Intensive Care Med (2015) 41:115–117
DOI 10.1007/s00134-014-3529-8

Yazdan Yazdanpanah
Jose Ramon Arribas
Denis Malvy

Treatment of Ebola virus disease

Received: 8 October 2014
Accepted: 23 October 2014
Published online: 11 November 2014

Y. Yazdanpanah (✉)
Service de Maladies Infectieuses et tropicales, Hôpital Bichat Claude Bernard, Paris, France
e-mail: yazdan.yazdanpanah@bch.aphp.fr
Tel.: +33 1 40 25 78 93

Y. Yazdanpanah
Decision Sciences in Infectious Disease: Prevention, Control, and Care, IAME, UMR 1137, Inserm, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

J. R. Arribas
Infectious Diseases Unit, Internal Medicine Service, Hospital La Paz, IdiPAZ, Madrid, Spain

D. Malvy
Service des Maladies Infectieuses et Tropicales, CHU de Bordeaux, Bordeaux, France

D. Malvy
Tropical Medicine Branch, INSERM 897, Bordeaux, France

As of October 17, 2014, a total of 9,216 cases of Ebola virus disease (EVD) and 4,555 deaths had been reported from five countries in West Africa, Spain, and United States [1]. Assuming no change in the control measures for this epidemic, which seems to be the most realistic scenario for several months, it is likely that EVD will become endemic among the human population of West Africa [2]. Although the highest priority must be given to infection-control measures, the current outbreak highlights the need for vaccines and effective treatment.

Current treatment for EVD consists of supportive care. The most prominent feature of EVD in this outbreak has been progressive gastrointestinal symptoms with vomiting and diarrhea that lead to intravascular volume depletion, profound electrolyte disorders, and shock [2]. Bleeding is a late manifestation that occurs in only a minority of patients (<20 % of cases) [2]. Thus, the most important aspect of supportive care is the maintenance of intravascular volume with intravenous fluids or oral rehydration and solutions that contain electrolytes [3]. Evidence-based appropriate sepsis management and blood transfusion could also be considered. Treatment of other concomitant diseases such as malaria infection is recommended along with empiric antibiotics for enteric pathogens especially at gastrointestinal phase of illness (such as IV third generation cephalosporins). For a condition with high baseline mortality, the potential effect of supportive care is important. However, one should keep in mind that supportive care might probably not be sufficient.

Currently, there are no approved antiviral treatments for EVD. Experimental therapies are under development (Fig. 1), but there is a lack of data on the efficacy and tolerance of these treatments in humans. In a WHO consultation meeting in Geneva, up to eight treatment strategies were allowed for experimental and compassionate use. Among these, WHO only approved the use of convalescent serum and whole blood products to treat affected patients [4, 5].

Recent work has shown that immunoglobulin preparations from Zaire Ebolavirus and Marburgvirus convalescent non-human primates (NHPs) protect NHPs against lethal challenge [6]. Treatment of patients with convalescent human blood has, however, been used in limited occasions in humans with controversial outcomes. Blood products from convalescent individuals were shown to be effective in an outbreak of EVD in the Democratic Republic of the Congo when eight patients

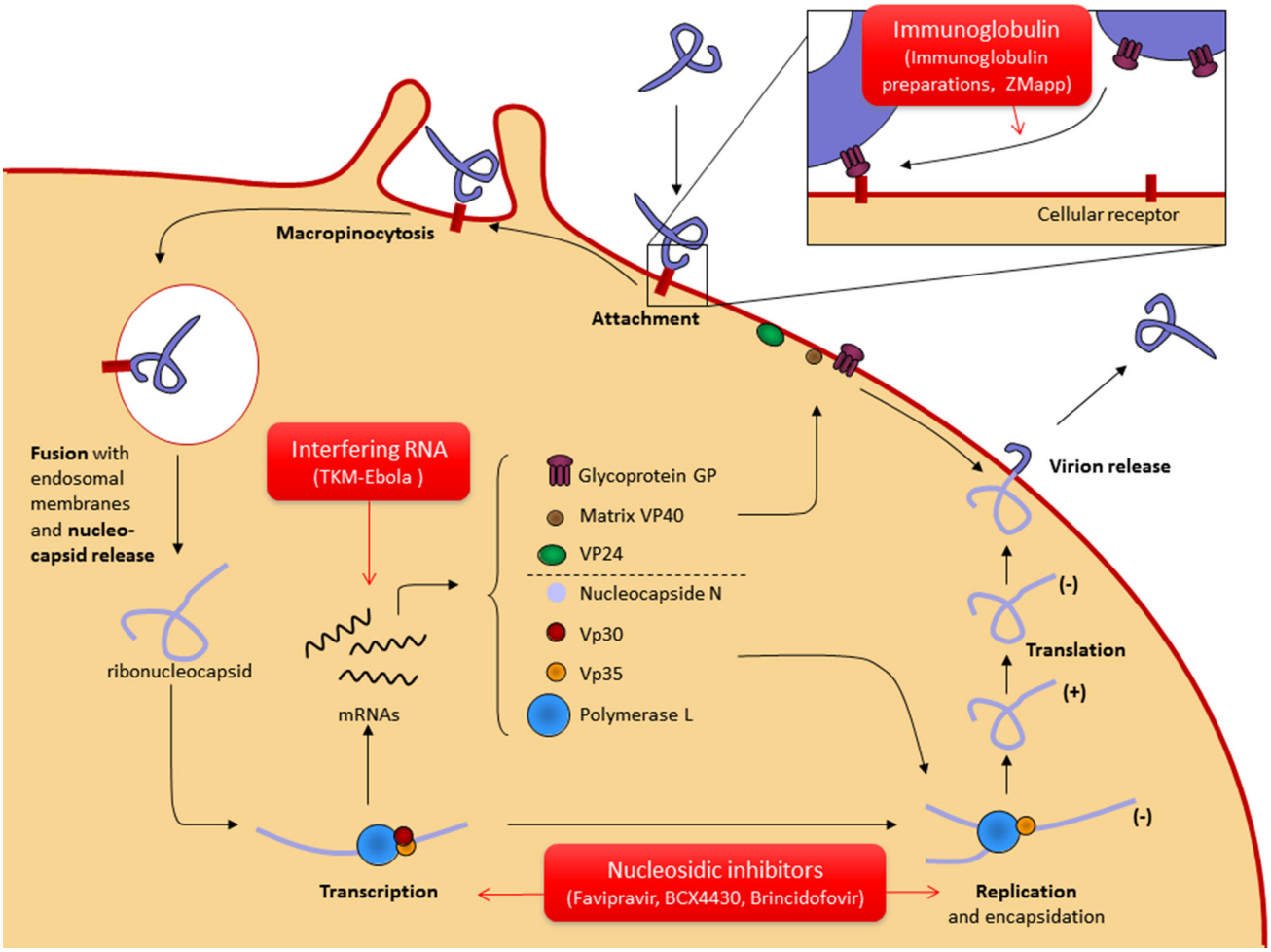

Fig. 1 Targets of experimental therapies

were given the blood of convalescent patients [7]. Just one of the patients died. But this positive outcome may had been related to the enhanced care that these patients received. Controversial outcomes in different studies may be related to differences in total and neutralizing anti-GP antibodies concentrations that need to be optimized. For the use of convalescent serum to be efficacious and safe, especially in countries where the epidemic occurs, capacity building for the collection and testing of convalescent blood or plasma from recovered Ebola patients is crucial. WHO has issued a guidance document regarding collection and use of convalescent plasma or serum as an element in filovirus outbreak response [5].

Regarding other passive immunotherapy strategies, the most promising is ZMapp that combines three humanized monoclonal antibodies. A recent trial of this product in NHPs suggests impressive efficacy at preventing lethal disease [8]. Based on these data, several health workers mostly in northern countries have received doses of ZMapp. Some of these patients may have benefited from the product, although this is based on a small number of patients. The available supply of this drug is depleted, and scaling production will take months, limiting broader access.

Among experimental antiviral treatments, there are three that are probably the most promising. First, TKM-Ebola, that uses an "interfering" RNA molecule to silence expression of two genes that the Ebola virus needs to replicate. In early studies, the drug prevented infection in all the laboratory animals given a lethal dose of Ebola virus [9]. The US Food and Drug Administration had placed a hold on TKM-Ebola after concerns about critical signs of cytokine release in patients who were given high doses of the drug, but later modified the clinical hold to a partial hold, allowing the experimental drug to be used in patients with EVD. However, if side effects related to cytokine release are confirmed, this may be of concern, given that they mimic EVD symptoms. It seems that there are firm plans to produce 900 treatment courses for this drug by early 2015 [10].

Second, Favipiravir (T-705), a viral RNA polymerase inhibitor, has shown efficacy against EV in mice, in vitro and in vivo [11]. Data are available on an important number of patients regarding the good tolerance of this drug used for treating novel or resistant influenza infections in Japan [12]. Moreover, this drug, which can be used orally, is immediately available. However, in an initial study, only one out of six NHPs using this drug survived, probably because doses used were not appropriate for EVD. It is possible that, for this drug, the doses required in humans with EVD should be higher than in humans with influenza infections. Another study using this drug in NHPs is currently being conducted by NIH with higher doses.

BCX4430, which is a nucleoside analog that blocks viral RNA synthesis, has shown promising results in rodents and monkeys. However, pre-clinical toxicology and phase 1 data for this drug are lacking [13]. Finally, very recently, brincidofovir, an oral nucleotide analog that has shown broad-spectrum antiviral activity against DNA viruses, including viruses in the herpes virus family and adenovirus, was authorized by the FDA for patients with EVD, but based on in vitro data only.

There is a controversy surrounding the "compassionate use" of these experimental therapies in the absence of human safety and efficacy data [14, 15]. WHO convened an expert panel in August 2014 to advise on its role. The panel "concluded unanimously that it would be acceptable on both ethical and evidential grounds to use as potential treatments or for prevention unregistered interventions." Those involved have, however, a moral obligation to evaluate these interventions and to collect and share all the scientifically relevant data generated by the "compassionate use" of these drugs. It is also important to recommend that experimental therapy should be introduced early and on a foundation of very good supportive care.

Acknowledgments We are indebted to Serge Paul Eholie for his comments on the manuscript and to Benoit Visseaux for his help with the figure.

References

1. WHO. Ebola response roadmap update (17 October 2014) [Internet]. 2014. Available from: http://apps.who.int/iris/bitstream/10665/136645/1/roadmapupdate17Oct14_eng.pdf?ua=1. Cited 20 Oct 2014
2. WHO Ebola Response Team (2014) Ebola virus disease in West Africa—the first 9 months of the epidemic and forward projections. N Engl J Med 371(16):1481–1495
3. Fowler RA, Fletcher T, Fischer WA, Lamontagne F, Jacob S, Brett-Major D et al (2014) Caring for critically ill patients with Ebola virus disease. Perspectives from west Africa. Am J Respir Crit Care Med 190(7):733–737
4. Gulland A (2014) First Ebola treatment is approved by WHO. BMJ 349:g5539
5. WHO Blood Regulators Network (BRN) (2014) Position paper on collection and use of convalescent plasma or serum as an element in filovirus outbreak response. WHO, Geneva
6. Dye JM, Herbert AS, Kuehne AI, Barth JF, Muhammad MA, Zak SE et al (2012) Postexposure antibody prophylaxis protects nonhuman primates from filovirus disease. Proc Natl Acad Sci USA 109(13):5034–5039
7. Mupapa K, Massamba M, Kibadi K, Kuvula K, Bwaka A, Kipasa M et al (1999) Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. International Scientific and Technical Committee. J Infect Dis 179(Suppl 1):S18–S23
8. Qiu X, Wong G, Audet J, Bello A, Fernando L, Alimonti JB et al (2014) Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp. Nature 514(7520):47–53
9. Geisbert TW, Lee ACH, Robbins M, Geisbert JB, Honko AN, Sood V et al (2010) Postexposure protection of non-human primates against a lethal Ebola virus challenge with RNA interference: a proof-of-concept study. Lancet 375(9729):1896–1905
10. Maurice J (2014) WHO meeting chooses untried interventions to defeat Ebola. Lancet 384(9948):e45–e46
11. Oestereich L, Lüdtke A, Wurr S, Rieger T, Muñoz-Fontela C, Günther S (2014) Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model. Antivir Res 105:17–21
12. Phase 3 efficacy and safety study of favipiravir for treatment of uncomplicated influenza in adults [Internet]. Available from: http://www.clinicaltrials.gov/show/NCT02008344. Cited 7 Oct 2014
13. Warren TK, Wells J, Panchal RG, Stuthman KS, Garza NL, Van Tongeren SA et al (2014) Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. Nature 508(7496):402–405
14. Joffe S (2014) Evaluating novel therapies during the Ebola epidemic. JAMA 312(13):1299–1300
15. Goodman JL (2014) Studying "secret serums"—toward safe, effective Ebola treatments. N Engl J Med 371(12):1086–1089