

Mesenchymal stromal cells and the acute respiratory distress syndrome (ARDS): challenges for clinical application

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In contemporary reports, approximately 30% of patients with acute respiratory distress syndrome (ARDS) will die¹ and up to 70% of survivors have persistent significant disability.² Several interventions which limit injurious ventilation have been shown to reduce mortality, primarily: low-tidal volume ventilation,³ prone positioning,⁴ early neuromuscular blockade⁵ and possibly extracorporeal membrane oxygenation (ECMO).⁶ To date, no intervention targeted at the underlying pathophysiological process has been shown to be beneficial, including recent studies of β -agonists and statins.^{7,8}

Given the failure of pharmacological interventions in ARDS, increasing interest has been shown in the potential of mesenchymal stromal cells (MSCs). While the complex actions of MSCs are not yet fully understood, they appear to attenuate lung injury via three broad mechanisms. First, they have an immunomodulatory ability, influencing both innate and adaptive immunity. This is achieved by the secretion of anti-inflammatory soluble factors, including interleukin 10 (IL-10), IL-1 receptor antagonist and prostaglandin E2.⁹ Second, MSCs directly augment the host response to sepsis. LL-37 is a peptide secreted by MSCs which has direct antimicrobial properties and has previously been shown to increase bacterial clearance in an *Escherichia coli* model of lung injury after the intratracheal administration of MSCs.¹⁰ Third, MSCs play an important role in the repair and regeneration of lung tissue following injury. This ability appears to be mediated by the secretion of several growth factors, including vascular endothelial growth factor and keratinocyte growth factor.⁹

In this edition of *Thorax*, Devaney *et al*,¹¹ in an elegant series of experiments have contributed important new evidence supporting a potential role for MSCs in ARDS. The administration of human bone marrow-derived MSCs (hMSCs) resulted in improved lung injury in animals treated with MSC as compared with those treated with saline or fibroblasts. These treated animals exhibited lower rates of alveolar neutrophil infiltration and higher levels of IL-10, demonstrating the immunomodulatory properties of hMSCs. Crucially, this study also found that hMSCs act to reduce the bacterial burden and enhance the function of macrophages. These data support results obtained from previous work in both *ex vivo* and animal models of ARDS.^{12,13} Importantly, the authors also present results, which have direct relevance to our future ability to translate MSC therapy to patients. Their study compared the use of cryopreserved hMSCs against fresh cells and showed no difference in efficacy. The ability to preserve cells for storage or transport would increase the feasibility of MSCs as a therapeutic option. Furthermore, the study showed no advantage to intratracheal instillation when compared with intravenous administration. In the setting of significant hypoxia associated with ARDS, intravenous administration offers a safer and more convenient method of administration.

One factor to consider in the translation of these data relates to the relevance of data from small animal models to patients with ARDS. It is recognised that ventilation in rodents differs from humans^{14,15} and moreover genomic responses in mouse models correlate poorly with human inflammatory diseases.¹⁶ One approach to compliment and advance the data from small animal models is to use a large animal ovine model of ARDS, which most closely represents human pulmonary physiology.¹⁷

In a previous editorial,¹⁸ reviewing pre-clinical studies on MSCs in ARDS,^{13,19} the argument was made that the time was appropriate for clinical trials of MSCs in

patients with ARDS. Two phase I trials have been completed demonstrating safety in the acute setting,^{20,21} and two phase IIa studies are in progress: (1) Matthay *et al*²² are undertaking a randomised, double-blind, placebo-controlled, multicentre trial, investigating a single dose of allogeneic bone marrow-derived MSCs (10 M cells/kg) in patients with ARDS in the USA (NCT02097641) and (2) Le Blanc and Grinnemo²³ are undertaking a non-randomised open-label, controlled multicentre trial, investigating a single dose of allogeneic bone marrow-derived MSCs (2 M cells/kg) in patients with viral-induced ARDS on ECMO (NCT02215811). There is also significant pharma interest in cell therapy in ARDS. However, a number of key questions remain unanswered.

First, while the current study investigators have used bone marrow-derived MSCs, other groups have reported MSCs derived from different tissue types.⁹ MSCs derived from bone marrow present logistical challenges as a source of cells for large-scale clinical applications. MSCs derived from other tissue types, such as umbilical cord, may be a better source of cells. In addition to being a relatively unlimited tissue source, umbilical cord-derived MSCs may possess additional attributes, including greater anti-inflammatory potential and better proliferation kinetics.²⁴ Further clinical studies are required to determine the optimal MSC source.

The ARDS population to be studied in clinical trials merits further consideration; to date, preclinical studies of MSCs have focused on moderately severe models of lung injury. Future studies should also concentrate on testing the potential of MSCs in more severe ARDS where mortality is highest such as those patients receiving ECMO. Given the rapid expansion in the use of extracorporeal techniques, the interaction between these two therapies should be tested in preclinical studies to help inform the appropriate design of future clinical trials of MSCs in patients receiving ECMO. Patients receiving ECMO also offer a unique opportunity to investigate the pulmonary mechanisms by which MSCs act, through the ready access to bronchoalveolar lavage regardless of the severity of hypoxia. There may also be the opportunity to deliver MSCs to the preprepared ECMO circuit rather than the lungs *per se*, as the extracorporeal circuit is a site of substantial inflammatory excess related to the hyperoxic environment which exists there. Organisations such as ECMONet will be invaluable in facilitating such clinical trials (<http://www.internationalecmonetwork.org>).

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Finally, the challenges posed by the potential heterogeneity of donated cells and our lack of a potency assay to define a consistent final cell product, in addition to the issues of scaling cell manufacturing and distribution to supply multiple clinical sites and potentially thousands of patients, need to be considered. Research should focus on improving the isolation and definition of MSCs to reduce heterogeneity, which will be required to fulfil expected future regulatory requirements for cell therapy.²⁵ In the UK, a recent Department of Health position paper on Regenerative Medicine²⁶ highlighted that the NHS Blood and Transplant (NHSBT), with its expertise in supplying safe blood and tissue products to hospitals across the UK, would make it a natural partner in any national regenerative medicine strategy. If cell therapies are proven to be effective, the infrastructure that bodies such as the NHSBT have in place will need to be used to ensure that cell therapies can be delivered as a standard of care.

In conclusion, MSC therapy holds the promise of becoming a revolutionary treatment for ARDS. Ongoing preclinical work, such as the work by Devaney *et al*, is needed to inform future clinical trials. The next challenges in clinical translation will be to deliver a consistent cell product, in a scalable manner, to treat the significant number of patients with ARDS who might benefit from this therapy. Patients with the most severe ARDS requiring ECMO may represent a group in which this promising therapy can provide important benefits.

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