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Reply to Fedson

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To the Editor:

We appreciate the interest in our recent article [1] on biomarkers in Ebola virus disease (EVD), and the editorial comments provided by Dr. Fedson. In his editorial, Dr. Fedson points out that the evidence of endothelial dysfunction that we reported in patients affected by EVD is also commonly observed in other forms of sepsis. He brings attention to a mouse study that indicated that selective inhibition of NFκB signaling in endothelial cells in the context of bacterial sepsis provided protection from disease [2], suggesting that down-regulation of the local inflammatory response at the endothelial cell level could be protective to patients. Additionally, he comments on a small clinical trial of statins in patients with sepsis; this study showed decreased progression to severe sepsis in statin-treated patients [3]. This result is attributed to the role of statins in stabilizing the endothelium and in its local anti-inflammatory effects on endothelial cells. Finally, Dr. Fedson suggests the use of statins as adjunctive therapy in managing patients who have EVD.

We agree that statins should be considered as adjunctive therapy for EVD. In fact, we suggested the use of statins in EVD patients in a subsequent study, in which we examined the differences in biomarkers and clinical outcomes between adult and pediatric patients with EVD [4]. In that study, we observed direct evidence of endothelial dysfunction, demonstrated by elevated levels of sICAM and sVCAM in pediatric patients who had fatal outcomes, and normal levels of these factors in pediatric patients who survived infection.

No treatment is without risk, however, and the benefits and risks of a given intervention or medication must always be considered. The risks of using statins include rhabdomyolysis, leading to acute renal failure, and many potential drug interactions, since statins are metabolized by the cytochrome P450 system. Also, patients with known elevation of hepatic transaminases are at increased risk of side effects. Since Ebola virus is known to be hepatotrophic, and severe disease is associated with elevated hepatic transaminases, patients would need to be carefully monitored if statins were initiated. This type of intensive monitoring could be very difficult to achieve in the areas of the world affected by EVD. On the other hand, statins in EVD patients could stabilize the endothelium by decreasing local inflammation, and thus lessen the risk of the patient developing shock. Additionally, although only 30–40% of patients develop hemorrhagic manifestations of EVD, and the presence of hemorrhage does not correlate with death, statin use might also decrease the incidence of hemorrhage by affecting components of the coagulation pathway.

Unanswered questions include the dose, frequency, duration, and choice of statin to use in EVD patients. Presumably, initiating statin treatment within 24 hours of the onset of symptoms would be best, although given the severity of untreated EVD, initiation of treatment at any point in the disease course would be reasonable. In the ASEPSIS trial 40 mg of atorvastatin was administered daily for the duration of hospitalization, up to 28 days. Patients who survive EVD tend to show recovery within 2 weeks of symptom onset, so this duration of therapy would theoretically be sufficient. Typically, a potentially useful drug would be

evaluated in several animal models of disease long before its use in humans is even considered. Then a rigorous, double-blinded, placebo-controlled trial would be conducted to evaluate that drug in humans. However, we are in the midst of the largest EVD outbreak ever recorded, and it shows no signs of abating. Therefore, the individual clinician is left with the decision to use a drug off-label that might be beneficial, while weighing the possible side effects of that drug. These decisions should be made very carefully, in consultation with the patient, and with full disclosure of the possible risks and benefits.

We have no conflicts of Interest.

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