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Review Article

# Coronavirus (SARS-CoV-2): Molecular Mechanism of Coronavirus and Therapeutic Approaches (Stem Cell Therapy and Vaccine) for the Treatment of COVID-19

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## Abstract

Coronavirus or SARS-CoV-2 is the causative agent of the pandemic viral pneumonia disease COVID-19, identified in the late 2019. It is said to have originated in Wuhan, China and has now spread throughout the world and is a global pandemic. SARS-CoV-2 belongs to β-coronavirus family and has an identical genomic structure to bat coronavirus. SARS-CoV-2 mediates the entry in to host cell through host angiotensin-converting enzyme 2 (ACE 2). SARS-CoV-2 S protein has higher affinity to ACE2 receptor and mainly spreads the infection in the respiratory tract. The specific drugs/vaccine or any therapeutics approaches are required to prevent the current pandemic. Unfortunately, till date, there is no specific vaccine or therapeutic which is available to control the disease. Research efforts for development of COVID-19 pandemic are unprecedented in terms of promising time period. In this regard, we conducted a review on SARS-CoV-2 to cover the molecular mechanism to improve and increase understanding of the virus and therapeutic approaches such as vaccine and mesenchymal stem cell therapy (MSCs), which may provide the basis of future management of COVID-19.

***Keyworks:*** *SARS-CoV-2; Angiotensin-Converting Enzyme 2 (ACE 2); Interferons and MSCs*

## Introduction

The pandemic COVID-19 disease caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) started in December 2019 from Wuhan, China, later on within few months this infectious disease had spread all over the world [1]. Coronavirus word is a Latin word corona that means "crown". SARS-CoV-2 belongs to the family Coronaviridae under the genus beta coronavirus [2]. Corona virus is classified into four genera viz., alpha (α), beta (β), gamma (γ) and delta (δ) [3]. There are total seven human coronaviruses, including the new pandemic SARS-CoV-2 which has been identified till date. It is similar to human severe acute respiratory syndrome corona virus (SARS-CoV), a species of coronavirus which infects humans, bats, and camels [4]. SARS-CoV, was first identified in the year 2003, which causes severe acute respiratory syndrome (SARS) and shows unique pathogenesis as respiratory tract infections [5]. In human, SARS-CoV-2 causes

respiratory tract infections that can be mild, but SARS- CoV-2, SARS and MERS can be lethal, if immune system is compromised. The scientific evidence of a continuous human-to-human transmission of SARS-CoV-2 represents the epidemic situation of disease [6]. SARS-CoV-2 has positive-sense single-stranded RNA genome, approximately 29,903 bp nucleotides long [7], including four major structural proteins, viz., spike (S), membrane (M), envelope (E) and nucleocapsid (N), sixteen non-structural proteins (NSP 1-16) and five to eight accessory proteins [8]. High predominance and wide distribution of coronaviruses influence the genetic diversity and frequent recombination in genome, increase the risk of pandemic situation [7,9].

The SARS-CoV-2 is a major source of disaster in the 21st century. Till date (10th August 2020), a total of 29,060,688 patients are infected and more than 7,34,667 confirmed deaths have been reported with 2.52% fatality rate [10]. According to the Centers for Disease Control and Prevention (CDC), SARS-CoV-2 occasionally causes complications in the lower respiratory tract. The infected respiratory droplets can spread up to 1 - 2 meter and deposit on surfaces. It can live on hard surface for an hour's to days in favorable conditions [31] (Table 1). Infection can be spread by inhalation of infected droplets (aerosolization/fecooral route) or touching contaminated surfaces having SARS-CoV-2 virus. Some reports suggest that this virus is also present in the stool and contaminated water [11]. Virus can be eliminated within a minute by common disinfectants like 0.1% sodium hypochlorite, 0.5% hydrogen peroxide, 70% ethanol or even methanol etc [12]. Therefore, washing your hands frequently with soap or detergents, especially after contact with infected person or environment is advised.

| S. No. | Surface | Survival period of virus |
|---|---|---|
| 1. | Air | 3 hours |
| 2. | Copper | 4 hours |
| 3. | Cardboard | 24 hours |
| 4. | Wood | 2 days |
| 5. | Cloth | 2 days |
| 6. | Stainless steel | 2-3 days |
| 7. | Polypropylene plastic | 3 days |
| 8. | Glass | 4 days |
| 9. | Paper money | 4 days |
| 10. | Outside of surgical mask | 7 days |

***Table 1:*** *Survival period of SARS- CoV-2 in different surfaces*
***Source:*** *New England Journal of Medicine, The Lancet Microbe [31].*

Pandemic situation caused the travel restriction and nationwide lock down in many countries that also causes economic loss internationally [13]. Therapeutic approaches viz., Vaccine and stem cell are some way to restrict the pandemic situation; an effective strategy is required that can induce the cell-mediated immunity and deliver the proper responses against SARS-CoV-2. Presently no approved cure is available for SARS-CoV-2; although, scientists from all over the world are doing their best efforts to develop protective therapeutics. This article represents a brief overview of molecular mechanism of virus and therapeutic approaches, which can be applying to find out a better cure for COVID-19.

## Genomic organization and molecular mechanism of coronavirus

SARS-CoV-2 has a diameter of about 120 nm [17]. It consist of a lipid bilayer membrane (E), enveloped and 5'-leader- UTR transcriptase-spike (S) structural proteins [14], with a positive-sense single-stranded RNA genome and a nucleocapsid (N) -3' UTR and a poly (A) tail (M) [15]. This structure helps to protect the virus when it is outside the host cell. It also has a shorter spike-like surface protein called

hemagglutinin esterase (HE). ORF1a and ORF1b are the open reading frames, cover the two-thirds of the whole genome and produce the two viral replicase proteins (polyproteins) [19] (Figure 1). Both ORFs encode total 16 Non-Structural Proteins (NSPs) which are highly conserved in the coronaviruses. These NSPs actively participate to produce replicase transcriptase complex. Transcriptase polyprotein has the ability to self-cleave to form non-structural proteins [20]. Coronaviruses consist one of the largest genome size of 27 to 34 kilo bases in the RNA virus family [16]. Its genomes have a 5′ methylated cap and a 3′ polyadenylated tail.

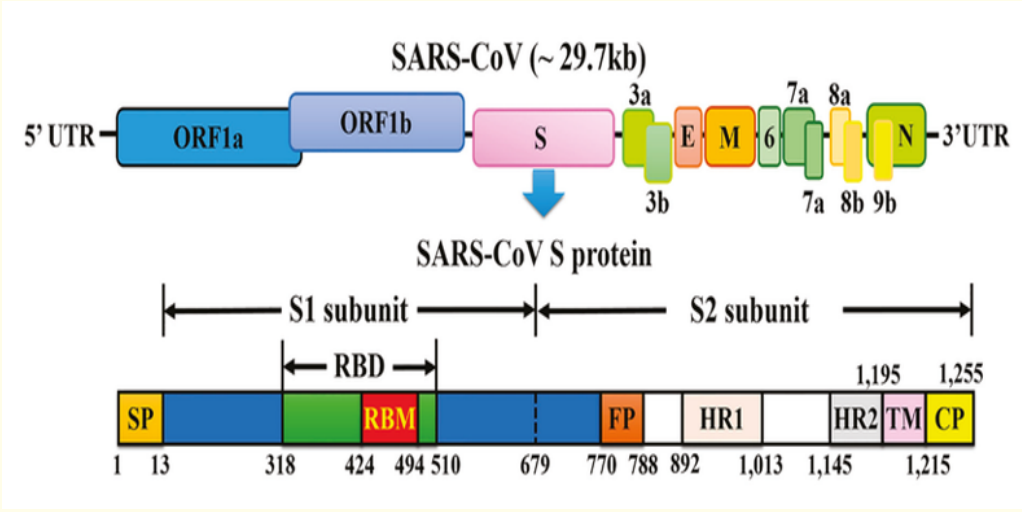


***Figure 1:*** *Genomic organization of SARS-CoV-2 [18].*

The S protein is heavily glycosylated protein, mainly contains the S1 and S2 subunits. These S subunit proteins are processed by host proteases [22]. The S1 subunit is responsible for receptor binding and S2 subunit for membrane fusion. SARS-CoV-2 consist two subunits within the S1 unit, which are capable of binding to host receptors. One is an amino (N)-terminal domain (NTD) and another is a carboxy (C)-terminal domain (CTD), are protein receptors for SARS-CoV-2 and MERS-CoV [19,20]. The M protein (25 - 30 kDa) is the most abundant structural protein in the virion structure and has 3 trans- membrane domains that give the virion its shape [23]. M protein has a small N-terminal glycosylated ectodomain and a much larger C-terminal endodomain that extends 6 - 8 nm into the viral particle [14,17]. The E protein with small portion about 8 - 12 kDa, are highly divergent [23] (Figure 1). E protein of virion has very limited data suggesting that it is a trans-membrane protein with an N-terminal ectodomain, a C-terminal endodomain and has ion channel activity. The ion channel activity in SARS-CoV-2 is required for pathogenesis. Studies suggested that E protein of coronavirus is not always lethal although depends upon virus type [14,19]. This protein facilitates assembly and release of the virus. N protein present in the nucleocapsid of virus has two domains an N-terminal domain (NTD) and a C-terminal domain (CTD) which helps RNA binding *in-vitro* [19]. N protein also binds NSP3 (Non Structural Protein 3, a key component of the replicase complex) [17,22] and the M protein [23]. These proteins help together the viral genome to form the Replicase Transcriptase Complex (RTC), and subsequently package the encapsulated genome into viral particles. Recent studies suggest that the mutation in NSP2 and NSP3 play a role in infectious capability and differentiation mechanism of COVID-19 [31].

In early stage of infection virus attaches to host cell with the viral spike with (S proteins) glycoprotein Receptor Binding Domain (RBD). After attachment, virus releases protease to cleave host cell and activates the receptor-attached spike protein or S protein receptor interaction. A recent study published in International Journal of Antimicrobials Agent and Science, showed that SARS-CoV-2 S protein

has higher affinity to ACE2 (Angiotensin-Converting Enzyme 2) than SARS-CoV, S protein [1,21]. The viral genome uses replicase-transcriptase protein RNA dependent RNA polymerase (RdRp) to replication and transcription of RNA from a RNA strand. Viral RNA genome has 5′ methylated cap and a 3′ polyadenylated tail bind to the host cell's ribosome for translation [21]. Continuously replications of RTC produce a nested set of sub genomic RNAs [22]. Further, these RNAs encode accessory proteins and structural proteins. Once sufficient amount of structural proteins and viral RNA are formed, viral RNA then assembles with the viral structural proteins into virion. Now, viral assembly and budding occur in smooth walled vesicles in the endoplasmic reticulum, Golgi intermediate compartment (ERGIC) [23] and virion-containing vesicles fuse with the plasma membrane to release the virus through exocytosis (Figure 2).

## Therapeutic approaches

There is no specific antiviral therapeutics/vaccine presently available that specifically targets human coronaviruses (SARS-CoV-2). The prospect of SARS-CoV-2 transmission to human populations suggests an urgent need to prepare a promising protective therapeutic approach. Studies suggested that *in-vitro* interferons (IFNs) are partially effective against coronaviruses including IFN-1, used as potential treatment of other positive ssRNA viruses [24]. *In-vitro* recombinant IFNs-α and IFNs-β inhibit the replication of both SARS-CoV and MERS-CoV in animal models [26,27]. Combination of both IFNs-α and IFNs-β along with other antivirals such as ribavirin can be used to treat patients with SARS. However, the effectiveness of this combination *in-vivo* requires further evaluation [24,25]. Presently many countries are widely using chloroquine (an anti-malarial drug, used to prevent or treat malaria), which have found some success in recovery of SARS-CoV-2 positive patients. Although, at present there are not enough scientific studies available to draw any conclusion on the effect of Chloroquine drug on COVID-19 [28]. Clinical trials with some of the promising approaches for treatment like nucleotide analog remdesivir and protease inhibitors are also ongoing in China and the United States. However, Remdesivir works against coronaviruses closely related to SARS-CoV-2 in animal models, as well as against the related MERS-CoV [7,18,27,35]. In previous studies it has been shown that Remdesivir was also tested for treatment of ebolavirus infections in humans therefore; safety data exist for the same agent, which should accelerate the process of clinical testing against SARS-CoV-2.

The SARS-CoV-2 has been identified by the National Institute of Allergy and Infectious Diseases of the US NIH (NIH-NIAID) as a category C pathogen, which has potential for high morbidity and mortality after bioengineered and could be used by bioterrorists as a biological weapon. Therefore, an effective vaccine or therapeutic approach is urgently needed to control the pandemic situation and also for biodefense stratagem. It is often stated that vaccination has made the greatest contribution to global health of any human intervention apart from the introduction of clean water and sanitation, although it required some qualification [29]. In India, seven different industries (Zydus Cadila, Serum Institute of India, Biological E, Bharat Biotech, Indian Immunologicals, Mynvax) are in race to develop a better vaccine candidate with support from the government organizations and academic institutions, researchers are working on 14 vaccine candidates on different levels [29,30]. Scientists are using specific significance platform for early development of an effective vaccine e.g. whole virus inactivated and live attenuated vaccine, nucleic acid (DNA, RNA) vaccine and viral vector based recombinant vaccine (Table 2).

| Vaccine type | Target | Candidate name | Company name | Trial stage |
|---|---|---|---|---|
| Non-Replicating Viral Vector | S-protein | ChAdOx1-S | Oxford/AstraZeneca Uni. | Phase 3 |
| | | Adenovirus Type 5 Vector | CanSino Bio. Inc./ Beijing Institute of Biotechnology | Phase 2 |
| | | Adeno-based | Gamaleya National Research center for Epidemiology and microbiology | Phase 1 |
| RNA | S-protein | LNP encapsulated | Moderna/NIAID | Phase 3 |
| | | mRNA 3 LNP-mRNAs | BioNTech/Fosun Pharma/Pfizer | Phase 1/2 |
| | | LNP-nCoVsaRNA | Imperial College London | Phase 1 |
| | | mRNA | Curevac | Phase 1 |
| | | mRNA | People's Liberation Army (PLA) Academy of Military Sciences/ Walvax Biotech | Phase 1 |

| | | | | |
|---|---|---|---|---|
| DNA | S-protein | DNA plasmid vaccine with electroporation | Inovio Pharmaceuticals | Phase 1/2 |
| | | DNA plasmid vaccine +Adjuvant | Osaka University/ AnGes/Takara Bio | Phase 1/2 |
| | | DNA Vaccine (GX19) | Genexine Consortium | Phase 1/2 |
| | | DNA plasmid Vaccine | Cadila Healthcare Limited | Phase 1/2 |
| Inactivated | Whole virion | Inactivated | Beijing Institute of Biological Products/ Sinopharm | Phase 3 |
| | | Inactivated | Wuhan Inst. of Biological Products/ Sinopharm | Phase 3 |
| | | Inactivated | Institute of Med. Bio., Chinese Acad. of Med. Sci. | Phase 1/2 |
| | | Inactivated + alum | Sinovac | Phase 3 |
| | | Whole-Virion Inactivated | Bharat Biotech | Phase 1/2 |
| Protein Subunit | S-protein | Adjuvanted recombinant protein (RBD-Dimer) | Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Acad. of Sciences | Phase 2 |
| | | Full length recombinant SARS-CoV-2 glycolprotein nanoparticle vaccine adjuvanted-Matrix M | Novavax | Phase 1/2 |
| | | RBD-based | Kentucky Bioprocessing, Inc. | Phase ½ |
| | | Native like Trimeric subunit Spike Protein vaccine | Clover Biopharmaceuticals Inc./GSK/ Dynavax | Phase 1 |
| | | Recombinant spike protein with Advax™ adjuvant | Vaxine Pty Ltd/Medytox | Phase 1 |
| | | Molecular clamp stabilized Spike protein with MF59 adjuvant | University of Queensland/CSL/Seqirus | Phase 1 |

***Table 2:*** *Platforms, under clinical evaluation for development of COVID-19 vaccine.*

## Stem cell approaches: Can stem cell therapy be effective for virus

Several studies reported that SARS-CoV-2 virus attack by identifying the ACE-2 receptor presents in the cells [32-34]. ACE-2 widely distributed on the surface of mammalian cells, such as alveolar type 2 (AT-2). AT-2 expresses the TMRRSSR-2 which is also allow the virus to entry of virus to host cell [33]. Hamming and co-workers reported that bone marrow, thymus, lymph nodes, spleen, and immune cells (T and B lymphocytes) and macrophages are always negative for ACE2 [33,35]. It should be noted that the pathogenicity of virus can be also minimized by cytokines therapy. SARS-CoV-2 triggered acute cytokine release of GSCF, MIP1A, IL-2, IL-7, IP10, MCP1, IL-6, and TNF results in pulmonary edema, dysfunctional distribution of air-exchange, acute respiratory distress syndrome (ARDS) and acute cardiac injury and leading to death [36].

Stem cell therapies and, more recently, their secreted extracellular vesicles (EVs), are emerging as new promising treatments, which could attenuate inflammation in COVID-19 patients. Stem cells could be beneficial, alone or in combination with other therapeutic agents,

in people infected with COVID-19 as they exert their immunomodulatory, anti-oxidant, and reparative therapeutic effects. Some studies suggest that mesenchymal stem cells (MSCs) could be the promising candidate for the treatment of SARS-CoV-2 [37,38]. MSCs are well-suited considering their main mechanism of action is through their immunomodulatory and anti-inflammatory properties [39]. There are currently 17 clinical trials underway to evaluating the therapeutic potential of MSCs for the treatment of COVID-19. The majority of patients including COVID-19 and pneumonia and utilizing allogeneic bone-marrow or umbilical cord-derived MSCs transplanted intravenously on three different occasions [37]. About 50% of the trials are undergoing in China. Trials NCT03042143 is being recruiting in Northern Ireland and another trial NCT04333368 is being planned in United Kingdom in France and NCT04345601 in the United States of America. Aim of these trials is to investigate the therapeutic potential of MSCs in SARS-CoV-2-induced acute respiratory distress syndrome (ARDS) [37]. Number of MSCs related trials in COVID-19 patients with respiratory complications are underway while, we have to wait for the outcomes from these trials to be reported. In the year of 2013 and 2015, MSCs have already been investigated in ARDS for the pre-clinical and clinical trials [40,41]. These studies reported the ability of MSCs to promote distal lung epithelial repair, albeit potentially limited in the presence of hypercapnic acidosis [42].

## Mechanism of stem cell therapy

Several studies mentioned that SARS-CoV-2 may trigger a destroying immune overreaction in the body. The immune system of COVID-19 patients produces large number of inflammatory factors (causing a cytokine storm) which causes an overproduction of immune cells and cytokines [43,44]. In this phenomenon MSCs therapy may play a crucial role in the COVID-19 treatment to prevent the overproduction release of cytokines by immune system and promote endogenous repair by the stem cells [45,46] (Figure 2).

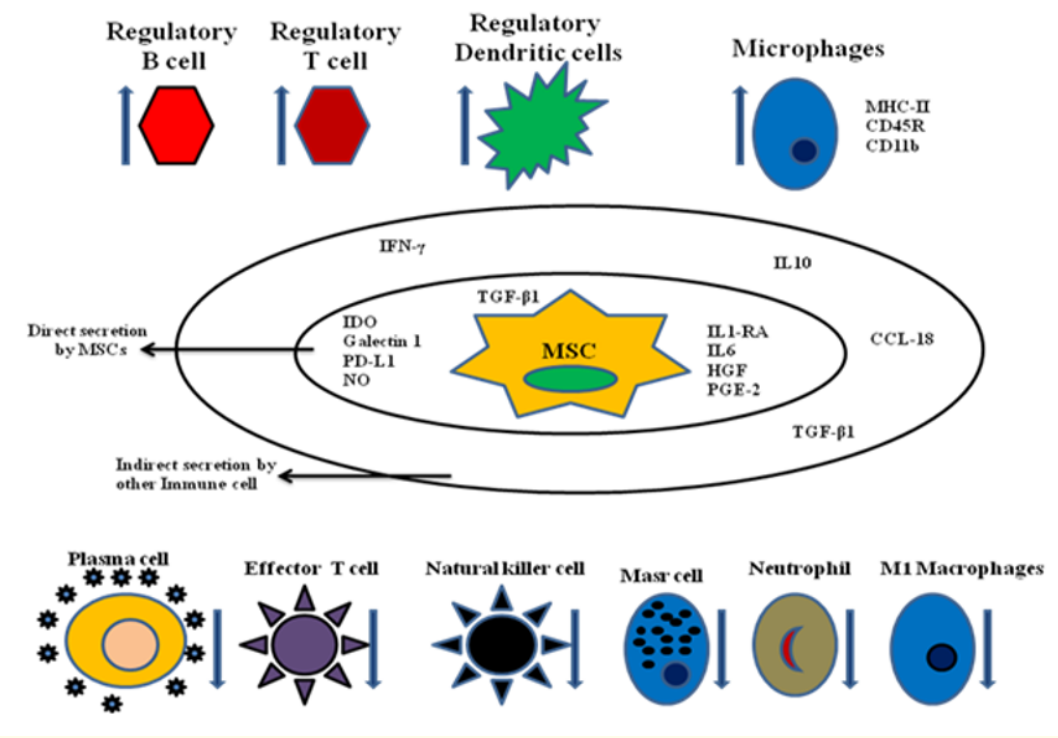


***Figure 2:*** *Figure showing the released cytokines after interaction of MSCs with the host immune system [45,46] (https://biorender.com).*

A significant population of MSC's cells will be accumulated in the lung after the intravenous transplantation of MSC's where they their immunomodulatory effect could protect alveolar epithelial cell, recover the pulmonary microenvironment, prevent the pulmonary fibrosis, and cure lung dysfunction [47]. However, one of the main restrictions in this approach is the suppling source of clinical-grade MSCs and subsequently the speed of preparation for clinical usage that here stem cell banks can play an important role.

## Clinical trial of MSC for COVID-19 treatment

At present, USA, China, Iran, Jordon, and several other countries are working on cell based therapy clinical studies and some reports have been published (Table 3). Some studies reported that MSCs therapy is widely used in the treatment of type 2 diabetes, spinal cord injury, Graft-versus-host disease (GVHD), autoimmune disease, and several other diseases associated with high immunity rates [43,48,49]. MSCs therapy can prevent lung tissue death by counteracting the cytokine overproduction and regeneration and reconstruction of damaged tissues due to their immunomodulatory properties and differentiation ability [43,44] (Figure 2).

| Cell type | Dosage | Number of patients | Outcome | Stage of study | Reference/NCT No. |
|---|---|---|---|---|---|
| MSCs (tissue source unspecified) | Single dose of $1 \times 10^6$ cells per kg, IV | 7 patients with severe COVID-19 Pneumonia | Regulation of inflammatory response (Decreased plasma C-reaction protein, reduced cytokine-secreting immune cells, reducing TNF-alpha, increased IL-10 and VEGF) | Complete | Leng., *et al*. 2020 |
| Adipose tissue-derived MSCs | Two serial doses of $1.5\times10^6$ cells per kg, IV | Estimated: 100 patients | N/A | Phase 2; Not yet Recruiting | NCT04348461 |
| Dental pulp stem cells | $3\times10^7$ cells IV on day 1,4, and 7 | Estimated: 20 patients | N/A | Phase 1 clinical trial; Recruiting | NCT04336254 |
| Dental pulp stem cells | $1 \times 10^6$ cells per kg IV on day 1, 3, and 7 | Estimated: 24 patients | N/A | Early Phase 1; Not yet recruiting | NCT04302519 |
| Wharton's Jelly MSCs | 3 doses of $1 \times 10^6$ cells per kg IV, 3 days apart from each other | Estimated: 5 patients | N/A | Phase 1 clinical trial; Recruiting | NCT04313322 |
| MSCs (tissue source unspecified) | $3 \times 10^7$ cells IV on day 0, 3, and 6 | Estimated: 20 patients | N/A | Phase 1 clinical trial; Recruiting | NCT04252118 |
| Umbilical cord MSCs | $9.9 \times 10^7$ cells IV on day 1, 3, 5, and 7 | Estimated: 10 patients | N/A | Phase 2 clinical trial; Recruiting | NCT04269525 |
| Umbilical cord MSCs | $0.5 \times 10^6$ cells per kg body Wt. IV on day 1, 3, 5, and 7 | Estimated: 48 patients | N/A | Not yet recruiting | NCT04273646 |
| Bone Marrow MSCs | Single dose of $1 \times 10^6$ cells per kg, IV | Estimated: 20 patients | N/A | Phase 1 clinical trial; Not yet recruiting | NCT04346368 |
| Human embryonic stem cells, matrix-regulatory cells | 3 cohorts who receive doses of 3, 5, 10 million cells per kg body weight IV | Estimated: 9 patients | N/A | Phase 1 clinical trial; Recruiting | NCT04331613 |

***Table 3:*** *Stem cell-based clinical trials for COVID-19.*

*Source: http://www.chictr.org.cn and https://clinicaltrials.gov (NCT numbers refer to Clinical trials.gov identifier numbers).*

Recently, Chen and coworkers reported the use of MSCc in the clinical treatment of H5N1 viral infections that have similar effects on the lung [39]. There was an another case study was reported in China, where the results were found extremely effective after 21 days of treatment with umbilical cord MSCs in a female patient with an acute COVID-19 syndrome. The patients facing the breathing and relieve muscle fatigue due to poor oxygenation are treated with cord MSCs alone and with α-1 thymosin $5 \times 10^7$ cells each three times. The results showed that after the second injection, serum albumin, CRP, and ALT/AST gradually decreased, as well as other vital signs improved, and improved the breathing system of the patients. It was found that the number of lymphocytes reached to their normal level. Most importantly, $CD8^+$ T cell, $CD4^+$ T cell and $CD3^+$ T cell numbers were significantly increased. The results showed that the pneumonia was very relieved on CT images obtained from after the 2nd and 3rd injections of cord stem cells. After two days the 3rd injection the patient discharged from the ICU and most of the vital signs and clinical laboratory parameters were normal [50]. The results from the studies suggested that umbilical cord mesenchymal stem cells could play an important role in the treatment for acute COVID-19 patients. The results showed that the clinical symptoms of all patients improved significantly two days after stem cell transplantation.

In another case study, three patient in which one has very acute and two patients with milder conditions were discharged within 10 days after stem cell transplantation. On day six after transplantation, their results also showed the increased peripheral lymphocyte levels and activated cytokine-secreting immune cells including $CXCR3^+$ $CD4^+$ T cells, $CXCR3^+$ $CD8^+$ T cells. At the same time, IL-10 was increased and TNF-α levels were decreased in the patients treated with MSCs therapy [47]. Therefore, it may be concluded that MSCs therapy is effective for treating patients with COVID-19 pneumonia with an acute conditions. Now a day there is a need for globally coordinated approach and support to conduct multicenter clinical trials to demonstrate safety and effectiveness of various types of stem cells to treat COVID-19 and other health complications. It also suggests that there is a need in biomedical research and development to establish the most effective stem cell types that are ideally suited for the treatment of aforementioned complications.

## Conclusion

Several research investigations have identified that SARS-CoV-2 belongs to β-coronavirus family with positive sense RNA genome and has a highly identical genomic structure to bat coronavirus. The novel coronavirus uses ACE2 receptor as a binding receptor for their entry to human host cell, and mainly spreads through the respiratory tract. Through a planned endocytosis and exocytosis pathway virus easily replicated their life cycle inside the living cell and transmitted to other cell. Scientists, doctors, medical staff and other scientific organization from all over the world are involved as frontline corona warriors against COVID-19 pandemic. Research on different vaccine approaches are still in progress for eliminating this pandemic situation. Vaccine candidates, including inactivated whole-viruses, live viruses, recombinant protein subunits, and nucleic acids may offer better protection against pandemic COVID-19. Immunomodulatory and anti-inflammatory properties of MSCs might be effective weapon for treating patients with COVID-19. As are multipotent in nature and can be easily isolated from various tissues. At present, 17 clinical trials are underway to evaluating the therapeutic potential of MSCs for the treatment of COVID-19. Studies suggest the ability of MSCs to promote distal lung epithelial repair, albeit potentially limited in the presence of hypercapnic acidosis. MSCs therapy can prevent the overproduction release of cytokines by immune system and promote endogenous repair by the stem cells. Several countries including USA, China, Iran, Jordon are working on cell based therapy clinical studies. Therapeutic approaches including Vaccine/MSCs therapy currently in progress have their advantages and disadvantages. Consequently, it is the priority that vaccine/MSCs therapy prepared by any of the promising approach will require a carefully evaluation for safety and efficacy. The data presented in this review provides a judicious summary on efforts to develop a Therapeutic approach for the SARS-CoV-2.

## Author Contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

## Competing Interests

No competing in interests.

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