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Backs against the Wall: Novel and Existing Strategies Used during the 2014-2015 Ebola Virus Outbreak

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SUMMARY

The 2014-2015 outbreak of Ebola virus (EBOV), originating from Guinea, is now responsible for the infection of >20,000 people in 9 countries. Whereas past filovirus outbreaks in sub-Saharan Africa have been rapidly brought under control with comparably few cases, this outbreak has been particularly resistant to containment efforts. Both the general population and primary health care workers have been affected by this outbreak, with hundreds of doctors and nurses being infected in the line of duty. In the absence of approved therapeutics, several caregivers have turned to investigational new drugs as well as experimental therapies in an effort to save lives. This review aims to summarize the candidates currently under consideration for postexposure use in infected patients during the largest EBOV outbreak in history.

INTRODUCTION

The genus *Ebolavirus* (family *Filoviridae*) consists of five distinct virus species: Ebola virus (EBOV), Sudan virus, Bundibugyo virus, Taï Forest virus, and Reston virus. Along with the related viruses Marburg virus (MARV) and Ravn virus (RAVV) of the *Marburgvirus* genus, filoviruses are among the deadliest pathogens known to humans and nonhuman primates (NHPs), with case fatality rates in humans reaching as high as 90% in several past outbreaks. The EBOV outbreak in West Africa, identified by the World Health Organization (WHO) in mid-March 2014, is the largest documented filovirus outbreak by a significant margin. The numbers of cases and fatalities from this outbreak have outnumbered those of all past filovirus outbreaks combined. As of 11 March 2015, a total of 9,976 deaths from 24,282 cases have been reported (1), although authorities believe that both numbers are likely underreported because of the inability of overwhelmed responders to report the epidemiological data accurately. One report estimated the outbreak toll to be closer to 2.5 times the number of cases currently being reported by the WHO (2). At the height of the outbreak, the transmission of EBOV was intense and widespread in Guinea, Sierra Leone, and Liberia, with densely populated capitals in all three countries recording cases. Approximately 500 new infections were reported weekly as of early October 2014, with the number expected to double every 30 days if effective interventions are not implemented (3). The geographic spread and sustained presence of EBOV in these three countries has, for the first time, led to the importation of cases to other countries and resulted in clusters of new infections. The first instance, in which 8 of 20 total cases eventually succumbed to EBOV, was that of a Liberian citizen who had traveled to Nigeria by plane (4). The second instance was a Guinean traveling to Senegal by road, and fortunately, there were no secondary cases resulting from this individual (5). The third importation involved a Liberian patient with EBOV who traveled to the United States by plane; 2 nurses were subsequently infected while providing med-

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ical care to the patient (6). The fourth importation was from a U.S. physician who returned to New York City from Guinea, with no additional cases (7). The fifth and sixth international importations occurred in Mali; both cases had traveled by road from Guinea. While the former did not result in transmission, the latter resulted in 6 deaths among 8 reported cases. A nurse who fell ill upon returning to Scotland from West Africa in late December 2014 was also diagnosed with EBOV (8). With the outbreak not yet at an end, more infections may be possible in this evolving situation (9, 10).

A number of primary health care workers battling this outbreak have also been infected with EBOV in the line of duty. In addition to the two U.S. nurses mentioned above, a Spanish nurse was infected while caring for a patient who had been medically evacuated from Sierra Leone. This was the first instance of human-to-human EBOV transmission outside Africa (11). Also, hundreds of medical workers, local or from deployed international organizations, have also contracted the disease. The toll currently stands at 495 deaths out of 838 health care worker cases (1), devastating the already weak health care infrastructure. In the absence of licensed medical countermeasures and vaccines against EBOV, barrier techniques such as personal protective equipment, thorough decontamination, and vigilance still play the major role in keeping health workers safe, but these strategies have not been sufficiently effective, as evidenced by the number of infections.

Effective postexposure therapies are desperately needed to treat patients confirmed to be infected with EBOV. As response groups struggle to deal with mounting losses, several health workers and missionaries have already been repatriated or transferred to more resourceful countries in the hopes that receiving a higher standard of medical care will increase their chances of survival. An increasing number of investigational new drug (IND) applications are being approved by the Food and Drug Administration (FDA) for compassionate use in humans, with the intention to fast-track the most promising interventions toward clinical approval in the shortest time possible. In this review, we summarize the available preclinical and clinical results behind different strategies utilized during this outbreak and contemplate the requirements behind an effective, approved EBOV treatment.

As previously summarized in a review of postexposure therapies for filovirus infections (12), strategies for developing experimental postexposure therapeutics against EBOV revolve around preventing the development of filovirus-associated coagulopathies (recombinant nematode anticoagulant protein [rNAPc2] and recombinant human activated protein C [rhAPC]) (13, 14), inhibiting virus processes such as replication or translation (small interfering RNA [siRNA], BCX4430, or PMOplus) (15–17), boosting host immune responses by postexposure prophylaxis (vesicular stomatitis virus [VSV]-vectored virus expressing EBOV glycoprotein [VSVΔG/EBOVGP]) (18), or limiting viremia and virus spread (monoclonal antibody [MAb] cocktails ZMAb and MB-003) (19, 20). During the current outbreak, a particularly desirable strategy is the off-label use of approved or nearly approved nonspecific small-molecule drugs to treat EBOV infections in humans. The rationale behind the use of these drugs is that they have already been shown to have an acceptable safety profile in humans, therefore bypassing the need for phase I trials. These drugs are available in large quantities and are typically given orally, which increases their desirability because of the ease of administration in the early stages of the disease. If shown to be protective, these nonspecific drugs may be effective against not only EBOV but potentially also other filoviruses as well. TKM-Ebola (siRNA)- and ZMapp (antibody)-based compounds have been used in this outbreak. These compounds are specifically designed against EBOV and are relatively well characterized in terms of efficacy in the "gold-standard" NHP model; however, their safety profile is unknown. Blood transfusions from human survivors of EBOV, a controversial method because of the lack of data and safety concerns such as adverse immune-related reactions and the possibility of other blood-borne diseases being transmitted, have also been employed during this outbreak, in addition to intensive supportive care.

SMALL-MOLECULE DRUGS

Lamivudine

Lamivudine (developed by GlaxoSmithKline, United Kingdom), a nucleoside analog of cytidine, is a reverse transcriptase inhibitor. Studies have shown that lamivudine can inhibit the human immunodeficiency virus type 1 (HIV-1), HIV-2, and hepatitis B virus (HBV) reverse transcriptases *in vitro* (21, 22). Lamivudine has been approved by the FDA to be used in combination with other drugs to treat HIV infections in adults and children (23, 24) or alone to treat acute and chronic HBV infections (25, 26).

During this outbreak, a Liberian doctor used lamivudine to treat 15 infected patients, with 13 eventually surviving EBOV disease. The clinical and preclinical data regarding the effectiveness of this compound against EBOV were not made public. However, the Scientific and Technical Advisory Committee for Ebola Experimental Interventions (STAC-EE), an advisory body of the WHO, did not recommend further use of lamivudine to treat EBOV disease, as data presented to the STAC-EE did not appear to find a survival benefit of this drug (27). Furthermore, a recent *in vitro* study found that treatment with lamivudine at concentrations of up to 320 μmol/liter in EBOV-infected human monocyte-derived macrophages or Vero E6 (African green monkey kidney) or HepG2 (human hepatoma) cells did not have any direct antiviral effects (28).

Favipiravir

Favipiravir (developed by Toyama Chemical, Japan), a pyrazinecarboxamide derivative, is well characterized as a drug against influenza virus infections and acts by selectively inhibiting the activity of the viral RNA-dependent RNA polymerase (29, 30). Favipiravir has completed phase III clinical trials for the treatment of influenza (31), and several studies have supported it as a broad-spectrum antiviral against a panel of arenaviruses and bunyaviruses (32), West Nile virus (33), yellow fever virus (34), and others, which have been summarized in a review (35).

Recent studies have also shown that favipiravir is effective against aerosol Ebola virus E718 infection in immunodeficient A129 alpha/beta interferon (IFN-α/β) receptor knockout ($IFNAR^{-/-}$) mice. When the drug was administered orally at a dose of 150 mg/kg of body weight, beginning at 1 h postchallenge and continuing twice daily for 14 days, all mice survived the challenge (36). Follow-up experiments investigated the ability of favipiravir to treat symptomatic EBOV disease in $IFNAR^{-/-}$ mice. At concentrations of 300 mg/kg/day, initiated 6 days after challenge and continuing for 1 week, all mice survived the lethal challenge. Importantly, this drug was able to reverse advanced Ebola

virus infection, as evidenced by decreasing levels of the liver enzymes aspartate transaminase (AST) and alanine aminotransferase (ALT) as well as viremia after treatment (37). Favipiravir was one of the drugs used to treat an infected health worker repatriated to France during the outbreak (38), and clinical results are pending. A phase II trial for favipiravir against EBOV was also started on December 2014 in Guinea (39).

Brincidofovir

Brincidofovir (developed by Chimerix, USA) is a lipid-conjugated analog of cidofovir, which is converted into the active compound cidofovir diphosphate upon intracellular release of the drug. The drug acts by inhibiting DNA polymerase through incorporation into the cDNA strand during virus replication, thereby slowing chain extension or resulting in termination. The proofreading 3′-to-5′ exonuclease activity is also inhibited (40). Brincidofovir was shown to possess antiviral activity against cytomegalovirus (CMV) (41), adenovirus (Ad) (42), herpes simplex virus (43), and poxvirus (44) in animal models and is currently in phase III clinical trials against CMV and Ad infections (45, 46).

Brincidofovir was one of the drugs given to patients diagnosed with EBOV in the United States after the FDA approved its use on an emergency basis (47). A Liberian citizen in the United States who received brincidofovir later in the EBOV disease course died; however, several other patients were also given the same drug earlier in the disease course and survived. However, the potential mechanisms of actions of this drug are unknown because EBOV is not a DNA virus and does not undergo a double-stranded DNA (dsDNA) intermediate phase at any stage in its life cycle. Studies will be necessary to elucidate whether brincidofovir is also effective at inhibiting replication in RNA viruses. Clinical, animal, and *in vitro* data regarding the effectiveness of brincidofovir against EBOV are currently unavailable. A planned clinical trial for brincidofovir was cancelled by Chimerix as of January 2015 due to a lack of participants in Liberia, and it was reported that the trial would not be extended to neighboring Sierra Leone (48, 49).

SMALL INTERFERING RNA

TKM-Ebola

TKM-Ebola (developed by Tekmira Pharmaceuticals, Canada) consists of a cocktail of three siRNAs in the form of lipid nanoparticles, designed specifically to target regions in three EBOV genes: EBOV membrane-associated protein 24 (VP24), the EBOV polymerase complex protein VP35, and polymerase (L). The mechanism of TKM-Ebola is to interfere with the translation of the EBOV VP24, VP35, and L proteins from viral mRNA, which are required for evasion of host IFN responses and several viral processes, including virus assembly, transcription, and replication (50–53).

An intravenous (i.v.) bolus infusion of TKM-Ebola at 2 mg/kg, beginning at 30 min after EBOV challenge and continuing daily for 7 days, was found to be protective, as all NHPs survived the infection (15). A phase I clinical trial was initiated for this drug (54); however, following the observation of unintended cytokine release in participants that was induced by TKM-Ebola, the trial was initially put on clinical hold by the FDA (55). A partial lift was subsequently granted, in which the drug could be tested in EBOV-infected patients in response to the 2014-2015 outbreak (56), and several patients were administered TKM-Ebola, although clinical data are unavailable.

MONOCLONAL ANTIBODIES

ZMapp

ZMapp (developed jointly by the Public Health Agency of Canada and Mappbio Pharmaceuticals, USA) is an improved IgG MAb cocktail comprising MAbs from two precursor cocktails, ZMAb (providing MAbs c2G4 and c4G7) and MB-003 (providing MAb c13C6). The plant-derived antibodies are specific for the viral glycoprotein, which is the sole surface protein on the EBOV virion (57) and a main target for vaccine design because of its ability to elicit specific immune responses (58).

In preclinical studies, ZMapp was found to be efficacious in nonhuman primates when administered as an i.v. bolus at a concentration of 50 mg/kg in three separate doses spread evenly over 9 days. Complete survival was observed when ZMapp therapy was initiated up to 5 days after EBOV infection, and ZMapp was effective at reversing advanced EBOV disease symptoms, as evidenced by decreases in rash and viremia and elevated liver enzyme levels (59).

ZMapp was administered to 7 patients during the current outbreak under an emergency compassionate-use provision from the FDA, and clinical information is available from two U.S. health care providers who received ZMapp, combined with aggressive supportive therapy including hydration and electrolyte correction. Both patients had hypovolemia, hypokalemia, hypocalcemia, and hypoalbuminemia, and one patient also had substantial liver injury, which were factors associated with increased mortality (60) and indicative of advanced EBOV disease. The conditions of both patients improved with this combined treatment, and both patients survived EBOV infection. It was noted that there was a correlation between increasing antibody levels and decreasing viremia, as determined by reverse transcription-quantitative PCR (RT-qPCR), and subjective as well as objective improvements were observed shortly after the administration of the first ZMapp dose (61). However, this improvement occurred with other treatments as well, and the authors of this study could not definitively conclude that the administration of ZMapp had any survival benefit in these patients (61).

WHOLE-BLOOD OR PLASMA TRANSFUSIONS FROM CONVALESCENT SURVIVORS

Whole-blood transfusions are widely used in developing countries with limited resources committed toward health care. However, there are several concerns with this technique, as leukocytes have been associated with adverse effects, including febrile transfusion reactions, alloimmunization to leukocyte antigens, graft-versus-host disease, and the possibility of becoming infected with other blood-borne diseases, such as HIV, hepatitis viruses, CMV, and other viruses (62). Whole-blood transfusions from convalescent to infected patients were successful during the 1995 EBOV outbreak in Kikwit, Democratic Republic of Congo. Seven out of eight patients who received the transfusions survived, although several of the survivors already had detectable antibodies when they received the transfusion (63). However, the transfused patients also received comparatively better supportive care than did others, including infusions of glucose and electrolytes, treatment with antibiotics and antimalarial drugs, and food supplementa-

tion, limiting conclusions that can be drawn about the potential benefits of this treatment (63). Furthermore, a study in which sera were passively transferred from EBOV-immune survivor macaques was not successful in conferring protection to naive NHPs, but it should be noted that three of four recipient animals exhibited IgG titers of only 1:100 at 3 days after passive immunotherapy (64). Therefore, further investigation into passive immune therapy during a future EBOV outbreak is needed.

Patients seldom require all the components found in whole blood. As a safer alternative, immunotherapy with convalescent-phase serum, plasma, and polyclonal antibodies was used historically for many bacterial and viral diseases, including *Haemophilus influenzae*, scarlet fever, pertussis, measles, mumps, polio, the 1918 pandemic H1N1 influenza virus, and others (65). In the laboratory, a number of studies were performed to demonstrate the impact of antibodies on EBOV infection. Passive transfer of IgG from horses hyperimmunized to EBOV was evaluated for survival benefit to NHPs when given immediately after a lethal challenge. Although all treated NHPs succumbed to disease, there was a delay in the onset of viremia and clinical symptoms compared with control animals (66). An additional dose of equine IgG given to NHPs 5 days after challenge did not have any additional beneficial effects (67). However, NHPs were fully protected when given three doses of concentrated, polyclonal IgG from NHP survivors purified to 96% purity by fractionation in protein G columns, beginning 48 h after infection, with additional treatments at 4 and 8 days postinfection (68).

Whole-blood or plasma transfusions were deemed an ethically acceptable treatment modality by the WHO for use in the current outbreak (69), provided that risk assessments were carried out to minimize any known associated risks. For instance, the potential donor patient must be clinically asymptomatic and have twice tested negative for EBOV RNA in two independent blood samples taken at least 48 h apart. Donor blood must be blood group compatible and also tested for the possible presence of any bloodborne infections. The blood must be collected, prepared, stored, and transfused at facilities experienced in handling such processes. The appearance of neutralizing antibodies is late in general (several weeks or months after recovery), and levels are variable between patients. Donor blood is likely to vary in protective efficacy; therefore, the levels of total and neutralizing EBOV antibodies should be titrated if possible (69). During this outbreak, several infected patients received whole blood or plasma from convalescent survivors. Clinical trials are under way to assess the clinical benefits associated with blood or plasma transfusions (27).

SUPPORTIVE TREATMENT

Supportive care is based primarily on the management of and relief from disease symptoms, physical stress, as well as mental stress and therefore can be used regardless of the disease. The typical protocol for febrile illness was used in past filovirus outbreaks. Initial treatments include antimalarial drugs and antibiotics to eliminate the possibility of malaria as well as to prevent and treat secondary bacterial infections. Antiviral drugs used in past outbreaks include acyclovir and ribavirin. Other treatments include painkillers, sedatives, as well as anti-inflammatory, antidiarrheal, and antipsychotic drugs administered at the medical doctor's discretion (70). Intravenous rehydration was routinely used in later outbreaks (71); however, oral rehydration was encouraged whenever possible because of the risk of EBOV transmission through contaminated needles used for i.v. fluid administration. Coagulants such as fibrinogen and prothrombin were given to prevent hemorrhaging during a previous outbreak of MARV (70), although their use may be more restricted in resource-poor locations, as i.v. administrations are more difficult to perform properly for the reasons mentioned above. Anticoagulants such as heparin were also administered to some patients in response to certain disorders, such as disseminated intravascular coagulation (70). For patients in high-resource medical settings, such as those airlifted to the United States and Europe for intensive treatment, it is possible to monitor and rapidly respond to changes in the patient's renal, hepatic, and pulmonary/respiratory functions (61, 72). This is in part related to the high medical-personnel-to-patient ratio as well as the added ability to provide critical care such as noninvasive and invasive mechanical ventilation and continuous renal replacement therapy (73). As of 7 January 2015, among the 24 patients who received medical care for EBOV disease in the United States or Europe, 18 (75%) recovered, 5 died, and 1 is still undergoing intensive treatment (74). This represents a higher survival rate than that in West Africa. Supportive therapy has not been rigorously tested for efficacy as part of a randomized trial due to ethical issues and is expected in general to be associated with better outcomes. However, the survivor benefits associated with the details of this strategy under these conditions remain based on a general perception built upon years of experience that supportive therapy is not believed to be harmful to the patient.

OTHER POTENTIAL DRUGS FOR USE IN THE 2014-2015 OUTBREAK

A meeting convened by the WHO with a panel of experts to prioritize experimental drugs resulted in the consideration of two additional compounds not described above that may also have beneficial effects against EBOV infections in humans. Therapy with type I IFN is commonly used in the clinic to boost host antiviral responses for the treatment of chronic HBV (75), hepatitis C virus (HCV) (76), as well as human herpesvirus 8 (HHV-8) for Kaposi's sarcoma (77). In preclinical studies with EBOV, the administration of IFN-α2b to NHPs at a dose of 2×10^7 IU/kg/day beginning 18 h after challenge resulted in a delay of viremia development as well as a slight extension in the time to death of treated NHPs by 1 to 2 days (67). IFN-β treatment also increased the survival time for NHPs. Animals given 10.5 μg/kg of IFN-β beginning 18 h after challenge, with subsequent doses at 1, 3, 5, 7, and 9 days after infection, had significantly prolonged survival times, on average 5.5 days longer than those of untreated control animals (78).

Another candidate is the drug toremifene, an FDA-approved selective estrogen receptor modulator (SERM) identified by an *in vitro* screen of drugs approved by the FDA and drugs approved outside the United States for anti-EBOV activity (79). Toremifene is approved for the treatment of advanced breast cancer (80). SERMs act by binding to the estrogen receptor, causing conformational changes that lead to the initiation or suppression of target genes through interactions with coactivator or corepressor proteins, respectively (81). However, as estrogen receptor expression was not required for *in vitro* EBOV inhibition by toremifene, the drug likely works independently of the classical estrogen pathway. The activity of toremifene was also evaluated *in vivo* by using a mouse model of EBOV infection. Treatment was initiated beginning 1 h after challenge at a dose of 60 mg/kg by intraperitoneal

injection, with subsequent doses at days 1, 3, 5, 7, and 9, which protected 50% of the infected animals (79).

POSTEXPOSURE PROPHYLAXIS WITH VSVΔG/EBOVGP

VSVΔG/EBOVGP is one of two vaccines that are currently undergoing phase I and II clinical trials in North America, Europe, and Africa as a potential candidate for the mass immunization of at-risk populations in response to the 2014-2015 outbreak (82, 83). With the recent exception of an adjuvanted adenovirus-vectored vaccine (84), VSVΔG/EBOVGP was at one time unique as the only vaccine that could also confer postexposure protection, with 50% efficacy in NHPs if given 30 min after EBOV challenge (18). The rapid protection induced by immunization with the VSV-vectored vaccine highlights its utility should instances of accidental exposure, such as a needlestick injury, occur in the laboratory or the field.

In 2009, the VSVΔG/EBOVGP vaccine was given under compassionate circumstances to a researcher who had a high-risk occupational EBOV exposure from a laboratory accident. The individual was given a single intramuscular (i.m.) dose of 5×10^7 PFU of VSVΔG/EBOVGP ~48 h after the incident. Aside from a fever 12 h later and the detection of vesicular stomatitis virus (VSV) viremia by PCR for 2 days, the vaccine recipient remained healthy (85). In September 2014, a physician was potentially exposed to EBOV through a needlestick injury while working at an EBOV treatment center in Sierra Leone. The individual received an i.m. injection of 1×10^8 PFU of VSVΔG/EBOVGP ~43 h after the accident. A fever as well as moderate to severe myalgia, chills, tiredness, and headache were noted 12 h after the injection but subsided over 3 to 4 days. VSV viremia was detectable by PCR for 4 days, and cytokine secretion as well as T-cell/plasmablast activation occurred early postvaccination (86). Both patients were not believed to have been infected with EBOV, as diagnostic tests for the EBOV nucleoprotein were consistently negative, and the VSVΔG/EBOVGP vaccine was not associated with any adverse effects in these two individuals.

DISCUSSION

The 2014-2015 EBOV outbreak has exposed the severe shortage of options in medical countermeasures at our disposal. The current process for the preclinical testing of candidate EBOV antivirals includes mouse, guinea pig, and NHP animal models, which fulfills the FDA's "two-animal rule." The two-animal rule stipulates that in emergency scenarios, a drug can be made available on compassionate grounds provided that (i) it has shown efficacy in two different animal models for EBOV infections or efficacy in one well-characterized animal model that recapitulates the major hallmarks of EBOV disease and (ii) it does not cause adverse side effects in humans (87). Based on past experiences, some candidate treatments have been shown to be protective in lower-animal models but are less effective in the gold-standard NHP model. For instance, the EBOV-neutralizing MAb KZ52 demonstrated complete pre- and postexposure protection in guinea pigs with one dose (88) but was not effective when administered to NHPs (89). Along similar lines, a recombinant adenovirus expressing IFN-α (Ad-IFN-α) was fully protective when administered to mice (90) but was not protective in guinea pigs (91) and NHPs (92). The difference in protective efficacy is attributed to the observation that wild-type EBOV is more virulent in NHPs and more closely mimics the hallmarks of disease in humans than the adapted EBOV variants used for rodent studies (93). Therefore, the most promising compounds should be tested for efficacy and safety in NHPs before use in humans, even under compassionate-use provisions.

Owing to the severity of the EBOV outbreak in West Africa, regulatory approval bodies have modified their position toward the testing of potential clinical options in infected humans. A panel of WHO experts has unanimously concluded that it is ethical to use unapproved drugs in this outbreak, provided that there are preclinical safety and efficacy data supporting such use (94). When ZMapp was administered for the first time to two EBOV-infected health workers in Liberia during the outbreak, it meant that those responsible felt that the possibility of severe adverse effects from an untested cocktail was an acceptable risk, given the high mortality rates associated with EBOV disease. This was in stark contrast to events only several days earlier, when authorities declined to use ZMapp to treat a physician in Sierra Leone, despite the drug being made available at that time for compassionate use. These proceedings highlighted the ethical dilemma that faces governing aid organizations all the way down to the physician responsible for administering an untested drug. However, as a potential positive outcome of these events, the level of informed consent required from patients to necessitate the testing of experimental drugs under atypical circumstances is now established as a precedent. These events have also triggered a much-needed ethical discussion regarding the use of potentially efficacious but untested compounds or the off-label use of approved drugs in humans, along with a significant push to rapidly advance EBOV vaccines and therapeutics toward clinical licensure.

Clinical data on the effect of some experimental products administered to patients evacuated from West Africa are not readily available, and in many cases, adequate controls are not available for comparison. Therefore, it is difficult to compare the efficacies of the different treatment regimens at this time. Another confounding factor is the fact that many of the surviving patients were given several experimental therapies in order to maximize their chances of survival. Therefore, it will be very challenging to assess each intervention independently in relation to its survival benefit. Under these circumstances, the next best alternative would be to compare the clinical statuses of the patients shortly after the administration of a certain compound to determine which intervention had the most profound effects. Aside from objective clinical observations, one significant indicator would be a direct drop in EBOV viremia after treatment, as lower viremia has been correlated with survival from infection (95). Other possible survival indicators include blood chemistry parameters such as AST, blood urea nitrogen (BUN), creatinine, and albumin; the secretion of proinflammatory cytokines; or elevated thrombomodulin and ferritin levels, which were found to be associated with hemorrhaging (96).

This is the first instance in which a drug exists that could be used to treat patients postexposure during an EBOV outbreak (Table 1). ZMapp shows the most promising preclinical data in terms of efficacy in NHPs. While untested in a controlled clinical trial, in a small sample of seven people, ZMapp was well tolerated overall, and five patients who had received all three ZMapp doses survived the infection (97). Of note, eight additional patients were treated with ZMAb after supplies of ZMapp had been exhausted, and all patients survived the infection (our unpublished data). Available data support further investigation of antibody-based

TABLE 1 Strategies used in the 2014-2015 EBOV outbreak in West Africa and their past and current statuses

Compound	Developer(s)	Status before the 2014-2015 EBOV outbreak		Current status
		Tested for efficacy against EBOV	Proof of safety in humans	
Lamivudine	GlaxoSmithKline	No	Yes, FDA approved against HIV	Not recommended by WHO for treatment of EBOV disease
Favipiravir	Toyama Chemical	Yes, in mice	Yes, phase III against influenza virus	Phase II
Brincidofovir	Chimerix	No	Yes, phase III against CMV and Ad infections	EBOV trial discontinued
TKM-Ebola	Tekmira Pharmaceuticals	Yes, in NHPs	No	Phase I (partial suspension)
ZMapp	Public Health Agency of Canada and MappBio Pharmaceuticals	Yes, in NHPs	No	Phase I/II
Whole-blood or plasma transfusion		No	Yes, routine medical procedure in resource-poor countries	Still in use
Supportive treatment		No	Yes, routine medical procedure	Still in use
Type I IFN		Yes, delayed time to death in NHPs	Yes, used in clinic to treat HBV, HCV, and HHV-8	Not yet used in patients during the 2014-2015 outbreak
Toremifene		Yes, in mice	Yes, FDA approved for use against breast cancer	Not yet used in patients during the 2014-2015 outbreak
VSVΔG/EBOVGP	Public Health Agency of Canada	Yes, in NHPs	No	Phase I/II (as a prophylactic)

therapies, and controlled clinical trials should take place, preferably in the countries affected by the outbreak. Since ZMapp is expensive to synthesize in large quantities and the production process requires several months, other strategies should be combined with ZMapp to test whether the clinical benefits could be enhanced and lead to a more efficacious treatment with lower ZMapp doses. A previous study showed that the protective effects of ZMAb are enhanced in NHPs when supplemented with an Ad-IFN-α adjuvant (92). Effective postexposure treatment will likely consist of several components, including aggressive supportive care and a nonspecific antiviral to hinder EBOV pathogenesis and spread, before the control of viremia is achieved with an efficacious specific treatment such as ZMapp.

The 2014-2015 EBOV outbreak has provided the world with many tough lessons regarding the speed of research and development of protective medical countermeasures, the ethical considerations of the use of experimental therapies in humans under compassionate-use provisions, and the circumstances under which licensed drugs can be used off-label for the treatment of other diseases. This outbreak has also highlighted the various levels of preparedness among different countries to combat the rapid spread of infectious diseases with relative high case fatality rates. These findings must be incorporated into revised guidelines in order to ensure that any barriers regarding the emergency use of experimental treatments will not be repeated in the future, whether with EBOV or with other pathogens.

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Her Majesty the Queen in right of Canada holds a patent on MAbs 1H3, 2G4, and 4G7 (PCT/CA2009/000070), monoclonal antibodies for Ebola and Marburg viruses. G.W. and G.P.K. have read and agree with the contents in the manuscript. G.W. and G.P.K. have been extensively involved in the preclinical development and testing of the antibody cocktails ZMAb and ZMapp as well as experiments with the VSVΔG/EBOVGP vaccine mentioned in this review. G.W. and G.P.K. are not included on any related patents, other intellectual property, or contracts that may benefit them financially in the future. We declare no other competing interests.

Additionally, the findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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