WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 8, 752-773. Review Article ISSN 2277– 7105

A REVIEW OF COVID-19: PATHOGENESIS, SYMPTOMS, TRANSMISSION, DIAGNOSIS AND TREATMENT

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Article Received on
01 June 2020,

Revised on 22 June 2020,
Accepted on 13 July 2020,

DOI: 10.20959/wjpr20208-18172

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ABSTRACT

The Coronavirus Disease Pandemic 2019 (COVID-19) caused by the novel acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses an ongoing task in identifying suitable treatments for prevention and diagnosis. Due to the rapid pace of scientific advancement and scientific research generated by a large group of individuals who are rapidly infected with SARS-CoV-2, physicians need efficient evidence of effective medical treatment for this infection. The origin, pathogenesis and immune responses, epidemiology, diagnosis, treatment and management of the disease are all assessed in this review.

KEYWORDS: Severe acute respiratory syndrome, COVID-19, pathogenesis, treatments.

1. INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread all over the world and has a significant impact on global public health and economies. According to the COVID-19 situation report published by the World Health Organization (WHO), a total of 6 931 000 confirmed cases and 400 857 deaths were identified globally until June 8, 2020.1 However, there is no antiviral medication or vaccine of proven efficacy to treat or prevent human coronavirus infection, hence the crucial and urgent need to identify effective, safe and available treatment strategy for the disease. SARS-CoV-2 is a novel human coronavirus identified in 2019. It is an enveloped, positive-sense, single-stranded RNA beta-coronavirus, and is structurally similar to SARS-CoV-1 and Middle East Respiratory Syndrome

coronavirus (MERS-CoV) which were identified in the 2003 SARS and 2012 MERS outbreak respectively. As long as the threat of the COVID-19 epidemic and past experience with the treatment of SARS and MERS, many production in vaccine and treatment strategy development are being made vigorously. This review focuses on the potential therapeutic agents and vaccine development that have been reported with experience in treating SARS-CoV-2 infection.

2. STRUCTURE OF SARS-COV-2

The SARS-CoV-2 genome (30 kb in size) encodes an outsized, non-structural polyprotein (ORF1a/b) that's further proteolytically cleaved to get 15/16 proteins, 4 structural proteins and 5 accessory proteins (ORF3a, ORF6, ORF7, ORF8 and ORF9)[1] (Fig. 1). The four structural proteins contains the spike (S) surface glycoprotein, the membrane (M) protein, the envelope (E) protein and therefore the nucleocapsid (N) protein, which are essential for SARS-CoV-2 assembly and infection. The spike surface glycoprotein plays a key role in its attachment to host cells and may be further cleaved by host proteases into an N-terminal S1 subunit and a membrane-bound C-terminal S2 region. Binding of the S1 subunit to a number receptor can destabilase the prefusion trimer, resulting in shedding of the S1 subunit and transition of the S2 sub- unit into a highly stable post fusion conformation.[2] So as to interact a number receptor, the receptor-binding domain (RBD) of the S1 subunit undergoes hinge-like conformational movements, which transiently hide or expose the determinants of receptor binding.[3] These two states of the S1 subunit are often considered the ‘down’ conformation and therefore the ‘up’ conformation. The previous represents an inaccessible state of the receptor, whereas the latter corresponds to an accessible state.[4] Therefore, understanding the structure and performance of the spike protein can help to develop antibody drugs and to guide the planning and development of vaccines.

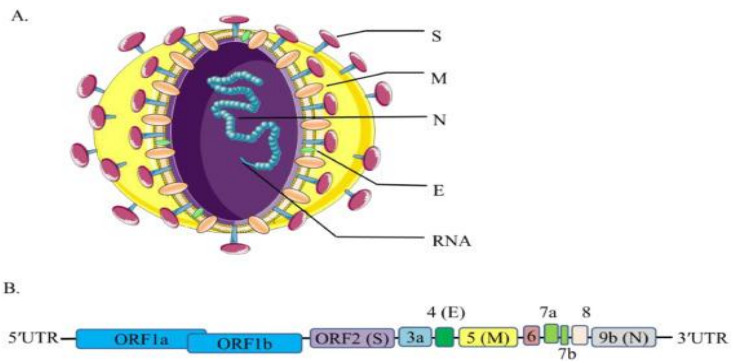

Fig. 1: Structure and genome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). (A) There are four structural proteins as follows: membrane (M)

protein (orange); spike (S) surface glycoprotein (purple); nucleocapsid (N) protein (blue); and envelope (E) protein (green). Genomic RNA is shown encased in the N protein. (B) The SARS-CoV-2 genome is arranged in the order of 5′-replicase (ORF1a/b)–structural proteins [spike (S)–envelope (E)–membrane (M)–nucleocapsid (N)] −3′.

3. ETIOLOGY AND PATHOGENESIS OF COVID-19

SARS-CoV-2 is that the seventh member of the family of CoVs that infect humans. Four human CoVs (HCoV-229E, HCoV-NL63, HCoV- OC43 and HCoV-HKU1) are ready to cause a large range of up- per tract infections (common cold), whereas SARS-CoV and MERS-CoV are liable for primary atypical pneumonia. The causes of various infection sites are likely associated with the presence of dipeptidyl peptidase 4 (DPP4) and angiotensin-converting enzyme 2 (ACE2) within the lower tract, which are the main human receptors for the surface spike (S) glycoprotein of MERS-CoV and SARS-CoV, respectively.[5] The genetic sequence of SARS- CoV-2 is ≥70% almost like that SARS-CoV, and SARS-CoV-2 is capable of using an equivalent cell entry receptor (ACE2) as SARS-CoV to infect humans.[6] However, there are more differences within the key S proteins that the viruses use to interact with host cells. SARS-CoV-2 spike binds to human ACE2 with approximately 10–20 fold greater affinity than the SARS-CoV spike.[3] Making it easier to spread from human to human.

Upon entry into alveolar epithelial cells, SARS-CoV-2 replicates rapidly and triggers a robust immune reaction, leading to cytokine storm syndromes and pulmonary tissue damage. Cytokine storm syndromes, also referred to as hypercytokinaemia, are a gaggle of disorders characterised by the uncontrolled production of pro-inflammatory cytokines and are important causes of acute respiratory distress syndrome (ARDS) and multiple organ failure.[7] The primary 99 confirmed cases of evaluation of SARS-CoV-2 infection revealed that cytokine storm syndromes occurred in patients with severe COVID-19; 17 patients (17%) had ARDS, among whom 11 (11%) deteriorated within a brief period of your time and died of multiple organ failure. additionally, the numbers of total T-cells, CD4 + T-cells and CD8 + T-cells are decreased in patients with SARS-CoV-2 infection, and therefore the surviving T-cells are functionally exhausted,[8] suggesting a decreased immune function in SARS-CoV-2-infected patients. ARDS, decreased secondary infection and immune function further worsens respiratory failure.

4. THE VIRUS: CLASSIFICATION AND ORIGIN

SARS-CoV-2 may be a member of the family Coronaviridae and order Nidovirales. The family exist 2 subfamilies, Coronavirinae and Torovirinae and their branch of subfamily Coronavirinae are subdivided into four genera: (a) Alphacoronavirus contains the human coronavirus (HCoV)-229E and HCoVNL63; (b) Betacoronavirus includes HCoV-OC43, Severe Acute Respiratory Syndrome human coronavirus (SARS-HCoV), HCoV-HKU1, and Middle Eastern respiratory syndrome coronavirus (MERS-CoV); (c) Gammacoronavirus includes viruses of whales and birds and; (d) Deltacoronavirus includes viruses isolated from pigs and birds.[9] SARSCoV- 2 belongs to Betacoronavirus alongside two highly pathogenic viruses, SARSCoV and MERSCoV. SARS-CoV-2 is an enveloped and positivesense single-stranded RNA (+ssRNA) virus.[10]

SARS-CoV-2 is taken into account a completely unique human-infecting Betacoronavirus.[11] Phylogenetic analysis of the SARS-CoV-2 genome indicates that the virus is closely related (with 88% identity) to 2 bat-derived SARS-like coronaviruses collected in 2018 in eastern China (bat-SL-CoVZC45 and bat- SL-CoVZXC21) and genetically distinct from SARS-CoV (with about 79% similarity) and MERS-CoV.[11] Using the genome sequences of SARS-CoV-2, RaTG13, and SARS-CoV[11], an extra study found that the virus is more associated with BatCoV RaTG13, a bat coronavirus that was previously detected in Rhinolophus affinis from Yunnan, with 96.2% overall genome sequence identity.[12] A study found that no evidence of recombination events detected within the genome of SARS-CoV-2 from other viruses originating from bats like BatCoV RaTG13, SARS-CoV and SARSr-CoVs.[12] Altogether, these findings suggest that bats could be the first host of this virus.[11,12]

However, a study is required to illuminate whether any intermediate hosts have facilitated the transmission of the virus to humans. Bats are unlikely to be the animal that's directly liable for transmission of the virus to humans for several reasons[11]: (1) there have been various non-aquatic animals (including mammals) available for purchase in Huanan Seafood Wholesale Market but no bats were sold or found; SARS-CoV-2 and its close relatives, bat-SLCoVZC45 and bat-SL-CoVZXC21, have a comparatively long branch (sequence identity of but 90%), suggesting those viruses aren't direct ancestors of SARS-CoV-2; and in other coronaviruses where bat is that the natural reservoir like SARS-CoV and MERS-CoV, other animals have acted because the host (civets and possibly camels, respectively). Nevertheless,

bats don't always need an intermediary host to transmit viruses to humans. For instance, Nipah virus in Bangladesh is transmitted through bats.[13]

5. SYMPTOMS

Symptoms of COVID-19 infection are seen after infiltration within approximately 5 days. The amount from the onset of CCID-19 symptoms to death from 6 to 40 days and 14 days. This era depends on the patient's age and system. It had been shorter among patients 70-years-old compared with those younger than 70 years.[14] The foremost common symptoms of early COVID-19 are fever, weakness and weakness, but other symptoms include infection, fever, hemoptysis, diarrhea, dyspnea and lymphopathy. The clinical manifestations of a chest CT scan showed pneumonia, however, with rare cases like RNAaemia, increasing the danger of infection, diarrhea. Coronary failure, and therefore the danger of crystal opacities results in it. It's important to notice that there are similar symptoms between COVID-19 and first beta coronaviruses like fever, severity, dyspnea and bilateral opaque glass on the CT of the chest.[15] In some cases, the large-scale low-glass opacities were observed in sub pleural to both lung regions. This may be related and therefore the response to mediation are going to be impaired. Unfortunately, some subjects treated with inhaled interferon didn't show any clinical signs and seemed to be ill thanks to β-molar flexibility. In fact, COVID-19 showed variety of other clinical features including the introduction of the lower tract as seen by upper tract symptoms like rhinorrhea, sneezing, and throat pain. The death rate among the 25-year-olds for COVID-19 incidents was 2.84% from Jan25, 2020 and therefore the median age of death was seventy-five (range 48-9). Patients exposed to C0VIDD-19 showed intracellular leukocytes, infections, and increased pro-inflammatory plasma cytokines. One among the CCID-19 cases showed weakness within 5 days of pain caused by cough, hypertension, and blood heat of 39.0 °C

6. TRANSMISSION

The role of the Huanan Seafood Wholesale Market in multiplying this disease is unclear. Many initial COVID-19 cases were linked to the current market suggesting that SARS-CoV-2 was transmitted from animals to humans.[16] However, a genomic study has provided manifest that the virus was introduced from another, still unknown region, into the market where it spread faster, although human-to-human transmission may have occurred earlier. Clusters of infected relations and medical workers have confirmed the presence of person-to-person transmission.[17] After January 1, but 10% of patients had market exposure and over

70% patients had no exposure to the market.[10] Person-to-person transmission is assumed to occur among close contacts mainly via respiratory droplets produced when person has coughs or sneeze. Fomites could also be an outsized source of transmission, as SARS-CoV has been found to persist on surfaces up to 96 hours and other coronaviruses for up to 9 days.[18]

Whether or not there's asymptomatic transmission of disease is controversial. One initial study published on January 30 reported asymptomatic transmission,[19] but later it had been found that the researchers had indirectly interviewed the patient, who did actually have symptoms before transmitting disease. On February 21 a newer study published, also purported asymptomatic transmission,[20, 21] but any such study might be limited by errors in self-reported symptoms or contact with other cases and fomites.

Findings about disease characteristics are rapidly changing and subject to selection bias. A study indicated the mean time period was 5.2 days (95% confidence interval [95%CI]: 4.1 to 7.0). The time period has been found to be as long as 19 or 24 days,[21,22] although case definitions typically believe a 14 day window.[22]

The basic reproductive number (R0) has been estimated with varying results and interpretations. R0 measures the typical number of infections that would result from one infected individual during a fully susceptible population.[24] Studies from previous outbreaks found R0 to be 2.7 for SARS[23] and a couple of.4 for 2009 pandemic H1N1 influenza.[24] One study estimated that that basic reproductive number (R0) was 2.2 (95% CI: 1.4 to 3.9). However, later during a further analysis of 12 available studies found that R0 was 3.28.[23] Because R0 represents a mean value it's also important to think about the role of super spreaders, who could also be hugely liable for outbreaks within large clusters but who wouldn't largely influence the worth of R0.[25] During the acute phase of an epidemic or pre pandemic, R0 could also be unstable.[24]

In pregnancy, a study of nine pregnancy women who developed COVID-19 in late pregnancy suggested COVID-19 didn't cause substantially worse symptoms than in non-pregnant persons and there's no evidence for intrauterine infection caused by vertical transmission.[26]

In hospital surrounding, a study involving 138 COVID-19 suggested that hospital associated transmission of SARS-CoV-2 occurred in 41% of patients.[27] Moreover, another study on 425 patients found that the proportion of cases in health care workers gradually raised by

time.[24] These cases likely reflect exposure to a better concentration of virus from sustained contact in close quarters.

Outside China, as of Lincoln's Birthday, 2020, there have been 441 confirmed COVID-19 cases reported in 24 countries of which the primary imported case was reported in Thailand on January 13, 2020.[28] Among those countries, 11 countries have reported local transmission with the very best number of cases reported in Singapore with 47 confirmed cases.

7. EPIDEMIOLOGY

7.1. Source of Infection

Currently, COVID-19 patients are the most source of infection, and severe patients are considered to be more contagious than mild ones. Asymptomatically infected persons or patients in incubation who show no signs or symptoms of respiratory tract infection proven to shed infectious virus, can also be potential sources of infection. Additionally, samples taken from patients recovered from COVID-19 continuously show a positive RT-PCR test,[28] which has never been seen within the history of human infectious diseases. Especially, asymptomatically infected persons and patients in incubation or recovered from COVID-19 may pose serious challenges for disease prevention and control.

7.2. Spectrum of Infection

COVID-19 has been considered as a kind of self-limiting communicable disease, and most cases with mild symptoms can recover in 1–2 weeks. SARS-CoV-2 infection can cause five distinctive outcomes they are as follows: asymptomatically infected persons (1.2%); mild to medium cases (80.9%); severe cases (13.8%); critical case (4.7%); and death (2.3% altogether reported cases). the newest study indicates that the proportion of asymptomatic infection in children under 10-years old is as high as 15.8%.[29] Therefore, the proportion of asymptomatic infection should be further uncovered within the future.

7.3. Clinical Features

In the initial 41 sufferers, fever (98%), cough (76%), and myalgia or fatigue (44%) have been the foremost not unusual signs and symptoms. Less common signs have been sputum production (28%), headache (8%), hemoptysis (5%), and diarrhea (3%). Over half patients advanced dyspnea. The typical incubation length and primary duplicate number (R0) have been envisioned to be 5.2 d (95% CI: 4.1–7.0) and 2.2 (95% CI, 1.4–3.9), respectively.[30]

Biopsy showed ordinary or reduced (25%) white blood corpuscle remember and lymphopenia (65%). An entire of 98% of patients had bilateral involvement underneath chest CT.

Typical checkups of chest CT pictures of ICU sufferers on admission were bilateral more than one lobular and subsegmental regions of consolidation. The consultant chest CT findings of non-ICU sufferers confirmed bilateral ground-glass opacity and subsegmental areas of consolidation. Analysis of 1324 laboratory confirmed instances confirmed that fever (87.9%) and cough (67.7%) had been nevertheless the foremost common symptoms, even as diarrhea is rare. Lymphopenia was observed in 82.1% of sufferers admitted to ICU.[31]

7.4 Other Regions

According to the WHO data updated on March 23, 2020[32], 190 countries or areas have reported 332,218 laboratory confirmed cases including 14,510 deaths. The entire case-fatality rate of worldwide cases outside China is 4.5%. More attention should be paid to Italy, Spain, the USA, Germany, France, and Iran with more severe epidemic.[32] The highest five countries with the best cumulative confirmed cases within the world are China (24.6%), Italy (17.8%), USA (9.5%), Spain (8.6%), and Germany (7.5%). Higher case-fatality rates were found in Italy (9.3%), Iran (7.8%), and Spain (6.0%).[32]

7.5. Routes of Transmission

Currently, respiratory droplets and get in touch with transmission are considered to be the most transmission routes. Recent reports indicate that SARS-CoV-2 are often detected within the urine and stool of laboratory confirmed patients, implying a risk of fecal–oral transmission.[33] However, it's not yet certain that the consumption of virus-contaminated foods will cause infection and transmission. There's still no evidence that SARS-CoV-2 are often transmitted through aerosols or from mother to baby during pregnancy or childbirth.

7.6 Herd Susceptibility

As an emerging infectious disease, the population of all races and ages is usually susceptible. In China, 30~65-year-old persons account for 71.45% and kids under 10-years-old account for 0.35%.[34] Elderly people and persons with underlying basic disorders like asthma, diabetes, cardiovascular diseases, and cancer could also be more vulnerable to SARS-CoV-2. Smoking and obesity also are susceptible factors.[35]

8. DIAGNOSIS

8.1. Nucleic Acid Test

Viral diagnostics is one important a part of our armamentarium against COVID-19. After initial outbreak, diagnostic tests supported the detection of the viral sequence by RT-PCR or next generation sequencing platforms soon became available. Afterward, many biotechnology companies have successfully developed nucleic acid detection kits, and therefore the China Food and Drug Administration (CFDA) has urgently approved a batch of fluorescent quantitative kits and sequencing systems. The most concern associated with the macromolecule test is fake negatives. To resolve the matter of low detection efficiency, some improved rapid viral nucleic acid diagnostic tests are invented. Specifically, a nucleic acid test paper, which may be used for the rapid detection of SARS-CoV-2 with the eye observation within three minutes, has been successfully developed.[36]

8.2. Serologic Diagnosis

The acute serological responses has been shown with patients of SARS-CoV-2 infection. Combined with immune chromatography, colloidal gold, and other technologies, relevant detection reagents are developed rapidly.[37]

8.3. CRISPR/Cas13 System

The Cas13-based SHERLOCK (specific high-sensitivity enzymatic reporter unlocking) platform has been widely wont to encounter the Zika virus (ZIKV) and dengue virus (DENV) in patient samples at concentrations as low as 1 copy per microliter.[38] Currently, Zhang et al. released a CRISPR/Cas13-based SHERLOCK technology to detect SARS-CoV-2. The CRISPR/Cas13 system is still remains to be verified because it's not been tested on clinical samples from COVID-19 patients.

8.4 Imaging Technology

Chest radiograph or CT is a vital tool for COVID-19 diagnosis in clinical practice. The bulk of COVID-19 cases have similar features on CT images including bilateral distribution of patchy shadows and ground glass opacity. The good value of using the deep learning machine to extract radiological graphical features for COVID-19 diagnosis has been introduced.[39] Artificial intelligence (AI) can accurately interpret the CT images of the suspected cases of the new crown within 20 s, and therefore the accuracy rate of the analysis results reached 96%, greatly improving the diagnostic efficiency. This method is already being employed in clinical practice.

9. TREATMENT

9.1 Potential therapeutic agents

Lopinavir/ritonavir (LPV/RTV) are antiretroviral protease inhibitors utilized in combination for the treatment of human immunodeficiency virus (HIV) infection since 2000. RTV is employed alongside LPV to extend the LPV half-life via inhibition of cytochrome P450 and acts only as its pharmacokinetic enhancer.[40] LPV acts against the viral 3-chymotrypsin-like protease (3CLpro) and has been reported with promising results against SARS-CoV-1 and MERS-CoV. LOTUS China trial (Lopinavir Trial for Suppression of SARS-CoV-2 in China), which may be a randomized, controlled, open-label study, was initiated to analyze the efficacy and safety of oral LPV/RTV for SARS-CoV-2 infection in 199 adult patients hospitalized with severe COVID-19. Patients were randomized during a 1:1 ratio to receive either LPV/RTV (400 mg/100 mg) twice daily additionally to standard care (n = 99) or standard care alone (n = 100) for 14 days. They showed no difference in clinical improvement between the 2 groups (HR 1.24, 95% CI, 0.90-1.72). Mortality at 28 days was also identical to both groups (19.2% vs. 25.0%, 95% CI, -17.3-5.7). Here they concluded that no benefit was observed with LPV/RTV treatment beyond standard care in adult patients hospitalized with severe COVID-19.[41]

Remdesivir (RDV) may be a novel anti-viral drug developed by Gilead Sciences, originally for the treatment of Ebola virus disease and Marburg virus infections. RDV is an adenosine nucleotide analogue with broad-spectrum antiviral activity, which acts as an inhibitor of RNA-dependent RNA polymerases (RdRps). RDV inhibits viral replication through premature termination of RNA transcription and has been demonstrated to enhance pulmonary function and reduce lung viral loads in mice infected with MERS-CoV.[42] A recent in-vitro study indicated that RDV potently inhibited SARS-CoV-2 (EC50 = 0.77 uM) in Vero E6 cells. One case report by Holshue et al. described clinical improvement after RDV wont to treat the primary U.S. case of COVID-19. There are several randomized control trials are currently being conducted to judge the efficacy and safety of RDV in patients with COVID-19. Two phase III clinical trial trials initiated in China in February 2020, aimed to judge RDV in hospitalized adult patients with mild/moderate (NCT04252664) or severe (NCT04257656) COVID-19 (RDV 200 mg on day 1 and 100 mg once daily for 9 days vs. placebo).[43]

Preliminary results of those trials are expected to be announced at the end of April, 2020. Thereafter, three international phase III clinical trial trials were launched within the U.S. and Asia, including hospitalized adult patients with COVID-19 (RDV 200 mg on day 1 and 100 mg once daily up to a ten days course vs. placebo, NCT04280705), patients with moderate COVID-19 (RDV200 mg on day 1 and 100 mg once daily for 4 days vs. RDV 200 mg on day 1 and 100 mg once daily for 9 days, NCT04292730) and patients with severe COVID-19 (RDV 200 mg on day 1 and 100 mg once daily for 4 days vs. RDV 200 mg on day 1 and 100 mg once daily for 9 days, NCT04292899). Two of those trials are estimated to finish in May 2020.[43]

Favipiravir (FPV) is a guanine analogue that selectively inhibits RNA-established RNA polymerase (RdRP) of RNA viruses and has been permitted for the remedy of novel influenza given that 2014.[44] In vitro study showed inhibition of SARS-CoV-2 by way of favipiravir. Cai et al conducted an open label, controlled analysis, take a look at the outcomes of FPV (1600 mg twice daily on day 1 and 600 mg twice daily on days 2–14) as opposed to LPV/RTV (four hundred mg/a hundred mg twice every day) similarly to intetferon-α1b 60 mg twice day by day with the aid of inhalation for the remedy of COVID-19. The preliminary effects reported widespread clinical differences between FPV (35 patients) and LPV/RTV (45 patients) with median viral clearance time (4 days vs. 11 days, $p<0.001$) and chest image improvement rate (91.43% vs. 62.22%, $p=0.004$).[45]

Chloroquine (CQ) and hydroxychloroquine (HCQ) are aminoquinolines that have been used to deal with malaria and autoimmune sicknesses for over 50 years. These two tablets are susceptible diprotic bases and might increase the pH of the endosome, which prevents viral fusion into the cell. Recent in vitro studies stated CQ and HCQ against SARS-CoV-2 at a multiplicity of infection (MOI) of 0.01 with EC50 2.71 uM and 4.51 uM in Vero E6 cells, respectively.

Several medical trials are being conducted in China to evaluate the efficacy and protection of CQ and HCQ in COVID-19, one among which found out that chloroquine is advanced to the control group in scientific improvement, promoting virus-poor conversion and shortening the sickness course.[46]

Meanwhile, the preliminary look at in France evaluated the efficacy of HCQ in COVID-19 patients. There have been 2 organizations in this look at, 26 sufferers acquired HCQ (2

hundred mg tid for 10 days) and 16 patients acquired trendy of care. Six HCQ group patients lostfollow-up because of early cessation of treatment. Six patients in HCQ group obtained additional azithromycin (500 mg on day 1, 250 mg once daily for 4 days) to save you bacterial superinfection. The result confirmed the virologicaly cured charge became significantly better in HCQ combined with azithromycin-handled patients comparing to the HCQ best organization or manipulate group (100% vs. 57.1% vs. 12.5%, P = 0.001).[47] Although this study established promising consequences, similarly large trials are still needed to affirm the efficacy and protection of HCQ by myself or in mixture with azithromycin in COVID-19. In addition, HCQ as post-exposure prophylaxis / preemptive remedy for SARS-CoV-2 contamination is now below evaluation inside the U.S. (NCT04308668), using the regimen of 800 mg orally once, followed in 6 to eight hours by 600 mg, then 600mg once a day for four consecutive days.[48]

Interferon is a broad-spectrum antiviral agent via interaction with toll-like receptors and inhibit viral replication.[49] Interferon-alfa and beta each proven an anti-SARS-CoV-1 activity in vitro. Interferon-beta displayed potent activity in lowering MERS-CoV replication (EC50= 1.37–17 IU/mL). Ribavirin is a guanosine analogue with a broad-spectrum antiviral agent and used in mixture with interferon for the treatment of persistent hepatitis C. Ribavirin in mixture with LPV/RTV were used to deal with SARS-CoV-1 infection with lower risk of acute respiratory misery syndrome (ARDS) and dying than LPV/RTV alone. However, in a current in-vitro study, the result revealed that ribavirin required high effective concentration (EC50= 109.50 uM) against SARS-CoV-2.[50]

An ongoing trial comparing the efficacy and protection of interferon-alpha used in combination with ribavirin, LPV/RTV or ribavirin plus LPV/RTV for SARS-CoV-2 contamination in China (ChiCTR2000029387) is currently being conducted.

Interleukin (IL)-6 turned into stated to be launched extensively in SARS and MERS sufferers and can play a role within the pathogenesis of those diseases.[51] A recent file on the clinical capabilities of COVID-19 sufferers additionally found better plasma ranges of cytokines in ICU patients. Tocilizumab is a recombinant humanized monoclonal antibody which acts as IL-6 receptor antagonist, and is used for the remedy of rheumatoid arthritis. One observe in China recruited 21 sufferers with extreme or important COVID-19, 75% of sufferers had decreased their want for oxygen complement after receiving tocilizumab (400 mg once thru IV infusion; 3 sufferers had every other dose administered due to persisted fever inside 12

hours).[52] Nineteen patients discharged on average 13.5 ± 3.1 days hospitalization time after the treatment with tocilizumab. The U.S. FDA also accepted a segment III clinical trial for evaluating tocilizumab in hospitalized sufferers with intense COVID-19 pneumonia (NCT04320615). Meanwhile, sarilumab, which is another IL-6 receptor antagonist has also released phase II/III clinical trial to evaluate its efficacy in sufferers with extreme COVID-19 infection (NCT04315298).[53]

9.2 Other Antivirals

Considering their antiviral activity towards influenza, significant attention has been paid to oseltamivir and a lower level of baloxavir as potential effective treatments for COVID-19.[54] Oseltamivir is a neuraminidase inhibitor recommended for the treatment of influenza but has no reported in vitro action against SARS-CoV-2. The correlation between oseltamivir and baloxavir and COVID-19 is completely coincidental. The pandemic of COVID-19 in China initially taken place during peak influenza, resulting in a large proportion of patients receiving empiric oseltamivir treatment until the exploration of SARS-CoV-2 as the cause of COVID-19. Neither oseltamivir nor baloxavir has any role to play in the management of COVID-19 in cases where influenza was already ruled out or is not chronic.[54]

9.3 Convalescent Plasma therapy

Convalescent plasma from sufferers who have recovered from viral infections has been used as a treatment in preceding virus outbreaks which include SARS, avian influenza, and Ebola virus infection. Clinical trials to work out the security and efficacy of convalescent plasma that contains antibodies to SARS-CoV-2 in patients with COVID-19 have started. A scientific review of 5 studies found that convalescent plasma may reduce mortality in critically sick sufferers, have a beneficial impact on clinical symptoms, and decrease viral load.[55] In the US, the FDA is facilitating get entry to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the method of single patient emergency investigational new drug applications, and has issued guidance for its use. The FDA is encouraging patients who have recovered (complete resolution of symptoms for a minimum of 2 weeks before donation; a negative reverse-transcription polymerase chain reaction [RT-PCR] test isn't necessary to qualify for donation) to donate their plasma. There’s currently insufficient evidence to recommend either for or against the utilization of convalescent plasma for the treatment of COVID-19. The authors of a Cochrane rapid review were uncertain on whether convalescent plasma is an efficient

treatment for COVID-19. The finished studies were of poor quality, and therefore the results might be associated with natural progression of the disease or to other treatments the patient receives.[56]

9.4 Stem cell therapy

Stem cell therapy is being examined to treat patients with COVID-19 during clinical trials. It's thought that mesenchymal stem cells can reduce the pathological changes that occur within the lungs, and inhibit the cell mediated immune inflammatory response.[57]

9.5 Bacille Calmette-Guerin (BCG) vaccine

The BCG vaccine is being trialled in a few countries for the prevention of COVID-19, consisting of in healthcare workers. There is some proof that BCG vaccination prevents other breathing tract infections in youngsters and older human beings mediated by induction of innate immune memory. However, there may be no proof to support its use in COVID-19, and the WHO does now not advocate it for the prevention of COVID-19.[58]

9.6 Bemcentinib

An experimental small molecule that inhibits AXL kinase. Bemcentinib has previously proven a role in the treatment of cancer, but has additionally been pronounced to have antiviral role in preclinical models, consisting of interest towards SARS-CoV-2. It is the primary candidate to be selected as a part of the UK's Accelerating COVID-19 Research and Development (ACCORD) study. The multicentre, phase 2, adaptive randomization platform trial aims to evaluate the protection and efficacy of a multiple candidates.[59]

9.7 Vitamin C

Vitamin C supplementation has shown assurance in the treatment of viral infections. High-dose of vitamin C by intravenous route is being trialed in some centers for the treatment of severe COVID-19.[60]

9.8 Vitamin D

Supplementation of Vitamin D has been associated with a reduced risk of respiratory tract infections such as influenza in some studies. A small retrospective observational study (not peer reviewed) recommended a link between vitamin D insufficiency and COVID-19 severity. However, further research is needed. Vitamin D is being trialed in patients with COVID-19.[61] Vitamin D is being trialed in sufferers with COVID-19. However, there's no

proof to advice vitamin D for the prophylaxis or treatment of COVID-19 as yet. Public Health England recommends that people remember taking a vitamin D nutrition supplement for bone and muscle health due to a scarcity of solar exposure as a result of lockdown measures.[62]

9.9 Hyperbaric oxygen

Preliminary evidence shows that hyperbaric oxygen treatment has been favorably used to treat deteriorating, seriously hypoxaemic patients with extreme COVID-19. Clinical trials are presently recruiting.[63]

9.10 Nitric oxide

Studies indicate that nitric oxide may help to decreased tract infection by inactivating viruses and inhibiting their replication in epithelial cells.[64] The US Food and Drug Administration (USFDA) has approved an after investigational drug application for inhaled nitric oxide to be studied during a phase lll. This study is completed of up to 500 patients with COVID-19. Other studies are currently recruiting.

9.11 Corticosteroids

The justification for using corticosteroids is to reduce the inflammatory response of the host in the lungs, which can result to acute lung injury and syndrome of acute respiratory distress (ARDS). After all, adverse effects, including delayed viral clearance and increased risk of secondary infection, can overshadow the benefit. Since there is little clear evidence for corticosteroids in COVID-19, it is instructive to analyze results of other viral pneumonias.[65] Observational trials in patients with SARS and MERS documented no correlation with corticosteroids with increased survival, but demonstrated correlation with impaired respiratory and blood respiratory clearance and elevated complications, including hyperglycemia, paranoia, and avascular necrosis.[66] In comparison, a 2019 meta-analysis of 10 prospective trials of 6548 influenza pneumonia patients showed that corticosteroids were associated with an elevated risk of mortality (risk ratio [RR], 1.75 [95 percent CI, 1.3-2.4]; P < .001) and a 2-fold greater risk of secondary infections (RR, 1.98 [95 percent CI, 1.0-3.8]; P = .04).[67] Although the effectiveness of corticosteroids in ARDS and septic shocks is more widely debated, Russell and associates concluded that those more likely to benefit from corticosteroids are those with bacterial instead of viral infections. A reported systematic study of 201 patients with COVID-19 in China showed that treatment with methylprednisolone was associated with a reduced risk of mortality for those who acquired ARDS (23/50 [46 per cent]

with steroid vs 21/34 [62 per cent] without methylprednisolone; HR, 0.38 [95 per cent CI, 0.20-0.72]). Furthermore, the results indicated that bias and residual uncertainty between those who did or did not receive steroids could occur in this prospective study. Therefore, the risk of harm and lack of proven benefit to corticosteroids prevents routine use of corticosteroids in patients with COVID-19 outside of the RCT unless there is a concurrent compelling evidence, such as chronic obstructive pulmonary disease.[67]

9.12 Anticytokine or Immunomodulatory Agents

Monoclonal antibodies targeted against core inflammatory cytokines or other facets of the innate immune response are another possible category of adjunctive therapies for COVID-19. The reason for their use is that the underlying pathophysiology of severe organ injury in the lungs and other organs is triggered by an intensified immune response and release of cytokine, or "cytokine outbreak."[68] IL-6 tends to be a primary regulator of this dysregulated inflammation based on the early prospective study from China. Hence, monoclonal antibodies to IL-6 could potentially dampen this mechanism and enhance clinical results. Tocilizumab, an IL-6 receptor antagonist amonoclonal antibody, is a licensed FDA for the treatment of RA and cytokine release syndrome following chimeric T-cell receptor antigen therapy. In view of this knowledge, tocilizumab was used in a brief number of extreme COVID-19 cases with early positive outcomes. A study of 21 patients with COVID-19 found that 400 mg of tocilizumab was consistent with clinical improvement in 91 per cent of patients as evaluated by increased respiratory efficiency, rapid defervescence and positive discharge, with most patients providing just single dose. The lack of an analog category restricts the understanding of the actual drug effect and requires caution until more detailed evidence becomes available. Many RCTs of tocilizumab, alone or in combination, are ongoing in patients with COVID-19 with extreme pneumonia in China (NCT04310228, ChiCTR200002976) and are included in the latest Chinese National Guidelines for Care.[69]

10. CONCLUSION

SARS-CoV initially emerged in 2002 and eventually spread to 32 regions and countries, during which the world realized the MERS-CoV outbreak in 2012. Presently, SARS-CoV-2 has spread quickly across various countries, caused chronic disease and prolonged human-to - human transmission, making it a serious and serious health care threat. In addition, it is important to make better use of currently available data for therapeutic agents and improve drugs use approaches and prevent and regulate the transmission of SARS-CoV-2. It has been

verified that the SARS-CoV-2 genome sequence shares a strong identity with that of bat and human SARS-CoVs. A number of antiviral medications and methods of treatment for SARS-CoV infection have also been considered for the treatment and prevention of COVID-19.

The speed and volume of clinical trials launched to investigate potential therapies for COVID-19 highlight both the need and capability to produce high-quality evidence even in the middle of a pandemic.

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