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LETTER TO THE EDITOR

Mesenchymal stem/stromal cells as adjuvant therapy in COVID-19-associated acute lung injury and cytokine storm: Importance of cell identification

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Abstract

Theoretically, mesenchymal stem cells (MSCs) are very promising as adjuvant therapy to alleviate coronavirus disease 2019 (COVID-19)-associated acute lung injury and cytokine storm. Several published studies, which used MSCs to alleviate COVID-19-associated acute lung injury and cytokine storm, reported promising results. However, the evidence came from a case report, case series, and clinical trials with a limited number of participants. Therefore, more studies are needed to get robust proof of MSC beneficial effects.

Key Words: COVID-19; Mesenchymal stem cells; Pneumonia; Cytokine storm; Acute respiratory distress syndrome

Core Tip: Several published studies, which used mesenchymal stem cells (MSCs) to alleviate coronavirus disease 2019-associated acute lung injury and cytokine storm, reported promising results. However, the evidence came from a case report, case series, and clinical trials with a limited number of participants. Therefore, more robust proof is needed. The studies and ongoing clinical trials used MSCs from various sources, and theoretically angiotensin-converting enzyme 2 negative subsets are preferable. Therefore, in future reporting of clinical trial results, the complete identity of the MSCs needs to be defined.

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TO THE EDITOR

I read with interest a minireview by Zhang *et al*[1], who elaborately discussed the prospects of mesenchymal stem/stromal cells (MSCs) in coronavirus disease 2019 (COVID-19)-associated acute lung injury/acute respiratory distress syndrome. In the beginning, the authors pointed out two recently reported MSC based therapies to deal with cytokine storm and pulmonary damage. The first report was by Leng *et al*[2], which enrolled 7 MSC treated subjects and 3 controls. The report showed favorable prognosis in terms of clinical recovery and serum cytokine profile. The second report of MSC based therapy for COVID-19 was a case report by Liang *et al*[3] that reported a favorable outcome.

Though the two reports showed favorable outcomes, I highly support the opinion of Zhang *et al*[1] that the systematic elaboration of the therapeutics and underlying mechanism is far from satisfactory. The first report, which enrolled only a few subjects, showed that the treatment and control group were unequal in terms of age of the patients and severity of disease. The second report is a case report of only 1 patient[2,3], which provides the lowest level of evidence. There were several other reports that were not assessed by the authors. A case series of 12 patients by Terry[4] used two intravenous infusions of bone marrow-derived MSCs (Ryoncil® from Mesoblast). The results showed that 75% of patients who were previously refractory to other experimental therapies were free from ventilators within 10 d, and overall survival was 83%. Further, a recent randomized clinical trial from Indonesia, which enrolled 40 patients, gave umbilical cord (UC)-derived MSCs, and the results showed that the survival rate in the treatment group was 2.5 times higher than in the control group. However, when only patients with comorbidities were assessed, the survival rate of the treatment group was 4.5 times compared to controls. Moreover, there was a significant decrease in interleukin-6 in the recovered patients, and this result was in line with the anti-inflammatory property of MSCs[5]. Interestingly, there are 70 clinical trials at various stages, which are ongoing, and these trials are using MSCs from various sources[1].

It is interesting to note that Zhang *et al*[1] pointed out the superiority of angiotensin-converting enzyme 2 (ACE2) negative subsets of UC-derived MSCs that were used by Leng *et al*[2]. Other studies that used MSCs for COVID-19 did not use ACE2 negative subsets of MSCs[3-5]. A study showed that ACE2 expression was significantly higher in adipose tissue and bone marrow-derived MSCs compared to UC or placenta-derived MSCs. In addition, culture conditions and passage also had an impact on ACE2 expression levels. At higher passages (3-5 passages) both UC and placenta-derived MSCs expressed higher levels of ACE2[6]. I highly support the opinion of Zhang *et al*[1] that highly bioactive subpopulations from the heterogeneous MSCs need to be identified[1]. Therefore, future studies that will use MSCs need to completely report the source, culture conditions, passage, identity, and properties of the MSCs that are used.

FOOTNOTES

Author contributions: Pawitan JA designed the research, performed the research, analyzed data, wrote the letter, and revised the letter.

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