PATHOGENS AND GLOBAL HEALTH
2019, VOL. 113, NO. 5, 207–208
https://doi.org/10.1080/20477724.2019.1679556

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COMMENTARY

Sofosbuvir use for yellow fever: a new perspective treatment

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ABSTRACT
Yellow fever is an acute febrile illness for which there is no specific antiviral treatment. Since 2016, Brazil has experienced two outbreaks, and collective health measures have been adopted to contain these grievances. However, published data about the drug sofosbuvir against flaviviruses are promising, suggesting the relevance of conducting future clinical trials.

KEYWORDS
sofosbuvir; yellow fever; arboviroses; *Flaviviridae*

Yellow Fever (YF) is an acute febrile disease caused by yellow fever virus (YFV). In Brazil, the YFV is transmitted by *Aedes spp*. mosquitoes in urban cycle, or *Haemagogus* and *Sabethes*, species in wild cycle. There are several clinical presentations in humans, which can be observed from mild or oligosymptomatic forms, to severe manifestations, such as febrile-icteric syndrome, that are involved with septic shock and death. Since 2016, Brazil has been experiencing continuous outbreaks, and collective health measures have been adopted in order to contain them. It is estimated that during the 2016–2018 period, almost 2,050 cases were documented, with approximately 680 deaths. Manifestations of urban YF have not yet been reported in the last decades, however, both the climatic conditions favorable to the proliferation of *A. aegypti* mosquitoes and the high lethality of YF are factors that alert the public health authorities. Although YFV vaccine prophylaxis is an effective process, failures in vaccination campaigns and geographic redistribution of cases have led to the reestablishment of the infection in 2017 and 2018, with widespread distribution throughout our country [1].

There is no specific antiviral treatment; so, the study of potential targets of anti-YFV drugs, as antigens that participate in viral replication, directs special attention to the formulation of compounds capable of preventing the proliferation of YFV in the human organism is of immediate importance. Furthermore, the drug Sofosbuvir, a uridine nucleoside prodrug compound against viral RNA polymerase (a chain terminator, in clinical treatment of hepatitis C), has demonstrated significant activity amid *in vitro* and *in vivo* experiments. Moreover, there were notable reductions in YFV-related lethality provided by both the quantitative decrease in infectious viral fragments and infected cells, as well as in hepatic cells of animal subjects [2].

Sofosbuvir is clinically approved for the Hepatitis C virus (HCV), a species of the Flaviviridae family, the same as the YFV. Its pharmacokinetics are described as a highly metabolized drug in the liver. In this organ, it forms the analogue of the pharmacologically active nucleoside, by sequential hydrolysis of the carboxyl ester portion catalyzed by cathepsin A or carboxylesterase 1, accompanied by phosphorylation through the uridine nucleoside biosynthesis pathway [3].

Since flaviviruses have similar morphology and replication mechanisms, other infectious agents of the same family, such as Zika virus (ZIKV) and dengue virus are also being evaluated in laboratory experiments *in vitro* and *in vivo*, regarding the response of Sofosbuvir in regulating each of these infections. Besides them, Alphavirus, like Chikungunya, may have the same response to antiviral.

In vitro analyzes of ZIKV-infected cells have indicated that by inhibiting ZIKV RNA polymerase, the drug Sofosbuvir has achieved efficacy in diverse cellular systems, such as hepatoma, neuroblastoma, neural stem and brain organoid cells. Similar investigations in CHIKV-infected human hepatoma cells have revealed that the drug has a selective potential in inhibiting CHIKV replication three times more than Ribavirin, a synthetic nucleotide analogue pan-antiviral that selectively inhibits the synthesis of DNA, RNA and other viral proteins [4,5]. *In silico* examinations, a significant inhibitory effect of Sofosbuvir on human cells infected with DENV was estimated, however, *in vitro* experiments to approximate the replication of DENV are still inconclusive [5].

In this regard, published data on the action of Sofosbuvir against flaviviruses are promising,

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suggesting the relevance of conducting future clinical trials to deepen the hypothesis of the increased potential of this drug as a universal polymerase inhibitor of species of the Family: Flaviviridae. This scenario, associated with the need for an efficient treatment for YF, due to the current epidemiological and clinical information of this disease. Additionally, it evinces the importance in studies that demonstrate both the benefit for liver function in YF patients and also the reduction of parasitemia levels and viral replication in subjects at acute stages of infection and in patients with neurotropic or viscerotropic involvement.

Acknowledgments

This study was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq – National Council for Scientific and Technological Development) and the Research Program of the Faculdade Dinâmica do Vale do Piranga (PROAPP/FADIP).

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

There is no financial support to report for this submission.

References

[1] Cupertino MC, Garcia R, Gomes AP, et al. Epidemiological, prevention and control updates of yellow fever outbreak in Brazil. Asian Pac J Trop Med. 2019;12(2):49.

[2] Freitas CS, Higa LM, Sacramento CQ, et al. Yellow fever virus is susceptible to sofosbuvir both in vitro and in vivo. PLoS Negl Trop Dis. 2019;13(1): e0007072.

[3] Sovaldi: sofosbuvir. Irlanda: gilead Sciences Ireland UC, 2014. Medicine bottle. [cited 2019 May 20]. Available from: https://www.ema.europa.eu/en/documents/product-information/sovaldi-epar-product-information_pt.pdf

[4] Ferreira AC, Reis PA, Freitas CS, et al. Beyond members of the Flaviviridae family, sofosbuvir also inhibits chikungunya virus replication. Antimicrob Agents Chemother. 2019;63(2):e01389–18.

[5] Gan CS, Lim SK, Chee CF, et al. Sofosbuvir as treatment against dengue? Chem Biol Drug Des. 2018;91 (2):448–455.