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Is there a need for emerging drugs for the acute respiratory distress syndrome?

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Abstract

The acute respiratory distress syndrome (ARDS) is a common and devastating syndrome of acute respiratory failure for which little effective pharmacotherapy exists. The authors describe some interventions that show promise as potential therapies for this condition, with particular reference to clinically relevant human models of ARDS. Aspirin, mesenchymal stromal (stem) cells, keratinocyte growth factor, IFN-β and oncostatin M inhibition are discussed.

Keywords

acute respiratory distress syndrome; aspirin; IFN-β; mesenchymal stromal cells; oncostatin M

The acute respiratory distress syndrome (ARDS) is a condition characterized clinically by acute respiratory failure in critically ill patients. Since ARDS was first described in 1967 [1], definitions have varied, with consequent discrepancy in the literature surrounding this condition. The 1994 American European Consensus Conference criteria [2] were broadly accepted, albeit with limitations, but since 2013 the 'Berlin definition' [3], created by a

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consensus panel of experts, has been in use. This defines ARDS as 'an acute diffuse, inflammatory lung injury,' with specific changes in description of oxygenation (mild, moderate or severe), timing (within 1 week), radiographic (chest radiograph or computed tomographic findings) and use of wedge pressure (abandoned). Many disease processes are associated with ARDS, the commonest being severe sepsis and pneumonia. There is a marked acute alveolar neutrophilic infiltrate, with the classic pathological finding being diffuse alveolar damage (DAD), although recent studies suggest a low sensitivity for DAD, especially in those with less severe ARDS [4,5]. Regardless of etiology, the hallmark of the disease is inflammation and injury at the alveolar epithelial and capillary endothelial junction, with neutrophil activation and cytokine release [6]. Neutrophils [7] and alveolar macrophages [8,9] are the key mediators of inflammation in ARDS, with emerging evidence that platelets and particularly neutrophil–platelet interaction is important [10]. The incidence of ARDS in the US is estimated at almost 200,000 cases per annum [11] with an unacceptably high mortality rate of ~ 30% [12], as well as substantial morbidity for survivors. Despite decades of research, however, there is no specific therapy for ARDS, and the few interventions that have been shown to reduce mortality in these patients have targeted ventilator-induced lung injury [13–16]. There is an urgent, unmet need for effective pharmacotherapy for ARDS.

Since the first report of ARDS almost 50 years ago [1], many pharmacological therapies have been assessed, but while some have shown promise in early investigations, to date none have been found to be effective in Phase III trials, including most recently, β2 agonist therapy [17,18] and statins [19]. This discrepancy may reflect the heterogeneity of this condition, but may also be due to the complexity underlying the pathogenesis of ARDS, with significant temporal overlap between inflammatory and resolution phases, hindering traditional attempts to categorize timing of interventions which target either excessive inflammation or impaired repair processes. A recent post-mortem study [20] indicated a rising incidence of inflammatory fibrotic change with time, with few patients demonstrating evidence of fibrosis within the first week, which may indicate that anti-inflammatory treatment might best be used later in ARDS, though obviously this subgroup of patients who succumbed to their illness may represent those with more severe disease. Also, the causative heterogeneity may be reflected in the existence of a number of discrete phenotypes of ARDS, which may differ in their manifestation of disease, as well as response to therapy. Analysis [21] of data from over 1000 patients with ARDS suggested the existence of a hyper-inflammatory sub-phenotype with exaggerated cytokine responses and more severe disease, and patients with this phenotype responded better to a ventilatory strategy using higher levels of positive end-expiratory pressure. Many drugs that have shown promise in animal or cellular models have not delivered positive results in clinical studies. Animal models are certainly a powerful research tool to facilitate study of complex pathways and give insight into mechanisms of illness, as well as giving some indication of the safety profile of a drug, but there are inherent problems associated with reproducing ARDS in animal models. These include difficulties reproducing key pathogenic abnormalities in animals, as well as controlling for age and comorbidity.

Clinically relevant human models of ARDS are increasingly being used to investigate new therapies in an effective and safe way, and give important insights into mechanisms of

inflammation and repair, as well as providing proof of concept data to inform subsequent clinical trials. The human *ex vivo* lung perfusion (EVLP) model is an effective platform to closely examine injury as well as responses to therapy without associated risk to patients [22]. This model utilizes whole human lungs, unsuitable for transplantation, which are perfused and inflated with continuous positive airway pressure or ventilated with standard or lung protective tidal volumes. This preparation allows the assessment of intact human lung tissue reaction to injury and repair, reproducing some of the complex milieu of the lung and enabling study of inflammation in a novel manner. Also, the use of the lipopolysaccharide (LPS) challenge in healthy volunteers to induce a subclinical alveolar inflammatory response has been shown to be a safe model of ARDS [23] and allows assessment of the early response to inflammation and injury *in vivo*.

A number of promising therapies are currently in investigation for ARDS, with varying mechanisms of action. A key feature of these interventions is that all of these do not simply target the excessive inflammation associated with ARDS.

Aspirin has been in use for many centuries as an analgesic, antipyretic and anti-inflammatory drug, as well more recently as an inhibitor of platelet aggregation for secondary prevention in coronary artery disease. It is a potent inhibitor of platelet activation. As alveolar neutrophils and platelets interact to cause inflammatory damage in the alveolus, antiplatelet therapy has a potential benefit in dampening down this injurious interaction. To support this hypothesis, observational studies have demonstrated that critically ill patients previously taking aspirin therapy have a significantly decreased likelihood of developing ARDS *de novo* [24]. Animal models support the use of aspirin in ARDS [10], as aspirin treatment decreases platelet sequestration in the lung, decreases lung vascular permeability and edema, and increases survival. Ongoing studies are currently underway to investigate this therapy as both treatment [ARENA NCT01659307] and prevention [25] of ARDS.

Mesenchymal stromal (stem) cells (MSCs) are derived from a number of sources, including human placental tissue, umbilical cord, bone marrow or adipose tissue. These cells have a high capacity for self-renewal, as well as the potential to develop into many cellular phenotypes and are interesting targets as ARDS therapy to modulate inflammatory responses, as well as promote repair in the lung. Potential mechanisms through which MSC therapy improves lung function include both cell contact dependent and independent immunomodulatory functions, although paracrine effects likely predominate [26] for improved epithelial function and augmented alveolar fluid clearance in ARDS [27]. Studies investigating MSCs have shown improved markers of cell injury in animal models of ARDS [28], while lung injury induced by LPS or with live *Escherichia coli* in the human *ex vivo* lung perfusion model showed MSC treatment decreased inflammation and reduced bacterial growth in the lung [29]. Clinical grade allogeneic MSCs have recently been demonstrated to enhance alveolar fluid clearance, an indicator of function, in *ex vivo* perfused human lungs that have been rejected as unsuitable for transplantation [30], with effects mediated at least partly via keratinocyte growth factor (KGF). MSCs may in the future be a useful treatment to increase the viability of donor lungs using the EVLP model, as well as a treatment for ARDS.

KGF is a fibroblast growth factor produced by mesenchymal cells and macrophages. *In vivo* it has an important role in lung inflammation and repair by increasing alveolar cellular proliferation [27]. KGF is a soluble mediator of MSCs and is already in use clinically as a therapy (palifermin: recombinant human KGF) as a treatment for radiation induced oral mucositis, where it has been shown to be safe and well tolerated [31]. In animal models of ARDS, pretreatment with KGF reduces injury and increases alveolar epithelial proliferation and repair [32,33]. A recent investigation of KGF in a healthy volunteer human model of ARDS showed that KGF treatment increased markers of type II alveolar epithelial cell proliferation and increased alveolar concentrations of reparative proteases and the anti-inflammatory cytokine IL-1Ra [34]. A Phase II clinical trial of palifermin in ARDS has recently concluded [ISRCTN95690673] and results are awaited.

IFN-β is an established therapy for the inflammatory demyelinating neurological disorder, multiple sclerosis, though the precise mechanisms through which it achieves its anti-inflammatory and immunomodulatory effects remain uncertain. Possible effects include alteration of T-cell activation and matrix metalloproteinase -9 stimulation [35], cytokine modulation [36] or prevention of abnormal leakage across the blood–brain barrier [37]. Ectonucleotidase (cluster of differentiation [CD]73) is a widely distributed enzyme on vascular endothelium, which produces the potent anti-inflammatory adenosine, and IFN's anti-inflammatory effects are likely at least partially mediated via upregulation of CD73 [38,39].

Because abnormal vascular leakage in the lung is a major pathological finding in ARDS, IFN-β has been investigated as an ARDS therapy. A recent Phase I clinical trial [40] demonstrated a 28-day mortality rate of 8% in a cohort of 26 patients with ARDS treated with IFN-β, while a control cohort of 59 patients with ARDS (comprising older, sicker patients) had an overall 28-day mortality rate of 32%. This was not a randomized controlled trial, but had a case–control design, which limits its immediate applicability [41]; but certainly raises interesting questions, and supports further investigation of IFN-β as a therapy for ARDS in Phase II clinical trials.

Oncostatin M (OSM) is a member of the IL-6 cytokine superfamily. It is expressed by neutrophils [42], dendritic cells [43] and macrophages [44,] and has been shown to synergize with other inflammatory cytokines in the lung to drive destructive proteases and inflammation [45]. OSM is expressed *ex vivo* by neutrophils from patients with ARDS, and is significantly elevated in bronchoalveolar lavage fluid from patients with ARDS [46]. It may have an important role in wound repair following inflammatory stimulus [47]. It is a potential therapeutic target to downregulate the inappropriate inflammation of ARDS as inhibition of its synergistic effects may decrease excessive inflammation, while leaving host responses to bacterial infection intact, and allowing protective and reparative processes to continue. OSM inhibition is being investigated in preclinical trials to determine its efficacy as a potential therapy for ARDS.

In summary, there are several new treatments being developed for ARDS, with encouraging early results. Use of clinically relevant translational models will improve our understanding of the complex environment of inflammation and repair in ARDS and aid the search for an

effective treatment. The model of inhaled LPS to induce a mild alveolar inflammatory response facilitates examination of early responses to injury *in vivo*, while the use of the human *ex vivo* lung perfusion model allows investigation of intact tissue response with maintained lung tissue architecture, and allows sampling from multiple sites, including bronchoalveolar lavage fluid, as well as histological examination. These promising methods to study the interface of injury and inflammation may facilitate a new paradigm of translational lung research.

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