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**Are nucleotide inhibitors, already used for treating hepatitis C virus infection, a potential option for the treatment of COVID-19 compared with standard of care? A literature review**

Spera AM. Sofosbuvir: An antiviral drug for a viral infection

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**Abstract**

Coronavirus disease 2019 (COVID-19) is global pandemic with various clinical presentations, ranging from cold to sometimes unrecoverable acute respiratory distress syndrome. Although urgently needed, currently there are no specific treatments for COVID-19. Repurposing existing pharmaceuticals to treat COVID-19 is crucial to control the pandemic. *In silico* and *in vitro* studies suggest that a nucleotide inhibitor called Sofosbuvir, has also antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), apart from suppressing other positive-strand ribonucleic Acid viruses with conserved polymerase (hepatitis C virus). The aim of this study was to assess if Sofosbuvir improves clinical outcomes in patients with moderate or severe COVID-19. A comprehensive overview of scientific literature has been made. Terms searched in PubMed were: COVID-19, SARS-CoV-2, nucleotide inhibitors, pandemic, Sofosbuvir. Results clinical trials conducted among adults with moderate or severe COVID-19 were analyzed. Patients were divided in treatment and control arms, receiving Sofosbuvir plus standard care and standard care alone respectively. The addition of Sofosbuvir to standard care significantly reduced the duration of hospital stay compared with standard care alone in clinical trials examined. If efficacy of these repurposed, cheap and easily available drug against SARS-CoV-2 is further demonstrated, it could be essential to refine the treatment of COVID-19.

**Key Words:** COVID-19; SARS-CoV-2; Pandemic; Nucleotide inhibitors; Sofosbuvir; Coronavirus

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**Core Tip:** Coronavirus disease 2019 represents a terrible, still unsolved, global problem affecting not only the healthcare system but also the economic and social one. All countries are facing and fighting against this pandemic but there is still no specific treatment for its eradication. Recently some nucleotide inhibitors, already approved and employed for the treatment of hepatitis c virus infection, have been repurposed for treatment of severe acute respiratory syndrome coronavirus 2 infection, because of some common features among coronaviruses and hepatitis c virus. Herein briefly I focused on the effects of this compound on coronavirus disease 2019, based on its pharmacokinetic properties and on results of several completed clinical trials.

**INTRODUCTION**

Coronavirus disease 2019 (COVID-19) is an infection caused by a coronavirus (CoV), an enveloped positive-sense ribonucleic acid (RNA) virus with a crown-like appearance due to spike-like projections on its surface[1]. The identification of 27 cases of pneumonia of unknown etiology on 31 December 2019 in Wuhan City, China, revealed a new virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19, as named by the World Health Organization (WHO)[2]. According to Zhou *et al*[3], SARS-CoV-2 can affect the respiratory, gastrointestinal, hepatic and central nervous system tracts of several organisms, such as humans, cattle, bats, rodents, birds and other wild animals. Given that COVID-19 has been preempted by two different events in the past (2002 and 2012) caused by crossover of animal betacoronaviruses to humans that resulted in severe disease, until the outbreak of severe acute respiratory syndromes, these zoonotic viruses were not considered highly pathogenetic to humans but only responsible for mild infections in immunocompetent people[4]. Such zoonotic spillover determines pathogen transmission from a vertebrate animal to a human. Furthermore, there is evidence of human-to-human virus transmission: Humans may change from hosts into new stable infection reservoirs[5]. Moreover, some people can act as superspreaders; overall, patients can be infectious not only during their symptomatic phase but also during their clinical recovery; as the viral loads found in the nasal cavity are higher than those of the throat, there is no difference in viral burden among symptomatic and asymptomatic patients, as Zou *et al*[6] recently clarified. According to Cheng *et al*[7], the receptor used by SARS-CoV-2 to enter the respiratory mucosa is angiotensin receptor 2 (ACE2), which is highly expressed in the Asian population; this finding may represent an interesting target for future therapeutic options, as reported. The clinical presentation of COVID-19 varies among individuals, ranging from an asymptomatic status to severe respiratory distress and multiorgan failure. SARS-CoV-2 also has neuroinvasive potential, as hypothesized by Li *et al*[8], entering the central nervous system, invading the olfactory nerve and bulb or the sensory fibers of the vagus nerve innervating the respiratory tract and thus causing hyposmia and dysgeusia. The disease can progress in a week to interstitial pneumonia, and in the worst cases, patients develop silent “happy” hypoxemia (respiratory failure without subjective perception of dyspnea) with evidence of hypocapnia by compensatory hyperventilation. Complications typically developed by elderly people and patients affected by underlying comorbidities include acute lung injury, acute respiratory distress syndrome, shock and acute kidney impairment[5]. Recovery begins in the 2nd or 3rd week, and the median duration of hospital stay for recovered patients is almost 10 d. Differential diagnosis of COVID-19 includes all types of respiratory viral infections, atypical organisms such as mycoplasma and chlamydia and bacterial infections[5].

**CURRENT TREATMENT ONGOING**

Clinical management of COVID-19 is based only on life support, treatment of symptoms and prevention of respiratory failure, as there are currently no registered drugs for treating this disease. Nevertheless, clinical trials based on antiviral, immunomodulatory and anti-inflammatory drugs are ongoing, moving from the SARS-CoV and MERS-CoV experience as well as *in vitro* observations. No conclusive evidence is available regarding the use of steroids; according to Russel *et al*[9] and Zhou *et al*[10], it is necessary to evaluate use on a case-by-case basis, considering both risks and benefits[9,10].  Lin *et al*[11] recommend the use of anticoagulation therapy at the early stage of the disease, particularly when the D-dimer value is 4 times higher than normal, as the infection and related factors can overactivate the coagulation cascade, possibly resulting in ischemic events and disseminated intravascular coagulation. The use of antiviral agents is controversial. In fact, although Chu *et al*[12], Lim *et al*[13] and Yao *et al*[14] demonstrated the efficacy of lopinavir/ritonavir (400/100 mg twice daily) against COVID-19, clinical evidence of its efficacy remains under debate. Al-Tawfiq *et al*[15] described the successful use of remdesivir, a nucleotide analog able to incorporate into the nascent viral RNA chain, causing its premature termination, but it is not yet recommended by the WHO[16]. Chloroquine and hydroxychloroquine, two drugs used for malaria and amoebiasis, demonstrate activity against SARS-CoV-2 *in vitro* and in animal models[17]. According to this study, the mechanism of action of these drugs seems to be an increase in endosomal pH, which prevents fusion between the virus and the host cell and also interferes with the ACE2 receptor targeted by the virus. Moreover, these drugs appear to have immunomodulatory activity. In addition to common side effects (nausea, vomiting, diarrhea, abdominal pain, extrapyramidal disorders), arrhythmogenic cardiotoxicity has been reported, and QT interval monitoring is mandatory with their use. When hypoxia or acute respiratory distress syndrome arises, oxygen therapy is required, basically administered through a nasal cannula, face mask or noninvasive CPAP. If an adequate arterial O2 level is not reached (SatO2 < 93%), invasive mechanical ventilation *via* intubation is necessary. Advanced techniques such as prone positioning should be considered[18], as should extracorporeal membrane oxygenation. The national multicenter clinical trial in Italy based on the use of tocilizumab, a monoclonal antibody against IL-6R, was prematurely interrupted[19] because no improvement in patients was shown. However, other possible therapeutic options represented by specific anti-inflammatory molecules and multiple monoclonal antibodies/immunostimulants are under investigation. Some options include anti-IL-17, interferon and mesenchymal stromal cells able to reduce inflammation and stimulate regeneration of tissues[20], amplification of anti-2019nCoV specific T lymphocytes[21], the use of anti-Th1-mediated inflammatory cascades such as canakinumab (anti IL-1B)[22] and roflumilast (inhibitor of enzyme phosphodiesterase-4 already used to control neutrophilic inflammation in patients with COPD)[23]. Gurwitz *et al*[24] suggested that sartanics (angiotensin receptor 1 blockers) may be considered for their ability to inhibit binding between the spike S protein of the virus and ACE2, though other studies hypothesized that sartanics may predispose patients toward COVID-19 by targeting ACE receptors in pulmonary tissue. Another interesting option is based on the use of molecules able to target structural genes encoding the S, envelope or membrane protein along with small interfering RNAs[25]. Moreover, some broad-spectrum antiviral agents (*e.g.*, dsRNA-activated caspase oligomerizers) can cause selective apoptosis of host cells containing the virus, which should be exploited in fighting COVID-19; however, combination with other therapies (such as thiopurine compounds, naphthalene and protease inhibitors, zinc or mercury) is necessary because antivirals alone cannot block the virus from entering the cell or disrupt viral nucleic acid[25]. COVID-19-related bradykinin-dependent local lung angioedema can be treated with bradykinin receptor B1 and B2 antagonists and anti-inflammatory agents or neutralizing strategies for anti-S antibody-induced effects[26]. In addition, the use of passive immunotherapy with plasma derived from convalescent patients is still debated[27]. Vaccination may constitute a solution, but vaccine development is ongoing. All drugs currently employed or suggested for the treatment of COVID-19 are summarized in Table 1.

The aim of this review is to evaluate the possible role of nucleotide analogs in the treatment of this dangerous pandemic, given that no drugs currently available for the treatment of SARS-CoV-2 infections seem to be effective.

**NUCLEOTIDE ANALOGS IN THE TREATMENT OF CORONAVIRUS DISEASE 2019: WHERE ARE WE NOW?**

A novel therapeutic approach for COVID-19 is based on the use of nucleotide analogs. One such analog is Sofosbuvir, a powerful anti-hepatitis C virus direct-acting agent that targets HCV polymerase NS5B, approved by national and international agencies. It has a demonstrated ability to suppress other positive-strand RNA viruses, such as members of Flaviviridae and Togaviridae, in addition to Coronaviridae[28].

Although not currently listed as a potential option for SARS-CoV-2 therapy, sofosbuvir may represent a key step in the control of the COVID-19 pandemic, as stated by Jácome *et al*[29]. Nevertheless, the winning strategy may instead be based on a multitargeted approach of different drugs targeting many viral proteins[29]. Sofosbuvir binds to the active site of HCV and is thus incorporated in the nascent strand, preventing the addition of the next nucleotide[29]. The replication mechanisms of coronaviruses, flaviviruses and togaviruses require an RNA-dependent RNA polymerase that is targeted by sofosbuvir, ribavirin and AZT[28]. This has been demonstrated by Elfiky *et al*[30] in a recent in silico study based on homology modeling: the docking scores that emerged from the study suggested the possible use of these antiviral drugs in the treatment of disease caused by SARS-CoV-2.

The RdRp enzyme of coronaviruses tightly embody biologically activated triphosphate forms of “four nucleotide/nucleoside analog” antiviral drugs (sofosbuvir, tenofovir alafenamide, alovudine and AZT), without further incorporation thereafter, as clearly reported by Chien *et al*[31]. Therefore, all these compounds may be considered permanent terminators for SARS-CoV-2 RdRp[31,32] and are of curative significance for COVID-19, though the authors did not suggest the best RdRp inhibitor.

***Sofosbuvir: An antiviral drug***

The antiviral effect of sofosbuvir and its potent, fast action[33], even against liver cirrhosis, is well known, even in the setting of a lack of response to other medications, such as interferon and ribavirin[34]. Pivotal trials of this pangenotipic DAA[35] (Fission, Positron, Fusion and Photon 1)[36-38] report its high rate of success, significant efficacy, low rate of side effects and tolerability. Moreover, this antiviral compound does not interfere with the cytochrome P450 system or other major drug-metabolizing enzymes and has low drug-drug interactions. With a good pharmacokinetic profile, sofosbuvir can be prescribed as a single oral daily dose. The antiviral activity of the active form of sofosbuvir is related to the intracellular production of its active triphosphate metabolite by intracellular nucleoside diphosphate kinase (NDK), an enzyme encoded by National Military Establishment that is present in all cells, including the alveolar epithelial type II cells targeted/infected by SARS-CoV-2. The main role of NDK is to maintain an equilibrium between the concentrations of several nucleoside/nucleotide triphosphates, which are thus the source of RNA and deoxyribonucleic acid precursors such as CTP, UTP and GPT[39]. The presence of NDK-A and NDK-B in airway epithelial membranes has been suggested by Muimo *et al*[40] using isoform-specific antibodies, whereby local COVID-19-mediated lung inflammation enhanced sofosbuvir endothelial permeability and improved epithelial uptake during SARS-COV-2 infection. The extremely high intracellular stability of sofosbuvir and its triphosphate metabolite is a main feature of this antiviral drug and explains its significant and persistent HCV effect in inhibiting HCV-NS5B polymerase[41]. Moreover, intracellular levels of its triphosphate metabolite in alveolar epithelial type II cells may inhibit SARS-CoV-2 RdRp (in accordance with its EC50).

Notably, it must be emphasized that use of the currently employed nucleoside analog remdesivir has recently been reduced. In fact, the living WHO guidelines on drugs for COVID-19[16] released on September 4 and then updated in November 2020 strongly suggest no remdesivir use for patients with COVID-19 at any severity; this was based on results of a systematic review and network meta-analysis including data for 4 randomized trials with 7333 adult patients hospitalized for COVID-19. No effect on mortality, need for mechanical ventilation, or time to clinical improvement was found among COVID-19 patients treated with remdesivir. The conclusion is that remdesivir does not improve important patient outcomes. Jockusch *et al*[42] reported in Nature that RNA terminated by sofosbuvir is more resistant to SARS-CoV-2 proofreading than RNA terminated by remdesivir.

Several randomized and nonrandomized clinical trials have been performed comparing DAA-based regimens and standard of care (SOC) in hospitalized COVID-19 patients[43]. Trials eligible for inclusion were identified by reviewing clinicaltrials government, WHO International Clinical Trials Registry Platform and Cochrane Central Register of Controlled Trials. Three[44-46] of eight studies reviewed were considered by Simmons *et al*[43] because they met the inclusion criteria (completed trials about the comparison of predetermined DAA-based regimens and SOC for the treatment of COVID-19). The primary outcomes highlighted were clinical recovery in 14 d and all-cause mortality from enrollment to the end of the follow-up; the findings along with secondary outcomes are summarized in Table 2. An individual patient data meta-analysis was produced, and treatment effects were reported as risk ratios and mean differences for binary and continuous outcomes, respectively. Cox proportional hazards models were used to estimate the cause-specific hazard ratios for recovery, and the Fine and Gray competing risk model was employed to account for death as a competing risk. A sensitivity analysis for the primary outcomes involved excluding nonrandomized trials because of the potential risk of bias. A second analysis for primary binary outcomes was performed, including the worst outcomes not yet considered in the Intention to treat analysis of all the studies included in the meta-analysis.

The effects of nonrandomized treatment assignment were studied in a final sensitivity analysis in which the effect of sofosbuvir/daclatasvir on clinical recovery and death was estimated using the inverse probability weighting estimator adjusted for age, sex and comorbidities (hypertension, chronic pulmonary illness, diabetes mellitus). Data were analyzed using STATA vers 14.2 and Rstudio vers 3.5.3.

Three Iranian studies of the eight available were conducted among 176 hospitalized patients, with equal reported baseline characteristics among the intervention and control groups. Two of the three studies were randomized[44,45] and included patients affected by severe disease. A combination of DAA + SOC at the time of trial (hydroxychloroquine + lopinavir/ritonavir) was administered to the intervention arm of each trial; the control groups received only SOC (hydroxychloroquine plus lopinavir/ritonavir, hydroxychloroquine plus lopinavir/ritonavir and ribavirin, hydroxychloroquine plus lopinavir/ritonavir plus or without ribavirin), as reported in Table 3. Ninety-three percent of patients in the intervention arm and 68% in the control arms achieved clinical recovery after 14 d of randomization. Five percent in the intervention arms and 20% in the control arms died during the trial: a higher frequency of comorbidities, though not significant, was detected in the control arm. Significant differences in secondary outcomes (duration of hospitalization and intensive care unit admission or intermittent mandatory ventilation requirement) in favor of the DAA treatment-based group were found. Although limited by the small number of studies included and lack of full blinding and uniform reported primary outcomes, the cited meta-analysis revealed significant differences in clinical recovery and all-cause mortality in favor of sofosbuvir/daclatasvir regimens for the treatment of COVID-19. In conclusion, considering that managing a placebo-controlled trial during a pandemic is difficult, it is important to underline that the Iranian authors of those clinical trials took up a tough challenge, raising awareness of the whole scientific community about the use of sofosbuvir for the treatment of COVID-19 and encouraging larger randomized trials to establish the potential utility of nucleotide inhibitors for this disease. Moreover, given that sofosbuvir has been used for treating early stages of COVID-19, further studies are needed to evaluate whether this nucleotide analog may even be used to prevent SARS-CoV-2 contagion suddenly after the first exposure to this specific antigen.

**CONCLUSION**

The addition of Sofosbuvir to standard care significantly reduced the duration of hospital stay compared with standard care alone in clinical trials examined. If efficacy of these repurposed, cheap and easily available drug against SARS-CoV-2 is further demonstrated, it could be essential to refine the treatment of COVID-19.

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**Table 1 Current ongoing treatment for coronavirus disease 2019**

|  |  |  |
| --- | --- | --- |
|  | **Rationale of use** | **Notes** |
| Steroids | Prevent and treat acute lung injury and respiratory distress due to host inflammatory response secondary to SARS-CoV-2 infection | May determine Hyper-glicemia, arterial hypertension |
| Anticoagulation therapy | Prevent and/or treat the over-activation of the coagulation cascade, responsible for ischaemic events and disseminated intravascular coagulation | May determines Hemorrhagic risk |
| Antiviral agents | Protease inhibitors (lopinavir), nucleotide analogue (remdesivir) | May determine Drug/drug interactions, allergic reactions, acquired resistance  |
| Chloroquine/hydroxychloroquine | Increasing in endosomal pH, avoiding the fusion between the virus and the host cell, but also the interference with the ACE2 cell receptor targeted by the virus. immunomodulatory activity | May determine common side effects (nausea, vomiting, diarrhea, abdominal pain, extrapyramidal disorders), and arrhythmogenic cardiotoxicity (thus monitor QT interval) |
| Oxygen therapy | Treatment of hypoxia basically administered through a nasal cannula, face mask or noninvasive CPAP. If an adequate arterial O2 level is not reached (SatO2 < 93%), invasive mechanical ventilation via intubation is necessary. Advanced technique such as prone positioning should be considered as well as extracorporeal membrane oxygenation |  |
| Antinflammatory molecules – multiple monoclonal antibodies/immunostimulants (anti IL-17, interferon and mesenchymal stromal cells) | Able to reduce inflammation and stimulate regeneration of tissues as well, the amplification of anti-2019nCoV specific T lymphocytes, the employment of anti-Th1-mediated inflammatory cascade such as canakinumab (anti IL-1B) and roflumilast (inhibitor of enzyme phosphodiesterase-4 already used to control neutrophilic inflammation in patients with COPD) |  |
| Sartanics (angiotensin receptor 1 blockers) | Could be considered for their ability to inhibit the link between the spike S protein of the virus and ACE2 |  According to other studies could predispose to COVID targeting ACE receptors on pulmonary tissue |
| Some broad spectrum antiviral agents (dsRNA-activated caspase oligomerizer) | Cause selective apoptosis of host cells containing virus, this skill could be exploited in fighting COVID-19 |  |
| Bradykinin receptors B1 and B2 antagonists | COVID related bradykinin-dependent local lung angioedema |  |
| Plasma | Passive immunotherapy |  |

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin receptor 2; RNA: Ribonucleic acid.

**Table 2 Primary and secondary outcomes of studies included in simmons’ meta-analysis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  | **Intervention arm (92 patients)** | **Control arm (84 patients)** |
| Outcomes | Primary | Clinical recovery in 14 d | 86 (93%) | 57 (68%) |
| All cause mortality | 5 (5%) | 17 (20%) |
| Secondary | Duration of hospitalization | 6 (IQR: 5-7) | 8 (IQR: 6-11) |
| ICU admission/imv needed | 9 (10%) | 24 (29%) |

ICU: Intensive care unit.

**Table 3 Therapeutic schedule of clinical trials considered in meta-analysis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Disease stage** | **Treatment arm** | **Control arm** | **duration** |
| Eslami | Severe | 35 patients: SOC (lopinavir/ritonavir + hydroxychloroquine) + Sof/dac started24-48 hlater (after PCR and TC confirmation of COVID-19) | 27 patients: SOC (lopinavir/ritonavir + hydroxychloroquine) + ribavirin | 14 d |
| Kasgari | Moderate | 24 patients: Sof/dac + ribavirin | 24 patients: Lopinavir/ritonavir + hydroxychloroquine ± Ribavirin  | 6 d? |
| Sadeghi | severe | 33 patients: Sof/dac + lopinavir/ritonavir | 33 patients: Lopinavir/ritonavir | 14 d |

SOC: Standard of care; COVID-19: Coronavirus disease 2019.



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