European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2020; 24: 5193-5194

Editorial – Sofosbuvir/Velpatasvir as a combination with strong potential activity against SARS-CoV2 (COVID-19) infection: how to use direct-acting antivirals as broad-spectrum antiviral agents

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Human coronaviruses (HCoVs) are positive-sense RNA (30 kb) viruses. Two types of proteins characterize HCoVs: structural [Spike (S), Nucleocapsid (N), Matrix (M), and Envelope (E)] and non-structural proteins (nsp1 up to nsp16) including the RNA dependent RNA polymerase (RdRp) (nsp12), the 3-chymotrypsin-like protease, and the papain like Protease[1].

Recently, an outbreak of interstitial pneumonia arose in Wuhan, China, since December 2019, due to the novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), and the related disease was named COVID-19[2]. The epidemic quickly spread all around the world, representing a severe global health threat[3]. WHO declared COVID-19 as a Public Health Emergency of International Concern (PHEIC), then, as a pandemic in March 2020[4]. Promptly started a rush towards discovery of compounds with therapeutic potential against COVID-19[5,6]. Actually, there is the urgent need to identify other already available compounds that can effectively inhibit SARS-CoV2 replication cycle.

Recently, viral lifecycle, potential drug targets and investigational compounds acting similarly of Directly Acting Antiviral Agents (DAAS) for Hepatitis C virus (HCV) infection, were focused[7].

Repurposing some of existing antivirals as broad-spectrum antiviral agents (BSAAs) could represent a viable alternative[8]. Moreover, a recent review pointed up the attention on the fact that discovery and development of safe-in-man BSSAs, including Sofosbuvir and Velpatasvir, able to targeting viruses belonging to two or more viral families (as flavivirus and coronavirus families) could provide additional protection of the general population from emerging and re-emerging viral diseases, reinforcing the arsenal of available antiviral options[9].

Similarly to HCV, SARS-CoV2 genome is characterized by a positive-sense single-strand RNA and share a similar replication mechanism requiring a RNA-dependent RNA polymerase (RdRp). This polymerase displays similar catalytic mechanisms and some key conserved amino acids in the active site among different positive sense RNA viruses[10,11]. Like HCV, SARS-CoV2 RdRps has no proofreading ability and is highly error-prone, which might increase its ability to accept modified nucleotide analogues as substrates. RdRp catalyzes the synthesis of viral RNA and thus plays a central role in the replication and transcription cycle of SARS-COV2. The polymerase domain, like HCV, is composed of three subdomains; a fingers subdomain (residues L366-A581 and K621-G679), a palm subdomain (residues T582-P620 and T680-Q815), and a thumb subdomain (residues H816-E920). The configurations of the template/primer entry paths, the nucleoside triphosphate (NTP) entry channel, and the nascent strand exit path are similar to those described for HCV polymerase[10]. Moreover, also the 3-chymotrypsin-like protease (3CLpro) is vital to virus replication and the 3CLpro cleavage sites are highly conserved, so it could be a promising drug target[12].

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Sofosbuvir (SOF) is a prodrug nucleotide uridine analogue inhibitor of the RdRp and acts as specific RNA chain terminator from the template strand to the primer strand. The active triphosphate form is incorporated by SARS-CoV-2 RdRp and blocks further incorporation[13-15].

Velpatasvir (VEL) is an inhibitor of the NS5A protein of HCV. The VEL inhibition activity, tailored upon the active sites of A chain and that of B chain of the 3CLpro was recently focused[12].

SOF/VEL is an effective and safe drug combination worldwide used as standard of care for HCV infection and could be an attractive candidate as SARS-CoV2 specific DAAs because of the contemporary inhibition of two viral enzymes, which substantially reduces the ability of the virus to develop resistance.

These computational results provide a strong rationale for experimental validation of SOF/VEL association as effective combination either in prophylaxis of exposed health care workers and in treatment of SARS-CoV2 infected patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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