Published in final edited form as:

Crit Care Med. 2012 May ; 40(5): 1661–1663. doi:10.1097/CCM.0b013e3182451fb2.

Statins and acute lung injury: Holy Grail or the next to fail?

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Keywords

Statins; acute lung injury; prevention; therapy; epidemiology; outcomes

Acute lung injury (ALI) and the more severe acute respiratory distress syndrome (ARDS) are life-threatening critical care syndromes which continue to consume substantial health care resources and profoundly impact patient-important outcomes.(1) Although recent epidemiologic studies suggest the incidence of lung injury may be on the decline,(2) even conservative estimates suggest the associated mortality continues to exceed 25%.(3) Mechanistically, the “lung attack” is characterized by abrupt injury to the alveolar-capillary barrier with resultant alveolar flooding and hypoxemic respiratory failure. Although our understanding of the precise mechanisms underlying this process continues to unfold, the available data suggests critical roles for inflammation, endothelial activation and injury, epithelial injury, intravascular coagulation and oxidative stress.

To date, substantial effort has been expended in an attempt to identify effective therapeutic options for patients with this serious critical care syndrome. Although numerous therapeutic interventions have shown great initial promise [N-acetylcysteine,(4) Ketokonazole,(5) lisofylline,(6) sivelestat, (7) and more recently inhaled beta agonists (8) and omega-3 fatty acids (9)], translation to clinical benefit has been frustratingly elusive. Despite our best efforts, we are mostly left with the avoidance of additional lung injury via protective ventilator settings(10) and conservative fluid approaches(11) as our only supportive therapies.

HMG-CoA reductase inhibitors (statins) are a class of medications that have been traditionally recommended and prescribed for the treatment of hypercholesterolemia and for the secondary prevention of cardiovascular disease.(12, 13) More recently, statins have been shown to possess a variety of non-lipid lowering effects, termed the pleiotropic effects of statin therapy. These non-lipid lowering properties are believed to affect a diverse set of cellular and metabolic pathways including inflammatory, oxidative, and thrombotic processes.(14) The characterization of these pleiotropic effects has led to the study of statins in a wide range of disease processes including cerebrovascular(15) and renal disease(16), cancer,(17) venous thromboembolism,(18) and a variety of infectious complications including bacteremia,(19) pneumonia,(20) and sepsis(21).

In light of the substantial concordance between our understanding of ALI pathophysiology and the described pleiotropic effects of statin therapy, a potential role for statins in the

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mitigation of ALI development and/or progression would certainly seem plausible as well. Furthermore, there is wealth of preclinical data which supports a role for statins in this setting.(22) Importantly, however, we have been here before and the history of ALI therapeutics has been quite unforgiving. So with a healthy degree of skepticism we ask, “will statin’s promising preclinical data translate into clinical benefit?”

Until now, there had been three observational studies (23–25) and two phase I/II clinical trials, (26, 27) all aiming to address the role of statins in the prevention and/or treatment of ALI. In the three investigations addressing statins in patients with established lung injury, the results have been inconsistent and mostly underwhelming. (23, 24, 27) Intuitively, we might expect to see improved efficacy with the administration of statins in patients at risk for ALI as compared to those with the fully established syndrome. Indeed, two recent investigations have specifically evaluated this question. In a small randomized clinical trial of 30 healthy volunteers, Shymansunder et al. evaluated the impact statin pretreatment on the inflammatory response in healthy volunteers who inhaled lipopolysaccharide.(26) When compared to the placebo group, the statin cohort was indeed noted to have an attenuated inflammatory response. In a second observational cohort study, O’neal et al. reported a reduced incidence of ALI in critically ill patients taking chronic statin therapy.(25) This protective affect was most notable in those with sepsis and the affect appeared to be potentiated by the co-administration of aspirin. Notably, prehospital statin use was not associated with improvements in patient-centered outcomes such as ventilator-free days nor ICU or hospital length of stay.

Several limitations exist in each of the aforementioned investigations. Both clinical trials were performed in a single center and were of limited sample size. The initial trial(26) enrolled healthy volunteers and the subsequent investigation noted improved late organ failures, but no improvements in early organ failures nor pulmonary or patient-important outcomes at any point during the assessment period.(27) The observational studies have also been generally limited by small sample size, indication bias, incomplete adjustment of confounding variables, and incomplete characterization of statin administration. Furthermore, differing study populations with varying ALI risk profiles, differing study methodologies, inconsistent outcome definitions and widely disparate statin dosing regimens preclude meaningful between-study comparisons.

In this issue of Critical Care Medicine, Dr. Bajwa and colleagues(28) aimed to shed additional light on the role of statins in both the prevention and treatment of ALI. The primary objective of the study was to evaluate the association between statin administration within 24 hours of ICU admission and development of ARDS in a high-risk ICU cohort. As a secondary aim, the investigators assessed the impact of statin therapy on patient-centered outcomes following development of ARDS. The initial results were encouraging as statin administration was indeed associated with a reduced incidence of ARDS. However, the initial enthusiasm would prove fleeting as the association was lost in the more robust propensity adjusted analyses. Furthermore, when evaluating patient-centered outcomes in those who developed ARDS, no benefits were seen in the statin cohort.

To what extent does the current investigation (28) refute a role for statins in the prevention and/or treatment of ALI? At the very least, it should cast a substantial shadow of doubt. Though previous studies have adjusted for confounding variables, none have included as detailed a statistical plan. The propensity models were robust, well thought, and effective in establishing baseline covariate balance. In addition, the sample size was large and the study population closely matched what most would agree is the desired target population. Specifically, critically ill patients with major risk factors for ALI.

To be sure, the study of Bajwa and colleagues (28) is well done and it addresses a number of the previously identified concerns. However, important limitations and several questions do remain. The observational nature of the investigation cannot rule out the potential influence of additional unmeasured confounding affects. In addition, most patients (92%) had their statin therapy discontinued following admission to the ICU. The impact of this practice on patient outcomes is unknown and will clearly require additional study. Potentially important details relating to the intervention of interest (e.g. specific statin agent administered, dosing regimen, etc.) are also lacking. Finally, a pervasive limitation in the study of ALI interventions is the ongoing desire to characterize the syndrome as a single disease entity. We must remember, ALI is not a well-characterized disease. Rather, it's a syndrome that arises in widely disparate clinical scenarios. Is it reasonable to expect that statin administration would be as effective for the prevention of ALI in patients with an aspiration event or a major surgical procedure as it is in the setting of septic shock? If we are to make meaningful progress in the prevention and treatment of ALI, it may well be time to begin evaluating the impact of preventative strategies and therapeutic interventions in specific clinical constructs rather than in the unified whole.

And so here we are now, more uncertain of statins role in ALI than ever before. As we await the results of more definitive clinical trials [e.g. Statins for Acutely Injured Lungs From Sepsis (SAILS) - Clinicaltrials.gov ID: NCT00979121; Simvastatin Effect on the Incidence of Acute Lung Injury/Adult Respiratory Distress Syndrome (ALI/ARDS) - Clinicaltrials.gov ID: NCT01195428], we hold out hope that statin's are indeed the Holy Grail. However, I would suggest a degree of caution as we anxiously await these study results. Unfortunately, history is not on our side!!

Acknowledgments

Dr. Kor received funding from the National Institutes of Health (NIH).

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