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Response to the letter of Shyamsundar et al.

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We appreciate the letter of Shyamsundar and colleagues regarding our manuscript entitled “Statin administration did not influence the progression of lung injury or associated organ failures in a cohort of patients with acute lung injury” [1]. The limitations of endpoints such as $\text{PaO}_2/\text{FiO}_2$ are indeed highlighted by trials such as ARMA [2]. The oxygenation index $[(\text{FiO}_2 \times \text{mean airway pressure} \times 100)/\text{PaO}_2]$ is an alternative to the $\text{PaO}_2/\text{FiO}_2$ ratio that we have shown to correlate better with patient-important outcomes [3]. Unfortunately, we were unable to perform meaningful statistical analyses for this endpoint as few patients were receiving ventilatory support at day 7.

Endpoints of greater clinical significance in the study of acute lung injury (ALI) include ventilator-free days, length of intensive care unit (ICU) stay, and mortality [4]. These endpoints were evaluated in our investigation as well and no significant differences between the statin and nonstatin cohorts were noted. These endpoints were considered secondary rather than primary outcomes due to a priori concerns regarding sample size. Our initial interest in the univariate trends toward more ventilator-free days, reduced length of ICU stay, and lower hospital mortality in the cohort receiving statin therapy was tempered by the lack of

effect in patients with low probability for statin administration.

We also agree with the extensive amount of preclinical data suggesting a beneficial anti-inflammatory effect with statin therapy. Indeed, this pre-clinical work provided a degree of motivation for our investigation of statin therapy in patients with established ALI [5]. Although our evaluation did not support the routine use of statin therapy in patients with established acute lung injury, it does not rule out a role in other pro-inflammatory conditions such as pneumonia or sepsis. Additionally, it does not exclude a role in the prevention of ALI.

Finally, Shyamsundar and colleagues raise the important questions of genetic variability and class versus drug effect in the study of statin administration in patients with ALI. Unfortunately, we are not able to comment effectively on either of these issues due to the retrospective nature of our study and limited number of patients receiving statin therapy ($n = 45$). Similar limitations preclude comment on the pharmacokinetics of statin therapy in various disease states and patient conditions. We are aware of the data presented by Kruger et al. [6] and agree that a variety of factors are likely to affect both serum levels and the end-organ effects of statins. This is likely to be particularly true in patients with critically illness.

In summary, we acknowledge the existing body of preclinical data and emerging body of clinical data suggesting benefit with statin therapy in a variety of clinical circumstances. We were unable to confirm such benefit in patients with established ALI. Our findings do not refute (or confirm) a potential role for statin therapy in the prevention of ALI, particularly in populations with high-risk conditions such as pneumonia and/or sepsis. The numerous ongoing randomized controlled trials will hopefully shed additional light on the potential role

of statins in these clinical circumstances.

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