Considerations of Favipiravir as a Medical Countermeasure in Future Randomized Controlled Trials Against Ebola Virus Disease

Colleen S. Kraft1,2
1Department of Pathology and Laboratory Medicine, and 2Division of Infectious Diseases, Department of Medicine, Emory University, Atlanta, Georgia

(See the Major Article by Bai et al on pages 1288–94.)

Keywords. favipiravir; Sierra Leone; clinical trials; Ebola virus disease; treatment.

In this issue of Clinical Infectious Diseases, Bai et al describe their trial in Jui Town of Freetown, Sierra Leone, utilizing the oral drug favipiravir to treat Ebola virus disease (EVD) in a historical control design. Since the discovery of Ebola virus in the Democratic Republic of Congo in 1976, outbreaks of EVD had been mainly confined to rural areas (http://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html). This includes the most recent outbreak that also occurred concurrently with the West African outbreak in the Democratic Republic of Congo where there were 66 reported human cases. The published literature regarding therapeutics used in these previous outbreaks has been limited to the 1995 Kikwit experience where 8 Ebola-infected females received the transfusion of convalescent whole blood from 5 male survivors [1]. Only 1 recipient died in this study, but it is unclear if the transfusion played a role in their survival given the small numbers and that some of the recipients already had antibodies to Ebola virus at the time of transfusion.

The West African Ebola epidemic was unlike any since 1976, with spread into large urban cities, where it had not been previously recognized as an endemic pathogen. Although these countries routinely care for Lassa virus infections in their eastern regions, the lethality and contagion of Ebola virus was different and warranted different practices of infection prevention. In Sierra Leone, where this trial was performed, the initial spread of Ebola into the country was from its rural areas near Kenema where it followed individuals who were present at the funeral of a traditional healer who had unknowingly died of EVD [2]. The outbreak spread into Sierra Leone in the regions where there had been Lassa and, ironically, near the Viral Hemorrhagic Fevers Consortium laboratory housed at Kenema, where the first diagnosis of EVD was made in the country on 25 May 2014 [2]. What followed that diagnosis in Kenema was exponential growth in the number of patients with EVD in Sierra Leone. At the end of the outbreak, Sierra Leone had the highest number of confirmed, probable, and suspected patients at 14,124. Sierra Leone reported 3,956 deaths attributed to the disease, which was the lowest case fatality rate of the 3 countries. Sierra Leone was declared to be Ebola free on 7 November 2015, with 2 additional cases that were presumed to be sexually transmitted from the semen of survivors [3].

The care of patients in the initial part of the epidemic was in the eastern, more rural areas that included Kenema, but in October 2014, the patients predominated in the more urban districts in the west, near Freetown, which is the context for this trial. The Sierra Leone–China Friendship hospital was opened on 10 January 2014, and all of the dispatched doctors and nurses from China were senior experts in infectious diseases.

The trial began on 10 October 2014, with the World Health Organization standard of care (http://www.who.int/csr/resources/publications/clinical-management-patients/en/; 30 March 2014 version) being given to all patients until the trial ended. From 1 to 10 November 2014, the patients who had confirmed EVD also received favipiravir with dosing of 1600 mg the first day, 1200 mg the second day, and at least 5 days of standard of care dosing (this dose is not referenced) for a total of 3–11 days until discharge, transfer, or death. The most common endpoint for stopping therapy was due to patients being transferred out of the Ebola treatment unit to another hospital due to preference of the patient, limited beds (capacity was 40 beds), and requirements for intravenous therapy. A full 67 of 85 (79%) patients in the control arm and 22 of 39 (56%) patients in the intervention group were transferred, leaving 18 patients in the control group and 17 patients in the treatment group to make it...
This manuscript comes on the heels of the JIKI trial, which was a historically controlled, single-arm, proof-of-concept trial in Guinea. The outcome from this study of 111 patients was that favipiravir monotherapy may have helped survival in patients with a cycle threshold value of ≥20 on admission [6]. In the Sierra Leone trial, all of the patients had viral loads that were in this range, supporting that favipiravir may help treatment in the range of moderate viremia, but many of these individuals would have likely survived regardless. These are the types of questions that can only be elucidated when a randomized controlled trial is performed.

The dosing in this study is also something for future trials. In the JIKI trial, the patients were given 1600 mg twice daily on the first day and 600 mg twice daily for an additional 4 days. Given the tolerability of favipiravir at the doses given in this study (and in the influenza studies), it seems that for a lethal viral disease the dosing could be increased and, again, should be an aspect of future randomized controlled studies. Favipiravir was used as a therapeutic in the evacuees in Europe, with 10 patients receiving at least 1 dose and 5 of those patients completing a course (dosages not recorded) [7]. In the United States, 1 patient was treated for eye disease with a 21-day course of oral favipiravir at a dose of 2000 mg orally every 12 hours for 2 doses, followed by 1200 mg (adjusted for >80 kg) [8, 9].

In conclusion, there is a great need for efficacious therapeutics to treat EVD. The supportive care management of the patient appears to remain the single most important variable in reducing mortality. This remains the biggest intervention that the global community can make for EVD. We must also come together as a global community to embrace the crucial benefits that only randomized controlled trials can afford, which is to determine true efficacy. There are adaptive study designs that can allow for fewer patients to be studied in each arm in order to make decisions on drug efficacy [10], and this may be how future studies are designed.

**Note**

**Potential conflict of interest.** Author certifies no potential conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**