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NOVEL THERAPEUTIC DRUG APPROACHES FOR COVID-19

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ABSTRACT-

This review study was conducted on the information of COVID-19 ethio-pathogenesis, clinical features, diagnosis, complication and Management, and we have compiled the most recent information on the methods and pharmacological agents used in the diagnosis and treatment of Coronavirus disease, including pharmacological approaches, fluid therapy, oxygen therapy, Adoptive T cell therapy, Mesenchymal stromal cell therapy, Nano medicine approaches in COVID-19 and Vaccination approaches.

Key words- Novel, Vaccinations, Covid 19, Therapeutic approaches .

AIMS AND OBJECTIVES:

This review paper aimed to compile the up-to-date information about the methods and pharmacological agents used in the diagnosis and treatment of coronavirus disease 2019 (COVID-19) and examine the methods used in the treatment of COVID-19 in patients in the intensive care unit by reviewing the treatment guidelines published by national health authorities worldwide.

We have gonethrough various published papers on the novel coronavirus (severe acute respiratory syndrome [SARS] coronavirus [SARS-CoV-2]) till date. The results of the study identified serological and molecular methods (e.g., real-time reverse transcriptase polymerase chain reaction) used by physicians for diagnosing COVID-19 and identified thorax computed tomography along with other imaging methods used for determining the severity of the disease. many of the agents used and studied for the treatment were drugs previously used for the treatment of Middle East respiratory syndrome and SARS. COVID-19 has higher levels of transmissibility and pandemic risk. The available information revealed that, given the size and scope of the pandemic, to date, there

has been no scientifically proven effective medicine and few vaccines have approved against SARS-CoV-2. There is also an urgent need for further research for finding an effective medicine for COVID-19 to manage the occurrence of an outbreak in future and manage such public health emergency of this magnitude in both short and long terms.

INTRODUCTION

Coronavirus(CoV) is a large family of positive-sense, single-stranded RiboNuclicAcid(RNA) viruses that belong to the Nidovirales order. The order includes Roniviridae, Arteriviridae, and Coronaviridae families. The Coronaviridae family is subdivided into Torovirinae and Coronavirinae subfamilies. Coronavirinae is further subclassified into alpha, beta, gamma and deltaCoronavirus[1]. A major difference from common flu virus to Corona virus disease(COVID-19) is that the latter one originates from including common cold to severe syndrome like middle east respiratory(MERS) and severe acute respiratory(SARS). COVID virus is a new strain that is first discovered in humans. It is a zoonosis type of infectious disease that spreads from nonhumans to humans. Even several known corona viruses are circulating in animals that are not yet infected to humans[2].In the month of December 2019, a novel human coronavirus outbreak started in Wuhan, Hubei Province, China and then subsequently spread to dozens of other countries becoming a global pandemic[3].On January 22, 2020, novel CoV has been declared tobe originated from wild bats and belonged to Group 2 of beta-coronavirus that contains Severe Acute Respiratory Syndrome Associated Coronavirus(SARS-CoV). Although COVID-19 and SARS-CoV belong to the same beta coronavirüs subgroup, similarity at genome level is only 70% and the novel group has been found to show genetic differences from SARS-CoV[4]. There are four classifications found in COVID-19: Alpha, Beta, Delta and Gamma Corona viruses, among them, beta Corona virus divides further into five subgenera. In general this virus contains almost 29000 nucleotides encoding for 9860 amino acids from a single strandedRibo Nucleic Acid(RNA). This genomic structure is organized in a positive sense single stranded RNA(+ssRNA) that can serve as a messenger RNA translates in to protein in the host[5]. There are a number of clinical trials ongoing to study the efficacy of older drugs to be repurposed for use against SARS-CoV-2. One such medication includes the anti malarial Chloroquine(CQ) which was recently cited as a potential treatment to shorten SARS-CoV-2 disease course, mitigate inflammatory responses to infection, inhibit the exacerbation of pneumonia, improve lung imaging findings, and promote a virus negative conversion[3,6,7].CoVs are a diverse family of viruses that interact at multiple levels with components of host cells taking this advantage of some of the cellular machineries for replication and proliferation. Various are known about the molecular biology of CoVs but more information is needed to learn. For example, many of the nonstructural and accessory proteins encoded by these viruses remain uncharacterized with no known function, and it will be important to identify mechanisms of action for these proteins as well as defining their role in viral replication and pathogenesis. Developing technology is going to be getting important insight about structure of CoVs protein to define the mechanism of how protein cause disease and understanding the protein-protein and protein RNA interaction will significantly improve our ability to design vaccines. In the meantime, molecular modelling methods provide important solutions to the struggle[8]

SOURCES AND ROUTE OF TRANSMISSION OF COVID-19:

In recent studies, it hasbeen observed that the novel virus causing epidemics coincides with the CoV isolated in bats. Presence of wild animal trade in Huanan Seafoods Market where the first cases appeared, supports this finding[4,9].Based on data from the first cases in Wuhan and investigations conducted by the China CDC and local CDCs, the incubation time could be generally within 3 to 7 days and up to 2 weeks as the longest time from infection to symptoms was 12.5 days (95% CI, 9.2 to 18)[10]. This data also showed that this novel epidemic doubled about every seven days, whereas the basic reproduction number (R0 - R naught) is 2.2. In other words, on average, each patient transmits the infection to an additional 2.2 individuals. Of note, estimations of the R0 of the SARS-CoV epidemic in 2002-2003 were approximately 3[11].Often, the human-to-human transmission occurs with close contact. The transmission primarily occurs when an infected person sneezes and through the respiratory droplets produced just as the spread of influenza and other respiratory pathogens. These droplets can settle in the mouth or nasal mucosa and lungs of people with inhaled air[12]. Currently, it is clear that a person can be infected by COVID-19 by touching an infected surface or object and then touching their mouth, nose, or possibly eyes.

PATHOPHYSIOLOGY:

Coronaviruses encode five structural proteins in their genomes(mentioned in fig.1). These are the

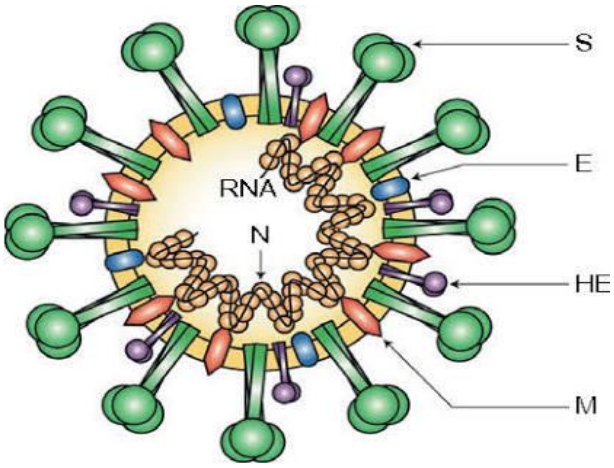

Fig.1.Coronavirusvirion structure shown with structural proteins N: Nucleocapsid protein; S: Spike protein,M: Membranprotein, HE: Hemagglutinin-Esterase andE: Envelope protein

Spike(S), Membrane(M), Envelope(E) glycoproteins, Hemagglutinin Esterase(HE) andNucleocapsid(N) protein.All envelope proteins and N protein is present in all virions but HE is only present in some beta coronaviruses[13]. S Glycoproteins are located outside the virion and give the virion the typical shape. The S proteins form homotrimers, which allow the formation of sun-like morphologies that give the name of Coronaviruses [14,15,16].The M protein plays a key role in regenerating virions in the cell. N protein forms a complex by binding to genomic RNA and M protein triggers the formation of interacting virions in this endoplasmic reticulum-Golgi apparatus intermediate compartment (ERGIC) with this complex [17,18,19].

The N proteins are phosphoproteins that are capable of binding to helix and have flexible structure of viral genomic RNA. It plays an important role in virion structure, replication and transcription of coronaviruses, because the N protein localizes in both the replication/ transcriptional region of the coronaviruses and the ERGIC region where the virus is collected [20][21].

The coronavirus spike contains three segments: a large ectodomain, a single-pass transmembrane anchor and a short intracellular tail. The ectodomain consists of a receptor-binding subunit S1 and a membrane-fusion subunit S2. Electron microscopy studies revealed that the spike is a clove-shaped trimer with three S1 heads and a trimeric S2 stalk[30-33]. During virus entry, S1 binds to a receptor on the host cell surface for viral attachment and S2 fuses the host and viral membranes, allowing viral genomes to enter host cells. Receptor binding and membrane fusion are the initial and critical steps in the coronavirus infection cycle; they also serve as primary targets for human inventions[34]. The life cycle of the virus is deplected in fig.2.

The replication of coronaviruses occurs in host cell cytoplasm. The viruses primarily bind to the receptor on the cell surface via the spike (S) protein. When S protein is bound to the receptor, a conformational structure occurs in the structure and the process of entry into the virus cell begin. This process with endocytosis is dependant of pH through the receptor. After entering the cytoplasm, the virus particle releases the RNA genome. This genome is a single-stranded, non-segmented RNA virus with the largest known RNA genome(gRNA), which is approximately 26-32 kb The genome consists of seven genes. It is organized into 5'non-structural protein coding regions comprising the replicase genes (gene 1), which are two-thirds of the genome, and 3' structural and nonessential accessory protein coding regions comprising the gene 2-7. Thereplicase gene 1 products are encoded two very large open reading frames ORF1a and 1b, which are translated into two large polypeptides pp1a and pp1b, which are synthesized directly from the 5' two-thirds of the genomic RNA of CoV. After synthesis of these proteins, consisting of 16 units, non-structural protein (nsp1to nsp16) is converted with the contribution of viral proteases pp1a and pp1b. These 16 proteins form Double-Membrane Vesicles(DMV). At the same time, this DMV is virus Replication and Transcription Complex (RTC). These nsp proteins, especially non-structural protein3 (nsp3), have an important role in the virion structure, the replication and transcription of CoV.

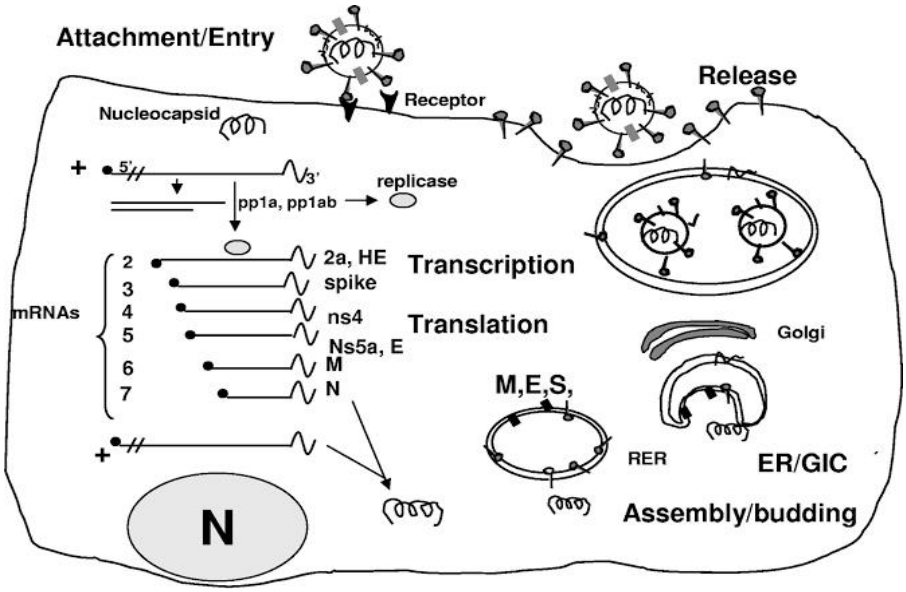

Fig.2: Coronavirus' life cycle [35]

CLINICAL FEATURES

COVID-19 manifests with a wide clinical spectrum ranging from asymptomatic patients to septic shock and multi-organ dysfunction[36]. COVID-19 is classified based on the severity of the presentation[36]. The disease may be classified into mild, moderate, severe and critical[38]. The most common symptoms of patients include fever (98.6%), fatigue (69.6%), dry cough, anddiarrhea[38]Patients with mild illness may present with upper respiratorytract viral infection like dry cough, mild fever, nasal congestion, sore throat, head ache, muscle pain and malaise. Among infected cases majority (81)% are mild[36]Patients with severe disease present withsevere pneumonia. Acute respiratory distress syndrome(ARDS) and septic shock[36]. Clinical presentations include the presence of severe dyspnea, tachypnea (respiratory rate > 30/minute), respiratory distress, SpO2 ≤ 93%, PaO2/FiO2 < 300, and/or greater than 50% lung infiltrates within 24 to 48 hours[36]. Signs of organ dysfunction include severe dyspnea, low oxygen saturation, reduced urine output, tachycardia, hypotension, cold extremities, skin mottling, and altered mentation[36].

DIAGNOSIS

The WHO recommends collecting samples from both the upper and lower respiratory tracts. This can be achieved through expectorated sputum, bronchoalveolar lavage or endotrachialaspirate,These samples are then assessed for viral RNA using polymerase chain reaction(PCR)[36].The symptoms of the early stages of the disease are nonspecific. Differential diagnosis should include the possibility of a wide range of infectious and non-infectious (e.g.vasculitis and dermatomyositis) common respiratory disorders like Adenovirus, Influenza, Human metapneumovirus(HmPV), Parainfluenza, Respiratory syncytial virus (RSV), Rhinovirus(common cold)For suspected cases, rapid antigen detection and other investigations should be adopted for evaluating common respiratory pathogens and non-infectious conditions[37].In addition to the clinical and ventilatory criteria, chest imaging modalities such as chest X-ray, computed tomography(CT) scan and lung ultrasound can be used to support the diagnosis. Laboratory evidence of other homeostatic dysregulation includes acidosis, high lactate, hyperbilirubinemia, thrombocytopenia, and evidence of coagulopathy[36]. Patients with septic shock are persistently hypotensive despite volume resuscitation. They may also have an accompanying serum lactate level of >2 mmol/L.

COMPLICATIONS AND FATALITY RATE:

Severe pneumonia, Acute respiratory distress syndrome(ARDS), sepsis or septic shock[36]. Even in severe forms of the disease, fever can be absent or moderate. In addition, 5% of patients can develop a critical disease with features of respiratory failure, RNAaemia, cardiac injury, septic shock or multiple organ dysfunction [36,38]. Data from the Chinese CDC suggest that the case fatality rate for critical patients is 49%[36]. Patients with pre-existing co-morbidities have a higher case fatality rate. These co-morbidities include diabetes (7.3%), respiratory disease(6.5%), cardiovascular disease(10.5%), hypertension(6%) and malignancy (5.6%). Patients without co-morbidities have a lower case fatality rate(0.9%)[38].

PREVENTIVE MEASURES:

Preventive measures must focus on optimizing infection control protocols, self-isolation, and patient isolation during the provision of clinical care. The WHO has advised against close contact with patients, farm animals, and wildPrevention[36] The WHO and other organizations have issued the following general recommendations:

- Avoid close contact with subjects suffering from acute respiratory infections.
- Wash your hands frequently, especially after contact with infected people or their environment.
- Avoid unprotected contact with farm or wild animals.
- People with symptoms of acute airway infection should keep their distance, cover coughs or sneezes with disposable tissues or clothes and wash their hands.
- Strengthen, in particular, in emergency medicine departments, the application of strict hygiene measures for the prevention and control of infections.
- Individuals who areimmuno-compromised, co-morbid conditions, using corticosteroids and organ transplanted should avoid public gatherings[37]

MANAGEMENT

Isolation remains the most effective measure for containment of COVID-19. No specific antiviral medication or vaccine is currently available[36]. Therefore, the treatment of COVID-19 includes symptomatic care and oxygen therapy. Patients with mild infections require early supportive management. This can be achieved with the use of acetaminophen, external cooling, oxygen therapy, nutritional supplements and sometimes anti-bacterial therapy[38]. Critically ill patients require high flow oxygen, extracorporeal membrane oxygenation(ECMO), glucocorticoid therapy and convalescent plasma[38]. The administration of systemic corticosteroids is not recommended to treat Acute respirato distress Syndrome[38].Therapeutically, aerosol administration of alpha-interferon (5 million units twicedaily), chloroquine phosphate and lopinavir/ritonavir have been suggested[36]. Other suggested anti-viralsinclude ribavirin and abidor.Preclinical studies suggested that remdesivir(GS5734)an inhibitor of RNA polymerase with in vitro activity against multiple RNA viruses, including Ebola could be effective for both prophylaxis and therapy of corona infections.[39].Treatment of septic shock requires hemodynamic support with theadministration of vasopressors. Organ function support is necessary for patients with multiple organ dysfunction[36].

NOVEL COVID-19 PHARMACOLOGICAL TREATMENTS AND CLINICAL RESEARCH

There is no disease-specific treatment scientifically proven to be effective treating COVID-19 [40]. However, many randomised controlled trials are underway regarding the use of some potential drugs in therapy [59]. Many of these published studies relate to the potential therapeutic effects of drugs that were previously used to treat Middle East respiratory syndrome (MERS) and SARS. Some of these studies are expected to be completed in the coming months [40]. This review provides information about some popular agents, some of which have not yet been proven in the treatment of COVID-19, some of which are used by some centres and some that are recommended by local authorities[41].

HYDROXYCHLOROQUINE/CHLOROQUINE:

Hydroxychloroquine and chloroquine are used in the treatment of malaria and autoimmune diseases. Despite positive in vitro data on the antiviral activity of chloroquine and hydroxychloroquine, there is insufficient evidence to publish a recommendation on their use in the treatment of COVID-19 [42]. The U.S. Food and Drug Administration (FDA) issued a warning to caution against using hydroxychloroquine or chloroquine for COVID-19 outside the hospital setting or in clinical trials owing to the risk of serious cardiac rhythm problems [42]. The efficacy of hydroxychloroquine and chloroquine treatment in COVID-19 has not yet been demonstrated in well-designed clinical trials [43].

REMDESIVIR

Remdesivir is a broad-spectrum antiviral agent against RNA viruses. It is included in the beginning viral RNA chains, causing early termination of the virus. It was used clinically in the treatment of Ebola virus infection. In vitro studies of remdesivir have shown effective inhibition against SARSCoV-2 [44]. Besides the in vitro studies, there are several ongoing clinical trials for COVID-19 therapy using different doses of remdesivir. Some of these studies are related to the safety and antiviral activity of remdesivir in patients with severe COVID-19 [45]. Remdesivir is currently under investigation for use in the treatment of COVID-19. Remdesivir is one of the promising potential treatments for COVID-19 [44]

FAVIPIRAVIR

Favipiravir is an RNA polymerase inhibitor licensed in Japan. It is an antiviral drug currently used in Japan to treat influenza. It has a broad spectrum of anti-RNA virus activity in vitro. In a recent study, in vitro antiviral activity of favipiravir against SARS-CoV-2 has also been demonstrated [46]. The recommended treatment dose is 1,200–1,800 mg twice daily, followed by a loading dose of 2,400–3,000 mg twice daily [46]. An alternative dosage schedule is 600 mg twice daily for 4 days, followed by an oral loading dose of 1,600 mg twice daily [47].

LOPINAVIR/RITONAVIR

Lopinavir is an antiretroviral protease inhibitor that inhibits the protease activity of the coronavirus. It is used in combination with ritonavir to provide adequate lopinavir exposure in the treatment of human immunodeficiency virus infection. It was found that lopinavir shows in vitro activity against SARS and MERS [48]. Lopinavir/ritonavir is considered a potential agent for the treatment of COVID-19 in WHO's list of research priorities of therapeutic agents [49]. There are some ongoing clinical trials, but there is insufficient evidence to publish a recommendation on the use of lopinavir/ritonavir in critically ill patients with COVID-19 [50].The recommended treatment dose for lopinavir/ritonavir is 400 mg/100 mg twice daily for up to 10–14 days. Lopinavir/ritonavir was associated with some common side effects such as gastrointestinal intolerance, nausea, vomiting and diarrhoea. Less common but more dangerous side effects include pancreatitis, hepatotoxicity and cardiac conduction abnormalities. Lopinavir/ritonavir is a potent cytochrome P3A4 inhibitor and can interact with many drugs commonly used in critically ill patients, such as apixaban, betrixaban, clopidogrel and vitamin K antagonists. [47]

RIBAVIRIN

Ribavirin is an RNA polymerase inhibitor that inhibits the viral RNA-dependent RNA polymerase. Its antiviral properties against fighting MERS and SARS are well known, but for these findings to come into effect, it should be used in high doses, especially in the treatment of COVID-19. Ribavirin can cause severe haematological and liver toxicity. Haematological toxicity effect is dose dependent, so most of the ongoing ribavirin studies include combination therapy with recombinant interferon. Because the side effects such as haemolyticanaemia and transaminase elevation are frequently seen in the therapeutic dose, the use of combining therapies is thought to be better in terms of clinical efficacy rather than individual drugs [47]. Inaddition, ribavirin is a teratogenic drug; its use is contraindicated in patients who are pregnant. There is insufficient evidence to publish a recommendation on the use of ribavirin in the treatment of COVID-19 [47]. Oseltamivir It is a neuraminidase inhibitor used in the treatment of influenza. Oseltamivir is not recommended for the treatment of COVID-19 [47]. Oseltamivir should be given to patients with clinical findings that are compatible with influenza, as well as to patients who are positive for the influenza diagnostic test. Umifenovir It is an antiviral drug used in influenza treatment in Russia and China, but it is not approved for use in other countries. Umifenovir is thought to inhibit the viral entry into target cells and stimulate the immune response. A limited number of studies have been described from China, but there is no sufficient evidence to publish a recommendation on COVID-19 treatment yet [51].

AZITHROMYCIN

Azithromycin is one of the macrolide antibiotics. It inhibits RNA-dependent protein synthesis, which causes an antibacterial effect. Although a non-randomised study [52] with a small number of participants found that the combination of hydroxychloroquine and azithromycin in patients with COVID-19 is significantly related to viral load reduction or loss, there is insufficient evidence about the therapeutic effect of azithromycin on COVID-19. [51]. Some local guidelines recommend the combination of hydroxychloroquine and azithromycin in patients with critical illness in COVID-19. The recommended treatment dose for azithromycin is a 500- mg loading dose once daily, followed by a 250-mg dose once daily for 4 days [49]. Both azithromycin and hydroxychloroquine prolong the QT interval and may be prone to ventricular tachycardia. [52].

ANTIMICROBIALS/ANTIBACTERIAL AGENTS

If the diagnosis of COVID-19 is uncertain or if a co-infection is suspected, antibiotics showing activity against both typical and atypical respiratory pathogens can be added to the treatment for community-acquired pneumonia [53]. Because the etiological agents that cause pneumonia vary according to the country where the patients live, the origin of the patient should be taken into account during the selection of the antibiotic type. Empirical antimicrobial/antibacterial agents are recommended for COVID-19 and mechanically ventilated patients with respiratory failure [53].

TOCILIZUMAB

The underlying pathophysiology of organ damage in patients with severe COVID-19 infection is thought to be due to an increased immune response and cytokine release (cytokine storm). IL-6 is thought to play a key role in irregular inflammation in the cytokine storm. Tocilizumab is a recombinant monoclonal antibody. It functions as an IL-6 receptor antagonist. Tocilizumab is already approved for the treatment of cytokine release syndrome and rheumatoid arthritis. Studies on the use of tocilizumab in COVID-19 infections include Italian anecdotes and case series from China. Some randomised controlled trials on the use of tocilizumab in patients with COVID-19 are still ongoing. The China diagnosis and treatment guideline for COVID-19 recommended a single intravenous dose of 4–8 mg kg–1 (maximum 400 mg) [54]. Tocilizumab may increase the risk of developing other respiratory infections and tuberculosis as well. Acetaminophen It is well known that most patients with COVID-19 will develop fever during hospitalisation. Acetaminophen remains the best option for the treatment of fever owing to the unproven reports on ibuprofen and non-steroidal anti-inflammatory drugs but confusing the preliminary reports [54].

CORTICOSTEROIDS

There is not yet sufficient evidence that corticosteroids are useful in COVID-19 treatment. Therefore, the recommendations are based on indirect evidence from critically ill patients, especially patients with ARDS. The purpose of using corticosteroids in patients with ARDS is to reduce the host inflammatory response in the lungs. However, the negative side effects of corticosteroids may outweigh this benefit. Common side effects of corticosteroids include respiratory and blood delay of viral clearance, hyperglycaemia, avascular necrosis, and psychosis. Current evidence has reported that low-dose corticosteroid therapy does not change mortality rates but

shortens the length of stay in the ICU and hospital [50]. Corticosteroids are not recommended for routine use in patients with acute respiratory failure with COVID-19 [50]. Patients with special conditions, such as the presence of septic shock or refractory shock and exacerbation of chronic obstructive pulmonary disease, will have alternative clinical indications suitable for the use of corticosteroids. Low-dose corticosteroid therapy is recommended for refractory shock. The recommended treatment dose is 200 mg day–1 as an infusion or intermittent doses [50]. Convalescent plasma It is believed that administration of plasma, serum or immunoglobulin concentrates derived from the recovered patientsmay be effective in the treatment of COVID-19. Application of convalescent plasma to patients for therapeutic purposes can be defined as passive immune transfer. This potential adjunctive therapy was used in SARS and MERS. On April 13, 2020, the FDA issued guidance on the application of convalescent plasma collected from the individuals recovering from COVID-19 [55].

FLUID THERAPY, HEMODYNAMIC SUPPORT AND VASO-ACTIVE AGENTS

Because there is no direct evidence for patients with COVID-19 and septic shock, the recommendations are generally based on indirect evidence from critical patients. Recommendations to evaluate fluid responsiveness offer the use of dynamic parameters such as skin temperature, capillary refill time and/or serum lactate measurement. It should be noted that high lactate levels may also be due to mitochondrial dysfunction, liver failure, beta-agonists, mesenteric ischaemia or epinephrine. Considering that fluid resuscitation is necessary in patients with COVID-19 and septic shock, conservative fluid therapy is recommended by guides first. The recommended fluid type for acute resuscitation of adults with COVID-19 is primarily crystalloids. Hydroxyethyl starches, gelatines, dextrans and albumin are not recommended [47]. The vaso-active agent recommended for COVID-19 and adult patients with septic shock is norepinephrine. If it is unavailable, vasopressin may be an alternative. Dopamine is no longer preferred as an alternative. If the target MAP cannot be achieved only with norepinephrine, vasopressin can be added as a second-line agent. Despite fluid resuscitation and norepinephrine administration, if cardiac dysfunction and persistent hypoperfusion still exist, it is recommended to add dobutamine instead of increasing the norepinephrine dose[50]. Despite fluid resuscitation, vasopressor support should be given in the presence of a septic shock or severe hypotension. Target MAP should be set to 65 mmHg [49].

OXYGEN THERAPY, NON-INVASIVE SUPPORT AND INVASIVE MECHANICAL VENTILATION

Lung damage seen in patients with COVID-19 has unique histopathological features: cellular fibromyxoid exudates and bilateral widespread alveolar damage, desquamation of pneumocytes, pulmonary oedema and hyaline membrane formation. Lung disease associated with COVID-19 can show different dynamics than typical ARDS; some patients show significantly higher compliance than typical for shunt fractions. Despite this high compliance, clinically severe hypoxemia is observed. This can be explained by the loss of lung perifusion regulation and hypoxic vasoconstriction. Considering all these aspects, some researchers have proposed a new ventilation strategy-buying time with minimal additional damage-which is the lowest possible positive end-expiratory pressure (PEEP) and gentle ventilation [56]. The recommended threshold value of peripheral oxygen saturation to initiate oxygen supplementation is specified as 90%. Target SpO2 is not higher than 96%. Despite conventional oxygen therapy, if acute hypoxemic respiratory failure is still present, high-flow nasal cannula (HFNC) is recommended instead of non-invasive positive pressure ventilation (NIPPV) [56] If HFNC is unavailable and there is no immediate indication for endotracheal intubation, NIPPV can be used with close monitoring. There is not yet enough data to make a recommendation on the use of the helmet NIPPV compared with the mask NIPPV (20). In invasive mechanical ventilation, it is recommended to use low tidal volume (Vt) ventilation (Vt 4-8 mL kg–1 estimated body weight); the purpose of the low Vt is to minimise the risk of ventilator-induced lung damage. For mechanically ventilated adults with COVID-19 and ARDS, it is recommended that the target plateau pressures be <30cm. However, some aspects remain uncertain about PEEP. There are 2 different suggestions about target PEEP values. Although some researchers suggest high values as in typical ARDSs, some recent studies have suggested that high PEEP values may increase the lung damage [57].

DEVELOPMENT OF SARS-COV-2 PREVENTIVE VACCINES

mRNA-1273 (Moderna TX, Inc.) is an mRNA vaccine that is composed of synthetic mRNA expressing the prefusion-stabilized SARS-CoV-2 spike trimer (mRNA1273) [58]. The efficacy and immunogenicity of Moderna vaccine investigated in a phase III clinical trial (NCT04470427). Moderna has announced its primary efficacy analysis (95%) and recently applied to the FDA (USA) for emergency use authorization. & ChAdOx1 nCOV-19 is another vaccine under evaluation in phase II/III clinical trials. This vaccine has been developed by Oxford University and produced due to the technology in which an adeno-viral vector encodes SARSCoV-2 S protein (NCT04400838) [59][60]. The pre-clinical investigations showed that ChAdOx1 nCOV-19 was immunogenic in vaccinated mice and rhesus macaques and triggered robust humoral and cell-mediated responses [61][62]. Its safety and immunogenicity were evaluated in a phase II/III trial in a prime-boost regimen in young and old adults. In 14 days after receiving the boost dose, > 99% of participants had neutralizing antibodies [63]. & BNT162b2 is a COVID-19 RNA vaccine candidate that has been announced by BioNTech/Pfizer. This vaccine encodes the receptor-binding domain (RBD) of theSARS-CoV-2 spike protein. Data from a phase III clinical trial showed vaccine efficiency over 95% [64]. &CoronaVac is inactivated SARS-CoV-2 manufactured by Sinovac Life Sciences (Beijing, China). Its safety, tolerability, and immunogenicity have been approved in healthy adults aged 18–59 years in a phase I/II clinical trial [65]; and now it is under investigation in a phase III clinical trial (NCT04582344). & Gam-COVID-Vac (Sputnik V) is a combined vector vaccine that consists of recombinant adenovirus type 26 (rAd26) and type 5 (rAd5) vectors. They carry the spike glycoprotein gene. Gam-COVID-Vac has been developed by Gamaleya National Research Center for Epidemiology and Microbiology (Moscow, Russia) [66]. Its safety and immunogenicity was approved in two formulations in a phase I/II clinical trial [82]. And now, the safety and efficiency of this vaccine is under assessment in a phase III clinical trial (NCT04530396). & Using Ad5 vector to carry the spike glycoprotein gene, CanSino Biologics Inc. (China) has developed a recombinant novel coronavirus vaccine which safety and efficiency has been being evaluated in a phase III clinical trial (NCT04526990). The progress in vaccine development is critically discussed in the following recently published reviews in detail [67][68].

MESENCHYMAL STROMAL CELLS IN COVID-19 TREATMENT

Due to the immunomodulatory effects of MSCs [69][70], clinical trials using MSCs from various sources including the umbilical cord, adipose tissue, and bone marrow have been registered for the treatment of acute respiratory distress syndrome (ARDS) caused by COVID-19 (NCT04341610, NCT04366063). Primary results showed that this strategy was safe and effective. The MSC therapyimproved lung function, downregulated inflammatory cytokines, increased anti-inflammatory ones, and decreased mortality rate [71][72][73]. MSCs exert their antiinflammatory properties through direct cell-cell contact, paracrine effects, and their extracellular vesicles such as exosomes [74][75]. It seems that application of MSCs and their exosomes could be a promising approach for the management of respiratory complications in COVID-19 [75].

ADOPTIVE T CELLS IN COVID-19 TREATMENT

Some studies reported lymphopenia and functional exhaustion due to the over-activation of the immune system during infection [76]. COVID-19 specific T and TCD8+ cells play an important role in the virus clearance by producing inflammatory cytokines and their cytotoxicity effects [77]. Moreover, virus-specific memory T cells were isolated from the serum of the recovered patients [78][79][80]. Based on this evidence, recent clinical trials designed and used the adoptive T cells in severe COVID-19 patients. Using this treatment protocol, HLA-matched T cells from fully recovered patients were transfused into newly infected individuals. This approach may help patients who are at the risk of requiring mechanical ventilation (NCT04457726, NCT04401410, and NCT04406064).

EXOSOMES DERIVED FROM ADOPTIVE T CELLS IN COVID-19 TREATMENT

In addition, another clinical trial used COVID-19-specific T cell-derived exosomes (CSTC-Exo) for the treatment of early infected patients in order to boost the IFN-γ production. Compared to the cells, CSTC-Exo does not need HLA-matching, and their administration route is an aerosol inhalation (NCT04389385). If it meets the endpoints, it could be a suitable alternative as an off-the-shelf product. & Since regulatory T cells (Treg) are known as major antiinflammatory T cell subsets, Treg cell therapy may be a novel regenerative and anti-inflammatory treatment strategy for COVID-19. Infusion of cord blood-derived Treg cells (CK0802) may improve the ARDS symptoms in these patients (NCT04468971). RAPA-501-ALLO is a hybrid Treg/Th2 off-the-shelf reprogrammed Treg cell product produced by the healthy donors. RAPA-501- ALLO could have a dual advantage by modulating Th1 and Th17 subpopulations and inhibiting the massive production of inflammatory cytokines, as well as regenerating the damaged alveolar tissues [81]. This product may be a useful therapeutic option for the treatment of severe COVID-19 (NCT04482699).NK cells in COVID-19 treatment & NK cells are an essential part of the innate immune system and play an important role in mediating virus-induced immune responses. So, interventional therapies using NK cells have been developed for the COVID-19 treatment. Recently, the adoptive transfer of allogenic NK cells has been developed to boost the antiviral immune responses and clearance of the infected cells in COVID-19 patients (NCT04344548, NCT04280224). NKG2DACE2 CAR-NK is an off-the-shelf product that has been investigated in a phase I/II clinical trial (NCT04324996). These cells simultaneously target ACE2 (the main receptor for SARS-CoV-2) [82] and NKG2D on the infected cells and removed them. Therefore, they could inhibit the SARS-CoV-2 infection through ACE2 blockade.

MONOCLONAL ANTIBODIES IN COVID-19 TREATMENT

It has been shown that monoclonal antibodies could be a promising treatment approach for COVID-19. Monoclonal antibodies against inflammatory cytokines such as anti-IL-1 receptor, IL-6 antagonist, anti-TNF-α,anti-GM-CSF, anti-IFN-γ, and C5a inhibitor have been studied in different clinical trials. Over 60 clinical trials have been registered to evaluate the treatment efficiency of Tocilizumab and Olokizumab (anti-IL-6 mAbs) [83-86]. The published studies showed that Tocilizumab (anti-IL-6 mAb) could improve the outcomes in COVID-19 patients and inhibit a cytokine storm [87]. Anakinra (IL-1ra) [88],[89] also showed beneficial effects for the treatment of COVID-19 patients and could decrease the mechanical ventilation need. Moreover, REGN-COV2 has been developed and consists of two neutralizing antibodies (REGN10987 + REGN10933) targeting SARS-CoV-2 spike protein [90][91].

NANO-MEDICINE IN COVID-19 TREATMENT

Using nano-medicine including aerosol inhalations of therapeutic agents attracts lots of attention. Recent studies have investigated the efficiency and safety of the MSCderived exosome (NCT04491240, NCT04276987) and interferon beta inhalation (NCT04385095).Now, most of the mentioned studies are ongoing. The growing number of clinical trials in this field could provide more validated designs and higher quality data. In this context, the increase in international collaborations to provide larger number of patients will be helpful to obtain more definite results [92]. Identifying the exact mechanisms of the COVID-19 immuno-pathogenesis will ensure the development of more effective therapies.

CONCLUSION:

The COVID-19 pandemic, which has been progressing rapidly since the first case was detected in China, has caused a major crisis in the world. Rapid progress was made in diagnosing the disease. There are many ongoing clinical trials related to COVID-19 therapy. A number of randomised controlled trials are underway regarding the use of some potential drugs for therapy, but, to date, there is no treatment scientifically proven to be effective in treating COVID-19. Few vaccines were approved for use.

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