19 patients were cured [62]. Currently hydroxychloroquine and chloroquine is under test trial in patients with pneumonia caused by coronavirus-2019 (2019-nCoV) and chloroquine as preventative medicine for COVID-19 patients [63, 64].

Azithromycin (Z-pak)

Azithromycin is an antibiotic commonly used to treat bacterial infections such as bronchitis and pneumonia. It has been shown to have some in vitro activity against viruses like inuenza A and Zika, but did not work against the coronavirus that causes MERS. One research group looked at azithromycin in combination with hydroxychloroquine for COVID-19. They reported that 93% of patients cleared the virus aer 8 days, but there was no control group so we don't know if people would have cleared the virus on their own without the medications. There are concerns about potentially serious side eects when using azithromycin and hydroxychloroquine together [65].

Immunoglobulins

Currently these are used against in several diseases (chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain-Barre Syndrome (GBS), idiopathic thrombocytopenia purpura (ITP), Kawasaki disease) and also used in multiple neurological autoimmune disorders refractory to standard immunosuppressive treatments [66]. The mechanism of broadly neutralizing antibodies is recognizing a wide variety of glycoproteins (GPs) on virus surfaces or the protein shell of a non-enveloped virus. However some viruses (Ebola virus (EBOV), HIV-1, hepatitis C virus (HCV), influenza viruses, and dengue virus (DENV), can mutate superficial glycoproteins by these mutations and they can evade the antibody response, an obstacle in the development of new therapies against such virus infections [67]. Trial NCT04261426 is utilizing human immunoglobulin in eighty 2019-nCoV participants having Pneumonia caused by 2019-nCoV, Sponsor Peking Union Medical College Hospital and its estimated end may be 30-06-2020 which is under Phase 2 and 3 [68].

Remdesivir

Remdesivir is an antiviral that is given by intravenous (IV) infusion in the hospital. This is a brand-new drug that has not been approved for use on the market yet, and is being tested in carefully controlled environments. It was previously shown to have some eect against SARS, MERS, and Ebola in cell and animal models. In a recent in vitro study (studies done in a petri dish or test tube rather than in animals or humans), remdesivir prevented human cells from being infected with SARS-CoV-2 (the virus that causes COVID-19). Two past clinical studies showed the use of this drug (Remdesivir) in severe or mild respiratory infections caused by SARS-CoV-2 [69, 70]. Dyer et al. 2019 described preliminary findings of a mortality rate of 33% in 499 patients treated with remdesivir against the EBOV disease in early infection stages [71] because remdesivir is a nucleotide analog inhibitor of the EBOV RNA-polymerase RNA-dependent (RdRp). They also noted (75%) mortality of almost 1,900 people among non-treated infected patients during the same epidemic period [72]. In the findings of Wang et al. in 2020 it was showing that remdesivir is effective drug against the 2019-nCoV in Vero E6 cells [25] and the suggested mechanism for remdesivir involves the host cells' post-entry stage [71].

Arbidol
This is also known as umifenovir and is approved drug for the treatment of influenza virus infections in Russia and China. It is patented for SARS treatment as it does not have any significant adverse effects [72]. The anti-viral mechanism of arbidol against influenza A and B involves viral fusion inhibition with the targeted membrane as it blocks virus entry into the cell [73]. Other approved drug (Oseltamivir) for influenza A and B treatment inhibits the viral neuraminidase and consequently blocks the release of viral particles from host cells which reduces the spread of it in the respiratory tract [74]. Four clinical trials are going to utilize this drug for COVID-19 treatment (a): one with arbidol in comparison with the basic treatment [75], (b): three studies comparing effects with oseltamivir, lopinavir ritonavir, and carrimycin in covid-19 patients [76-78].

Epidemic
In COVID-19 epidemic, the use of oseltamivir was already reported in China, either alone or with antibiotics and corticosteroids [79]. Oseltamivir is also used in a clinical trial along with multiple combinations of chloroquine and favipiravir [80], a nucleoside analog that is well-known as a broad spectrum antiviral drug; it has shown [72] an EC50 of 61.88 μM against SARS-CoV-2 with low toxicity.

lopinavir-ritonavir
Several countries approved lopinavir-ritonavir combination for the treatment of AIDS as both drugs are HIV protease inhibitors. But the ritonavir is also a cytochrome P450 and GP inhibitor which is a fact that endorses the lopinavir pharmacokinetic and pharmacodynamic activities against HIV [81]. This combination, plus β-1b interferon is in the phase 2 for the MERS treatment [82]. Several trials involve lopinavir-ritonavir treatment in comparison with the use of other drugs (arbidol (carrimycin, TCM, xiyanping, danoprevir-ritonavir and interferon inhalation) for COVID-19 treatment [75-77 & 83-88].

Carrimycin
This is a macrolide antibiotic which effects against some gram-positive bacteria and in vitro effects on Mycobacterium tuberculosis [89].

Danoprevir
This is an HCV NS3 protease inhibitor and is approved in China for the treatment of non-cirrhotic genotype 1b chronic hepatitis C, in combination with ribavirin, peginterferon-α, and ritonavir [90].

Traditional Chinese medicine
These are using phytotherapeutic formulations such as teas, powders, pills or tinctures, and cultural components that originated 5000 years ago in Chinese medicine [91]. These Traditional Chinese medicine (TCMs) were already used in 2000 for SARS-CoV infection as coadjuvant therapy with the enhancement of patient's symptoms, increased oxyhemoglobin arterial saturation. They were also proved useful in the early stages of this infection [91].

Interferons (IFNs)
These Interferons (IFNs) are proteins that bind to cellular surface receptors and initiate JAK-STAT signaling cascades, with transcriptional regulation of genes controlled by interferons and effects against some viruses like hepatitis B virus and HCV [92].

Xiyanping: This is a TCM preparation with andrographolide as a principal component and it has significant antibacterial and antiviral effects [93].

Darunavir
Darunavir is another HIV protease inhibitor, and cobicistat, like ritonavir, is a booster for enhancing the pharmacokinetics and pharmacodynamics of darunavir by cytochrome P450 (CYP3A) inhibition [94]. The United States Food and Drug Administration (FDA) currently approve a combination of Darunavir and cobicistat in AIDS treatment [95]. The combination of Darunavir and cobicistat will be used in trial number NCT04252274 in patients with COVID-19 pneumonia with 30 participants at Shanghai Public Health Clinical Center [96].

Recombinant human interferon α2β
Recombinant human interferon α2β is described to have inhibitory effects on MERS-CoV and SARS CoV [97] and the purpose of the clinical trials found is to evaluate the efficacy and safety of recombinant human interferon α2β in treating patients with this new coronavirus infection [98].

Thalidomide
This drug will be used in two trials against COVID-19 [98, 99], as thalidomide can increase the secretion of interleukins, such as IL-12, and activate natural killer cells. Thalidomide has an anti inflammatory action due to its ability to speed up the degradation of messenger RNA in blood cells and thus reduce tumor necrosis factor-α (TNFα) [100].

The corticosteroid methylprednisolone
This will be tested against COVID-19 [101]. In 2016 Long et al. reported that corticosteroid therapy (methylprednisolone, dexamethasone, and hydrocortisone) is beneficial in treating SARS-CoV patients because it can significantly prolongs the survival time of clinical cases [102]. However others of other research studies described the use of corticosteroids in early stages of SARS infection with rising values of viral load [103]. In addition some studies with corticosteroids in the adjuvant therapy of MERS-CoV infection were unable to verify efficacy because all patients died [104]. Methylprednisolone drug has already been used in the treatment of COVID-19 patients in combination with antibiotics (oseltamivir, and oxygen therapy) [105].

Vitamin C (ascorbic acid)
These are going to be tested on COVID-19, it may be due to its antioxidant activity and may reduce oxidative stress and inflammation effects that improve vasopressor synthesis, enhance immune cell function, improve endovascular function, and provide epigenetic immunologic modifications [106 – 108].

Fingolimod
Fingolimod is a sphingosine-1-phosphate receptor regulator (FTY720) with an effective immunology modulator which is useful in multiple sclerosis [109]. According to some pathological findings of pulmonary edema and hyaline membrane formation, the use of immune modulators, together with ventilator support, should be considered for severe patients to prevent the development of acute respiratory distress syndrome (ARDS). Study (NCT04280588) in Affiliated Hospital of Wenzhou Medical University including 30 participants with COVID-19 aims to determine the efficacy of fingolimod for COVID-19 [108].

Bevacizumab
Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF) [110, 108], and it may reduce the levels of VEGF caused by hypoxia, severe inflammation, and up-regulation of the infected respiratory tract epithelium, all of which might suppress the edema in patients

with COVID-19 [108].

Pirfenidone

It has been used in the treatment of idiopathic pulmonary fibrosis diseases because of its anti-inflammatory and anti-oxidant effects by inhibiting IL-1β and IL-4 [111]. Study (NCT04282902) in Huilan Zhang including 294 participants with severe pneumonia caused by 2019-nCoV claimed that anti-inflammatory effects may be helpful in SARS-CoV-2 infection [111].

bromhexine hydrochloride

This is a transmembrane protease serine inhibitor; such a protease is responsible for the activation of S-glycoprotein of SARS-CoV and MERS-CoV for viral entry through the plasma membrane [107, 112]. One study will evaluate the efficacy of bromhexine combined with standard treatment in patients with COVID-19 [109].

The U.S. FDA recently approved convalescent plasma from patients recovered from Covid-19 for the treatment of severe or life-threatening Covid-19 infections. "Considering the lack of efficacious treatments for Covid-19 and the epidemic situation with high mortality rate, the U.S. FDA has approved convalescent plasma for COVID-19 for clinical trials, expanded access and single patient emergency investigations.

Conclusions

This new virus outbreak has challenged the economic, medical and public health infrastructure of China and of other countries especially, its neighbors. Time alone will tell how the virus will impact lives round the world. More so, future outbreaks of viruses and pathogens of zoonotic origin are likely to continue. Therefore, apart from curbing this outbreak, efforts should be made to devise comprehensive measures to prevent future outbreaks of zoonotic origin. From Research studies and review papers it was concluded that Base line testing for symptomatic and asymptomatic patient should be started so that preliminary screening at large scale will be started. Although further research is warranted as the weight of the evidence increases, with the limited available data, and although the results of research studies are unadjusted for other factors that may impact disease progression of COVID-19. WHO declared an epidemic of pneumonia caused by the SARS-CoV-2 in 2020. Different clinical trials have already started with the repositioning of more than 20 medicines for COVID-19 treatment, such as human immunoglobulin, interferons, chloroquine, hydroxychloroquine, arbidol, remdesivir, favipiravir, oseltamivir, thalidomide, methylprednisolone, bevacizumab, TCM and combination of different drugs with excellent results in clinical trials against SARS-CoV-2. Besides its limitations, repositioning clinical trials are still an attractive strategy: they may facilitate the discovery of new classes of medicines; they may reduce the costs and time to reach the market; we hope that upcoming trials may help to find solutions for COVID-19 treatment by this year.

In the face of this rapidly emerging global threat, there are several reasons for optimism about future control. A number of antiviral drugs have shown promise in vitro. Even a partially effective antiviral could allow sufficient reduction in viral load so that the immune system can recover and respond to prevent lethal disease.

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