Medycyna Pracy 2021;72(6):693–700
http://medpr.imp.lodz.pl/en

https://doi.org/10.13075/mp.5893.01207

REVIEW PAPER

POTENTIAL THERAPEUTIC APPLICATION OF MESENCHYMAL STEM CELLS IN COVID-19 COMPLICATIONS

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Abstract

Mesenchymal stem cells (MSCs) have remarkable immunomodulatory properties, low immunogenicity, and paracrine properties as well as the ability to differentiate into multiple cell lines. These properties make them potential candidates for clinical applications in the treatment of neurodegenerative, cardiovascular, and lung diseases, which may be occupational diseases. Preclinical studies using experimental animal models have demonstrated regenerative properties of MSCs in diseases such as silicosis and occupational asthma. Currently, treatment of the novel disease COVID-19 could be enhanced by using MSC therapies. This disease affects many professional groups with great intensity and its consequences might be considered as an occupational disease. It is a significant public health problem and a therapeutic challenge. Despite the development of vaccines against COVID-19, there is growing concern about the emergence of new mutations of the SARS-CoV-2 virus in addition to the known alpha, beta, gamma, and delta variants. There is still no effective COVID-19 treatment and the existing ones only play a supporting role. MSCs offer treatment possibilities as an alternative or complementary therapy. The clinical trials to date using MSCs in patients with COVID-19 give hope for the safe and effective use of this stem cell population. Med Pr. 2021;72(6):693–700

Key words: occupational diseases, mesenchymal stem cells, cell therapy, complementary therapy, COVID-19, SARS-CoV-2 mutations

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Received: August 18, 2021, accepted: November 12, 2021

INTRODUCTION

In recent months, there has been a growing discussion about the role of the coronavirus disease 2019 (COVID-19) and its complications, especially long-term and irreversible ones, in the assessment of occupational risk in healthcare workers. However, this particular disease has a huge impact on the work environment not only in healthcare but also in many other workplaces, increasing the risk of severe lung disease and multi-organ complications. Generally, people whose job requires working in closed workplaces or in large groups are more susceptible to SARS-CoV-2 exposure compared to the rest of the population [1]. The problem was first noted at the start of the pandemic among animal wholesalers in Wuhan [2]. In addition, many of those who have experienced acute respiratory distress syndrome and thromboembolic complications in the course of COVID-19 will develop a restrictive or progressive pulmonary fibrosis, vascular disease, or post-infectious myositis [3–5]. The exact scale of the problem is not yet precisely defined but the cases observed so far are relatively common and may result in reduced work ability [6].

We have high hopes to contain the SARS-CoV-2 epidemic with effective prophylactic vaccination but the number of vaccinated people remains far below expectations. The emergence of new variants of the SARS-CoV-2 virus additionally increases the risk of further pandemic waves. Moreover, an effective drug for COVID-19 has yet to be developed. The existing treatments only play a supporting role.

MSCs could be a promising therapeutic or supplementary agent for treatment of COVID-19 (Figure 1). These are multipotent cells that have been used successfully in regenerative medicine. Thanks to their effective acquisition from a variety of tissues of the human body, including bone marrow, adipose tissue, synovial membranes of joints, umbilical cord, and placenta, mesenchymal stem cells (MSCs) constitute a therapeutic agent

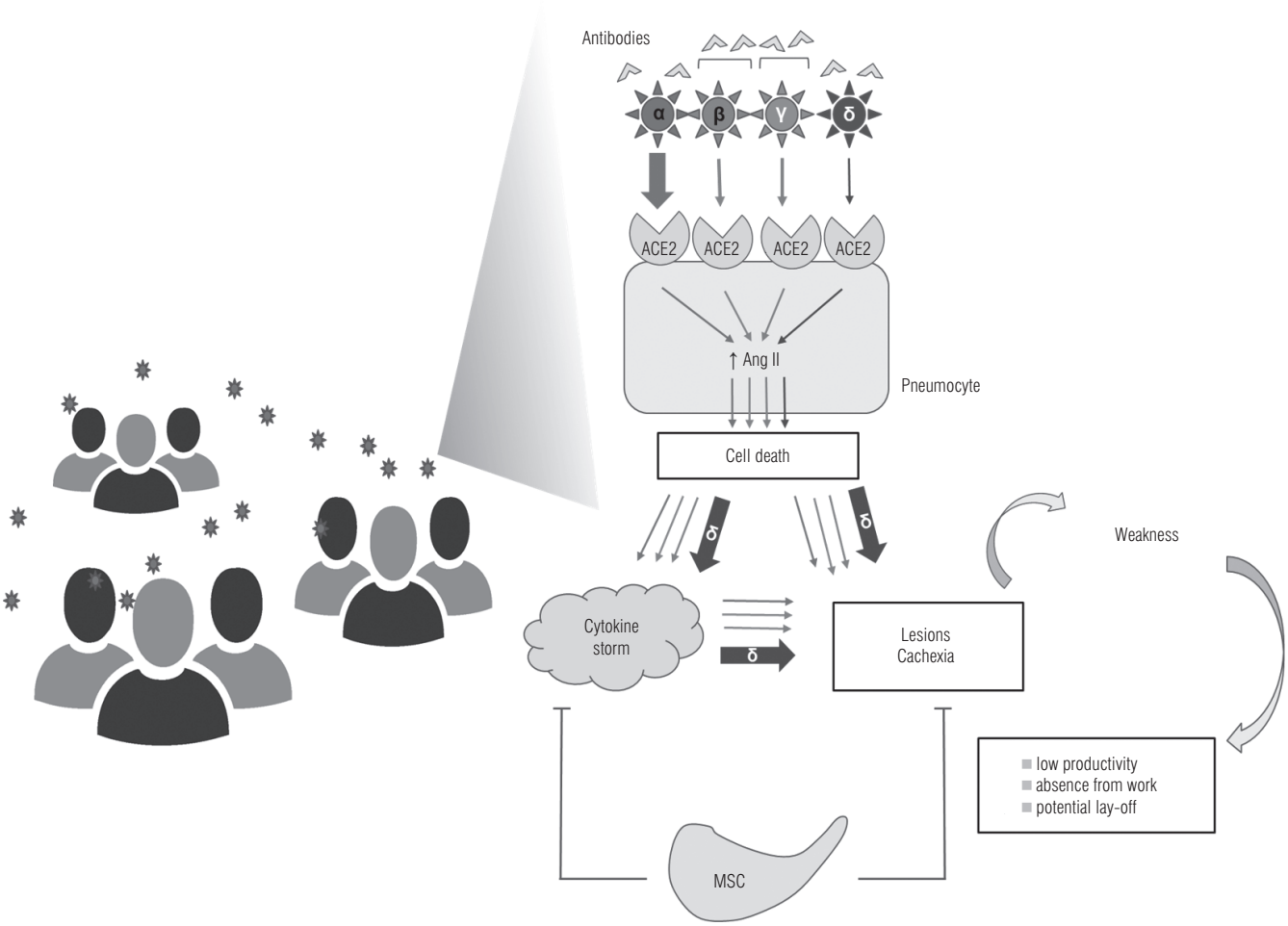

Figure 1. Potential application of mesenchymal stem cells (MSCs) in the treatment of different variants of SARS-CoV-2 infection

that is relatively accessible, safe for the patient, and devoid of ethical concerns [7]. They owe their wide application to, among others, their low immunogenicity. Due to the low expression of major histocompatibility complex (MHC) particles and undetectable levels of MHC II, MSCs are not recognized by the human immune system [8]. Their use in the treatment of COVID-19 and other infectious diseases of the respiratory system is possible thanks to the unique immunomodulatory properties resulting from the prostaglandins, cytokines, chemokines, and growth factors they produce. One of the most important factors mentioned above is prostaglandin E2 (PGE2), which inhibits the maturation of dendritic cells, presentation of antigens, and secretion of cytokines as well as reduces the activity of natural killer (NK) lymphocytes [9]. Indoleamine 2,3-dioxygenase and nitric oxide inhibit the proliferation and maturation of many different types of immune cells, including cytotoxic lymphocytes. Tumor Growth Factor β (TGFβ) promotes immunosuppression by increasing the activity of regulatory T cells (Treg). On the other hand, hepatocyte growth factor (HGF) helps in the regeneration of organs damaged by a cytokine storm, including lungs [10]. Some of the substances produced by MSCs are secreted via exosomes, i.e., membrane-bound vesicles released into the immediate vicinity of the cells. Exosomes also contain genetic material in the form of microRNA (miRNA) and transfer RNA (tRNA), and their lipid envelopes allow them to fuse with the membranes of adjacent cells [11]. These vesicles have the same immunogenic properties as MSCs themselves.

So far, MSCs have been successfully used in animal models of pulmonary fibrosis in the course of silicosis and occupational bronchial asthma. A study using a rat model of pulmonary fibrosis following administration of silica showed significant reduction in fibrosis in animals additionally treated with MSCs derived from bone marrow. The study also showed reduced levels of inflammatory cytokines such as tumour necrosis factor α (TNF-α), interleukin 1β (IL-1β), and interleukin 6 (IL-6)

in lung tissue [12]. A study using a murine model of occupational bronchial asthma showed that administration of adipose-derived MSCs significantly reduces lung neutrophilic infiltrates and reduces IgE levels [13].

Clinical trials conducted on COVID-19 patients with the use of MSCs confirmed the possibility of their use in the acute phase of the disease [14]. It is not known whether it will be possible to use these cells also in the post-acute COVID-19 syndrome (PACS) to reduce long-term complications and whether MSCs will be similarly effective against complications arising from infection with each virus variant. Some reports suggest that individual SARS-CoV2 variants may differ significantly not only in their immunogenicity but also in the degree of induction of the cytokine storm generated during infection [15].

METHODS

The literature review was based on the PubMed database. The following combination of keywords: "Mesenchymal Stem Cells in COVID19 treatment," "COVID19 pathogenesis and complications," "Mesenchymal Stem Cells in occupational diseases treatment," "SARS-CoV-2 mutations," and "COVID-19 as an occupational disease," were used. Papers published in English were selected for the review. As many as 40 publications, the most recent covering the analyzed topic, were reviewed and discussed in this publication.

RESULTS

COVID-19 pathogenesis

SARS-CoV-2 is an RNA virus from the betacoronavirus group, whose genome is 79.5% compatible with the SARS virus [16]. The surface of the SARS-CoV-2 virion is covered with spike glycoproteins (S proteins) through which infectious particles enter the host cells. Viruses most commonly target pneumocytes, which show high expression of angiotensin-converting enzyme 2 (ACE2) membrane enzymes (though not the highest in the body) [17]. S proteins show an affinity for these enzymes, making them receptors for viruses [18]. Viruses enter the lungs when infectious material is inhaled in aerosol form. Other ACE2-expressing cells in the body may also become infected. This applies to mucous membranes of the mouth, eye, and nose as well as the gastrointestinal tract, although this route of infection is less common and occurs mainly in children [16].

The combination of the virus with ACE2 results in its entry into the cell via endocytosis. The viral capsid is shed into the cytoplasm [19]. The viruses then modify the cell to produce proteins to synthesise more infectious particles that are eventually released via exocytosis. In the case of SARS viruses, the main cell-damaging mechanism is the increase in angiotensin II concentration resulting directly from the virus binding to ACE2. Under normal conditions, these enzymes regulate the levels of angiotensin, converting it into inactive metabolites. Combining viruses with receptors blocks the enzymatic activity of the latter, which results in an increase in the concentration of the hormone inside the cells and ultimately their death [20].

Dead pneumocytes and their debris attract macrophages to the infection site, which initiate the phagocytosis process. Absorption of damaged cells results in the release of small alarmins, also known as damage-associated molecular patterns (DAMPs). These molecules are recognized by toll-like receptors located on the surface of dendritic cells and leukocytes [20]. Binding of DAMPs activates in these cells the MyD88 adapter protein-dependent signalling pathway through which the nuclear factor kappa-light-chain-ehancer of activated B cells (NFκB) is activated. This factor enters the cell nucleus and induces transcription of pro-IL-1β and procaspase-1, which are then trimmed to active IL-1β and capsase-1. These proteins are involved in the formation of a complex called inflammasome, which is responsible for the production of cytokines that are then released from cells.

Among the cytokines significant for cytokine storm development, the following are particularly important: IL-6, interferon γ (INF-γ), TNF-α, and IL-1 [21]. Their combined action produces effects usually seen in severe COVID-19. Interleukin 6 is a factor that induces lymphopenia occurring in a cytokine storm, increases the proportion of the lymphocyte population in favour of cytotoxic NK and T lymphocytes, and inhibits the formation of Treg lymphocytes. Also, by stimulating cytotoxic cells, it not only increases their toxic activity but also causes massive apoptosis due to functional exhaustion [22]. Interferon γ is associated with an increased number of neutrophils and their infiltration in the lungs, and its level is an important indicator of the severity the disease [21]. Tumour necrosis factor α stimulates lung epithelial cells to secrete hyaluronates that draw fluid into the pulmonary alveoli, which is a common cause of respiratory failure in severe COVID-19. Interleukin 1 stimulates the activity of Th17 lymphocytes, increasing their secretion of interleukin 17 (IL-17), which causes fibrosis of the lungs and other organs [23].

So far there are no known pharmacological agents that could effectively quench the cytokine storm. A potential drug would have to act on many of the cytokines involved in the storm to suppress their effects. The drugs available for use in adjunctive therapy block single cytokines. One of such drugs is tocilizumab – an antibody against the IL-6 receptor. It is used in the treatment of COVID-19 but the therapy with its use carries the risk of serious side effects in the form of neutropenia, thrombocytopenia, and liver injury [18].

SARS-CoV-2 has many genetic variants, primarily defined by different conformations of S proteins. These mutations modify the properties of the virus, so that each variant has slightly different clinical significance. The World Health Organization (WHO) considers 4 variants of SARS-CoV-2 to be of concern: B.1.1.7 (Alpha), first reported in the UK in September 2020; B.1.351 (Beta), first found in South Africa in October 2020; P.1 (Gamma), first identified in Brazil in December 2020; and least understood B.1.617.2 (Delta), first identified in India in October 2020 but recognized as a variant of concern in May 2021. In May and June 2021 Delta became the dominant variant in the UK [24].

All 4 variants are derived from the strain with the D614G mutation, whose appearance in January 2020 coincided with the declaration of the pandemic by the WHO. This mutation is characterised by the activation of not 1 but 2 or 3 S protein receptor binding domains, which significantly accelerates the penetration of viruses into cells and their spread. This strain completely dominated the population in late April and early May 2020, giving rise to the so-called "G group" that includes all of the above-mentioned variants and replacing the groups L, S, 0, and V that were present before the declaration of the pandemic and lacked the D614G mutation [25].

The emergence of the Alpha variant in September 2020 coincided with the second wave of the pandemic in many countries, including Europe. September brought a significant increase in new cases, which may be related to the properties of this virus variant. In addition to the D614G mutation, B.1.1.7 also has a change in the ACE2 binding site on the receptor binding domain (N501Y), which significantly increases its affinity for the enzyme. As a result, this variant spreads up to 90% faster than the original strain from Wuhan [26]. It has been shown to be highly sensitive to immunization with the Pfizer-BioNTech vaccine, but patients may become infected within 2 weeks after receiving the first dose and within 1 week after receiving the second dose [27].

Beta and Gamma variants have several similar mutations in the S protein (K417N/K417T, E484K, N501Y), resulting in similar properties. Both variants are characterised by a change in aminoacid sequence in the ACE2 binding region. Both of these mutations most likely reduce the affinity for ACE2 compared to the Alpha variant (although it is still higher than in the original D614G strain) but allow the viruses to escape neutralisation by antibodies induced by a vaccine or natural infection, resulting in probably lower effectiveness of the Pfizer BioNTech, Moderna, and AstraZeneca vaccines against these variants [28]. The E484K mutation further reduces the affinity between viruses and antibodies. For those reasons, these variants may not spread as quickly as Alpha but may cause more repeat infections in people who have been infected with the Alpha variant [25].

The Delta variant is the least understood. The exact differences separating it from the rest of the "G group" are unclear, but animal model studies showed that infection with this variant results in more weight loss, more extensive pulmonary inflammation, and more haemorrhages than infection with the D614G strain. The course of this infection may therefore be more severe than in the other variants [15]. Delta caused a massive second wave of infections in India and then led to a third wave in the UK [29]. Epidemiological data also show that this variant spreads approx. 60% faster than Alpha and is less susceptible to immunisation with the available vaccines [30].

The use of MSCs in the treatment of COVID-19

The immunomodulatory properties of MSCs have made them of interest to researchers in terms of treatment options for infectious diseases of the respiratory system, including COVID-19 [31]. In the context of COVID-19 treatment, the conducted research included pilot [32], phase 1 [33,34], and phase 2 [35] studies (Table 1). None of the studies reported serious adverse events associated with the administration of MSCs to patients [36]. Two studies reported minor side effects in the form of rash, convulsions, and light fever [33,34]. This confirms the safety of MSC therapies also in patients with COVID-19.

Clinical trials demonstrated several positive effects of MSCs in COVID-19 patients. Some of the studies included placebo-controlled groups [2], and in non-controlled studies the results were compared with the observations from other centres [37]. However, assessment of the effects of MSC therapies is hampered by the fact that the study groups were usually heterogeneous.

Table 1. Clinical application of mesenchymal stem cells (MSCs) in the treatment of COVID-19 (based on the data published since March 2020)

Form of trial	Patients [n]	Cell type	Results	Reference
Phase 1 clinical trial	9	umbilical cord MSCs	↓ pro-inflammatory cytokines ↑ blood oxygenation minor adverse reactions in 2 patients	33
Randomized, double-blind, placebo-controlled phase 2 clinical trial	65	umbilical cord MSCs	↓ lung lesions ↑ physical ability no adverse reactions	35
Experimental treatment	1	umbilical cord MSCs	↓ neutrophiles, lung lesions ↑ lymphocytes, general condition no adverse reactions	38
Pilot study	7	umbilical cord MSCs	↓ lung lesions, pro-inflammatory cytokines ↑ survival rate, general condition no adverse reactions	32
Phase 1 clinical trial	11	umbilical cord and placenta MSCs	↓ pro-inflammatory cytokines and CRP ↓ lung lesions minor adverse reactions in 2 patients	34
Prospective nonrandomized open-label cohort study	24	bone marrow MSCs exosomes	↓ acute-phase proteins ↑ survival rate, blood oxygenation no adverse reactions	37

CRP – C-reactive protein, MSCs – mesenchymal stem cells.
↑ increase, ↓ decrease.

The patients who participated in the studies were of different ages and sexes and were in advanced stages of the disease of varying severity.

One effect observed in several independent studies regardless of the patient profile was the acceleration of lung regeneration. During COVID-19, inflammatory infiltrates and necrotic foci were found in the lungs, which later became fibrotic [13]. In a randomized phase 2 study by Shi et al. [35], the lung status of the study group patients was monitored using high-resolution computed tomography and compared with the results of the same examination performed on patients in the control group. It turned out that over the same time interval, the volume of pathological structures in the lungs of MSC-treated patients decreased statistically more than in placebo-treated patients. Consolidation of changes decreased particularly significantly [35]. It is believed that lung regeneration may be encouraged by a reduction of proinflammatory interleukin levels, but no significant decreases were observed in this particular study. However, the authors were not able to monitor the activity of MSCs in the lungs and the substances secreted by them into the tissues may not have entered the venous blood on which the tests were conducted. It is therefore most likely that improvement in lung tissue regeneration was due to the release of anti-inflammatory and regenerative substances (such as HGF, VEGF, and IL-10) by stem cells into the surrounding lung tissue, which did not translate into significant biochemical changes in the blood. This study was conducted at a time when the D614G strain was increasingly contributing to the virus population, shortly before it became the dominant strain.

Another effect of cell therapy that emerged in the research was the biochemical and cellular signs of resolution of the cytokine storm. Patients treated with MSCs showed an increase in the number of lymphocytes, eliminating lymphopenia, and in the case of the experimentally treated female patient described by Liang et al. [38] there was also a decrease in the number of neutrophils. Many studies also showed decreases in the concentrations of proinflammatory cytokines (IL-6, TNF-α, IL-8) and acute-phase proteins (CRP, D-dimers) [32,38]. The decrease in CPRs is likely an indirect effect resulting from decreased levels of IL-6, TNF-α, and IL-8, which stimulate its secretion in the liver. This protein is not believed to be dangerous in itself but merely serves as a marker of the inflammation intensity. In one of the studies by Hashemian et al. [34], a few patients experienced slight increases in anti-inflammatory cytokines IL-4 and IL-10, although the statistical analysis did not find them to be significant (Figure 1).

Treatment with MSCs significantly improved patient survival, attenuated the disease process, and accelerated

convalescence and discharge from hospital [37]. This is likely due to the rapid decline in the levels of proinflammatory cytokines, which cause cachexia, and facilitated regeneration processes. Patients treated with MSCs also recovered faster. In a study by Shi et al. [35], the control and test subjects were subjected to a 6-minute walk test, which measures the distance covered by the subject over a period of 6 min of leisurely walking. On average, MSC-treated patients covered a greater distance than their placebo-treated counterparts (420 m vs 403 m) [35]. This was likely due to an improvement in respiratory function achieved by faster removal of inflammatory lesions from the lungs and accelerated regeneration of their structure, making gas exchange more efficient. This is also supported by the improvement (by an average of 191%) in blood oxygenation observed in a study by Sengupta et al. [37]. The study used exosomes and was conducted during the dominance of the D614G strain.

It is highly likely that an MSC therapy can also prevent the development of some stages of PACS. The most important aspect of this syndrome is chronic fatigue that persists for months, resulting from, among others, structural muscle weakness caused by high IL-6 levels and decreased excitability of motor neurons caused by long periods of low physical activity due to the disease [39]. By inhibiting IL-6 secretion and accelerating physical recovery, MSCs can protect patients against these effects. They can also protect them from developing one of the most serious complications of PACS, i.e., permanent pulmonary fibrosis. It is believed to affect about 5% of patients, permanently reducing their respiratory function [40]. The onset of fibrosis is a consequence of inflammatory necrosis. Factors produced by MSCs help regenerate lung tissue and remove inflammatory infiltrates before the onset of necrosis, thus significantly reducing the risk of fibrosis.

CONCLUSIONS

From the perspective of new hazards that may occur in the workplace, COVID-19 is one of the most serious factors having a negative impact on the health of employees in many industries where face-to-face teamwork is essential for business operation. Due to the COVID-19 pandemic, many problems have emerged that complicate work organisation as well as occupational ergonomics, physiology, and psychology. The biggest problem, however, has been the periodic or permanent absence of many employees suffering from COVID-19 or PACS. Business operations have also been affected by quarantines of employees that may have been infected with the SARS-CoV-2 virus. Unfortunately, despite the existing vaccination programme, the number of COVID-19 patients worldwide is high and there is still a risk of new mutations of the SARS-CoV-2 virus against which prophylactic vaccination may not be effective. Moreover, there is still no effective cure for COVID-19, and existing treatments have been largely symptomatic and aimed at preventing complications. The application of cell therapy using MSCs could be helpful in solving this problem. As demonstrated by clinical studies, such therapy is safe and, in many cases, effective.

The therapeutic potential of MSCs in COVID-19 consists mainly in 2 aspects: repairing damage caused by cell death due to ACE2 blockage by viruses and preventing further damage caused by the cytokine storm. It this way, MSCs appear to be useful in treating infections with the Alpha, Beta, Gamma, and Delta variants. The first 3 variants, due to the mutation-enhanced affinity for ACE2 enzymes, may not only spread faster but also kill more cells, accelerating the development of inflammatory lesions and necrosis. MSCs can offset these effects by accelerating tissue regeneration. The Delta variant, on the other hand, is characterised by the formation of larger inflammatory lesions and greater cachexia, suggesting that infection with this variant causes a more severe cytokine storm. In this case, the action of MSCs may be even more important. By rapidly suppressing the cytokine storm and inhibiting the production of new proinflammatory substances, they can stop severe damage caused by the latest SARS-CoV-2 variant. In addition, MSCs have antifibrotic effects and thus have the potential to prevent permanent health damage by allowing the lungs to regenerate completely in PACS.

Considering all these effects, MSCs may become a factor supporting COVID-19 therapy as well as recovery after COVID-19 and may contribute to minimizing socio-economic consequences resulting from the absence of COVID-19 patients in their workplaces.

Particularly dangerous variants of the SARS-CoV-2 virus (variants of concern) include Alpha, Beta, Gamma, and Delta. Modifications to their S proteins result in differences in the properties. A virus-induced cytokine storm impairs the function of key organs. After and during COVID-19, patients experience fatigue, cognitive dysfunction, and dyspnoea, which impair their physical fitness, resulting in absence from work and

long-term decrease in productivity. This generates additional costs for the employer and may disrupt the operation of workplaces. Through their immunomodulatory secretome, MSCs can reduce the effects of infection with all SARS-CoV-2 variants, inhibiting the cytokine storm and promoting regeneration of damaged tissues. This would allow patients to regain fitness quicker, thus enabling faster return to work. Therefore, research into cell therapies in the treatment of COVID-19 should continue.

REFERENCES

1. Carlsten C, Gulati M, Hines S, Rose C, Scott K, Tarlo SM, et al. COVID-19 as an occupational disease. Am J Ind Med. 2021;64(4):227–237. https://doi.org/10.1002/ajim.23222.
2. Middleton J, Reintjes R, Lopes H. Meat plants – a new front line in the COVID-19 pandemic. BMJ. 2020;370:m2716. https://doi.org/10.1136/bmj.m2716.
3. Shah AS, Wong AW, Hague CJ, Murphy DT, Johnston JC, Ryerson CJ, et al. A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations. Thorax. 2020;76(4):402–404. https://doi.org/10.1136/thoraxjnl-2020-216308.
4. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. N Engl J Med. 2020;383:120–128. https://doi.org/10.1056/NEJMoa2015432.
5. Paliwal VK, Garg RK, Gupta A, Tejan N. Neuromuscular presentations in patients with COVID-19. Neurol Sci. 2020;41(11):3039–3056. https://doi.org/10.1007/s10072-020-04708-8.
6. Zhao Y, Shang Y, Song W, Li QQ, Xie H, Xu QF, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. 2020;25:100463. https://doi.org/10.1016/j.eclinm.2020.100463.
7. Han Y, Li X, Zhang Y, Han Y, Chang F, Ding J. Mesenchymal Stem Cells for Regenerative Medicine. Cells. 2019;8(8):886. https://doi.org/10.3390/cells8080886.
8. Tsuchiya A, Takeuchi S, Iwasawa T, Kumagai M, Sato T, Motegi S, et al. Therapeutic potential of mesenchymal stem cells and their exosomes in severe novel coronavirus disease 2019 (COVID-19) cases. Inflamm Regen. 2020;40:14. https://doi.org/10.1186/s41232-020-00121-y.
9. Gao F, Chiu SM, Motan DA, Zhang Z, Chen L, Ji HL, et al. Mesenchymal stem cells and immunomodulation: current status and future prospects. Cell Death Dis. 2016;7(1):e2062. https://doi.org/10.1038/cddis.2015.327.
10. Zeng L, Yang XT, Li HS, Li Y, Yang C, Gu W, et al. The cellular kinetics of lung alveolar epithelial cells and its relationship with lung tissue repair after acute lung injury. Respir Res. 2016;17(1):164. https://doi.org/10.1186/s12931-016-0480-y.
11. Jayaramayya K, Mahalaxmi I, Subramaniam MD, Raj N, Dayem AA, Lim KM, et al. Immunomodulatory effect of mesenchymal stem cells and mesenchymal stem-cell-derived exosomes for COVID-19 treatment. BMB Rep. 2020;53(8):400–412. https://doi.org/10.5483/BMBRep.2020.53.8.121.
12. Martínez-González I, Cruz MJ, Moreno R, Morell F, Muñoz X, Aran JM. Human mesenchymal stem cells resolve airway inflammation, hyperreactivity, and histopathology in a mouse model of occupational asthma. Stem Cells Dev. 2014;23(19):2352–63. https://doi.org/10.1089/scd.2013.0616.
13. Yang Q, Liu Q, Xu H, Lu H, Liu S, Li H. Imaging of coronavirus disease 2019: A Chinese expert consensus statement. Eur J Radiol. 2020;127:109008. https://doi.org/10.1016/j.ejrad.2020.109008.
14. Shu L, Niu C, Li R, Huang T, Wang Y, Huang M, et al. Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. Stem Cell Res Ther. 2020;11(1):361. https://doi.org/10.1186/s13287-020-01875-5.
15. Yadav PD, Mohandas S, Shete AM, Nyayanit DA, Gupta N, Patil DY, et al. SARS CoV-2 variant B. 1.617. 1 is highly pathogenic in hamsters than B. 1 variant. bioRxiv. 2021. https://doi.org/10.1101/2021.05.05.442760.
16. Wang MY, Zhao R, Gao LJ, Gao XF, Wang DP, Cao JM. SARS-CoV-2: Structure, Biology, and Structure-Based Therapeutics Development. Front Cell Infect Microbiol. 2020;10:587269. https://doi.org/10.3389/fcimb.2020.587269.
17. Ashraf UM, Abokor AA, Edwards JM, Waigi EW, Royfman RS, Hasan SA, et al. SARS-CoV-2, ACE2 expression, and systemic organ invasion. Physiol Genomics. 2021;53(2):51–60. https://doi.org/10.1152/physiolgenomics.00087.2020.
18. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol. 2021;93(1):250–256. https://doi.org/10.1002/jmv.26232.
19. Samudrala PK, Kumar P, Choudhary K, Thakur N, Wadekar GS, Dayaramani R, et al. Virology, pathogenesis, diagnosis and in-line treatment of COVID-19. Eur J Pharmacol. 2020;883:173375. https://doi.org/10.1016/j.ejphar.2020.173375.
20. Wei J, Zhao Q, Yang G, Huang R, Li C, Qi Y, et al. Mesenchymal stem cells ameliorate silica-induced pulmonary fibrosis by inhibition of inflammation and epithelial-mesenchymal transition. J Cell Mol Med. 2021;25(13):6417–28. https://doi.org/10.1111/jcmm.16621.

21. Fara A, Mitrev Z, Rosalia RA, Assas BM. Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines. Open Biol. 2020;10(9):200160. https://doi.org/10.1098/rsob.200160.
22. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). Front Immunol. 2020;11:827. https://doi.org/10.3389/fimmu.2020.00827.
23. Ramani K, Biswas PS. Interleukin-17: Friend or foe in organ fibrosis. Cytokine. 2019;120:282–288. https://doi.org/10.1016/j.cyto.2018.11.00.
24. World Health Organization [Internet]. Geneva: The Organization; 2021 [cited 2021 Jul 10]. Tracking SARS-CoV-2 variants. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants.
25. Winger A, Caspari T. The Spike of Concern-The Novel Variants of SARS-CoV-2. Viruses. 2021;13(6):1002. https://doi.org/10.3390/v13061002.
26. Kustin T, Harel N, Finkel U, Perchik S, Harari S, Tahor M, et al. Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2-mRNA-vaccinated individuals. Nat Med. 2021;27(8):1379–1384. https://doi.org/10.1038/s41591-021-01413-7.
27. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021;372(6538):eabg3055. https://doi.org/10.1126/science.abg3055.
28. Chen C, Boorla VS, Banerjee D, Chowdhury R, Cavener VS, Nissly RH, et al. Computational prediction of the effect of amino acid changes on the binding affinity between SARS-CoV-2 spike protein and the human ACE2 receptor. bioRxiv. 2021. https://doi.org/10.1101/2021.03.24.436885.
29. Torjesen I. COVID-19: Delta variant is now UK's most dominant strain and spreading through schools. BMJ. 2021;373:n1445. https://doi.org/10.1136/bmj.n1445.
30. European Centre for Disease Prevention and Control [Internet]. Stockholm: The Organization, 2021 [cited 2021 Jul 10]. Implications for the EU/EEA on the spread of the SARSCoV-2 Delta (B.1.617.2) variant of concern. Available from: https://www.ecdc.europa.eu/en/publications-data/threat-assessment-emergence-and-impact-sars-cov-2-delta-variant.
31. Golchin A, Seyedjafari E, Ardeshirylajimi A. Mesenchymal Stem Cell Therapy for COVID-19: Present or Future. Stem Cell Rev Rep. 2020;16(3):427–433. https://doi.org/10.1007/s12015-020-09973-w.
32. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, et al. Transplantation of ACE2- Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia. Aging Dis. 2020;11(2):216–228. https://doi.org/10.14336/AD.2020.0228.
33. Meng F, Xu R, Wang S, Xu Z, Zhang C, Li Y, et al. Human umbilical cord-derived mesenchymal stem cell therapy in patients with COVID-19: a phase 1 clinical trial. Signal Transduct Target Ther. 2020;5(1):172. https://doi.org/10.1038/s41392-020-00286-5.
34. Hashemian SR, Aliannejad R, Zarrabi M, Soleimani M, Vosough M, Hosseini SE, et al. Mesenchymal stem cells derived from perinatal tissues for treatment of critically ill COVID-19-induced ARDS patients: a case series. Stem Cell Res Ther. 2021;12(1):91. https://doi.org/10.1186/s13287-021-02165-4.
35. Shi L, Huang H, Lu X, Yan X, Jiang X, Xu R, et al. Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: a randomized, double-blind, placebo-controlled phase 2 trial. Signal Transduct Target Ther. 2021;6(1):58. https://doi.org/10.1038/s41392-021-00488-5.
36. Hashemian SR, Aliannejad R, Zarrabi M, Soleimani M, Vosough M, Hosseini SE, et al. Mesenchymal stem cells derived from perinatal tissues for treatment of critically ill COVID-19-induced ARDS patients: a case series. Stem Cell Res Ther. 2021;12(1):91. https://doi.org/10.1186/s13287-021-02165-4.
37. Sengupta V, Sengupta S, Lazo A, Woods P, Nolan A, Bremer N. Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe COVID-19. Stem Cells Dev. 2020;29(12):747–754. https://doi.org/10.1089/scd.2020.0080.
38. Liang B, Chen J, Li T, Wu H, Yang W, Li Y, et al. Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells: A case report. Medicine (Baltimore). 2020;99(31):e21429. https://doi.org/10.1097/MD.0000000000021429.
39. Rudroff T, Fietsam AC, Deters JR, Bryant AD, Kamholz J. Post-COVID-19 Fatigue: Potential Contributing Factors. Brain Sci. 2020;10(12):1012. https://doi.org/10.3390/brainsci10121012.
40. Kamal M, Abo Omirah M, Hussein A, Saeed H. Assessment and characterisation of post-COVID-19 manifestations. Int J Clin Pract. 2021;75(3):e13746. https://doi.org/10.1111/ijcp.13746.

Publisher: Nofer Institute of Occupational Medicine, Łódź, Poland