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Immunomodulatory adjunctive treatment options for Ebola virus disease patients

Accepted: 6 March 2015
Published online: 2 April 2015
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Dear Editor,
With interest, we read the recent article by Yazdanpanah et al. [1] describing that currently the treatment of Ebola virus disease consists mainly of supportive care. Additionally, experimental therapies focus completely on antiviral therapy. In the absence of safety and efficacy data in humans, there is controversy surrounding the compassionate use of these compounds [2]. To the best of our knowledge, no therapies aimed at influencing the host response appear to be considered for EVD patients.

In our view, infection with the Ebola virus shows signs indicative of macrophage activation syndrome, including fever, cytopenia (thrombocytopenia), low fibrinogen levels, low NK cells and markedly increased ferritin levels. A recent study correlated inflammatory biomarkers with clinical outcome, and found that death was associated with elevated concentrations of cytokines, elevated d-dimer levels, and elevated thrombomodulin and ferritin concentrations, being associated with hemorrhage and death [3].

Macrophage activation syndrome (MAS) is a potentially fatal clinical

syndrome caused by an excessive activation and proliferation of macrophages and T lymphocytes. The resultant exaggerated, but ineffective, inflammatory reaction may complicate the course of different conditions, including viral and bacterial infectious diseases.

As one of the features of MAS is its persistence following treatment of the underlying condition, EVD patients may benefit from a pathophysiologically-targeted approach. In EVD patients, the sustained high levels of cytokines likely account for the observed pancytopenia, hypertriglyceridemia and capillary leakage, and correlate with impaired clinical outcome [4]. Hyperferritinemia levels in EVD patients of approximately 10,000 µg/L in non-survivors and 2500 µg/L in survivors are observed. Ferritin levels this high have a sensitivity of 90 % and specificity of 96 % to diagnose MAS [5].

Based on these observations, the treatment of MAS with immunomodulatory compounds aimed to down-regulate the cytokine storm might benefit EVD patients. Non-specific interventions, e.g. corticosteroids, have been proposed, but also a more specific therapy; for example, with anakinra to inhibit IL-1-induced hyperinflammation is an option. Of interest, in patients with sepsis suffering from MAS, anakinra also improved mortality (Shakoory B SCCM 2014 poster presentation #1105). In EVD patients fulfilling the criteria for MAS, compassionate use of known compounds with remarkable effectiveness and an excellent safety record is, in our view, warranted.

Diagnostic criteria for macrophage activation syndrome (deemed present when five out of eight criteria fulfilled):

Clinical: fever; spleen enlargement

Laboratory: cytopenia (≥ 2 of the 3 lineages); hypertriglyceridemia; hyperferritinemia; low/absent natural killer cell activity; increased soluble CD-25 levels

Histological: hemophagocytosis

Conflicts of interest The authors declare that they have no conflicts of interest.

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