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Biomarkers of Ebola Viral Disease

Abstract

Ebola virus (EBOV) is a non-segmented negative stranded-RNA virus of the filovirus genus made of four subtypes. EBOV was first isolated in 1976 in Zaire, DRCs [1,2]. It is the most pathogenic for humans and non-human primates [3]. It has caused several outbreaks of Ebola haemorrhagic fever with the most recent occurring in West Africa [4]. EBOV disease (EVD) is characterized by onset of non-specific symptoms such as fever, asthenia, abdominal pain, myalgia, diarrhea, arthralgia, and vomiting. This usually occurs 4-7 days after exposure to infected biological fluids such as blood. Hemorrhagic signs including melaena, epistaxis, gingivorrhagia, petechiae, conjunctivitis, and spontaneous bleeding occurs in some patients, most of who die 5-9 days after the clinical onset.

Case fatality ration is between 30% and 90% [5,6]. As a result of the efforts by many investigators, potential vaccines and therapeutics have been developed for EVD but till date no commercial product have been developed and are unlikely to do so in the near future due to the cost involved in developing novel products for human use and challenge of conducting clinical trials during an outbreak in developing countries who lack the necessary healthcare infrastructure. The most cost-effective and timely method to manage future outbreaks is to identify an already approved drug that might be used in combating disease caused by EBOV and other emerging pathogens [7,8] . In order to identify whether currently licensed drugs might be useful, we need to know about the pathophysiology of the disease. Analysis of biomarkers of EVD will be a useful for purpose.

Keywords: Ebola virus; Disease; EVD; EBOV disease; EBOV infection

Mini Review

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Abbreviations: EBOV: Ebola Virus; EVD: EBOV Disease; POC: Point of Care; ROC: Receiver Operator Characteristics; NRI: Net Reclassification; GP: Glycoprotein

Introduction

What are Biomarkers?

Biomarkers have been defined by Hulk et al as "cellular, biochemical or molecular alterations that are measureable in biological media such as human tissue, cells or fluids" [9]. In recent times, this definition has been expanded to include biological characteristics that can be measured objectively and evaluated as an indicator of the normal biological process, pathogenic process or pharmacological response to therapeutic intervention. Biomarkers are becoming increasingly important tool in all areas of medical science. Potential application of biomarkers includes monitoring therapy response, predicting outcome and measuring pathogenesis. An ideal biomarker should distinguish between various stages of infectious diseases, inform further diagnostic test, improve time to treatment and provide information about prognosis.

There are 2 main types of biomarkers: biomarkers of exposure, used in risk prediction and biomarker of disease, used in screening, diagnosis and monitoring of disease progression. In recent times, advances in genomics and proteomics technology has led to identification of numerous transcript and proteins associated with various viral infections and our understanding of immune response has led to many proposal for viral infection. Majority of these biomarkers are yet to be evaluated as diagnostic markers. One issue that needs to be cleared is whether a proposed biomarker in viral hemorrhagic fever such EBOV should be a single biomarker or combination of biomarkers. Many of the markers that have been investigated are costly and time-consuming to measure. Studies of panel of biomarkers have yielded encouraging results but none of them have shown any potential to be measured as affordable point of care (POC) test.

The performance of biomarkers is usually assessed using receiver operator characteristics (ROC) curves. The ROC curve evaluate the discrimination of a test or combination of tests but maybe insensitive to the addition of new biomarkers especially if good biomarkers is already included in the model. Net reclassification (NRI) quantifies improvement in the model as a result of adding one or more biomarkers. This approach has been used in acute lung injury and cardiovascular disease to improve the accuracy of risk prediction [10-13].

What do we have?

Changes in the clinical and serological parameters of an infected individual can be used as basis for diagnosis of EBOV infection. Below is an analysis of some of these measurable cellular alterations which has been described in EBOV infection. The current data on EBOV biomarkers is limited. In two separate studies, investigators used ELISAs or multiplex assay, of serum and plasma samples as well as RT-PCR from PBMC RNA in order to determine biomarkers in EBOV-infected individuals from 6 different outbreaks. They found that there were increased levels

of IL-1β, IL1-RA,IL-2,IL-6, IL-8, IL-10, MIP-1α, MIP-1β,MCP-1, MCSF,MIF, IP-10, GRO-α, eotaxin, neopterin, STNF-R1, TNF-α, sFasL, IFN-α, IFN-γ and most significantly, absence of IFNα2 [14-16].

These shows that excessive immune activation (so-called cytokine storm) is associated with detrimental effect in infected individuals. But the result is not specific as we cannot determine the specific role of each cytokine in the pathogenesis of EVD. Studies have shown that cytokine response is not detrimental per se. In studies of individuals with asymptomatic EBOV infection, it was shown that pro-inflammatory cytokine level weigh higher than those seen in symptomatic individuals but only in asymptomatic samples that were collected weeks after viral exposure [16].

Further studies of PMBC RNA of the same asymptomatic patients, it was shown that biomarkers of T-cell activation such as IL-2, IL-4, CD-28, CD-40L, and CTL-4 were all upregulated immediately after initial pro-inflammatory cytokine storm. Further analysis using RNA biomarkers of apoptosis and T cell activation, including perforin, Fas, FasL, and IFN-γ showed evidence of reduction in T-cell population which occurred at the same time as antibody developed in the patients.

This was consistent with an appropriate adaptive response [17]. Platelet change is a common phenomenon in EVD. In a letter, Wiwanitkit outlined some of the changes associated platelet profile associated with EBOV infection. Of the 20 patients hospitalized for EVD, 7 had thrombocytopenia on the day of admission which confirmed the hemorrhagic nature of the infection. Between 14 and 17 days of the disease, 3 patients had decreased platelet level on day 14 and 17. The authors concluded reduction in platelet count is usually between l2 and 3 weeks of EVD [18]. This conclusion might be biased as controlled platelets count measurement was not performed.

Biomarkers can be used as prognostic biomarkers of survival. In a study, Garamszegi et al. [19] showed that based on analysis of mRNA expression of changes between NHP survivors and non-survivors that received anticoagulant therapy and not , six genes: CLDN3, KF2, IL3, NDUFAI2, RUVBL2, and SLC38A5 were upregulated while ten other genes: CEBPE, CRHR2, FAM63A, HMP19,IL2RA, LTF, PSMA1, RCHY1, and SLC9A7 were down-regulated. In addition microRNAs, AC009283, and LOC100289371 were also down-regulated. Survivors exhibited "significant and opposing regulation of expression" when compared to non-survivors. Analysis of genes that were identified suggests that genes associated with cellular immune and inflammatory response were upregulated in non-survivors.

This is in conformity with the hypothesis that non-survivors experience acute, deregulation of cellular immune surveillance. A study by McElroy et al to identify biomarkers specific to pediatric EVD reported that pediatric patients who survived had higher levels of IL-10, IP-10, RANTES, sICAM, sVCAM, and PAI-1 than pediatric patients who died [20]. Adult patients had similar level regardless of the disease outcome. RANTES demonstrated an association with higher survival rate in children. The study also analyzed factors that control coagulation and fibrinogen (coagulopathy) and endothelial (endothelial function).

They found that in coagulopathy, PAI-1 levels were elevated in pediatric patients, in those who died, and those who had hemorrhagic manifestations. TF levels were slightly elevated also. For endothelial function, ICAM and VCAM were expressed on endothelial cells and upregulated in response to proinflammatory cytokines. At 0-10 days post-symptoms onset, pediatric patients who died had higher levels of both factors than those who survived.

Isolation of the virus is the strongest indication of infection. A study found the levels of viral RNA in PMBC higher in patients who died from the infection. Similar results was obtained when plasma and serum specimen were used. The higher viral load can be associated with inability to control the viral replication in target organs and cells of the mononuclear phagocytic system. The viral surface glycoprotein (GP) can be targeted as biomarker. A unique feature of EBOV is that following infection, virus encoded GP are detected in the blood of patients and experimentally infected animals. A study by Escudero-Perez et al showed that shed GP of EBOV is associated immune activation and increased vascular permeability [21]. GP can be used to generate monoclonal antibody that can be used in diagnosis and potential therapeutic for EBOV infection.

Conclusion

Biomarkers have many potential applications in EBOV infection. These includes risk assessment, screening, differential diagnosis, prediction of survivors and therapeutic interventions, and monitoring of disease progression. Due to the importance of a potential biomarker, it is essential that they undergo rigorous evaluation, including analytical evaluation, clinical analysis, and assessment for clinical use.

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