A Randomized, Controlled Trial of Ebola Virus Disease Therapies

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| **Introduction** | | |
| Background | Introduction: Ebola virus gets its name from the Ebola river which neighbors the two cities (Nzara, South Sudan and Yambuku, Democratic Republic of the Congo) where the first two cases of the infections were identified. Symptoms typically present 3 days after infection which include fever, sore throat, muscle pain, headache, vomiting diarrhea and bleeding. The disease has a high risk of death, killing 25% to 90% of those infected, with an average of about 50%.1 This is often due to [low blood pressure from fluid loss](https://en.wikipedia.org/wiki/Hypovolemic_shock) which typically follows six to 16 days after symptom onset. Fruit bats are assumed to be the primary pathogenic vector. Diagnosis of infection includes clinical presentation, viral RNA, or viral antibodies. Standard of care includes [oral rehydration or](https://en.wikipedia.org/wiki/Oral_rehydration_therapy) [intravenous fluids](https://en.wikipedia.org/wiki/Intravenous_fluids) for volume replenishment.  Pathogenesis: Ebola virus -> VP40 + VP24, these proteins interfere with JAK1 and STAT1 which are involved in transcription antiviral proteins.2 Interfering with these immunomodulators reduces innate immunity from engaging apoptosis and T-cell activity. This allows for infected virus cells to continue to proliferate which burdens organ systems. End results is death from septic shock. Several other mechanisms of disease are well documented. Vaccine: rVSV-ZeBOV (Ervebo) neutralizes infection risk by exposing subjecting to Zaire Ebola’s GP (efficacy 70-100) Side effects occur within 7 days of administration and included headache, muscle pain/joint pain and injection site reactions. Adverse events usually resolve within 7 days. Approved in December 2019 for use in the United States.3 Interventions:  - Remdesivir is an RNA-dependent-RNA-polymerase inhibitor which prevents production of viral RNA  - ZMapp is a cocktail of three antibodies which neutralize the virus by binding to GP1 and GP2 which inhibit conformational changes required viral-host fusion + antibody dependent cytotoxicity4  - Mab-114 is a single MAB which neutralizes the virus by binding to non-cathepsin cleaved and cleaved GP1 and GP2 protein4  - Inmazeb (REGN-3Eb) is a cocktail of three antibodies with neutralizes virus through antibody dependent cell mediated cytotoxicity and/or phagocytosis (no GP binding)4 | |
| Bias | Bias pertains to generalizability of results. Generalizability appears high as exclusion criteria includes only subjects without RT-RNA confirmed Ebola diagnosis and little pertaining of medical conditions or baseline characteristics. Subject recruitment included neonates, adults, and pregnant women. However, patients were recruited from a confined geographic region and interventions targeted one ebolavirus strain (Zaira). Efficacy could vary based on an outbreaks geographic location or different populations infected.  *“Outbreaks with filovirus species other than Zaire ebolavirus will require reconsideration of study arms with agents that have known activity for that species. The monoclonal therapies currently targeted for study are specifically designed for Zaire ebolavirus variants.”* | |
| Study objective | Compare efficacy and safety of four antiviral interventions in patients with a confirmed Ebola infection diagnosis per the study protocol. | |
| **Methods** | | |
| Design | 1:1:1:1 randomization of remdesivir, Mab114, REGN-EB3 and ZMapp as control. Trail was originally designed with three arms in November 2018 but augmented in 2019 with addition of REGN-EB3. An independent data and safety monitoring board (DSMB) will actively monitor interim data to make recommendations about early study closure or changes to study arms. Trial-group assignment were placed in sequentially numbered envelopes and distributed during enrollments. Bar-coded paper care-report forms were transmitted from the site to a server, where they were digitally recorded. Subjects were enrolled though multiple study centers. | |
| Inclusion criteria | - Inclusion required confirmed ebolavirus infection by RT-PCR assay to detect nucleoprotein of Ebola virus by Xpert Ebola Assay (Cepheid) and Piccolo Xpress Chemistry Analyzer (Abbott).  - Patients of any age, including pregnant women, were eligible if they had a positive result on RT-PCR with 3 days before screening and if they had not received other investigational agents (except experimental intervention) within the previous 30 days.  - Neonates were included if mother had documented EVD. | |
| Exclusion criteria | - No diagnosis of Ebola infection by RT-RNA.  - Treatment with other Ebola treatment within 30 days of screening (excluded experimental intervention) | |
| Interventions | - All patients SOC (IV fluid, daily clinical laboratory testing, correction of hypoglycemia, broad spectrum antibiotics and antimalarial agents as indicated).  - ZMapp = 50 mg/kg Q3D for 3 doses.  - Remdesivir 200mg in adults (adjusted for children by body weight) and 100 mg on day 2 continuing for 9 to 13 days depending on viral load.  - Mab114 = 50 mg/kg on day 1  - REGN-EB3 = 150 mg/kg on day 1. | |
| Primary  outcome | To compare the 28 day mortality in patients with Ebola virus disease who receive one of two different investigational therapeutics with those who receive ZMapp in the control arm. | |
| Secondary outcomes | To compare the change in viral load between study arms.  To compare safety features of the intervention.  To compare mortality rates among patients whose baseline predictors of disease place them in high-risk versus low-risk categories for disease severity. | |
| **Statistical analysis** | | |
| Sample Size | Planned: ZMapp = 185, remdesivir = 170, Mab114 = 170, REGN-EB3 = 170. (Total =725)  Analyzed: ZMapp = 169, remdesivir = 175, Mab114 = 174, REGN-EB3 = 155. (Total =673) | |
| Primary and Secondary  endpoint | - Boschloo’s test for hypothesis testing, estimated 145 patients per study arm for 80% power to show 50% reduction in mortality between each of the groups and the control (ZMapp group).  - Two-sided type I error rate of 5%, without adjustment for multiplicity.  - Four interim analyses of efficacy and safety that were performed based on prespecified enrollment targets. | |
| Subgroup | Same statistical analysis was applied to subgroup analysis | |
| **Results** | | |
| Baseline  characteristics | - Neonate=0.7%, 5 years <=2.8%, 6 to 17 years of age=12.8%, 18 year or> =74.4%  - 55.6%=females (6.1% pregnant)  - Mean Ct value was 24.9 (sD=5.6)  - Enrolled 5.5 days on average after the onset of symptoms  - Diarrhea (53%), fever (51%), abdominal pain (46%), headache (44%) and vomiting (39%), malaria coinfection (10%) [10.2% - 25% reported receiving malaria vaccine]  - SrCr=2.5 (dS=2.9), AST=668 (dS=700), ALT=379 (dS=464) | |
| Primary results | ZMapp = 84/169 **(49.7%%)**  Remdesivir = (49.7) 93/175 **(53.1%)**  Mab114 = 61/174 **(35.1%)**  REGN-EB3 = 52/155 **(33.5%)**  REGN-EB3 vs. ZMapp = −17.8 (−28.9 to −2.9)  Mab114 vs. ZMapp = -14.6 (-25.2 to -1.7) | |
| Secondary results | REGN-EB3 = 15 days (medium)  Mab114 = 16 days (medium)  ZMapp = 27 days (medium) | |
| Sub‐group analysis | - Interim analysis (August 19, 2019) suggest D/C of ZMapp and remdesivir because Mab114 and REGN-EB3 were superior.  - Odds of death increased by 11% for each day of not presenting  - Odds of death increased (1.43; 95% CI, 1.31 to 1.56) with 1 mg/dL increase in SrCr  - Odds of death decreased (0.66; 95% CI, 0.62 to 0.71) per Ct unit decrease  - Odds of death increased (1.15; 95% CI, 1.11 to 1.20) per 100U/L APT increase  - Odds of death increased (1.43; 95% CI, 1.33 to 1.54) per 100U/L ALT increase  - Remdesivir vs. ZMapp (0.99; 95% CI 0.46-2.14)  - Mab114 vs. ZMapp (0.24; 95% CI, 0.10-0.53)  - REGN-EB3 vs. ZMApp (0.21; 95% CI, 0.08-0.53) | |
| **Critiques of Study** | | |
| Strengths  - Randomization was stratified by nucleoprotein cycle-threshold (Ct) value (<22.0 or >22.0, corresponding to higher and lower viral loads)  - Sub-group analysis of indicators for disease progressions (SrCr and LFTS)  - Well populated for first-in-human trail REGN-EB3  - Delivered interesting insight about trends in subjects seeking health care | | Weaknesses  - Not blinded  - Lack of consist and complete reporting of baseline values  - ZMapp and remdesivir groups had higher levers of SrCr and AST |
| **Conclusions and Application** | | |
| Conclusions | There was a statistically significant difference between REGN-EB3 (0.21; 95% CI, 0.08-0.53), MAB-144 (0.24; 95% CI, 0.10-0.53) compared to ZMapp. Important to consider, differences in efficacy could be due to dosing strategies of ZMapp compared to REGN-EB3 as 97% of deaths occurred within 9 days. This study delivered insights of Ebola disease progression predictors through sub-group analysis (Ct, SrCr and ASP/AST) It remains unexplained that ZMapp mortality was 22% in PREVAIL II trail and 50% in this trial. This is possibly due to differences in strain virulence. This study exemplifies the synergist potential of healthcare, scientists, and government agencies in overcoming logistical and political challenges. Finally, this trial delivered insights on requirements for future improved anti-Ebola treatments considering efficacy of multiple MOA and importance of escape mutation consideration. | |
| Application in clinical practice | A virulent outbreak can be a good opportunity to evaluate risks vs. benefit for novel therapies, especially if the interventions can deliver lifesaving benefits. For these interventions, relative efficacy over safety would be the purpose of clinical application as 34% of subjects died in of both Mab114 and REGN-EB3 groups and 67% of all patients with high viral loads died (Ct>22). Importance of community health awareness and preparedness was evidenced as there was increased mortality when patients presented 1 days after symptom onset. Patients receiving vaccine (n=155) 10 days before symptoms presentation were sooner to enroll after symptoms presentation. | |

References:

* 1. [Ebola virus disease, Fact sheet N°103, Updated September 2014"](https://web.archive.org/web/20141214011751/https:/www.who.int/mediacentre/factsheets/fs103/en/). [World Health Organization](https://en.wikipedia.org/wiki/World_Health_Organization) (WHO). September 2014. Archived from the original on 14 December 2014. Retrieved 15 December 2014.
  2. Kühl A, Pöhlmann S (September 2012). ["How Ebola virus counters the interferon system"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7165950). *Zoonoses Public Health*. **59** (Supplement 2): 116–31. [doi](https://en.wikipedia.org/wiki/Doi_(identifier)):[10.1111/j.1863-2378.2012.01454.x](https://doi.org/10.1111%2Fj.1863-2378.2012.01454.x). [PMC](https://en.wikipedia.org/wiki/PMC_(identifier)) [7165950](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7165950). [PMID](https://en.wikipedia.org/wiki/PMID_(identifier)) [22958256](https://pubmed.ncbi.nlm.nih.gov/22958256).
  3. ["First FDA-approved vaccine for the prevention of Ebola virus disease, marking a critical milestone in public health preparedness and response"](https://www.fda.gov/news-events/press-announcements/first-fda-approved-vaccine-prevention-ebola-virus-disease-marking-critical-milestone-public-health). *U.S.*[*Food and Drug Administration*](https://en.wikipedia.org/wiki/Food_and_Drug_Administration)*(FDA)* (Press release). 20 December 2019. Retrieved 22 December 2019.
  4. Hoenen, T., Groseth, A. & Feldmann, H. Therapeutic strategies to target the Ebola virus life cycle. *Nat Rev Microbiol* **17,**593–606 (2019). https://doi-org.proxy.hsl.ucdenver.edu/10.1038/s41579-019-0233-2