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Antibody Therapeutics for Ebola Virus Disease

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Abstract

With the unprecedented scale of the 2014–2015 West Africa outbreak, the clinical and scientific community scrambled to identify potential therapeutics for Ebola virus disease (EVD). Passive administration of antibodies has a long successful history for prophylaxis and therapy of a variety of infectious diseases, but the importance of antibodies in EVD has been unclear and is the subject of some debate. Recent studies in non-human primates have renewed interest in the potential of antibodies to impact EVD. Currently ongoing clinical evaluation of polyclonal and monoclonal antibody therapy in EVD patients in West Africa may finally offer a definitive answer to this debate.

Graphical Abstract

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Introduction

The 2014–2015 West African outbreak of Ebola virus (EBOV) has been the largest and most challenging to contain since identification of the filoviruses. During this outbreak, over 28,000 people have been infected and over 11,000 of these patients have died from Ebola virus disease (EVD). With no licensed vaccines or therapeutics available for treating EVD, the clinical and scientific community mobilized to determine whether any experimental drugs could be effective. Antibody-based treatments, both blood-based (e.g. whole blood, plasma) and recombinantly manufactured (i.e. monoclonal antibodies; mAbs), have previously been shown to provide benefit in non-human primate (NHP) models of EVD, and in early 2015 several of these began clinical evaluation in EVD patients. This review focuses on the historic evidence for and against the utility of antibodies in EVD as well as the clinical evaluation of polyclonal and monoclonal antibody based products during the current outbreak.

Passive Immunization

Mammals have been exploiting the benefits of passive delivery of antibodies for millions of years: colostrum and breast milk have very high concentrations of antibodies of specificities ideal for the specific environment the newborn is introduced to (i.e. the mother's antibody repertoire is against the pathogens she has been exposed to and that the newborn is likely to encounter). Much more recently, humans have made use of blood-based antibody products for treating a variety of infectious diseases [1–3]. The clinical use of antibody therapy declined with the introduction and wide availability of antibiotics. However, with recent advances in manufacturing of mAbs, the clinical and commercial success of oncology and autoimmunity mAb products, and the increasing occurrence of antibiotic resistance, interest in antibody therapy for infectious disease has experienced a resurgence. Polyclonal blood-derived antibody products have been developed for a variety of infectious disease indications (e.g. anthrax, cytomegalovirus, hepatitis B, rabies, tetanus toxin, varicella-zoster), and mAb products are available for anthrax (Raxibacumab; GSK) and Respiratory Syncytial Virus (Palivizumab; MedImmune).

Antibodies have several appealing characteristics as a drug platform. Antibody based drugs have a lower risk of failure through the development process [4,5], in part because of their high specificity and the resulting reduced likelihood of off target binding. With over 40 mAb products licensed in the U.S. and Europe, many of the inherent risks in manufacturing, formulation, and characterization have been addressed compared with other classes of new chemical entities.

Despite the historic successes of passive immunization, its value for EVD has been a subject of debate. In a report of eight patients treated with convalescent blood during the 1995 Kikwit outbreak, seven survived [6]. However, a number of concerns were raised by the authors and others [7] as to what conclusions could be drawn from these uncontrolled data. NHP studies that have continued to examine antibody therapy for EVD are reviewed below, followed by a summary of the ongoing antibody therapy clinical studies that may finally settle this uncertainty.

Efficacy of Passive Immunization in Non-Human Primates

This review is limited to antibody treatments that have been evaluated in NHPs, the model generally agreed to be most representative of human EVD. An important caveat is that the standard NHP model employs an intramuscular (IM) challenge, a reasonable surrogate for needlestick injuries. However to mimic more typical exposures that family members and healthcare workers experience with infectious fluids (e.g. mucus, blood) a useful alternative model would be a mucosal challenge (e.g. intranasal). Directly breaching the mucosa and skin with a needle for an IM challenge is likely to serve as a higher bar for evaluating potential therapeutics than mucosal exposure, so the regimens that were effective (Table 1) against IM challenge could be expected to be at least as effective against a mucosal challenge.

In what was likely the first NHP EVD study with passive immunization, Russian scientists tested an equine hyperimmune IgG preparation using a baboon model and a low viral challenge (10–30 LD₅₀). The equine IgG provided 100% protection when given prior to, or up to one hour after challenge, with survival dropping to 29% when animals were dosed two hours post-infection [8]. This product was subsequently evaluated by USAMRIID scientists using a more robust (and now standard) challenge (1000 pfu) in cynomolgus macaques [9,10]; Table 1) and found to provide no protection when given prior to or on the day of challenge, and partial protection (33%) when given on the day of infection and on day five post-infection (dpi).

After clinical failures with murine monoclonal antibodies for several different indications, the belief in the importance of species matching (e.g. human antibodies for human administration) increased. By the mid to late 1990s, most antibody drug developers were moving towards more human-like antibody products, either by chimerization of murine mAb variable regions with human constant regions, humanization of murine mAbs (“CDR grafting”), or by use of fully human mAbs. Indeed, in the late 1990s Maruyama *et al.* identified a potent neutralizing mAb (designated KZ52) from an EVD survivor [11] that protected guinea pigs when delivered at a dose of 25 mg/kg one hour after challenge, but not when dosing occurred six hours after infection [12]. When KZ52 was tested in NHPs with dosing one day prior and four days post infection (dpi), no evidence of protection was observed in three of four treated animals [13]. In addition to an absence of a survival benefit in these animals, no change in viral replication or any impact on the course of disease was observed. The fourth animal was euthanized when it became moribund 28 dpi at which point no virus was detected in serum, but viral loads were detected in various organs. The authors did not find evidence of neutralization escape mutants complicating the reconciliation of the

observed high serum levels of neutralizing mAb with the lack of impact on the viral load in serum detected by plaque assay. It appeared in this study that neutralization of free virus in blood had minimal impact on the course of EVD and viral load.

To investigate, in part, whether species matching in NHPs could be relevant, in 2007 Jahrling *et al.* treated four naïve macaques with whole blood from convalescent-phase macaque donors immediately after challenge [7]. Two of the recipients received a second transfusion on day three after challenge with EBOV, and the other two received the second transfusion on day four after challenge. Although serum levels of antibody comparable to those associated with effective vaccination were obtained, all treated animals succumbed to infection in the same time frame as controls. Given the results to date with polyclonal and monoclonal antibodies, the authors reasonably suggested that continued investment in antibody therapeutics for EBOV should be questioned.

It was another five years before the first success with antibody post-exposure prophylaxis was demonstrated by Dye *et al.* [14]. In this study, IgG was purified from convalescent serum of macaques vaccinated with an experimental vaccine and survived subsequent challenge. With 80 mg/kg doses of total IgG administered two, four, and eight dpi, 100% protection was observed. The purified IgG preparation had EC₅₀ and EC₈₀ values of approximately 5 and 15 µg/ml in a plaque reduction neutralization assay. Interestingly, the purified IgG was less potent in plaque reduction than reported for KZ52 which failed to provide protection to NHPs [13]. Although dosing in the Dye *et al.* study was similar in total IgG compared to Jahrling *et al.* (2007), the efficacy was dramatically better for reasons that are unclear. There may have been antibody titer and/or specificity differences between the two studies, or there may be some benefit to dosing with purified IgG as opposed to serum.

The efficacy observed with the purified polyclonal NHP IgG was quickly followed by demonstrations of partial protection with a two mAb cocktail with pre-exposure dosing [15], and of partial or complete protection with post-exposure treatment one to two dpi with cocktails of three murine (ZMAb) or three chimeric (MB-003) mAbs. Qiu *et al.* reported 100% and 50% protection when post-exposure treatment was initiated one or two dpi in cynomolgus macaques [16], a species that experiences faster EVD progression than rhesus macaques. Olinger *et al.* reported 67% efficacy with a mouse-human chimeric mAb cocktail (MB-003) initiated one or two dpi [17]. Notably the MB-003 mAbs were produced in a novel expression system that yields afucosylated mAbs. A comparison of fucosylated and afucosylated versions of MB-003 suggested that afucosylation was important for the efficacy of the MB-003 mAbs, indicating a role for ADCC in protection [17,18]. With the success of the *post-exposure* evaluation of MB-003, the mAb cocktail was subsequently evaluated in a *therapeutic* study in which both a PCR positive test and a fever were required triggers for treatment [19]. Animals received their first of three doses on day four after infection. Three of seven treated animals survived, demonstrating partial therapeutic efficacy.

The developers of ZMAb and MB-003 subsequently collaborated to chimerize the ZMAb mAbs and to identify the best combination of three mAbs from the two cocktails [20]. Using the guinea pig model for initial down-selection and the NHP model for identifying the final combination now known as ZMapp™, the authors showed 100% protection when the mAb

cocktail was administered as late as five dpi and described examples of reversion of EVD in rhesus macaques. This study was performed in June of 2014 just as the 2014–2015 West Africa Ebola outbreak was gaining momentum. As such, no dose optimization studies (e.g. frequency or number of doses) had occurred by the time ZMapp was first used compassionately in August 2014.

Clinical Evaluation of Passive Immunization during the 2014–2015 West Africa Outbreak

In August 2014, the World Health Organization (WHO) published a report supporting the use and evaluation of experimental treatments for EVD [21]. Among the various trials initiated, six trials were begun using either whole blood or plasma infusion to treat EVD patients. Dosing in most of these studies is a single transfusion with blood or plasma from one or two convalescent donors. A 400 mL unit of convalescent blood or plasma contains roughly 4 grams of total IgG, only a fraction of which would be expected to be specific for EBOV. For a 70 kg patient, this translates to a 57 mg/kg total IgG dosage (and likely an EBOV-specific IgG dosage of < 1 mg/kg). This total IgG dose is similar to that used in NHP studies by Jahrling *et al.* and Dye *et al.* [7,14], but both of these NHP studies included multiple doses and in only one of these two studies was protection observed. Assuming the NHP model has predictive value for humans, it is likely that the amount of EBOV-specific antibody transfused in these clinical studies was insufficient to have an impact on EVD. For the purposes of comparison, 100–750 mg/kg total IgG doses (approximately 2–6-fold more than in a unit of blood), are used for three FDA licensed anti-viral polyclonal products (RespiGam for RSV; CMV-IGIV for cytomegalovirus; VIGIV for vaccinia/smallpox). The levels of viral load and the extent of dissemination of infections by RSV, CMV and vaccinia are dramatically lower than those observed in EVD patients [22–24], who can experience fully disseminated viral loads of well above 10^7 viral particles/mL [25]. Further, these polyclonal immunoglobulin products are prepared from a much larger pool of donors than used in the EVD studies, where preparation of more diverse pools is logistically challenging. These observations in total suggest that larger antibody doses may be required to observe a clinical effect in EVD. Indeed, data from an EVD patient treated at Royal Free Hospital (London, UK) sequentially with polyclonal antibody (in the form of convalescent plasma; CP) and the ZMAb monoclonal antibody cocktail support this hypothesis (Figure 1). Infusion of CP (~ 60 mg/kg of total IgG) resulted in a minor increase in measurable blood anti-Ebola IgG levels and had no discernible impact on the increasing viral load in the patient. In contrast, treatment with ZMAb (50 mg/kg of EBOV-specific IgG) resulted in a dramatic increase in anti-Ebola IgG levels temporally associated with reversal of the patient's increasing viral load. An 8-fold reduction in viral load (Ct value change from 13 to 16) was observed within a day of the first ZMAb dose, and the reduction continued until the patient cleared virus and was released. Considering that the level of anti-EBOV glycoprotein IgG was the main immune correlate of protection in NHPs identified by several groups [26–28], these data highlight the likely importance of characterizing, controlling, and maximizing the anti-Ebola IgG levels in CP clinical efforts.

In addition to blood-based products, one recombinant mAb cocktail product, ZMapp, is currently under clinical evaluation. A three dose regimen of ZMapp (50 mg/kg of EBOV-specific IgG) is the first therapeutic being evaluated under a Master Trial Protocol being run

by the National Institutes of Health in partnership with U.S. and West African academic institutions and health authorities of Liberia, Sierra Leone and Guinea [29].

Conclusions

Antibodies have played a critical role in the evolution of our species, and over the past 100 years passive immunization has been exploited by humans for treating a variety of infectious diseases. Recent evidence from NHP studies has demonstrated that post-exposure and therapeutic antibody treatment is capable of impacting the course of EVD. Given the aggressive nature and high viral loads in EVD as well as data from NHPs and an anecdotal case study in a human EVD patient, it is our opinion that whole blood or plasma infusions are unlikely to have an impact in EVD patients unless significantly higher doses are administered. Whether more potent preparations of recombinantly manufactured mAbs can be effective clinically will hopefully be determined in the currently ongoing trial in West Africa.

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Highlights

- Antibody therapy has historically been successful against a wide variety of pathogens
- Only recently have antibodies shown efficacy in non-human primates against Ebola
- Ongoing trials may determine if antibodies are clinically effective against Ebola

Figure 1. Changes in plasma viral load (qPCR Ct) and in Ebola Makona protein reactivity (Antibody Reactivity), post convalescent plasma (CP) and ZMAb administration in an EVD patient

Sequential patient plasma and sera taken days post illness onset were tested by quantitative RT-PCR to Zaire species viruses and indirect ELISA against Ebola Makona infected cell and control lysates (replicates; qPCR n=2 for Ct<30, n=6 for Ct>30. n=3 for EIA). Patient received a unit of convalescent plasma (CP) on days 2 and 3 post illness onset and a dose of ZMAb (50 mg/kg) on days 6 and 9 post illness onset.

Table 1**Macaque EVD Studies with Antibodies**

	NHP Species	Antibody Species	Antibody Dose ¹	Timing of dosing (days) with respect to challenge	Survival (%)	Reference
Equine hyperimmune IgG	Cynomolgus	Equine	120 mg/kg	-2	0/3 (0)	[9,10]
				0	0/6 (0)	
				0, +5	1/3 (33)	
Blood from convalescent NHPs	Rhesus	NHP	6 mL/kg ²	0, +3	0/2 (0)	[7]
				0, +4	0/2 (0)	
				-1, +4	0/4 (0)	
Purified IgG from convalescent NHPs	Rhesus	Human	50 mg/kg	+2, +4, +8	4/4 (100)	[14]
				-1, +1, +3	1/3 (33)	
				+1, +4, +7	4/4 (100)	
ZMAb (1H3, 2G4, 4H7)	Cynomolgus	Murine	25 mg/kg	+2, +5, +8	2/4 (50)	[16]
				+1, +4, +7, +10	2/3 (67)	
				+2, +5, +8, +10	2/3 (67)	
MB-003 (c13C6, c6D8, h13F6)	Rhesus	Chimeric	50 mg/kg	+4, +7, +10	3/7 (43)	[19]
				+3, +6, +9	6/6 (100)	
				+4, +7, +10	6/6 (100)	
ZMapp (c13C6, c2G4, c4G7)	Rhesus	Chimeric	50 mg/kg	+5, +8, +11	6/6 (100)	[20]

Viral challenge in all experiments was 1000 pfu delivered intramuscularly. Although an LD₅₀ has not been established, 1000 pfu is frequently equated with ~1000 LD₅₀.

¹This represents total antibody dose. For the polyclonal examples (hyperimmune IgG, blood, purified IgG from convalescent plasma), only an unknown fraction – likely no greater than 1% – of the antibody would be EBOV-specific.

²NHP serum contains ~15 mg/mL IgG [30].