MINI-REVIEW

A mini-review on sofosbuvir and daclatasvir treatment in coronavirus disease 2019

M. Shabani[1], B. Sadegh Ehdaei[2], F. Fathi[3] and R. Dowran[1]

1) *Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran,* 2) *Microbiology and Immunology Department, Faculty of Medicine, Kashan University of Medical Sciences, Kashan and* 3) *Department of Immunology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran*

Abstract

Sofosbuvir and daclatasvir have been used successfully since 2013 for hepatitis C treatment. It has been shown by different studies that sofosbuvir can inhibit RNA polymerase of other positive-strand RNA viruses including Flaviviridae and Togaviridae. Homology between hepatitis C virus RNA polymerase and severe acute respiratory syndrome coronavirus 2 has also been established. The efficacy of sofosbuvir and daclatasvir as potential choices in treating patients with coronavirus disease 2019 and their recovery can be hypothesized.

Keywords: COVID-19, daclatasvir, HCV, SARS-CoV-2, sofosbuvir
Original Submission: 7 April 2021; **Revised Submission:** 1 May 2021; **Accepted:** 4 May 2021
Article published online: 7 May 2021

Corresponding author: R. Dowran.
E-mail: raziehdowran@yahoo.com

Introduction

Public health is affected by a number of single-stranded positive-sense RNA viruses; among these are hepatitis C virus (HCV), dengue virus, Zika virus, yellow fever virus, chikungunya virus, severe acute respiratory syndrome virus, and Middle East respiratory syndrome virus [1]. Chronic hepatitis C has affected approximately 70 million people worldwide [2]. Hepatitis C is a major cause of cirrhosis and hepatocellular carcinoma and is the leading indication for liver transplantation [3]. Globally, the third leading cause of cancer-induced death is hepatocellular carcinoma, which is the leading cause of mortality in patients with cirrhosis, and hepatitis C is the major risk factor [4].

HCV is classified into seven genotypes [5]. Noteworthy is the fact that genotypes 1, 2, and 3 have worldwide distribution, with the predominance of subgroups 1a in the United States and 1b in Europe, Japan, and China [6,7]. Genotype 1 was the most frequent one in Iran [8]. With the advent of diagnostic tests for hepatitis A and hepatitis B, hepatitis C was first revealed to be a clearly recognizable form of liver disease in the mid-1970s [9]. Hybridization and nuclease digestion experiments indicated that the HCV genome consisted of a single-stranded, positive-sense RNA of approximately 9600 nucleotides in length encoding a polyprotein precursor of about 3000 amino acids [10]. Analyses of the cloned sequences revealed that HCV is related to members of the family Flaviviridae, which includes two other genera, i.e. Flavivirus and *Pestivirus*. All of these viruses have small, enveloped virions and positive-sense RNA genomes that are translated as single, long polyproteins. Then, their polyproteins are cotranslationally and post-translationally processed by cellular and viral proteases to yield the mature structural and nonstructural (NS) proteins, with the structural proteins (core, E1, E2, and p7) grouped together in the N-terminal heptad repeat terminal portion, followed by the NS proteins [11].

The NS proteins include two viral proteases, i.e. a zinc-stimulated NS2-3 protease and the NS3 serine protease, which are responsible for cleavages in the NS region of the HCV polyprotein, an RNA helicase located in the carboxy-terminal region of NS3, the NS4A polypeptide, the NS4B and NS5A proteins, and a RNA-dependent RNA polymerase (RdRp) represented by NS5B [12].

https://doi.org/10.1016/j.nmni.2021.100895

The standard treatment for hepatitis C was pegylated interferon with ribavirin (RBV) for 48 weeks. However, this was effective in only 30% of patients. The combination of a first-generation protease inhibitor (telaprevir or boceprevir) with peg-interferon and RBV subsequently improved sustained virological response (SVR) rates to 50–65% in genotype 1 HCV-infected recipients [13]. However, the addition of boceprevir or telaprevir is limited to HCV genotype 1 and is associated with side effects, intricate dose regimens, and viral resistance [14].

Sofosbuvir and daclatasvir, which are second-generation direct-acting antiviral agents, were approved by the French Agency for the safety of medicines and health care products, being available through an early access program in 2013 [15].

Daclatasvir inhibits HCV replication by binding to the N-terminus of NS5A. It also inhibits virion assembly, with powerful potent pan-genotypic antiviral activity in vitro (HCV genotypes 1-6), and sofosbuvir inhibits the HCV RNA polymerase NS5B [16,17].

The 12-week administration, i.e. once-daily oral daclatasvir plus sofosbuvir, with or without RBV (DCV+SOF±RBV), was satisfactorily tolerated, and SVR12 rates were achieved, exceeding 90% in patients in whom it has been challenging to treat effectively, including those with advanced cirrhosis, HCV genotype 3 infection, HIV/HCV coinfection, and HCV recurrence after liver transplantation and patients with no response to prior therapy with telaprevir or boceprevir [18,19].

The other life-threatening public health challenge that belongs to the single-stranded positive-sense RNA virus is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), formerly designated as 2019 novel coronavirus, which emerged in December 2019 in Wuhan, China, and then rapidly spread across China to many other countries [1].

Four crucial structural proteins are encoded by four Open Reading Frames (ORFs) of the SARS-CoV-2 genome: (a) spike (S) glycoprotein (S1 and S2 subunits), attaching to the host receptor through the receptor-binding domain of S1 subunit, determining the virus host range (S1 subunit), and mediating virus-cell membrane fusion (S2 subunit); (b) matrix (M) protein, mediating transport of nutrients across the transmembrane, bud release, and envelope formation; (c) small envelope (E) protein; and (d) nucleocapsid (N) protein, which interfere with the host's innate immune response [20]. The spike glycoprotein from coronaviruses forms homotrimers, protruding from the viral surface and mediating entry of the virus genome into the host cells [21]. SARS-CoV-2 uses the same host receptor, angiotensin-converting enzyme 2 (ACE2), used by SARS-CoV to infect humans [22]. ACE2 is a metalloprotease expressed in the cells of the lung, intestine, liver, heart, vascular endothelium, testis, and kidney. In addition, SARS-CoV-2 seems to have a receptor-binding domain that binds with high affinity to ACE2 of humans and other species with high receptor homology [23].

Although special measures such as quarantine and social distancing have so far been able to decrease the rates of transmission, antiviral drugs and effective vaccines obviously seem to be the only solution to long-term control and prevention of coronavirus disease 2019 (COVID-19) [24].

While the prevalence of COVID-19 continues to spread worldwide, the lack of a clinically proven antiviral treatment is a serious challenge of the disease [25]. The search for drugs by scientists, which would procure effective treatment for the disease, continues. Among more than thirty agents which have seemed promising in treatment of COVID-19, inculding Western medicine, natural products and Chinese medicine, only remdesivir has so far been approved for treatment of SARS-CoV-2 infection [26].

As previously mentioned, some of the most reliable antiviral agents against HCV are direct-acting antiviral agents, which have an acceptable safety profile and have been used since 2011 [27]. With its binding to the N-terminus of NS5A, daclatasvir presents itself as a powerful HCV NS5A replication complex inhibitor that affects both viral RNA replication and virion assembly [16,17]. In the HCV replicative cycle, NS5A has multiple functions including recruitment of cellular lipid bodies, RNA binding and replication, protein phosphorylation, cell signalling, antagonism of interferon pathways, and virion assembly [28]. In large-genome viruses, such as SARS-CoV-2, these activities are performed by different viral proteins, especially nsp1 to 14, but there is not an exact orthologous of NS5A in the SARS-CoV-2 genome and their activities may be exerted by other multiple proteins [29].

The docking score suggested possible eligibilities of sofosbuvir and daclatasvir as a potent drug against SARS-CoV-2 [30].

Sofosbuvir is a 2′Me-F uridine monophosphate nucleotide that undergoes intracellular metabolism in human hepatocytes to a pharmacologically active uridine triphosphate form (GS-461203) [31]. Indeed, hydrophobic protections in its phosphate allow sofosbuvir to enter a pathway to yield sofosbuvir triphosphate, the pharmacologically active antiviral compound. Then, sofosbuvir is incorporated into HCV RNA by NS5B polymerase, where it acts as a chain terminator [32].

Under normal circumstances, the liver harbours cellular enzymes such as cathepsin A, carboxylesterase 1, and histidine triad nucleotide-binding protein 1 that have a role in removing monophosphate protections [33]. These enzymes are also present in other tissues, such as the respiratory tract. The features of sofosbuvir include a significant rate of recovery, few side effects, high efficacy, and potent resistance defence [34], e.g. FISSION [35], POSITRON [36], FUSION [36], and PHOTON-1 [37]. Noteworthy is the fact that sofosbuvir, which is an antiviral drug,

does not interrupt the activity of the main drug-metabolizing enzymes, for example, the cytochrome P450 system [38]. Furthermore, it is reported that sofosbuvir revealed no bone marrow or mitochondrial toxicity, when dosed at multiples over the effective dose, and that it does not inhibit human DNA or RNA polymerases or mitochondrial RNA polymerase [39]. This is a safe drug that has been shown to be capable of inhibiting RNA polymerase of other positive-strand RNA viruses, e.g. Zika virus, yellow fever virus, and chikungunya virus. It is highly probable, therefore, that sofosbuvir would satisfactorily inhibit SARS-CoV-2 RdRp. It is indeed the case that the replication mechanisms of severe acute respiratory syndrome virus, Middle East respiratory syndrome virus, SARS-CoV-2, HCV, and other single-stranded positive-sense RNA viruses are alike and need an RdRp; in addition, the chances of sofosbuvir binding strongly to SARS-CoV-2 RdRp are high [40–42].

As shown by Sacramento et al. [43], daclatasvir frequently inhibited the production of infectious SARS-CoV-2 in various cells such as Vero cells, hepatoma cell lines (HuH-7), and type II pneumocytes (Calu-3), with potencies of 0.8, 0.6, and 1.1 μM, respectively, targeting early events during the viral replication cycle and preventing the induction of interleukin-6 and tumor necrosis factor α (TNF-α), inflammatory mediators associated with the cytokine storm characteristic of SARS-CoV-2 infection. However, no efficiency was shown, when the virus was quantified by copies per millilitre [43].

But they showed that sofosbuvir is inactive in Vero cells and displayed EC50 values of 6.2 and 9.5 μM in HuH-7 and Calu-3 cells, respectively. Thus, it inhibits SARS-CoV-2 replication more effectively in liver cells than in respiratory cells. The efficiency of daclatasvir compared with sofosbuvir with regard to the inhibition of viral RNA synthesis was twofold more [24]. This research showed that sofosbuvir inhibits SARS-CoV-2 replication 35% more in liver cells than in lung cells [24].

There is no precise and specific information nowadays about 50% of maximum inhibitory concentration of sofosbuvir against coronavirus, but there is information for hepatitis C virus, hepatitis E virus, hepatitis A virus, Zika virus, dengue virus, and West Nile virus [44]. Dragoni et al. [45] studied the effects of sofosbuvir against West Nile virus using different cell lines. The maximum inhibitory concentration values of sofosbuvir were 1.2 μM and 63.4 μM for West Nile virus in hepatic and lung cells, respectively. In lung cells, sofosbuvir was less active, indicating significant concern [45].

Conclusion

To sum up, it can be hypothesized that as far as the treatment and recovery of patients with COVID-19 is concerned, sofosbuvir and daclatasvir can be considered as potential candidates. A number of studies are being carried out to test the potential effect of antiviral treatments on suppression of SARS-CoV-2. In the treatment of COVID-19, daclatasvir and sofosbuvir have been presented as potential candidates. Docking studies showed remarkable binding interactions of daclatasvir and sofosbuvir with COVID-19 enzymes. Daclatasvir inhibited the production of infectious SARS-CoV-2 in different cells; this was especially significant during the initial stages of the disease and before the invasion of the virus into parenchymal cells of the lung. The replication of SARS-CoV-2 in HuH-7 and Calu-3 cells is also inhibited by sofosbuvir; its efficiency in the liver, however, is higher than in the lung. In future clinical trials, the two issues of effectiveness and safety should be considered in the treatment of COVID-19 with sofosbuvir and daclatasvir.

Transparency declaration

The authors declare no conflict of interests.

References

[1] Masters PS. The molecular biology of coronaviruses. Adv Virus Res 2006;66:193–292.
[2] Han R, Zhou J, François C, Toumi M. Prevalence of hepatitis C infection among the general population and high-risk groups in the EU/EEA: a systematic review update. BMC Infect Dis 2019;19(1):655.
[3] Thuluvath P, Guidinger M, Fung J, Johnson L, Rayhill S, Pelletier S. Liver transplantation in the United States, 1999–2008. Am J Transplant 2010;10(4p2):1003–19.
[4] El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012;142(6):1264–1273. e1.
[5] Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. Hepatology 2014;59(1):318–27.
[6] Negro F, Alberti A. The global health burden of hepatitis C virus infection. Liver Int 2011;31:1–3.
[7] Cornberg M, Razavi HA, Alberti A, Bernasconi E, Buti M, Cooper C, et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver Int 2011;31:30–60.
[8] Mahmud S, Akbarzadeh V, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Iran: systematic review and meta-analyses. Sci Rep 2018;8(1):1–25.
[9] Alter H, Holland P, Morrow A, Purcell R, Feinstone S, Moritsugu Y. Clinical and serological analysis of transfusion-associated hepatitis. Lancet 1975;306(7940):838–41.
[10] Choo Q-L, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989;244(4902):359–62.
[11] Miller RH, Purcell RH. Hepatitis C virus shares amino acid sequence similarity with pestiviruses and flaviviruses as well as members of two plant virus supergroups. Proc Nat Acad Sci 1990;87(6):2057–61.

[12] Neddermann P, Clementi A, De Francesco R. Hyperphosphorylation of the hepatitis C virus NS5A protein requires an active NS3 protease, NS4A, NS4B, and NS5A encoded on the same polyprotein. J Virol 1999;73(12):9984–91.
[13] Coilly A, Roche B, Dumortier J, Leroy V, Botta-Fridlund D, Radenne S, et al. Safety and efficacy of protease inhibitors to treat hepatitis C after liver transplantation: a multicenter experience. J Hepatol 2014;60(1):78–86.
[14] Poordad F, McCone Jr J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. New England J Med 2011;364(13):1195–206.
[15] Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. New England J Med 2014;370(3):211–21.
[16] Gao M, Nettles RE, Belema M, Snyder LB, Nguyen VN, Fridell RA, et al. Chemical genetics strategy identifies an HCV NS5A inhibitor with a potent clinical effect. Nature 2010;465(7294):96–100.
[17] Gao M. Antiviral activity and resistance of HCV NS5A replication complex inhibitors. Curr Opin Virol 2013;3(5):514–20.
[18] Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology 2015;61(4):1127–35.
[19] Wyles DL, Ruane PJ, Sulkowski MS, Dieterich D, Luetkemeyer A, Morgan TR, et al. Daclatasvir plus sofosbuvir for HCV in patients coinfected with HIV-1. New England J Med 2015;373(8):714–25.
[20] Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe 2020.
[21] Tortorici MA, Veesler D. Structural insights into coronavirus entry. Advances in virus research, vol. 105. Elsevier; 2019. p. 93–116.
[22] Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579(7798):270–3.
[23] Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020;94(7).
[24] Sacramento CQ, Fintelman-Rodrigues N, Temerozo JR, Dias SdSG, Ferreira AC, Mattos M, et al. The in vitro antiviral activity of the anti-hepatitis C virus (HCV) drugs daclatasvir and sofosbuvir against SARS-CoV-2. bioRxiv 2020.
[25] Sayad B, Sobhani M, Khodarahmi R. Sofosbuvir as repurposed antiviral drug against COVID-19: why were we convinced to evaluate the drug in a registered/approved clinical trial? Archiv Med Res 2020;51(6):577–81.
[26] Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Dis Therapeut 2020;14(1):58–60.
[27] Geddawy A, Ibrahim YF, Elbahie NM, Ibrahim MA. Direct acting anti-hepatitis C virus drugs: clinical pharmacology and future direction. J Translat Inter Med 2017;5(1):8–17.
[28] Smith MA, Regal RE, Mohammad RA. Daclatasvir: a NS5A replication complex inhibitor for hepatitis C infection. Ann Pharmacother 2016;50(1):39–46.
[29] O'Meara MJ, Guo JZ, Swaney DL, Tummino TA, Hüttenhain R. A SARS-CoV-2-human protein-protein interaction map reveals drug targets and potential drug-repurposing. BioRxiv 2020.
[30] Shah B, Modi P, Sagar SR. In silico studies on therapeutic agents for COVID-19: drug repurposing approach. Life Sci 2020:117652.
[31] Keating GM. Sofosbuvir: a review of its use in patients with chronic hepatitis. C Drugs. 2014;74(10):1127–46.
[32] Rodríguez-Torres M. Sofosbuvir (GS-7977), a pan-genotype, direct-acting antiviral for hepatitis C virus infection. Exp Rev Anti-Infect Ther 2013;11(12):1269–79.
[33] Murakami E, Tolstykh T, Bao H, Niu C, Steuer HMM, Bao D, et al. Mechanism of activation of PSI-7851 and its diastereoisomer PSI-7977. J Biol Chem 2010;285(45):34337–47.
[34] Svarovskaia E, Dvory H, Hebner C, Doehle B, Gontcharova V, Martin R, et al. No resistance detected in four phase 3 clinical studies in HCV genotype 1-6 of Sofosbuvir+ ribavirin with or without peginterferon: 1843. Hepatology 2013;58.
[35] Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. New England J Med 2013;368(20):1878–87.
[36] Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. New England J Med 2013;368(20):1867–77.
[37] Sulkowski M, Rodriguez-Torres M, Lalezari J, Fessel J, Mounzer K, Shuhort M, et al. All-oral therapy with sofosbuvir plus ribavirin for the treatment of Hcv Genotype 1, 2, and 3 infection in patients co-infected with Hiv (photon-1): 212. Hepatology 2013;58.
[38] Mariño Z, van Bömmel F, Forns X, Berg T. New concepts of sofosbuvir-based treatment regimens in patients with hepatitis C. Gut 2014;63(2):207–15.
[39] Mangia A, Piazzolla V. Overall efficacy and safety results of sofosbuvir-based therapies in phase II and III studies. Dig Liver Dis 2014;46:S179–85.
[40] Chien M, Anderson TK, Jockusch S, Tao C, Kumar S, Li X, et al. Nucleotide analogues as inhibitors of SARS-CoV-2 polymerase. bioRxiv; 2020.
[41] Ju J, Li X, Kumar S, Jockusch S, Chien M, Tao C, et al. Nucleotide analogues as inhibitors of SARS-CoV polymerase. BioRxiv 2020.
[42] Ferreira AC, Reis PA, de Freitas CS, Sacramento CQ, Hoelz LVB, Bastos MM, et al. Beyond members of the Flaviviridae family, sofosbuvir also inhibits chikungunya virus replication. Antimicrob Agents Chemother 2019;63(2).
[43] Sacramento CQ, Fintelman-Rodrigues N, Temerozo JR, da Silva Gomes Dias S, Ferreira AC, Mattos M, et al. The in vitro antiviral activity of the anti-hepatitis C virus (HCV) drugs daclatasvir and sofosbuvir against SARS-CoV-2. bioRxiv 2020. 2020.06.15.153411.
[44] Nourian A, Khalili H. Sofosbuvir as a potential option for the treatment of COVID-19. Acta Bio Medica: Atenei Parmensis 2020;91(2):239.
[45] Dragoni F, Boccuto A, Picarazzi F, Giannini A, Giammarino F, Saladini F, et al. Evaluation of sofosbuvir activity and resistance profile against West Nile virus in vitro. Antiviral Res 2020;175:104708.