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Perspective

Treating Ebola patients: a 'bottom up' approach using generic statins and angiotensin receptor blockers

David S. Fedson [a,*], Ole Martin Rordam [b]

[a] 57, chemin du Lavoir, 01630 Sergy Haut, France
[b] Fjordgata 50, Trondheim, Norway

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SUMMARY

The international community has responded to the Ebola outbreak in West Africa with a 'top down' approach. This has contributed to outbreak control, but has done much less to reduce the high mortality rate in individual patients. Ebola patients experience a breakdown in endothelial barrier integrity that leads to massive fluid losses and vascular collapse. Statins and angiotensin receptor blockers (ARBs) maintain or restore endothelial barrier integrity. Local physicians in Sierra Leone have treated approximately 100 consecutive Ebola patients with atorvastatin and irbesartan, and all but two inadequately treated patients have survived. The results of this experience have not been released and they need to be reviewed and validated. Unlike other treatments that target the Ebola virus itself, this 'bottom up' approach to treatment represents a paradigm shift by targeting the host response to infection. Treatment with these safe, inexpensive generic agents could be implemented readily throughout West Africa.

1. Introduction

The international community has responded to the Ebola outbreak in West Africa with an approach that could be described as 'top down'. Small groups of elite scientists, health policy makers, pharmaceutical company executives, and the staff of the World Health Organization (WHO), governmental agencies, and non-governmental institutions have decided how to implement interventions for outbreak control and containment and develop new Ebola vaccines and treatments. These 'top down' interventions have built Ebola treatment units and organized the delivery of supplies, communications, and surveillance that have been essential for outbreak control. However, they have had only a modest impact on the survival rate for individual patients. In most treatment units, overall case fatality rates have been 60% or greater, and they have been even higher in patients who have been treated in the community.[1]

Studies in non-human primates have shown that experimental antiviral agents and antibody preparations reduce Ebola virus replication and prolong or improve survival, and clinical trials of several of these agents have begun in West Africa. These trials are supported by hundreds of millions of dollars provided by companies, governmental agencies, and foundations in developed countries. However, by themselves, these agents will probably not have a major impact on the high case fatality rate of Ebola. Early results from a clinical trial of one antiviral agent (favipiravir) suggest that compared to historical controls, overall mortality was reduced by less than 20%.[2] If Ebola survival rates are to improve significantly, something else will be needed.

2. Lessons learned from evacuated healthcare workers

Four foreign healthcare workers in West Africa were infected with the Ebola virus and evacuated to the USA and European countries. Reports of their treatment have provided new insight into the pathophysiology of human Ebola virus disease.[3–5] These patients developed severe internal and external fluid losses that signalled a breakdown in endothelial barrier integrity (plasma leak syndrome). Left untreated, these losses would have led to vascular collapse, multi-organ failure, and death. Fortunately, these patients received meticulous care, and all survived.

* Corresponding author.
E-mail address: dfedson@wanadoo.fr (D.S. Fedson).

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In West Africa, most Ebola patients receive minimal supportive care, including intravenous fluid replacement, and consequently mortality is high. The observations on the evacuated healthcare workers suggest that if a simple treatment could be found that maintains or restores normal endothelial barrier integrity, patient survival might improve dramatically. Unlike antiviral agents, this treatment would not target the Ebola virus; instead, it would target the host response to infection.

3. Treating the host response to Ebola virus disease

Treating the host response to a disease is not a new idea. For example, almost all cardiovascular diseases are not caused by acute bacterial or viral infections, so treatment must target the damage caused by the disease itself. Cardiovascular scientists have developed several drugs that do this, and they include statins and angiotensin receptor blockers (ARBs). Statins were initially thought to work because they lower blood levels of low-density lipoprotein (LDL) cholesterol, and ARBs were developed to treat hypertension. Yet both drugs have anti-inflammatory activities,[6,7] and both are known to maintain or restore endothelial barrier integrity.[8–11]

More than a decade ago, Ebola scientists noted similarities between human Ebola virus disease and sepsis.[12,13] Increased vascular permeability, multi-organ failure, and a high mortality are found in both diseases.[12–15] Many severe virus infections share the same characteristics.[16] Endothelial dysfunction is central to the pathophysiology of sepsis and many viral diseases. Experimental evidence strongly indicates that it is also central to the pathophysiology of human Ebola virus disease.[17] Figure 1 illustrates the endothelial effects of Ebola virus infection.[18]

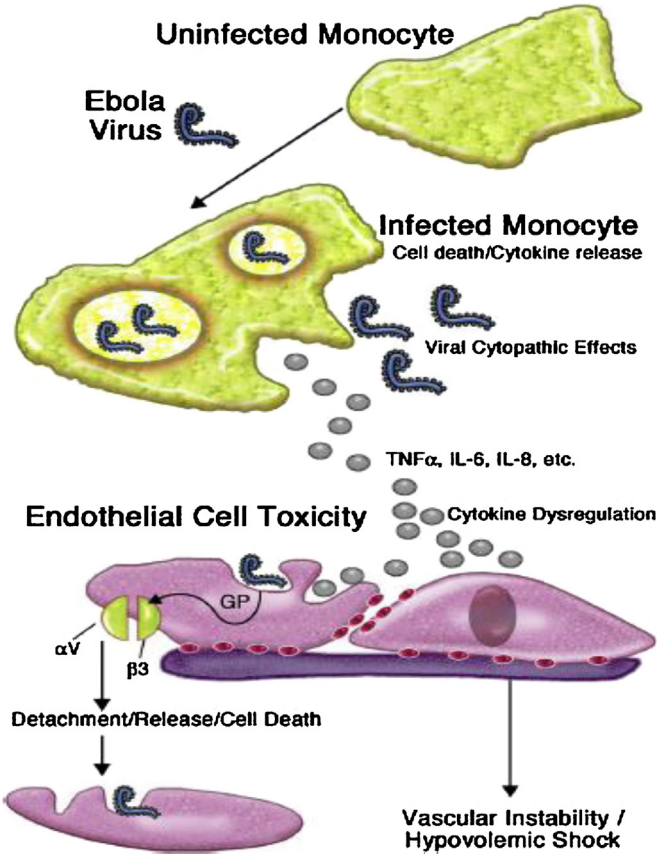

Figure 1. Ebola virus infection and endothelial dysfunction. Ebola viruses initially infect myeloid cells, which release numerous pro-inflammatory cytokines. These cytokines target endothelial cells, destabilize the actin cytoskeleton, and damage adherens and tight junctions, leading to a loss of endothelial barrier integrity, internal and external fluid losses, and vascular collapse. (From Roca et al.[18]).

Observational studies have shown that in patients hospitalized with community-acquired pneumonia[19] and seasonal influenza,[20] treatment with either a statin or an ARB significantly reduces all-cause mortality within the next 30 days. More directly, a randomized controlled trial conducted in 100 statin-naïve patients who were hospitalized with sepsis showed that treatment with atorvastatin (40 mg/day) led to an 83% reduction in evidence of multi-organ dysfunction.[21] Experimental evidence indicates clearly that sepsis-related multi-organ dysfunction can be prevented and survival increased by stabilizing endothelial function alone.[22] Numerous clinical studies have shown that statin and ARB treatment of patients with sepsis, pneumonia, and influenza is safe and well tolerated. Moreover, combined treatment with both agents has been shown to have a greater effect on biomarkers of inflammation and endothelial function than using either agent by itself.[23,24]

These experimental and clinical findings suggest that treatment with a statin, an ARB, or a combination of both, might improve survival in Ebola patients.[25]

4. A trial of statin and ARB treatment of Ebola virus disease

In November this past year, thanks to a private donation by one of the authors of this report (OMR), local physicians in Sierra Leone were able to treat approximately 100 Ebola patients with a combination of a statin and an ARB. Patients were treated in several centres: the Port Loko Government Hospital, the 34 Military Hospital in Freetown, the Hastings Ebola Treatment Centre, and a few other locations. Treatment consisted of administering atorvastatin (40 mg) and irbesartan (150 mg) daily for six or more days, along with the usual care provided in Ebola treatment units. (Several patients were also treated with clomiphene (50 mg/day) for the first 3 days. Clomiphene has been shown to have antiviral activity against Ebola virus.[26] Its effects on endothelial dysfunction are not known.) Only two inadequately treated patients died. One was extremely ill when first seen and he died after only 1 or 2 days of treatment. The other was a physician who was treated with atorvastatin and irbesartan for 3 days and showed improvement. His treatment was then stopped and he was started on an experimental antiviral treatment, following which he relapsed and died. All of the other (approximately 100) treated patients survived. A memorandum written by one of the treating physicians noted their 'remarkable improvement' on treatment (D.S. Fedson; unpublished observation).

A clinical study of Ebola virus patients seen during the 2000–2001 outbreak of Sudan Ebola virus disease showed that viral loads were higher in patients who died compared with those who survived, but starting on days 5–7, viral loads in both groups started to decline (Figure 2).[27] Recently, clinicians in Liberia reported that the large volume watery diarrhoea in Ebola patients rarely persisted beyond day 7 of illness, and clinical improvement in survivors was noticeable a few days later.[28] An important study of Ebola patients evacuated to Atlanta in the USA showed that instead of immunosuppression, these patients had robust humoral and cellular immune responses.[29] Taken together, these studies help us understand the effects of atorvastatin and irbesartan treatment. These agents maintained or restored endothelial barrier integrity, shutting down excessive fluid losses and preventing vascular collapse. By prolonging survival, treatment allowed patients to live long enough to develop an immune response and eliminate the virus on their own. This outcome was achieved in almost all treated patients without requiring the use of one of the experimental antiviral agents now being tested in West Africa.