Competing Interests

The author declares no competing interests.

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Can the Continuous Hemofiltration Control Ebola-induced Systemic Inflammatory Response Syndrome?

To the Editor:

The Ebola virus (EBOV) causes a serious hemorrhagic fever with mortality rates of 50 to 90%. During the clinical evolution, there is a sudden appearance of a multiple organ dysfunction syndrome, which leads to a state of multiple organ failure.[1]

The immune system is incapable of detecting the virus during the early stages of its replication. Indeed, the inflammatory response is inadequate and immunoparalysis supervenes. However, the specific immune response of survivors is capable of developing antibodies at an early stage.[1] Yet later, there is a massive activation of monocytes and macrophages and, in the final phases, destruction of endothelial cells with coagulopathy due to the interaction of the released cytokines.[1]

EBOV produces a systemic inflammatory response syndrome (SIRS) that can be defined as severe viral sepsis. The viral glycoproteins (GPs) (*N-linked high-mannose oligosaccharides*) intervene in a process in which the expression of the adhesion molecules of the endothelial glycocalyx and immune cells is inhibited, and this triggers the release of the cytokines as described above (fig. 1).

Advanced Ebola infection causes a profound acidosis: the replication of the virus is enhanced and the GPs are activated.

If severe SIRS does not develop, or if it is controlled and immunoparalysis is reversed, there may be sufficient time and capacity to generate individual immunity to the virus. This situation is comparable with severe bacterial sepsis,[2,3] and if SIRS and multiple organ dysfunction develops, death may occur due to multiple organ failure.

Hemofiltration and EBOV

We propose a strategy to remove inflammatory mediators and virus components based on convection and adsorption[3] that avoids "dialytrauma."

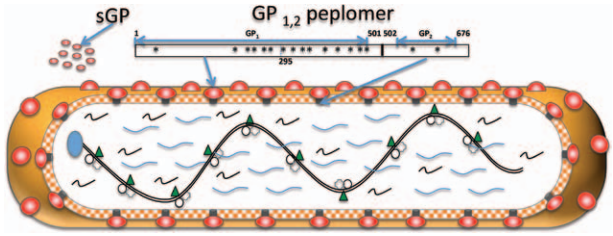

Fig. 1. Schematic illustration of the Ebola virus. The glycoprotein (GP) gene of the virus is translated in to structural GPs, $GP_{1,2}$, and mainly in a small soluble GP (sGP; 41 kDa) that shares its first 295 residues with the glycoprotein 1,2 ($GP_{1,2}$) (indicated by *dotted lines* in the $GP_{1,2}$). The maturation of the GP involves posttranslational splicing. This gives rise to glycoprotein 1 (GP1) and glycoprotein 2 (GP2) fragments that are linked by disulfide bonds. The surface GPs, $GP_{1,2}$, trigger the release of the cytokines by infected monocytes. sGP is also highly glycosylated (not shown) and is secreted in big quantities as a homodimer by the infected cells and fulfills an as yet controversial role. * Potential sites for *N*-glycosylation on the $GP_{1,2}$ molecule.

The size of soluble glycoprotein is 41 kDa, which can be filtered by convection using a membrane with a pore size of 60 kDa. Viral GPs have a negative electric charge, the intensity of which depends on the number of disulfide bonds facilitating adherence to the polyethyleneimine (PEI (+)) in the AN69-ST heparin-coated hemofiltration membrane. $GP_{1,2}$ may also show electrical affinity for the PEI (+).

The virus would be eliminated if the virus-free fraction was large, and because the virus has a size of 267 kDa, the pores of the membrane should be large (*plasmafilter*). To control albumin loss, a slow dialysis method would be used, which would mean a reduction of convective capacity against inflammatory mediators. Another possibility is a hemoperfusion system with the adsorption capacity to eliminate GPs rich in mannose sugars. In this way, we would eliminate the plasma viral load, to be able to continue with the convective treatment.

The AN69-ST heparin-coated membrane has the ability to adsorb negatively or positively charged molecules (endotoxins or inflammatory mediators), owing to its layered composition (sulfonate groups (–) and PEI (+)).[3]

Such hemofiltration is an approach sometimes used in serious sepsis SIRS of infectious. The indication is immunomodulatory, and in the case of Ebola, the disposal bags could be sterilized by sodium hypochlorite.

Possible Application

Possible application includes EBOV infection and signs of instability or organ dysfunction. The duration of the therapy might be based on the time survivors have taken to generate specific immunity.

Hemofiltration Proposal

- Technique: continuous venous hemodiafiltration.
- Catheter: 13.5- to 14-French × 24-cm femoral vein catheter.

- Membrane: the AN69-ST heparin-coated membrane with programmed replacement every 6 h. Thereafter, replacements can be scheduled further apart, depending on the state of the patient. If there is no improvement in 24 to 36 h, a hemoperfusion system should be added.
- Convection: 40 to 45 ml kg^{-1} h^{-1}. Initial balance zero.
- Replacement solution with a bicarbonate buffer, which reverses acidosis.
- Heparinization: not initially.
- Hemodynamic monitoring: when there is a negative fluid balance, the systolic volume index should be continuously monitored.
- Adaptation of the therapy to the state of the patient.

Conclusions

1. EBOV infection produces severe viral sepsis in patients, who die as a result of multiple organ dysfunction syndrome.
2. The immunoparalysis produced by SIRS prevents the generation of a specific immune response; this does not develop in patients who have survived.
3. Controlling SIRS by removing the inflammatory mediators can reduce its severity and stimulate the generation of an appropriate immune response.

Competing Interests

The authors declare no competing interests.

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