Acute Respiratory Distress Syndrome and Stem Cells
A Small Beginning or a Strategy Doomed to Never Gestate?

Acute respiratory distress syndrome (ARDS) remains a heterogeneous and very common cause of respiratory failure requiring intensive medical care. An enormous amount of research into ARDS has delivered some dividends (1); however, the mortality rate remains unacceptably high with estimates ranging from 15 to 50% in recent studies (2–5). More recently attention has also focused on poorer long-term health outcomes in ARDS survivors (4, 6–8). Much of the improvement in ARDS hospital mortality rates has been attributed to the use of pressure-controlled ventilation limiting secondary lung injury, a strategy suggested by experimental models, which has now been the standard of care for well over a decade (1). Despite a large amount of research, we have so far failed to develop any strategies that prevent the development of ARDS after an ARDS-prone insult, ameliorate ARDS when lung injury is evolving (i.e., as patients progress through acute lung injury to ARDS), or reduce the proportion of patients that go on to develop fibroproliferative ARDS and its associated prolonged use of mechanical ventilation.

In recent years, clinical trials with stem cells have taken the emerging field in many new directions. There is an emphasis on the use of bone marrow, hematopoietic, and mesenchymal stem cells. Both neural and pluripotent stem cells are under study in early phase I/II trials. In this issue of the Journal, Lee and colleagues (pp. 751–760) present a detailed series of experiments in an ex vivo human lung ARDS model and show that human mesenchymal stem cells may be beneficial, at least in part through the action of keratinocyte growth factor (KGF) (9). At face value, the results of Lee and colleagues seem promising, with substantial reductions in lung edema, lung inflammation, and bacterial load from a single intratracheal or intraperfusate (effectively intravenous) installation of human mesenchymal stem cells (MSCs) (9). However, it is when you start to consider how such an intervention would move toward clinical trials that you realize how poor our current understanding of ARDS is and the enormous gulf between what we can study in the laboratory and what happens in the “real” world.

ARDS is not a disease but a clinical–radiological–pathological phenotype that can be arrived at from a diverse array of insults to the lung. Is ARDS due to bacterial sepsis really the same as ARDS due to trauma or inhalational injury? This becomes a critical issue when we consider that the model used by Lee and colleagues (9) was a large bolus of Escherichia coli, and part of the effect of the intervention was to reduce bacterial load. A successful intervention through ameliorating bacterial-induced lung injury may not work in other situations. Indeed, the large bolus of E. coli required to cause injury in the ex vivo lung model bears little resemblance to the more gradual process of bacterial accumulation in the lung in normal human pneumonia, and we have no idea whether the immune processes brought into play are even comparable.

Moving from the bench to the bedside, the most critical issue becomes the window of opportunity to use the intervention. Experimental models offer the possibility to test the effect of potential therapeutic agents on regeneration of type I pneumocytes, which are nearly impossible to culture in vitro. Lee and colleagues (9) instilled their MSC 1 hour after the introduction of E. coli. A host of interventions have been shown to reduce pulmonary injury if given before, at the time of, or shortly after a significant insult, but all have so far failed to be effective when given at more realistic time points (e.g., 6, 12, or even 24 h after the initial insult). Although studying the human ex vivo lung has significant benefits, the inherent problem of keeping it viable for longer periods is also a major barrier to truly understanding the potential for MSC in clinical practice.

Providing sufficient clinical supply of MSC for any intervention represents a challenge, hence the importance of the finding by Lee and colleagues (9) that KGF provides much of the benefit. Even so, recombinant KGF is unlikely to be a cheap intervention and therefore restricted to patients with a high likelihood of developing ARDS. Therein lies the next problem, as our current ability to predict which patients will develop ARDS is poor. First, we have limited ability to predict which patients with impaired gas exchange will deteriorate further to the PaO2/FiO2 “cutoff” defining acute lung injury. In patients who meet the criteria for acute lung injury, we have very limited tools to determine who will

progress further to ARDS. Even in patients with ARDS, many have a very short duration of illness and have excellent outcomes, but our ability to clearly define this group of patients at the outset remains limited. If we cannot be sure in whom to intervene, any economic benefit from successful therapy quickly deteriorates due to massive overtreatment.

Finally we have to consider what downstream adverse effects there may be from intervening. Both glucocorticoids and anti-tumor necrosis factor therapies offered promise, but ultimately failed to show benefit both in bacterial and viral pneumonia in part due to excess side effects such as secondary infections (10). Although shutting down pulmonary inflammation may provide acute benefits, it may increase the risk of downstream complications. There is evidence that patients with ARDS are now older and have more comorbidities (11, 12). Another interesting issue is the possibility of genetic modification to secrete a specific protein that plays an important role in the control and pathogenesis of ALI/ARDS (13, 14). Will reducing the severity of ARDS, without affecting the underlying disease(s) responsible, produce real mortality and economic benefits, or will we be just keep some patients alive a little longer at great expense?

Overall Lee and colleagues are to be commended for their very detailed study and their new findings. KGF, given that it could be easily produced in large quantities and can be given systemically, avoiding the need to start mechanical ventilation preemptively, shows some promise. We should, however, recognize the severe limitations this and other experimental models of ARDS have and continue to try and produce data that answer the key questions: What is the window of opportunity to give the intervention? How long does the intervention continue to depress the immune response? What subgroup(s) of patients at risk for ARDS does this truly benefit? The increasing participation of large pharmaceutical companies in stem cell therapies and strong funding from research foundations and governmental agencies (15) is likely to expand new clinical trials in this field.

Author disclosures are available with the text of this article at www.atsjournals.org.

Grant W. Waterer, M.D., PhD  
School of Medicine and Pharmacology  
University of Western Australia  
Perth, Australia  

Jordi Rello, M.D.  
Universitat Autonoma de Barcelona  
Hospital Universitari Vall d’Hebron  
Barcelona, Spain

References


The Berlin Definition of ARDS versus Pathological Evidence of Diffuse Alveolar Damage

A reliable definition of acute respiratory distress syndrome (ARDS) is essential for clinical trials, epidemiologic studies, and biological studies of pathogenesis. A reasonable working definition of ARDS is also needed for clinicians to make the diagnosis of ARDS and initiate treatments that will improve clinical outcomes, including lung protective ventilation. ARDS is a form of acute lung injury characterized by inflammation and increased endothelial and epithelial permeability to protein (1). The corresponding pathologic findings are lung edema, inflammation and hemorrhage, hyaline membranes, and alveolar epithelial cell injury (i.e., diffuse alveolar damage [DAD]); these findings on post mortem examination or lung biopsy have represented the gold standard. The 1994 American European Consensus Conference definition was the first definition to be widely adopted after