Special Communication

Updates on Treatment of Ebola Virus Disease

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Abstract

Ebola viral disease is one of the major threats world wide. But the treatment option is merely supportive and symptomatic therapy. Vaccination and drug therapies are still under trial. This article throws light into the various emerging treatment options for the Ebola viral disease.

Keywords: *Ebola virus, treatment, reconvalescent plasma, drug therapy, vaccine*

Ebola viral disease is a virulent human viral hemorrhagic fever that has become a global threat due to its high fatality rates. Unfortunately, management of Ebola outbreaks is limited to palliative care and preventive measures. Supportive treatments include fluid resuscitation, correcting electrolyte imbalances, and treating secondary infections. Blood transfusion therapy, immunological therapy, drug therapies, and vaccines are all currently under development. This article discusses several approaches to treat Ebola virus (EBOV) infections that are currently being explored.

Some animal model data suggest that hyperimmune intravenous immunoglobulin preparations fractionated from reconvalescent plasma could be used as an Ebola treatment because this blood contains antibodies against EBOV (1). Treatment strategies using reconvalescent plasma are currently undergoing Phase II and III clinical trials. Comparisons of the efficacy of whole blood and plasma transfusions suggest that plasma transfusion is the preferable approach (2).

Michelow et al. proposed that recombinant human Mannose Binding Lectin (rhMBL) therapy can be used as a novel broad spectrum antiviral approach for treating Ebola patients (3). Some experimental strategies that have shown promising results in treating EBOV-challenged non-human primates (NHPs) after Ebola infection are: i) recombinant human activated protein C (rhAPC) (4); ii) recombinant nematode anticoagulant protein c2 (rNAPc2) (5); iii) small interfering RNA (siRNA) (6); iv) positively-charged phosphorodiamidatemorpholino oligomers (PMO*plus*) (7); and v) ZMAb (consisting of murine mAbs m1H3, m2G4, and m4G7) (8). Follow-up studies found that ZMAb combined with an adenovirus-based adjuvant may help provide full protection in rhesus macaques when treatment was administered up to 72 h after infection (9).

ZMapp is a humanised monoclonal antibody that targets the EBOV glycoprotein (10). This drug was first used in the 2014 West Africa Ebola virus outbreak and is currently in phase II clinical trials. To date, the safety and efficacy of ZMapp has not yet been fully demonstrated and thus the drug is not yet licensed. Drugs such as Zmapp can have several side effects, including fever, nausea, vomiting, diarrhoea, rashes, and in rare cases, life-threatening shock (11). The nucleotide analogue favipiravir and siRNA TKM 100802 are two other antiviral drugs that were approved for emergency use during EBOV outbreaks (12). These drugs are currently in phase II and III clinical trials. Favipiravir is proposed to be safe when taken orally and shows rapid distribution and uptake in cases arising during inhalational EBOV outbreaks (13). The peptide FX06 and monoclonal antibody mixture ZMab as well as several other drugs are currently being administered on a compassionate basis as the safety and efficacy of these drugs in patients is still undergoing evaluation. MIL-77 and BCX-4430 (14),which are a monoclonal antibody and adenosine analog, respectively, are in phase I clinical safety trials and currently have no planned efficacy trials until the safety data have been analysed. Interferons also have potential for treating EBOV and are undergoing phase II clinical trials. Meanwhile, trials of the nucleotide

analogue, brincidofovir, which was used as an emergency treatment in EBOV outbreaks (15), have been halted and World Health Organization (WHO) deprioritised this compound for treating Ebola infections. Some non-antiviral drugs such as chloroquine, clomiphene, and statins are also being explored for use in EBOV outbreaks (16–18), and the antimalarial drug amodiaquine is being prioritised by WHO for use in NHPs(17).

Although no licensed vaccine is currently available to prevent EBOV infections, vaccine research is ongoing in various countries and has produced several promising candidates. Initial characterisations of classical formulations of inactivated EBOV with adjuvants, such as Ribi or lipid A-containing liposomes, did not produce encouraging results (19–21). However, trials of viral-vector-based vaccines, DNA vaccines, and virus-like particles (VLPs) are currently underway. The advantage of these novel vaccine approaches over classical approaches is that they induce both innate and adaptive immune responses that result in better vaccine efficacy (22).

Recent studies suggest that a combination of humoral immune responses with sufficient activation of CD4+ and CD8+ T lymphocytes would protect against EBOV infection (23,24). A suitable protective immune response in mice (25)] and partial response in guinea pigs (26) was elicited by a DNA vaccine expressing Zaire Ebola virus glycoprotein (ZEBOV-GP). In humans, a three-plasmid DNA vaccine encoding Zaire-GP (ZEBOV-GP), Sudan-GP (SEBOV-GP), and -NP (nucleoprotein) elicited a cellular and humoral immune response after three injections of the vaccine in a phase I clinical trial (27). Moreover, chimpanzee adenovirus serotype 3 (cAd3-EBO), and recombinant vesicular stomatitis virus (rVSV–EBO) are important vaccines that may be effective in preventing the transmission of EBOV in NHPs (28,29). Phase III clinical trials are ongoing for ChAd3-ZEBOV and rVSV-ZEBOV in West African countries (30–32), and these rVSV-based EBOV vaccines may be beneficial aspost-exposure treatments. When rVSV together with ZEBOV-GP or SEBOV-GP was administered to NHPs after 30 minutes of homologous EBOV challenge, the rVSV vaccine protected 50% of ZEBOV-infected animals and 100% of SEBOV-infected animals (31,32). In phase I clinical trials, rVSV-ZEBOV showed mild-to-moderate reactogenicity, but no serious vaccine-related side effects were reported (33). Another completed phase I clinical trial showed that recombinant adenovirus serotype 5 expressing ZEBOV and SEBOV-GP was safe for use in humans (34). In another trial, EBOV virus like particle (VLP) vaccines combined with Ribi adjuvant were administered three times to NHPs and protected against homologous ZEBOV challenge (35). In addition, two vaccinations with the replication-deficient ZEBOV lacking the VP30 gene protected mice and guinea pigs from lethal ZEBOV challenge (36). Ad26-EBOV, MVA-EBOV, and recombinant protein Ebola vaccine candidates are only a few of the other EBOV vaccines that are currently in phase I clinical trials.

In conclusion, supportive and symptomatic treatment of EBOV infection is critical for managing EBOV cases, since drug therapies as well as immunological and blood transfusion treatments have not yet been licensed. WHO is committing significant resources and effort toward developing potential drugs and vaccines in order to deploy novel Ebola therapies, although research with EBOV is challenging due to its high virulence requiring biosafety level 4 laboratories with special safety equipment to protect researchers who work with the virus. A safe and effective vaccine against EBOV infection can play a critical role in preventing future Ebola outbreaks. Many studies are underway to explore the safety and efficacy of various drugs and vaccines for treating EBOV infections. Moreover, community engagement, disease surveillance, contact tracing, and good laboratory service may help control future EBOV outbreaks.

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Conflict of Interest

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References

1. Dye JM, Herbert AS, Kuehne AI, Barth JF, Muhammad MA, Zak SE. Postexposure antibody prophylaxis protects nonhuman primates from filovirus disease. *Proc Natl Acad Sci U S A*. 2012;**109(13)**:5034–5039. doi: 10.1073/pnas.1200409109.

2. Kreil TR. Treatment of Ebola virus infection with antibodies from reconvalescent donors. *Emerg Infect Dis*. 2015;**21(3)**:521–523. doi: 10.3201/eid 2103.141838.

3. Michelow IC, Lear C, Scully C, Prugar LI, Longley CB, Yantosca LM, et al. High-Dose Mannose-Binding Lectin Therapy for Ebola Virus Infection. *J Infect Dis*. 2011;**203(2)**:175–179. doi: 10.1093/infdis/jiq025.

4. Hensley LE, Stevens EL, Yan SB, Geisbert JB, Macias WL, Larsen T, et al. Recombinant human activated protein C for the postexposure treatment of Ebola hemorrhagic fever. *J Infect Dis*. 2007;**196(Suppl 2)**. S390–S399. doi: 10.1086/520598

5. Geisbert TW, Hensley LE, Jahrling PB, Larsen T, Geisbert JB, Paragas J, et al. Treatment of Ebola virus infection with a recombinant inhibitor of factor VIIa/ tissue factor: a study in rhesus monkeys. *Lancet*. 2003;**362(9400)**:1953–1958. doi: 10.1016/S0140-6736(03)15012-X.

6. Geisbert TW, Lee AC, Robbins M, Geisbert JB, Honko AN, Sood V, et al. Postexposure protection of non-human primates against a lethal Ebola virus challenge with RNA interference: a proof-of-concept study. *Lancet*. 2010;**375(9729)**:1896–1905. doi: 10.1016/ S0140-6736(10)60357-1.

7. Warren TK, Warfield KL, Wells J, Swenson DL, Donner KS, Van Tongeren SA, et al. Advanced antisense therapies for postexposure protection against lethal filovirus infections. *Nat Med*. 2010; **16(9)**:991–994 . doi: 10.1038/nm.2202.

8. Qiu X, Audet J, Wong G, Pillet S, Bello A, Cabral T, et al. Successful treatment of ebola virus-infected cynomolgus macaques with monoclonal antibodies. *Sci Transl Med*. 2012;**4(138)**:138ra181. doi: 10.1126/ scitranslmed.3003876.

9. Qiu X, Wong G, Fernando L, Audet J, Bello A, Strong J, et al. mAbs and Ad-vectored IFN-α therapy rescue Ebola-infected nonhuman primates when administered after the detection of viremia and symptoms. *Sci Transl Med*. 2013;**5(207)**:207ra143. doi: 10.1126/scitranslmed.3006605.

10. Qiu X, Wong G, Audet J, Bello A, Fernando L, Alimonti JB, et al. Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp. *Nature*. 2014;**514(7520)**:47–53. doi: 10.1038/nature13777.

11. Erika CH, Sara R. Should experimental drugs be used in the Ebola outbreak?[Internet].United States (US): Nature. 2014. Available from: http://www.nature.com/news/should-experimental-drugs-be-used-in-the-ebola-outbreak-1.15698.

12. Bouazza N, Treluyer JM, Foissac F, Mentre f, Taburet AM, Guedi J, et al. Favipiravir for children with Ebola. *Lancet*. 2015;**385(9968)**:603-604. doi: 10.1016/ S0140-6736(15)60232-X.

13. Smither SJ, Eastaugh LS, Steward JA, Nelson M, Lenk RP, Lever MS. Post-exposure efficacy of oral T-705 (Favipiravir) against inhalational Ebola virus infection in a mouse model. *Antiviral Res*. 2014;**104**:153–155. doi: 10.1016/j.antiviral.2014.01.012.

14. Warren TK, Wells J, Panchal RG, et al .Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. *Nature*. 2014;**508(7496)**:402–405. doi: 10.1038/nature 13027.

15. Florescu DF, Keck MA. Developm.ent of CMX001 (Brincidofovir) for the treatment of serious diseases or conditions caused by dsDNA viruses. *Expert Rev Anti Infect Ther*. 2014;**12(10)**:1171-1178. doi: 10.1586/14787210.2014.948847.

16. Madrid PB, Chopra S, Manger ID, Gilfillan L, Keepers TR, Shurtleff AC, et al. A systematic screen of FDA-approved drugs for inhibitors of biological threat agents. *PLoS One*. 2013;**8(4)**:e60579. doi: 10.1371/ journal. pone.0060579.

17. Gehring G, Rohrmann K, Atenchong N, Mittler E, Becker S, Dahlmann F, et al. The clinically approved drugs amiodarone, dronedarone and verapamil inhibit filovirus cell entry. *J Antimicrob Chemother*. 2014;**69(8)**:2123–2131.

18. Fedson DS. A Practical Treatment for Patients With Ebola Virus Disease. *J Infect Dis*. 2015;**211(4)**:661–662. doi: 10.1093/infdis/jiu474.

19. Geisbert TW, Pushko P, Anderson K, Smith J, Davis KJ, Jahrling PB. Evaluation in nonhuman primates of vaccines against Ebola virus. *Emerg Infect Dis*. 2002, **8(5)**:503–507.

20. Lupton HW, Lambert RD, Bumgardner DL, Moe JB, Eddy GA. Inactivated vaccine for Ebola virus efficacious in guineapig model. *Lancet*. 1980;**2(8207)**:1294–1295.

21. Rao M, Bray M, Alving CR, Jahrling P, Matyas GR. Induction of immune responses in mice and monkeys to Ebola virus after immunization with liposome-encapsulated irradiated Ebola virus: protection in mice requires CD4(+) T cells. *J Virol.* 2002;**76(18)**:9176–9185. doi: 10.1128/JVI.76.18.9176-9185.2002.

22. Wit ED, Feldmann H, Munster VJ. Tackling Ebola: new insights into prophylactic and therapeutic intervention strategies. *Genome Med.* 2011;**3(1)**:5. doi: 10.1186/gm219.

23. Warfield KL, Olinger G, Deal EM, Swenson DL, Bailey M, Negley DL, Hart MK, Bavari S: Induction of humoral and CD8+ T cell responses are required for protection against lethal Ebola virus infection. *J Immunol.* 2005;**175(2)**:1184–1191.

24. Warfield KL, Perkins JG, Swenson DL, Deal EM, Bosio CM, Aman MJ, Yokoyama WM, Young HA, Bavari S: Role of natural killer cells in innate protection against lethal ebola virus infection. *J Exp Med.* 2004;**200(2)**:169–179.

25. Vanderzanden L, Bray M, Fuller D, Roberts T, Custer D, Spik K, et al. DNA vaccines expressing either the GP or NP genes of Ebola virus protect mice from lethal challenge. *Virology.* 1998;**246(1)**:134–144. doi:10.1006/viro.1998.9176.

26. Xu L, Sanchez A, Yang Z, Zaki SR, Nabel EG, Nichol ST, Nabel GJ. Immunization for Ebola virus infection. *Nat Med.* 1998;**4(1)**:37–42.

27. Martin JE, Sullivan NJ, Enama ME, Gordon IJ, Roederer M, Koup RA, et al. A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial. *Clin Vaccine Immunol.* 2006;**13(11)**:1267–1277. doi:10.1128/CVI.00162-06.

28. Stanley DA, Honko AN, Asiedu C, Trefry JC, Lau-Kilby AW, Johnson JC, et al. Chimpanzee adenovirus vaccine generates acute and durable protective immunity against Ebolavirus challenge. *Nat Med.* 2014;**20(10)**:1126–1129. doi: 10.1038/nm.3702.

29. Geisbert TW, Geisbert JB, Leung A, Daddario-DiCaprio KM, Hensley LE, Grolla A, et al. Single-injection vaccine protects nonhuman primates against infection with Marburg virus and three species of Ebola virus. *J Virol.* 2009;**83(14)**:7296–7304. doi: 10.1128/JVI.00561-09.

30. Kanapathipillai R, Henao Restrepo AM, Fast P, Wood D, Dye C, Kieny MP, et al. Ebola vaccine -- an urgent international priority. *N Engl J Med.* 2014;**371(24)**:2249–2251.

31. Feldmann H, Jones SM, Daddario-DiCaprio KM, Geisbert JB, Stroher U, Grolla A, et al. Effective post-exposure treatment of Ebola infection. *PLoS Pathog.* 2007;**3(1)**:e2. doi: 10.1371/journal.ppat.0030002.

32. Geisbert TW, Daddario-DiCaprio KM, Williams KJ, Geisbert JB, Leung A, Feldmann F, et al. Recombinant vesicular stomatitis virus vector mediates postexposure protection against Sudan Ebola hemorrhagic fever in nonhuman primates. *J Virol.* 2008;**82(11)**:5664–5668. doi: 10.1128/JVI.00456-08.

33. Agnandji ST, Huttner A, Zinser ME, Njuguna P, Dahlke C, Fernandes JF, et al. Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe — Preliminary Report. *N Engl J Med.* 2015. doi: 10.1056/NEJMoa1502924

34. Ledgerwood JE, Costner P, Desai N, Holman L, Enama ME, Yamshchikov G, et al. A replication defective recombinant Ad5 vaccine expressing Ebola virus GP is safe and immunogenic in healthy adults. *Vaccine.* 2010;**29(2)**:304–313. doi: 10.1016/j.vaccine.2010.10.037.

35. Warfield KL, Swenson DL, Olinger GG, Kalina WV, Aman MJ, Bavari S: Ebola virus-like particle-based vaccine protects nonhuman primates against lethal Ebola virus challenge. *J Infect Dis.* 2007;**196(Suppl 2)**:S430–S437.

36. Halfmann P, Ebihara H, Marzi A, Hatta Y, Watanabe S, Suresh M, et al. Replication-deficient ebolavirus as a vaccine candidate. *J Virol* 2009;**83(8)**:3810–3815. doi: 10.1128/JVI.00074-09.