Paris, 24 February 2015

Press release

Preliminary results of the JIKI clinical trial to test the efficacy of favipiravir in reducing mortality in individuals infected by Ebola virus in Guinea.

Preliminary data from the JIKI clinical trial, which is testing the efficacy of favipiravir in reducing mortality associated with Ebola, provide two important pieces of information:

- **absence of efficacy in individuals who arrive at treatment centres with a very high level of viral replication and who already have serious visceral involvement,**
- **and encouraging signs of efficacy in individuals arriving at treatment centres with a high or moderate level of viral replication, who have not yet developed overly severe visceral lesions.**

With this classification into two groups, we have a much better understanding of Ebola virus disease, and can redefine the role of antiviral monotherapies in the therapeutic arsenal used against the disease.

The trial, sponsored by Inserm and funded by the European Commission from the Horizon 2020 Initiative under the project title REACTION, is supported by two NGOs, Médecins Sans Frontières/Doctors Without Borders (MSF) and Alliance for International Medical Action (ALIMA); two laboratory networks, Belgian First Aid and Support Team (B-FAST) and European Mobile Laboratory (EMLab); the French Red Cross, and the French Military Health Service.

These preliminary data are being presented on Wednesday 25 February as a late-breaking abstract at the CROI international conference (Conference on Retroviruses and Opportunistic Infections) in Seattle.

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Given the high mortality associated with Ebola virus despite high-quality symptomatic treatment, study of specific innovative therapeutic agents is essential. Potentially useful drugs against the virus include favipiravir (T-705), an antiviral drug already tested against influenza virus in adult humans (and well tolerated). The latter (no more than other potential treatments) has never been tested in humans for treating Ebola, but its efficacy has been demonstrated in vitro and in mice.

As part of the mission given to Aviesan to organise the research as a matter of urgency, the JIKI clinical trial, a phase II multicentre noncomparative trial, began in Guinea on 17

December 2014, to test the ability of favipiravir to reduce mortality in individuals infected by Ebola virus.

Sponsored by Inserm, and jointly funded by the European Commission, the JIKI trial is being conducted in partnership with MSF, ALIMA, the French Red Cross, EMLab, B-Fast and the French Military Health Service, and is taking place in four Ebola treatment centres in Guékédou (MSF), Nzérékoré (ALIMA), Macenta (French Red Cross) and Conakry (carers' treatment centre).

In these centres, adults and children over one year of age with a positive Ebola PCR test who agree to take part (parental consent in the case of minors) receive treatment with favipiravir for 10 days along with basic care. Favipiravir is provided by FUJIFILM Corporation/Toyama Chemical Co., Ltd. Favipiravir comes in the form of 200 mg tablets (the tablets can be dissolved in a drink) and is administered according to the following dose regimen[1]:

- Adults: Day 0: 2,400 mg at H0, 2,400 mg at H8 and 1,200 mg at H16, then 1,200 mg twice a day for 9 days;
- Children: doses adjusted to body weight.

The JIKI trial is being followed by an independent monitoring committee, which met on 11 December 2014, and on 5 January, 14 January and 26 January 2015. At this last meeting, the committee authorised the investigators to publish the interim data, which they judged to contain messages that should be quickly shared with the international community. These messages, obtained from the first 80 participants (69 adolescents or adults, and 11 children) are as follows:

- 42% of participants arrived at the treatment centres with a strongly positive PCR test (cycle threshold value, CT, < 20), reflecting a very high viral load[2]. Of these patients, 81% had refractory renal failure and 93% died. In the three months preceding the trial, mortality among individuals presenting with the same features was 85%. Comparison of the trial and pretrial data shows that it is highly unlikely that favipiravir monotherapy will ultimately be proven to reduce mortality in this population with advanced disease.
- 58% of participants arrived in the treatment centres with a cycle threshold (CT) ≥ 20, reflecting a high or moderate viral load. Of these patients, 42% had renal failure, but only 15% died. In the three months preceding the trial, mortality among individuals presenting with a CT ≥ 20 was 30%. Comparison of the trial and pretrial data therefore leads us to hope that favipiravir monotherapy may reduce mortality in this population with less advanced disease.

For the researchers, these preliminary data encourage us:

- to continue the trial while trying to provide favipiravir treatment as soon as possible after the symptoms appear, so as to treat patients in whom viral multiplication can be controlled, and who have not yet developed visceral lesions (especially renal lesions);
- to explore other therapeutic options for patients who come to the treatment centres when their disease is too far advanced.

Yves Levy, the chairman and CEO of Inserm said: *"The results of this non-comparative trial have to be confirmed using a larger number of patients. However, they open up other therapeutic opportunities in drug combinations, in particular for the treatment of patients suffering from more advanced stages of this disease. They also clearly show that research plays an essential role in tackling such epidemics. I would also like to stress that without the excellent Guinean-French cooperation, the pioneering role of the Médecins Sans Frontières (MSF) in this research, the fruitful partnerships with all NGOs involved, and the European Commission's responsiveness, this progress could not have been accomplished."*

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[1] Details of this dose regimen are the subject of a publication in the journal The Lancet Infectious Diseases.
[2] In the laboratories taking part in the trial, a CT < 20 is equivalent to a viral load of over 10^8 copies of the virus per ml of blood.

European Commissioner for Research, Science and Innovation Carlos Moedas said: *"I am excited about the encouraging results of one of our EU-funded projects to tackle Ebola. We have preliminary evidence that the antiviral drug 'favipiravir' may be effective against early Ebola disease. If these results are confirmed by the ongoing clinical trial, it will be the first-ever treatment to be deployed against this deadly disease during the current outbreak. These results show the success of the European Commission's quick reaction to the Ebola outbreak to support urgent research on several potential treatments and vaccines against Ebola with funding from our Horizon 2020 research programme. This is an astounding example of what the best brains can achieve with EU support when there is so much at stake. It shows how EU funding can lead to discoveries that save people's lives and which are the result of rapid EU, international and industry cooperation."*

According to Augustin Augier, Secretary-General of Alima, *"Those positive results will reinforce the confidence between affected populations and the treatment center. This therapeutic solution, even if partial, will significatively attract ebola patients to the treatment center. It is a significative step towards tackling the outbreak in the villages where it still goes on."*

"MSF is pleased to see that favipiravir seems to have a positive effect for certain patients suffering from EVD. But it also seems that the most vulnerable patients, the people that are most likely to die from the disease, don't benefit at all from favipiravir. That fact, and the fact that these are only preliminary results, show that it is really too soon to start using favipiravir outside a trial environment. Research into favipiravir, and into other potential treatments for EVD, must be continued, and MSF is willing to play a role in these clinical trials," says Dr. Bertrand Draguez, medical director of MSF.

This project has received funding from the European Union's Horizon 2020 research and innovation programme

Source

Late-breaking abstract, "Favipiravir in Patients with Ebola Virus Disease: Early Results of the JIKI trial in Guinea"
Conference on Retroviruses and Opportunistic Infections (CROI)
Abstract Number: 103-ALB
Session Title: Factors Affecting HIV Care and Outcome: Global Perspective
Session date and time: 25 February 2015 from 10:00 am to 12:30 pm

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Material

Photos and video rushes from the JIKI trial available on request from the Inserm press service