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Highlights

- There is an 80% overlap in the amino acids of Zika and hepatitis C virus RNA polymerase that bind sofosbuvir
- We propose the use of the anti-HCV drug, sofosbuvir, to treat symptomatic Zika infections
- Sofosbuvir (12 week regimen) has a favorable safety profile in HCV patients
- Sofosbuvir has not been reported to produce teratogenic or mutagenic effects in humans
- Sofosbuvir may reduce neurological problems in infants born to symptomatic mothers
Sofosbuvir: an anti-viral drug with potential efficacy against Zika infection

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Currently, there are no effective licensed vaccines or drugs available for the treatment of Zika virus infections and financial support for their development is running short. We suggest that sofosbuvir be considered for Zika infection. Sofosbuvir is used with other drugs for the treatment of hepatitis C virus (HCV) genotypes 1-6 infections. Zika is a member of the flaviviridae family of viruses, which includes yellow fever virus, West Nile virus, dengue virus, St. Louis encephalitis virus and HCV. The most common manifestations include macular or papular rash, fever, arthralgia, retro-orbital pain, conjunctivitis, myalgia and headache and these resolve within two weeks. However, Zika viral outbreaks in the Americas and Pacific have been reported to be temporally linked to Guillain-Barré syndrome. Also, acute myelitis and meningoencephalitis have occurred in patients infected with Zika virus. There is substantial evidence indicating the Zika virus can be transmitted from the mother to the fetus, resulting in adverse fetal effects, including stillbirths, miscarriages, microcephaly and ocular abnormalities. On February 1, 2016, the WHO declared Zika virus to be a public health emergency of international concern.

Zika virus, as with other flaviruses, is an enveloped, single-stranded positive-sensed RNA virus. It has been hypothesized that Zika virus uses the enzyme RNA-dependent RNA polymerase (RdRp or the nonstructural protein, NS5), along with cofactors, to replicate, maintain and express its RNA genome. The three dimensional structure of flavivirus RdRp resembles that of a cupped right hand and contains a finger, thumb and palm domain and is conserved. Currently, the structure of the Zika viral RdRp remains to be
elucidated. However, the predicted three dimensional structure and amino acids for Zika virus RdRp indicates that hepatitis C virus (HCV) RdRp (NS5B protein), particularly at the active site, shares many residues in common with Zika RdRp. Furthermore, the pharmacologically active metabolite of sofosbuvir, 2’-fluoro-2-C-methyl-UTP, which inhibits HCV RdRp, docks into the active site of NS5. Thus, it is possible that certain nucleoside and nucleotide compounds that inhibit HCV RdRp may have inhibitory potency against Zika virus. Zika virus RdRp is an excellent pharmacological target as 1) its inhibition will prevent RNA synthesis and decrease viral replication; 2) there is no similar protein target in human cells.

Sofosbuvir is a uridine nucleotide analog that is biotransformed in hepatocytes to a triphosphate metabolite that inhibits HCV RdRp-catalyzed RNA synthesis, thereby inhibiting viral replication and transcription. Interestingly, the triphosphate metabolite of the nucleoside analog 7-deaza-2’-C-methyladenosine, which inhibits HCV RdRp in vitro, has been shown to: 1) inhibit the in vitro replication of Zika virus, as well as other flaviviruses; 2) significantly decrease Zika viremia and delay morbidity and mortality in Zika-infected mice. Congruent with the above findings, certain 2’-C-methylated nucleosides have been shown to inhibit Zika virus replication in cell cultures. Two recent studies indicate that sofosbuvir significantly fits or docks into the Zika virus RdRp. Furthermore, there is an 80% overlap in amino acid sequence for the Zika and HCV RdRp’s that bind sofosbuvir. In vitro data indicate that sofosbuvir inhibits 1) Brazilian Zika virus RdRp in a concentration-dependent manner; 2) Brazilian Zika viral
replication in BHK-21 (baby hamster kidney) and SH-Sy5y (human neuroblastoma) cells. Finally, a recent study has shown that BCX4430, an adenosine nucleoside analog, significantly 1) reduces the cytopathic effect of three different Zika strains in vitro; 2) decreases mortality in AG129 mice (which lack Type I and Type II interferon receptors, 300 mg/kg/day); 3) protects AG129 mice from mortality when given one day after Zika virus challenge.

We propose that prior to clinical trials, sofosbuvir’s efficacy, along with the positive control, 7-deaza-2’-C-methyladenosine, be tested: 1) in vitro against the most common circulating strains of Zika virus to determine if sofosbuvir inhibits viral replication; 2) in vivo in AG129 mice infected with Zika, where its effect on viremia and morbidity and mortality would be assessed. If these results are positive, sofosbuvir’s efficacy in humans could be tested in randomized controlled trials by recruiting non-pregnant patients (female patients would be tested for pregnancy) aged 18 or older with Zika virus infection proven by RT PCR of blood or urine and clinical manifestation of the disease present for a minimum of two days. Patients would be screened for other arboviruses (notably Dengue and Chikungunya) as these viruses can elicit similar signs and symptoms as Zika virus. Viral load would be assessed in blood, urine, semen and vaginal secretions throughout treatment. Based on our hypothesis that sofosbuvir will produce significant attenuation of symptoms as compared to placebo control in at least 50% of patients (with a 95% confidence interval of 40 to 60%), treatment and placebo control groups of 100 participants each would be sufficient to detect a statistically significant effect of the drug. Sofosbuvir could be administered orally, 400 mg per day for one week.
If this initial trial were successful, symptomatic pregnant women with proven Zika virus infection could then be recruited for a similar trial of 400 mg of sofosbuvir per day for one week.

Sofosbuvir has a pharmacokinetic profile that would be suitable for treating the potential variety of patients with Zika virus. For example, at least 80% of a dose of sofosbuvir is absorbed systemically and can be given without regard to food. The primary metabolite of sofosbuvir, GS-331007, is pharmacologically inactive, non-toxic and primarily excreted unchanged into the urine. The kinetics of sofosbuvir are not significantly altered by age (19 to 75 years of age), ethnicity, gender, body mass index or cirrhosis. In addition, sofosbuvir and GS-331007 have linear pharmacokinetics with minimal accumulation after multiple dosing. Sofosbuvir has a large volume of distribution (127 liters), thereby increasing the likelihood that sufficient concentrations will be present in potential reservoir areas. Sofosbuvir can be used in patients with severe liver impairment and mild-moderate impairment of renal function.

Safety would not appear to be of major concern as the majority of adverse effects reported for 400 mg of sofosbuvir were of grade 1 severity in HCV patients and only 1% of patients discontinued treatment. Nonetheless, if sofosbuvir produced intolerable or severe adverse effects or increased mortality, then treatment would be promptly discontinued. Patients should be screened for HCV as using sofosbuvir alone for the treatment of HCV would not be considered optimal therapy. Currently, no well
controlled or adequate studies have been done using sofosbuvir in pregnant women. However, to date, no teratogenic effects in humans have been reported. Animal data indicate that at area under the curve exposures far exceeding those seen with normal clinical doses, sofosbuvir does not produce carcinogenesis, mutagenic effects, or an impairment of fertility.\textsuperscript{13}

In summary, we propose that sofosbuvir is a safe pharmacotherapeutic approach for a currently escalating global health threat for which there is currently no effective treatment. If sofosbuvir significantly reduces or eliminates Zika viral load, this approach could 1) in symptomatic cases, eliminate the presence of the virus in plasma, saliva, semen and other body fluids and the risk of transmission between individuals; 2) potentially reduce the severe neurological complications currently seen in infants born to symptomatic mothers. The use of sofosbuvir, in combination with other health-related measures (e.g. control of Zika viral vectors), has the potential to attenuate the health problems and consequences associated with Zika viral infection.

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