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Ebola: a review on the state of the art on prevention and treatment

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ABSTRACT

The aim of this paper is to highlight the current development in the research field for helping people just exposed to Ebola virus survive (treatment) and to prevent the disease when given at various times after exposure (vaccine). Concerning the treatment, recombinant anti-Ebola monoclonal antibodies and small interfering RNAs that block the expression of essential viral proteins, are the most promising way in stopping the disease when it has already reached the humans. As far as concerns the prevention field, two candidate vaccines have clinical-grade vials available for phase 1 pre-licensure clinical trials, and demonstrated to have a 100% efficacy in studies on non human primates. Well-informed communities can reduce the main ways of spread the infection, by avoiding unprotected home-based care of people who are infected and also by completely modifying traditional burial practices that are way of diffusion of the contagion.

1. Introduction

The current outbreak started officially on March 23, 2014, when the World Health Organization (WHO) was notified of an outbreak of Ebola virus disease (EVD) in Guinea, even if the epidemics started on October 2013[1]. Almost five months later, on August 8, the WHO declared the epidemic reached the level of a public health emergency of international concern[2].

But why are we so interested in the evolving of this outbreak? The forecast of the WHO Ebola response team says that at the beginning of November 2014, and assuming no change in the control measures for this epidemic, the cumulative reported numbers of confirmed and probable cases will exceed 20 000 (5 740 in Guinea, 9 890 in Liberia, and 5 000 in Sierra Leone)[3].

By September 14, 2014, a total of 4 507 probable and confirmed cases, including 2 296 deaths from EVD (Zaire species) had been reported from five countries in West Africa-Guinea, Liberia, Nigeria, Senegal, and Sierra Leone.

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The WHO recently underlined that "Ebola virus disease currently has no vaccines or medicines approved by national regulatory authorities for use in humans save for the purpose of compassionate care"[4].

Lamontagne *et al*. have argued that the role of public health in stopping Ebola is and will be important also in the next future, through the characterization of the outbreak epidemiology, of contact tracing, social mobilization, and public education[5]. It is well known that public health intervention are capable of saving many more lives than can be saved by individual patient care. However, the prevention and the treatment of EVD are essential issues to take into account in the control of the outbreak, and the objective of this paper is to review the current scientific literature on the treatment and prevention of EVD.

Essentially, this paper will highlight the ways researchers are following for helping people just exposed to Ebola virus survive (treatment) and to prevent the disease when given at various times after exposure (vaccine).

2. Treatment

Current treatment for EVD consists of supportive care. As the virus

reproduces and spreads in the body, it interferes with blood clotting and disrupts electrolyte balance. As a result, severely ill patients are frequently dehydrated and need intravenous fluids or oral rehydration with solutions that contain electrolytes. Such interventions can help sustain some patients and allow them to recover, but in many cases, patients progress toward multiorgan failure, shock, and death.

Recombinant anti-Ebola monoclonal antibodies and small interfering RNAs that block the expression of essential viral proteins, are the most promising way in stopping the disease when it has already reached the humans.

The research on finding effective drug for this diseases suffered from the fact that EVD until now should be considered a rare disease. Theoretically, the most effective way in stopping the disease when it has been already acquired by humans is the administration of specific antibodies. In this field, Mapp Biopharmaceutical, a small biotechnology enterprise, conducted preclinical testing of ZMapp, a passive immunotherapy that combines 3 humanized monoclonal antibodies produced in genetically modified *Nicotinia* plants.

A trial of this product conducted by Qiu *et al*. administered up to 5 d after experimental administration of macaque monkeys with a virulent Ebola virus strain, indicates a 100% efficacy in preventing lethal disease[6].

On the basis of these results, two different things happened in recent days: first of all, 6 health workers and a priest received doses of ZMapp, and secondly, the US government signed a multimillion dollar contract for several million dollar with the maker of the experimental Ebola drug ZMapp with the aim of accelerating the drug's development[7].

At this point in time, the scarce availability of the product needs to be taken into account for tackling efficaciously the disease at the epidemic level in Africa.

On the other hand, we have to consider that new drugs are under development[8]. One of this novel drugs is TKM-Ebola[9]. This drug is now under Phase I clinical trial conducted by Tekmira, a pharmaceutical corporation. The randomized, single-blind, placebo-controlled study involves single ascending doses and multiple ascending doses of TKM-Ebola, and aims to assess safety, tolerability and pharmacokinetics of administering TKM-Ebola to healthy adult volunteers without administering any steroid pre-medications[10].

Other experimental therapies include BCX4430, a synthetic adenosine analogue with high *in vitro* and *in vivo* activity against filoviruses and other RNA viruses. This drug inhibits viral RNA polymerase activity and protects cynomolgus macaques from Marburg virus infection if inoculated as late as 48 h after infection[11]. However, we have to report that no data safety in humans are still available from clinical trials.

Other well known drugs, such as chloroquine and imatinib, have been tested in prelimnary *in vitro* studies, showing activity against Ebola virus and in rodent models[12].

Finally, Tan *et al*. emphasized the potential utility for the use of melatonin in the treatment of individuals who were affected by EVD[13]. Since the pathological changes associated with an Ebola infection include endothelial disruption, disseminated intravascular coagulation and multiple organ hemorrhage, they suggest that melatonin could be used, based on the fact it targets these alterations. However, this use of melatonin has not been tested for safety and efficacy, even if this drug is characterized to have a high safety profile, to be readily-available and be orally-self administered.

When thousands of people are confronted with a life-threatening disease, and no specific therapies or preventive measures exist, it can be ethically acceptable to assume greater risks and offer patients unproven interventions[14].

3. Prevention

There is evidence that several non-human species, including primates and fruit bats, can be infected with the Ebola virus. Moreover, wild animals are the likely source of infection for outbreaks in humans[15]. However, the mortality rates after Ebola infection is high in the primates (25% in a chimpanzee community in the 1990's in Cote d'Ivoire)[16] and it is difficult to argue that these animals could constitute the reservoir of the infection in wild life. On the other hand, bats are considered the better candidate for this role. Fruit bats could act as source of infection since, even infected with Ebola, they do not became ill, probably because they develop protective antibodies against the Ebola virus[17,18]. Another point is concerning the transmission of the infection from bats to humans. How could this happen? Leroy *et al*. argued that the start of at least one Ebola outbreak in humans has been linked to people consuming bat meat[19].

If so, a better knowledge of this mean of transmission among the population and mapping Ebola in wild animals[20] could be useful for controlling the spread of the infection.

As far as concerns the availability of a vaccine, at the end of September 2014, WHO consultation on Ebola vaccines in Geneva has stated that two candidate vaccines have clinical-grade vials available for phase 1 pre-licensure clinical trials[21], and demonstrated to have a 100% efficacy in studies on non human primates[22].

The first candidate, cAd3-ZEBOV, has been conceived by Nicosia and Cortese and developed by GlaxoSmithKline in collaboration with the US National Institute of Allergy and Infectious Diseases. This vaccine uses a chimpanzee-derived adenovirus vector with an Ebola virus gene inserted[23].

The second candidate, rVSV-ZEBOV, has been developed by the Public Health Agency of Canada in Winnipeg. rVSV-ZEBOV uses an attenuated or weakened vesicular stomatitis virus, a pathogen found in livestock; one of its genes has been replaced by an Ebola virus gene[24].

As discussed in the WHO meeting in Geneva[21], phase 1 trials should be expedited and their results shared broadly in order to facilitate rapid progression to phase 2. There is a substantial agreement on the fact that if the results of phase 1 will be favorable, phase 2a studies should be conducted in Africa but outside the current Ebola outbreak zone and should proceed in parallel with phase 2b studies to carry out in exposed populations to the current outbreak.

A final consideration is due. We agree with the Nature editorial that it's time to act[25]. We are pretty sure that well-informed communities can reduce the main ways of spread the infection, by avoiding unprotected home-based care of people who are infected and also by completely modifying traditional burial practices that are way of diffusion of the contagion.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Briand S, Bertherat E, Cox P, Formenty P, Kieny MP, Myhre JK, et al. The international Ebola emergency. *N Engl J Med* 2014; **371**: 1180-1183.

[2] World Health Organization. WHO statement on the meeting of the International Health Regulations Emergency Committee regarding the 2014 Ebola outbreak in West Africa. Geneva: World Health Organization; 2014. [Online] Available from: http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/ [Accessed on 20th October, 2014]

[3] WHO Ebola Response Team. Ebola virus disease in West Africa - the first 9 months of the epidemic and forward projections. *N Engl J Med* 2014; **371**: 1481-1495.

[4] World Health Organization. Experimental therapies: growing interest in the use of whole blood or plasma from recovered Ebola patients (convalescent therapies). Geneva: World Health Organization; 2014. [Online] Available from: http://www.who.int/mediacentre/news/ebola/26-september-2014/en/ [Accessed on 20th October, 2014]

[5] Lamontagne F, Clément C, Fletcher T, Jacob ST, Fischer WA 2nd, Fowler RA, et al. Doing Today's work superbly well-treating Ebola with current tools. *N Engl J Med* 2014; doi: 10.1056/NEJMp1411310.

[6] 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.

[7] McCarthy M. US signs contract with ZMapp maker to accelerate development of the Ebola drug. *BMJ* 2014; doi: 10.1136/bmj.g5488.

[8] Hampton T. Largest-ever outbreak of Ebola virus disease thrusts experimental therapies, vaccines into spotlight. *JAMA* 2014; **312**(10): 987-989.

[9] 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**: 1896-1905.

[10] Tekmira. FDA modifies Tekmira's TKM-Ebola clinical hold to partial hold. Vancouver: Tekmira; 2014. [Online] Available from: http://investor.tekmirapharm.com/releasedetail.cfm?ReleaseID=865208 [Accessed on 20th October, 2014]

[11] Warren TK, Wells J, Panchal RG, Stuthman KS, Garza NL, Van Tongeren SA, et al. Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. *Nature* 2014; **508**: 402-405.

[12] Uebelhoer LS, Albarino CG, McMullan LK, Chakrabarti AK, Vincent JP, Nichol ST, et al. High-throughput, luciferase-based reverse genetics systems for identifying inhibitors of Marburg and Ebola viruses. *Antiviral Res* 2014; **106**: 86-94.

[13] Tan DX, Korkmaz A, Reiter RJ, Manchester LC. Ebola virus disease: potential use of melatonin as a treatment. *J Pineal Res* 2014; **57**(4): 381-384.

[14] Rid A, Emanuel EJ. Ethical considerations of experimental interventions in the Ebola outbreak. *Lancet* 2014; doi: 10.1016/S0140-6736(14)61315-5.

[15] Funk S, Piot P. Mapping Ebola in wild animals for better disease control. *Elife* 2014; doi: 10.7554/eLife.04565.

[16] Formenty P, Hatz C, Le Guenno B, Stoll A, Rogenmoser P, Widmer A. Human infection due to Ebola virus, subtype Côte d'Ivoire: clinical and biologic presentation. *J Infect Dis* 1999; **179**(Suppl 1): S48-S53.

[17] Leroy EM, Kumulungui B, Pourrut X, Rouquet P, Hassanin A, Yaba P, et al. Fruit bats as reservoirs of Ebola virus. *Nature* 2005; **438**: 575-576.

[18] Hayman DTS, Yu M, Crameri G, Wang LF, Suu-Ire R, Wood JLN, et al. Ebola virus antibodies in fruit bats, Ghana, West Africa. *Emerg Infect Dis* 2012; **18**: 1207-1209.

[19] Leroy EM, Epelboin A, Mondonge V, Pourrut X, Gonzalez JP, Muyembe-Tamfum JJ, et al. Human Ebola outbreak resulting from direct exposure to fruit bats in Luebo, Democratic Republic of Congo, 2007. *Vector Borne Zoonotic Dis* 2009; **9**: 723-728.

[20] Pigott DM, Golding N, Mylne A, Huang Z, Henry AJ, Weiss DJ, et al. Mapping the zoonotic niche of Ebola virus disease in Africa. *eLife* 2014; doi: 10.7554/eLife.04395.

[21] World Health Organization. Experimental Ebola vaccines. Geneva: World Health Organization; 2014. [Online] Available from: http://www.who.int/mediacentre/news/ebola/01-october-2014/en/ [Accessed on 20th October, 2014]

[22] Kanapathipillai R, Restrepo AM, Fast P, Wood D, Dye C, Kieny MP, et al. Ebola vaccine-an urgent international priority. *N Engl J Med* 2014; doi: 10.1056/NEJMp1412166.

[23] 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 Ebola virus challenge. *Nat Med* 2014; **20**(10): 1126-1129.

[24] 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**: 7296-7304.

[25] Ebola: time to act. *Nature* 2014; **513**(7517): 143-144.