Journal of Infectious Diseases Advance Access published August 25, 2014

A Practical Treatment for Patients with Ebola Virus Disease

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The re-emergence of Ebola virus disease (EVD) in Guinea and its spread to urban centers in neighbouring West African countries has caused international alarm [1]. The fatality rate of cases attributable to EVD has been at least 60%. In the absence of any licensed prophylaxis or treatment [1, 2], supportive care for individual patients has been fraught with difficulty and evoked widespread suspicion and fear in affected communities. As yet, there has been no sign the outbreak is abating.

In an article published recently in this journal, McElroy and colleagues updated previous studies of biomarker correlates of outcomes in patients seen during the 2000-2001 EVD outbreak in Uganda [3]. They confirmed many well-known findings and identified some that were new. Fatal cases were associated with severe abnormalities of liver and kidney function, marked CD8 lymphocytopenia and elevated plasma levels of several cytokines and chemokines (IL-1α, IL-1RA, IL-6, MCP-1, MCSF and MIP-1α). Unexpectedly, higher levels of sCD40L were seen in patients who survived compared with those who died. (sCD40L is a member of the TNF superfamily that has prothrombotic and pro-inflammatory activities.) Evidence of endothelial activation (elevated levels of sICAM) was observed in those with hemorrhagic disease, and abnormal elevations in biomarkers of coagulopathy (thrombomodulin, D-dimer) were seen in those who died. These observations of endothelial dysfunction and coagulopathy confirm the findings of other studies of clinical EVD and experimental Ebola virus infection of non-human primates [4]. Moreover, similar findings are seen in experimental and human sepsis [4-6].

A recent report demonstrated the central importance of endothelial barrier integrity in determining the outcome in sepsis. Liu and colleagues studied transgenic mice that conditionally overexpress a mutant form of I-κBα (an inhibitor of NF-κB) only in endothelial cells [7]. Ordinarily, activation of NF-κB leads to the up regulation of pro-inflammatory cytokines followed by endothelial cell dysfunction and loss of barrier integrity. Seven hours after *E. coli* infection, control mice showed significantly elevated plasma levels of pro-inflammatory cytokines, increased tissue levels of pro-inflammatory cytokines and evidence of multi-organ failure in heart, lungs, liver and kidneys, and increased mortality. In transgenic mice, I-κBα-mediated blockade of

NF-κB-activation had no effect on the increase in pro-inflammatory cytokines in plasma or in the four target organs, but biomarkers of endothelial activation (ICAM-1, VCAM-1) in these organs were reduced. As a result, multi-organ failure did not develop and survival improved. Thus, blockade of NF-κB activation preserved endothelial barrier integrity, demonstrating that endothelial cells were the targets, not necessarily the origin, of sepsis-induced inflammation.

These experimental findings help us understand the results of a randomized controlled trial conducted by Patel and colleagues in 100 patients hospitalized with sepsis [8]. Patients with severe sepsis, as indicated by failure of one or more organs, were excluded from the trial. On the first hospital day, 49 patients were given atorvastatin (40 mg/day orally) and 51 were given placebo (all had been statin-naive for at least two weeks). The primary outcome was progression to severe sepsis. The atorvastatin group experienced an 83% reduction in progression to severe sepsis compared with the placebo group (2 vs. 12; p =0.007). The sample size for the trial was too small to evaluate the effects of treatment on other outcomes such as mortality, ICU admission and hospital length of stay.

In addition to their known effects in reducing plasma levels of LDL cholesterol, statins have additional anti-inflammatory and immunomodulatory activities that include up regulation of I-κBα, down regulation of NF-κB and reduced levels of sCD40L and sICAM [5, 6, 8]. Statins also decrease expression of tissue factor and thrombin, decrease cleavage of fibrinogen and increase activation of thrombomodulin [9]. All of these activities promote and maintain normal endothelial cell function and coagulation pathways.

Investigators have not developed an effective vaccine against EVD and post-exposure treatments targeting the virus or the host response are in the early stages of development [2]. Although these interventions might eventually benefit laboratory and healthcare workers, they will be expensive, in short supply, and it is unclear how they might be used in patient care during an EVD outbreak. Statins, however, are widely available to African physicians as inexpensive generics and are used to treat patients with cardiovascular disease every day. Along with other generic

immunomodulatory agents (e.g., ACE inhibitors, angiotensin receptor blockers), statins have been proposed for syndromic treatment of the host response in patients with influenza, pneumonia and sepsis [10]. They should also be considered for treating patients with EVD.

Conflict of interest: The author declares no conflict of interest.

Funding source: The author declares no outside funding was used to support the writing of this article.

Presentation at meetings: The material covered by this manuscript has not been presented at any meeting.

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