to directly worsen endothelial permeability. Mice with one functional Ang-2 allele are protected from lung injury and vascular leak (7). Serum from both patients with sepsis (7) and those with ALI (6) disrupts endothelial barrier function, via a mechanism that is blocked via Ang-2 blockade (6, 7). These deleterious effects of Ang-2 on the endothelial barrier function appear to be mediated via a conditional antagonism of the tyrosine kinase receptor Tie 2, which is important in maintaining endothelial junctional integrity.

There are some limitations to be considered. The proportion of patients within the cohort who developed ALI within the target time frame is relatively small, emphasizing the need for validation of these important findings in a larger cohort. The patient cohort is quite specific, namely critically ill patients presenting to the emergency department that do not have ALI at intensive care unit admission. Additional studies will be required to determine whether these findings are generalizable to other critically ill patient populations. Unfortunately, the lack of a bedside assay for Ang-2 means that it is difficult to operationalize this knowledge at this time. Finally, despite the authors making considerable effort to collect blood samples early in the course of critical illness in these patients, many samples were drawn after the actual development of ALI.

In conclusion, the current study yields important insights regarding the utility of Ang-2 as a biomarker to predict ARDS. Ang-2 appears to be particularly useful when used in combination with the LIP score. Given the potential for a pathogenic role of Ang-2, these findings suggest that alterations in endothelial permeability may be a key early event in ARDS. More broadly, the development of strategies to prevent ARDS is becoming a key research priority in our efforts to reduce the disease burden of ARDS (9). One example of a prevention trial is the LIPS-A trial evaluating the efficacy of aspirin to prevent ALI (10). A key step in enhancing the feasibility of these studies is the accurate identification of patients at high risk for developing ARDS. Agrawal and colleagues deserve congratulations for their important new insights into the early identification of ALI in the critically ill.

Author disclosures are available with the text of this article at www.atljournals.org.

John G. Laffey, M.D.
Department of Anesthesia
Keenan Research Centre in the Li Ka Shing Knowledge Institute
St. Michael’s Hospital
Toronto, Ontario, Canada
and
University of Toronto
Toronto, Ontario, Canada

Daniel Talmor, M.D., M.P.H.
Department of Anesthesia, Critical Care, and Pain Medicine
Beth Israel Deaconess Medical Center and Harvard Medical School
Boston, Massachusetts

Statins and Sepsis
Potential Benefit but More Unanswered Questions

Statins modulate pathogenic mechanisms important in the development of severe sepsis (1). In this issue of the Journal, the ANZ-STATInS Investigators (pp. 743–750) report the findings of a high-quality phase-2 randomized, placebo-controlled, multicenter trial of 250 patients with severe sepsis if enteral atorvastatin 20 mg daily for up to 14 days improved biological and clinical outcomes (2). The study investigated two cohorts of patients, those who were statin naive (n = 173) and those who had received predmission statins (n = 77). The primary outcome was plasma interleukin-6 (IL-6). There was no difference in plasma IL-6 or other secondary clinical outcome in the overall population or in the subgroup of patients who were statin naive. However in the subgroup of prior statin users, atorvastatin decreased IL-6 and reduced mortality.

This study raises several important questions.

WAS THE TREATMENT REGIMEN USED IN THIS STUDY APPROPRIATE?

Why, in this well-designed and executed study, did atorvastatin fail to show any biological or clinical evidence of effectiveness in statin-naive patients with established sepsis? A simple answer may be that statins are not effective in this population. However it is worth considering the treatment regimen used in this study.

References


Copyright © 2013 by the American Thoracic Society
DOI: 10.1164/rccm.201301-0168ED
Pleiotropic actions have been demonstrated for most statins to date (1, 3), but there have been no studies directly comparing the immunomodulatory effects of different types of statins. Furthermore, there are limited data that demonstrate efficacy of statins in clinically relevant human models or in critically ill patients to inform the optimal statin, dose, and duration of treatment to be used in these studies. Interestingly, a recent nested cohort study found that statin therapy reduced hospital mortality in patients with sepsis, but mortality reduction was only observed with simvastatin and not with atorvastatin. In addition, the mortality reduction was largely seen with higher doses of statins (4). The finding that higher doses may be more effective is supported by data from a study that compared pretreatment with two doses of simvastatin (5 or 20 mg/kg) in an lipopolysaccharide (LPS)-induced murine model of acute lung injury (ALI) where only the higher dose was effective in attenuating lung injury (5). Pretreatment with simvastatin 40 and 80 mg for 4 days reduced inflammatory responses to inhaled LPS in healthy human subjects. In this study, there was no difference between the 40- and 80-mg simvastatin groups, although the study was not powered to determine if there was a difference between the two simvastatin doses (6). Two recent studies support the use of high doses of statins for more prolonged periods. In the ASEPSSIS trial in patients with sepsis, atorvastatin 40 mg daily during their hospital stay reduced the rate of sepsis progressing to severe sepsis during hospitalization (7). In a small proof-of-concept study in patients with ALI, of whom half had sepsis, simvastatin 80 mg daily for up to 14 days improved sequential organ failure scores. However, improvements were only significant at Day 14 in contrast to Day 7, suggesting that more prolonged therapy was required (8). In the current study the median number of doses of atorvastatin 20 mg administered was only four. Although the atorvastatin levels achieved are adequate for the cholesterol-lowering effects of statins, it is unclear if these levels are sufficient to achieve the pleiotropic antiinflammatory effects of statins.

Taken together, these data, as discussed by the authors, raise the possibility that the treatment regimen in the current study might not have been effective in the treatment of established sepsis in statin-naive patients and that higher doses of a statin other than atorvastatin, given for a more prolonged period, may be required for a beneficial effect. Ongoing studies in patients with ALI using high-dose simvastatin 80 mg (HARP-2 ISRCTN88244364) (9) and rosvastatin 20 mg (SAILS NCT00979121) for up to 28 days will help address these questions.

**IS PRETREATMENT WITH STATINS IN CRITICALLY ILL PATIENTS WITH SEPSIS LIKELY TO BE MORE EFFECTIVE THAN TREATING ESTABLISHED SEPSIS?**

Another possible explanation for the absence of an effect in statin-naive patients with established sepsis is that the timing of statin use may have been too late to modulate the inflammatory changes of sepsis. The majority of data indicate that statins are effective when used as a pretreatment in animal models of sepsis and ALI. The data from the current study that prior statin use was associated with a lower baseline plasma IL-6 in patients with severe sepsis, and that atorvastatin 20 mg in prior statin users was associated with improved 28-day survival raises the hypothesis that pretreatment with statins in critically ill patients at risk of sepsis may be more effective than treating established sepsis. A metaanalysis of 13 studies involving 254,950 patients found that treatment with statins in community-acquired pneumonia was associated with improved survival but that the effect was more pronounced if treatment was initiated in the community prior to hospital admission (10). This is supported by data that pretreatment with simvastatin attenuated the systemic and pulmonary inflammatory response to LPS in healthy human subjects (6, 11). Future studies should focus on randomizing either a population of preexisting statin users with established severe sepsis to receive statins or alternatively statin-naive patients at high risk of severe sepsis, such as patients undergoing esophagectomy or complex colorectal surgery, to pretreatment with high doses of statins.

**SHOULD STATINS BE CONTINUED IN CRITICALLY ILL PATIENTS?**

Given that prior statin use was associated with a reduced mortality in patients with severe sepsis, the question arises of whether statin therapy should be continued in the critically ill. Importantly, in this current study, the cessation of established statin treatment was found to be associated with worse survival. The current study also provides preliminary evidence of safety of the use of statins in this cohort. Given that other observational data have demonstrated that discontinuing statins in preexisting statin users is associated with the worst outcome in patients with bacteremia (12), this supports the recommendation that statins should be continued in the critically ill. However, it is important to remember that statins can be associated with life-threatening rhabdomyolysis and liver dysfunction, particularly in the setting of the frequency of concomitant medications given in the intensive care unit, where there is a potential for adverse drug interactions, and in certain patient cohorts such as those with hypothyroidism. Therefore, pending the results of further clinical trials, continuing statins should be considered if there is no contraindication, although it is important to carefully monitor creatine kinase and liver function on a regular basis.

In conclusion, this important study by the ANZ-STATInS Investigators adds important new data to the body of data regarding the use of statins in sepsis. However, more research is needed, namely, investigating high-dose statins for a more prolonged period in patients with sepsis. Future research should focus on three cohorts of patients: those with established sepsis, preexisting statin users with severe sepsis, and statin-naive patients at high risk of developing sepsis who would be pretreated with statins. Studies should continue to carefully monitor for potential toxicity. In the interim, with appropriate safety monitoring, continuation of preexisting statin use in the critically ill with sepsis should be considered.

**Author disclosures** are available with the text of this article at www.atsjournals.org.

**Cecilia M. O’Kane, M.B.Ch.B., Ph.D.**
Centre for Infection and Immunity
Queen’s University of Belfast
Belfast, United Kingdom

**Gavin D. Perkins, M.B.Ch.B., M.D.**
University of Warwick
Warwick Medical School
Warwick, United Kingdom

**Daniel F. McAuley, M.B.Ch.B., M.D.**
Centre for Infection and Immunity
Queen’s University of Belfast
Belfast, United Kingdom

**References**

Acute Respiratory Distress Syndrome and Stem Cells
A Small Beginning or a Strategy Doomed to Never Gestate?

Acute respiratory distress syndrome (ARDS) remains a heterogeneous and very common cause of respiratory failure requiring intensive medical care. An enormous amount of research into ARDS has delivered some dividends (1); however, the mortality rate remains unacceptably high with estimates ranging from 15 to 50% in recent studies (2-5). More recently attention has also focused on poorer long-term health outcomes in ARDS survivors (4, 6-8).

Much of the improvement in ARDS hospital mortality rates has been attributed to the use of pressure-controlled ventilation limiting secondary lung injury, a strategy suggested by experimental models, which has now been the standard of care for well over a decade (1). Despite a large amount of research, we have so far failed to develop any strategies that prevent the development of ARDS after an ARDS-prone insult, ameliorate ARDS when lung injury is evolving (i.e., as patients progress through acute lung injury to ARDS), or reduce the proportion of patients that go on to develop fibroproliferative ARDS and its associated prolonged use of mechanical ventilation.

In recent years, clinical trials with stem cells have taken the emerging field in many new directions. There is an emphasis on longed use of mechanical ventilation.

Go on to develop fibroproliferative ARDS and its associated pulmonary injury to ARDS), or reduce the proportion of patients that lung injury is evolving (i.e., as patients progress through acute from a single array of insults to the lung. Is ARDS due to bacterial sepsis really the same as ARDS due to trauma or inhalational injury? This becomes a critical issue when we consider that the model used by Lee and colleagues (9) was a large bolus of Escherichia coli, and part of the effect of the intervention was to reduce bacterial load. A successful intervention through ameliorating bacterial-induced lung injury may not work in other situations. Indeed, the large bolus of E. coli required to cause injury in the ex vivo lung model bears little resemblance to the more gradual process of bacterial accumulation in the lung in normal human pneumonia, and we have no idea whether the immune processes brought into play are even comparable.

Moving from the bench to the bedside, the most critical issue becomes the window of opportunity to use the intervention. Experimental models offer the possibility to test the effect of potential therapeutic agents on regeneration of type 1 pneumocytes, which are nearly impossible to culture in vitro. Lee and colleagues (9) instilled their MSC 1 hour after the introduction of E. coli. A host of interventions have been shown to reduce pulmonary injury if given before, at the time of, or shortly after a significant insult, but all have so far failed to be effective when given at more realistic time points (e.g., 6, 12, or even 24 h after the initial insult). Although studying the human ex vivo lung has significant benefits, the inherent problem of keeping it viable for longer periods is also a major barrier to truly understanding the potential for MSC in clinical practice.

Providing sufficient clinical supply of MSC for any intervention represents a challenge, hence the importance of the finding by Lee and colleagues (9) that KGF provides much of the benefit. Even so, recombinant KGF is unlikely to be a cheap intervention and therefore restricted to patients with a high likelihood of developing ARDS. Therein lies the next problem, as our current ability to predict which patients will develop ARDS is poor. First, we have limited ability to predict which patients with impaired gas exchange will deteriorate further to the PaO2/FiO2 “cutoff” defining acute lung injury. In patients who meet the criteria for acute lung injury, we have very limited tools to determine who will

References:

Copyright © 2013 by the American Thoracic Society
DOI: 10.1164/rccm.201212-2305ED