Correspondence

A Practical Treatment for Patients With Ebola Virus Disease

To the Editor—The emergence of Ebola virus disease (EVD) in Guinea and its spread to urban centers in neighboring West African countries has caused international alarm [1]. The case-fatality rate of EVD has been 50 to 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 et al 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 (interleukin 1α, interleukin 1RA, interleukin 6, monocyte chemotactic protein 1, macrophage colony-stimulating factor, and macrophage inflammatory protein 1α). Unexpectedly, higher levels of soluble CD40L, a member of the tumor necrosis factor superfamily that has prothrombotic and proinflammatory activities, were seen in patients who survived, compared with those who died. Evidence of endothelial activation (ie, elevated levels of soluble intercellular adhesion molecule [sICAM]) was observed in those with hemorrhagic disease, and abnormal elevations in levels of biomarkers of coagulopathy (ie, thrombomodulin and 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 nonhuman 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 et al studied transgenic mice that conditionally overexpress a mutant form of I-κBα (an inhibitor of nuclear factor κB [NF-κB]) only in endothelial cells [7]. Ordinarily, activation of NF-κB leads to the upregulation of proinflammatory cytokines, followed by endothelial cell dysfunction and loss of barrier integrity. Seven hours after *Escherichia coli* infection, control mice showed significantly elevated plasma levels of proinflammatory cytokines; increased tissue levels of proinflammatory cytokines; evidence of multiorgan 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 proinflammatory cytokines in plasma or in the 4 target organs, but levels of biomarkers of endothelial activation (ie, ICAM-1 and vascular cell adhesion protein 1) in these organs were reduced. As a result, multiorgan 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 et al in 100 patients hospitalized with sepsis [8]. Patients with severe sepsis, as indicated by failure of 1 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 2 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; $P = .007$). The sample size for the trial was too small to evaluate the effects of treatment on other outcomes, such as mortality, intensive care unit admission, and hospital length of stay.

In addition to their known effects in reducing plasma levels of low-density lipoprotein cholesterol, statins have additional antiinflammatory and immunomodulatory activities that include upregulation of I-κBα, downregulation 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 postexposure 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 and 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 generic drugs and are used to treat patients with cardiovascular disease every day. Along with

other generic immunomodulatory agents (eg, angiotensin-converting enzyme inhibitors and 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.

Note

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Received 27 July 2014; accepted 18 August 2014; electronically published 25 August 2014.

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The Journal of Infectious Diseases® 2015;211:661–2

DOI: 10.1093/infdis/jiu474