Treating the Host Response to Ebola Virus Disease with Generic Statins and Angiotensin Receptor Blockers

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ABSTRACT Treatments targeting the Ebola virus may eventually be shown to work, but they will not have an impact on overall Ebola mortality in West Africa. Endothelial dysfunction is responsible for the fluid and electrolyte imbalances seen in Ebola patients. Because inexpensive generic statins and angiotensin receptor blockers restore endothelial barrier integrity, they can be used to treat the host response in these patients. In Sierra Leone, approximately 100 Ebola patients were treated with this combination, and reports indicate that survival was greatly improved.

The Ebola outbreak that has devastated West Africa this past year may be receding, but it is far from over. Clinical trials of experimental antiviral agents, antibody preparations, and vaccines have begun, but even if these agents are effective, supplies will be limited and all of them will be costly (1). By themselves, they will not affect the course of the current outbreak or have much impact on its overall mortality. To improve patient survival, a different approach to treatment will be needed.

ENDOTHELIAL DYSFUNCTION IN EBOLA VIRUS DISEASE AND SEPSIS

Reports of the care given to Ebola virus-infected health care workers who were evacuated to Germany and the United States have been invaluable. They document severe internal (third spacing) and external (vomiting, diarrhea) fluid losses and electrolyte disturbances (2–4). These findings reflect the profound endothelial dysfunction and vascular barrier breakdown that are the central features of human Ebola virus disease. Left untreated, these changes usually lead to profound hypovolemia, multiorgan failure, and death (5). Fortunately, these health care workers received meticulous care and all survived.

Animal models of Ebola virus infection, including those in nonhuman primates (6), have not duplicated the fluid and electrolyte disturbances seen in human Ebola virus disease. Noninfectious Ebola virus glycoproteins (GPs) are shed from infected cells (7) and activate myeloid and endothelial cells via a TLR4-mediated mechanism. This leads to endothelial dysfunction and increased vascular permeability. A recent study in Collaborative Cross mice has demonstrated the importance of endothelial dysfunction and increased vascular permeability in causing lethal Ebola virus infection (8).

Sepsis is another condition that, as in Ebola virus disease, is characterized by endothelial dysfunction, multiorgan failure, and high mortality (5). Several lines of experimental evidence suggest that maintaining or restoring endothelial barrier integrity can improve survival (9). For example, one study was conducted with transgenic mice engineered to overexpress IκBα in endothelial cells alone (10). Overexpression of IκBα blocks the activation of NF-κB, which, when allowed to activate, translocates to the nucleus and leads to the release of proinflammatory cytokines and chemokines. When these mice were subjected to *Escherichia coli* sepsis, selective blockade of endothelial NF-κB activation via overexpression of IκBα had no effect on the appearance of systemic cytokines and chemokines, but it prevented the development of endothelial dysfunction and multiorgan failure and improved survival (10). This and other studies suggest that treatments targeting the endothelial response to sepsis might improve survival. The same might be true for Ebola virus disease.

TREATING ENDOTHELIAL DYSFUNCTION WITH STATINS AND ARBs

In vitro studies have shown that statins (11, 12) and angiotensin receptor blockers (ARBs) (13) preserve or restore endothelial barrier integrity. In older adults hospitalized with community-acquired pneumonia (a disease also characterized by endothelial dysfunction), an observational study suggested that inpatient treatment with statins and ARBs reduced 30-day all-cause mortality by 32% and 53%, respectively (14). (For most of these patients, outpatient treatment was continued after hospital admission.) However, in patients with sepsis-related acute respiratory distress syndrome requiring intensive-care unit (ICU) admission and mechanical ventilation, randomized controlled trials of statin treatment have shown no improvement in survival (15). In these patients, statin treatment was probably "too little, too late." To be effective, statins probably have to be started earlier, as suggested by the findings of a randomized controlled trial of 100 patients hospitalized with early sepsis (16). At the time of enrollment, none of the patients had evidence of organ failure and all had been statin naive for at least 2 weeks. As soon as they were hospitalized, they were treated with either atorvastatin (40 mg/day) or a placebo. The trial showed that atorvastatin reduced the occurrence of multiorgan failure by 83%, a result that was likely due to stabilization of endothelial function.

Cardiologists have known for more than a decade that when statins and ARBs are given in combination to patients with cardiovascular disease, they have additive or synergistic activities in counteracting endothelial dysfunction (17, 18). Both drugs can be

Published 23 June 2015

Citation Fedson DS, Jacobson JR, Rordam OM, Opal SM. 2015. Treating the host response to Ebola virus disease with generic statins and angiotensin receptor blockers. mBio 6(3):e00716-15. doi:10.1128/mBio.00716-15.

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administered orally once a day, and they have been shown to be safe when given to thousands of patients with acute critical illness. A full discussion of the mechanisms by which statins and ARBs preserve or restore endothelial barrier integrity is beyond the scope of this article. Nonetheless, the studies cited above suggest that the increased vascular permeability and the fluid and electrolyte abnormalities seen in Ebola patients might improve after treatment with these agents (19). Because they have direct effects on the response of endothelial cells to Ebola virus infection, they might improve survival.

CONCERNS ABOUT USING STATINS AND ARBs TO TREAT EBOLA PATIENTS

Most Ebola scientists seek to develop new treatments for Ebola virus disease that directly target the virus (1). They first test potential treatments in animal models and then evaluate promising agents in clinical trials. They are hesitant about treatments that target the host response because these treatments are based on extrapolations from findings obtained from patients with other conditions (20). They are uncertain about the safety of using agents that they believe might increase virus replication. They worry about disillusionment if treatment is found to be ineffective.

The results of the first clinical study of an antiviral treatment for Ebola virus disease were recently reported. A proof-of-concept phase 2 study of favipiravir was conducted in two Ebola treatment units in Guinea (21). Favipiravir is a nucleoside polymerase inhibitor that *in vitro* and animal studies have shown to have antiviral activity against Ebola viruses. In 69 PCR-positive adults and adolescents of ≥14 years of age, a loading dose of favipiravir (6,000 mg orally) was given in divided doses on day 1, and then 1,200 mg was given twice a day for the next 9 days. Ebola virus loads were determined by cycle threshold (C_T) values, with C_T values of <20 and ≥20 indicating high and low virus loads, respectively. Mortality rates after 14 days in consecutively treated patients were compared with those in untreated patients seen in the two units during the previous 3 months. Among favipiravir-treated patients with low virus loads, mortality was 15%, compared with 30% in historical controls. However, among treated patients and historical controls with high virus loads (approximately 40% of all treated patients), mortality rates in both groups were 85%. Although this study is not definitive, it suggests that antiviral treatment of Ebola patients might yield only modest improvements (<20%) in overall survival.

There are no data on the efficacy of combination treatment with statins and ARBs in animal models of Ebola virus disease, including nonhuman primates. Although statin effects on Ebola virus replication are unknown, statins have been shown to reduce the replication of at least five other RNA viruses (D. S. Fedson, unpublished observations); there are no data on the effect of ARBs on the replication of any virus. Moreover, these agents are produced as inexpensive generics in developing countries and are available in West Africa (19). If given in combination, a 10-day course of treatment for an individual Ebola patient would cost only a few dollars. There is no guarantee that such treatment would convincingly reduce Ebola mortality or forestall complications in those given preventive treatment, and failure to show efficacy would be disappointing. However, given their promise and known safety, it is reasonable to think that they might improve survival in Ebola patients.

It must be emphasized that treating the host response would not prevent or cure Ebola virus infection itself, but it might allow individual patients to survive long enough to develop an immune response that eliminates the virus. These agents could be used in combination with antivirals if they are available.

TREATING EBOLA PATIENTS IN SIERRA LEONE WITH ATORVASTATIN AND IRBESARTAN

In September 2014, one of the authors of this report (O.M.R.) facilitated the delivery of a supply of atorvastatin and irbesartan and arranged to have the drugs delivered to officials in Sierra Leone. In an arrangement negotiated with several governmental ministers and staff of the Office of National Security, it was agreed that this agency would conduct initial trials in police and military hospitals in Freetown, Sierra Leone. The drugs were not to be used without the approval of an agency such as the Pharmacy Board of Sierra Leone. The agreement did not stipulate that signed informed consent be obtained from each patient because it was assumed that physicians and the government would be acting in the best interests of their patients. Instructions that accompanied the donation stipulated that records of treatment should be kept and reviewed on a continuous basis to determine whether treatment was safe or might increase mortality rates. It also stipulated that all results were to be made public, regardless of outcome. In addition, two of the coauthors (D.S.F. and S.M.O.) wrote detailed letters to the Pharmacy Board in November outlining the rationale for treatment and providing guidance on the use of the drugs.

The circumstances for testing these drugs were not ideal; for example, there was no financial or logistical support for proper clinical trials. Nonetheless, local physicians were able to treat consecutively approximately 100 patients with laboratory-confirmed Ebola virus disease at the 34 Military Hospital in Freetown, the Port Loko Government Hospital, the Hastings Ebola Treatment Centre, and other sites in Sierra Leone. Patients were given atorvastatin (40 mg/day) and irbesartan (150 mg/day). Reports indicate that rapid clinical improvement was seen in almost all patients, and only two who were inadequately treated are known to have died (O.M.R., unpublished observations). One was critically ill when first seen and died soon thereafter. The other initially responded to 3 days of combination treatment, but when treatment was stopped and he was given an antiviral agent, he relapsed and died.

Unfortunately, supervising physicians and health officials in Sierra Leone have not released reports of the treatment results, although they exchanged letters and memoranda describing their experience, with one letter noting "remarkable improvement" on treatment (O.M.R., unpublished observation). It will be up to others to rigorously review and validate these findings.

A recent article by Ansumana et al. reported on 581 patients at the Hastings Ebola Treatment Centre (22). All patients were treated with intravenous fluids and oral rehydration solution. The case fatality rate was 47.7% during the period from 20 September 2014 to 13 October 2014, but it declined to 23.4% during the period from 5 November 2014 to 7 December 2014. The authors could not explain this 51% decrease in mortality. Interestingly, reports from 34 Military Hospital and the Port Loko Government Hospital in November suggested that atorvastatin and irbesartan treatment was associated with improved survival, and some patients at the Hastings Center were also given the same treatment during November (O.M.R., unpublished observation). An-

sumana et al. did not acknowledge this in their report (22). Perhaps atorvastatin and irbesartan treatment of some of these patients helps explain the decrease in the Ebola case fatality rate observed at the Hastings Center.

WHAT TO DO NEXT

Given the highly encouraging but poorly documented results of atorvastatin and irbesartan treatment in Sierra Leone, it is important to decide what should be done next. At least four things should be considered.

Undertake research on the host response to Ebola virus infection and its treatment. Current international programs for improving the care of Ebola patients are focused on the development and testing of experimental treatments that target the Ebola virus (1). These programs are generously supported by government, foundation, and corporate grants and contracts. In the United States alone, for the years 2003 to 2013, NIAID-sponsored research and development for medical countermeasures targeting Ebola virus disease totaled $333 million (23). For 2015, Congress appropriated an additional $238 million for NIAID-sponsored research and development for Ebola countermeasures. An additional $870 million was appropriated for other agencies (FDA, DOD, BARDA), for a total of $1.1 billion. In contrast, studies of treatments that target the host response to Ebola virus disease have received no such support.

This imbalance in Ebola research and development should change. Funding agencies should redirect some of their resources to studies of the host response to Ebola virus disease. This work should involve scientists outside the Ebola community, especially those who understand endothelial cell biology and how it is affected in other diseases, such as sepsis, pneumonia, and influenza. They should determine whether inexpensive generic drugs that modify endothelial cell function might be used to treat Ebola patients.

Perform clinical studies in West Africa. Health care workers in West Africa should undertake pragmatic clinical trials to test combination treatment with statins and ARBs in Ebola patients and their contacts. The candidates who should be considered for treatment with statins and angiotensin receptor blockers are Ebola patients cared for in hospitals and other treatment units that are staffed by trained health care workers, Ebola patients treated at home, health care workers (to prevent severe illness in those who are at high risk and might become infected while caring for Ebola patients), family caregivers and other close contacts, and community surveillance and burial workers. The primary goal of treatment is to reduce patient mortality. Secondary goals are to reduce requirements for fluid and electrolyte replacement and prevent severe disease in health care workers and other contacts who become infected. Treating all patients consecutively would be the most straightforward approach, and results could be compared with those seen in historical controls. Clinical oncologists often use the same approach when they evaluate new treatments, and it can be highly efficient. For example, if the goal is to achieve a statistically significant (95% confidence interval) reduction in case fatality rates from 50% to 25%, only 52 patients would have to be treated. One problem with this method is uncertainty about mortality rates in historical controls in settings where better supportive care has already improved survival. This concern has already led to uncertainty about the results of the favipiravir study in Guinea (21). If clinical record keeping in the centers in Sierra Leone where Ebola patients were treated had been adequate, a matched-set case-control study might be used to retrospectively evaluate the effectiveness of atorvastatin and irbesartan treatment.

A randomized controlled trial might also be undertaken, although with 1:1 randomization, a statistically significant reduction in mortality from 50% to 25% would require 210 patients, and only half would receive active treatment. Given the known high mortality rate of untreated patients, investigators might instead choose an adaptive trial design. This would minimize the number of untreated placebo subjects and allow different treatment regimens to be tested simultaneously for efficacy and safety.

Consider the implications of successful treatment of the host response for clinical trials of other interventions that target the Ebola virus. If convincing evidence that statin and ARB treatment reduces Ebola mortality is forthcoming, this might have major implications for clinical trials of all interventions that target the Ebola virus. Treating the host response with these agents would become a new standard of care in clinical trials; both control and intervention subjects would have to be given statins and ARBs. This would necessarily increase sample size requirements and might make it difficult to conduct a successful trial.

Recognize the implications of treating the host response for other diseases. If combination treatment with statins and ARBs is convincingly shown to reduce Ebola mortality, it will suggest that these agents might be used in the syndromic treatment of other forms of acute severe illness, much like oral rehydration solution is used to treat the host response to severe diarrheal illness, regardless of cause (24). The combination of statins and ARBs might eventually be used to treat other filovirus infections. These agents might find a place in treating dengue hemorrhagic fever, hantavirus infections, and severe acute respiratory syndrome/Middle East respiratory syndrome coronavirus infections. Observational studies have already suggested that statins and ARBs may reduce mortality in patients with community-acquired pneumonia (14) and that statins may reduce mortality in patients with influenza (24). Combination treatment might be especially useful for a global response to an avian influenza pandemic. It might also find use in treating nonviral diseases, such as pneumococcal sepsis and severe malaria, and it might provide an effective medical countermeasure against potential agents of bioterrorism, such as those for smallpox, plague, and anthrax (24). All of these possibilities deserve study.

CONCLUSIONS

The Ebola crisis in West Africa has highlighted the contributions that new technologies are making to the identification of emerging viruses, the rapid diagnosis of disease, and the development of new vaccines and antiviral agents (25). These technologies are being used to develop several treatments that target the Ebola virus, but even if they are effective, they will be expensive and in short supply. As an alternative, inexpensive generic agents that counteract endothelial dysfunction could be used to treat Ebola patients. Reports from Sierra Leone suggest that combination treatment with atorvastatin and irbesartan reduced mortality. These agents are safe and inexpensive, and if the results of treatment can be validated, their use would transform the way Ebola virus disease is managed. These agents might also find use in the syndromic treatment of other severe infectious diseases.

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