Sofosbuvir for Covid-19 infection: A Potential Candidate

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Abstract

SARS COV-2 and its related disease COVID 19 has led to a major global pandemic and in absence of no known effective therapeutic agents against it, virus is having a free run. Sequence analyses, homology modelling and docking have suggested potential drugs which can be used against this virus. Sofosubivir is a direct-acting antiviral agent with NS5B RNA-dependent RNA polymerase (RdRp) inhibitory activity used in management of Hepatitis-C infection. This drug has potential role in managing this viral disease. Safety and efficacy of this drug is already established in patients of Hepatitis-C where it is given for long periods of time. Favourable pharmacokinetic profile of this drug also favors it use in this infection. This report summarises information available which can be explored further in clinical trials.

SARS COV-2 and its related disease COVID 19 has led to a major global pandemic. Currently, absence of a clinically proven antiviral therapy or effective vaccine is a serious challenge for the control of this pandemic.

Coronaviruses, including SARS-CoV2, are enveloped viruses. Their genome is comprised of a single, large (27-34 kilobase) positive-sense single-stranded RNA, which is directly translated by host cells. The SARS-CoV2 genome encodes 4 structural proteins, 16 non-structural proteins (NSPs) which carry out crucial intracellular functions, and 9 accessory proteins [1]. One of the important non-structural proteins is RNA dependent RNA polymerase (RdRp) (nsp12) [2]. Structural and phylogenetic analysis indicates that all known viral RdRps preserve a high degree of structural conservation. There are several drugs that bind to the RdRp active site and that have shown efficacy, in vitro and animal models, for treating other RNA viral diseases, including Favipiravir [3] and Remdesivir [4]. In fact, recently, Remedesivir has shown efficacy in decreasing the disease duration in adult patients with severe COVID 19 infection [5].

Sofosbuvir is a clinically approved drug with potent antiviral effects against hepatitis-C virus (HCV) which is also a positive sense RNA virus [6]. Sofosbuvir is a direct-acting antiviral agent with NS5B RNA-dependent RNA polymerase (RdRp) inhibitory activity. The phosphorylation of sofosbuvir within the host cell (hepatocyte) converts it to the active from, nucleoside triphosphate, which terminates RNA replication in the nascent viral genome through the competition with the nucleotides of virus [6]. Sofosbuvir has also been shown to have high efficacy and safety profile [7]. Sofosbuvir can be prescribed as single daily dose, orally, due to its promising pharmacokinetic profile [8].

Recently, some preliminary studies have been conducted, in vitro, to evaluate the possible role of sofosbuvir in inhibiting Rdrp of SARS-Cov-2. In a study by Elfiky [9], sequence analyses, homology modelling and docking were used to build a new SARS-CoV 2 RdRp model which was then targeted by anti-polymerase drugs, including Sofosbuvir and Remedsivir. The docking scores suggested possible eligibilities of Sofosbuvir and Remdesivir as potent drugs against the new coronavirus.

Using polymerase extension experiments, Chien M, et al. [10] demonstrated that the biologically active triphosphate forms of Sofosbuvir was incorporated by RNA-dependent RNA polymerase (RdRp) enzymes of SARS-CoV as well as SARS-CoV-2, and permanently blocked further polymerase extension.

In another in-vitro study, it was demonstrated that the activated triphosphate form of Sofosbuvir was incorporated by low-fidelity polymerases and SARS-CoV RNA-dependent RNA polymerase (RdRp), and blocked further incorporation by these polymerases; the activated triphosphate form of Sofosbuvir did not incorporate a host-like high-fidelity DNA polymerase [11].

With the worldwide availability of Sofosbuvir and excellent safety profile and preliminary studies suggesting its potential role in Covid -19, there is urgent need to conduct control trials to test the efficacy and safety of this drug in patients of COVID-19 disease.

Conflict of Interest

None of the authors have any conflict of interest.

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