CASE REPORT / OLGU SUNUMU

DOI: 10.4274/mjima.galenos.2021.2021.54 Mediterr J Infect Microb Antimicrob 2021;10:54

Erişim: http://dx.doi.org/10.4274/mjima.galenos.2021.2021.54



Our Experience with Mesenchymal Stem Cells in Patients with COVID-19

COVID-19 Hastalarında Mezenkimal Kök Hücre Deneyimimiz

Sema SARI¹, Tuğçe MENGi¹, Yahya TAHTA²

 1 Ömer Halisdemir University Training and Research Hospital, Clinic of Intensive Care, Niğde, Turkey

²Erciyes University Institute of Health Sciences, Department of Anatomy, Kayseri, Turkey

Abstract

Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2), which causes Coronavirus disease-2019 (COVID-19), has rapidly spread all over the world and has become a public health emergency. Coronavirus disease-2019 has a wide clinical spectrum, from asymptomatic infection to Acute respiratory distress syndrome, sepsis, metabolic acidosis, coagulation disorder, multi-organ failure and even death. The dysregulated and hyperimmune response to SARS-CoV-2 could possibly explain the highly variable disease manifestations and play an important role in the pathogenesis of COVID-19. Since there is no specific antiviral treatment in the treatment of COVID-19, treatments for inflammation against the virus and sharing experience are important. Mesenchymal stem cells (MSCs) have potent anti-inflammatory and immunomodulatory abilities that can migrate to damaged tissues, promote tissue regeneration, and inhibit tissue fibrosis. Today, MSCs are widely used in many clinical studies on immune-mediated inflammatory diseases such as Graft-versus-Host disease, systemic lupus erythematosus, and perianal Crohn's disease. MSC treatment in COVID-19 is a promising option. In this study, we would present four patients with COVID-19 who were treated with MSCs and who were found to be positive for real-time polymerase chain reaction tests on nasopharyngeal swab or tracheal aspirate. All patients were critically ill were followed up with mechanical ventilator due to severe hypoxemia. One patient was extubated and discharged. Other patients died. In this study, MSCs were used as salvage therapy in the late period, so benefit might not be seen. In previous studies, this treatment was used earlier and there were results showing the benefits of MSCs. Based on this study, MSCs can be a promising treatment option when used in the appropriate patient at the appropriate time.

Keywords: COVID-19, cytokine storm, immunomodulatory therapies, mesenchymal stem cell

Öz

Koronavirüs hastalığı-2019'a (COVID-19) neden olan Şiddetli akut solunum sendromu-Koronavirüs-2 (SARS-COV-2), hızla tüm dünyaya yayılarak bir halk sağlığı acil durumu haline gelmiştir. Koronavirüs hastalığı-2019, asemptomatik enfeksiyondan Akut solunum sıkıntısı sendromu, sepsis, metabolik asidoz, pıhtılaşma bozukluğu, çoklu organ yetmezliği ve hatta ölüm de dahil geniş bir klinik spektruma sahiptir. Şiddetli akut solunum sendromu-CoV-2'ye karşı disregüle ve aşırı immün yanıt, muhtemelen oldukça değişken hastalık belirtilerini açıklayabilir ve COVID-19 patogenezinde önemli bir rol oynayabilir. Koronavirüs hastalığı-2019 tedavisinde spesifik antiviral tedavi olmadığı için virüse karşı gelişen enflamasyona yönelik tedaviler ve deneyim paylaşımı önem arz etmektedir. Mezenkimal kök hücreler (MKH), hasarlı dokulara göç edebilen, doku rejenerasyonunu destekleyen ve doku fibrozisini inhibe edebilen güçlü anti-enflamatuvar ve immünomodülatör yeteneklere sahiptir. Günümüzde MKH'ler, Graft-versus-Host hastalığı, sistemik lupus eritematozus, perianal Crohn hastalığı gibi immün aracılı enflamatuvar hastalıklarla ilgili birçok klinik çalışmada yaygın olarak kullanılmaktadır. Koronavirüs hastalığı-2019'da MKH tedavisi umut verici bir seçenektir. Bu çalışmada, MKH'lerle tedavi edilen, nazofarengeal sürüntüde ya da trakeal aspiratta bakılan gerçek zamanlı polimeraz zincir reaksiyonu testi pozitif saptanan dört COVID-19 olgusunu sunacağız. Tüm olgular, ciddi hipoksemi nedeniyle mekanik ventilatörle takipli kritik derecede hasta olan hastalardı. Bir hasta ekstübe edilerek taburcu edilebildi. Diğer hastalar kaybedildi. Bu çalışmada MKH'ler geç dönemde kurtarma tedavisi olarak uygulamış olup bu nedenle fayda görülmemiş olabilir. Daha

Cite this article as: Bakır Ekinci P, Kurtaran M, Kara E, Avcı H, Demirkan K, Metan G. Our Experience with Mesenchymal Stem Cells in Patients with COVID-19. Mediterr J Infect Microb Antimicrob. 2021;10:54.



Address for Correspondence/Yazışma Adresi: Sema SARI MD, Ömer Halisdemir University Training and Research Hospital, Clinic of Intensive Care, Niğde, Turkey

Phone: +90 530 146 05 95 E-mail: semadmc@gmail.com ORCID ID: orcid.org/0000-0002-1977-8547 Received/Geliş Tarihi: 01.01.2021 Accepted/Kabul Tarihi: 13.09.2021

©Copyright 2021 by the Infectious Diseases and Clinical Microbiology Specialty Society of Turkey Mediterranean Journal of Infection, Microbes and Antimicrobials published by Galenos Yayınevi. Presented in: This study was presented as an oral presentation in the 9th Scientific Platform of Infectious Diseases and Clinical Microbiology Speciality Society of Turkey, 20-23 May 2021-Online Congress.

Published: 15 September 2021

Öz

önceki çalışmalarda bu tedavi daha erken dönemde kullanılmış olup tedavinin faydalı olduğu yönünde sonuçlar bulunmaktadır. Bu çalışmadan yola çıkılarak MKH'lerin uygun zamanda uygun hastada kullanıldığında umut verici bir tedavi seçeneği olabileceğini söyleyebiliriz.

Anahtar Kelimeler: COVID-19, sitokin fırtınası, immünmodülatör tedaviler, mezenkimal kök hücre

Introduction

The Coronavirus disease-2019 (COVID-19), caused by Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2), was first detected in China at the end of 2019 and soon affected the whole world. Severe COVID-19 often progresses to Acute respiratory distress syndrome (ARDS), sepsis, coagulation dysfunction and multi-organ failure, resulting in death in a short time^[1]. Limited treatment options and low response rates in ARDS due to COVID-19 have led to alternative treatments^[2,3]. Mesenchymal stem cells (MSCs), which have strong antiinflammatory and immunomodulatory effects, have been widely used in many diseases such as type 2 diabetes mellitus (DM), autoimmune diseases, graft versus host disease, and spinal cord damage^[4]. It was also used in influenza-related lung injury before, and there were positive results about it[5]. After intravenous (IV) infusion, MSCs are confined to the pulmonary vasculature before entering other organ systems. Therefore, it is thought to be effective in the treatment of lung diseases[6].

Mesenchymal stem cells are expected to reduce the risk of complications and mortality in patients with COVID-19 by improving the microenvironment in the lung, supporting neovascularization and tissue repair, preventing pulmonary fibrosis, and treating lung dysfunction and pneumonia^[7]. In this study, we aimed to present 4 patients with severe COVID-19 who were treated with MSCs and followed up with mechanical ventilator support.

Case Reports

Case 1

A 47-year-old female patient with known hypertension (HT) and obesity was admitted to the emergency department on 09.04.2020 with complaints of shortness of breath and cough. The patient, whose oxygen saturation without support was around 65% and who was tachypneic, was admitted to the intensive care unit. Real-time polymerase chain reaction (RT-PCR) test was positive in the nasopharyngeal swab taken in the emergency room. Heart rate was 117/min, arterial blood pressure was 130/80 mmHg, respiratory rate was 30/min, and body temperature was 37 °C. There were bilateral diffuse rales and rhonchi in oscultation of the lungs. There were bilateral diffuse ground glass opacities in thorax computed tomography

(CT) (Figure 1). The clinical, laboratory, management and outcome data of the patient are given in Table 1. The patient, whose saturation was around 75%, was intubated on the second day of hospitalization under 8 lt/min oxygen support with a mask in the intensive care unit. On the third day of hospitalization, when the FiO₂ was 100% and the saturation was around 60%, 100 mg methylprednisolone was given in addition to the hydroxychloroquine, favipravir and moxifloxacin treatments. Since there was no response, a single dose of 400 mg tocilizumab was administered on the same day. With 100% fractional inspired oxygen (FiO₂) and 15 positive end-expiratory pressure (PEEP), the saturation of the patient increased to 90% and FiO₂ could be reduced to 70%. However, due to her continued need for PEEP, 7x10⁵ cells/kg IV MSC treatment was applied on the sixth day of her hospitalization. Intravenous immunoglobulin treatment, which was started on the seventh day, was administered at a dose of 0.4 g/kg/day for four days. Tracheal aspirate sample was taken due to increased secretion and on the eighth day, K. pneumoniae growth occurred in the tracheal aspirate culture (TAC). Since she was resistant to empirical piperacillin-tazobactam treatment, her treatment was arranged as colistin (sensitive) and meropenem (intermediate sensitive). The patient, whose PEEP requirement and oxygen requirement decreased gradually, was extubated on the eleventh day. The patient, who was transferred to the ward on the 15th day, was discharged on the 28th day of her hospitalization with spontaneous breathing in room air.

Case 2

A 67-year-old obese male patient with HT, DM and chronic obstructive pulmonary disease (COPD) was admitted to the emergency department with the complaint of shortness of breath for two days on 30.03.2020. Oxygen saturation was 94% and vital signs were stable. The patient was admitted to the ward because of mild involvement in thorax CT. Real-time PCR test was found positive in the nasopharyngeal swab taken in the emergency room. The patient who had a fever of 40 °C in the ward, had a oxygen saturation of 80% and was tachypneic, was transferred to the intensive care unit on the 7th day of his hospitalization. His anteroposterior (AP) chest X-ray is shown in Figure 2A1. Favipravir and 100 mg methylprednisolone were started in the patient who was treated with hydroxychloroquine in the ward. On the 8th day, he was intubated and connected to a mechanical ventilator. The clinical, laboratory, management

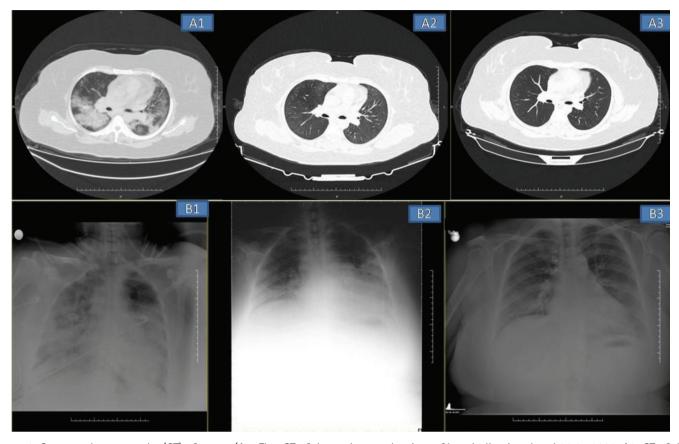


Figure 1. Computed tomography (CT) of case 1 (A1: First CT of the patient at the time of hospitalization dated 09.04.2020, A2: CT of the patient dated 01.06.2020 after discharge, A3: Last CT of the patient dated 19.02.2021) and chest X-rays (B1: Anteroposterior chest X-ray (APCX) of the patient dated 12.04.2020 during hospitalization, B2: APCX before discharge dated 03.05.2020, B3: Control posteroanterior chest X-ray dated 24.11.2020)

Table 1. Clinical, laboratory, management and outcome data of case 1

Days of hospitalization	1	2	3	4	5	6	7	8	10	11	12	14	15	16	21	28
Intensive care unit																
Invasive ventilation																
PaO ₂ /FiO ₂ (mmHg)	170	90	38	86	104	131	121	150	216	277	260	257	331	350	380	400
MSC																
IVIG																
Tocilizumab																
Leukocyte (10³/mcl)	9.3		14		10	8.2	7.9	14	8.9	8.7	9.9	7.3	5.4	3.7	4.3	3.2
Lymphocyte (10³/mcl)	0.6		0.9		0.8	0.6	0.9	0.5	0.8	1.1	1.5	1.4	1.5	1.4	1.4	1.1
CRP (mg/l)	268		110			31	13	9.6	3	2	2	2	2	1.5	6	6
Ferritin (ug/l)	93		91			59	62	74	75	81	93	114	94	51	42	33
LDH (U/I)	571		828			581	625	676	625	609	620	460	359	365	390	314
D-dimer (ng/ml)	281		1657			599	933	967	853	790	772	625	582	1851	358	217
Date	10.04	11.04	12.04	13.04	14.04	15.04	16.04	17.04	19.04	20.04	21.04	23.04	24.04	25.04	30.04	07.05

^{*}The days of intensive care unit hospitalization, the days of invasive ventilation, the days of MSC, IVIG and tocilizumab treatments are colored in blue.

PaO₂/FiO₂: Partial oxygen pressure/fractionated oxygen level, MSC: Mesenchymal stem cell, IVIG: Intravenous immunoglobulin, CRP: C-reactive protein, LDH: Lactate dehydrogenase

and outcome data of the patient are given in Table 2. Klebsiella pneumoniae grew in the TAC on the 14th day of hospitalization and in the blood culture on the 19th day. Empirically initiated meropenem was sensitive and infection parameters regressed. Intravenous immunoglobulin treatment, which was started on the 15th day of his hospitalization, was administered at a dose of 0.4 g/kg/day for two days. The patient whose oxygenation did not recover with FiO, 100% and PEEP 15, in addition to other treatments, a single dose of 7x105 cells/kg IV MSC was administered to the patient on the 22nd day of his hospitalization. On the 28th day of hospitalization, the cultures of the patient who developed hypotension and increased secretion were taken, and meropenem treatment was changed with colistin and tigecycline, taking into account the hospital flora. In TAC, Acinetobacter baumannii growth was found to be sensitive to colistin and intermediate sensitive to tigecycline. The patient, whose oxygenation and clinical findings did not improve, died from septic shock on the 7th day after MSC treatment.

Case 3

A 51-year-old male patient, who did not have any additional disease other than known COPD, was admitted to the emergency department on 21.07.2020 with complaints of shortness of breath and cough for one week. The patient, who was admitted to the ward, was admitted to the intensive care unit the next day due to increased shortness of breath and decreased saturation. Anteroposterior chest X-ray is shown in Figure 2B1. The clinical, laboratory, management and outcome data of the patient are given in Table 3. The patient who was intubated on the day of

admission to the intensive care unit was followed up with a FiO_a of 60% and a PEEP of 15. Piperacillin-tazobactam, levofloxacin, hydroxychloroguine, favipravir and dexamethasone (2x8 mg) treatments which were started in the ward were continued. On the 7th day of hospitalization, tocilizumab was administered in addition to other treatments. Positive end-expiratory pressure could be reduced up to 10 and FiO₂ could be reduced up to 50%. As fever and infection parameters increased on the 9th day, cultures were taken and piperacillin-tazobactam treatment was changed to meropenem and tigecycline. Infection parameters of the patient regressed in whom Kocuria kristinae grew in blood and TACs. The patient, who could not be extubated due to diffuse lung involvement, was treated with 7x105 cells/ kg IV and 3x10⁵ cells/kg intratracheally (IT) on the 11th day of his hospitalization. The patient, whose oxygenation gradually worsened and FiO₂ had to be increased to 100%, died at the 58th hour of MSC treatment.

Case 4

An 87-year-old male patient with HT, coronary artery disease, prostate cancer had been followed up with oxygen support at home for a week due to COVID-19. He was admitted to the intensive care unit on 23.08.2020 due to increased shortness of breath. The AP chest X-ray is shown in Figure 2C1. The clinical, laboratory, management and outcome data of the patient are given in Table 4. Piperacillin-tazobactam, moxifloxacin, dexamethasone (2x8 mg) treatments were started for the patient who completed the favipravir treatment at home. The patient, who was followed up with high-flow oxygen,

Table 2. Clinical, laboratory, management and outcome data of case 2

Days of hospitalization	1	6	7	10	12	14	15	16	17	19	21	22	23	24	26	28	29
Intensive care unit																	
Invasive ventilation																	
PaO ₂ /FiO ₂ (mmHg)	330	230	96	118	137	124	113	97	116	88	87	76	92	97	75	106	74
MSC																	
IVIG																	
Leukocyte (10³/mcl)	7.4	8.7	11.4	10.3	9.4		11.7	9.3	7.1	7.5	14.8	11.1	9.8	9.9	5.2	5.2	11.6
Lymphocyte (10³/mcl)	1.9	0.4	0.68	0.64	0.56		0.76	0.69	0.43	0.92	0.61	1.12	0.61	0.49	0.9	0.74	1.7
CRP (mg/l)	51	66	149	56	14		214	217	280	156	221	103	142	165	349	338	183
Ferritin (ug/l)	684	1080	1400		821		1366	1294	1404	1834	2000	1273	1117	1176	734	981	2000
LDH (U/I)		725	658		477		594	599	385	402	491	526	340	373	287	319	485
D-dimer (ng/ml)		397	1203		573		1185	2345	2322	5018		2315	3919	2492	2787	1840	1711
Date	01.04	06.04	07.04	10.04	12.04	14.04	15.04	16.04	17.04	19.04	21.04	22.04	23.04	24.04	26.04	28.04	29.04

^{*}The days of intensive care unit hospitalization, the days of invasive ventilation, the days of MSC, IVIG and tocilizumab treatments are colored in blue.

was intubated on the third day of hospitalization due to increased oxygen demand and respiratory effort. The patient, who was extubated on the 16th day, was re-intubated two days later because he could not tolerate it. On the 26th day of hospitalization, 7x10⁵ cells/kg MSC was administered IV to the patient who could not be weaned from the mechanical ventilator. The patient with better oxygenation was extubated three days after the MSC treatment. The patient, who was transferred to the ward seven days after the treatment, was reintubated and taken to the intensive care unit, after nine days due to increased secretion and not being able to remove the secretions. There was *A. baumannii* growth in TAC. The patient, who could not be extubated again, died on 18.10.2020 on the 56th day of his hospitalization and on the 31st day of MSC treatment due to additional comorbidities.

Discussion

The clinical spectrum of COVID-19 ranges from asymptomatic infection to ARDS, multi-organ failure and death. Clinical evidence is that proinflammatory cytokines and chemokines triggered by SARS-CoV-2 cause cytokine storm, worsening the clinical status and causing irreversible damage or death. The use of MSCs in many inflammatory diseases, especially autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, neurodegenerative diseases, cardiovascular diseases and various diseases such as cancer is being investigated^[8,9]. In a study conducted in the 2013 pandemic, it was shown that MSC treatment in patients with ARDS due to H7N9 significantly reduced mortality. Numerous studies have been conducted on the use of MSCs in pulmonary diseases and COVID-19^[10,11].

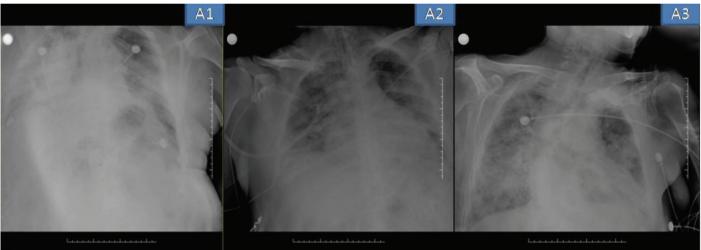


Figure 2. First anteroposterior chest X-rays of cases 2, 3 and 4 at the time of hospitalization

Table 3. Clinical, laboratory, management and outcome data of case 3

Days of hospitalization	1	2	3	4	5	6	7	8	9	10	11	12	13
Intensive care unit													
Invasive ventilation													
PaO ₂ /FiO ₂ (mmHg)	125	64	96	116	141	120	123	170	151	115	117	67	61
MSC													
Tocilizumab													
Leukocyte (10³/mcl)	8.6	11	8.2	7.5	7.6	7	8.6	6.4	7.2	7	7.2	8.5	8.3
Lymphocyte (10³/mcl)	0.4	1	0.46	0.6	0.65	0.45	0.45	0.91	1.1	0.8	1.4	1.3	1
CRP (mg/I)	100	150	220	112	64	36	32	23	11	8.6	7.5	9	34
Ferritin (ug/I)		1278	1570	1695	1391	1694	1789	1386	1276	1060	1204	1184	964
LDH (U/I)		586	595	617	561	584	760	606	729	724	815	792	868
D-dimer (ng/ml)		14230	1636		50108			12963		8193	6502	4530	4275
Date	21.07	22.07	23.07	24.07	25.07	26.07	27.07	28.07	29.07	30.07	31.07	01.08	02.08

^{*}The days of intensive care unit hospitalization, the days of invasive ventilation, the days of MSC, IVIG and tocilizumab treatments are colored in blue.

Pa0_/Fi0_: Partial oxygen pressure/fractionated oxygen level, MSC: Mesenchymal stem cell, IVIG: Intravenous immunoglobulin, CRP: C-reactive protein, LDH: Lactate dehydrogenase

Table 4. Clinical, laboratory, management and outcome data of case 4

Tube II climed, about 61,7 management and outcome data of ease 1																	
Days of hospitalization	1	4	7	10	17	18	19	22	26	27	28	29	30	33	35	45	56
Intensive care unit																	
Invasive ventilation																	
PaO ₂ /FiO ₂ (mmHg)	90	56	211	172	212	160	111	125	143	160	205	240	170	177	168	156	75
MSC																	
Leukocyte (10³/mcl)	1.6	1.2	3.3	5.2	4.8	9	4.5	5	7.8	4.3	3.1	5.3	6.1	5.8	4.6	3	15.7
Lymphocyte (10³/mcl)	0.2	0.14	0.25	0.5	0.4	0.8	0.3	0.4	0.2	0.4	0.3	0.7	0.5	0.4	0.45	0.57	1.36
CRP (mg/l)	161	74	35	30	41	33	69	93	62	45	47	34	50	92	66	74	96
Ferritin (ug/l)	351	347	388	439	411	391	388	1087	488	395	366	349	328	403	403		
LDH (U/I)	475	356	343	282	332	315	190	214	222	238	256	271	298	334	316		
D-dimer (ng/ml)	681	1018	1431	1525	709	1441	461	753	1546	1009	598	577	537	393	355		
Date	23.08	26.08	29.08	01.09	08.09	09.09	10.09	13.09	17.09	18.09	19.09	20.09	21.09	24.09	26.09	06.10	17.10

^{*}The days of intensive care unit hospitalization, the days of invasive ventilation, the days of MSC, IVIG and tocilizumab treatments are colored in blue.

Pa0_/Fi0_; Partial oxygen pressure/fractionated oxygen level, MSC: Mesenchymal stem cell, IVIG: Intravenous immunoglobulin, CRP: C-reactive protein, LDH: Lactate dehydrogenase

Severe cytokine storm in COVID-19 is one of the main causes of organ damage. MSCs are thought to be an effective treatment option, not only to calm the cytokine storm, but also to activate endogenous regenerative mechanisms due to their strong immunomodulatory effects^[12]. In this study, only the case 1 underwent MSC during the cytokine storm period and he was extubated five days later. Similarly, in other studies, patients who benefited most were in the cytokine storm period^[13].

All of our four patients with positive RT-PCR test on nasopharyngeal swab or tracheal aspirate were in severe ARDS, were intubated, and were followed up with mechanical ventilator support. Allogeneic MSCs originating from the umbilical cord were used in our patients. In all our patients, IV MSC treatment was administered as a single dose, and only case 3 was administered IT and IV MSC together. In most of the studies, MSC treatment was administered via the IV route. In a publication in which 120 articles were analyzed, it was shown that IV route was used in 73 of the studies, IT route was used in 18, and other routes were used in the remainder^[10].

In our study, the patients were in severe ARDS and all of them were intubated. In other studies, MSC was generally performed in the early period, and most of the patients were not intubated. In the randomized controlled study conducted by Shu et al.^[14], there was no mortality in the group in which MSC was applied, while mortality was found to be 10.34% in the control group. However, none of the patients were intubated before the study. In the control group, 13.79% of the patients were intubated during the follow-up. In the MSC group, none of the

patients required intubation. In the double-blind randomized controlled study conducted by Shi et al.^[15], severe patients with lung involvement were included in the study, but intubating the patient was accepted as an exclusion criterion. The reason why MSC treatment was not found to be effective in this study might be that we used it as a rescue treatment in our patients with severe ARDS. In mild-moderate ARDS period, the use of MSCs may be more effective.

Conclusion

In conclusion, MSC treatment is a promising treatment method when used in the appropriate time and in the appropriate patient. A large number of clinical studies on the use of MSCs are ongoing. There is a need for a practical guide defining the cell source, number of cells, injection frequency, and injection site, etc.

Ethics

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: P.B.E., Concept: P.B.E., E.K., Design: P.B.E., E.K., Data Collection or Processing: P.B.E., M.K., E.K., Analysis or Interpretation: P.B.E., M.K., Literature Search: P.B.E., M.K., Writing: P.B.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

- Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020:180:934–43.
- Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, Shan G, Meng F, Du D, Wang S, Fan J, Wang W, Deng L, Shi H, Li H, Hu Z, Zhang F, Gao J, Liu H, Li X, Zhao Y, Yin K, He X, Gao Z, Wang Y, Yang B, Jin R, Stambler I, Lim LW, Su H, Moskalev A, Cano A, Chakrabarti S, Min KJ, Ellison-Hughes G, Caruso C, Jin K, Zhao RC. Transplantation of ACE2- Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia. Aging Dis. 2020;11:216-28.
- Sadeghi S, Soudi S, Shafiee A, Hashemi SM. Mesenchymal stem cell therapies for COVID-19: Current status and mechanism of action. Life Sci. 2020;262:118493.
- Golchin A, Seyedjafari E, Ardeshirylajimi A. Mesenchymal Stem Cell Therapy for COVID-19: Present or Future. Stem Cell Rev Rep. 2020;16:427-33.
- Chen J, Hu C, Chen L, Tang L, Zhu Y, Xu X, Chen L, Gao H, Lu X, Yu L, Dai X, Xiang C, Li L. Clinical Study of Mesenchymal Stem Cell Treatment for Acute Respiratory Distress Syndrome Induced by Epidemic Influenza A (H7N9) Infection: A Hint for COVID-19 Treatment. Engineering (Beijing). 2020:6:1153-61.
- Jeyaraman M, John A, Koshy S, Ranjan R, Anudeep TC, Jain R, Swati K, Jha NK, Sharma A, Kesari KK, Prakash A, Nand P, Jha SK, Reddy PH. Fostering mesenchymal stem cell therapy to halt cytokine storm in COVID-19. Biochim Biophys Acta Mol Basis Dis. 2021;1867:166014.
- Yao D, Ye H, Huo Z, Wu L, Wei S. Mesenchymal stem cell research progress for the treatment of COVID-19. J Int Med Res. 2020;48:300060520955063.

- Zhou T, Yuan Z, Weng J, Pei D, Du X, He C, Lai P. Challenges and advances in clinical applications of mesenchymal stromal cells. J Hematol Oncol. 2021;14:24.
- Wilson A, Webster A, Genever P. Nomenclature and heterogeneity: consequences for the use of mesenchymal stem cells in regenerative medicine. Regen Med. 2019;14:595–611.
- Ji HL, Liu C, Zhao RZ. Stem cell therapy for COVID-19 and other respiratory diseases: Global trends of clinical trials. World J Stem Cells. 2020;12:471-80.
- Yen BL, Yen ML, Wang LT, Liu KJ, Sytwu HK. Current status of mesenchymal stem cell therapy for immune/inflammatory lung disorders: Gleaning insights for possible use in COVID-19. Stem Cells Transl Med. 2020;9:1163-73.
- Shetty AK. Mesenchymal Stem Cell Infusion Shows Promise for Combating Coronavirus (COVID-19)- Induced Pneumonia. Aging Dis. 2020;11:462-4.
- 13. Lanzoni G, Linetsky E, Correa D, Messinger Cayetano S, Alvarez RA, Kouroupis D, Alvarez Gil A, Poggioli R, Ruiz P, Marttos AC, Hirani K, Bell CA, Kusack H, Rafkin L, Baidal D, Pastewski A, Gawri K, Leñero C, Mantero AMA, Metalonis SW, Wang X, Roque L, Masters B, Kenyon NS, Ginzburg E, Xu X, Tan J, Caplan Al, Glassberg MK, Alejandro R, Ricordi C. Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: A double-blind, phase 1/2a, randomized controlled trial. Stem Cells Transl Med. 2021;10:660-73.
- Shu L, Niu C, Li R, Huang T, Wang Y, Huang M, Ji N, Zheng Y, Chen X, Shi L, Wu M, Deng K, Wei J, Wang X, Cao Y, Yan J, Feng G. Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. Stem Cell Res Ther. 2020:11:361.
- 15. Shi L, Huang H, Lu X, Yan X, Jiang X, Xu R, Wang S, Zhang C, Yuan X, Xu Z, Huang L, Fu JL, Li Y, Zhang Y, Yao WQ, Liu T, Song J, Sun L, Yang F, Zhang X, Zhang B, Shi M, Meng F, Song Y, Yu Y, Wen J, Li Q, Mao Q, Maeurer M, Zumla A, Yao C, Xie WF, Wang FS. 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;6:58.