Published in final edited form as:

Crit Care Med. 2016 June ; 44(6): e453–e454. doi:10.1097/CCM.0000000000001573.

Trials and Tribulations of Therapies for the Acute Respiratory Distress Syndrome

Mahendra Damarla, M.D.¹ and **Paul M. Hassoun, M.D.¹**

¹Department of Medicine, Johns Hopkins University School of Medicine

Keywords

p38 mitogen activated protein kinase; acute respiratory distress syndrome; severe trauma; diltapimod; clinical trials design; therapy

To the Editor

We read with great interest the article by Christie et al. entitled ‘A Randomized Dose-Escalation study of the Safety and Anti-Inflammatory Activity of the p38 Mitogen-Activated Protein Kinase Inhibitor Diltapimod in Severe Trauma Subjects at Risk for Acute Respiratory Distress Syndrome’(1).

A major hurdle in designing clinical trials of pharmaceutical therapies for patients with the acute respiratory distress syndrome (ARDS) is the difficulty in translating promising findings from pre-clinical animal experiments to human clinical trials. This is likely due in part to tremendous heterogeneity in ARDS. Recent work has identified discrete molecular patterns of injury based on the etiology of ARDS, where direct causes of lung injury lead to significantly more epithelial damage while indirect causes lead to more endothelial damage(2). The clinical importance of this distinction was highlighted in the recent clinical trials of beta-agonists for the treatment of ARDS. The β -Agonist Lung Injury Trial (BALTI) demonstrated a significant reduction in lung water with salbutamol treatment compared to placebo(3). However, these promising results could not be replicated in the BALTI-2 trial. In fact, patient recruitment was interrupted early due to safety concerns(4). Interestingly, 64% of patients in BALTI-2, compared to only 15.8% in BALTI, randomized to the salbutamol group had a direct cause of injury identified as the source of ARDS. As beta-agonists rely on functioning epithelial cells to promote adequate clearance of extravascular lung water, it is reasonable to think that when there is significant epithelial injury, as is the case with direct lung injury, beta-agonists may be ineffective.

Another important factor to consider in designing clinical trials of ARDS is infectious versus non-infectious causes of ARDS. This is even more relevant when the intervention studied affects inflammation. While over-exuberant inflammation may result in endothelial barrier dysfunction leading to ARDS, a limited inflammatory response is critical in killing

Address correspondence: Mahendra Damarla, Department of Medicine, Division of Pulmonary and Critical Care Medicine, 5501 Hopkins Bayview Circle, Baltimore, MD, USA, Tel.: (410) 550-0545; Fax: (410) 550-2612; ; Email: mdamarl1@jhmi.edu.

infectious pathogens to prevent overwhelming sepsis. Lastly, the timing of the intervention is also critical as molecular mechanisms that underlie the pathogenesis of ARDS may be entirely different from pathways necessary for recovery from pulmonary dysfunction.

The authors should be commended for their meticulous trial design. They focused on diltapimod use for prevention of ARDS, based on preclinical animal models of p38 mitogen activated protein kinase inhibition(5). Given the heterogeneous nature and complexity of the pathogenesis of ARDS, the authors chose a study design that closely mimics that of preclinical experiments thereby limiting potential confounding factors. They were also rigorous in enrolling only patients with non-infectious and indirect causes of inflammation, i.e. trauma, as the risk factor for ARDS. In doing so, the authors resisted the urge to broaden inclusion criteria to maximize enrollment, which could have led to heterogeneous populations thus diluting the potential effects of promising therapeutic targets. As diltapimod moves forward to the next phase of drug development, hopefully the investigators continue to use the same rigor in clinical trial design to assess its potential efficacy in ARDS treatment.

Acknowledgments

This work was supported by grants from the National Institutes of Health R01HL049441 (PH), KO8HL097024 (MD).

Copyright form disclosures: Dr. Damarla received support for article research from the National Institutes of Health (NIH). Dr. Hassoun received funding from Gilead (advisory board) and from Merck (advisory board) (for activities unrelated to current project).

References

1. Christie JD, Vaslef S, Chang PK, et al. A Randomized Dose-Escalation Study of the Safety and Anti-Inflammatory Activity of the p38 Mitogen-Activated Protein Kinase Inhibitor Diltapimod in Severe Trauma Subjects at Risk for Acute Respiratory Distress Syndrome. *Crit Care Med.* 2015; 43(9):1859–1869. [PubMed: 26102252]
2. Calfee CS, Janz DR, Bernard GR, et al. Distinct Molecular Phenotypes of Direct Versus Indirect ARDS in Single and Multi-Center Studies. *Chest.* 2014
3. Perkins GD, McAuley DF, Thickett DR, et al. The beta-agonist lung injury trial (BALTI): a randomized placebo-controlled clinical trial. *Am J Respir Crit Care Med.* 2006; 173(3):281–287. [PubMed: 16254268]
4. Gao Smith F, Perkins GD, Gates S, et al. Effect of intravenous beta-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. *Lancet.* 2012; 379(9812):229–235. [PubMed: 22166903]
5. Damarla M, Hasan E, Boueiz A, et al. Mitogen activated protein kinase activated protein kinase 2 regulates actin polymerization and vascular leak in ventilator associated lung injury. *PLoS One.* 2009; 4(2):e4600. [PubMed: 19240800]