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Umbilical Cord-Mesenchymal Stem Cell Therapy for COVID-19 Related Acute Respiratory Distress Syndrome: A Mini-Review

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Abstract

Introduction: *Acute respiratory distress syndrome (ARDS) is the leading cause of death among coronavirus disease 2019 (COVID-19) patients, mainly due to the cytokine storm and the rearrangements in coagulation and immune responses. Accordingly, the immunomodulatory and regenerative properties of umbilical mesenchymal stem cells (UC-MSCs) have been studied for the treatment of COVID-19.*

Methods: *This mini-review evaluated adults with moderate-severe COVID-19 infection and compared the results of placebo plus standard of care (SOC) therapy with those obtained from the administration of umbilical cord mesenchymal cells (UC-MSCs). We searched the following databases: Cochrane, Central Register of Controlled Trials, and PubMed; subsequently, 8 clinical trials were included in this mini-review. Some statistically significant difference was found in the levels of clinical and inflammatory markers between the intervention and the control groups.*

Conclusion: *Early phase trials have shown the promising efficacy and safety of UC-MSC therapy for COVID-19-associated moderate-to-severe ARDS. Large multicenter phase III randomized controlled clinical trials will further confirm these findings.*

Introduction

Acute respiratory distress syndrome (ARDS) is the leading cause of death among Coronavirus disease 19 (COVID-19) patients, mainly due to the cytokine storm (Ragab et al., 2020) and the rearrangements in coagulation and immune responses (Li et al., 2020). Accordingly, the immunomodulatory and regenerative properties of Umbilical Mesenchymal Stem Cells (UC-MSCs) have been studied for the treatment of COVID-19 (Adas et al., 2021; Dilogo et al., 2021; Saldanha-araujo et al., 2020).

The main mechanism of the immunomodulatory action of MSCs is a shift from pro-inflammatory T-helper 1 (Th1) to anti-inflammatory T-helper 2 (Th2) cells (Weiss et al., 2019). MSCs also promote the repair of type 2 alveolar epithelial cells (Shi et al., 2021). MSCs can be isolated from various sources, including umbilical cord, adipose tissue, bone marrow, and human dental pulp. However, only umbilical cord-derived-mesenchymal stem cells (UC-MSCs) have been tested in phase I and II studies, which resulted in their promising efficacy and safety (Shi et al., 2021).

Currently, most of the studies on ARDS have reported the use of UC-MSCs for therapy, and the amount of such data is increasing rapidly. UC-MSC therapy appears to be effective against ARDS (Rebelatto et al., 2022). However, despite the increased popularity of UC-MSC therapy, no current review has assessed the updated results of this therapy. Therefore, the purpose of this study was to review the current knowledge on UC-MSCs infusion in COVID-19-induced ARDS. We focused on analyzing the safety and efficacy of this intervention.

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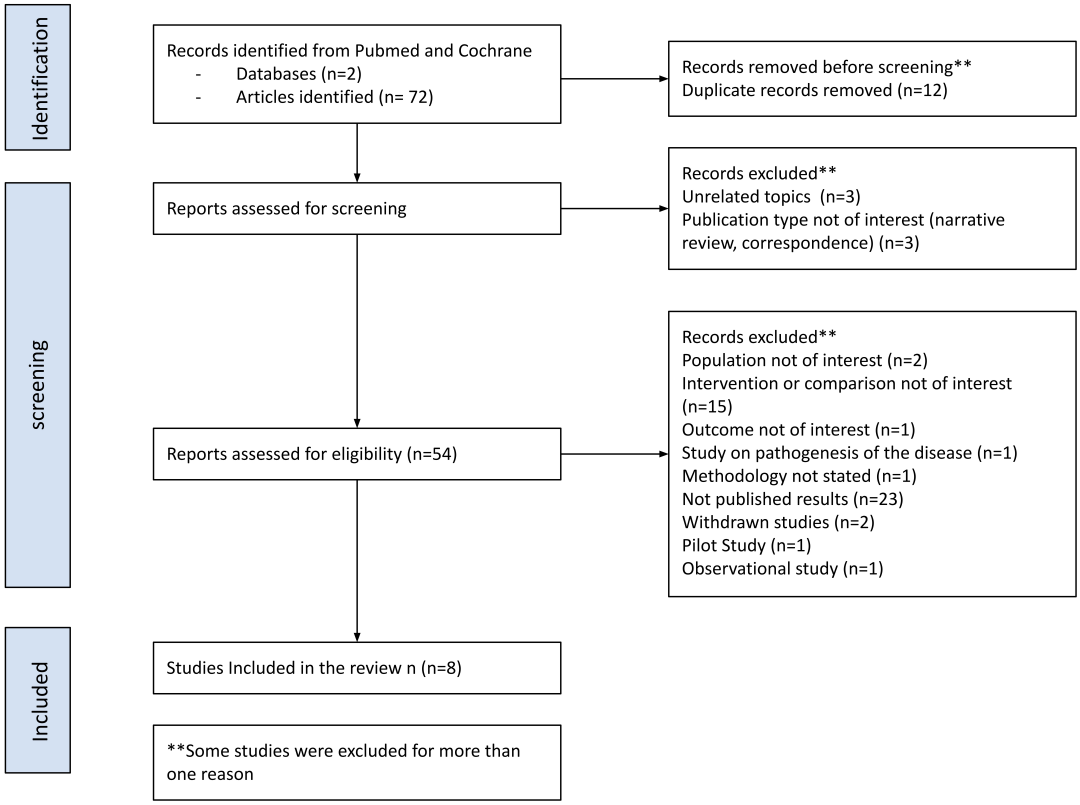

Figure 1: *PRISMA flowchart of literature search.*

Materials and Methods

We searched Cochrane, Central Register of Controlled Trials, and PubMed databases since inception February 1, 2020, to October 4, 2022, using the keywords UC-MSC therapy for patients with COVID-19 and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (See Table 2S: Research strategy, in supplementary appendix). The search strategies were conceived by two researchers of the team and adapted according to the databases' features. Duplicate records were eliminated. The identified records written in English were screened by titles and abstracts, as well as keywords. Papers with potential eligibility were then obtained for full-text review. This two-step screening process for eligibility was performed by two authors. Eligibility was firstly assessed by population: patients with COVID-19 infection confirmed by polymerase chain reaction; intervention; effects of UC-MSC therapy: comparators standard of care or placebo; outcomes: adverse events, safety, imaging, and/or inflammatory factors; study design: Phase I, I/II, and II clinical trials. Studies that did not meet the eligibility criteria were excluded. Because no phase III trials had been performed at the time of this mini-review, they were not included in the strategy.

We included 8 published English phase I–II clinical trials; we evaluated adults aged 20–85 years of age with moderate to severe COVID-19 infection and compared the results of placebo plus standard of care (SOC) therapy with those obtained from intravenous (IV) administration of UC-MSCs. The eligibility criteria can be found in the supplementary appendix (See Table S1: Eligibility criteria, in supplementary appendix). This review adhered to the PRISMA reporting guidelines (Page et al., 2020; Figure 1).

Results

Immunological markers outcomes

The goal of UC-MSCs administration is to exert regenerative and anti-inflammatory effects in damaged lung tissue. Inflammatory markers like interleukin 6 (IL-6; a major contributor to cytokine storm response) presented a significant reduction compared to the control group (P=0.023, Dilogo et al. 2021). Adas et al. (2021) also report a significant reduction of IL-6 in critically ill patients with COVID-19 treated with UC-MSCs compared to those treated with standard care only (mean of 91.3 vs. 117.3mpg/ml, P<0.05) on day 7. Assessment of levels of inflammatory markers (granulocyte-macrophage colony-stimulating factor

(GM-CSF), interferon-gamma (IFN-γ), IL-5, IL-7, TNF-α, TNF-β, platelet-derived growth factor-BB [PDGF-BB], and chemokine ligand 5 [CCL5]) on day 6 after UC-MSC infusion revealed a significant reduction in the concentration of these markers (P<0.05). Adas et al (2021) and Lanzoni et al. (2021) also reported a decrease in other proinflammatory cytokines like IL-5, IL-7, IL-12, tumor necrosis factor alpha (TNF-α), and TNF-β in patients treated with UC-MSCs additional to standard therapy (P<0.05). Nevertheless, the IL-2 levels in the UC-MSC-treated group were not statistically significantly different from the control group (P=0.051, Lanzoni et al. 2021). Similar results were obtained for IL-2, macrophage inflammatory protein-1 alpha- Chemokine ligand 3 (MIP1α-CCL3), and Granulocyte Colony-Stimulating Factor (G-CSF) levels, as no significant differences between the levels in the two groups were observed (Rebelatto et al., 2022).

Primary safety outcomes

Adas, et al. (2021), described no serious adverse events (SAEs) with UC-MSCs therapy. The death occurred commonly due to bacterial pneumonia and thrombotic events (myocardial infarction, thromboembolism). Comorbidities such as hypertension and diabetes mellitus were seen in the deceased patients.

Lanzoni, et al. (2020), measured safety as their primary outcome; described it as an event that happened within the first 6-hour infusion and 24 hours post-infusion of the UC-MSCs therapy infusion. Compared to the control group, SAEs were seen in the control group compared to UC-MSC therapy (p= 0.04). The only reported adverse events (AEs) included infusion-related reactions in one patient and a bradycardic event, solved by vasopressor use, in a second patient.

Rebelatto, et al. (2022), compared UC-MSCs therapy vs. placebo, and their primary endpoint was to measure infusion-related AEs [-15.5 to 93.3] vs 25.3 [-33.3 to 104.6], respectively, within the first 24 hours of infusion. The only AEs reported was transient hypotension in one patient after the first infusion only. Death was reported due to bacterial infection, ARDS, and multiorgan failure in both groups.

Meng, et al. (2020), reported no SAEs related to UC-MSCs therapy. Infusion-related AEs included flushing and fever. Monsel, et al. (2022) reported 6 SAEs non-related to UC-MSCs therapy or placebo.

Clinical performance outcomes

Shi et al. (2021) observed no significant differences were found between the values of lung parameters, including diffusing capacity for carbon monoxide (DLCO), the status of oxygen therapy, maximum forced vital capacity (VCmax), residual volume, total lung capacity, and vital capacity levels, in the placebo plus SOC group and the group treated with UC-MSCs. UC-MSC therapy in the intervention group caused a reduction in the extent of the total lung volume injury of -19.40% (95% CI, -53.40%, -2.62%) compared to the lesser repair of the SOC group with -7.30% (95% CI, -46.58%, +19.12%) 28 days after the evaluation used as the baseline. Similar results in the median differences in solid lung components lesions; parenchymal and interstitial tissue; 28 days after baseline (-57.70 vs. -44.35%, in UC-MSC and SOC groups, respectively; Shi et al., 2021). The CT scan results presented complete lung lesion improvement from 100% of patients with severe lung damage observed 2 weeks after infusion of UC-MSC, compared lung damage persistence at discharge to 33% of patients from the control group (Meng et al., 2020).

The six-minute walk test (6-MWT) is used to assess lung function. Shi et al. (2021) demonstrated that patients who received MSC therapy could walk for longer distances after 1 month of treatment compared to those in the placebo group (420 m vs. 403 m, respectively, P=0.05). In a study by Shu et al. (2020), time-to-discharge from the onset of symptoms was significantly lesser for patients who received UC-MSC therapy than for those who received SOC (P=0.01), a significant improvement in clinical symptoms was observed on days 7 (P=0.02) and 14 (P=0.03) in patients who received UC-MSC therapy compared to that in patients who received SOC. Monsel et al. (2022) found no significant differences in partial pressure of oxygen to fractional inspired oxygen ratio (PaO_2/FiO_2) from days 0-7 between the UC-MSCs therapy and placebo groups (Interquartile range 54.3 [-15.5 to 93.3] vs 25.3 [-33.3 to 104.6]; respectively.

Lanzoni et al. (2021) evaluated the rates of patient survival using Kaplan-Meier survival estimates. In the trial, rates of survival significantly improved 31 days after UC-MSC administration in the intervention group compared to that in the control group (91 vs. 42%, respectively, P=0.015). Additionally, the recovery times also improved after UC-MSC administration in the intervention group. In the UC-MSC-treated group, it took less time to recover than those in the control arm (P=0.03). In the subgroup of patients older than 65 years, the average recovery time of the UC-MSC-treated group was 13 (95% IC, 11.75, 14.00) days, whereas that of patients in the control group was 23 (95% IC, 18.50, 29.00; Shu et al., 2020). However, Meng et al. (2020) observed no significant differences between the groups treated

with UC-MSCs and treated with SOC only (20 vs. 23 days, P=0.306).

Discussion

The primary objective of this mini-review was to evaluate adults with moderate severe COVID-19 infection and compare the results of placebo plus SOC therapy with those obtained from the administration of UC-MSCs. Following a comprehensive literature search and the identification of relevant clinical trials, a narrow number of studies suggest that the administration of UC-MSCs on the pathophysiology of SARS-CoV-2 constitutes a promising therapeutic method of combating the COVID-19 virus, increasing patient survival rates. Having a general beneficial effect of UC-MSC it can be considered a safe and effective method to treat COVID-19 in this early phase of research.

Little to no occurrence of SAEs in the UC-MSCs therapeutic arm was also observed, confirming the administration of UC-MSCs is relatively safe in addition to the SOC. To our knowledge, this is the first mini-review that assessed the different clinical trials evaluating the efficacy and safety of UC-MSCs as a possible treatment for COVID-19. The findings are clinically important since different current clinical trials show that UC-MSC administration is a safe and effective method. Despite the heterogeneity of efficacy outcomes among different trials, the overall results show a significant improvement in persistent COVID-19 symptoms in the UC-MSCs arm, along with an improvement in recovery times after UC-MSC administration. At the molecular level, we find the description of a significant reduction in the cellular response of lymphocytes observed in the UC-MSC-treated group.

There are many limitations of the studies included in this review. The number of studies included in the review that answered the main question is restricted. The sample size of most studies was limited and did not allow stratification of patients. Furthermore, many patients were lost to follow-up or died. Unknown potential confounders were not equally measured at entry into the study, which makes it challenging to evaluate subsequent differences in results. All analyzed studies are written in English, and no other language was included in this review. Additionally, all studies are obtained from a few open-access databases. Lack of generalizability should be targeted on the inclusion of phase I and phase II trials, therefore, studies with small sample sizes, single-center settings, and without a standard protocol for the intervention. Based on such limitations, the authors suggest that further studies are needed to determine the mechanism of action of UC-MSC therapy in severe cases with mechanical ventilation, to standardize the timing of administration and criteria for therapeutic improvement and failure, and to have longer follow-up periods.

Conclusions

The present findings based on early-phase trials suggest that UC-MSCs result in promising efficacy and safety in COVID-19-related ARDS. Large-scale, long-term multicenter phase III RCTs are needed to confirm the effectiveness of this intervention.

Supplementary materials

The following supporting information can be downloaded: Table S1: Eligibility criteria; Table S2: Research strategy; Table S3: Main characteristics of the included studies.

Author Contributions

The authors are ordered based on their contribution to the study. The first author was decided after concluding the manuscript based on the performance quality and quantity during the development. The corresponding author's name is written at last, functioning as senior author and contributor of the project.

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Conflicts of Interest

The authors declare no conflict of interest.

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