In reply

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LETTER TO THE EDITOR

STEM CELLS TRANSLATIONAL MEDICINE

In reply

We appreciate the interest in our recent publication[1] from Ji and colleagues[2] and thank them for their letter. The authors report on initiating a clinical trial (NCT04252118) to use umbilical cord-derived mesenchymal stem cells (UC MSC) as cell therapy to treat COVID-19 infected patients who have developed pneumonia. One of the mechanisms by which coronaviruses cause extensive lung damage and mortality is due to the induction of unregulated inflammatory response leading to development of acute respiratory distress syndrome (ARDS). In view of the recent WHO declaration of COVID-19 as a pandemic, there is an urgent need to find methods to alleviate the severity of COVID-19-induced acute lung injury, which represents the major cause of mortality in infected patients.

MSCs-based therapy is being considered as a promising approach for ARDS because of robust preclinical evidence of MSC's ability to target major aspects of ARDS pathophysiology.[3,4] Furthermore, data from early phase clinical trials suggest that it is safe to give MSCs to patients with ARDS.[5,6] In addition, the MUST-ARDS study conducted by Athersys Inc with a patented bone marrow-derived adult multipotent progenitor cell product "MultiStem" reported a significant reduction in 28-day mortality accompanied by an increase in both ventilator- and intensive care unit-free days in patients who had received cell therapy.[7] Ji and colleagues also refer to the UC MSC effectiveness in the NCT03608592 trial; however, no published data on the results of this trial have been made available yet, and according to ClinicalTrials.gov, this trial has a recruitment phase status with estimated completion date of December 1, 2020.

Unfortunately, preclinical data on the effects of MSCs in viral-induced lung injury are limited. That is predominantly due to the fact that it is very difficult to model human viral infections in animals. The available data suggest that effects of MSCs appear to depend on the specific viral strain. MSCs significantly attenuated H9N2 avian influenza, as well as H5N1 virus-induced acute lung injury and inflammation, in mice.[8,9] In contrast, MSCs failed to protect mice from lung injury caused by influenza A pneumonia (a mouse-adapted H1N1, PR8).[10,11] To the best our knowledge, there are no data on MSC effectiveness in coronavirus-induced lung injury. This further reiterates the need for establishment and wider adoption of in vivo animal models with natural human target cells to accelerate the development and testing of effective therapeutics for many highly relevant human pathogens. One such model, based on subcutaneous implantation of human lung tissue into humanized mice, was recently reported by Wahl et al.[12]

Another important aspect to consider is that MSCs themselves might be susceptible to viral infections, and such infection may alter their immunomodulatory and reparative properties.[13,14] In this regard, MSC cell products and specifically MSC-derived extracellular vesicles (EVs) could represent a better alternative to the MSC whole cell therapy. In fact, a recent publication by Loy et al suggests that MSC-EVs were effective in attenuating influenza A(H5N1)-induced acute lung injury in pigs.[15]

In conclusion, the safety of MSC administration has been confirmed in numerous clinical trials, so it is unlikely that their administration would cause unwanted adverse effects in the COVID-19 patients' cohort. At the same time, well-established immunomodulatory and reparative capacities of MSCs (although not directly tested in preclinical models for this particular application) make them promising candidates to test in this urgent scenario. Further effective development of MSC-based therapy will be important to investigate the mechanisms of their therapeutic effects in the context of viral pneumonia using clinical samples from patients enrolled in this trial.

We wish the authors success in their study and, most importantly, full recovery to all COVID-19 infected patients.

CONFLICT OF INTEREST

The author indicated no financial relationships.

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