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Promising Therapeutics against Ebola Virus Disease

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Ebola Virus Disease (EVD) has become a major threat to global peace and security. Since 1976, when Ebola virus was discovered, over 20 outbreaks have been reported. Most of these outbreaks occurred in rural areas of East and Central Africa. But the current 2014 outbreak, which started in Guinea in March 2014, spread to Liberia, Sierra Leone, Nigeria, Senegal and Mali, and traveled beyond Africa into Europe and US. Thus far, there have been no approved therapeutics and preventive vaccines and hence response is limited to supportive care, barrier nursing, and management of patient complications. Spurred by the global threat, research has identified promising drug candidates against the disease. This review presents the current status of promising drug candidates against EVD. The current development status of the experimental drugs ZMapp, TKM-Ebola, Favipiravir (T-705 or Avigan), AVI 6002, BCX 4430 and Brincidofovir (CMX-001) is given. In the absence of licensed drugs, these first generation anti-Ebola virus experimental drugs, which are currently in phase 1 clinical trial, were administered to a limited number of healthcare workers during the current EVD outbreak.

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1. INTRODUCTION

One of the disease that threatened the economy and people of West Africa in 2014 is Ebola Virus Disease (EVD) formerly called Ebola Hemorrhagic Fever (EHF) caused by Ebola virus. Ebola virus was discovered in 1976 with simultaneous outbreaks in Zaire (now Democratic Republic of Congo, DRC) and Sudan (World Health Organization) [1]. Thereafter, several sporadic outbreaks have occurred in different years and different parts of Africa including DRC (1977, 1995, 2001–2003, 2007, 2008–2009, 2012), Sudan (1979, 2004), Gabon (1994, 1996–1997, 2001–2002), Uganda (2000–2001, 2007–2008 and 2012) and Cote d'Ivoire (1994). The current 2014 outbreak of Ebola virus disease (EVD) in West Africa was alleged to have first occurred in a 2 year baby who died on 6 December 2013 in a remote Gueckedou prefecture of Guinea [2,3], a forested area near the border with Sierra Leone and Liberia [4]. Thereafter, nothing was heard of the disease, until a major outbreak was reported in West Africa 3 months after. EVD outbreak was reported in Guinea on 22 March 2014, Liberia on 31 March 2014 and Sierra Leone on 26 May 2014. The disease subsequently spread to Nigeria on 20 July 2014 [5,6], DRC on 24 August 2014, Senegal on 26 August 2014, and Mali on 25 October 2014 [7]. In the current outbreak, the first imported case of EVD from Africa was recorded in the US on 30 September 2014 and a second case was reported in Spain on 6 October 2014, when a Spanish nurse developed EVD after treating an infected priest that contacted EVD while working on voluntary/humanitarian basis in West Africa. Other cases of EVD were also reported in other parts of the world including United Kingdom (UK). EVD was spread due to virus characteristics, religion, culture, customs, as well as the rapidity of modern travel [8,9].

The 2014 EVD outbreak which was caused by Zaire Ebola virus [10-12], is considered the largest outbreak of the disease since 1976, when it was first discovered [11,13,14]. Bishop [15] and WHO Ebola Response Team [12] reported that the current epidemic is larger than all the previous epidemics of EVD combined. Sarwar et al. [9] described the current epidemic as the worst outbreak to date and the first to be localized primarily in urban areas. On 8 August 2014, the WHO declared EVD outbreak to be an epidemic of public health emergency of international concern [12]. Statistics abound on the devastating effects of EVD in West Africa. In July 2014, the total cases of Ebola were 1,407 with 743 deaths [1]. As of 15 August 2014, there were 2,127 total cases of EVD with 1,145 deaths in Guinea, Sierra Leone, Liberia and Nigeria [14] and by 14 September 2014, the total number of cases had increased to 4,507 with 2,296 deaths [12]. By 28 December, a total of 20,206 cases and 7,905 deaths from EVD have been reported worldwide, with the largest incidence and fatalities in the 3 West African countries of Guinea (2,707 cases with 1,709 deaths), Liberia (8,018 cases with 3,423 deaths) and Sierra Leone (9,446 cases with 2,753 deaths) [4]. While, the spread of Ebola virus have been contained in Nigeria and Senegal, the disease is still ravaging Guinea, Sierra Leone and Liberia.

Ebola virus disease is a severe and often fatal disease in humans and other primates caused by the virus in the genus Ebola and belonging to the Filoviridae family. Five species of Ebola virus have been documented including Zaire Ebola virus, Sudan Ebola virus, Bundibugyo Ebola virus, Tai Forest Ebola virus and Reston Ebola virus [1,16]. Of these, the Sudan and Zaire Ebola virus are the most virulent [17].The current outbreak in West Africa is caused by the Zaire Ebola virus. According to WHO [1], the commonest symptoms of EVD are sudden, onset of fever, intense weakness, muscles pain and sore throat, which is followed by vomiting, diarrhea, bleeding (internal and external) and multi-organ damage particularly the kidney, spleen and liver especially in advanced stage. In the 2014 EVD outbreak, the commonest symptoms were fever (87.1%), fatigue (76.4%), loss of appetite (64.5%), vomiting (67.6%), diarrhea (65.5%), head ache (53.4%), abdominal pain (44.3%), and unexplained bleeding (18%) [10]. The virulence of Ebola virus appears to differ among these virus species, with case fatality being highest in Zaire species (60 – 90%) followed by Sudan species (40-60%) [18]. Many other authors have reported the case fatality of Zaire Ebola virus to be up to 90% [9,19–25].

Recently, studies show that host genetic diversity affects Ebola virus pathogenesis and resistance [26]. But the fatality rate of the 2014 EVD outbreak is less being 55 – 60% globally [13] and 40% in Nigeria [5–7] as against the well documented 90% fatality rate of Zaire Ebola virus.

The Filoviruses, particularly the Ebola virus have been listed among emerging and re-emerging viral disease of global threat [27,28]. Ebola viruses are evasive, with the capacity of inhibiting type I interferon activity, and therefore reducing or destroying the host immune response [19,20,29], and these viruses then reduce or destroy the host capacity to combat the infection. Though, research has revealed promising therapeutics and vaccines for EVD, none have been approved by US Food and Drug Agency (FDA) or WHO. Hence, Ebola virus has been described as a possible target for bioterrorism/bio-weapon [9,21,30,31]. Ebola virus have been classified as biosafety level 4 (BSL4) pathogen [32,33] and "Category A" agents of bioterrorism [32,34,35], which therefore requires urgent attention. Because of the antecedents of Ebola virus including its virulence, high fatality rates, evasiveness and the potential for global spread through air travel, it has become urgent to develop therapeutics for treatment and vaccines for prevention of EVD. Hence, this review is focused on potential anti-EVD drugs including antibodies, plasma/serum and antiviral and non-anti-viral drugs with reported activity against EVD. The study methodology was based on critical review of literature including published journals, newspaper reports and broadcast media. The study used the following recent background literature among others: Beeching et al. [10], Bishop [15], Butler [36], Feldmann and Geisbert [18], IDCRP [37], Norwegian Institute of Public Health [38], WHO [39–41]. Prior to presenting the list of possible drugs and their current development status, Ebola genomes, which are linked to the mode of action of the drugs, shall be first summarized.

2. EBOLA VIRUS GENOME

The genome of Ebola virus, which is about 19kb long, consists of genes that encode for 7 proteins [18,20,28,33,42]. Four of the genes encode for structural proteins including virion envelope glycoprotein (GP), nucleoprotein (NP) and 2 viral (matrix) proteins VP24 and VP40, while the nonstructural proteins include VP30 and VP35, and the RNA dependent viral polymerase (L) [43]. The order of occurrence of the gens is as follows; 3' Leader, NP, VP35, VP40, GP, VP30, VP24, L and 5' trailer [20]. A simplified version of the genome is presented in Fig. 1.

Most of these genes have various functions (Table 1), some are potential targets for novel therapeutic agents. For instance, the glycoprotein is responsible for binding and viral entry [20,29,33,42], NP, VP35, VP30 and L are responsible for replication and transcription of viral RNA [29,33,42], while VP 40 and VP 24 are responsible for assembly, budding and release of virion particles [33,42].

The NP encapsulates the genome and forms a complex with VP30, VP35 and L, which are required for both genomic replication and transcription of viral genes [44]. The three other proteins, GP, VP40, and VP24 are membrane associated proteins [29], which may be important in the expression of antibodies against Ebola virus antigens. Watanabe et al. [29] suggested that VP24 is very important for Ebola virus to evade the antiviral activities of interferons. Also, VP24, NP and VP35 are involved in the formation of nucleocapsid [29]. Geisbert et al. [20] reported that VP24 and VP35 are potential targets for antiviral interventions since both genes have inhibitory effects against host type I interferon response. Also, according to Geisbert et al. [20], the L proteins which provides the RNA dependent RNA polymerase is a potential target for antiviral drugs because of two reasons, 1) suppression could result in the inhibition of viral replication and, 2) such protein is not found in mammalian systems.

3. POTENTIAL EVD THERAPIES

Promising therapies against EVD based on Research and Development can be broadly classified into antibody therapies, specific antiviral therapies for Ebola virus, anti-inflammatory therapy and anticoagulants. Others include mannose binding lecithin and sepsis-related therapies (Table 2). Promising therapeutics were tested in small animal and non-human primates before being considered in human clinical trials. Table 3 presents the leading/ first generation experimental drugs with proven efficacy against EVD that have started preclinical or clinical trials. Though not yet licensed, the WHO and /or FDA have endorsed their limited use on compassionate grounds during an outbreak. Table 4 listed some FDA approved drugs for other treatments that have exhibited antiviral activities, which could also be tried against EVD during outbreaks because of the unavailability of approved therapeutics and vaccines.

3.1 Antibodies

Treatments based on antibodies will be the first to be tried and approved for EVD despite the

limited validity and scientific conflicts of the therapy. Research results abounds on the use of blood from convalescent patients for the treatment of EVD [45-48]. The use of blood transfusion from convalescent patients confers passive immunity on the recipients [48].

During the 1995 EVD outbreak in DRC, 8 patients who were severely ill of EVD were transfused with blood from convalescent patients. Most of these patients fully recovered (87.5%) i.e. 12.5% fatality in contrast with the overall case fatality rate of 80% in 1995 [48].

An occasion when serum from convalescent patient given with human interferon was used to successfully treat an EVD patient, viremia decreased rapidly and the patients recovered [45,46,48]. The success of these cases and many other unreported cases in West Africa, have fuelled the black market trading of convalescent blood. Despite the successes in humans, few authors have reported failures of blood from convalescent patients to protect humans, mice and guinea pigs against EVD. For instance, Jahrling et al. [49] reported fatality of all the monkeys transfused with whole blood from convalescent monkeys that were challenged with EVD. Sadek et al. [50] reported an instance where over 80% of the 250 patients given blood from convalescent patients died of EVD in DRC in 1995. Other authors presented conflicting results on the use of hyperimmune serum for prophylaxis and treatment of EVD [47,49]. Jahrling et al. [49] reported that guinea pig were completely protected by injection of hyper immune equine IgG when treatment was initiated early but not after viremia had developed. The authors also reported that the immune IgG could not protect mice and monkeys. Kudpyarova-Zubavichene et al. [47] used multiple immunization of sheep and goats to obtained hyper immune serum, which demonstrated effective prophylaxis during challenge experiments in guinea pigs and baboon. This therapy was demonstrated to be safe in phase I clinical trials. Convalescent serum was successfully used to treat EVD patients in Spain during the current 2014 EVD outbreak [51]. Notwithstanding the conflicting scientific findings, WHO have approved the use of hyper-immune serum and blood from convalescent patients for the treatment of EVD [39–41,52]. The WHO Blood Regulators Network (BRN) subsequently released the guidelines for the collection and use of convalescent plasma or serum for response against EVD [53]. A study testing the use of convalescent serum started in Guinea in February 2015 [54].

Antibodies produced by convalescent patients, against Ebola virus primarily targeted viral proteins, NP, VP40, and GP [42]. For instance, Sobarzo et al. [79] reported that anti-Ebola IgG was primarily targeted to viral proteins NP, VP 40 and GP. In NHP (non-human primates) and other smaller animal models, it was demonstrated that the adaptive immunity, which contributes to the protection against EVD, is associated with both cellular and humoral immunity [42,79]. Neutralizing monoclonal antibodies can provide protection against viruses in animal models [22,64].

3′ Leader	NP	VP35	VP40	GP	VP30	VP24	L	5′ Trailer

Fig. 1. Simplified structure of Ebola virus genome

Key: NP= Nucleoprotein; VP= Virus Protein; GP= Glycoprotein; L= RNA dependent RNA polymerase VP35=Phosphoprotien IFN antagonist; VP40= Membrane-Associated matrix protein; VP30=Ribonucleoprotein. VP24= Membrane-Associated protein

Table 1. Functions of Ebola virus genes

Gene	Functions	References
NP	Transcription and replication	[20,29,33,42]
VP35	Transcription and replication	[33,42]
	RNA synthesis, type 1 interferon antagonist	[2933,55]
VP40	Virus assembly and budding	[33,44]
GP	Mediate viral entry into cell	[33,42,56]
VP30	Transcription and replication	[29,33,42]
VP24	Virus assembly and budding	[29,33]
	Type 1 interferon antagonist	[20,55]
L	Transcription and replication	[29,33,42]

Table 2. Research towards the development of therapies for Ebola virus disease

Therapy		Humans	Non-Human Primates (NHP) model	Small animal (rodent) model	Remarks/ references
Antibodies	Convalescent plasma	[40,41,45,48, 50]	[57]		
	Immunoglobulin	[47]	[58,59]		
	Monoclonal Antibodies	[60]	[8,14,24,25,61,62]	[63,64]	
	Polyclonal antibodies			[46]	[1839–41]
	Hyperimmune serum				[39–41]
Anti-Viral	LNP/siRNA		[20,65]	[66]	
	PMOs	[34]	[31,67]	[68]	
	Polymerase inhibitors		[67]	[23,69]	
	Garcinai kola (bitter kola)	[70]			The kola has antiviral activity, but has not been tested with Ebola virus
	Nanosilver				[71]
Anti-Inflammatory modulators	Interferons (Type 1 (α, β))		[25,72]	[25]	Modulation of immune system [18]
	S-adenosyl homocysteine hydrolase inhibitors				Modulation of immune system [18]
Anti-Coagulants	rhAPC		[73,74]		Limited success with NHP. 33% efficacy in the treatment of Zaire Ebola virus infected macaque
	rNAPc2, Tissue factor pathway inhibitors		[73–76]		Not tested in rodents but confer partial protection in NHPs [18]
	Heparin sulphate				[18]
Others	Sepsis-Related Therapies		[75]		
	Mannose-binding lectin				[77,78]

Abbreviations: PMOs=Anti-sense phosphoro-diamidatemorpholino oligomers, LNP/siRNA= Lipid nanoparticle/ smallinterfering RNA, rhAPC =Recombinant human activated protein C, rNAPc2 = Recombinant nematode anti-coagulant protein c2

Hence, the survival of patients has been linked to the early and robust production of antibodies [42]; alternately, the antibodies produced may have been consumed due to viral replication [22]. Parren et al. [64] reported an instance when a neutralizing human monoclonal antibody, KZ52, protected guinea pigs from lethal Ebola Zaire virus infection. Hence, KZ52 was able to confer pre- and post-exposure prophylaxis against Ebola virus in a small animal model by passive transfer of a neutralizing human antibody. But Oswald [61] demonstrated that transfer of neutralizing human monoclonal antibodies failed to protect macaque monkeys against a clinical challenge with Ebola virus and also failed to halt the replication of the virus. Qiu et al. [25] demonstrated that monoclonal antibodies combined with Adenovirus-vectored interferon

significantly extended the treatment window in Ebola virus infected guinea pigs. Dye et al. [58] obtained polyclonal IgG from NHP that survived EVD and used it as post exposure treatment (delayed for 48 hours) for NHP challenged with Ebola virus. Results show that the IgG protected the macaques. Cocktails of monoclonal antibodies have been successful used for the treatment of NHP infected with Ebola virus. Qui et al. [63] reported the successful treatment of cynomolgus macaques using a combination of 3 neutralizing antibodies. A cocktail of humanized monoclonal antibodies protected NHP from EVD [8,24,25,35]. Based on these success stories, ZMapp was developed. ZMapp is composed of three monoclonal antibodies that have been humanized by genetic engineering and contains monoclonal antibody C13C6 from MB003 and C2G4 and C4G7 from Zmab [61,80]. ZMapp components are produced in tobacco plant *Nicotiana benthamianca* [14,62,80]. Qiu et al. [14] demonstrated that administration of ZMapp to Ebola virus infected rhesus macaques exhibiting advanced disease symptoms with high viremia and liver enzymes was rescued 100%. ZMapp was able to rescue the monkeys even after 5 days of infection. Though, no approval has been given, but the FDA has permitted its limited use on compassionate ground [13,36]. In the current outbreak, 7 patients were given ZMapp and 2 of these patients died [36]. ZMapp contains neutralizing antibodies conferring passive immunity by specifically targeting and reacting with Ebola virus glycoprotein [80,81]. The US has signed a contract with Mapp Biopharmaceuticals to accelerate the development of the drug [81]. Testing of ZMapp on EVD patients is scheduled to begin in Liberia in February 2015, while Guinea and Sierra Leone could follow after resolving some issues pertaining to research design [54].

3.2 Antiviral Agents

A number of promising antiviral substances with proven efficacy against EVD are being developed (Table 2). Some of the leading antiviral substances are polymerase inhibitors, anti-sense oligomers, lipid nanoparticles/small interfering RNA and selective estrogen receptors. RNA interference (RNAi) based therapies are fast becoming a viable tool for the treatment of many diseases. RNAi is the process of sequence specific, post-transcriptional gene silencing, which suppress the expression of pathologically or physiologically important genes by using small interfering RNA (si RNA) [82]. RNAi represents a powerful natural occurring biological strategy for the inhibition of gene expression and has the ability to inhibit viral replication [83]. Ursic-Bedoya et al. [84] reported protection of guinea pigs against lethal Marburg virus mediated by lipid encapsulated siRNA. Similarly, Geisbert et al. [83] reported that post exposure protection of guinea pigs against lethal Ebola virus challenge using siRNAs targeting the polymerase (L) gene of Zaire Ebola virus. The siRNA therapy completely protected guinea pigs against viremia and death. After being successful in small animal models, the use of RNAi was tried in NHP.

In a proof of concept study, Geisbert et al. [20] demonstrated the post-exposure protection of NHP against a lethal Zaire Ebola virus challenge using siRNA targeted at L, VP 24 and VP 35 genes. The drug TKM-Ebola manufactured by Tekmira Pharmaceutical Corporation, Vancouver, Canada was developed based on RNAi technology. The drug was produced targeting 3 Zaire Ebola virus proteins L, VP 35 and VP 24 [80]. These 3 molecules were formulated as stable nucleic acid-lipid particles (SNALPs) in a novel lipid nanoparticle delivery technology. In 2010, Tekmira Pharmaceutical Co signed a contract of $140 million with US government to fast track the development of the drug. The company started phase 1 clinical trials in January 2014 and as of May 2014 has successfully completed the ascending single dose portion of the phase 1 clinical trials in healthy patients. TKM-Ebola was administered to a limited number of patients during the 2014 EVD outbreak.

Another method for the development of antiviral drug is antisense technology. The potential of oligo-deoxynucleotides to act as antisense agents that inhibit viral replication [85] has great promise against EVD. Phosphoro-diamediate-morpholino oligomers (PMOs) are synthetic molecules used to inhibit viral replication by specifically binding to RNA, which suppress the expression of selected genes by steric blockage [55]. The use of antisense PMOs as gene-specific counter measures against EVD in have been well demonstrated in rodents [30,31,33]. Warfield et al. [31] used a combination of Ebola virus specific PMO, targeted at viral mRNAs for VP 24, VP 35 and L protected rodents in both pre- and post–exposure therapeutics regimes. In a proof of prophylaxis, the authors showed that PMOs also protected 75% of rhesus macaques from lethal Ebola virus infection. Warren et al. [86] had demonstrated that AVI-6002 containing

two PMOs, one targeting VP24 (AVI-7537) and the other targeting VP35 (AVI-7539) protected over 60% of rhesus monkeys against lethal Ebola virus challenge. Warren et al. [55] further demonstrated that a single PMO targeting VP24 protected rhesus monkeys against lethal Ebola virus infection. Iversen et al. [68] reported the discovery and early development of PMO AVI-6002 comprising of AVI-7357 and AVI-7539 against Ebola virus. Sarepta Therapetics (USA) is developing and commercializing AVI-6002 containing AVI-7357 and AVI-7539. Results of phase 1 clinical studies indicated that AVI-6002 is effective against Ebola virus and is safe and well tolerated.

Drugs with broad spectrum antiviral activity are also being considered as possible therapy for EVD. For instance, favipiravir, 6-fluoro-3-hydroxy-2-pyrazine carboxamide (T-705 or Avigan) have broad spectrum antiviral properties against many RNA viruses including influenza virus, Arenaviruses, Bunyaviruses, flaviviruses, Alphaviruses, Picornaviruses and Noroviruses [87]. The authors also described favipiravir as a novel compound that selectively and potently inhibit the RNA-dependent RNA polymerase of influenza and many other RNA viruses. Caroline et al. [88] demonstrated the efficacy of favipiravir for protection from highly lethal inhalation Rift Valley fever in rats. Oestereich et al. [23] demonstrated the efficacy of favipiravir against Zaire Ebola virus in small animal model both *in-vitro* and *in-vivo*. In the small animal model experiments, this author also reported initiation of favipiravir administration at 6 day post infection induced rapid virus clearance, reduced biochemical parameters of disease severity and prevented fatality in 100% of the tested animals. In a mouse model for norovirus infection, Arias et al. [89] showed that the broad-range antiviral nucleoside favipiravir mode of action involves the reduction of viral load *in vivo* by exerting antiviral mutagenesis. In mice infected with Ebola virus, results have shown that the initiation of 150 mg/kg favipiravir twice daily within 6 days of infection induced rapid virus clearance, reduced biochemical parameters of disease severity, which led to 100% survival [23,69,90].

Favipiravir, which is produced by Toyama chemicals, Japan is currently under phase III clinical evaluation for influenza in Japan and has completed phase II in US [87] and has commenced phase 1 clinical trial for Ebola virus. During the 2014 EVD outbreak, a French nurse who contracted the disease recovered after taking favipiravir. Favipiravir was recently reported to have halved mortality in one group of Ebola virus patients in Guinea [54].

Another promising therapy for EVD is BCX.4430 produced by Biocryst Pharmaceuticals, USA. BCX.4430 is an analog of adenosine (a nucleotide) that has broad spectrum antiviral properties. BCX.4430 acts as a broad spectrum RNA polymerase inhibitor with activity against over 20 RNA viruses in various families [91]. According to Bishop [15], BCX-4430 indirectly inhibit the RNA polymerase of viruses through non-obligate RNA chain termination resulting in the termination of transcription and replication of the virus. BCX-4430 blocks viral RNA synthesis. Warren et al. [67] demonstrated that BCX-4430 could confer protection of mouse against lethal doses of Ebola virus challenge up to 96 hours post exposure. BCX-4430 also protected monkeys infected with lethal doses of Marburg virus after 48 hours post infection.

Brincidofovir (CMX 001) manufactured by Chimerix Inc. is also listed among the leading therapeutics against EVD (Table 3). Brincidofovir has antiviral activity against Ebola virus, which is an RNA virus, because Brincidofovir is a phosphonate derivative of Cidofovir, under deverlopment for Cytomegalovirus, Adenovirus and other DNA viruses. Though, there are no published data on the safety and efficacy of Brincidofovir in the treatment of EVD in human, NHPs or small animal models, it was recommended for use on compassionate grounds. In the 2014 EVD outbreak, it was used to treat 5 [15] Americans infected with Ebola virus. Other drugs that have been recently discovered showing broad-spectrum antiviral, but still under preclinical development include FGI-106 (USAMRIID), FGI-104 (functional Genetics/ USAMRIID), FGI-103 (UCLA) and LJ-001 (UCLA) [38].

3.3 Anti-inflammatory Modulators

Anti-inflammatory modulators have also been listed as effective against EVD including Type I (α,β) interferons, and S-adenosyl homocysteine hydrolase inhibitor (Table 2). Interferons are protein synthesized by the body to fight infections and have been used to successfully treat some diseases such as hepatitis and certain cancers. However, filovirus can evade the protective effects of interferons.

Table 3. Leading first generation experimental therapies for Ebola virus disease

Therapy	Manufacturer	Mode of action	Phase of development	Administration route	Remarks
ZMapp	Mapp Biopharmaceuticals Inc, USA	Cocktail of 3 monoclonal antibodies (c13c6, h-13F6, c6D8) binds and inactivates virus	Phase 1	Intravascular	Administered to 7 people of which 2 died. Completely protected monkeys from EVD
TKM Ebola	Tekmira Pharmaceuticals, Canada	si RNA which interferes with L, VP24, VP35. Gene silencing	Phase 1	Intravascular	Protect monkeys infected with Ebola virus. Used for humans under emergency in the 2014 EVD outbreak
Favipiravir (T-705 or Avigan)	Toyama Chemical/Fuji Film, Japan and Medi vector USA	Nucleotide analog that inhibits L. Broad spectrum antiviral agent. RNA chain terminator or lethal mutagenesis	Phase 1 (Ebola virus); Phase 3 (influenza)	Oral	Protect mice infected with Ebola virus
AVI 6002	Sarepta Therapeutics, USA	Antisense PMO which inhibits VP24. Gene silencing	Phase 1	Oral or intramuscular	
BCX 4430	Biocryst Pharmaceuticals, USA	Nucleoside which inhibits L. Broad spectrum antiviral agent. RNA chain terminator	Phase 1	Oral or intramuscular	Protect monkeys infected with Ebola virus
Brincidofovir (CMX-001)	ChimerixInc, USA	Ebola: unknown; CMV inhibits DNA synthesis	Phase 1 for Ebola virus, Phase 3 for CMV & ADV	Oral	Used for humans under emergency in the 2014 EVD outbreak

Sources: Bishop [15]; Butler [36]; Goeijenbier et al. [92]); Norwegian Institute of Public Health [38]; WHO [39 – 41]; Yelle [91]

Ying et al. [93] reported that when Ebola virus attacks reticuloendothelia cells, it over-produces cytokines that cause exaggerated inflammatory response, which is not protective. Smith et al. [72] reported that EVD is associated with robust production interferon-α with plasma concentrations that greatly exceed those observed in other viral infections (61–100 fold), but little IFN-β production. Kondratowicz and Maury [44] reported that filovirus encodes 2

different proteins that block induction of cytokine. Ebola virus VP 24 directly blocks IFN-α/β and IFN- γ synaling, while VP 35 inhibits Type I IFN induction. Sullivan et al. [43] reported VP 35 acts as an IFN-α/β antagonist. Similarly, Reid et al. [94] demonstrated that VP 24 inhibits interferon signaling. Furthermore, Kondratowicz and Maury [44] reported that Ebola virus directly inhibits the antiviral activities of RNAi pathway through the actions of VP 30, VP 35 and VP 40. Hence, the complete absence or reduction of type I interferons in infected macrophages and dendritic cells, which is associated with the dysregulation of the immune system, and the pronounced and aberrant cytokine profile is thought to be responsible for the inappropriately stimulated and quickly depleted immune response characteristics of fatal cases. Smith et al. [72] reported that the imbalance interferon production (robust production of IFN- α and absence of IFN-β) during Ebola virus infection leads to inefficient antiviral activity and dysregulated lymphocyte apoptosis. Smith et al. [72] demonstrated that early post-exposure treatment with IFN-β significantly increased survival time (i.e., treatment window) of rhesus macaques infected with a lethal dose of Ebola virus, but failed to prevent fatality/mortality. Similarly, Jahrling et al. [49] demonstrated that recombinant interferon –α2b delayed viremia and death several days in monkeys challenged with Ebola virus. Leung et al. [95] reported that EBOV VP 35 contributes to virulence through the evasion of host immune system and viral RNA synthesis. Similarly, Watanebe et al. [29] reported that V 24 is important for EBOV to evade the antiviral effects of IFNs. Hence, interferon therapies is often considered in combination with other therapies. For instance, Qiu et al. [25] demonstrated that monoclonal antibodies combined with Adenovirus-vectored interferon significantly extend the treatment window in Ebola virus infected guinea pigs. Administration of the combination therapy at 3 days post infection (dpi) provided 100% survival, which was a significant improvement over survival with either treatment alone. In a follow up study, Qiu et al. [25] demonstrated that administration of monoclonal antibodies (ZMAS) combined with Adenovirus vectored IFN-α therapy rescued Ebola virus infected cynomolgus and rhesus macaques and 100% rhesus macaques survived when treatment was administered after detection of viremia at 3 dpi.

Huggins et al. [96] reported that S-Adenosyl homo-cysteine hydrolase inhibitors inhibit Ebola virus *in vitro* in a lethal mouse model. They demonstrated 100% survival when treatment was initiated at 0 or 1 dpi, 90% survival at 2 dpi and 40% survival at 3dpi. Based on these results, they claimed that carbocyclic 3- deazadenosine is the first compound demonstrated to cure animals with a lethal Ebola virus infections.

Due to the dysfunctional effect of Ebola virus on the blood system (coagulopathy), anti-coagulants are also being considered as possible cure for EVD. Some of the commonest anticoagulants with demonstrated efficacy include recombinant human activated protein C (rhAPc) and recombinant nematode protein C2 (rNAPC2) and to a lesser extent heparin sulphate (Table 2). Hensley et al. [75] reported that infection of primate with ZEBOV leads to hypertension, coagulation disorders and impaired immune system similar to Serra sepsis, which is characterized by rapid decreases in plasma levels of protein C. The authors demonstrated that human activated protein C (Xigris, licensed for treating patients with severe sepsis) delayed death of monkeys to about 12.6 days while only 2 out of 11 treated monkeys i.e. 18% survived. Geisbert et al. [73] reported that Ebola virus infection induces over expression of pro-coagulant tissue factor in primate monocytes and macrophages, suggesting an inhibition of the tissue-factor pathway. The authors further demonstrated that treatment with rNAPc2 (a potent inhibitor of tissue factor initiated blood coagulation) results in prolong survival of rhesus monkeys challenged with Ebola virus with 33% survival rates. These modest results obtained could be enhanced by the use of combination therapies. Other anti-coagulants such as melatonin have been tested in rats and humans [97–99]. According to Tan et al. [100], melatonin is a potent free radical scavenger and an anti-inflammatory agent. Masters-Israilov et al. [101] reported the potential usefulness of melatonin in the treatment of EVD. The authors reported that melatonin has certain features useful against complications arising from EVD such as antioxidant, anti-inflammatory and anti-coagulopathic properties.

3.4 Other Purpose Drugs

The FDA has approved drugs for other purposes, and some of these have potential usage against Ebola virus (Table 4). These drugs include anti-malarial drugs such as chloroquine and amodiaquine [102,103], selective estrogen receptor modulators; clomiphene and toremifene

[21] and cationic amphiphiles, which induce a Niemann-Pick C phenotype that inhibit Ebola virus entry and infection [104]. Kouznetsova et al. [103] screened several FDA approved drugs for other purposes and found about 53 candidates that can block Ebola virus entry. Of these, about 11 have been demonstrated for anti-Ebola virus activity (Table 4). Other purpose drugs that have been considered against Ebola virus disease include antivirals (Lamivadine), vitamins (vitamin P/Rutin, Vitamin C, retimazone/vitamin A and statins (Table 4). Kesel et al. [105] reported that refinazone inhibit certain blood-borne human virus including ZEBOV. Mannose-binding lectins have been reported to be effective against Ebola and Marburg viruses [77,78].

Table 4. FDA approved other purpose drugs with potential use against Ebola virus disease

Treatment types	Drugs	Usual uses	Mechanism against Ebola virus	References
Cationic amphiphilis	Clomiphene ^ Toremifene*^ Amiodarome Dronedarone Verapamil	Ovulation reduction Breast cancer Anti-arrhythmics Anti-arrhythmics Anti- hypertension	Induce a Niemann-Pick C-like phenotypes and block the entry of Ebola virus through late endosomes	[15,21,104,106,107]
	Clomiphene* Toremifene*	Ovulation reduction Breast cancer	Inhibits virus entry	[15,21,103]
Anti-malaria	Chloroquine*	Anti-malaria	It prevents acid dependent cleavage of Ebola virus $GP_1$by endosomal proteases. Attacks Ebola virus VP35	[15,102,103,106]
	Amodiaquine*	Anti-malaria	Attacks Ebola virus VP35	[102,103,106]
Antiviral	Lamivudine	Antiviral drug approved for the treatment of HIV and hepatitis B virus		[15]
	Ribavirin	Broad spectrum antiviral agent. It is a synthesized guanosine analog that could inhibit RNA dependent RNA polymerase used for the treatment of hepatitis C and several other viral hemorrhagic diseases		[18,46,48,49,76,93,96]
Statins		A class of drugs used to lower cholesterol levels	Anti-inflammatory and anti immuno-modulatory agent; positive effect on coagulation	[15,107,108]
Vitamins	Vitamin P /Rutin	Used to treat Crimean-Congo hemorrhagic fever	Protect barrier integrity via its ability to inhibit	[107]

Treatment types	Drugs	Usual uses	Mechanism against Ebola virus	References
			adhesion of viral particles	
	Vitamin C	Used to treat Crimean-Congo hemorrhagic fever	Prevent endothelial dysfunction	[76,107]
	Retinazone*	Antiviral agent		[105]
Na^+/K^+-ATPase pump inhibitors	Ouabain, digoxin, digitoxin,	Cardiac glycosides	Inhibit viral replication	[106]
Na^+/K^+ exchangers	Amiloride& its derivatives	Used as potassium sparing diuretics to treat hypertension and congestive heart failure	It inhibits entry and infection of Ebola virus. It inhibit RNA synthesis	[106]
Antioxidants	N-acetyl-cysteine	Pregnancy drug	Possibly manage Ebola virus induced cytokine dysregulation	[106]
Other approved drugs	Melatonin*	An hormone used to cure sleeping disorders	Anti-inflammatory and anti-coagulant , free radical scavenger	[97-100,107]
	Nocodazole*	Widely-used as a cell cycle synchronizing agent to induce mitotic arrest		[103]
	Tamoxifen*	used to treat some types of breast cancer		
	Cepharanthine*	used for the treatment of many acute and chronic diseases. Antitumor agent		
	Zoloft (Sertraline)*	used to treat depression, obsessive-compulsive disorder, panic disorder, anxiety/stress disorders		
	Raloxifene*^	Treats and prevents osteoporosis (weak or thin bones) in women who are past menopause.		
	Nilotinib*	used to treat certain types of chronic myeloid leukemia		
	Imipramine*	Treats depression		

** tested for anti-Ebola virus activity [103], ^ also called Selective Estrogen Receptor Modulators (SERMS)*

Finally, three potential anti-EVD therapies that have been strongly criticized are: bitter kola (*Garcina kola*), Ribavirin and nanosilver. Ribavirin is a broad spectrum antiviral agent that has been used to treat many viral infections including other hemorrhagic fevers, but some authors have reported that the drug is ineffective against Ebola virus [48,96]. Ribavirin when incorporated into the viral genome causes lethal mutagenesis and a subsequent decrease in the specific infectivity of RNA viruses [109]. It is therefore surprising that ribavirin, which is an antiviral nucleoside analog that is mutagenic to several RNA viruses is not effective against Ebola virus. More research is therefore required to demonstrate the infectiviteness of Ribavirin against Ebola virus.

Iwu et al. [70] reported the antiviral properties of bitter kola, but the botanical has never been demonstrated as effects against EVD in small animals, NHPs or human models. No published report on the use of nanosilver against EVD apart from un-published 2009 US Department of Defense funded study [71]. It has been well demonstrated that nanosilver is effective against monkey pox virus [110], HIV [111], Tacaribe virus [112] and some bacteria [113,114]. Since there are still no approved therapies or prevention vaccines against EVD, and the death toll continues to increase, the research community and drug manufacturing companies should not be in haste to discard any potential lead, but all options should remain on the table for consideration.

4. CONCLUSION

Ebola virus that emerged in West Africa in March 2014 has caused the death of about 8,000 persons as of 31 December 2014, with the highest cases being reported in Sierra Leone, Guinea and Liberia. Ebola virus disease is a severe and often fatal disease in humans and other primates caused by the virus in the genus Ebola and belonging to the Filoviridae family. Ebola viruses are evasive, with the capacity of inhibiting type I interferon activity, and therefore reducing or destroying the host immune response. The genome of Ebola virus has genes that encode for proteins including GP, NP, VP24, VP40, VP30 and VP35, which facilitate the evasiveness and pathogenesis of the virus. But there have been no licensed drug or preventive vaccine for combating EVD. The scientific community has intensified research on potential therapeutics against EVD. Promising therapies against EVD can be broadly classified into antibody therapies, specific antiviral therapies for Ebola virus, anti-inflammatory therapy and anticoagulants. First generation EVD experimental drugs that have emerged include ZMapp, TKM-Ebola, Favipiravir (T-705 or Avigan), AVI 6002, BCX 4430 and Brincidofovir (CMX-001). These first generation therapeutics have been tested in small animal and non-human primates before being considered in human clinical trials. Though not yet licensed, the WHO and /or FDA have endorsed their limited use on compassionate grounds during an outbreak.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist. The mention of products/drugs in this manuscript does not mean that the author or publishers have endorsed their use.

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