World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2022 June 26; 10(18): 6338-6340

DOI: 10.12998/wjcc.v10.i18.6338

ISSN 2307-8960 (online)

LETTER TO THE EDITOR

Stem cells as an option for the treatment of COVID-19

Maria Veronica Cuevas-González, Juan Carlos Cuevas-González

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Al-Omari B, United Arab Emirates; Emran TB, Bangladesh

Received: February 6, 2022
Peer-review started: February 6, 2022
First decision: March 23, 2022
Revised: April 1, 2022
Accepted: May 12, 2022
Article in press: May 12, 2022
Published online: June 26, 2022

Maria Veronica Cuevas-González, Institute of Biomedical Sciences, Universidad Autonoma de Ciudad Juarez, Juarez 32310, Chihuahua, Mexico

Juan Carlos Cuevas-González, Institute of Biomedical Sciences, Autonomous University of Ciudad Juárez, Ciudad Juarez 32310, Chihuahua, Mexico

Corresponding author: Juan Carlos Cuevas-González, PhD, Academic Research, Institute of Biomedical Sciences, Autonomous University of Ciudad Juárez, Av. Benjamín Franklin No. 4650, Zona Pronaf Condominio La Plata, Ciudad Juarez 32310, Chihuahua, Mexico. cuevas_gonzalez@hotmail.com

Abstract

The application of stem cells is among the many strategies currently available for the treatment of multiple diseases. Stem cells are characterized as undifferentiated cells that have the ability to differentiate towards multiple lineages and self-renewal, among other attributes. Since the first umbilical cord stem cell transplant for the treatment of Fanconi anemia, the use of stem cells for the treatment of multiple diseases, including coronavirus disease 2019, has increased, showing promising results that require evaluation through research studies that include a longer follow-up time. Therefore, the main objective of this Letter is to provide an update on the use of stem cells in the treatment of severe acute respiratory syndrome coronavirus 2, as well as identify the main challenges and limitations presented by this type of therapy.

Key Words: COVID-19; Stem cells; Multiple diseases; Undifferentiated cells; Appropriate treatment; Cytokines granulocyte-macrophage colony-stimulating factor

Core Tip: The stem-cell-derived microvesicles improve the oxygenation conditions of patients, thereby avoiding mechanical oxygenation methods. They demonstrate the ability to modulate the inflammatory response by reducing the levels of proinflammatory cytokines within the first few hours of their intravenous application because these microvesicles contain cytokines, growth factors, and microRNAs, which function as anti-inflammatory agents.

Citation: Cuevas-González MV, Cuevas-González JC. Stem cells as an option for the treatment of COVID-19. *World J Clin Cases* 2022; 10(18): 6338-6340
URL: https://www.wjgnet.com/2307-8960/full/v10/i18/6338.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i18.6338

TO THE EDITOR

The current pandemic we are experiencing due to coronavirus disease 2019 (COVID-19) undoubtedly represents a significant challenge for medical and research domains. The magnitude of the disease is evident with millions of lives lost; therefore, the need to find appropriate treatment is urgent. One of the main effects that this type of virus triggers in the human body is the overproduction of pro-inflammatory cytokines [interleukins (ILs)], such as IL-1α/β, IL-2, IL-6, IL-12, interferon (IFN)-α/β/γ, and the anti-tumor necrosis factor (TNF), which cause damage to multiple organs[1]. Zheng[2] published a very interesting study in which they carried out a review of the effects of stem cells in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It covers the ability of stem cells to secrete immunomodulatory factors and to improve the adverse effects of respiratory syndrome by reducing fibrosis.

Since the first umbilical cord stem cell transplant for the treatment of Fanconi anemia[3], the use of stem cells for the treatment of multiple diseases, including COVID-19, has increased. Among the various positive effects of stem cells is their capacity for immunoregulation by controlling inflammatory processes. The evidence we have on the use of stem cells for the SARS-CoV-2 infection is from transplanting mesenchymal cord cells by intravenous infusion, in which there is a significant decrease in the cytokines granulocyte-macrophage colony-stimulating factor, IFN-γ, IL-5, IL-6, IL-7, TNF-α, TNF-, platelet-derived growth factor-BB, and RANTES, which in turn decrease the mortality rate and the recovery time of patients[4]. Also, the application of umbilical stem cells has shown—through imaging analysis—that it improves the damage to lung tissue by reducing the solid component, which may be related to fibrosis[5].

Stem cells influence the regulation of cytokine expression by promoting the polarization of macrophages from a pro-inflammatory to an anti-inflammatory phenotype through the production of different types of cytokines, such as prostaglandin E2, TNF-stimulated gene 6 protein lactate, kynurenic acid, and spermidine, all of which in turn have an effect on the adaptive immune system by preventing the activation of effector T cells and promoting the regulation of regulatory T cells[6].

The efficacy and safety of the application of stem-cell-derived microvesicles have also been evaluated, which improve the oxygenation conditions of patients, thereby avoiding mechanical oxygenation methods and demonstrating the ability to modulate the inflammatory response by reducing the levels of proinflammatory cytokines within the first few hours of their intravenous application[7]. This is because these microvesicles contain cytokines, growth factors, and microRNAs that function as anti-inflammatory agents[8].

Although clinical trials have shown that stem-cell-based therapy has great advantages that have a direct impact on the survival of patients with severe disease, there are significant technical and biological limitations with this type of therapy: (1) The methods of obtaining stem cells—for example, those that come from adults; and (2) The quantity and quality of these stem cells depend on the age of the donor and their exposure to environmental stress, which could affect cell proliferation and differentiation[9]. Obtaining stem cells is still a challenge due to the lack of consensus of ethics committees. Another major challenge is the *in vitro* manipulation given to the cells: Keeping them in expansion for long periods of time can limit the characteristics of the cells regarding their regeneration potential and genomic stability[10].

The conclusion of this Letter is that although encouraging results have been obtained, we believe it is necessary to continue with long-term clinical trials that (1) Include a greater number of patients that allow adequate evaluation; (2) Design studies with a longer follow-up time, months or years, which allows an adequate assessment of the possible biological risks of the application of stem cells; and (3) Include the evaluation of molecular studies in order to analyze the gene expression of stem cells within the body These three clinical trial points will aid in obtaining approval from the international institutions that sanction the use of medical drugs (including stem cells).

FOOTNOTES

Author contributions: Cuevas-González MV and Cuevas-González JC wrote the manuscript.

Conflict-of-interest statement: None.

Country/Territory of origin: Mexico

ORCID number: Maria Veronica Cuevas-González 0000-0003-3112-4893; Juan Carlos Cuevas-González 0000-0002-6981-8025.

S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

REFERENCES

1 **Yang B**, Fan J, Huang J, Guo E, Fu Y, Liu S, Xiao R, Liu C, Lu F, Qin T, He C, Wang Z, Qin X, Hu D, You L, Li X, Wang T, Wu P, Chen G, Zhou J, Li K, Sun C. Clinical and molecular characteristics of COVID-19 patients with persistent SARS-CoV-2 infection. *Nat Commun* 2021; **12**: 3501 [PMID: 34108465 DOI: 10.1038/s41467-021-23621-y]
2 **Zheng ZX**. Stem cell therapy: A promising treatment for COVID-19. *World J Clin Cases* 2021; **9**: 11148-11155 [PMID: 35071545 DOI: 10.12998/wjcc.v9.i36.11148]
3 **Charitos IA**, Ballini A, Cantore S, Boccellino M, Di Domenico M, Borsani E, Nocini R, Di Cosola M, Santacroce L, Bottalico L. Stem Cells: A Historical Review about Biological, Religious, and Ethical Issues. *Stem Cells Int* 2021; **2021**: 9978837 [PMID: 34012469 DOI: 10.1155/2021/9978837]
4 **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 AI, 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**: 660-673 [PMID: 33400390 DOI: 10.1002/sctm.20-0472]
5 **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 [PMID: 33568628 DOI: 10.1038/s41392-021-00488-5]
6 **Shi Y**, Wang Y, Li Q, Liu K, Hou J, Shao C. Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases. *Nat Rev Nephrol* 2018; **14**: 493-507 [PMID: 29895977 DOI: 10.1038/s41581-018-0023-5]
7 **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**: 747-754 [PMID: 32380908 DOI: 10.1089/scd.2020.0080]
8 **Yu B**, Zhang X, Li X. Exosomes derived from mesenchymal stem cells. *Int J Mol Sci* 2014; **15**: 4142-4157 [PMID: 24608926 DOI: 10.3390/ijms15034142]
9 **Brown C**, McKee C, Bakshi S, Walker K, Hakman E, Halassy S, Svinarich D, Dodds R, Govind CK, Chaudhry GR. Mesenchymal stem cells: Cell therapy and regeneration potential. *J Tissue Eng Regen Med* 2019; **13**: 1738-1755 [PMID: 31216380 DOI: 10.1002/term.2914]
10 **Saleh FA**, Ghazzawi J. Clinical update on the use of mesenchymal stem cells in COVID-19. *Am J Transl Res* 2021; **13**: 12195-12205 [PMID: 34956446]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com