Intensive Care Med (2015) 41:322–326
DOI 10.1007/s00134-014-3578-z

Gerard F. Curley
John G. Laffey

Future therapies for ARDS

Received: 12 November 2014
Accepted: 19 November 2014
Published online: 4 December 2014

G. F. Curley · J. G. Laffey (✉)
Department of Anesthesia, Critical Illness and Injury Research Centre, Keenan Research Centre for Biomedical Science, The Li Ka Shing Knowledge Institute, St. Michael's Hospital, 30 Bond Street, Toronto, ON M5B 1W8, Canada
e-mail: laffeyj@smh.ca
Tel.: 1-416-864-5071

G. F. Curley · J. G. Laffey
Department of Anesthesia, University of Toronto, Toronto, Canada

Introduction

Despite more than 150 randomized clinical trials (RCTs) of multiple potential therapies, the only interventions for acute respiratory distress syndrome (ARDS) that reduce mortality are those that minimize ventilator-induced lung injury [1]. This 'translational failure' may have a number of explanations. Firstly, ARDS is a syndrome, and interventional trials in ARDS generally include a heterogenous patient group with a wide spectrum of disease etiology and disease severity. Second, deficits exist in our understanding of key aspects of the pathogenesis of ARDS. Notwithstanding these challenges, a number of promising therapies are currently under investigation for ARDS, and offer hope for the future.

Future therapies for ARDS

Aspirin

Platelets are important in ARDS pathogenesis. In preclinical studies, aspirin reduces thromboxane A_2, 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.

Table 1 Early phase clinical studies of emerging therapies for acute respiratory distress syndrome

Title/description	Design	ARDS population	No. of patients	Intervention	Primary outcome	Status/key findings
Lung Injury Prevention Study with Aspirin (LIPS-A:NCT01504867)	Phase 2 RCT	Adults admitted to hospital at high risk for ARDS	400	Aspirin 325 mg Day 1, then 81 mg daily to day 7	Development of ARDS	Recruiting
Nebulized heparin for lung injury (ACTRN12612 000418875)	Phase 2 RCT	Patients within 24 h of mechanical ventilation with PaO_2 to FiO_2 ratio <300	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	Patients within 48 h of developing ARDS	Phase 1–5; Phase 2a–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	Patients within 48 h of developing ARDS	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	Patients within 24 h of developing ARDS	60	2–10 million cells/kg allogeneic bone marrow-derived hMSCs	Safety and tolerability. PaO_2/FiO_2 ratio and oxygenation index at day 3	Recruiting

ARDS, Acute respiratory distress syndrome; RCT, randomized clinical trial; ACE2, (angiotensin I converting enzyme 2; KGF, keratinocyte growth factor; hMSCs, human mesenchymal stem cells; FiO_2, fraction or percentage of oxygen; PaO_2, partial pressure of oxygen in arterial blood

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.

Acknowledgments J. Laffey and G. Curley are funded by the Canadian Institute of Health Research and hold a Merit Award and a Clinician Scientist Transition Award, respectively, from the University of Toronto Department of Anesthesia. G. Curley holds an award from the International Anesthesia Research Society and from the Canadian Anesthesiology Society. J. Laffey holds an award from Physicians Services Incorporated.

Conflicts of interest The authors have no conflict of interest in relation to the subjectmatter of this manuscript.

References

1. Tonelli AR, Zein J, Adams J, Ioannidis JP (2014) Effects of interventions on survival in acute respiratory distress syndrome: an umbrella review of 159 published randomized trials and 29 meta-analyses. Intensive Care Med 40(6):769–787
2. Erlich JM, Talmor DS, Cartin-Ceba R, Gajic O, Kor DJ (2011) Prehospitalization antiplatelet therapy is associated with a reduced incidence of acute lung injury: a population-based cohort study. Chest 139:289–295
3. Kor DJ, Talmor DS, Banner-Goodspeed VM, Carter RE, Hinds R, Park PK, Gajic O, Gong MN, US Critical Illness and Injury Trials Group: Lung Injury Prevention with Aspirin Study Group (USCIITG: LIPS-A) (2012) Lung injury prevention with aspirin (LIPS-A): a protocol for a multicentre randomised clinical trial in medical patients at high risk of acute lung injury. BMJ Open:2(5)
4. Craig TR, Duffy MJ, Shyamsundar M, McDowell C, O'Kane CM, Elborn JS, McAuley DF (2011) A randomized clinical trial of hydroxymethylglutaryl-coenzyme a reductase inhibition for acute lung injury (The HARP Study). Am J Respir Crit Care Med 183:620–626
5. McAuley DF, Laffey JG, O'Kane CM, Perkins GD, Mullan B, Trinder TJ, Johnston P, Hopkins PA, Johnston AJ, McDowell C, McNally C, HARP-2 Investigators, Irish Critical Care Trials Group (2014) Simvastatin in the acute respiratory distress syndrome. N Engl J Med 371:1695–1703
6. National Heart L, Blood Institute ACTN, Truwit JD, Bernard GR, Steingrub J, Matthay MA, Liu KD, Albertson TE, Brower RG, Shanholtz C, Rock P, Douglas IS, de Boisblanc BP, Hough CL, Hite RD, Thompson BT (2014) Rosuvastatin for sepsis-associated acute respiratory distress syndrome. N Engl J Med 370:2191–2200
7. Dixon B, Schultz MJ, Smith R, Fink JB, Santamaria JD, Campbell DJ (2010) Nebulized heparin is associated with fewer days of mechanical ventilation in critically ill patients: a randomized controlled trial. Crit Care 14:R180
8. Bellingan G, Maksimow M, Howell DC, Stotz M, Beale R, Beatty M, Walsh T, Binning A, Davidson A, Kuper M, Shah S, Cooper J, Waris M, Yegutkin GG, Jalkanen J, Salmi M, Piippo I, Jalkanen M, Montgomery H, Jalkanen S (2014) The effect of intravenous interferon-beta-1a (FP-1201) on lung CD73 expression and on acute respiratory distress syndrome mortality: an open-label study. Lancet Respir Med 2:98–107
9. Bertok S, Wilson MR, Morley PJ, de Wildt R, Bayliffe A, Takata M (2012) Selective inhibition of intra-alveolar p55 TNF receptor attenuates ventilator-induced lung injury. Thorax 67:244–251
10. Proudfoot AG, O'Kane CM, Bayliffe A, Serone AP, Bareille P, Smith SP, Brown V, Wright TJ, Chen Y, Wilson R, Cordy JC, Morley PJ, Elborn S, Hind M, Chilvers ER, Griffiths MJ, Summers C, McAuley DF (2014) A novel TNFR1-targeting domain antibody attenuates pulmonary inflammation in a human model of lung injury, via actions on the lung micro-vascular endothelium. Am J Respir Crit Care Med 189:A6589
11. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui CC, Hein L, Uhlig S, Slutsky AS, Jiang C, Penninger JM (2005) Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 436:112–116
12. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM (2005) A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 11:875–879
13. Adamzik M, Frey U, Sixt S, Knemeyer L, Beiderlinden M, Peters J, Siffert W (2007) ACE I/D but not AGT (-6)A/G polymorphism is a risk factor for mortality in ARDS. Eur Respir J 29:482–488
14. Temmesfeld-Wollbruck B, Hocke AC, Suttorp N, Hippenstiel S (2007) Adrenomedullin and endothelial barrier function. Thromb Haemost 98:944–951

15. Shyamsundar M, McAuley DF, Ingram RJ, Gibson DS, O'Kane D, McKeown ST, Edwards A, Taggart C, Elborn JS, Calfee CS, Matthay MA, O'Kane CM (2014) Keratinocyte growth factor promotes epithelial survival and resolution in a human model of lung injury. Am J Respir Crit Care Med 189:1520–1529
16. Curley GF, Scott JA, Laffey JG (2014) Therapeutic potential and mechanisms of action of mesenchymal stromal cells for acute respiratory distress syndrome. Curr Stem Cell Res Ther 9:319–329
17. Curley GF, Ansari B, Hayes M, Devaney J, Masterson C, Ryan A, Barry F, O'Brien T, Toole DO, Laffey JG (2013) Effects of intratracheal mesenchymal stromal cell therapy during recovery and resolution after ventilator-induced lung injury. Anesthesiology 118:924–932
18. Curley GF, Hayes M, Ansari B, Shaw G, Ryan A, Barry F, O'Brien T, O'Toole D, Laffey JG (2012) Mesenchymal stem cells enhance recovery and repair following ventilator-induced lung injury in the rat. Thorax 67:496–501
19. Zheng G, Huang L, Tong H, Shu Q, Hu Y, Ge M, Deng K, Zhang L, Zou B, Cheng B, Xu J (2014) Treatment of acute respiratory distress syndrome with allogeneic adipose-derived mesenchymal stem cells: a randomized, placebo-controlled pilot study. Respir Res 15:39