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

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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. © 2021 The Authors. Published by Elsevier Ltd.

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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].
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, including 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.

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