

The Latest Information on Antiviral Therapy, Immunotherapy and Cell Therapy for COVID-19

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ABSTRACT

The cases of COVID-19 have been found in many countries around the world. Corona virus disease 2019 (COVID-19), being an emerging infectious disease, is a serious threat to human health. Current clinical management includes infection prevention and control measures and supportive care including supplemental oxygen and mechanical ventilatory support. Evolving research and clinical data regarding the virologic SARS-CoV-2 suggest a potential list of repurposed drugs with appropriate pharmacological effects and therapeutic efficacies in treating COVID-19 patients. The structure of the SARS-CoV-2 virus comprises of S proteins, M proteins, E proteins, hemagglutinin esterases, nucleocapsid proteins, and RNA genome. Viral proteases cleave these polyproteins and RNA-dependent polymerases replicate the genome. Numerous investigators are developing novel protease inhibitors, some of which have made it into clinical trials. In addition to therapeutic properties of these anti-COVID-19 compounds, some adverse effects were observed in different human organs as well. Not only several attentions were paid to antiviral therapy and treatment of COVID-19, but also nanomedicine, immunotherapy, and cell therapy were conducted against this viral infection. In this review paper, We discussed the latest therapeutic developments against COVID-19.

Keywords: COVID-19; Drugs; Vaccines; Treatment

INTRODUCTION

The COVID-19 outbreak made the entire world frightened in late 2019, which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), belongs to single stranded RNA viruses having spike-like projections of glycoprotein. The virus infection was first reported in Wuhan, People's Republic of China during December 2019 [1]. COVID-19 is the official name of the coronavirus declared by the World Health Organization (WHO). Even though the source of coronavirus has not been declared officially, bats and snakes are considered as the potential host. Wuhan institute of virology confirmed that 96% of similarity coronavirus with the gene sequence of bat coronavirus. Coronavirus infects humans via the binding of S-protein with angiotensin-converting enzyme-2 (ACE-2) with higher affinity [2]. Transmission of coronavirus is through

respiratory droplets of infected persons. The common symptoms include fever, throat infection, cough, headache and breathlessness even some may be asymptomatic. The average incubation period of coronavirus ranges from three days to twenty-four days [3], but the prevalence is more in elderly people with medical comorbidities.

During this pandemic outbreak, several countries adopt preventive measures and their own treatment methodologies. Avoiding contact with infected persons, unnecessary travel and personal hygiene practices are the basic preventive measures followed to avoid the transmission of coronavirus. RT-PCR and chest computed tomography scan are the diagnostic tools used along with the combination of symptom relevant treatment [4]. Viral infections are the major threat to the human kind. As of now, antiviral therapy, symptomatic and oxygen therapy are followed for treating SARS-CoV-2. Nano-based approaches are

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the promising tool for the diagnosis and treatment of such viral diseases. Based on the statistical analysis of StatNano, out of patents filed related to SARS-CoV-2 diagnostics and treatments, 5.2% belong to nano-based technology [5]. With this background, the present review focuses on emerging approaches including drug repurposing, vaccine development including peptide and nano based approaches for COVID-19 therapeutics.

VACCINE DEVELOPMENT APPROACH

Vaccine development involves different strategies including live attenuated or inactivated virus, virus-like particles or other protein-based approaches, viral vector-based vaccines or nucleic acid-based vaccines [6]. In live attenuated vaccines, virulence of the virus is removed but viability is retained which in turn helps the immune system to develop memory cells [7]. Virus-like particles are molecules that closely resemble viruses which are synthesized by the expression of the viral structural protein. The synthesized molecules can assemble themselves to virus-like particles and help the body to boost immunity [8]. Viral vector-based vaccines and nucleic acid-based vaccines incorporate the antibody expressing gene into the cell to produce necessary antibodies to acquire immunity against infections. Drug discovery and development for SARS-CoV-2 can be facilitated by artificial intelligence and other computational tools [9].

Jiang and colleagues have demonstrated that RBD in the SARS-CoV S protein is the major target of neutralizing antibodies in SARS patients and is able to induce highly potent neutralizing antibody responses and long-term protective immunity in animal models. It contains 6 different conformational neutralizing epitopes, to which a series of mouse monoclonal antibodies (mAbs) with different neutralizing activity were generated. Interestingly, these mAbs exhibited cross-neutralizing activities against divergent SARS-CoV strains isolated from SARS patients at different stages of SARS epidemics and those from palm civets [10,11]. This group has also shown that these SARS-CoV-RBD-specific neutralizing mAbs can cross-neutralize bat SL-CoVs, such as bat SL-CoV-WIV1 [12], indicating that these antibodies may also cross-neutralize 2019-nCoV. Most importantly, RBD-based vaccine could induce neutralizing antibody responses and protection against SARS-CoV infection in the immunized animals, while it did not elicit ADE or other harmful immune responses, unlike the virus inactivated vaccines or full-length S protein-based vaccines as discussed above. Therefore, this RBD-based SARS vaccine is expected to be safer and more effective than the vaccines targeting other sites in S protein. Jiang and Du's groups have collaborated with Hotez's group at Baylor College of Medicine in Houston and Tseng's group at the University of Texas Medical Branch at Galveston, Texas, USA in development of an effective and safe vaccine at the late stage of preclinical study [13].

TOCILIZUMAB

Tocilizumab (TCZ) or Actemra is a monoclonal antibody which is widely used in treatment of rheumatic diseases such as rheumatoid arthritis. TCZ is one of the drugs approved in the United States on August 30, 2017, for severe life-threatening

cytokine release syndrome caused by chimeric antigen receptor (CAR) T-cell Immunotherapy. Interleukin-6 (IL-6) is highly expressed in patients with SARS and MERS as well as COVID-19 [14]. TCZ can be prescribed to patients with COVID-19 who are in the risk of cytokine storm. TCZ as a recombinant human monoclonal antibody binds to soluble and membrane-bound IL-6 receptors (IL-6R), and stops IL-6 signals and production of intermediate inflammatory molecules [15]. TCZ is considered a pharmaceutical option for treating patients with COVID-19, however, during the treatment procedures; clinicians should evaluate the safety and efficacy of TCZ. During the administration of TCZ in patients with COVID-19, screening and monitoring parameters, especially latent tuberculosis test (TB) should be performed by IFN- γ release assay (IGRA) before and during the treatment. Studies on phase III trials associated with TCZ revealed that it will be crucial in the reduction of severe respiratory symptoms in patients with COVID-19 [16]. During the treatment of patients with COVID-19 through TCZ therapy, some laboratory parameters including C-reactive protein (CRP) and IL-6 concentrations should be assessed before and after TCZ therapy. In addition, TCZ was used along with methylprednisolone in some patients with COVID-19. The studies have shown that the level of IL-6 decreased in patients after taking TCZ, while the level of IL-6 increased significantly in patients who were not treated with TCZ. TCZ appears to be an effective treatment option in patients with COVID-19 at high risk of M.S. Mirtaleb et al. cytokine storm. Meanwhile, a repeated dose determination of TCZ is recommended for patients with high IL-6 [17].

BARICITINIB

Baricitinib is one of the leading pharmaceuticals recommended for treating pneumonia associated with COVID-19. This compound is known as a safe drug with high affinity to infected cells. Regarding the SARS virus, the most important receptor for glycoprotein S binding was the angiotensin-converting enzyme 2 (ACE2) in the human cells. In the SARS-CoV-2 and due to the structural similarity of glycoprotein S with that found in SARS virus, ACE2 plays the major receptor for viral entrance. This viral receptor is widely present in kidney cells, heart, blood vessels and especially in lung AT2 alveolar epithelial cells. These cells are prone to viral infections such as SARS, so, they are effective in the reproduction and transmission of viral particles through endocytosis. Co-infection, as well as the risk of reactivation of latent infections, is an important risk in the management of COVID-19 [17]. Studies have shown that baricitinib reactivates viruses, including the varicella zoster, herpes simplex, and Epstein-Barr virus strains. There is also a risk of reactivation of latent infections. Zhou et al. proved that approximately 50% of the patients with COVID-19, also experienced a secondary infection [17,18].

ABIDOL-UMIFENOVIR

One of the approved antiviral agents in China and Russia is Abidol. This compound works against a large number of enveloped and non-M.S. Mirtaleb et al. enveloped viruses such as influenza, SARS, and Lassa viruses. Abidol exerts its antiviral

properties by inhibiting the fusion of viral particles into the target cell membrane and preventing the virus from entering the target cell. There have been few reports of this drug's effect on patients with COVID-19. A limited number of COVID-19 studies report data about patients receiving LPV/r and arbidol. It is challenging to identify whether patients have recovered naturally or the recovery process is associated with medications. Studies by Zhen Zhu et al. have shown that arbidol monotherapy is more effective than LPV/r for treating patients with COVID-19 [19]. Contrary to that, Deng's reported that the efficacy of LPV/r alone is higher than the combination of arbidol and LPV/r for treating patients with COVID-19 [20].

RUXOLITINIB

Ruxolitinib is commonly used for treating patients with intermediate or high-risk myelofibrosis. Ruxolitinib as a Janus kinase (JAK) inhibitor was prescribed in a phase III clinical trial of patients with COVID-19 associated with cytokine storm. However, due to the broad immunosuppressive effects of JAK kinase inhibitors, the US National Institute of Health (NIH) did not recommend the application of ruxolitinib for control of cytokine storm in patients with COVID-19 [21].

PLASMA THERAPY

As newer antibiotics, antivirals, and vaccines emerged, the use of convalescent serum or plasma as a frontline therapy decreased. The sera of the infection recovered patients contain plenty of antibodies against the pathogens. In this treatment method, the patient's serum is infused to the recently infected patient with the same pathogen, so that the specific antibodies neutralize the pathogen in the recipient [22]. Some evaluations were performed to analyze the clinical effectiveness of convalescent plasma, serum, or hyperimmune immunoglobulin for the treatment of severe viral acute respiratory infections including those due to SARS coronavirus, Spanish influenza A (H1N1), avian influenza A (H5N1), and pandemic influenza A (H1N1) in 2009. In all cases, hyperimmune immunoglobulin was able to demonstrate a statistically significant reduction in the odds of mortality among those who were treated with convalescent plasma or serum [23].

During SARS-CoV infection, it was thought that convalescent plasma improve the outcome of infected patients. Previous studies on patients with SARS-CoV infection suggested that convalescent plasma may be useful for patients with SARS so showed improvements in survival and resulted in a shorter hospital stay. A protocol for the application of convalescent plasma as a therapeutic option for MERS was suggested [24]. The recent outbreak of Ebola virus disease (EVD) in West Africa has been the worst ever witnessed. By September 9, 2015, a total of 28,183 cases and 11,306 deaths had been reported. The high case fatality rate (40%-60%) highlights the need for effective EVD-specific treatments. Such interventions would facilitate the rapid tracing of contacts of patients and the implementation of measurements to control the spread of an outbreak. The WHO has prioritized the evaluation of treatment with convalescent whole blood or plasma derived from patients who have recovered from EVD. Such treatment has been used successfully

for other serious infectious diseases with appropriate safeguards. In 1995, the largest case series involved eight patients who were treated with convalescent whole blood during the Kikwit outbreak of EVD that seven patients were survived. However, it was not possible to assess whether the low case fatality rate was due to treatment with convalescent whole blood or other factors, such as characteristics of the patients or the period during the illness at which treatment was given. In the Pandemic of COVID-19, plasma therapy has been used for treating COVID-9 patients. In an initial study, five patients with COVID-19 with ARDS underwent plasma therapy and clinical outcomes were compared before and after convalescent plasma (CP) transfusion the results showed improvement in the patients' clinical condition [25].

Due to the limitations in the sample and the experimental design, it is not possible to give a definite opinion about the potential effectiveness of this type of treatment and more clinical observations will be needed. In a study by Duan et al. in ten severe adult cases, the results showed that a dose of 200 mL CP was well tolerated and could significantly increase or maintain neutralizing antibodies at a desirable level. This treatment was capable of reducing viremia within 7 days. After the application of this treatment method, clinical and paraclinical symptoms improved rapidly within 3 days. Radiological studies also showed varying degrees of absorption of lung lesions within 7 days. According to these observations, CP can be expected as a life-saving option in patients with severe COVID-19 [26].

CYTOKINE-BASED IMMUNOTHERAPY

Interferon (IFN)-based immunotherapy could be a safe choice for multiple sclerosis (MS) patients with mild-to-moderate disease activity during the COVID-19 pandemic. At the first stage of viral disease, the expression of IFNs could be an appropriate innate immune response to the virus. Afterward, the main immune response to the virus is mediated by lymphocytes, monocytes, and macrophages. IFNs induce interference with viral replication and previous evidence suggests that IFN- β is mildly effective in animal models of MERS-CoV whenever used along with lopinavir and ritonavir, so the capability of IFN- β for treating COVID-19 could be a useful investigation [27]. The prescription of IFNs in the early stages of COVID-19 can elicit a stronger antiviral response and prevent infection spreading to other cells. However, the use of IFNs in the severe phase of the immune response can trigger hyperactivation of immune response and intensify the cytokine storm. Therefore, this treatment is not recommended in the acute phase of infection. SARS-CoV-2 inhibits the production of type 1 IFNs by disrupting IFN signaling pathways through the inhibition of signal transducers and transcription activators such as signal transducer and activator of transcription 1 (STAT1) and Interferon regulatory factor 3 (IRF3) [28].

According to the IFN-I therapy studies conducted on the SARS-CoV and MERS-CoV infections, type 1 IFNs show high-potential for treating patients with COVID-19. In this regard, IFN- α 2b was used as a therapeutic agent for treating patients with COVID-19 according to a study conducted in Wuhan,

China. In this study, 77 hospitalized adults with COVID-19 were treated with IFN- α 2b (5 mU b.i.d.), or arbidol (200 mg t.i.d), or a combination of both pharmaceuticals. Hematological, biochemical and immunological parameters were evaluated. IFN- α 2b therapy, either alone or concomitantly with arbidol, significantly reduced the duration of the detection of SARS-CoV-2 virus in the upper respiratory tract and also reduced the blood levels of the inflammatory markers such as IL-6 and CRP. Referring to the conducted studies, IFN could be considered as a pharmaceutical option for treating patients with COVID-19 [29].

STEM CELL THERAPY

Nowadays, cell-based therapy methods such as stem cell therapy are considered potential therapeutic strategies for treating some severe diseases. Due to the superior properties of mesenchymal stem cells (MSCs) and their conditioned medium compared to other cellular therapies, the application of MSC-based therapy has further expanded in the field of cell therapy. MSCs are readily available and can be isolated and stored from various tissues such as bone marrow and adipose tissue. MSCs are multipotent stem cells and can be easily expanded to clinical applications in a desired period. Therapeutic application of MSCs has been documented in several clinical trials. Clinical trials using MSCs have not shown any adverse effects in the patients [30].

In patients with COVID-19, the cytokine storm occurs after overproduction of inflammatory agents by the immune system. MSCs control the release and activity of cytokine in this condition which is provided through endogenous repair with compensatory properties of the stem cell products. By intravenous injection of MSCs, the pulmonary environment is restored, alveolar epithelial cells are protected, pulmonary fibrosis is inhibited and COVID-19 pneumonia is treated. Therefore, MSC-based therapy can be a potential novel treatment ideal for clinical trials or at least along with other treatment methods for patients with COVID-19 [30].

In a study by Liang et al. on a 65-year-old woman with COVID-19, human umbilical cords MSCs (hUCMSCs) were used. The allogenic hUCMSCs were given three times (5×10^7 cells each time) with a 3-day interval, with daily injection of thymosin α 1 and antibiotics. After treatment with MSCs, most experimental indicators and computerized tomography (CT) images showed an improvement in the inflammation and symptoms. The patient was then transferred out of intensive care unit (ICU) and the throat swab test for RT-PCR test was reported negative 4 days later. The results suggested that hUCMSCs could be a potential treatment option alone or in combination with other immune modulators for acute patients with COVID-19 [31].

In a study by Leng et al., they investigated the effect of MSC transplantation on pneumonia-associated patients with COVID-19. The period of treatment lasted for 14 days. Within 2 days post-transplantation, the patients' pulmonary function had improved dramatically. After treatment, the CRP level decreased, peripheral lymphocyte count was increased, cytokine-

secreting immune cells such as CXCR3+CD4+ T and CXCR3+CD8+ T cells were over-activated, and CXCR3+ natural killer (NK) cells disappeared within 3–6 days. Meanwhile, the group of immunological cells including CD14+, CD11c+, CD11b mid, and regulatory dendritic cells (DCs) dramatically increased. During the treatment, the level of IL-10 as an immunomodulatory cytokine was increased, while, the level of TNF- α was decreased. Therefore, intravenous transplantation of MSCs can be a potential and safe treatment method against acute pneumonia-associated patients with COVID-19. Exosomes are secretory components studied for their similarity to the paracrine effect of MSCs for treating various diseases. These 30-150 nm nanoparticles are involved in cellular communication and are responsible for transporting many biological materials, including mRNA and protein molecules. The use of MSC-derived exosomes as cell-free therapeutics offers several advantages over their cellular counterparts, including high stability, low immunogenicity, ease of storage, and ability to cross the blood-brain barrier. MSCs-derived exosomes could be a new intervention idea to treat severe conditions of COVID-19 through modulation of the immune system and antimicrobials [32].

NK cells are a subset of innate immunity lymphocytes that comprise 10%-15% of total peripheral blood leukocytes. They are categorized as first-line defense components against viruses. They are naturally activated during the initial immune response to virus-infected cells and promote the infected cells toward apoptosis. The most distinct features of the NK immune response are MHC independence and ready availability to combat virally infected cells. Their functionality could be enhanced by macrophage-derived cytokines and type I IFNs. Since the outbreak of COVID-19, scientists have considered the use of NK cells as an effective cell therapy method for treating patients with COVID-19 [28]. The chimeric antigen receptor (CAR) is a genetically engineered receptor that is widely used for treating various cancers. Engineered NK cells expressing CAR molecules can specifically target virus anti-gene expressing cells. Since NK cells play an important role in antiviral immune response to SARS-CoV-2, CAR-NK engineered cells have been proposed as a new approach to the treatment of COVID-19. ACE-2 can be a target antigen that can be used to design CAR-NK cells against SARSCoV-2. NCT04324996 is a phase I/II clinical trial study initiated to evaluate the efficacy of Universal Off-the-shelf NKG2D-ACE2 CAR-NK cells for treating COVID-19 pneumonia [33].

DC THERAPY

As members of the innate immune system, type 1 DCs (DC-1) exert their antiviral immune response by producing IL-6 and IFN, and acting as antigen-presenting cells. The application of engineered DCs is mainly a hot topic in cancer therapy; however, its application in infectious disease is possible, too. DCs may activate NK cells by expressing NKG2D. However, the hypersecretion of IL-6 is considered the major mechanism that contributes to the progression of respiratory inflammation and lung tissue damage in ARDS. Application of DC-blocking

agents and using engineered DCs could be considered for inhibition of the proinflammatory effects of patients with severe COVID-19 [28].

MACROPHAGE THERAPY

Macrophages are categorized into type 1 macrophages (M1) with proinflammatory functions, and type 2 macrophages (M2) with anti-inflammatory properties. Commonly, these cells could be developed from monocytes in the *in vitro* conditions. Similarly, in the *in vivo* condition the circulating monocytes enter tissues and differentiate into macrophages. During the COVID-19 pandemic, M1 macrophages contribute to severe inflammation by secretion of proinflammatory cytokines such as IL-6 and IL-1 β . To suppress the hyperinflammatory condition, macrophages can be modified in two ways. The first method could be the modulation of the M1 macrophages to secrete lower levels of proinflammatory cytokines and the second approach could be the application of M2 macrophages to suppress the inflammation of the lungs. Considering the application of macrophages for treating COVID-19, macrophage therapy could be considered in further studies [28].

CONCLUSION

To date, the transmission of COVID-19 is still uncontrollable with the fact that numbers of confirmed and death cases keep increasing. The novel nature of COVID-19 has challenged the scientific research and development sector as well as pharmaceutical industries with unprecedented demand to accelerate therapeutics and vaccine development. The treatment approaches discussed has reflected the current knowledge at the time of writing the manuscript, but the field is rapidly evolving. Combination treatment has been encouraged as part of the management of critical COVID-19 patients in this pandemic. In the future, more specifically designed randomized, controlled clinical trials are necessary to determine the most effective evidence-based treatment and management of COVID-19. Since the emergence of COVID-19 in December 2020, many academic groups and pharmaceutical companies focused their efforts and budgets on designing of the pharmaceutical compounds for treatment and production of various forms of anti-COVID-19 vaccines. Although some pharmaceutical companies such as Pfizer-BioNTech, Moderna, and AstraZeneca reported the production of anti-COVID-19 vaccines with different definitive immunogenicity percentages.

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The authors declares that they have no competing interests.

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