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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. (www.actabiomedica.it)

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 1of 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 $3CL^{pro}$ 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 (IC_{50}) of sofosbuvir against coronavirus but there are for hepatitis C, hepatitis E, hepatitis A, zika, dengue and West Nile virus. Different values of IC_{50} 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 IC_{50} of 0.016 – 0.048μM (9). In another in-vitro study, IC_{50} of sofosbuvir against HCV was 1.2μM (10).

The inhibitory activity of sofosbuvir against HEV has been reported with an IC_{50} 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_{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_{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_{50} values of sofosbuvir were1.2μM 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_{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_{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_{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_{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

References

1. Schinazi, RF, J Shi, and T. Whitaker, Sofosbuvir (Sovaldi): The First-in-Class HCV NS5B Nucleotide Polymerase Inhibitor. Innovative Drug Synthesis 2016: p. 61-79.
2. Zuccaro V, et al. PK/PD and antiviral activity of anti-HCV therapy: is there still a role in the choice of treatment? Expert Opinion on Drug Metabolism & Toxicology 2020. 16(2): p. 97-101.
3. Pockros PJ. Nucleoside/nucleotide analogue polymerase inhibitors in development. Clinics in liver disease 2013. 17(1): p. 105-110.
4. Hilgenfeld R and M Peiris. From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses. Antiviral research 2013. 100(1): p. 286-295.
5. Elfiky AA, SM Mahdy and WM Elshemey, Quantitative structure-activity relationship and molecular docking revealed a potency of anti-hepatitis C virus drugs against human corona viruses. Journal of medical virology, 2017. 89(6): p. 1040-1047.
6. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life sciences 2020: p. 117477.
7. Chen YW, C.-P.B. Yiu, and K.-Y. Wong. Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CL pro) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates. F1000Research, 2020. 9.
8. Xu, H.-T., et al., Purification of Zika virus RNA-dependent RNA polymerase and its use to identify small-molecule Zika inhibitors. Journal of Antimicrobial Chemotherapy 2017. 72(3): p. 727-734.
9. Lam AM, et al., Genotype and subtype profiling of PSI-7977 as a nucleotide inhibitor of hepatitis C virus. Antimicrobial agents and chemotherapy 2012. 56(6): p. 3359-3368.
10. Fenaux M, et al., Antiviral nucleotide incorporation by recombinant human mitochondrial RNA polymerase is predictive of increased in vivo mitochondrial toxicity risk. Antimicrobial agents and chemotherapy 2016. 60(12): p. 7077-7085.
11. Thi VLD, et al. Sofosbuvir inhibits hepatitis E virus replication in vitro and results in an additive effect when combined with ribavirin. Gastroenterology 2016. 150(1): p. 82-85. e4.
12. Netzler NE, et al., Antiviral candidates for treating hepatitis E virus infection. Antimicrobial agents and chemotherapy 2019. 63(6): p. e00003-19.
13. Wang W, et al. Distinct antiviral potency of sofosbuvir against hepatitis C and E viruses. Gastroenterology 2016. 151(6): p. 1251-1253.
14. Jiang W, et al. Sofosbuvir inhibits hepatitis A virus replication in vitro assessed by a cell-based fluorescent reporter system. Antiviral research 2018. 154: p. 51-57.
15. Dragoni F, et al. Evaluation of sofosbuvir activity and resistance profile against West Nile virus in vitro. Antiviral research 2020: p. 104708.
16. Bullard-Feibelman KM, et al., The FDA-approved drug sofosbuvir inhibits Zika virus infection. Antiviral research 2017. 137: p. 134-140.
17. Vicenti, I, et al. Development of a Cell-Based Immunodetection Assay for Simultaneous Screening of Antiviral Compounds Inhibiting Zika and Dengue Virus Replica-

tion. SLAS DISCOVERY: Advancing the Science of Drug Discovery 2020: p. 2472555220911456.
18. Sacramento CQ, et al. The clinically approved antiviral drug sofosbuvir impairs Brazilian zika virus replication. BioRxiv 2016: p. 061671.
19. Mumtaz N, et al. Cell-line dependent antiviral activity of sofosbuvir against Zika virus. Antiviral research 2017. 146: p. 161-163.

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