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Review

Ebola and its yet unproven therapeutic regimens

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Ebola is a viral disease transmitted by bats and a species of rat to human. It was discovered in Zaire and latter spread to Zambia, Congo, Sierra Leone and Nigeria. The outbreak of Ebola in some parts of African countries posed therapeutic challenges, due to lack of ideal therapeutic agent against Ebola. In view of this, molecular and cellular pathogenesis of Ebola virus, therapeutic modalities as well as immunopreventive potential of anti-ebola were reviewed. The severe pathogenicity of Ebola virus may be due to its antigenic shift, glycoprotein, polymerase 1, nucleoprotein, viral protein and surface expression protein. The possible therapeutic and vaccine against Ebola should target all the proteins present in Ebola virus. General and subpopulation affected should be monitored during the period of epidemics in order to prevent generation of a new variant. Prompt diagnosis, quarantine and multifacet treatment intervention that involve the use of analgesics, haematonics, plasma expander, blood transfusion and some anti-ebola drugs under trial could save lives.

Key words: Ebola, anti-ebola drug, genome, vaccine, Zmapp.

INTRODUCTION

Ebola virus belongs to the family filoviridae with Marburg virus (WHO, 2017). About 11,000 deaths from 28,000 cases and 50 years old of Ebola have shown that the virus has seriously replicated (de La Vega et al*.,* 2015). Reston Ebola virus found in Philippines is not pathogenic in human but case fatalities of African species in man are up to 90% without prophylaxis and treatment. It causes immune suppression, inflammatory response, coagulopathy, vasculopathy and immunopathy leading to multiple organ failure and septic shock (Feldmann and Geizbert, 2011). Ebola virus (EBOV) glycoproteins tropism has been increased for human cells and reduced for bat cells, invariably enhancing the ability of transmission among humans and contributing to wide geographic spread of some of the viral lineages (Urbanowicz et al., 2016).

MOLECULAR STRUCTURE OF THERAPEUTIC TARGET IN EBOLA VIRUS

The Zaire strain of the virus has nucleoprotein gene proximal to the 3' end of the genome. The coding region has 2217 bases and contains 739 amino acids with molecular weight of 83.3kda. The protein has a net charge of -30, divided into hydrophobic N-terminal half and hydrophilic, highly acidic c-terminal (Sanchez et al*.,*1989), suggesting that a variant of Ebola virus may be able to penetrate central nervous system because of low molecular weight and presence of heteroatoms in the

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structure (Saganuwan, 2017). Ebola virus may defy therapeutics because of its ability to edit genome. Genome editing may cause mutation via nucleases which may cause gain or loss of function affecting DNA or RNA that is relevant at clinical and preclinical level (Cox et al., 2015) of drug development against pathogenic microorganisms. Though, its protein precursor functions and virulent factors are poorly understood especially as there are various strains such as Bundibugyo, Reston, Sudan, Tai Forest, Zaire (Swetha et al., 2016) and perhaps Nigeria Ebola virus. The variation in the strains may be due to antigenic shift and drift, which may make genetic editing of the virus easier. For example, CpG motif (5' GTCGTT-3) is very prominent and the GC content is up to 2,399 positions in Zaire strain (Swetha et al., 2016). Ebola polymerase, a protein that synthesizes the viral RNA becomes difficult to move at specific locations; creating additional nucleotides resulting in new edited RNAs (ASM, 2014) which may not be recognized by an ideal anti-ebola virus, if the world had had one! This may contribute to Ebola viremia kinetics that is quadratic having 0.94 logarithm copies per ml present in higher quantity in non-survivors than in survivors day 2 from onset of symptoms (Lanini et al., 2015). Hence Ebola viral infection could be contained, despite its transmission dynamics and its therapeutic interventions have not been clearly known (Cross et al., 2018) making the disease a great concern in both affected and non-affected regions. The incubation period of Ebola is 2-21days and temperature may run over 38.5 degree centigrade with diarrhea and bleeding (WHO, 2014). Based on genetic coefficient and percentage of immunized population, duration of the epidemic can be deduced (Akwafuo et al., 2018), invariably giving room for prevention and control of Ebola infection. Polypharmacy including the use of fluid, blood, analgesic, antipyretic, inhibitory tissue factor have resulted in curing 35% of monkeys (Kondratowicz and Maury, 2012).

THE ANTI-EBOLA DRUGS ON TRIAL

Ebola drugs have been in the process of development and validation using experimental process, when the sudden resurgence of Ebola occurred in 2011. Although there was hope for survival when the drug in the process of development and validation proved successful in 2011 outbreak of Ebola, prioritizing access of some certain experimental drugs to certain populations or countries at risk of specific, highly contagious, transmissible diseases (Rid and Emmanuel, 2014). TKM-130803 (0.3 mg/kg i.v.) did not improve the survival of patients with Ebola viral disease. The probability for survival of the disease for 16 days is 0.27 (Dunning et al., 2016). Anti-Ebola virus under trial is favipiravir (T-705) which inhibits RNA polymerase that prevents viral replication active against influenza virus given orally. Convalescent plasma from live Ebola patient stimulates polyclonal antibodies with unconfirmed efficacy. ZMapp, a cocktail of monoclonal antibody-based drugs with 100%efficacy against Kiwit strain of Ebola virus is administered parenterally. Brain cidofovir interferes with DNA replication, though tested in guinea pigs, monkey and mice with uncertain results. Hence, combination of the above drugs (polypharmacy) may prove effective against Ebola (Hagne et al.,2015). Because of the menace caused by Ebola virus, WHO has recommended proposals for providing as yet unproven therapy under emergency (Hampton, 2014). Clomiphene, toremiphene and U18666A (a cationic amphiphilic) that induce accumulation of cholesterol in endosomes are given intraperitoneally. TKM-Ebola, AV1-7537and BCX443 inhibit RNA, VP24 protein and RNA polymerase activity respectively, whereas Fla1-103 caused delayed cytokine when given intraperitoneally (Haque et al., 2 015). But rIFNB1agiven subcutaneously 30 µg for 10 days reduced oral load. However, there is need for adequate information of toxic potentials of anti-ebola drugs under trial before application to avoid high mortality rate of Ebola in pregnant women and neonates (Hayden et al., 2017). The outbreak of 2011-2016 period has a great landmark for beginning of development of therapeutic agents against Ebola. BCX 430, GS-5734, and amodiaquine inhibit polymerase and interfere with ion transport, respectively. Chloroquine, hydroxychloroquine, aminoquiline-13, amiodarone, azithromycin, sertraline, bepridil, lectin, rhAPC, rNAPc2, AVI 6002 and AVI-7537 have been investigated in laboratory withoutdesired efficacy and safety (Bixler et al., 2017). Hence development of vaccine against the haemorrhagic fever could also be tried. Some medicinal plants such as *Abrus precatorius* have immunotherapeutic and haematonic potential (Saganuwan and Onyeyili, 2012; Saganuwan et al., 2014) and could be used in the treatment of Ebola.

MOLECULAR STRUCTURE OF EBOLA VIRUS FOR VACCINE DEVELOPMENT

The pathogenesis of hemorrhagic fever is vital for development of effective vaccine and drug against prevention, elimination and treatment of the disease, respectively (Michalek et al., 2015). Since Ebola virus genome encodes seven genes that produce nucleoprotein, viral protein (VP 35, V40) glycoprotein and polymerase 1 (Kondratowicz and Maury, 2012), the mechanism of anti-Ebola may be via one or more of these proteins. Hence the proteins could also be used for vaccine development. The Complex RNA- free to RNA bound oligomer and helical form of Zaire ebola virus nucleoprotein as revealed by nuclear- atomic resolution cryoelection microscopy (NARCEM) (Sugita et al., 2018) may indicate high virulence of the virus as a major determinant of the burden of viral infections in animals (Geoghegan and Holmes, 2018). This is evidenced by

identification of Ebola virus glycoprotein, as a target for antibodies leading to antigen-binding fragment that may serve as a rational basis for design of crossprotective vaccines and therapeutics against the disease (Janus et al. 2018). Genomics has characterized new ebola virus with glycoprotein similar to Bumbali virus that further buttresses implication of bat as a reservoir host (Goldstein et al., 2015). This further indicates that phylodynamism of Ebola virus could interfere with its therapeutic intervention strategies against prevention, elimination and treatment (Dellicomr et al., 2018). Therefore, elimination of the reservoir host may be the first step that should be considered for global eradication ofebola virus and hemorrhagic fever at large. But mistrust in outbreak zone could hamper post exposure treatments (Maxmen, 2018a, b, c). Hence genome sequencing has informed the health professionals and public about the risk-benefit-assessment of Ebola (Van Puyvelde and Argimon, 2018), leading to a clinical trial of protein for testing the three ebolamedicines that were used in the latest African outbreak (Maxmen, 2018b), which WHO said was not an international emergency (Butler, 2018). So what do we call outbreak? when there is need to rise to the Ebola challenges, even though there has been a better preparedness to meet the unprecedented challenge than ever before – especially in the war zone were vaccines should be effectively dispensed (Maxmen, 2018c). Zaire Ebola virus acts on GP and L genes. The GP gene was incriminated in the 2014 outbreak. The putative sites identified inthe GP are located in the mucin-like domain of the protein indicating the likely role in the immune system. Epitope binding sites could be a good target for vaccine development. These sites could be identified by glycosylation especially for therapeutic strategies (Jun et al., 2015). Glycoprotein and polymerase genes show the most sequence variation (Bell et al., 2015).

PREVENTIVE MEASURE AGAINST EBOLA

ZEBOV variants are reproduced in human to human during epidemic (Liu et al., 2015).This may connote the possibility of emerging more new variants. Therefore, there should be adequate surveillance and quarantine during any outbreak. We could only hope that the responses to the recent outbreaks were commensurate to the Ebola burdens (Lamplard and Valiquette, 2014). Clinicians should quarantine the persons on travel for few days for proper diagnosis and prevention of spread of the disease (Kadanali and Karagoz, 2015). Therefore, relevant laboratories should be aware of emergency authorized tests for prompt diagnosis and management (Bard, 2015). Ebola virus GP alters target cells, which are macrophages and endothelial cells disrupting their inflammatory function. Cell surface expression protein and immune recognition, activation molecules, cytolitic-T-cell function were all disrupted (Sullivan et al., 2003). Hence it is a sole responsibility of health care agencies to ensure safe efficient management, tracking and reporting (Broadhurst et al., 2016). Trained staff should be responsible for sample taking, diagnosis and management of the disease (Formenty, 2018).

CONCLUSION

Discovery of pathogenic molecular sites in Ebola virus could serve as source for definitive diagnosis, control, prevention and treatment of Ebola disease.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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