

Umbilical cord-derived mesenchymal stem cell transplantation for COVID -19 patients: long-term benefits for lung regeneration

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has affected hundreds of millions of people worldwide. Currently, mortality due to COVID-19 is significantly reduced by vaccination, antiviral drugs, and some improved treatments. Mesenchymal stem cell (MSC) transplantation—particularly umbilical cord-derived MSC (UC-MSC)—has been used as an adjuvant therapy for COVID-19 with some clinical evidence (reviewed in the publication). Moreover, a recent piece published in eBiomedicine (part of The Lancet, <https://doi.org/10.1016/j.ebiom.2021.103789>) in the previous month showed the long-term effects of UC-MSC transplantation in COVID-19 in a 1-year follow-up randomized, double-blind, placebo-controlled trial, demonstrating significantly recovered lung lesions and symptoms compared to the control group (*i.e.*, without UC-MSC transplantation). In this commentary, we would like to discuss the value of UC-MSC transplantation for COVID-19 patients based on the results from this study and suggest applying this therapy for COVID-19 patients.

Key words: Covid-19, Cytokine storm, Lung fibrosis, UC-MSC, Umbilical cord derived mesenchymal stem cell

COMMENT

Our previous publications about UC-MSCs and their immune modulations include hypothesizing the benefits of UC-MSCs in COVID-19 treatment in 2020¹ and summarizing clinical trials using UC-MSCs for COVID-19 in 2021². Examining 16 publications covering 395 COVID-19 patients treated with UC-MSCs overall, we found that all publications showed that UC-MSC transplantation is safe, well tolerated, improves COVID-19 symptoms, and significantly decreases mortality².

The latest publication of Lei Shi *et al.* (2022) in eBiomedicine (part of The Lancet, <https://doi.org/10.1016/j.ebiom.2021.103789>) from the previous month about the 1-year follow-up results of a randomized, double-blind, placebo-controlled trial strongly confirmed our observations shared in previous reviews³. In this study, there were 65 COVID-19 patients transplanted with UC-MSCs and 35 COVID-19 patients in the placebo group. The authors focused on the effects of UC-MSC transplantation on lung recovery, which was evaluated based on CT images and the 6-MWD test at 3, 6, 9, and 12 months. Note that at Month 6, 6 patients (6/51 patients) in the UC-MSC transplantation group had normal CT images; in contrast, none of the patients in the placebo group had normal CT images ($p = 0.087$). At Month 12, the number of patients with normal CT images increased

to 10 in the UC-MSC transplantation group, but not in the placebo group ($p = 0.013$). The CT imaging results were supported by the 6-MWD tests in both groups. Although the 6-MWD scores gradually increased in both groups over time at 3, 6, 9, and 12 months, the patients in the UC-MSC transplantation group increased from 440 m at Month 3 to 478 m at Month 12, compared to 420 m at Month 3 to 441 m at Month 12 for the placebo group³.

These results showed that patients with UC-MSC transplantation displayed good lung function and structure recovery compared to the non-transplantation group. Thus, alongside some previous publications, these observations confirm the roles of UC-MSCs⁴⁻⁷. However, whether UC-MSCs can help recover or regenerate damaged lungs in COVID-19 patients is not yet well understood.

With their strong modulation potentials, UC-MSCs can suppress cytokine storms in COVID-19 patients. Accordingly, we proposed some hypotheses regarding the effects of UC-MSCs on lung recovery as a result of minimizing damage during the cytokine storm and inhibiting fibrosis.

Cytokine storms and cytokine release syndrome are life-threatening systemic inflammatory syndromes related to elevated levels of circulating cytokines and immune cell hyperactivation, which can be triggered by various therapies, pathogens, can-

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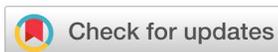
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lung cancer. This review confirmed that MSC transplantation is a promising therapeutic approach for treating lung disease²². Furthermore, in a case report by Silva et al. (2021), UC-MSC transplantation corresponded to immunomodulatory and anti-fibrotic effects in a critically ill patient with COVID-19 presenting with lung fibrosis²³. Based on the current results, UC-MSC transplantation should be considered as an adjuvant treatment in patients at high risk for cytokine storms, which includes those with COVID-19. Indeed, UC-MSC transplantation minimizes the lung damage caused by cytokine storms and inhibits lung fibrosis in post-COVID-19 patients. Although more large studies are required on this topic, the current data about the safety and long-term effects of UC-MSC transplantation for COVID-19 patients are sufficient for this therapy to be considered as an option in such cases.

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ABBREVIATIONS

6-MWD test: The 6-min walk test, **COVID-19:** Coronavirus disease 2019, **CT:** Computed tomography, **UC-MSC:** Umbilical cord derived mesenchymal stem cell

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AUTHOR'S CONTRIBUTIONS

Authors equally contributed to this work, read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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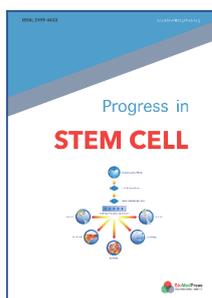
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