Sofosbuvir as a potential option for the treatment of COVID-19

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Summary. Sofosbuvir may be a potential option in the treatment of COVID-19 based on the similarity between the replication mechanisms of the HCV and the coronavirus. According the limited experimental evidences, it is hypothesized that sofosbuvir might be a potential option to improve care of patients with COVID-19 especially at the start of the disease and before invasion of the virus into the lung parenchymal cells. Efficacy and safety of sofosbuvir in treatment of COVID-19 may be considered in future clinical studies.

Key words: Sofosbuvir, COVID-19

To Sir Editor

Sofosbuvir is a direct-acting antiviral agent with NS5B RNA-dependent RNA polymerase (RdRp) inhibitory activity that was approved for the treatment of HCV infection in 2013. In 2014 the combination of sofosbuvir and ledipasvir (a NS5A protein inhibitor) received US FDA approval for the treatment of viral hepatitis caused by genotype 1 of HCV (1). Sofosbuvir may be a potential option in the treatment of COVID-19 based on the similarity between the replication mechanisms of the HCV and the coronavirus.

HCV NS5B RdRp requires nucleotide triphosphates as substrates to synthesize RNA, a process without proofreading function (2). Drugs such as sofosbuvir act like these substrates, which terminate the RNA synthesis process by incorporating into the RNA chain (3).

Coronaviruses are single-stranded RNA viruses (4). The RNA is translated into numerous proteins including structural proteins (S, N, M and E proteins), non-structural proteins (NSP) such as nsp12 (RdRp) and proteases (PLpro and 3CLpro) (4).

There are only two docking studies regarding the potential activity of sofosbuvir against coronavirus RdRp. One has been reported in 2016, 4 years after Middle East respiratory syndrome coronavirus outbreak, and the other one has been targeted in 2020 (5-6). Sofosbuvir can inhibit RdRp by fitting into the active site of the structural model of coronavirus and forms the bond with the virus polymerase.

There is also a virtual screening for ledipasvir, an inhibitor of the NS5A protein, to assess its ability to attach to 3CLpro of the 2019 coronavirus (7). It is suggested that ledipasvir (in combination with sofosbuvir) may be a candidate to inhibit the proteins of coronavirus.

There is no specific data about the 50% of maximum inhibitory concentration (IC₅₀) of sofosbuvir against coronavirus but there are for hepatitis C, hepatitis E, hepatitis A, zika, dengue and West Nile virus. Different values of IC₅₀ have been measured by different methods for some virus subtypes and cell lines. Activity of sofosbuvir against the recombinant viruses also has been examined (8).

Several replicons of HCV inhibited with IC₅₀ of 0.016 – 0.048µM (9). In another in-vitro study, IC₅₀ of sofosbuvir against HCV was 1.2µM (10).

The inhibitory activity of sofosbuvir against HEV has been reported with an IC₅₀ of 1.2µM and 10 µM, based on the different replicons (11). There is also an-
other report of dose-dependent inhibition of sofosbuvir on HEV with an IC\textsubscript{50} of 1.97µM (12). However, it was claimed that sofosbuvir did not effective against HEV even at high concentrations (13).

Sofosbuvir may also be active against hepatitis A virus (14). This drug inhibited HAV polymerase with IC\textsubscript{50} of 6.3µM in hepatic but not in kidney cell line.

Activity of sofosbuvir against West Nile virus (WNV) was also examined on different cell lines by Dragoni et al. (15). The IC\textsubscript{50} values of sofosbuvir were 1.2µM and 63.4µM for WNV in hepatic and lung cells respectively. As a concern, activity of sofosbuvir was inferior in the lung cells.

There are some experiences regarding efficacy of sofosbuvir against zika virus (ZIKV). The IC\textsubscript{50} values of 1-5µM were reported for 3 strains of ZIKV in hepatic cell lines and 12-44µM in placental cell lines (16). In hepatic cell line, sofosbuvir IC\textsubscript{50} values were 2.0µM and 3.8µM against ZIKV and Dengue virus (DENV), respectively (17). In another report sofosbuvir inhibited ZIKV replication with IC\textsubscript{50} value of 0.38µM (18).

Mumtaz et al evaluated the effectiveness of sofosbuvir against ZIKV in different cell lines (Huh7, Vero and A549) (19). They detected IC\textsubscript{50} of 4µM for sofosbuvir but only in hepatic cells. The concentration of the drug was much lower in kidney and lung cell lines. Other examinations on different cell lines are needed to evaluate the activity of sofosbuvir in tissues other than hepatic cells.

In conclusion, it is hypothesized that sofosbuvir might be a potential option to improve care of patients with COVID-19 especially at the start of the disease and before invasion of the virus into the lung parenchymal cells. Efficacy and safety of sofosbuvir in treatment of COVID-19 may be considered in future clinical studies.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Received: 24 April 2020
Accepted: 27 April 2020
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