Mesenchymal Stem Cell Therapy for Acute Respiratory Distress Syndrome

A Light at the End of the Tunnel?

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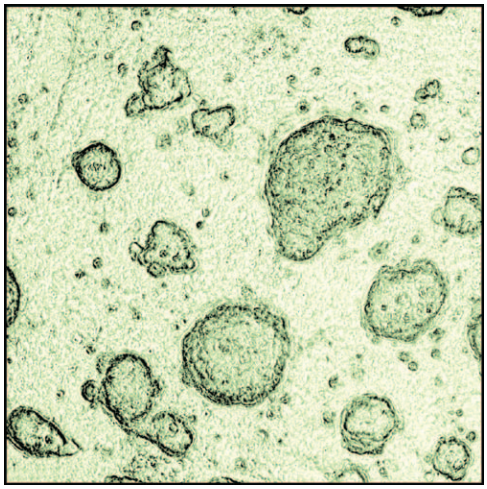
ACUTE respiratory distress syndrome (ARDS) is a major cause of acute respiratory failure in critically ill patients. Despite improvements in understanding the pathophysiology of ARDS, its mortality remains high.[1,2] Current treatments rely on supportive measures, such as lung-protective ventilation, conservative fluid management, and prone positioning.[3–5] No pharmacological therapies from preclinical models have been translated to effective clinical treatment options. Mesenchymal stem or stromal cells (MSCs) may be an innovative therapy for ARDS. However, questions remain concerning the optimal dose, route, and timing of MSC administration after acute lung injury (ALI). In this issue of Anesthesiology, Hayes *et al.*[6] address these concerns by studying the therapeutic characteristics of human bone marrow–derived MSCs in a validated animal model of ALI: ventilator-induced lung injury (VILI) in rats.



"… two clinical trials are underway to test the safety and feasibility of using MSCs in ARDS."

MSCs are adult, nonhematopoietic precursor cells derived from a variety of tissues (*e.g.,* bone marrow, adipose tissue, and placenta) and have been used as therapy in multiple conditions (myocardial infarction and graft-*versus*-host disease). We, and other investigators, have reported that MSCs are effective in preclinical models of ALI due to their ability to secrete paracrine factors that regulate lung endothelial and epithelial permeability, including growth factors, anti-inflammatory cytokines, and antimicrobial peptides.[7–10] These soluble factors can treat the major abnormalities underlying ALI, including impaired alveolar fluid clearance, altered lung permeability, dysregulated inflammation, and infection.

Based on promising preclinical data, two clinical trials are underway to test the safety and feasibility of using MSCs in ARDS. One (NCT01775774) is a multicenter study which will assess the safety of escalating intravenous doses ($1–10 \times 10^6$ cells/kg) of allogeneic human bone marrow–derived MSCs in patients with moderate or severe ARDS. Another randomized, double-blind, placebo-controlled trial (NCT01902082) will assess safety and efficacy outcomes of allogeneic adipose-derived MSC therapy (1×10^6 cells/kg). However, questions remain as to the optimal dose and route of MSC delivery.

Optimal Dose and Route of MSC Delivery

Preclinical ALI studies have used mean MSC doses of $29.9 \pm 20.4 \times 10^6$ cells/kg in mice and $20.3 \pm 22.5 \times 10^6$ cells/kg in rats during the early phase of lung injury, suggesting that the effective dose is approximately $20–30 \times 10^6$ cells/kg.[11] Most clinical trials using MSCs in lung disease, such as for idiopathic pulmonary fibrosis (NCT01385644) or bronchopulmonary dysplasia (NCT01632475), administered doses in the $1–20 \times 10^6$ cells/kg range, which appeared to be largely based on previous trials of MSCs in myocardial infarction, graft-*versus*-host disease, *etc*. To address this discrepancy between preclinical animal models and ongoing clinical trials, Curley *et al.*[12] tested the efficacy of different doses of human MSCs ($1–10 \times 10^6$ cells/kg) in the rat model of VILI. The authors found that intravenous administration

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of 10×10^6 MSCs/kg improved lung compliance, reduced alveolar edema/lung permeability, and helped restore lung architecture and oxygenation as compared with vehicle or fibroblasts.[6] MSCs also decreased the influx of inflammatory cells into the injured alveolus, reducing expression of cytokine-induced neutrophil chemoattractant-1 and interleukin-6, while increasing the secretion of keratinocyte growth factor, which is known to enhance alveolar fluid clearance. More importantly, they found that MSC dose–response curve was not linear and the lowest effective dose of human MSCs, that is, the threshold above which greater efficacy was not seen, was 2×10^6 cells/kg. Therefore, MSC doses above this threshold provide no additional therapeutic benefits, but may increase the potential for complications. It is well known that, when administered intravenously, MSCs are initially trapped in the pulmonary circulation due to their size, which can precipitate embolic phenomena with increased right ventricular strain and elevated pulmonary artery pressures, complications that ARDS patients may not tolerate.

Most preclinical studies using endotoxin or bacterial pneumonia models of ALI administrated MSCs intratracheally, while those using bleomycin, ischemia/reperfusion, ventilator-induced, or other lung injury models delivered MSCs intravenously.[11] To address the optimal route of MSC delivery, Hayes *et al.*[6] compared the intravenous route to the intratracheal and intraperitoneal routes in VILI. They found that both intravenous and intratracheal MSC administration more effectively enhanced the recovery of arterial oxygenation and lung compliance, reduced lung permeability and influx of inflammatory cells into the injured alveolus, and restored lung structure compared to the intraperitoneal route. Although intrabronchial MSC instillation may not be optimal in hypoxemic ARDS patients, one Phase I clinical trial is underway to test the intratracheal administration of up to 20×10^6 cells/kg in neonates with severe bronchopulmonary dysplasia (NCT01632475). Additionally, for patients with pneumonia-associated ARDS, it is now known that MSCs possess direct antimicrobial activity through the secretion of antimicrobial peptides/proteins, such as cathelicidin-related antimicrobial peptides or lipocalin-2, as well as the ability to enhance macrophage/monocyte phagocytosis of bacteria. Thus, intrapulmonary delivery may ultimately be the most effective route to enhance bacterial clearance.[13]

Timing of MSC Administration

Although preclinical animal models cannot replicate the natural course of ARDS, MSCs are usually given within 6 h of ALI, during the acute inflammatory phase.[11] However, it is unlikely that any therapy for ARDS be administered so early in its course but once lung injury is firmly established.[9] To address this issue, Hayes *et al.* administered MSCs at 0.25, 6, and 24 h after VILI, to coincide with both the acute inflammatory and the subsequent resolution phase of VILI. They found that MSCs significantly enhanced repair even when administered at 24 h after injury, suggesting the therapeutic effect was not solely anti-inflammatory.[6]

Bone Marrow–derived Mononuclear Cells *versus* MSCs

To generate enough cells for administration, MSC preparations require *in vitro* culture expansion, which increases risks and entails several weeks of preparation. Therefore, most clinical trials have used human MSCs frozen in DMSO, which could negatively affect the therapeutic immunomodulatory effects of these cells.[14] As an alternative, several investigators have focused on investigating the therapeutic potential of bone marrow–derived mononuclear cells (BMDMCs). Compared to MSC, the potential advantages of BMDMCs include autologous harvest on the day of administration, avoiding the need for an allogeneic source and lowering the cost in acute diseases such as ARDS; expression of genes involved in inflammatory response and chemotaxis by BMDMCs; and potential for crosstalk among multiple cell types in these preparations.[15,16] In preclinical studies, BMDMCs from experimental donors with pulmonary and extrapulmonary ALI, although different in characteristics, were as effective as cells obtained from healthy donors in reducing inflammation and remodeling, suggesting a role for autologous BMDMC transplantation in clinical settings. BMDMC administration was also found to reduce lung inflammation and fibrosis regardless of the timing of injection after endotoxin-induced ALI.[17–20]

Conclusion

Despite these advancements from preclinical studies, substantial challenges remain before MSC therapy can be used in clinical practice. As a relatively small number of patients with lung injury have received MSC therapy to date, further investigations are required to characterize its safety profile in terms of MSC quality control, bacteriological testing, viability, phenotype, and oncogenicity tests. The optimal timing and duration of administration, dose, source, delivery route, and schedule need to be evaluated. Finally, MSCs are produced by different companies; thus, regulations for their production require better definition because differences in cell production (*e.g.*, passaging) may result in different effects. In conclusion, MSCs are potentially a very promising treatment for ARDS. Although it is difficult to extrapolate animal studies to bedside, the Hayes *et al.* study should help clinician scientists evaluate stem cell–based therapies for ARDS by defining the optimal dose, route, and timing of MSC administration.

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Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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