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Editorial

Is strengthening the endothelial barrier a therapeutic strategy for Ebola?

1. Introduction

In a provocative article published in this issue, Fedson and Rordam argue that statins and angiotensin II receptor blockers (ARBs) could be used as therapeutic agents in Ebola virus disease (EVD). The authors assert that the loss of vascular integrity represents a critical step in the pathophysiology of EVD, leading to hypovolemia and multi-organ failure. Since every blood vessel in the body is lined by endothelial cells and since, according to the authors, statins and ARBs work to maintain or enhance endothelial barrier integrity, these drugs might keep the patient alive long enough for the immune system to clear the virus. Essentially, this strategy seeks to modulate the host response to the infection rather than combating the virus itself. The authors point out that the loss of vascular integrity that is characteristic of human EVD is not reproduced in most animal models. Because of this, the authors note that the notion of targeting endothelial activation or leak in EVD has not been widely accepted. In this editorial we will address the biological plausibility of this approach and then address the clinical evidence of its efficacy.

2. Biological plausibility

The premise that the endothelium is critical to the pathogenesis of severe infections is not new. In animal models of bacterial sepsis, endothelial cell activation and increased endothelial permeability contribute to mortality.[1,2] Similar findings have been reported in certain viral infections.[3] For instance, activation of the endothelium is critical to the pathogenesis of influenza,[4] and we and others have reported on the importance of lung endothelial barrier integrity in murine models of influenza virus- induced acute lung injury.[2,5,6]

Diarrhea and poor oral intake are major contributors to the hypovolemia that characterizes human cases of EVD;[7,8] however, the loss of endothelial barrier integrity may also contribute. While viral infection of the endothelium itself could conceivably cause endothelial leak, in vitro experiments,[9] as well as necropsy studies on cynomolgus monkeys[10] and autopsy studies on human patients,[11] suggest that this occurs only late in the disease. However, monocytes are an early target of the Ebola virus,[12] and the massive activation of these cells and macrophages results in the secretion of pro-inflammatory cytokines[13,14] that can increase endothelial permeability. In addition, secreted Ebola virus glycoproteins have both direct and paracrine effects, including inducing endothelial cell activation, loss of cellular adhesion, and direct cytotoxicity.[15–18] Finally, a recent study in mice reported that genes associated with endothelial signaling and vascular leakage correlated with resistance to a mouse-adapted strain of Ebola.[19] Together, these observations suggest an important and perhaps unappreciated role for the endothelium in the pathogenesis of EVD.

3. Evidence of efficacy

In their article, Fedson and Rordam present data from a case series of approximately 100 consecutive patients in Sierra Leone treated for six or more days with a combination of atorvastatin 40 mg and irbesartan 150 mg daily. Remarkably, the authors report that "(o)nly two... died". While intriguing, these observations must be interpreted cautiously. Importantly, no information is provided as to the oversight and consent processes and no control data are available—a particular shortcoming given that EVD mortality varies significantly in different clinical contexts.[20,21] The authors provide very little detail about these patients, making a critical appraisal of the results difficult. Other published case series emphasize the importance of adequate fluid and electrolyte replacement,[8] and it is unclear whether statins and/or ARBs would confer additional benefit in the setting of optimal supportive care.

Furthermore, we are unsure whether statins and ARBs can actually improve endothelial leak or activation in vivo. Statins have been suggested to have pleiotropic anti-inflammatory effects (reviewed by Tousoulis et al.[22]), including the ability to modulate endothelial activation in sepsis,[23] and observational trials initially suggested that statin therapy had a protective effect in this context (see meta-analysis by Wan et al.[24]). Unfortunately, randomized controlled trials do not support this hypothesis. Indeed, in the trial cited by Fedson and Rordam in which statin-naïve septic patients were treated with atorvastatin, there was no difference in the length of hospital stay or the mortality rate between treatment and control groups.[25] Other larger trials have shown that statins do not alter mortality[26] from sepsis or the acute respiratory distress syndrome.[27] Several meta-analyses now suggest that statins do not have clinically significant effects on the outcome of severe infection.[24,28,29]

The literature on ARBs as modulators of endothelial permeability is not as complete. Angiotensin II has potent effects on the vascular endothelium (reviewed by Salgado et al.[30]); for instance, in rat tissue, angiotensin II modulates vascular leak,[31] while mice deficient in Angiotensin Converting Enzyme, the enzyme that generates angiotensin II, exhibit reduced susceptibility to acute lung injury.[32] Consistent with these findings, ARBs have been shown to have lung-protective effects in a murine model of

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sepsis.[33] However, there are no data from randomized controlled trials in humans with sepsis or lung injury. Human genetic studies suggest that a polymorphism that would be expected to attenuate angiotensin II signaling is actually associated with lower blood pressure and increased mortality from sepsis.[34] From a practical standpoint, ARBs could be dangerous in severe infections, as inhibition of angiotensin II signaling could contribute to renal insult[35] and hemodynamic instability.[30]

Ultimately, the efficacy of statins and ARBs for EVD cannot be properly evaluated without a formal, well-designed clinical trial. Nonetheless, modulation of the endothelial response to Ebola infection is a potentially promising approach that merits further investigation. Finally, the development of better animal models for Ebola-mediated vascular leak could be an important next step towards the development of future therapeutics.

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Conflict of interest:.

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