Mulangu S, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics[1]

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BACKGROUND – THE STUDY QUESTION?	

Background	• After the end of the outbreak in West Africa in 2016, the World Health Organization (WHO) initiated a series of discussions to develop an R&D Blueprint for Ebola virus disease (EVD) research that included a working group focused on how experimental therapeutics should be assessed in the context of the next EVD outbreak (2018 outbreak)
	• These and other discussions led to a consensus that when a new outbreak occurred, the most promising experimental therapeutics should be studied in the context of a randomized, controlled trial, if possible.
	• This groundwork facilitated the uniting of the international community and Democratic Republic of Congo (DRC) leadership to develop and implement the trial described in this report that compared:
	  ○ Triple monoclonal antibody ZMapp (the control group-see "previous trials")
	  ○ The antiviral agent remdesivir
	  ○ The single monoclonal antibody MAb114 from an EVD survivor
	  ○ The triple monoclonal antibody REGN-EB3
	• The current trial was originally designed in November 2018 as a three-group trial, and the protocol was updated in January 2019 to add REGN-EB3 as a fourth group; data from this group were compared with those of patients in the ZMapp group who were enrolled on or after the time the REGN-EB3 group was added (the ZMapp subgroup).
	• EVD:Filoviridae family, 3 spp→outbreaks: Bundibugyo ebolavirus (BDBV), Zaire ebolavirus (EBOV), Sudan ebolavirus (SUDV)[2]

Previous trials	• Ongoing trials for remdesivir and convalescent plasma-no FDA-approved antiviral for either Ebolavirus or SARS-CoV-2 • PREVAIL II: ZMapp vs. SOC for 71 pts w/ EVD; ZMapp appeared beneficial but did not meet statistical threshold for efficacy[3]
Why this study?	• RCT comparing remdesivir and monoclonal antibody products to a control agent (ZMapp) for another single-stranded RNA virus • Though EVD and COVID19 are different diseases, this study may shed light on how effective experimental therapies (including remdesivir and a convalescent plasma-like agent may be for another SS-RNA virus
Null Hypothesis	• No difference between any treatment group and SOC

GENERAL STUDY OVERVIEW		
	Summary	Critique
Funding	• Biomedical & Advanced Research & Development Authority of U.S. DHHS (funded production of ZMapp & REGN-EB3) • NIAID & Defense Advanced Research Projects Agency of the U.S. DoD (funded production of MAb114)	• None
Trial design	• Prospective, multicenter, randomized superiority trial • 1:1:1:1 enrollment to 4 experimental therapies • Randomization was stratified according to baseline nucleoprotein cycle-threshold (Ct) value (≤22.0 or >22.0,corresponding to higher and lower viral loads, respectively, as determined by quantitative RT-PCR) and Ebola treatment center	• None
Objectives	• Compare 3 experimental EVD therapies to control (ZMapp)	• None

Enrollment	• Receipt of SOC PLUS 1:1:1:1 ZMapp (control group), remdesivir, Mab114, or REGN-EB3
	  • Triple monoclonal antibody ZMapp (the control group)
	  • Antiviral agent remdesivir (nucleotide analogue RNA polymerase inhibitor)
		• The current trial was originally designed in November 2018 as a three-group trial, and the protocol was updated in January 2019 to add REGN-EB3 as a fourth group; data from this group were compared with those of patients in the ZMapp group (both are triple monoclonal antibody products) who were

	• Single monoclonal antibody MAb114 fm an EVD survivor • The triple monoclonal antibody REGN-EB3 • SOC (IVF, daily lab testing, hypoglycemia and lyte correction, broad-spectrum abx and anti-malarial agents prn)	enrolled on or after the time the REGN-EB3 group was added (the ZMapp subgroup)
METHODS		
Inclusion criteria	• Positive RT-PCR w/in 3 days of screening AND no receipt of other investigational agents w/in previous 30 days • *Included* pregnant women, neonates ≤ 7d old if EVD+ mom	• Stratified pts according to higher vs. lower viral load→impt b/c higher viral load assoc w/ higher mortality in PREVAIL II[3]
Exclusion criteria	• Patients who did not have positive RT-PCR or >3 days btw (+) RT-PCR and screening • Receipt of other investigational agents w/in previous 30 days (experimental vaccines allowed)	• Sensitivity analyses adjusted for differences in age and sex between groups
Interventions	• 1:1:1:1 randomization: • ZMapp-50 mg/kg Q72h X 3 doses • Remdesivir 200mgX1→100mg QDX9-13d (dep on viral load) • MAb114 50 mg/kg X1 dose • REGN-EB3 150 mg/kg X 1 dose	• ZMapp required 3 infusions over 6 days for complete course • Remdesivir required 10-14 days to complete therapy • Both MAb114 and REGN-EB3 are given as a complete course in 1 dose→could benefit these since fast mortality w. EVD
Primary Endpoints	• 28-day mortality	• None
Secondary Endpoints	• Time to first negative RT-PCR • Safety endpoints-adverse effects related to study drugs	• If patient died, considered not having achieved viral clearance
Statistical analyses	• 145 pts needed in each group for a power of 80% to show a 50% reduction of mortality in each group vs. ZMapp • Boschloo's test used for primary outcome of 28d mortality • Propensity score analyses using baseline predictors of mortality to stratify patients • Differences between control and experimental groups were assessed with a 95% bilateral CI • Log-rank test was used to compare time to death (up to 28d)	• Amendment of protocol in July 2019 to increase sample size to increase the sample size to 725 to improve the power of the trial while taking into account the availability of ZMapp. The sample size was revised to 185 pts each in the ZMapp, remdesivir, & MAb114 groups & 170 in the REGN-EB3 group. • Interim analysis recommended terminating random assignment to ZMapp and remdesivir b/c mortality was lower with REGN-EB3 an MAb114 vs. ZMapp and Remdesivir • Boschloo's test vs. Fisher's exact 2/2 less conservative small-sample performance • Performed sensitivity analyses to adjust for BL differences in site, CT, age, and sex
RESULTS		
Enrollment	• 681 pts randomized at interim analysis, 8 excluded • Of the remaining 673 participants, 169 were assigned to receive ZMapp, 175 to receive remdesivir, 174 to receive MAb114, and 155 to receive REGN-EB3. A total of 154 patients were assigned to the ZMapp group after the REGN-EB3 group had been added (the ZMapp subgroup), and data from these patients were used in the comparison of REGN-EB3 with ZMapp (table 1)	• On August 9, 2019 (681 pts had been enrolled), the data & safety monitoring board conducted an interim analysis on data from 499 pts &, on the basis of two observations (results in the REGN-EB3 group crossed an interim boundary for efficacy for surrogate for primary endpoint, & mortality analysis showed clear separation between MAb114 & REGN-EB3 groups vs. ZMapp & remdesivir groups), recommended terminating random assignment to ZMapp and remdesivir. • Majority of pts from 2 centers (85%) vs the other 2 centers • Only 8 pts were excluded→seems to be a "real-world" representation of patients w/ EVD

Baseline characteristics	• 74.4% age 18+ years, 55.6% female (6.1% pregnant)
	• Overall mean age 28.8 ± 17.6 yrs
	• Most patients (74.4%) were 18 years of age or older, 12.8% were 6 to 17 years of age, and 12.8% were 5 years of age or younger, of whom 0.7% were neonates (≤7 days old).
	• Overall mean weight 47 ±19.3 kg
	• 10.2% overall co-infection with malaria
	• Baseline (BL) cycle threshold (CT) ≤ 22.0 in 42.1% pts
	• Mean SCr and AST higher in ZMapp and remdesivir groups
	  • SCr: ZMapp=2.9±3.3, remdesivir=2.7±3.0, MAb114= 2.1±2.6, REGN-EB3=2.5±2.8 (ZMapp sub=2.7±3.0)
	  • AST: ZMapp=767±745, remdesivir=713±702, MAb114= 546±617, REGN-EB3=648±726 (ZMapp sub=775±749)
		• Young age-does not reflect COVID population
		• Mean wt much lower than U.S. population
		• Unclear the role of malaria co-infection
		• Investigators used a cycle threshold (CT) cutoff of >22 to define "low" viral load (VL). Though the majority (57.9%) of pts had a "low" VL (lower mortality risk), this study still included a large % pts with a "high" VL-did not report quantitative values
		• Higher SCr and AST may suggest further progression of disease and inc'd risk of mortality, BUT 18.6% pts and 40.6% of pts did not have BL SCr and AST recorded, respectively. AND, 70.1% BL samples had some degree of hemolysis

Monitoring	• Baseline (BL) labs, other labs prn	• BL labs collected inconsistently & a high degree of hemolysis

Primary Outcome	• Results reflect findings from analysis in 671 patients
	• ZMapp mortality (49.7%): control
	  • No diff vs. remdesivir (53.1%), diff 3.4% (95%CI -7.2, 14.0)
	  • ↓in MAb114 (35.1%), diff -14.6% (-25.3, -1.7)
	  • ↓in REGN-EB3 (33.5%), diff -17.8% (-28.9, -2.9)
	• High viral load adj, no mortality diff btw ZMapp & remdesivir
	  • ↓in MAb114 (69.9% vs. 85.3%), diff -14.6% (-33, -0.5)
	  • ↓in REGN-EB3 (63.6% vs. 86.2%), diff -22.5% (-41.8, -5.1)
	• Low viral load adj, no mortality diff btw ZMapp & remdesivir
	  • ↓in MAb114 (9.9% vs. 24.5%), diff -14.6% (-32.4, -2.6)
	  • ↓in REGN-EB3 (11.2% vs. 25.8%), diff -14.6%(-32.6, -2.3)
		• On August 9, 2019 (681 pts had been enrolled), the data & safety monitoring board conducted an interim analysis on data from 499 pts &, on the basis of two observations (results in the REGN-EB3 group crossed an interim boundary for efficacy for surrogate for primary endpoint, & mortality analysis showed clear separation between MAb114 & REGN-EB3 groups vs. ZMapp & remdesivir groups), recommended terminating random assignment to ZMapp and remdesivir.
		• Appreciated adjustments for high and low viral loads since higher VL is associated with higher mortality in EVD
		• The survival benefits seen in the MAb114 and REGN-EB3 groups were also seen in sensitivity analyses adjusted for potential baseline imbalances

Secondary Outcomes	• Median time to first negative RT-PCR vs. ZMapp (27d)
	  • Shorter in MAb114 (16d) & REGN-EB3 (15d)
	  • Remdesivir: >28d because mortality >50%
	• 29 serious adverse events potentially related to study drugs, only 4 (all resulted in death) persisted after committee review
		• Patients who expired during the study were documented as having not had a negative RT-PCR
		• Serious AEs: GI symptoms, infusional hypotension & hypoxia, hypotension →cardiac arrest. Difficult to distinguish btw fulminant EVD

Other Clinical events	• Lower mortality in those who rec'd an EVD vaccine (27.1% vs. 48.4%) • 19% of patients who arrived at the treatment center within 1 day after the reported onset of symptoms died, as compared with 47% of patients who arrived after they had had symptoms for 5 days. • Multivariate analysis showed BL CT value, SCr, and duration of symptoms at enrollment were significant prognostic indicators of death	• Pts who rec'd a vaccine presented earlier; presentation delay inc'd mortality (11% per day, 95%CI 5, 16), possible treatment seeking behaviors vs. vaccine efficacy
AUTHORS' CONCLUSIONS		

- Standard of care plus either MAb114 or REGN-EB3 were each superior to ZMapp plus SOC with regards to 28-day mortality. This benefit persisted despite high or low viral load at presentation.

GENERALIZABILITY/CRITIQUE/DISCUSSION

- Generalizability:
  - This study evaluated EVD, specifically EBOV variant during an outbreak in the DRC. Mortality can be markedly different even between different EVD variants (e.g. mortality in PREVAIL II study was ~ 22% vs. ~50% in this study), so difficult to apply to a completely different RNA virus (SARS-CoV-2) that has thus far exhibited lower mortality rates than EVD.
  - The mean age in this study is much lower than patients at highest risk of hospitalization and more severe disease caused by SARS-CoV-2. We must consider the changes in PK/PD of the experimental agents between this younger cohort vs. what we would expect to see in older patients in the US
  - The mean weight of pts in this study is much lower than a typical patient in the US, who could be 2-3X heavier than the patients in this study. Again, the PK/PD may be different in this patient population vs. a typical American, and it is unclear if these agents would need to be dose-adjusted in the setting of obesity
  - Malaria co-infection was reported as ~ 10% in this study, which is not commonly encountered in the US. Likewise, patients in the US likely experience comorbidities that were not seen in this study's population. It is unclear how these may influence patients' responses to the therapeutic agents
- Critique:
  - Authors tried to balance the inconsistent capture of baseline data by performing sensitivity analyses, after which, MAb114 and REGN-EB3 were still favored
  - When vaccine data was available, 25% of pts reported they received an EVD vaccine-this was self-reported and unable to be confirmed. Additionally, patient enrollment was not stratified for receipt of vaccination, which could have affected mortality risk. Of note, patients in the MAb114 and REGN-EB3 groups reported lower receipt of vaccination (22.9% and 22.9% respectively) vs. 26.6% for ZMapp and 27.6% in the Remdesivir groups.
  - 97% of pts expired w/in 10 days of enrollment, which may favor MAb114 & REGN-EB3, which are given as a 1X dose vs. ZMapp (Q72h X3 doses) or remdesivir (10-14 days of therapy depending on viral load). Patients in the MAb114 and REGN-EB3 groups received a complete course of therapy
- Discussion:
  - The authors list the following barriers, which are not a concern for most practitioners in the US: regional violence, mistrust of government, mistrust of the Ebola response, and unstable electrical power grid, transportation difficulty, & a history of high morbidity from other infectious diseases.
  - This study was well-designed, & authors corrected for potential confounders (e.g. randomized, stratified for viral load, age, site, sex compared same time-frame of control when REGN-EB3 group was added, excluded patients who received drug when the chain of cold could not be confirmed, etc).
  - One of the most limiting factors in this study is the imbalance of baseline SCr and AST, which could be markers of worse disease progression, and which favored the 2 groups that performed better in this study (MAb114 and REGN-EB3)
  - Another limiting factor was the inability to stratify patients into the randomized groups based on receipt of the EVD vaccine, though there appeared to be lower rates of vaccination in the MAb114 and REGN-EB3 groups.
  - Despite high rates of survival with these agents in a non-human primate animal model, patients in this study still experienced a high rate of mortality
  - Though the study was not designed to make conclusions about the efficacy of remdesivir vs. MAb114 or REGN-EB3, it performed similarly to ZMapp
    - Remdesivir may be more effective in pts with COVID19 with its slower progression, which might allow patients to receive a full course of therapy
    - This may encourage clinicians to preferentially give convalescent plasma vs. remdesivir to pts w/ more severe COVID19 & shorter life expectancy
    - Unclear if same dose of remdesivir is adequate for SARS-CoV-2 as well as a different patient population (older, heavier, more co-morbidities)
  - The mortality reduction seen with 2 of the monoclonal antibody products-especially MAb114, which is a single monoclonal antibody from an EVD survivor-is especially encouraging considering convalescent plasma from COVID19-recovered donors is currently being studied and considered as therapy for SARS-CoV-2

References:

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3. PREVAIL II Writing Group. A randomized, controlled trial of ZMapp for Ebola virus infection. N Engl J Med. 2016;375:1448-56.