International Journal of Basic & Clinical Pharmacology
Garg R. Int J Basic Clin Pharmacol. 2022 May;11(3):285-289
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20221047

New Drug Update

Inmazeb: new hope for Zaire Ebola virus disease

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Received: 30 January 2022
Accepted: 28 February 2022

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ABSTRACT

Ebola virus disease first appeared in 1976 in Zaire (now democratic republic of Congo). Since then virus outbreaks occurred periodically in African countries. The cases notified in March 2014 in west Africa was largest outbreak till now. In 2020 there is ongoing outbreak of Zaire Ebola virus in democratic republic of Congo. Ebola virus is single stranded RNA virus which causes viral hemorrhagic fever in humans presenting as high fever, chills, loss of appetite, myalgia, headache. Till now there was no specific treatment, symptomatic treatment methods including infusion of electrolyte and/or antibiotics were mainly used. In October 2020 FDA approved the first treatment for Zaire Ebola virus disease in adult and pediatric patients, including neonates born to a mother who is RT-PCR positive for Zaire ebolavirus infection. The treatment is called Inmazeb, combination of three recombinant human IgG1κ monoclonal antibodies (Atoltivimab, Maftivimab, and Odesivimab-ebgn) each targeting the Zaire ebolavirus glycoprotein.

Keywords: Ebola virus, Inmazeb, Atoltivimab, Maftivimab, Odesivimab

INTRODUCTION

In the year 1976, first outbreak of Ebola virus disease was in Zaire (now The democratic republic of Congo).[1] Since then, virus outbreaks have occurred periodically in African countries.[2] The cases notified in March 2014 in West Africa were the largest outbreak till now.[3] Again there was a Kivu Ebola outbreak in 2018 in the democratic republic of Congo. In 2020 there is an ongoing outbreak of the Zaire Ebola virus in the democratic republic of Congo.[4]

Ebola virus genome is single-stranded negative-sensed RNA. The virion contains seven proteins: nucleoprotein, viral proteins 24, 30, 35, 40, glycoprotein (GP), and L protein.[5] Figure 1 shows structure of the Ebola virus.[6]

The single stranded RNA of the Ebola virus is wrapped around proteins NP, VP35, VP30, and L. VP40 and VP24 lie below lipid layer. Glycoproteins spike outside from the envelope.

Five species of the Ebolavirus have been identified belonging to the family *Filoviridae* and genus Ebola virus: Zaire, Bundibugyo, Sudan, Reston, and Tai Forest).[5,7] The virus causing 2014 West African outbreak belongs to Zaire species. The new strain of Ebola is called Ebola Tai (WHO).[8]

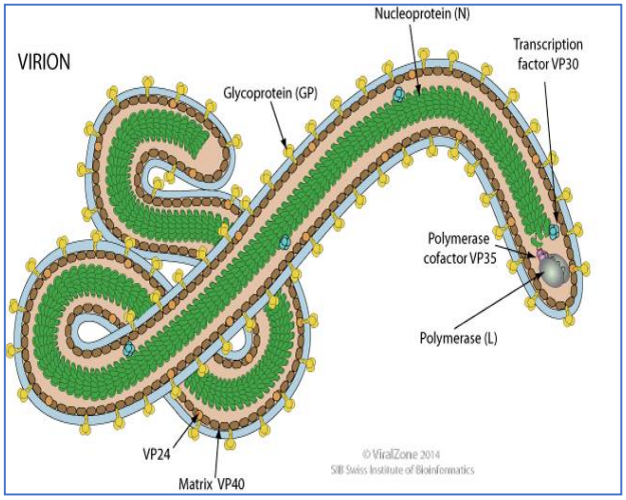

Figure 1: Structure of Ebola virus.[6]

TRANSMISSION ROUTES

Transmission of Ebola occurs through Fruit bats of the *Pteropodidae* family, which are natural Ebola virus hosts.[9] Ebola gets introduced into humans through close contact with the blood, secretions, organs of infected animals such as chimpanzees, gorillas, fruit bats, monkeys, forest antelope, and porcupines found ill or dead or in the rainforest. Human-to-human transmission of Ebola is by direct contact (through broken skin or mucous membranes) with the blood, or body secretions (e.g., saliva, mucus, vomit, feces, sweat, tears, breast milk, urine, and semen) from symptomatic/dead patients, organs or other bodily fluids of infected people, and with surfaces and materials (e.g., bedding, clothing) contaminated with these fluids.[3]

EBOLA VIRUS DISEASE

Ebola virus disease presents as viral hemorrhagic fever in humans beginning 4 to 10 days after the infection. Symptoms are high fever, chills, loss of appetite, myalgia, headache, etc. As the disease advances, symptoms like vomiting, diarrhea, chest pain, cough, bleeding, and coma may occur.[10,11] Till now there was no specific treatment; symptomatic treatment methods, including infusion of electrolyte and antibiotics, were mainly used.[10,12]

The first drug used experimentally against Ebola virus disease was an agent called ZMapp developed in the tobacco plant *Nicotiana benthamiana* in the bioproduction process known as "pharming." ZMapp is a drug cocktail of antibodies made against the Ebola virus. Leaf Biopharmaceutical (LeafBio, Inc.), a San Diego-based arm of Mapp Biopharmaceutical, is developing the composite drug.

ZMapp (investigational drug) was first used during the 2014 West Africa Ebola virus outbreak, having not previously undergone any human clinical trials to determine its efficacy or potential risks.[13]

In December 2019 FDA (Food and drug administration) approved Ervebo, the 1st vaccine for preventing Ebolavirus disease.[14]

After that, in October 2020 FDA approved the first treatment for Zaire Ebola virus disease in adult and pediatric patients, including neonates born to a mother who is RT-PCR positive for Zaire ebolavirus infection.[14]

The treatment is called Inmazeb (formerly called REGN-EB3 (REGN3470-3471-3479), by Regeneron pharmaceuticals is the combination of three recombinant human IgG1κ monoclonal antibodies (Atoltivimab, Maftivimab, and Odesivimab). The drug is granted orphan drug and breakthrough therapy designation by FDA.[14,15]

MECHANISM OF ACTION

All three monoclonal antibodies target the Zaire ebolavirus glycoprotein (GP). Surface protein or glycoprotein mediates virus attachment and membrane fusion with the host cell membranes. Three antibodies that makeup Inmazeb bind to this glycoprotein simultaneously and block attachment and entry of the virus. Maftivimab is a neutralizing antibody that blocks the entry of the virus into susceptible cells. Odesivimab is a non-neutralizing antibody that induces antibody-dependent effector function through FcγRIIIa signaling when bound to its target. Odesivimab also binds to the soluble form of Zaire ebolavirus glycoprotein (sGP). Atoltivimab combines both neutralization and FcγRIIIa signaling activities.

Also, GP is expressed on the surface of Zaire ebolavirus infected host cells, making it a target for antibodies that can mediate killing of these cells by antibody dependent-cellular cytotoxicity and other effector functions.[15,16]

CLINICAL PHARMACOLOGY

Pharmacodynamics

Atoltivimab, Maftivimab, and Odesivimab exposure-response relationships and the time course of pharmacodynamic response are unknown.[16]

Pharmacokinetics

No pharmacokinetic data are available in patients with Zaire ebolavirus infection. Pharmacokinetics in renal and hepatic impairment patients is unknown. Pharmacokinetics was linear and dose-proportional over the range of 1 mg of atoltivimab, 1 mg of maftivimab, and 1 mg of odesivimab per kg to 50 mg of atoltivimab, 50 mg of maftivimab, and 50 mg of odesivimab per kg (0.02 to 1 times the approved recommended dosage) of Inmazeb following a single intravenous (IV) infusion. The pharmacokinetics of atoltivimab, maftivimab, and odesivimab given as single intravenous infusion in 18 healthy subjects 21 to 60 years of age is summarized in Table 1.[16]

Table 1: Pharmacokinetic parameters of INMAZEB administered IV in healthy subjects.[16]

Variables	Atoltivimab, 50 mg/kg[a]	Maftivimab, 50 mg/kg[a]	Odesivimab, 50 mg/kg[a]
Systemic exposure, (n=6)			
Mean (SD) $C_{max,}$ mg/L	1,220 (101)	1,280 (68.0)	1,260 (81.2)
Mean (SD) AUC inf, mg day/L	17,100 (4,480)	18,700 (4,100)	25,600 (5,040)

Continued.

Variables	Atoltivimab, 50 mg/kg[a]	Maftivimab, 50 mg/kg[a]	Odesivimab, 50 mg/kg[a]
Distribution			
Mean (SD) volume of distribution at steady state, mL/kg	58.2 (2.66)	57.6 (3.89)	56.0 (3.16)
Elimination			
Mean (SD) elimination half-life (days)	21.2 (3.36)	22.3 (3.09)	25.3 (3.86)
Mean (SD) clearance (mL/day/kg)	3.08 (0.719)	2.78 (0.558)	2.02 (0.374)

[a]Inmazeb was administered at a total dose of 50 mg of atoltivimab, 50 mg of maftivimab, and 50 mg of odesivimab per kg in a 1:1:1 ratio

DRUG INTERACTIONS

Vaccine interactions

No vaccine-therapeutic interaction studies have been performed in human subjects using Inmazeb. Inmazeb inhibit replication of live vaccine virus indicated for prevention of Zaire Ebola virus infection and reduce the efficacy of the vaccine, avoid the concurrent administration of a live vaccine during treatment with Inmazeb.[16]

Immuno-genecity

The development of anti-atoltivimab, anti-maftivimab, and anti-odesivimab antibodies was evaluated in 24 healthy adults in a single dose, randomized, double-blind, placebo-controlled, dose escalation study. Immunogenic responses against atoltivimab, maftivimab, and odesivimab were not detected at baseline or through 168 days post-dose in any subjects.[16]

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenicity, genotoxicity, and fertility studies have not been conducted with Inmazeb.[16]

Use in special population[16]

Zaire ebolavirus infection is life-threatening for both the mother and fetus and treatment should not be withheld due to pregnancy. High rate of maternal and fetal/neonatal morbidity have been shown with Inmazeb. Data are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal/fetal outcome. Animal reproduction studies with Inmazeb have not been conducted. Inmazeb, is transported across the placenta and has potential to be transferred from the mother to the developing fetus.

Patients with confirmed Zaire ebolavirus should not breastfeed their infants to reduce the risk of postnatal transmission of Zaire ebolavirus infection. There are no data on the presence of Inmazeb in human milk. The safety and effectiveness of Inmazeb have been established in pediatric patients from birth to less than 18 years of age. For Geriatric age group, clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

DRUG DOSAGE AND FORMULATION

Inmazeb is clear to slightly opalescent and colorless to pale yellow solution available as injection.[16] Inmazeb is a combination of three human monoclonal antibodies co-formulated in a 1:1:1 ratio of atoltivimab, maftivimab, and odesivimab. The recommended dosage is 50 mg of atoltivimab, 50 mg of maftivimab, and 50 mg of odesivimab per kg diluted and given as single intravenous infusion.[16] Dilution should be done in either 0.9% sodium chloride Injection, USP, 5% dextrose injection, USP, or lactated Ringer's injection, USP. For neonates, 5% dextrose Injection, USP is recommended. Mix the diluted solution by gentle inversion. Do not shake.

Inmazeb does not contain preservatives. It is recommended to administer intravenous medication immediately after preparation when possible.[16]

ADVERSE EFFECTS

Adverse events reported were pyrexia, chills, tachycardia, tachypnea, and vomiting. Hypersensitivity reactions including infusion-associated events have been reported during and post-infusion.[16]

CONTRAINDICATIONS

No contraindications have been reported.[16]

CLINICAL TRIALS

Clinical trial conducted to assess the safety and efficacy of Inmazeb

FDA approval of Inmazeb was based on PALM trial, a multi-center, open-label, randomized controlled trial sponsored by the national institute of allergy and infectious diseases (NIAID; NCT03719586). The trial enrolled 681 subjects of all ages, including pregnant women with documented Zaire ebolavirus infection. Trial was conducted in the democratic republic of Congo, where an outbreak began in August 2018. The safety and efficacy of Inmazeb was evaluated in 382 adult and pediatric subjects. The 154 subjects (115 adult subjects and 39 pediatric subjects) received Inmazeb [50 mg of atoltivimab, 50 mg

of maftivimab, and 50 mg of odesivimab per kg (3 mL/kg)] intravenously as a single infusion and 168 subjects received an investigational control, 50 mg/kg intravenously every third day, for a total of 3 doses. Eligible subjects had a positive reverse transcriptase polymerase chain reaction (RT-PCR) for the nucleoprotein (NP) gene of Zaire ebolavirus and had not received other investigational treatments within the previous 30 days. Neonates ≤7 days of age were eligible if the mother had documented infection

The primary efficacy endpoint was 28-day mortality. Patients receiving Inmazeb showed a mortality rate of 34% at day 28, while those in the control group showed a 51% mortality rate. The PALM trial showed statistically significant reduction in mortality for Inmazeb compared to control.[16]

Mortality efficacy results are summarized in Table 2.[16]

Table 2: Mortality rates in PALM trial.[16]

Efficacy endpoints	Inmazeb[a], (n=154)	Control[a], (n=153)
Overall		
28-day mortality, n (%)	52 (34%)	78 (51%)
Mortality rate difference relative to control (95% CI)	-17.2 (-28.4, -2.6)	
P value[b]	0.0024	
Baseline viral load		
High viral load (CtNP ≤22)[c]	N=66	N=64
28-day mortality, n (%)	42 (64%)	56 (88%)
Mortality rate difference relative to control (95% CI)	-23.9 (-43.8, -6.4)	
Low viral load (CtNP >22)[c]	N=88	N=88
28-day mortality, n (%)	10 (11%)	22 (25%)
Mortality rate difference relative to control (95% CI)	-13.6 (-31.8, -1.4)	

[a]Both INMAZEB and control were administered with an optimized standard of care. [b]Result is significant according to the interim stopping boundary, p<0.028. [c]Cepheid GeneXpert Ebola® Assay used for detection of Zaire ebolavirus RNA.

The most common adverse events reported in at least 20% of subjects who received Inmazeb were pyrexia (or elevation in fever), chills, tachycardia, tachypnea, and vomiting. The adverse event profile in adult and pediatric subjects treated with Inmazeb was similar.

The adverse events reported during Inmazeb infusion are summarized in Table 3.[16]

Table 3: Summary of adverse events during Inmazeb infusion.[16]

Adverse event[a]	Inmazeb, (n=154) (%)	Control[c], (n=168) (%)
Pyrexia (Elevation in fever)	54	58
Chills	39	33
Tachycardia	20	32
Tachypnea	19	28
Vomiting[b]	19	23
Hypotension	15	31
Diarrhea [b]	11	18
Hypoxia [b]	10	11

[a] Adverse events in this table were reported as preferred terms from a list of pre-defined or other adverse events that occurred on the day of infusion and included signs and symptoms that occurred during or immediately after infusion. [b] Adverse events that were not pre-specified. [c] Investigational therapy administered as three separate infusions.

CONCLUSION

Ebola virus disease outbreaks have devastated the West African countries since March 2014 and are still ongoing. There was no specific treatment till now; only symptomatic treatment methods were used, which were having higher mortality rates. Inmazeb represents progress in Ebola virus disease treatment and has shown a significant reduction in mortality rates. The safety and efficacy of Inmazeb has been well established in the PALM trial. However, further studies are warranted to further affirm the safety of drugs concerning adverse maternal, fetal outcomes, geriatric use, carcinogenicity, genotoxicity, and fertility studies. The efficacy of Inmazeb has not been established for other species of the Ebola virus and Marburg virus genera. Zaire ebolavirus virulence could change over time or drug resistance can emerge. Considering available information on the drug, Inmazeb has shown promising evidence in reducing mortality in Zaire Ebolavirus infection and is the greatest advancement in the treatment of Ebola virus disease.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Garg R. Inmazeb: new hope for Zaire Ebola virus disease. Int J Basic Clin Pharmacol 2022;11:285-9.