Commentary

Clinical trials in an Ebola outbreak seek to find an evidence-based cure

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ARTICLE INFO

Article History:
Received 25 November 2019
Accepted 16 December 2019
Available online 14 January 2020

Ebola virus (EBOV) outbreaks are unpredictable, sporadic, and historically occur in remote locations of equatorial Africa. Traditionally, outbreak control consists of identifying EBOV-infected patients and contact tracing. Ebola treatment centers provide limited supportive care with rigorous infection control. Communication, education, and establishing trust with the community to allow continued surveillance and altering funeral rituals to ensure safe and dignified burials have been the focus for stopping EBOV spread since its discovery in 1976.

High case fatality rates of EBOV infection have justifiably administering unproven candidate therapeutics, convalescent plasma, or repurposed medicines on a compassionate use basis. In 2014, WHO declared the Ebola outbreak in West Africa (the largest to date) an international public health emergency. Subsequently, international institutes began requesting unproven but promising experimental therapeutics to combat EBOV [1]. Federal and academic research programs had been evaluating candidate therapies in cell culture, small animal, and non-human primate models of EBOV infection, but there had not been a registered clinical trial.

While compassionate use guidelines were accepted, ethics of performing clinical trials during an outbreak were heavily debated [2]. Patients’ need for the highest therapeutic benefits precluded placebo controls. Reallocation of limited resources from supportive care was a concern, and sufficient quantities of trial therapeutics were needed. Regulatory, ethical, pharmaceutical, and governmental committees had to be coordinated to approve clinical guidelines, in hindsight causing significant delays in starting trials. The outbreak peaked between August and December 2014, and the earliest trials began in 2015. As case numbers declined, matching location of trial centers with sufficient numbers of infected patients became problematic. Despite these enormous hurdles, diligent scientists insisted that Ebola patients deserved evidence-based effective treatment. Clinical trials were initiated evaluating small molecular inhibitors favipiravir and brincidofovir; host response modulator interferon beta; monoclonal antibody cocktail Zmapp; and convalescent plasma [3,4]. Most incorporated an initial safety study and were multi-staged to rapidly (typically within 14 days) assess benefits or harm of the experimental treatment versus historical case fatality rates. Conservative, low-dose regimens were chosen based on pre-clinical animal experiments or available phase 1 safety data on healthy human volunteers. Trials were conducted within Ebola treatment centers run by different aid agencies, used different laboratory tests, and provided varied supportive care.

A single-arm, phase 2 trial testing the efficacy of TKM-130803 (TKM-Ebola) was conducted in Sierra Leone in March 2015 [5]. TKM-Ebola is a lipid nanoparticle (LNP) containing small interfering RNAs (siRNAs) targeting the viral polymerase and VP35. Pre-clinical studies evaluated the formulation, TKM-100802, based on virus from the 1995 EBOV outbreak in Kikwit, DRC. One siRNA out of two failed to inhibit the West African EBOV strain, which differed from target siRNA sequences [6]. This highlights the importance of testing therapeutics using appropriate outbreak virus [7]. siRNAs redesigned to match the outbreak sequence were named TKM-130803; 14 patients enrolled to receive a 7-dose regimen. After 14 days, a conservative dose of TKM-Ebola provided no survival benefit, the trial was terminated, and researchers concluded that advanced EBOV disease was not susceptible to TKM-Ebola therapy. This failure to provide therapeutic benefit was attributed to several potential factors. Most strikingly, trial patients’ viral RNA levels at the time of enrollment were several logs greater than those tested in pre-clinical animal studies.

Questions remained if TKM-Ebola siRNAs were present in adequate levels during treatment. Here, Janet Scott et al. reevaluated clinical samples from the TKM-Ebola trial, developed and applied a new test to count the siRNA molecules and relate the amount to EBOV RNA in patient blood [8]. Previous animal studies measured the activity of circulating siRNAs and in macrophage target cells, and had found TKM-Ebola to provide survival if delivered within 3 days of infection [6]. Scott et al. found a molar excess of TKM-Ebola siRNA molecules relative to virus RNA [8]. However, the patients had much higher initial viral load and were in the later stages of EBOV infection. The authors next performed a pharmacokinetic model of dosing regimens and conclude the drug was delivered in abundance relative to virus in circulation, yet patients with severe Ebola infection had sustained TKM-Ebola levels, and thus were failing to clear the drug. This has implications for other LNP-based siRNA therapies where the siRNAs may not reach the intracellular targets, and thus be ineffective in patients with compromised organ function.

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2019.102601.
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https://doi.org/10.1016/j.ebiom.2019.102614
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This follow-up study of the TKM-Ebola clinical trial revisits and highlights how initial experiences conducting research in an outbreak are necessary to advance clinical care to Ebola patients [8]. They successfully worked with industry, academic, humanitarian and government agencies following newly developed regulations and protocols. They gained the trust of the local community to enroll patients under proper ethical guidelines. They delivered the investigational treatment within the extreme conditions of an Ebola treatment center. Results and limitations were presented to the scientific community [3,5]. Precious Ebola patient samples were collected, shared with enhanced laboratories with biosecurity allowing additional research to be performed and knowledge gained.

Lessons learned in West Africa are being applied in the current Ebola outbreak in the eastern provinces of DRC, now the second largest with over 3300 cases. A four-arm, multi centered, phase 2 clinical trial was initiated to evaluate efficacy of the nucleotide analogue prodrug remdesivir (GS-5734), the monoclonal antibody mAb114, and cocktail REGN-EB3 with Zmapp as the control [9]. Using same lab assays ensured comparable results and multiple trial locations allowed sufficient enrollment (681 patients) to conclude that REGN-EB3 and mAb114 were 89% and 90% effective, respectfully, promoting survival in patients with low viral loads, and should therefore continue to be administered for the duration of the outbreak [10].

Scientifically proven, effective treatments can dramatically change future EBOV outbreaks, encouraging patients to seek care in treatment centers, lowering viral loads and quelling person-to-person transmission, and saving lives. With proper treatment, Ebola can be cured.

Declaration of competing interest

The author declared no conflicts of interest.

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