Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Supported with Extracorporeal Membrane Oxygenation
Lost in Translational Research?

Acute respiratory distress syndrome (ARDS) is the clinical result of a broad variety of acute insults to the lung that can primarily injure the pulmonary epithelial cells (e.g., inhalation injury and pneumonia) or endothelial cells (e.g., sepsis) (1, 2). Regardless of the origin and route of injury, the common result is the development of a severe inflammatory response and consequent damage to vascular, interstitial, alveolar, and airway structures (3, 4). The inflammatory response is characterized by the rapid release of proinflammatory mediators and involvement of local lung tissue macrophages as well as the recruitment of blood cells, particularly neutrophils, from the bloodstream into the lung parenchyma. The most common feature seen in autopsies of ARDS patients is diffuse alveolar damage, with severely altered permeability of the alveolar capillary membrane, damage of the small airways, and formation of microthrombi (5). The injury is typically inhomogeneously distributed through the lung parenchyma, and the extension of the injury distribution is important in determining its severity (6).

Despite the large body of research in ARDS, no targeted treatment has proven efficacious in improving patient outcome (7). The prognosis of patients with ARDS hence mainly depends on treating, when possible, the primary cause of injury and on the efficacy of life-sustaining treatments (8), and mortality remains unacceptably high (9). A tremendous effort is, therefore, underway to identify specific therapies effective in preventing the progression of lung injury or in accelerating its resolution. The considerable challenge in this field is provided by the pathophysiological complexity of ARDS, whereby it is difficult to identify one single target that may be responsive among the whole spectrum of possible injurious mechanisms.

In this regard, the research on the therapeutic effect of mesenchymal stem cells (MSC) generated a considerable enthusiasm (10). MSC can exert pleiotropic effects, including their ability to transfer mitochondria, addressing several of the mechanisms of lung injury resulting in ARDS (11). Specifically, in experimental models of lung injury, MSC have been demonstrated to have considerable antiinflammatory, antimicrobial, and antifibrotic properties, which were very effective in reducing or resolving lung injury.

Only a few clinical trials have tested the effect of MSC administration in patients with ARDS, demonstrating safety without being appropriately powered to show improvement in patient-centered outcomes (12, 13). However, these trials excluded patients with the severe ARDS requiring extracorporeal membrane

oxygenation (ECMO). However, ARDS patients requiring ECMO could be the perfect candidates to investigate the therapeutic potential of MSC given the underlying severity of their lung injury and the stable gas exchange afforded by ECMO support.

In this issue of the *Journal*, Millar and colleagues (pp. 383–392) performed an experimental study using a complex sheep model of severe ARDS with intravenous oleic acid combined with endobronchial administration of *Escherichia coli* LPS (14). ECMO was started to normalize gas exchange, and then 3×10^8 of clinical-grade induced pluripotent stem cell–derived human MSCs (hMSC) were endobronchially delivered. Seven animals received hMSC and were compared with seven that received only the vehicle as control. The animals were supported with mechanical ventilation (V_T 4 ml/kg and positive end-expiratory pressure 10 cm H_2O) and were monitored for 24 hours. In the last hour of the experiment, ECMO was stopped, a lung recruitment maneuver was performed, and gas exchange was monitored to assess lung function in the absence of the confounding effect of extracorporeal gas exchange.

The results of the study showed that endobronchial administration of hMSC did not significantly improve gas exchange and lung function in this model. However, the animals treated with hMSC had less histologically evident lung injury, lower IL-8 levels in the BAL fluid, and less vasopressor requirements. Interestingly, hMSC were able to migrate from the endobronchial space into the bloodstream and adhere to the oxygenator fibers of the ECMO circuit.

Overall, these findings do not confirm the greater effect of hMSC demonstrated in other preclinical models despite similar sample size. Specifically, none of the primary outcomes of the study showed a positive outcome. Although not necessarily injurious, the adherence of hMSC on to the ECMO oxygenator with the consequent increase of the transmembrane pressure triggers important concerns about the potential life-threatening reduction in efficiency and durability of this piece of equipment, particularly if the study had continued for a longer duration. Concerning is also the findings of increased pulmonary thrombi in the hMSC-treated group. Moreover, hMSC in this model showed a surprisingly poor antiinflammatory effect, which should have been provided by the secretion of paracrine antiinflammatory factors from the cells adherent to the oxygenator. In addition, no effect was demonstrated on systemic inflammation or end-organ dysfunction.

Several issues may explain these results. The endobronchial route of administration of the cells may have not been the most effective in a model of ARDS caused by the intravenous administration of oleic acid, affecting primarily endothelial cells. Furthermore, although the cells transmigrated into the bloodstream and could have blunted the endothelial injury, no significant antiinflammatory effect was seen. Moreover, the reduction of IL-8 in the BAL fluid may have resulted from the scavenging action of the hMSC on the endobronchially delivered LPS. However, the ECMO support made this route of administration feasible and safe despite

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the severity of lung injury. The timing of administration may have not been optimal in this complex model. Whereas 1 hour after ECMO deployment may be an optimal timing for LPS-induced lung injury, it is unclear what the optimal timing would be for oleic acid–induced lung injury, as the molecular mechanism by which lung injury occurs in this circumstance is still not well defined. Experiments with multiple different time points of administration would have clarified this issue. Interestingly, in an acid aspiration model of lung injury, MSC have shown to have either a therapeutic or injurious effect according to the time of delivery because of changes in the microenvironment (15). Another potential issue is that the technique used to cause ARDS may be less sensitive to the therapeutic hMSC effect because the severity of the oleic acid–induced ARDS is less predictable and is neutrophil independent (16). Alternatively, the type of MSC used in these studies may not be effective in this specific model of injury. One size may not fit all for MSCs; several types of stromal cells of different origin (e.g., bone marrow–derived, umbilical cord–derived, adipose tissue–derived, and liver tissue–derived cells, endothelial progenitors, etc.) have been studied for their distinctive potential therapeutic mechanism and role in different types of lung injury (e.g., direct vs. indirect). The combined administration of MSCs and endothelial progenitors could have potentially more specifically addressed the inflammatory as well the endothelial injury in this model. Finally, it is possible that even if beneficial, the therapeutic effect of hMSC is not adequate to meaningfully alter the extent and severity of lung injury seen in this model. These questions will need to be answered in future research.

Given the number of unresolved questions, important safety concerns, and the lack of a convincing therapeutic effect, hMSC should not be considered for clinical use in patients with severe ARDS supported with ECMO and mechanical ventilation. Millar and colleagues should be congratulated for devising and executing an experimental model with high clinical relevance and, hence, an extraordinary level of complexity. Importantly, preclinical studies such as these will be needed to clarify the future role of hMSC administration in heterogeneous syndromes such as ARDS. ∎

Lorenzo Del Sorbo, M.D.
Eddy Fan, M.D., Ph.D.
Interdepartmental Division of Critical Care Medicine
University of Toronto
Toronto, Ontario, Canada
and

Extracorporeal Life Support (ECLS) Program
Toronto General Hospital
Toronto, Ontario, Canada

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