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Wharton's jelly-mesenchymal stem cells treatment for severe COVID 19 patients: 1-year follow-up

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SUMMARY

Background: Recently, attention has been focused on mesenchymal stem cells (MSC) because of their unique ability to suppress inflammation induced by cytokine storms caused by COVID-19. Several patients have been successfully treated in this manner. After one year of treatment with Wharton's jelly-derived MSC injections, this study evaluated the safety and efficacy of injecting MSCs intravenously in patients with COVID-19.

Methods: This study treated four patients with severe COVID-19 with Wharton's jelly-derived mesenchymal stem cells. In this study, patients were followed up for routine tests, tumor markers, and whole-body imaging (spiral neck CT scan (with contrast), spiral chest CT scan (with & without contrast), and spiral abdominopelvic CT scan (with IV & Oral contrast)) one year after cell therapy.

Results: The results indicated that lymphocyte; lymph count significantly increased, and neutrophil, ESR, ferritin, and CRP significantly decreased. LDH showed a non-significant decrease (P-value < 0.05). One year after the WJ-MSC injection, the tumor markers were normal, and no tumors were observed in patients after one year. Also, the CT scan result was normal.

Conclusions: In patients, no serious complications were observed after a one-year follow-up. After monitoring the patient via laboratory tests, tumor markers, and whole-body imaging, we concluded that the Wharton jelly-derived mesenchymal stem cells did not cause severe complications, including tumor formation, in severe COVID19 patients within a year. More clinical trials with higher sample sizes need to be performed on cell therapy with Wharton jelly-derived mesenchymal stem cells in the future.

1. Introduction

Coronavirus disease 2019 (COVID-19) has emerged as a global epidemic and has caused diverse clinical conditions, from asymptomatic carriers to severe acute respiratory distress syndrome (Huang et al., 2020; Tang et al., 2020; Xu et al., 2020). COVID-19 symptoms subside within 2 to 3 weeks, but approximately 10 % of patients experience symptoms several months after the infection. Long-term follow-up studies have been reported for severe COVID-19 patients discharged from hospitals (Huang et al., 2021; Wu et al., 2021). COVID19 is categorized into three categories based on the severity of the symptoms (Huang et al., 2020; Wu and McGoogan, 2020; Shi et al., 2020). Mild cases present symptoms such as fatigue, cough, fever, diarrhea, headache, and whether or not mild pneumonia is present. Dyspnea, decreased blood oxygen saturation, pulmonary infiltrates, acute respiratory stress, multiple peripheral ground-glass patches on both lungs, and so forth are symptoms of severe cases. Septic shock and respiratory failure are symptoms of critical cases. COVID-19 is estimated to have a

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mortality rate of 2.3 %, ranging from 6 to 41 days after the onset of symptoms (Shi et al., 2020; Wang et al., 2020).

Most cases are treated with supportive and symptomatic measures, but several antiviral agents, an antimalarial drug (chloroquine), and antibiotics have been used to treat milder and more severe cases. In addition to convalescent plasma therapy and mesenchymal stem cell therapy, other options have also been proposed to modulate the immune response in severely and critically ill patients (Shen et al., 2020; Leng et al., 2020; Orleans et al., 2020).

Mesenchymal stem cells can self-regeneration and differentiate into numerous types of cells (Metrellies et al., 2006; Chamberlain et al., 2007). Because MHC-I is not expressed to a high degree, and MHC-II is expressed in low numbers, mesenchymal stem cells are not immunogenic (Lee et al., 2014; Hass et al., 2011). That is why MSCs can be used for allogeneic cell transplantation. Several disease models have shown that MSCs can modulate the immune system and regenerate tissue (Corcione et al., 2006; Le Blanc and Davies, 2015; Wang et al., 2013; Forbes et al., 2014). There have been significant developments in stem cell technology with promising therapeutic prospects for treating various diseases, such as respiratory diseases (Fatima and Nawaz, 2015).

In a previous study in 2020 conducted by our research team, Wharton Jelly-derived mesenchymal stem cells were performed in 5 patients with severe forms of COVID19. After a 1-month follow-up, Wharton's jelly-derived stem cells were safe and well-tolerated by the patient (Saleh et al., 2021).

This study examined patients for one year for routine laboratory tests, tumor markers, and whole-body imaging examinations.

2. Materials and methods

Five patients with severe COVID-19 were treated with Wharton Jelly-derived mesenchymal stem cells in a previous pilot study at Shariat Hospital. By signing the consent form, patients entered the study from July 21, 2020, to August 21, 2020. HWj-MSC cells prepared by cell Tech Pharmed were injected into patients in 150 × 106 cells via IV in 3 doses on days 0, 3, and 6 (Saleh et al., 2021). In the previous study, these patients were monitored after cell injection for 0, 3, 6, and 14 days (myocardial enzymes, hematologic parameters, biochemistry, and inflammatory tests) and one year after cell therapy. In this study, patients (4 patients and one patient's information is not available) were followed up for routine tests, tumor markers, and whole-body imaging (spiral neck CT scan (with contrast), spiral chest CT scan (with & without contrast) and spiral abdominopelvic CT scan (with IV & Oral contrast)) one year after cell therapy. The Ethics Committee approved this study at the Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1400.035).

One year after cell therapy, all patients were evaluated for adverse events through clinical examinations, measurements of vital signs, and routine tests. One year after cell therapy, the following parameters were monitored: heart rate, respiration, blood pressure, body temperature, and oxygen saturation. Routine blood tests, biochemical indicators, myocardial enzymes, and Inflammatory Markers were performed before and after one year of cell therapy.

Beta-hCG, AFP, CEA, CA125, CA19-9, CA15-3, TPSA, and FPSA levels were measured in serum samples one year after cell therapy (ECL, HITACHI).

3. Statistical analysis

GraphPad Prism version 8.00 (GraphPad Software, Inc.) analyzed the data. We compared the means of two related groups using paired t-tests and one-way ANOVA for multi-group comparisons. The data were analyzed as mean ± S.D. P < 0.05 was considered to be statistically significant.
Table 2
Laboratory tests (base, Day3, Day6, Day14 & 1 year).

| Variables                  | Patient 1 Day0 | Patient 1 Day3 | Patient 1 Day6 | Patient 1 Day14 | Patient 1 Year | Patient 2 Day0 | Patient 2 Day3 | Patient 2 Day6 | Patient 2 Day14 | Patient 2 Year | Patient 3 Day0 | Patient 3 Day3 | Patient 3 Day6 | Patient 3 Day14 | Patient 3 Year | Patient 4 Day0 | Patient 4 Day3 | Patient 4 Day6 | Patient 4 Day14 | Patient 4 Year |
|----------------------------|---------------|---------------|---------------|----------------|--------------|---------------|---------------|---------------|----------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Routine blood tests        |               |               |               |                |              |               |               |               |                |              |               |               |               |               |               |               |               |                |              |
| WBC count                  | Normal range  | 3400 - 12,500 | 10,940        | 14,910         | 16,710       | 14,220        | 7500          | 9600          | 7560           | 10,620        | 8050          | 5400          | 10,400        | 11,040        | 10,950        | 11,630        | 6200          | 6100          | 12,740        | 10,050        | 9640          | 7190          |
| Hb (g/L)                   | M:14-18      | 12.7          | 12.7          | 13.7           | 12.5         | 11.5          | 11            | 11            | 13.5           | 13            | 13.1          | 14.2          | 13.5          | 15.1          | 15            | 14.7          | 15.1          | 14.4          | 13.8          | 16.9          |
| PLT count (×10^9/L)        | F:12-16      | 146           | 195           | 227            | 218          | 204           | 233           | 321           | 428            | 295           | 220           | 287           | 243           | 192           | 205           | 228           | 307           | 328           | 183           | 189           | 226           |
| Neutrophil (%)             | NA           | 88            | 88            | 70             | 54           | 90            | 80            | 83            | 62             | 50            | 90            | 82            | 70            | 71            | 54            | 86            | 91            | 71            | 81            | 57            |
| Lymphocyte (%)             | 45-75        | 2              | 10            | 19             | 39           | 4             | 9             | 11            | 26             | 38           | 5             | 10            | 20            | 20            | 33            | 8             | 2             | 21            | 14            | 35            |
| LYM count (×10^9/L)        | 20-40        | NA            | 298.2         | 1671           | 2702         | 2925          | 384           | 680.4         | 1168.2         | 2093          | 2052          | 520           | 1104          | 2190          | 2326          | 2046          | 640           | 254.8         | 2110.5        | 1265.6        | 2517          |
| ESR                        | M: 0 to 20   | 96            | 73            | 23             | 26           | 20            | 104           | NA            | NA             | 51            | 15            | 74            | 9             | 25            | 10            | 6             | 37            | 5             | 64            | 17            | 1             |
| Myocardial enzymes         |               |               |               |                |              |               |               |               |                |              |               |               |               |               |               |               |              |               |               |               |               |               |               |
| LDH (U/L)                  | 240-480      | 723           | 939           | 462            | 374          | 269           | 860           | 483           | 427            | 545           | 350           | 542           | 465           | 392           | 398           | 313           | 1458          | 1117          | 615           | 417           | 354           |
| Biochemical indicators     |               |               |               |                |              |               |               |               |                |              |               |               |               |               |               |               |               |              |               |               |               |               |               |
| Total Bili (mg/dL)         | 0.1-1.2      | 0.26          | 0.7           | 1              | 0.6          | 0.7           | 1.1           | 0.54          | 0.43           | 0.9           | 0.8           | 0.7           | 0.6           | 0.7           | 1.3           | 0.8           | 1.6           | 1.6           | 1.6           | 0.9           | 1             |
| Direct Bili (mg/dL)        | Up to 0.3    | 0.1           | 0.3           | 0.3            | 0.1          | 0.2           | 0.3           | 0.2           | 0.02           | 0.1           | 0.1           | 0.1           | 0.2           | 0.2           | 0.2           | 0.3           | 1.2           | 0.6           | 0.3           | 0.2           | 0.3           |
| ALT (U/L)                  | M: up to 41  | 55            | 29            | 40             | 43           | 11            | 98            | 41            | 42             | 39           | 21            | 16            | 43            | 30             | 11            | 15            | 136           | 106           | 55            | 75            | 29            |
| AST (U/L)                  | F: up to 31  | 23.5          | 20            | 25             | 20           | 17            | 68            | 47.5          | 25             | 18           | 26            | 19            | 40            | 15             | 35            | 18            | 145           | 50            | 29            | 27            | 23            |
| BUN (mmol/L)               | M: up to 38  | 6             | 23            | 24             | 16           | 13            | 23            | 54            | 43             | 21           | 14            | 25.2          | 16            | 21             | 21            | 16            | 25            | 14            | 11            | 11            | 11            |
| Cr (μmol/L)                | F: up to 31  | 0.8           | 0.8           | 0.7            | 0.8          | 0.6           | 0.5           | 0.9           | 1              | 1.1          | 0.74          | 0.9           | 0.8           | 1.1            | 0.9           | 0.8           | 0.8           | 0.7           | 0.8           | 0.7           | 1             |
| Inflammatory markers       |               |               |               |                |              |               |               |               |                |              |               |               |               |               |               |               |              |               |               |               |               |               |               |
| CRP                        | UP TO 10     | 60.5          | 6             | 3              | 0.48         | 2             | 107           | 101           | 20             | 3.84         | 2             | 87            | 53.5          | 24.5           | 4.44          | 3.9           | 45            | 82            | 25            | 147           | 2             |
| Ferritin                   | M: 24 to 336 | 1979          | 959           | 231            | 169          | 55            | 798           | 986           | 686            | 659          | 120           | 896           | 707           | 6200           | 500           | 142           | 1087          | 2666          | 742           | 878           | 229           |
| Cr: 11 to 307              | F: 24 to 336 | 1979          | 959           | 231            | 169          | 55            | 798           | 986           | 686            | 659          | 120           | 896           | 707           | 6200           | 500           | 142           | 1087          | 2666          | 742           | 878           | 229           |
Laboratory Tests in all patients (base, Day3, Day6, Day14 & 1 year)

**Neutrophil**

**Lymphocyte**

**LYM count**

**ESR**

**CRP**

**Ferritin**

**LDH**

ESR: Erythrocyte sedimentation rate, CRP C-reactive protein, LDH: Lactate dehydrogenase

Fig. 1. Laboratory tests at day 0, 3, 6, 14, and 1 year after WJ-MSC injection.
In the spiral abdominopelvic CT scan, the Liver was within normal limit, and no intrahepatic focal mass lesion was noted. Gall bladder, bile ducts, spleen, kidneys, and pancreas appeared normal. No obvious abdominopelvic abnormality was found.

5. Discussion

The growing evidence of MSCs’ therapeutic effectiveness has been shown in preclinical and clinical studies. Many studies indicate that the short-lived viability of MSCs after the injection may also account for low engraftment (Wang et al., 2014; Von Bahr et al., 2012). MSCs have started to appear as a new treatment option for COVID-19 patients (Haslemian et al., 2021; Feng et al., 2020). After MSCs are injected, many of them are trapped in the lungs, resulting in reduced cells that reach the target site (Makela et al., 2015). Since the most common infection of the COVID-19 virus is the lung, intravenous injection of these mesenchymal stem cells is beneficial in these patients.

However, new therapies, such as cell therapy, face several challenges. The tumorigenic properties of stem cells are essential to consider when using them. Several studies have evaluated the risk associated with tumorigenesis following stem cell transplantation. Both stem cells, and tumor cells can survive, proliferate, and prevent death (Bellagamba et al., 2016). After one year of cell therapy, we evaluated beta-hCG, AFP, CEA, CA125, CA19-9, CA15-3, TPSA, and FPSA. We did not include any patients with cancer diagnoses in this study. Therefore, we cannot correlate the elevation of these biomarkers with preexisting tumorigenesis conditions.

There is evidence that cancer biomarkers, such as CEA, and CA, are elevated during various inflammatory conditions of the lungs. For instance, smoking increases CEA levels, and chronic obstructive pulmonary disease increases CA125 levels (Stockley et al., 1986; Barouchos et al., 2015).

In this study, there were no complications, including tumor formation. Tumor marker results besides whole-body imaging demonstrate the safety of Wharton jelly-derived mesenchymal cells after one year.

In another study, in line with our safety results on a large scale, UC-MSC cells were used in patients with severe COVID-19. These patients were monitored for one year. They concluded that administering UC-MSCs to severe COVID-19 patients for some time could reduce lung...
Fig. 2. a. Chest CT scan.
a-1: A-D: A: day 0, B: day 14, C: day 30, and D: 1 year after WJ-MSC infection.
P1: Patient 1.
a-2: A-D: A: day 0, B: day 14, C: day 30, and D: 1 year after WJ-MSC infection.
P4: Patient 4.

b. CT scan of thoracic and abdominopelvic with contrast.
b-1: CT scan of thoracic and abdominopelvic with contrast: No pathology is seen.
Follow up 1 year chest CT scan, revealed complete resolution of parenchymal involvement without any Sequela.
P1: Patient 1.
b-2: CT scan of thoracic and abdominopelvic with contrast: No pathology is seen.
Follow up 1 year chest CT scan, revealed complete resolution of parenchymal involvement without any Sequela. P4: Patient 4.
b. CT scan of thoracic and abdominopelvic with contrast

b-1: CT scan of thoracic and abdominopelvic with contrast: No pathology is seen.

Follow up 1 year chest CT scan, revealed complete resolution of parenchymal involvement without any Sequela.

P1: Patient 1

b-2: CT scan of thoracic and abdominopelvic with contrast: No pathology is seen.

Follow up 1 year chest CT scan, revealed complete resolution of parenchymal involvement without any Sequela.

P4: Patient 4

Fig. 2. (continued)
lesions and offer good symptom improvement, indicating that UC-MSC administration as adjunctive therapy for COVID-19 patients is feasible (Shi et al., 2022).

6. Conclusion

This study showed that cell therapy using Wharton jelly-derived mesenchymal stem cells after one year did not have serious complications, including tumorigenesis, and the patient tolerated the patient well. It is best to do this study on a larger scale and do more research on tumor formation.

Abbreviation

| Acronym | Definition |
|---------|------------|
| WJ-MSC  | Wharton’s jelly derived MSCs |
| COVID-19 | coronavirus disease 2019 |
| ALT     | alanine aminotransferase |
| AST     | aspartate aminotransferase |
| Cr      | creatinine |
| CRP     | C-reactive protein |
| CT      | computed tomography |
| MSCs    | mesenchymal stem cells |

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2

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Ethics approval and consent to participate

Written informed consent was obtained from each patient or the patient’s legally authorized surrogate before the conduct of study-specific procedures.

Consent for publication

Not applicable.

Code availability

Not applicable.

CRediT authorship contribution statement

MS proposed initial idea, study design and writing of the manuscript. MS, AAV, LA, NA, MB, AAS and JV were responsible for the reference selection and writing of the manuscript. MS, NA, MB, and LA took care of the patients and performed the follow-up checks. MS collected and analyzed the data. MS and LA analyzed the CT. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

All of the data generated and analyzed during this study are included in our manuscript.

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