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OPINION

Sofosbuvir as Repurposed Antiviral Drug Against COVID-19: Why Were We Convinced to Evaluate the Drug in a Registered/Approved Clinical Trial?

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COVID-19 is a devastating global pandemic around the world. While the majority of infected cases appear mild, in some cases individuals present respiratory complications with possible serious lung damage. There are no specific treatments for COVID-19 as yet, though a number are under evaluation, including experimental antivirals. Sofosbuvir, the clinically approved anti-hepatitis C virus (HCV) drug, is also capable of suppressing other families of positive-strand RNA viruses; Flaviviridae and Togaviridae. Coronaviruses are a family of positive-strand RNA viruses with conserved polymerase, so SARS-CoV-2 RdRp is very likely to be effectively inhibited by sofosbuvir. More importantly, sofosbuvir is safe and well tolerated at 400 mg daily in a 24 week therapeutic regimen. Sofosbuvir active metabolite, however, shows an extremely high intracellular stability So, it is hypothesized that SARS-CoV-2 infection could also be susceptible to sofosbuvir and we were convinced to design and run a clinical trial to evaluate the effect of sofosbuvir 400 mg (in combination with velpatasvir 100 mg, as add-on treatment, in addition to standard of care) on the COVID-19. However, we believe that this manuscript/correspondence should be made available to the international scientific community as soon as possible, with the help of this esteemed journal.

Key Words: Drug repurposing, Sofosbuvir, COVID-19, SARS-CoV-2.

COVID-19 is a devastating global pandemic around the world. While the majority of infected cases appear mild, in some cases individuals present respiratory complications with possible serious lung damage. There are no specific treatments for COVID-19 as yet, though a number are under evaluation, including experimental antivirals. Sofosbuvir, the clinically approved anti-hepatitis C virus (HCV) drug, is also capable of suppressing other families of positive-strand RNA viruses; *Flaviviridae* and *Togaviridae*. Coronaviruses are a family of positive-strand RNA viruses with conserved polymerase, so SARS-CoV-2 RdRp is very likely to be effectively inhibited by sofosbuvir. More importantly, sofosbuvir is safe and well tolerated at 400 mg daily in a 24 week therapeutic regimen. Sofosbuvir active metabolite, however, shows an extremely high intracellular stability So, it is hypothesized that SARS-CoV-2 infection could also be susceptible to sofosbuvir and we were convinced to design and run a clinical trial to evaluate the effect of sofosbuvir 400 mg (in combination with velpatasvir 100 mg, as add-on treatment, in addition to standard of care) on the COVID-19. However, we believe that this manuscript/correspondence should be made available to the international scientific community as soon as possible, with the help of this esteemed journal.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its related disease, COVID-19 is terribly spreading to 206 countries, areas or territories. Till April 2nd, 2020, the values of confirmed cases and total deaths were more than 896,000 and ~45,500 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019).

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Human pathogenic coronaviruses (SARS-CoV and SARS-CoV-2) bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels (1−3). The ability of SARS-CoV2 to enter and infect the human nervous system, based on the strong expression of the ACE2 target throughout the brain (4), should be also considered. However, despite decades of extensive research, there are no specific/effective therapies approved by the US. Food and Drug Administration (FDA) for serious coronavirus infections such as SARS, MERS, and now COVID-19. *In vitro* and limited clinical data suggest potential benefit for chloroquine and hydroxychloroquine. Nevertheless, FDA on March 27th, 2020, issued an emergency authorization for experimental coronovirus treatment using these anti-malarial drugs. On the other hand, although *in vitro* and limited clinical data suggest potential benefit for Kaletra (Lopinavir; Ritonavir), and its actual role in the treatment of COVID-19 is still unclear, some preclinical data suggested potential benefit. However, more recent data has failed to confirm Kaletra efficacy for COVID-19 treatment (5) (https://www.elsevier.com/__data/assets/pdf_file/0007/988648/COVID-19-Drug-Therapy_Mar-2020.pdf). While the COVID-19 outbreak continues to spread around the world, the absence of a clinically proven antiviral therapy is a serious challenge for the treatment of severe COVID-19 cases (6).

According to (7,8), SARS, MERS and SARS-CoV-2 coronaviruses, like HCV and the flaviviridae (9), are positive-sense single-strand RNA viruses and these viruses share a similar replication mechanism requiring a RNA-dependent RNA polymerase (RdRp). So, there is a strong possibility that Sofosbuvir, Ribavirin, AZT (and other HCV/HIV nucleoside/nucleotide analogues such as Remdesivir) can tightly bind to SARS-CoV-2 RdRp. In a recent *in silico* (preliminary) study, sequence analyses as well as homology modeling were used to build a new SARS-nCoV RdRp model which then targeted by anti-polymerase drugs, including the approved drugs Sofosbuvir and Ribavirin (10). The docking scores suggested possible eligibilities of Sofosbuvir, Ribavirin, (and Remdesivir) as potent drugs against the new coronavirus. These theoretical data needed to be confirmed by the experimental observations. Using polymerase extension experiments, *in vitro*, Chien M, et al. also demonstrated that the biologically activate triphosphate forms of four well-known nucleotide/nucleoside analogue anti-viral (anti-HCV/HBV, anti-HIV/AIDS) drugs; Sofosbuvir (Figure 1), Tenofovir alafenamide, Alovudine, and AZT were incorporated by RNA-dependent RNA polymerase (RdRp) enzymes of SARS-CoV as well as SARS-CoV-2, and permanently blocked further incorporation (further polymerase extension was terminated). They considered all these compounds as permanent/strong terminators for the SARS-CoV-2 RdRp (7,8). Due to widely availability of these FDA approved drugs (Sofosbuvir, Tenofovir and AZT), they expressed hope that the drugs would be more evaluated quickly in laboratory and clinical trials for COVID-19 treatment. But the above researchers (Chien M, et al.) could not offer one (or more) of them as the best RdRp inhibitor(s) to introduce to the scientific community.

Sofosbuvir is a clinically approved drug with potent antiviral effects against hepatitis C virus (HCV) with

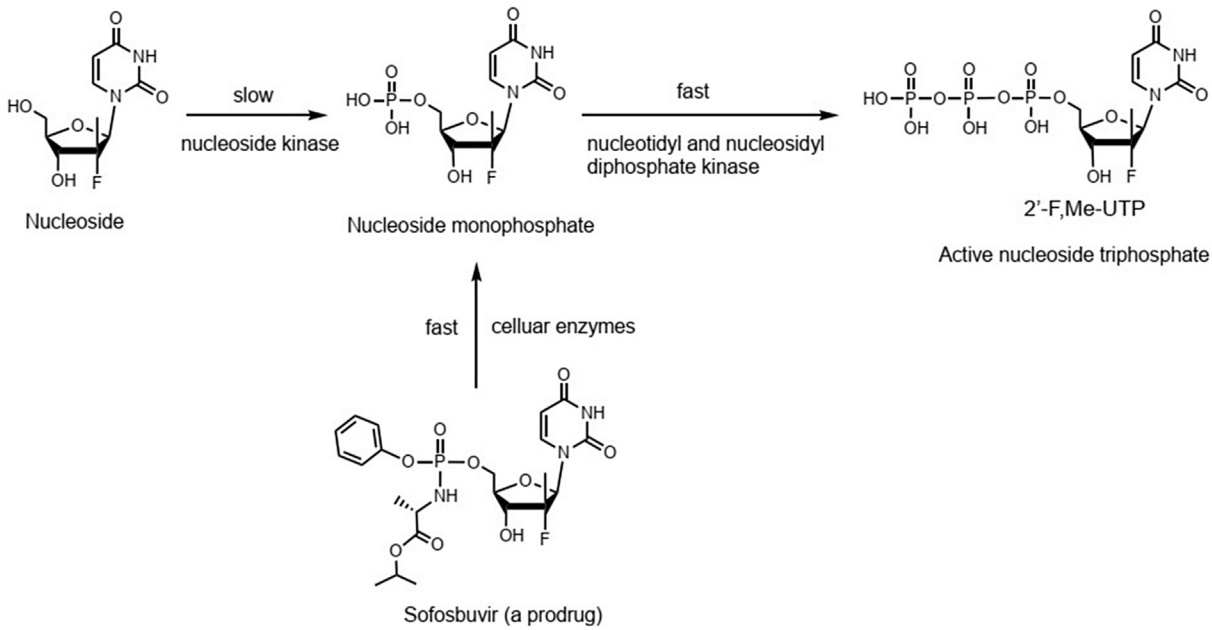

Figure 1. Conversion of Sofosbuvir pro-drug to the triphosphate drug *in vivo*. This UMP prodrug requires the removal of phosphate protection to enter a pathway to yield sofosbuvir triphosphate, the pharmacologically active antiviral compound. Adapted from (8).

diverse genotypes (11). The acid dissociation constant (*pKa*) of sofosbuvir is around 9.3 and as the class 3 compound possess high-solubility and low-permeability (12). The phosphorylation of sofosbuvir within the host cell (hepatocyte) converts it to the active from, nucleoside triphosphate, which terminates RNA replication in the nascent viral genome through the competition with the nucleotides of virus (11). Sofosbuvir exhibits potent antiviral activities, >90%, even against liver cirrhosis, as well as prior null response to ribavirin and IFN (13). Moreover, sofosbuvir is fast response and estimated that during the mean 0.8 and 2 d it exerts it 99 and 99.9 % potency (14). Sofosbuvir offers high healing rate, low side effects, significant efficacy, short administration period good tolerability, and potent resistance defense (15) (e.g. FISSION (16), POSITRON (17), FUSION (17), PHOTON-1 (18). It is reported that the patients receiving combination of sofosbuvir and ribavirin with or without interferon-α did not express primary sofosbuvir resistance mutation in NS5B, S282T (15,19). Moreover, sofosbuvir exerts pan-genotypic antiviral effects against HCV genotypes 1−6 (20).

This antiviral drug does not interfere with major drug metabolizing enzymes, such as the cytochrome P450 system, therefore has low drug-drug interactions, including with antiretrovirals, opioid substitution therapy, and calcineurin inhibitors, which is beneficial for treatment of who have traditionally been difficult to treat. Sofosbuvir has rapid clinical development due to its high efficacy and safety profile (21). Moreover, sofosbuvir can be prescribed in an oral single daily dose due to its promising pharmacokinetic profile. The bioavailability of sofosbuvir is high with maximum plasma concentrations (C_{max}) at ≈ 0.5−2 h in the oral administration (22).

It is interesting that Sofosbuvir, the clinically approved anti-hepatitis C virus (HCV) drug, has the ability to suppress different families of viruses. Different research groups have demonstrated that this safe drug inhibits the replication of flaviviruses (including ZIKV and DENV, and yellow fever virus (YFV) (23−28). Moreover, Ferreira AC, et al. (9) observed that, beyond members of the *Flaviviridae* family, sofosbuvir also inhibits chikungunya virus replication. They found that sofosbuvir was three times more selective in inhibiting Chikungunya virus (CHIKV) production and also was 25% less cytotoxic, in human hepatoma cells, than ribavirin. CHIKV is a member of the *Togaviridae* family has a positive-sense single-stranded RNA genome and its RdRp enzyme (is coded by NsP4 gene), as with other RNA polymerases from positive-sense RNA viruses (29), has well-conserved motifs. In this regard, since coronaviruses are a family of enveloped positive-strand RNA viruses with conserved polymerase, SARS-CoV-2 RdRp is very likely to be effectively inhibited by sofosbuvir. So, we hypothesized that SARS-CoV-2 infection could also be susceptible to this drug.

Prior to the discovery of sofosbuvir, a variety of nucleoside analogs had been examined as anti-hepatitis C (HCV) treatments, but this exhibited relatively low potency. Owing to the substrate specificity of the kinases, the activation of nucleoside analogues often proceeds insufficiently. The design of sofosbuvir, avoids this slow step by building the first phosphate group into the structure of the drug during synthesis. Moreover, additional groups are attached to this phosphate (to temporarily mask the negative charges of the phosphate group, thereby) facilitating entry of the pro-drug into the infected cell (30). Although hepatic cells have the most effective system for removing sofosbuvir phosphate protection, functional assays have revealed that other cells, relevant to SARS-CoV-2 infection, also activate sofosbuvir (9,31).

One of principle cell types productively infected by CHIKV are epithelial cells and variety of non-human and human epithelial cell lines (32). As mentioned above, sofosbuvir is (metabolized to the active drug and) capable of efficient controlling of this type of virus inside the epithelial cells. Furthermore, sofosbuvir appears to be highly active against ZIKV in human neuroepithelial stem cells (24,26) Antiviral activity of sofosbuvir against Zika virus or SARS-CoV-2 depends on the (cellular uptake and) intracellular enzymatic processing of the compound (33) and correlates with the intracellular concentration of the active triphosphate metabolite of the drug. As indicated in Figure 1, active triphosphate metabolite is produced by intracellular nucleoside-diphosphate-kinases (NDKs). The question may be raised: is NDK enzyme present in alveolar epithelial type II cells and the other cells, infected by SARS-CoV-2?

NDKs, encoded by *NME* (also named *NM23*) genes, are a family of multifunctional enzymes that are evolutionarily highly conserved among different species (from bacteria to humans), are found in all cells, and their activities maintain an equilibrium between the concentrations of different nucleoside triphosphates, so are the source of RNA and DNA precursors (except ATP), CTP for lipid synthesis, UTP for polysaccharide synthesis and GTP for protein elongation, signal transduction and microtubule polymerization (34).

Using isoform-specific antibodies, Muimo R, et al. suggested that NDK-A and NDK-B are present bound to the airway epithelial membranes (31). In an interesting study on pneumocyte and hepatic cell lines, Mumtaz R, et al. hypothesized that the conflicting results of sofosbuvir-mediated virus suppression, in different infected cell lines, could be explained by differences in intracellular processing of the pro-drug, leading to different concentration of the active triphosphate metabolite (33). The extent of drug uptake and cytosolic levels of metabolizing enzymes (such as NDK), involved in the metabolic activation of sofosbuvir in the infected cells, are two main determinants. Other important enzyme is carboxylesterase 1 (CES1) which is needed for activation of sofosbuvir. The hepatic cells

strongly express CES1 and lower levels of the enzyme expression, however, is documented in the lung cells (35,36). Though, sofosbuvir, developed for treatment of a hepatotropic virus, is designed to facilitate the intracellular penetration in liver tissue, the above statements can, in part, explain the successful uptake and intracellular activation of sofosbuvir in alveolar epithelial cells, as a viral reservoir.

We may also assume that cellular uptake of the pro-drug (sofosbuvir) as well as intracellular concentrations of biologically active triphosphate metabolites within lung epithelial cells are low, though local lung inflammation may enhance endothelial permeability and then improve epithelial uptake of the drug in the disease state. Which feature of sofosbuvir may give hope? That may be intracellular stability of the triphosphate metabolite. The surprising differences in stability of nucleoside analogue triphosphates of nucleotide analogues have been reported. It has been shown that the triphosphate of the Sofosbuvir showed an extremely high intracellular stability (~35 h), which was also made responsible for the significant and persistent anti-HCV effect of active drug to inhibit NS5B-polymerase (37). Babusis D, et al. also confirmed this observation and evaluated *In vitro* metabolism of sofosbuvir and ribavirin in primary human hepatocytes (38). They showed that activation was efficient for two investigated drugs, but the triphosphate metabolite of sofosbuvir persisted with a half-life of 24 h while ribavirin triphosphate had a short initial half-life of approximately 4 h. Considering phosphatases (on the opposite side of kinases) in alveolar epithelial type II cells, in accordance with the potent antiviral activity of sofosbuvir, the above statements demonstrate that the intracellular triphosphate levels achieved following sofosbuvir administration may equal or exceed the inhibition constant (EC_{50}) for SARS-CoV-2 RdRp. Velpatasvir, which is other inhibitor of the NS5A protein of HCV, may inibit SARS-CoV-2 RdRp enzyme (39).

Overall, although sofosbuvir is not currently listed as potential option of COVID-19 drug therapy, till now (https://www.elsevier.com/__data/assets/pdf_file/0007/988648/COVID-19-Drug-Therapy_Mar-2020.pdf), the evidence on the advantageous action of this drug on viral RdRp *in vitro*, stability of triphosphate drug metabolite and "the least interaction with standard of care" constituted the rationale to perform a trial on patients with SARS-CoV-2 infection. Moreover, sofosbuvir is safe and well tolerated at 400 mg daily in a 24 week therapeutic regimen (9), clinically relevant drug-drug interactions are rare and its important drug interaction is with amiodarone, which causes bradycardia (Sovaldi [Sofosbuvir]: Prescribing information. Foster City, CA: Gilead Sciences; 2013). Sofosbuvir presents an unusually clean safety profile for a nucleotide therapeutic. The safety profile of sofosbuvir, either in combination with Peg-IFN and RBV or in combination with ribavirin alone in all-oral regimen, was excellent, even in cirrhotic patients. Also, *In vitro*, sofosbuvir exhibits no cytotoxicity, mitochondrial toxicity, or bone marrow toxicity when dosed at multiples above the effective dose (40,41).

So, we were convinced to design and run a clinical trial to evaluate the effect of sofosbuvir 400 mg (in combination with velpatasvir 100 mg, as add-on treatment, in addition to standard of care) on the COVID-19. The written research proposal was submitted to the University research council/Ethics Committee, then the approved proposal registered in the Iranian Registry of Clinical trials (code: https://www.irct.ir/trial/46790). The clinical trial is currently in process. In agreement with (9), we advocate generic sofosbuvir beyond treatment of HCV-infected patients. As it represents a safe and effective antiviral option, compared to similar anti-viral agents, we encourage clinical investigators to consider these dual-component HCV drugs, (velpatasvir/sofosbuvir), as re-purposed treatment against SARS-CoV-2 infection. However, we believe that this manuscript/correspondence should be made available to the international community as soon as possible, with the help of this esteemed journal.

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