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Marburg virus disease treatments and vaccines: recent gaps and implications

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Dear Editor,

Marburg virus disease (MVD), caused by the Marburg virus (MARV) of the *Filoviridae* family, is characterized by a significant mortality rate ranging from 23 to 90%, making it one of the deadliest viruses[1,2]. Clinically, MVD patients commonly present with fever, malaise, arthralgia, and headache[3,4]. In addition, they may exhibit severe hemorrhagic symptoms, which can eventually cause severe bleeding leading to death within days[4]. Various pharmacological candidates have been developed and tested for potential use[5]. However, no current vaccines against MARV have been approved for usage so far[6]. In this study, we aimed to summarize the recent evidence in addition to literature gaps about available treatments and vaccines against MVD.

The management of severe cases is usually done through monitoring the vital signs and health status stability of these patients. It is essential to maintain blood pressure and oxygen levels within stable parameters, in addition to correcting any blood electrolyte imbalance[3]. Moreover, since MVD can present with hemorrhagic symptoms, blood and clotting factors should be urgently replaced when needed[1,4].

Currently, experiments are being carried out to determine the most viable and safe treatments for MVD. Some of these are still being tested on nonhuman primates (NHPs) with questionable efficacies, while others reached full human trials[7]. These different potential treatments include antivirals, phosphorodiamidate morpholino oligomers (PMOs), polyclonal and monoclonal antibodies, small-interfering RNA (siRNA), tumor necrosis factor and interlukin-1 (IL-1) antagonists, and interferons[7,8].

Galidesivir, an antiviral drug, works by terminating RNA chains and inhibiting the action of viral RNA polymerase[4]. Its efficacy has been proven in six cynomolgus macaques challenged with MARV. As a result, increased survival rates and decreased viremia levels and clotting times. Nevertheless, the findings of human trials have not been published yet[8].

Favipiravir, a broad-spectrum antiviral drug, was used to treat the Ebola virus disease (EVD) in the West African outbreak[4]. Regarding MVD, promising results were achieved when IV favipiravir was administered to six cynomolgus macaques challenged with the virus, five of which survived the infection[8]. In addition, remdesivir has also been proven to be effective against both EVD and MARV in NHPs[8].

Besides antivirals, monoclonal antibodies against the viral glycoprotein have also been proven to be effective in NHPs[4]. MR 191-N is a monoclonal antibody that was used once in a lab exposure, but no results have been disclosed yet. ZMapp, REGN-EB3, and mAb114 have been successful in treating EVD and may consider as an option to treat MVD[8]. Moreover, the results of interferon beta showed an increase in survival time without a difference in mortality rates, suggesting that interferon beta may be useful as an adjuvant therapy only[8].

siRNA are other potential agents tested to treat MVD. NP-718m is an example of siRNAs tested in guinea pigs infected with MARV[8]. This molecule targets the viral nucleoprotein and shows broad protection against the virus[7]. No siRNAs against the filovirus family are currently being tested in humans[8]. This is mainly attributed to the inability to develop sufficient methods to deliver these molecules correctly to the target cells[8]. A tumor necrosis factor alpha and IL-1 suppressor showed protective findings in treating infected guinea pigs. Additionally, ridostin, IL-1 antagonist, rNAPc2, and prednisone were also used[7].

Lastly, antisense PMOs are one of the most promising therapies for the MARV, they act particularly on genes that have been proven to be most susceptible to antisense interference[9]. These PMOs work by inhibiting mRNA translation. This is possible due to the ability of the PMOs to bind tightly to the mRNA, which in turn stops the translation machinery from accessing the mRNA molecule. This highly stable bond also allows the drug to achieve a high inhibition level with low levels of toxicity[8].

Regarding vaccines, several clinical trials for Ebola virus (EBOV) and MARV vaccine production have been conducted (Fig. 1). However, the vaccines do not cross-protect, although numerous tests in cynomolgus macaques have shown protection against both viruses (EBOV and MARV)[8,10]. Presently, ongoing studies focus on the utilization of diverse recombinant vectors for the supply of genes that express filovirus proteins to generate protective immunity against them. Adenoviruses, vaccinia

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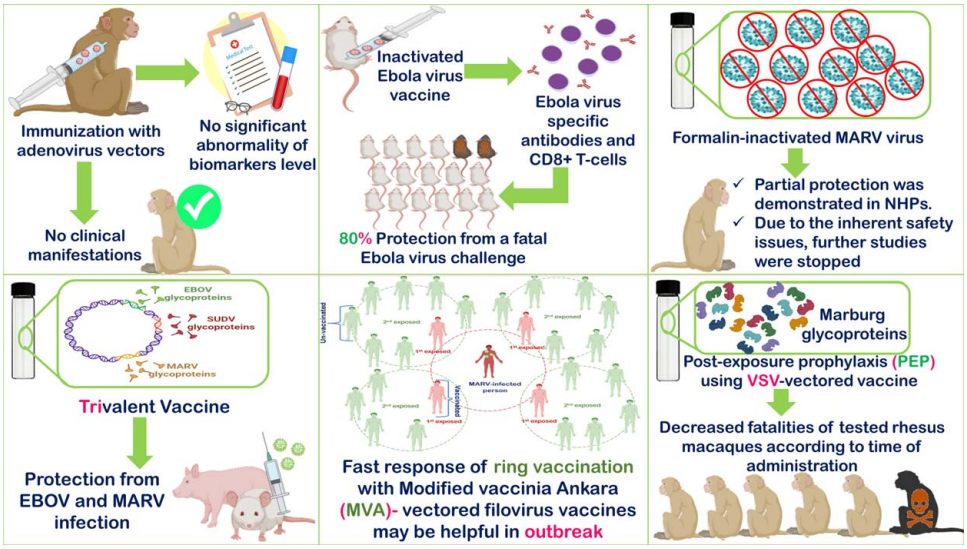

Figure 1. Marburg vaccine trials. EBOV, Ebola virus; MARV, Marburg virus; NHPs, nonhuman primates; VSV, vesicular stomatitis virus.

viruses, DNA-based vaccines, virus-like particles, human parainfluenza virus type 3, and vesicular stomatitis virus are some examples of the delivery mechanisms utilized to generate filovirus proteins for these aims[7,8].

In the early stages of MARV vaccine development, the formalin-inactivated virus was utilized, and partial protection was reported in NHPs[4]. However, attempts to further develop this method have stopped due to the inherent safety issues[4]. In rhesus macaques, post-exposure prophylaxis using a vesicular stomatitis virus-vectored vaccine that contains Marburg glycoprotein decreased fatalities in five out of five recipients when administered within 20–30 min after infection[8]. Moreover, administering the vaccine 24–48 h after infection also succeeded in protecting five out of six recipients, and even succeeded when given as late as 48 h by protecting two out of six recipients[7,8].

The modified vaccinia Ankara vector has shown better results. Two models have been created, and clinical trials for them are still in their preliminary stages[11]. It is crucial to remember that modified vaccinia Ankara-vectored filovirus vaccines may be helpful in outbreak scenarios when fast reaction ring vaccination techniques are preferred[11].

Finally, regarding DNA vaccines, it has been shown that a trivalent vaccination made up of plasmids encoding sequences from the glycoproteins of EBOV and MARV preserves mice and guinea pigs from EBOV and MARV dispute when administered intramuscularly[11].

Ethical approval

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Patient consent

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Author contribution

K.A.: the conception and design of the study; K.A., M.A.H., O.S., and A.M.A.: made the first draft; H.H., A.B.M., C.A.S., and N.N. A.: updated the manuscript; R.A.F. and A.K. reviewed the final draft. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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