Future therapies for ARDS

Aspirin

Platelets are important in ARDS pathogenesis. In preclinical studies, aspirin reduces thromboxane A2, P-selectin, and platelet-derived chemokine (e.g., CCL5 and CXCL4) production, reduces platelet–neutrophil aggregates and neutrophil extracellular traps, and enhances anti-inflammatory lipid mediators such as 15-epi-lipoxin A4. Aspirin reduces the risk of developing ARDS in critically ill patients [2]. A clinical study of aspirin in human volunteers undergoing endotoxin inhalation (ARENA NCT01659307) and a RCT of aspirin for ARDS prevention [3] are ongoing (Table 1).

Statins

HMG CoA-reductase inhibitors (statins) exert diverse ‘pleiotropic’ effects beyond their ‘pharmacologic’ effect in cholesterol reduction, including anti-inflammatory and endothelial protective effects. Results from both preclinical and observational studies support a potential role for statins in ARDS. Simvastatin improved pulmonary and systemic organ function in a phase 1/2 RCT in ARDS [4], but two larger phase 2/3 trials of statin therapy, carried out in Ireland/UK [5] and the USA [6], respectively, did not demonstrate benefit. Rosuvastatin, a hydrophilic statin, did not improve clinical outcomes in sepsis-associated ARDS and may have increased hepatic and renal dysfunction [6]. The lipophilic statin simvastatin did not worsen hepatic or renal function, it non-significantly reduced mortality, but it did not increase the number of ventilator-free days (VFD, the primary outcome) [5]. A definitive large trial of simvastatin, powered for mortality as a primary outcome, may be warranted.
| Title/Description | Design | No. of patients | Intervention | Primary outcome | Status/key findings |
|-------------------|--------|----------------|--------------|-----------------|------------------|
| Lung Injury Prevention Study with Aspirin (LIPS-A:NCT01504867) | Phase 2 RCT | 400 | Aspirin 325 mg on Day 1, then 81 mg daily to Day 7 | Development of ARDS | Recruiting |
| Nebulized heparin for lung injury (ACTRN12612000418875) | Phase 2 RCT | 256 | Nebulized heparin 25,000 IU every 6 h for up to 10 days | Physical function (SF-36 Health Survey) | Not yet recruiting |
| Investigation of GSK2586881 (recombinant human ACE2) in ARDS (NCT01597635) | Phase 1–2 RCT | 60 | Dose response ACE2 followed by highest tolerated dose | Safety and tolerability | Recruiting |
| Keratinocyte growth factor in Acute lung injury to REduce pulmonary dysfunction (KARE: ISRCTN95690673) | Phase 2 RCT | 60 | KGF 60 μg/kg IV daily for up to 6 days | Oxygenation index at Day 7 | Recruitment completed |
| Human Mesenchymal Stem Cells For Acute Respiratory Distress Syndrome (START: NCT01775774) | Phase 1–2 RCT | 60 | 2–10 million cells/kg allogeneic bone marrow-derived HMSCs | Safety and tolerability; PaO2/FiO2 ratio and PaO2/FiO2 ratio and oxygenation index at day 3 | Recruiting |
Heparin

Activation of coagulation plays a key role in the pathogenesis of ARDS, resulting in alveolar fibrin deposition which impairs gas exchange. In pre-clinical studies, heparin has been found to reduce alveolar fibrin deposition and exert anti-inflammatory effects. In one small RCT, heparin decreased the number of VFD in patients at risk for ARDS [7]. Further studies investigating the efficacy of nebulized heparin in patients at risk of ARDS (ACTRN12612000418875) (Table 1) are underway.

Interferon-beta

Interferon beta (IFN-β) increases endothelial expression of CD73, the rate-limiting enzyme in the conversion of adenosine monophosphate to adenosine, which in turn binds to pulmonary A2B receptors and exerts multiple protective effects in pre-clinical models. In a recent open-label dose-escalation study, only two (8 %) of 26 ARDS patients treated with 10 μg per day of IFN-β-1a died by day 28, compared to a 32 % mortality in a parallel control group [8]. Although the study was not randomized or blinded, and there were some baseline differences between the treated and control cohorts, further investigation of IFN-β for ARDS is warranted.

Tumor necrosis factor receptor 1 blockade

Tumor necrosis factor (TNF) exerts its effects by binding to one of two TNF receptors, designated TNFR1 and TNFR2. TNF-activated pro-inflammatory pathways and the programmed cell death pathways that result in tissue injury are largely mediated through TNFR1, while TNFR2 signaling plays a role in tissue repair and angiogenesis. Promising pre-clinical data support the efficacy of anti-TNFR1 monoclonal antibodies [9]. In one study, inhaled anti-TNFR1 antibodies decreased the pulmonary inflammation induced by endotoxin in healthy volunteers [10]. Early phase studies in ARDS patients are awaited.

Angiotensin converting enzyme 2

Angiotensin-converting enzyme (ACE) cleaves angiotensin-I to generate angiotensin-II, which causes vasoconstriction, inflammation, and increased vascular permeability via type 1 (AT1R) and type 2 receptors. ACE-2, a homolog of ACE, cleaves a single residue from Ang-II to generate Ang1–7 [11], which blocks many AT1R-mediated actions. Imai et al. [11] found that ACE, Ang-II, and AT1R function as lung injury-promoting factors, whereas ACE-2 protects the lung from injury. ACE2 is a receptor for severe acute respiratory syndrome-coronavirus (SARS-CoV), while SARS-CoV induces downregulation of ACE2, which is an important step in the development of severe lung failure [12]. In addition, mortality is increased in patients with ARDS who have the ACE DD phenotype, which results in greater ACE activity [13]. A human phase I/II clinical trial of recombinant human ACE2 therapy in patients with early ARDS is in progress (NCT01597635) (Table 1).

Adrenomedullin

Adrenomedullin (AM), an endogenous 52 amino acid peptide belonging to the calcitonin gene-related peptide family, is expressed in multiple tissues, including endothelial cells, and plays a crucial role in endothelial barrier integrity. AM acts via binding of the calcitonin receptor-like receptor, thereby raising intracellular cAMP levels in endothelial cells and reducing myosin light chain (MLC) phosphorylation. Thus, AM may prevent endothelial contraction and intercellular gap formation [14]. AM expression is upregulated in inflammatory diseases including ARDS and sepsis, and endogenous AM may contribute to the protection of vascular function in inflammation [14]. AM therapy reduces pulmonary permeability injury and decreases inflammation in experimental ARDS and sepsis. The Committee for Orphan Medicinal Products of the European Medicines Agency (EMA) recently recommended AM as an orphan drug for the treatment of ARDS (EMA/COMP/104704/2010). Clinical trials with AM are in the planning stage.

Keratinocyte growth factor

Keratinocyte growth factor (KGF) is a fibroblast growth factor expressed predominantly by mesenchymal cells, and its receptor (KGFR) is expressed on epithelial cells and macrophages. Results from pre-clinical studies suggest that intra-tracheal KGF reduces lung injury induced by hyperoxia, ventilator-induced lung injury, and bacterial pneumonia. In a recent study, KGF treatment (Palifermin®) increased markers of type II alveolar epithelial cell proliferation and increased alveolar concentrations of reparative proteases and the anti-inflammatory cytokine IL-1Ra following endotoxin inhalation by volunteers [15]. A Phase II clinical trial of palifermin® in ARDS has recently been concluded (ISRCTN95690673), and the results are awaited (Table 1).

Mesenchymal stem/stromal cells

Mesenchymal stem/stromal cells (MSCs) can regulate both the innate and adaptive immune systems and can
modulate macrophage phenotype, inhibit the production of inflammatory cytokines by activated CD4 and CD8 T cells, and stimulate the generation of FoxP3+ regulatory T cells, potentially reducing pro-inflammatory cytokines in ARDS [16]. MSCs directly attenuate bacterial sepsis, the commonest and most severe cause of ARDS, by enhancing macrophage phagocytosis and increasing antimicrobial peptide secretion, thereby increasing bacterial clearance [16]. MSCs also repair the injured lung following ventilation-induced lung injury, via paracrine mechanisms [17, 18]. A recent pilot study of MSC therapy for ARDS demonstrated no adverse effects [19]. A phase 1/2, open-label, dose-escalation, multi-center clinical trial of allogeneic BM-MSCs in patients with moderate to severe ARDS is underway in the USA (NCT01775774) (Table 1).

Conclusions

Although there have been many failed therapies to date, new therapies based on improved understanding of the mechanisms implicated in the development of ARDS are emerging, and may provide a treatment option in the near future.

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