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Therapeutic challenges of COVID-19: strategies of empirical treatment

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ABSTRACT: Coronavirus pandemic, is a progressing worldwide pandemic of coronavirus disease 2019 (COVID-19), brought about by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The episode was first distinguished in Wuhan, China, in December 2019. The World Health Organization announced a Public Health Emergency of International Concern on 30 January 2020, and a pandemic on 11 March. Scientists around the world are working to establish an effective treatment against SARS-CoV-2 to control the spread of this pandemic. In this review, we summarized the potential therapeutic strategies for treatment of COVID-19 and dividing the treatments to several categories including antiviral drugs which act on decreasing the viral load inside the body of patients, immunotherapy and immunomodulatory which relive the inflammatory process of viral infection.

Keywords: SARS-CoV-2; COVID-19; Treatment; Antiviral; Remdesivir; Immunotherapy.

1. INTRODUCTION

Coronaviruses (CoVs) appeared in East Asia and the Middle East in three significant outbreaks during 2002 and 2019. The severe acute respiratory syndrome (SARS), the Middle East respiratory syndromes (MERS) and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing the Coronavirus Disease 2019 (COVID-19) and the last emerge globally with pandemic characterizations [1]. The most common symptoms associated with COVID-19 including fever, cough, expectoration, dyspnea, headache, and myalgia or fatigue. Interestingly, loose bowels, hemoptysis, and windiness were the less common symptoms at the time of clinical affirmation [2]. As of late, individuals with asymptomatic contamination were also concerned with conceivably transmitting contamination, which further contributing to the multifaceted nature of disease transmission elements in COVID-19 [1]. COVID-19 is a complex disease and need extraordinary measures for controlling spreading of the virus and providing special cure procedures. Reduce the inflammatory condition that caused by SARS-CoV-2 inside the body is one of the methods to control the pandemic of the disease and using different types of antiviral drugs and immunotherapy for rapid cure of patients and decrease the fatality rate of the disease [3]. Such proficient reactions need inside and out information on an infection, that is currently a novel operator; thereafter, more examinations are required.

2.STRUCTURE AND MECHANISM OF ACTION FOR SARS-CoV-2

Understanding the fundamental structural binding mechanism of the virus to the host suggests that the virus will bind to a wide range of hosts (virus reservoirs), which will further lead us to establish countermeasures against the virus [4]. The name of Coronaviruses is derived from the crown shape of spikes [5]. Viral structure of coronavirus consists four proteins, including glycoprotein (S protein), small envelope (E) glycoprotein, membrane (M) glycoprotein and nucleocapsid (N) protein, as well as many accessory proteins and all these are enveloped by lipid bilayer derived from host cell membrane [6]. S glycoprotein is a transmembrane protein that forms homotrimers that protrude from the viral surface. Host proteases cleave this S glycoprotein into 2 subunits, namely S1 and S2. S1 is responsible for binding to the host cell receptor while S2 functions to mediate the fusion of the viral and cellular membranes [7]. The capsid is the protein shell, inside the capsid, there is nuclear or N-protein that bind to the viral RNA [8]. Another important part of this virus is the membrane or M protein, which is a transmembrane protein located in the viral membrane and is the most abundant structural protein in a virion. The last component is the envelope or E protein, which is the smallest of all structural proteins found in the viral membrane and localizes to the endoplasmic reticulum and the Golgi complex in the host cells [9].

As SARS-CoV-2 belong to the order of the Nidovirus family, coronavirus infection can be contracted from animals such as bats and fellow humans. This virus can enter the human body in two ways, either through endosomes or through plasma membrane fusion. In both ways, the coronavirus S protein binds to angiotensin converting enzyme 2 (ACE2) receptors, which found on the surface of many human cells, such as heart, lungs, kidneys, and gastrointestinal tract, thus enabling the viral entry into target cells [10]. SARS-CoV S1 contains a receptor-binding domain (RBD) that specifically recognizes ACE2 as its receptor. The RBD constantly switches between a standing-up position for receptor binding and a lying-down position for immune evasion [11,12]. After attachment, host proteases, such as type II transmembrane serine protease (TMPRSS2), which is present on the surface of the host cell, must activate the SARS-CoV spike proteolytically at the S1/S2 boundary. So, S1 dissociates and S2 undergoes a drastic change in structure. S protein activation results in conformational changes that allow the viral membrane and host cell to fuse and the virus to enter the cells [13,14]. Entered-SARS-CoV-2 is then released its genomic material into the cytoplasm and translated in the nuclei [15].

The genome organization of SARS-CoV-2 is a positive-sense single-stranded genomic RNA comprises 14 open reading frames (ORFs) with transcriptional regulatory sequences (TRSs) [16]. Two major transcriptional units, ORF1a and ORF1ab, are encoded for replicase polyprotein 1a (PP1a) and polyprotein 1ab (PP1ab), respectively. The largest polyprotein PP1ab embeds non-structural proteins (Nsp1-16), including RNA Dependent RNA Polymerase (RdRp) and Helicase that form the Replicase-Transcriptase Complex [17]. RdRp and Helicase localize to double-membrane vesicles and produce sub-genomic RNA (sgRNA), from which other proteins such as Structural Proteins are produced by translation. At the same time, the full-length positive-strand RNA is synthesized as genomic RNA. The structural viral proteins M, S and E are synthesized in the cytoplasm and then transferred to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) [18]. Nucleocapsids are formed in the cytoplasm by N protein, accompanied by budding into the lumen of ERGIC. Finally, in smooth walled vesicles, novel virions are exported from infected cells by transport to the cell membrane and then secreted through a process called exocytosis, so that other cells can be infected. However, the mechanism of action for the new COVID-19 is still unclear [19].

3.THERAPEUTIC STRATEGIES FOR COVID-19

Presently, there are no specific antiviral drugs or vaccines for SARS-CoV-2 control. However, according to the different genomic organizational studies and molecular mechanisms of SARS-CoV-2 pathogenesis, there are numerous targets that can be used in various ways as therapeutic agents to inhibit the replication of the virus or to create an intervention that may be successful against SARS-CoV-2 [20]. Here, the possible therapeutics available for the treatment of SARS-CoV-2 are summarized.

3.1. Antiviral therapy

Different antiviral treatments with variable mechanism of actions have been experimented by WHO, including Remdesivir; Chloroquine /Hydroxychloroquine; a combination of Human Immunodeficiency Viruses (HIV) drugs such as Lopinavir and Ritonavir; and a combination of HIV drugs linked to Interferon-beta [21].

3.1.1. Lopinavir / ritonavir

Lopinavir / ritonavir is a combination of drugs used primarily in the treatment of HIV infection, which serve as protease inhibitors. In 2000, this mixture was first marketed by Abbott under the Kaletra brand name. Lopinavir inhibits viral protease that results in immature/non-infectious virus particles; ritonavir inhibits liver degradation of lopinavir and thus prolongs the half-life of lopinavir [22]. More recently, a randomized clinical trial of lopinavir/ritonavir (400 mg/100 mg, twice daily for 14 days) in in the treatment of COVID-19 by Cao et al. [11] found that treatment with lopinavir/ritonavir did not significantly accelerate clinical progress, decrease mortality and decrease the identification of viral RNA in the throat in patients with extreme COVID-19. In case of the serious COVID-19 adult patients, [23] there was no benefit from treatment with lopinavir-ritonavir relative to the standard group. This study found that lopinavir-ritonavir does not seem to be successful in patients with COVID-19 and that these combinations caused more side effects. Results from *in vitro* studies showed some evidence of effectiveness against SARS and MERS, but their effectiveness against COVID-19 is unknown [23].

3.1.2. Remdesivir

Remdesivir, a novel nucleotide simple prodrug, was produced for the treatment of Ebola infection illness (EVD). In the essential human aviation route epithelial cell culture framework, it was found to tie to the viral RdRpt and repress the replication of SARS-CoV and MERS-CoV. *In vitro* explores have as of late demonstrated that remdesivir has better antiviral movement analyzed than lopinavir and ritonavir [24]. Furthermore, in vivo concentrates in mice have indicated that remdesivir treatment has upgraded pneumonic capacity and diminished viral burdens and pathology of the lungs in both prophylactic and restorative regimens contrasted and lopinavir/ritonavir-IFN-γ in MERS-CoV contamination [24]. Various COVIDs, including coursing human CoV, zoonotic bat CoV and pre-pandemic zoonotic CoV, are likewise restrained by remdesivir. Remdesivir is likewise accepted to be the main restorative item that significantly diminishes aspiratory pathology [24].

3.1.3. Arbidol

Arbidol is a small indole-derivative molecule. It is a broad-spectrum antiviral drug with demonstrated efficacy against a variety of enveloped and non-enveloped viruses such as hepatitis B and C, SARS and MERS. Arbidol has also been approved for the prophylaxis and treatment of influenza and other viral respiratory infections by binding to haemagglutinin (HA) protein [25, 26]. Any sequence or structural similarities between

SARS-CoV-2 spike glycoprotein and influenza virus (H3N2) HA may have a positive drug effect. The most recent study stated that the sequence and structural similarities between the SARS-CoV-2 spike glycoprotein and H3N2 HA binding sites of Arbidol seem promising and indicated that Arbidol may be useful in treating COVID-19. Arbidol can effectively block or inhibit SARS-CoV-2 spike glycoprotein trimerization, which is crucial to cell adherence and entry. The blockage of SARS-CoV-2 spike glycoprotein trimerization often contributes to the development of naked or immature virus, which is less infectious. This study has important implications, but clinical investigation is still necessary for the efficacy and safety of Arbidol against SARS-CoV-2 [27, 28].

3.1.4. Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine are old medicines that have been used for more than sixty years in the treatment of malaria, rheumatoid arthritis, lupus and sun allergies. As the mechanism of action of these two molecules is similar, the activity of hydroxychloroquine on viruses is possibly the same as that of chloroquine [29]. Chloroquine and hydroxychloroquine have received intense attention worldwide due to the positive results obtained from preliminary studies of their use in the treatment of SARS-CoV-2 patients [30]. Chloroquine and hydroxychloroquine can reduce endosome and lysosome acidity, which is necessary for membrane fusion between the virus and the host cell. This suggests that the endosome maturation mechanism has been changed, preventing endocytosis, leading to the failure of further transport of virions to the site of replication [31]. Moreover, the terminal glycosylation of the ACE2 receptor can also be impaired by chloroquine and hydroxy-chloroquine, thereby inhibiting viral cell penetration [30]. They can also inhibit the proper maturation and recognition by antigen-presenting cells (APCs) of viral antigens that require endosomal acidification for the processing of antigens. This could explain why they also have an immunomodulatory effect by attenuating cytokine production and inhibiting autophagy and lysosomal activity in host cells [31]. Currently, a clinical trial has shown that chloroquine and remdesivir are highly successful in the control of COVID-2019 infection *in vitro*. Since these compounds have been used in human patients with a safety track record and shown to be effective against different ailments [32]. Therefore, chloroquine and hydroxychloroquine have been proposed as available weapons for combating COVID-19 [33].

3.2. Immunotherapy

The immune status of patients with COVID-19 have two sides of view, the first view is that the viral infection activates immune cells, contributing to a cytokine storm that is associated with the severity of the disease. The second view that the COVID-19 primarily affects elders or people with chronic diseases, some of whom have very low numbers of lymphocytes, especially CD4+ T cells, suggesting immune system deficiency [34]. Therefore, immunomodulation or anti-cytokine antibody may also be considered an effective technique for minimizing COVID-19 symptomes, given the state of the patient's immune system at various stages of the disease. Such immunomodulatory interventions can be achieved using vaccines, interferons, convalescent plasma, anti-inflammatory agents, interleukin blockers, and other classes of immunomodulators [3].

3.2.1. Convalescent plasma therapy (CPT)

Convalescent plasma from patients who have recuperated from SARS-CoV-2 infection has likewise been proposed as a potential treatment for COVID-19. Gaining strength plasma has been utilized in numerous extreme infections, for example, SARS, MERS, and Ebola, as one of only a handful few remedial methodologies without antibodies or other explicit medicines [35]. The explanation for the effectiveness of convalescent plasma therapy is that viremia can be suppressed by antibodies from convalescent plasma

through free viral clearance, blockade of new infection, and acceleration of infected cell clearance. The use of CPT should be with considerations, including patients with moderate or end-stage disease are not benefit from CPT. Also, mild patients can be self-recovered, and CPT would not be needed [36]. The SARS-CoV-2 neutralizing antibodies titer in the CP may also be another important factor to increase the efficacy of the treatment. While there is no determination of amount of antibodies in the donor plasma prior to transfusion, some studies have shown that specific IgG increases approximately three weeks after symptom onset and peaks at week 12. Therefore, the CP from donors who are at week 12 after the onset of the symptoms is estimated to be more efficient [36].

3.2.2. Monoclonal antibodies

SARS-CoV-2 monoclonal antibodies have the potential for both therapeutic and prophylactic applications and can help direct the design and production of vaccines. Several research groups have isolated monoclonal antibodies (most commonly from the B cells of patients who have recently recovered from SARS-CoV-2 and, in some cases, from those who were infected with SARS-CoV in 2003) [37]. Monoclonal antibodies designed against SARS-CoV-2 can be classified into three major categories based on their targets: 1) antibodies that inhibit the attachment and entry of the virus by either targeting the structure of the virus or host receptors; 2) antibodies that interfere with the replication and transcription of the virus; 3) antibodies that inhibit different stages of immune system response [30].

S proteins found on the surface of the virus are the main target of neutralizing SARS-CoV-2 monoclonal antibodies and can therefore prevent the virus from entering the host epithelial cells and consequently prevent the amplification of the virus [38]. MAbs often alter the host organism's immune system response, i.e. a decrease in IL-6 plasma level, which is frequently elevated by mechanical ventilation in COVID-19 patients [39].

3.2.3. Immunomodulators

3.2.3.1. Interferons

There are two types of interferons (IFNs), type I IFNs and type II IFNs, type I IFNs designate a group of cytokines consisting of the ubiquitous subtypes α and β (themselves subdivided into many isoforms). It has been shown that type I IFNs can inhibit both SARS and MERS-CoV replication [40]. Suppression of interferon I-mediated immune responses by SARS-CoV-2 is already verified. Although interferon has been shown to combat the virus and is suggested for the treatment of the disease, some conflicting data have demonstrated that interferon can increase the expression of ACE2 and thus the viral entry. In addation good findings were found by using type I IFN, including INF-β-1a, in several clinical trials [41]. A recent study detected that IFNβ1 can be used to treat COVID-19 safely and effectively in the early stages of infection. Similar therapies had a mixed efficacy against MERS-CoV and SARS-CoV viruses, but *in vitro* studies indicate that SARS-CoV-2 may be significantly more sensitive to IFN-I than other coronaviruses [32]. IFN-β is already being tested in a combination protocol in the international clinical trial initiated by WHO, called the "Solidarity" trial, in the partner countries [42].

Moreover, due to the structural similarities between SARS-CoV-1 and SARS-CoV-2, INF-α can improve the innate immunity of SARS-CoV-2 patients. The sensitivity of SARS-CoV-2 to IFN-α is far higher than that of previously emergent SARS-CoVs [39]. In the beginning phase of disease, IFN-α would preferably control countless infection replication, decrease the manifestations of the intense stage, permit patients to endure the intense stage, and forestall the rate of decay. An investigation has demonstrated that

IFN-α2b splashes can limit the pace of SARS-CoV-2 disease, so they can be utilized as prophylaxis against SARS-CoV-2 [43].

3.2.3.2. IL-6 Inhibitors

IL-6 is a pleiotropic, pro-inflammatory cytokine formed from a number of types of cells, including lymphocytes, fibroblasts, and monocytes. When extreme systemic inflammatory responses in patients with SARS-CoV-2 infection occur, the elevations in IL-6 levels may be considered a significant indicator [44, 45]. Cytokine blockers (tocilizumab, sarilumab, and siltuximab) are being investigated as a disease prevention technique [46].

Tocilizumab a humanized anti-IL-6 receptor antibody, has been produced for the treatment of different autoimmune diseases like rheumatoid arthritis and juvenile idiopathic arthritis. Moreover, tocilizumab has been shown to be effective against cytokine release syndrome triggered from CART cell infusion against B cell acute lymphoblastic leukemia. Blocking of anti-human IL-6R by tocilizumab administration has been approved by China for the treatment of COVID-19 [3, 47, 48].

Sarilumab is a completely-humanized monoclonal antibody that inhibits the IL-6 signaling pathway by binding to and blocking IL-6R [49]. Sarilumab can potentially prevent SARS-CoV-2 infection-driven or accelerated cytokine-mediated pulmonary injury, thereby alleviating the severity and/or decreasing the mortality of patients with COVID-19 pneumonia when given in combination with antiviral therapy. Sarilumab an inhibitor of soluble and membrane IL-6Rα that can help to reduce the severity of respiratory difficulty of SARS-CoV-2 infection, but there is no evidence that it has anti-viral potential [50].

Siltuximab can be considered as a therapeutic strategy for the treatment of severe cases of SARS-CoV-2 infection with elevated levels of IL-6. Siltuximab is a humanized recombinant chimeric monoclonal antibody distinctive and specific for the IL-6 R and may potentially hammer symptoms of cytokine release syndromes (CRSs) such as fever, trouble breathing, weakness, fatigue, organ failure, and death in patients severely infected with COVID-19 [51]. Where it prevents the binding of IL-6 to both soluble and membrane-bound IL-6R and thereby inhibits IL-6 signaling [30].

3.2.3.3. IL-1 Inhibitors

In COVID-19 conditions, the IL-1 family of receptors activates an innate immune response and is associated with harmful inflammation, and IL-1 is elevated. Anakinra is an IL-1 receptor antagonist that inhibits the action of proinflammatory cytokines IL-1α and IL-1β and is used to treat autoinflammatory disorders such as adult-onset Still's disease, systemic-onset juvenile idiopathic arthritis, and familial Mediterranean fever [52]. A recently retrospective cohort study showed that patients with COVID-19 and ARDS managed with non-invasive ventilation outside of the ICU, high-dose anakinra therapy was safe and associated with clinical improvement in 72% of patients [53].

Canakinumab is a human monoclonal antibody that specifically targets and neutralizes IL-1β, thus preventing its interaction with IL-1 receptors [54]. A review investigation of 10 patients with affirmed SARS-CoV-2 infection found that canakinumab treatment was related with a quick and generous reduction in serum C-responsive protein on day 1 and day 3 and improved oxygenation, with an expansion in the PaO2: FiO2 proportion among benchmark and day 3 and day 7 after treatment [55].

3.2.3.4. Janus-associated kinase (JAK) inhibitors

Since that SARS-CoV-2 can likewise enter the cell by means of endocytosis, it tends to be vanquished through hindering endocytosis. Numb-related kinase (NAK) relatives, including AP2-related protein kinase

1 (AAK1) and Janus-related kinase (JAK), are two of the key endocytosis controllers that can be hindered and proposed as a possible objective for controlling different viral diseases, for example, SARS-CoV-2 infection [56].

In COVID-19, JAK inhibitors have an alleged benefit over other immunomodulatory strategies because they can exert dual anti-inflammatory (simultaneously blocking several pro-inflammatory cytokines) and anti-viral (impairing cellular viral endocytosis) effects and have convenient oral administration, with a relatively short half-life. The signalling of many pro-inflammatory cytokines involved in the pathogenesis of hyperinflammation, including IL-6, which has been the subject of several COVID-19 clinical trials, may be interrupted by JAK inhibitors [57,58]. Because of the great immunosuppressive effect of JAK inhibitors. The National Institute of Health (NIH) has suggested that it be used to treat patients with COVID-19. The JAK inhibitors recommended are baricitinib, tofacitinib, upadacinib, ruxocitinib and fedracitinb [59].

3.2.3.5. Corticosteroids

Corticosteroids, have anti-inflammatory, antipyretic and vasoconstrictive effects, which intensivists have been trying to leverage for decades to improve outcomes in patients with acute respiratory distress syndrome (ARDS) and septic shock [60]. Based on results from a study data analysis, the WHO has updated its guidance on the use of corticosteroid drugs in COVID-19 patients. An analysis of seven international clinical trials found that in critically ill COVID-19 patients, corticosteroids mitigated the risk of death by 20%. Data on hydrocortisone, dexamethasone and methylprednisolone were included in the study. Steroids were found to increase survival rates in patients with COVID-19 who needed hospital intensive care admission. Moreover, a recent meta analysis study indicated that COVID-19 patients with severe conditions are more likely to require corticosteroids. Corticosteroid use is associated with increased mortality in patients with coronavirus pneumonia [61,62].

4. CONCLUSION

Until now, no approved drug has been available against SARS-CoV-2 and hundreds of the vaccines and antiviral drugs are still under clinical trials that will take several months or longer to become available in the market. Furthermore, all of the drug choices are focused on the experience in the treatment of SARS, MERS or some other previous influenza viruses. However, remdesivir appears to be the most promising drug for the treatment and control of COVID-19 infection.

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