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Perspective

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

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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.

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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]

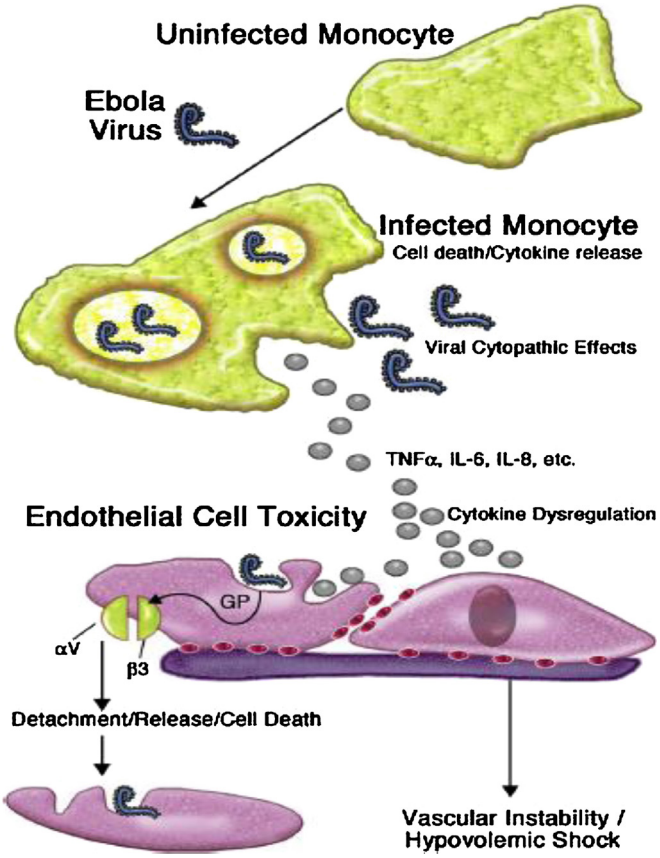

Figure 1. Ebola virus infection and endothelial dysfunction. Ebola viruses initially infect myeloid cells, which release numerous pro-inflammatory cytokines. These cytokines target endothelial cells, destabilize the actin cytoskeleton, and damage adherens and tight junctions, leading to a loss of endothelial 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.

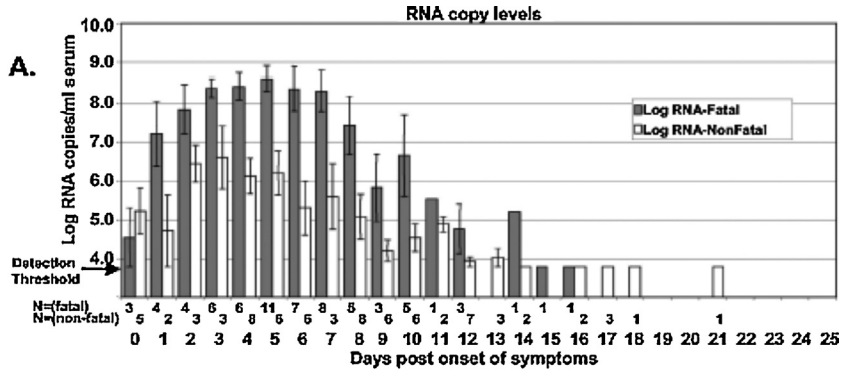

Figure 2. Ebola virus load (mean $\log_{10}$ RNA copies per ml of serum) in 18 survivors and 27 non-survivors of Sudan Ebola virus disease in 2000–2001. Viral loads started to decline in both survivors and non-survivors 5–7 days after the onset of clinical symptoms. (From Towner et al.[27]).

The drugs were donated at the request of government officials in Sierra Leone on the condition that (1) local officials would approve of their use, (2) healthcare professionals would keep accurate treatment records, and (3) the results would be made public, regardless of outcome. Unfortunately, there was no financial or logistical support for organized clinical trials, so patients were treated consecutively. Treatment results were documented informally and reported in letters and memoranda exchanged among local physicians and health officials. These communications included individual treatment records for 15 patients (Table 1; D.S. Fedson, unpublished observation). The clinical and treatment records of all treated patients need to be examined in order to validate the results. Unfortunately, this has not been possible because local supervising health officials have refused to release information on the treatment.

The idea of treating the host response has not been supported by Ebola scientists and health officials who have defined the international response to Ebola virus disease.[30,31] They are sceptical about a treatment based largely on an extrapolation of findings obtained in other conditions like sepsis, pneumonia, and influenza. They are uncertain about treatment safety and its effects on virus replication. They insist on first obtaining evidence of treatment efficacy in animal models of Ebola virus disease, and these interventions target only the virus. This approach to clinical development has been sanctioned by the WHO and underlies all of the clinical trials of antiviral agents now underway in West Africa.[32] Only agents that have shown promise in non human primates (NHPs) are considered for human clinical trials. Ebola scientists have used only rhesus macaques to test candidate agents. This approach is unlike that of other investigators who have shown that different NHP species respond differently to infection with the same virus. For example, simian immunodeficiency virus infection of rhesus macaques is uniformly fatal, whereas sooty mangabeys all survive, although viral loads in both are the same.[33] Most important, no NHP model of Ebola virus disease has reproduced the endothelial dysfunction and fluid losses seen in human patients.[34] Nonetheless, the reluctance of Ebola scientists to target the host response remains. The results of statin and ARB treatment of Ebola patients in Sierra Leone suggest that their concerns are misplaced.

Table 1
Summary of treatment for 15 Ebola patients in the Port Loko Government Hospital[a,b]

Patient	Age/sex	Duration of treatment, days
1	30 F	5
2	30 F	4[c]
3	40 M	5[c]
4	10 F	4[c]
5	12 M	5[c]
6	25 F	6
7	23 F	6
8	12 F	6
9	20 F	6
10	42 F	8
11	12 F	6
12	35 M	6
13	45 F	6
14	20 F	8
15	15 M	6

[a] Summary of 15 individual patient treatment records. Five patients were admitted on November 21, 2014 and 10 were admitted on November 25, 2014. All patients survived. They were discharged either home ($n=5$) or to a holding unit ($n=10$) to await a negative Ebola test result.

[b] All patients were treated with atorvastatin (40 mg/day) and irbesartan (150 mg/day). In addition, all patients received clomiphene (50 mg/day) for the first 3 days of treatment.

[c] Patient received an additional day of clomiphene treatment.

5. Treating the host response with statins and ARBs represents a 'bottom up' approach to managing Ebola virus disease

The Ebola outbreak is West Africa is regarded as a major humanitarian crisis.[35] The outbreak was unrecognized for several months, and then it was met with denial and hesitation by both local and international health officials.[36] When foreign healthcare workers became infected and were evacuated, the international response changed rapidly. Extensive population-based measures have achieved a large degree of outbreak control. Similarly extensive efforts to provide clinical care for individual Ebola patients have achieved much less.

The Editor of this journal recently noted that lower case fatality rates in some Ebola treatment units appear to be associated with the greater use of intravenous fluids.[37,38] He called for new treatment guidelines that emphasize the principles of fluid replacement and the correction of electrolyte imbalance "that can be implemented under field conditions in West Africa, provided staff are trained in high volume fluid replacement".[37] Others have also called for similar changes.[39–41] One group of investigators with experience in West Africa commented, "the most important aspect of supportive care is aggressive prevention of intravascular volume depletion, correcting profound electrolyte abnormalities, and preventing the complications of shock. This is an underlying tenant (sic) of critical care medicine, and one that can and should be applied in both resource-constrained and resource-rich settings ...".[39] They added, "with more personnel, basic monitoring and supportive treatment, many of the sickest patients with Ebola virus disease do not *need* to die. Ebola virus disease represents an illness ready for a paradigm shift in care delivery and outcomes ...".[39]

Treating Ebola patients with statins and ARBs represents this paradigm shift. By correcting the fundamental pathophysiological abnormality caused by Ebola virus infection, these agents should greatly reduce the need for intravenous fluids, and this should increase caregiver safety. All physicians in West Africa who treat patients with heart disease and high blood pressure should be familiar with their use and safety. Treating Ebola patients with these orally administered agents would require no additional training, personnel, or equipment. Debates over whether to provide intensive organ support (e.g., mechanical ventilation, renal dialysis) would become largely unnecessary.[42–44] Statins and ARBs are produced as inexpensive generics by companies located in developing countries. A 10-day course of combination treatment for an individual patient should cost no more than a few dollars (D.S. Fedson; unpublished observation).

Treating Ebola patients with inexpensive generic agents like statins and ARBs represents a 'bottom up' alternative to patient management.[45] Instead of relying on experimental agents that might not dramatically improve survival,[2,46] or those not yet developed,[47] it would rely on generic drugs that are widely available in West Africa. Treatment could be implemented readily for all patients who are treated by healthcare workers in Ebola treatment units or by family members who care for patients at home. These agents might also be used prophylactically to prevent severe disease in healthcare workers and other contacts who inadvertently become infected. They would provide caregivers with a simple treatment that could be used in settings that have little else to offer, radically transforming the management of Ebola patients. They would even call into question the need for expensive new treatments that target the Ebola virus.

6. A need for change

The WHO and all of the agencies and institutions involved in the Ebola response have an obligation to obtain the best scientific advice if they are to carry out their missions. For the Ebola response, this means seeking advice not only from Ebola scientists, but also from scientists in other disciplines; for example, endothelial cell biology, fluid and electrolyte metabolism, cell signalling effects of statins, ARBs and other generic agents, and the clinical and epidemiological effects of these agents in other forms of acute critical illness. It means being open to the idea that an effective treatment might target the host response, not the virus. By establishing the 'proof of principle' that treating the host response can be effective, this approach might be applied to patient care for other emerging and re-emerging diseases,[48] including an avian influenza pandemic.[45,49,50]

The German physicist Max Planck once wrote, "A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it." In other words, science advances one funeral at a time. This might be acceptable if it meant only the funerals of scientists themselves. It is a different matter if it means the funerals of many others.

In West Africa, more than 10 000 patients have died since early August 2014, when WHO declared Ebola a public health emergency of international concern and Ebola scientists and WHO staff first learned about the possibility of inexpensive generic treatment.[25,30] More than 4000 patients have died since late November, when physicians and health officials in Sierra Leone observed the effectiveness of atorvastatin and irbesartan treatment.

Clinical trials of agents like statins and ARBs should be part of current efforts to confront Ebola virus disease in West Africa. A trial protocol that includes atorvastatin and irbesartan treatment has recently been approved,[51] but a decline in the number of cases may make it difficult to undertake.[52] If pockets of Ebola virus disease persist, investigators must do everything possible to ensure that this trial goes forward. If the number of new cases declines even further, it will be critical for the results of the November treatment experience in Sierra Leone to be independently analyzed and validated. Only then will we be certain that treating the host response to Ebola virus disease really works.

Conflict of interest

The author declares no conflict of interest.

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