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LETTER TO THE EDITOR

When should antiviral drugs be used for the patient with an Ebola virus infection?

Infection with the Ebola virus (EBOV) causes a severe hemorrhagic fever syndrome with a case-fatality rate of up to 90%. Kant recently proposed a research program entitled "Pharmacophore modeling, database mining and biological evaluation to identify novel structurally diverse compounds as potential anti-Ebola drugs".[1] However, the optimal timing of medication with these antiviral drugs remains unclear.

Wong et al. recently reported the cases of six physicians and nurses with occupational exposure to Ebola virus in West Africa who received the antiviral agent rVSV-ZEBOV (rVSV-vectored vaccine expressing Ebola surface glycoprotein) or TKM-100802 (a lipid-bound small interfering RNA) for post-exposure prophylaxis.[2] All of these patients had self-limited symptoms after treatment, but none developed Ebola virus disease, indicating the effectiveness of these antiviral drugs.[2]

However, there are also some controversial reports. Oral favipiravir therapy showed a small benefit in patients with medium to high viremia (RT-PCR cycle threshold value <20), but was not effective in those with very high viremia .[3] An interim analysis of a trial of rVSV-ZEBOV in Guinea indicated that in the immediate vaccination group, there were no cases of Ebola virus disease with symptom onset at least 10 days after randomization, whereas in the delayed vaccination group (21 days later) there were 16 cases of Ebola virus disease from seven clusters.[4] Moreover, there are only two case reports for the drug TKM-100802. It is still unclear what role the TKM-100802 had in the recovery of these patients.[5]

Why were these anti-EBOV agents sometimes ineffective? A previous study showed that viral RNA copy levels in patients who died averaged 2 $\log_{10}$ higher than those in patients who survived.[6] Furthermore, this extraordinarily high viral load is associated with an aberrant innate immunity characterized by a 'cytokine storm' (e.g., high levels of interleukin 6), which leads to a massive loss (cell death) of CD4 and CD8 lymphocytes[6,7] and a fast-developing hemorrhage (e.g., higher levels of D-dimer) during the later stage of infection, such as at the time of the first clinic visit (Figure 1).[8]

In contrast, before the onset of symptoms, the viral load is much lower in both survivors and non-survivors. For example, patients at the time of the first clinic visit have 2 $\log_{10}$ higher levels of viral RNA than those at the onset of symptoms, and 4 $\log_{10}$ higher levels than those at 7 days before the onset of symptoms (Figure 1).

For the later-stage patients, host-directed therapeutic strategies may be more effective than the anti-EBOV agents. For example, local physicians in Sierra Leone treated approximately 100 consecutive Ebola patients with atorvastatin and irbesartan, and all but two inadequately treated patients survived, although these data need to be reviewed and validated.[9] A hypothetical treatment protocol to treat EBOV infection with the combined use of miglustat and toremifene has also been proposed recently.[10]

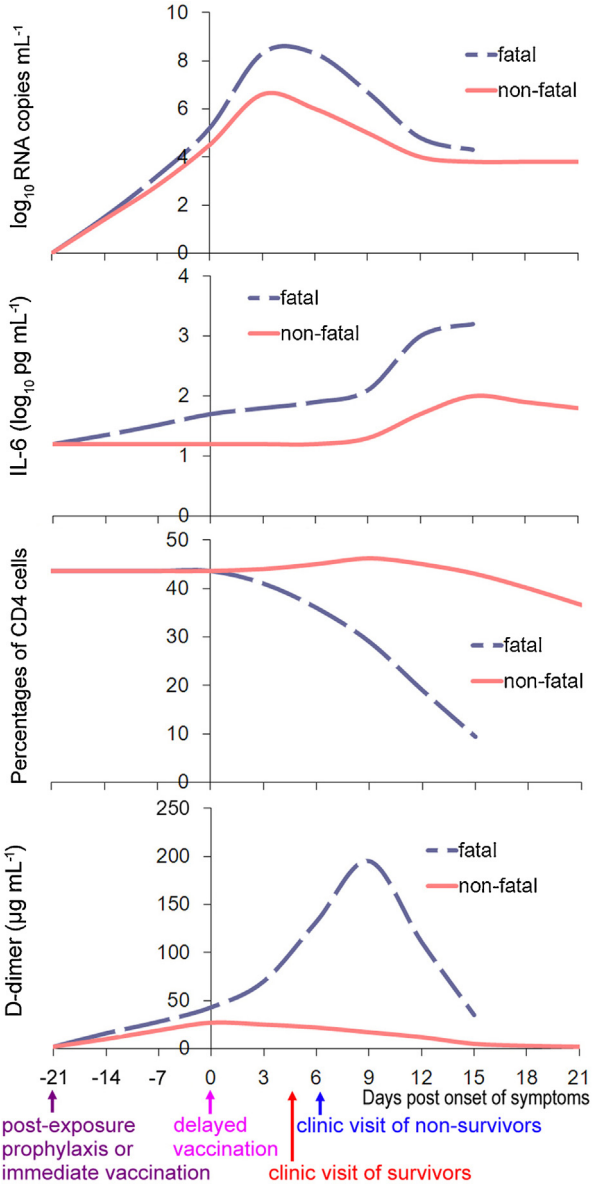

Figure 1. Summary of RNA copy, cytokine levels (represented by interleukin 6 (IL-6), lymphocyte levels (represented by CD4 cells), and hemorrhage severity (D-dimer as an indicator) in EBOV infection cases with fatal and non-fatal outcomes. Data for these four parameters were retrieved from the references.[6–8] Arrows show the times of antiviral agent application and the clinic visit.

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In summary, antiviral drugs should be used as early as possible (ideally before the onset of symptoms). Combinations of antiviral treatments and host-directed therapeutic strategies may be helpful for the late-stage patients.

Conflict of interest: We declare that we have no conflicts of interest.

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