

RESEARCH LETTER

Open Access



Administration of umbilical cord mesenchymal stem cells in patients with severe COVID-19 pneumonia

Zhinian Guo, Yunlong Chen, Xiaoyu Luo, Xiaolong He, Yong Zhang and Jiang Wang*

There are no specific drug therapies or vaccines for the pandemic of coronavirus disease 2019 (COVID-19), which is associated with substantial mortality. Attenuating or reversing the cytokine storm is critical for treating patients with severe COVID-19 pneumonia. Mesenchymal stem cells (MSCs) have been shown to have powerful immunoregulation and reparative properties in injured tissue with good safety [1]. This report aims to investigate whether umbilical cord MSC (UC-MSC) therapy improves the outcomes of 31 patients with severe or critical COVID-19 pneumonia.

We wish to report our experience using UC-MSCs for the treatment of severe COVID-19 pneumonia at Taikangtongji Hospital in Wuhan, China, from January 3, 2020, to April 4, 2020. Patient data, including demographics, clinical data, laboratory indices, treatment, and in-hospital outcomes, were collected. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) results of all patients were positive before UC-MSCs infused. Patients were diagnosed and treated according to national guidelines. Before the intravenous drip was established, UC-MSCs (1×10^6 cells per kilogram of weight) were suspended in 100 ml normal saline. We report numbers (percentages) for categorical variables and the median (interquartile range [IQR]) or mean \pm standard deviation (SD) for continuous variables. Intergroup comparisons were performed with paired *t* tests.

We treated 31 COVID-19 patients with UC-MSCs. The median age was 70 years (IQR, 61–71 years); 25 patients (80.6%) were male. The proportion of treatment

with oxygen was the highest (31 [100%]), followed by antivirals (26 [83.9%]), antibiotics (23 [74.2%]), intravenous immunoglobulin (8 [25.8%]), intravenous albumin (8 [25.8%]), and methylprednisolone (6 [19.4%]). The median (IQR) volume of infused UC-MSCs was 200 mL (100–300 mL). No adverse events were attributable to intravenous transplantation of UC-MSCs. After the first infusion of UC-MSCs, the SARS-CoV-2 PCR results of 30 patients (96.8%) became negative after a mean time of 10.7 days (SD, 4.2 days) (Table 1). Laboratory parameters tended to improve after UC-MSC therapy compared to the status before UC-MSC therapy, including elevated lymphocyte count (median [IQR], $1.09 [0.68-1.35] \times 10^9/L$ vs $1.43 [1.02-2.20] \times 10^9/L$; $P < 0.001$), decreased C-reactive protein level (median [IQR], 13.39 [1.30–38.86] mg/L vs 0.50 [0.50–6.40] mg/L; $P = 0.003$), decreased procalcitonin level (median [IQR], 0.07 [0.05–0.09] ng/mL vs 0.04 [0.03–0.06] ng/mL; $P < 0.001$), decreased interleukin-6 level (median [IQR], 13.78 [5.69–25.26] pg/mL vs 4.86 [2.13–8.19] pg/mL; $P < 0.001$), decreased D-dimer level (median [IQR], 495 [320–727] ng/mL vs 288 [197–537] ng/mL; $P = 0.010$), and elevated PaO₂/FiO₂ (median [IQR], 242 [200–294] vs 332 [288–364]; $P < 0.001$) (Table 2).

Our experience showed that UC-MSC therapy may restore oxygenation and downregulate cytokine storms in patients hospitalized with severe COVID-19 without any infusion reaction. This approach is a promising candidate for the treatment of severe COVID-19 [2]. During the outbreak of COVID-19 in Wuhan, China, the number of patients increased sharply. However, the hospital capacity was limited, and many patients could not be admitted to the hospital. Hence, days between onset of symptoms and hospital admission were long. UC-MSCs can improve the lung microenvironment, pulmonary

* Correspondence: 504641821@qq.com

Department of Cardiology, Xinqiao Hospital of Army Medical University, 183 Xinqiao Street, Chongqing 400037, China



© The Author(s). 2020 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Table 1 Baseline characteristics, treatments, and outcomes of patients with COVID-19 with UC-MSc therapy

	Total (n = 31)
Demographics and clinical characteristics	
Age, median (IQR), years	70 (61–71)
Sex, male	25 (80.6%)
BMI, mean ± SD, kg/m ²	24.5 ± 2.9
Symptoms at admission	
Fever	24 (77.4%)
Cough	25 (80.6%)
Dyspnea	17 (54.8%)
Chest congestion	14 (45.2%)
Fatigue	12 (38.7%)
Comorbidities	
Hypertension	13 (41.9%)
Chronic obstructive pulmonary disease	6 (19.4%)
Coronary artery disease	5 (16.1%)
Diabetes	5 (16.1%)
Chest computed tomographic findings	
Bilateral pneumonia	31 (100%)
Multiple mottling/ground-glass opacity	26 (83.9%)
Main complications	
Respiratory failure	10 (32.3%)
Acute respiratory distress syndrome	8 (25.8%)
Cardiac injury	12 (38.7%)
Disease severity status	
Severe	23 (74.2%)
Critical	8 (25.8%)
Days between onset of symptoms and hospital admission, mean ± SD, days	37.2 ± 17.6
Days between onset of symptoms and UC-MSc therapy, mean ± SD, days	50.7 ± 12.6
Days between hospital admission and UC-MSc therapy, median (IQR), days	10.0 (6.0–22.0)
Intensive care unit admission	16 (51.6%)
Treatments	
Oxygen	31 (100%)
Oxygen inhalation	19 (61.3%)
Noninvasive mechanical ventilation	4 (12.9%)
Invasive mechanical ventilation	8 (25.8%)
Antivirals	26 (83.9%)
Arbidol	20 (64.5%)
Interferon alfa-2b	9 (29.0%)
Oseltamivir	3 (9.7%)
Chloroquine	3 (9.7%)
Antibiotics	23 (74.2%)
Methylprednisolone	6 (19.4%)

Table 1 Baseline characteristics, treatments, and outcomes of patients with COVID-19 with UC-MSc therapy (Continued)

	Total (n = 31)
UC-MSc therapy	
UC-MSc volume, median (IQR), mL	200 (100–300)
Single infusion of UC-MScs	11 (35.5%)
Two infusions of UC-MScs	9 (29.0%)
Three infusions of UC-MScs	11 (35.5%)
Intravenous immunoglobulin therapy	8 (25.8%)
Intravenous albumin therapy	8 (25.8%)
Outcomes	
SARS-CoV-2 clearance	30 (96.8%)
Discharged	27 (87.1%)
Death	4 (12.9%)

UC-MScs umbilical cord mesenchymal stem cells, IQR interquartile range, SD standard deviation, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2

fibrosis, and lung function, probably due to the regulation of the inflammatory response and the promotion of tissue repair and regeneration [3]. A recent report of 7 patients found that bone marrow MSC therapy was an effective treatment for severe COVID-19 [3]. Moreover, another recent study indicated that bone marrow MSC therapy can improve hypoxia, immune reconstitution, and cytokine storms in patients with severe COVID-19 [4], which was consistent with our results. Further large multiple-center prospective trials are needed to confirm our results in the future.

Table 2 Comparison of laboratory parameters before and after UC-MSc therapy

Characteristics	Before UC-MSc therapy	After UC-MSc therapy	P value
White blood cell count, × 10 ⁹ /mL (normal range, 3.5–9.5)	6.72 ± 2.62	6.43 ± 1.72	0.346
Lymphocyte count, × 10 ⁹ /mL (normal range, 1.1–3.2)	1.09 (0.68–1.35)	1.43 (1.02–2.20)	< 0.001
C-reactive protein, mg/L (normal range, < 10)	13.39 (1.30–38.86)	0.50 (0.50–6.40)	0.003
Procalcitonin, ng/mL (normal range, < 0.05)	0.07 (0.05–0.09)	0.04 (0.03–0.06)	< 0.001
Interleukin-6, pg/mL (normal range, < 7)	13.78 (5.69–25.26)	4.86 (2.13–8.19)	< .001
D-dimer, ng/mL (normal range, < 243)	495 (320–727)	288 (197–537)	0.010
PaO ₂ /FiO ₂	242 (200–294)	332 (288–364)	< 0.001

UC-MScs umbilical cord mesenchymal stem cells, PaO₂/FiO₂ ratio of the partial pressure of arterial oxygen to the percentage of inspired oxygen

Acknowledgements

We thank all the medical staff of Taikangtongji Hospital for the diagnosis and treatment of patients with COVID-19.

Authors' contributions

Concept and design: JW and ZG. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: JW and ZG. Critical revision of the manuscript for important intellectual content: JW. Statistical analysis: ZG. Administrative, technical, or material support: JW. Supervision: JW. All authors have read and approved the final manuscript.

Funding

None

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics approval and consent to participate

The Clinical Research Ethics Commissions of Taikangtongji Hospital approved the study and granted a waiver for the need to obtain written informed consent from the study participants as COVID-19 is an emerging infectious disease.

Consent for publication

Not applicable.

Competing interests

All authors declare no competing interests.

Received: 15 June 2020 Accepted: 1 July 2020

Published online: 11 July 2020

References

1. Galipeau J, Sensebe L. Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. *Cell Stem Cell*. 2018;22(6):824–33.
2. Marini JJ, DeBacker D, Gattinoni L, Ince C, Martin-Loeches I, Singer P, Singer M, Westphal M, Vincent JL. Thinking forward: promising but unproven ideas for future intensive care. *Crit Care*. 2019;23(Suppl 1):197.
3. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, Shan G, Meng F, Du D, Wang S, et al. Transplantation of ACE2(-) mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging Dis*. 2020;11(2): 216–28.
4. Sengupta V, Sengupta S, Lazo AJ, Woods P, Nolan A, Bremer N. Exosomes derived from bone marrow Mesenchymal stem cells as treatment for severe COVID-19. *Stem Cells Dev*. 2020.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

