

# World Journal of *Virology*

*World J Virol* 2021 March 25; 10(2): 30-85



**EDITORIAL**

- 30 New Year's greeting and overview of *World Journal of Virology* in 2021

*Wang DM, Chen EQ, El-Bendary M*

**REVIEW**

- 34 Bottom-up analysis of emergent properties of N-acetylcysteine as an adjuvant therapy for COVID-19

*Dominari A, Hathaway III D, Kapasi A, Paul T, Makkar SS, Castaneda V, Gara S, Singh BM, Agadi K, Butt M, Retnakumar V, Chittajallu S, Taugir R, Sana MK, KC M, Razzack S, Moallem N, Alvarez A, Talalaev M*

**MINIREVIEWS**

- 53 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*

- 62 Trends in the management of infectious disease under SARS-CoV-2 era: From pathophysiological comparison of COVID-19 and influenza

*Seki M*

**META-ANALYSIS**

- 69 Epidemiological characterization and geographic distribution of human immunodeficiency virus/acquired immunodeficiency syndrome infection in North African countries

*Daw MA, Ahmed MO*

**ABOUT COVER**

Editorial Board Member, Sharof M Tugizov, DSc, PhD, Professor, Department of Medicine, University of California, Division of Infectious Diseases, San Francisco, CA 94143, United States. sharof.tugizov@ucsf.edu

**AIMS AND SCOPE**

The primary aim of *World Journal of Virology* (WJV, *World J Virol*) is to provide scholars and readers from various fields of virology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJV mainly publishes articles reporting research results obtained in the field of virology and covering a wide range of topics including arbovirus infections, viral bronchiolitis, central nervous system viral diseases, coinfection, DNA virus infections, viral encephalitis, viral eye infections, chronic fatigue syndrome, animal viral hepatitis, human viral hepatitis, viral meningitis, opportunistic infections, viral pneumonia, RNA virus infections, sexually transmitted diseases, viral skin diseases, slow virus diseases, tumor virus infections, viremia, and zoonoses.

**INDEXING/ABSTRACTING**

The WJV is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Yan-Xia Xing, Production Department Director: Yu-Jie Ma, Editorial Office Director: Jia-Ping Yan.

**NAME OF JOURNAL**

*World Journal of Virology*

**ISSN**

ISSN 2220-3249 (online)

**LAUNCH DATE**

February 12, 2012

**FREQUENCY**

Bimonthly

**EDITORS-IN-CHIEF**

Mahmoud El-Bendary, En-Qiang Chen

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2220-3249/editorialboard.htm>

**PUBLICATION DATE**

March 25, 2021

**COPYRIGHT**

© 2021 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/gerinfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/gerinfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/gerinfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## 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

Anna Maria Spera

**ORCID number:** Anna Maria Spera  
0000-0003-1292-3040.

**Author contributions:** Study conception and design, literature review, analysis and interpretation of data, drafting of manuscript and its critical revision was provided by Spera AM.

**Conflict-of-interest statement:**  
Authors declare no conflict of interests for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Specialty type:** Infectious diseases

**Country/Territory of origin:** Italy

**Anna Maria Spera**, Department of Infectious Diseases, University of Salerno, Salerno 84131, Italy

**Corresponding author:** Anna Maria Spera, MD, Doctor, Department of Infectious Diseases, University of Salerno, Largo Ippocrate, Salerno 84131, Italy.  
[annamariaspera@hotmail.it](mailto:annamariaspera@hotmail.it)

### 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

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
 Grade B (Very good): B  
 Grade C (Good): C  
 Grade D (Fair): 0  
 Grade E (Poor): 0

**Received:** December 12, 2020

**Peer-review started:** December 12, 2020

**First decision:** January 27, 2021

**Revised:** January 28, 2021

**Accepted:** March 8, 2021

**Article in press:** March 8, 2021

**Published online:** March 25, 2021

**P-Reviewer:** Fernández-Cuadros ME, Luqman Z

**S-Editor:** Zhang L

**L-Editor:** A

**P-Editor:** Xing YX



**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.

**Citation:** Spera AM. 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. *World J Virol* 2021; 10(2): 53-61

**URL:** <https://www.wjgnet.com/2220-3249/full/v10/i2/53.htm>

**DOI:** <https://dx.doi.org/10.5501/wjv.v10.i2.53>

## 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<sup>[1]</sup>. 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)<sup>[2]</sup>. According to Zhou *et al*<sup>[3]</sup>, 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<sup>[4]</sup>. 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<sup>[5]</sup>. 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*<sup>[6]</sup> recently clarified. According to Cheng *et al*<sup>[7]</sup>, 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*<sup>[8]</sup>, 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<sup>[9]</sup>. Recovery begins in the 2<sup>nd</sup> or 3<sup>rd</sup> 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<sup>[5]</sup>.



## 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*<sup>[9]</sup> and Zhou *et al*<sup>[10]</sup>, it is necessary to evaluate use on a case-by-case basis, considering both risks and benefits<sup>[9,10]</sup>. Lin *et al*<sup>[11]</sup> 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*<sup>[12]</sup>, Lim *et al*<sup>[13]</sup> and Yao *et al*<sup>[14]</sup> 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*<sup>[15]</sup> 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<sup>[16]</sup>. Chloroquine and hydroxychloroquine, two drugs used for malaria and amoebiasis, demonstrate activity against SARS-CoV-2 *in vitro* and in animal models<sup>[17]</sup>. 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 O<sub>2</sub> level is not reached (SatO<sub>2</sub> < 93%), invasive mechanical ventilation *via* intubation is necessary. Advanced techniques such as prone positioning should be considered<sup>[18]</sup>, 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<sup>[19]</sup> 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<sup>[20]</sup>, amplification of anti-2019nCoV specific T lymphocytes<sup>[21]</sup>, the use of anti-Th1-mediated inflammatory cascades such as canakinumab (anti IL-1B)<sup>[22]</sup> and roflumilast (inhibitor of enzyme phosphodiesterase-4 already used to control neutrophilic inflammation in patients with COPD)<sup>[23]</sup>. Gurwitz *et al*<sup>[24]</sup> 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<sup>[25]</sup>. 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<sup>[25]</sup>. 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<sup>[26]</sup>. In addition, the use of passive immunotherapy with plasma derived from convalescent patients is still debated<sup>[27]</sup>. 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.

**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 O <sub>2</sub> level is not reached (SatO <sub>2</sub> < 93%), invasive mechanical ventilation <i>via</i> intubation is necessary. Advanced technique such as prone positioning should be considered as well as extracorporeal membrane oxygenation	
Antiinflammatory 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.

## 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<sup>[28]</sup>.

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*<sup>[29]</sup>. Nevertheless, the winning strategy may instead be based on a multitargeted approach of different drugs targeting many viral proteins<sup>[29]</sup>. Sofosbuvir binds to the active site of HCV and is thus incorporated in the nascent strand, preventing the addition of the next nucleotide<sup>[29]</sup>. The replication mechanisms of coronaviruses, flaviviruses and togaviruses require an RNA-dependent RNA polymerase that is targeted by sofosbuvir, ribavirin and AZT<sup>[28]</sup>. This has been demonstrated by Elfiky *et al*<sup>[30]</sup> 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*<sup>[31]</sup>. Therefore, all these compounds may be considered permanent terminators for SARS-CoV-2 RdRp<sup>[31,32]</sup> 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<sup>[33]</sup>, even against liver cirrhosis, is well known, even in the setting of a lack of response to other medications, such as interferon and ribavirin<sup>[34]</sup>. Pivotal trials of this pangenotypic DAA<sup>[35]</sup> (Fission, Positron, Fusion and Photon 1)<sup>[36-38]</sup> 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 GTP<sup>[39]</sup>. The presence of NDK-A and NDK-B in airway epithelial membranes has been suggested by Muimo *et al*<sup>[40]</sup> 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<sup>[41]</sup>. 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<sup>[16]</sup> 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*<sup>[42]</sup> 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<sup>[43]</sup>. Trials eligible for inclusion were identified by reviewing clinicaltrials.gov, WHO International Clinical Trials Registry Platform and Cochrane Central Register of Controlled Trials. Three<sup>[44-46]</sup> of eight studies reviewed were considered by Simmons *et al*<sup>[43]</sup> 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



**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/inv needed	9 (10%)	24 (29%)

ICU: Intensive care unit.

control groups. Two of the three studies were randomized<sup>[44,45]</sup> 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.

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 started 24-48 h later (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.

## REFERENCES

- Richman DD, Whitley RJ, Hayden FG. Clinical Virology, 4th ed. Washington: ASM Press; 2016. Available from: <https://www.wiley.com/en-us/Clinical+Virology,+4th+Edition-p-9781683673163>
- World Health Organization, WHO Director-General's Remarks at the Media Briefing on 2019-nCoV on 11 February 2020 (cited February 23, 2021). Available from: <https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020>
- Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270-273 [PMID: 32015507 DOI: 10.1038/s41586-020-2012-7]
- Chan-Yeung M, Xu RH. SARS: epidemiology. *Respirology* 2003; **8** Suppl: S9-14 [PMID: 15018127 DOI: 10.1046/j.1440-1843.2003.00518.x]
- Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). *Indian J Pediatr* 2020; **87**: 281-286 [PMID: 32166607 DOI: 10.1007/s12098-020-03263-6]
- Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, Yu J, Kang M, Song Y, Xia J, Guo Q, Song T, He J, Yen HL, Peiris M, Wu J. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med* 2020; **382**: 1177-1179 [PMID: 32074444 DOI: 10.1056/NEJMc2001737]
- Cheng ZJ, Shan J. 2019 Novel coronavirus: where we are and what we know. *Infection* 2020; **48**: 155-163 [PMID: 32072569 DOI: 10.1007/s15010-020-01401-y]
- Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol* 2020; **92**: 552-555 [PMID: 32104915 DOI: 10.1002/jmv.25728]
- Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020; **395**: 473-475 [PMID: 32043983 DOI: 10.1016/S0140-6736(20)30317-2]
- Zhou W, Liu Y, Tian D, Wang C, Wang S, Cheng J, Hu M, Fang M, Gao Y. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia. *Signal Transduct Target Ther* 2020; **5**: 18 [PMID: 32296012 DOI: 10.1038/s41392-020-0127-9]
- Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect* 2020; **9**: 727-732 [PMID: 32196410 DOI: 10.1080/22221751.2020.1746199]
- Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, Kao RY, Poon LL, Wong CL, Guan Y, Peiris JS, Yuen KY; HKU/UCH SARS Study Group. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; **59**: 252-256 [PMID: 14985565 DOI: 10.1136/thorax.2003.012658]
- Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, Choe KW, Kang YM, Lee B, Park SJ. Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. *J Korean Med Sci* 2020; **35**: e79 [PMID: 32056407 DOI: 10.3346/jkms.2020.35.e79]
- Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. *J Med Virol* 2020; **92**: 556-563 [PMID: 32104907 DOI: 10.1002/jmv.25729]
- Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. *Travel Med Infect Dis* 2020; **34**: 101615 [PMID: 32145386 DOI: 10.1016/j.tmaid.2020.101615]
- Siemieniuk R, Rochwerf B, Agoritsas T, Lamontagne F, Leo YS, Macdonald H, Agarwal A, Zeng L, Lytvyn L, Appiah JA, Amin W, Arabi Y, Blumberg L, Burhan E, Bausch FJ, Calfee CS, Cao B, Cecconi M, Chanda D, Cooke G, Du B, Dunning J, Geduld H, Gee P, Hashimi M, Hui DS, Kabra S, Kanda S, Kawano-Dourado L, Kim YJ, Kisson N, Kwizera A, Laake JH, Machado FR, Mahaka I,

- Manai H, Mino G, Nsutedu E, Pshenichnaya N, Qadir N, Sabzwari S, Sarin R, Sharland M, Shen Y, Sri Ranganathan S, Souza J, Ugarte S, Venkatapuram S, Quoc Dat V, Vuyiseka D, Stegemann M, Wijewickrama A, Maguire B, Zeraatkar D, Bartoszko J, Ge L, Brignardello-Petersen R, Owen A, Guyatt G, Diaz J, Jacobs M, Vandvik PO. A living WHO guideline on drugs for covid-19. *BMJ* 2020; **370**: m3379 [PMID: [32887691](#) DOI: [10.1136/bmj.m3379](#)]
- 17 **Savarino A**, Di Trani L, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine. *Lancet Infect Dis* 2006; **6**: 67-69 [PMID: [16439323](#) DOI: [10.1016/S1473-3099\(06\)70361-9](#)]
- 18 **Munshi L**, Del Sorbo L, Adhikari NKJ, Hodgson CL, Wunsch H, Meade MO, Ulerik E, Mancebo J, Pesenti A, Ranieri VM, Fan E. Prone Position for Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. *Ann Am Thorac Soc* 2017; **14**: S280-S288 [PMID: [29068269](#) DOI: [10.1513/AnnalsATS.201704-343OT](#)]
- 19 **Agenzia Italiana del Farmaco**. COVID 19: Studio randomizzato italiano, nessun beneficio dal tocilizumab, 2020 (cited February 23, 2021). Available from: <https://www.aifa.gov.it/web/guest/-/covid-19-studio-randomizzato-italiano-nessun-beneficio-dal-tocilizumab>
- 20 **Horie S**, Gonzalez HE, Laffey JG, Masterson CH. Cell therapy in acute respiratory distress syndrome. *J Thorac Dis* 2018; **10**: 5607-5620 [PMID: [30416812](#) DOI: [10.21037/jtd.2018.08.28](#)]
- 21 **Zumla A**, Hui DS, Azhar EI, Memish ZA, Maeurer M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. *Lancet* 2020; **395**: e35-e36 [PMID: [32035018](#) DOI: [10.1016/S0140-6736\(20\)30305-6](#)]
- 22 **Chakraborty A**, Tannenbaum S, Rordorf C, Lowe PJ, Floch D, Gram H, Roy S. Pharmacokinetic and pharmacodynamic properties of canakinumab, a human anti-interleukin-1 $\beta$  monoclonal antibody. *Clin Pharmacokinet* 2012; **51**: e1-18 [PMID: [22550964](#) DOI: [10.2165/11599820-000000000-00000](#)]
- 23 **Wedzicha JA**, Calverley PM, Rabe KF. Roflumilast: a review of its use in the treatment of COPD. *Int J Chron Obstruct Pulmon Dis* 2016; **11**: 81-90 [PMID: [26792988](#) DOI: [10.2147/COPD.S89849](#)]
- 24 **Gurwitz D**. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res* 2020; **81**: 537-540 [PMID: [32129518](#) DOI: [10.1002/ddr.21656](#)]
- 25 **Khan S**, Siddique R, Shereen MA, Ali A, Liu J, Bai Q, Bashir N, Xue M. Emergence of a Novel Coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2: Biology and Therapeutic Options. *J Clin Microbiol* 2020; **58** [PMID: [32161092](#) DOI: [10.1128/JCM.00187-20](#)]
- 26 **van de Veerdonk F**, Netea MG, van Deuren M, van der Meer JW, de Mast Q, Bruggemann RJ, van der Hoeven H. Kinins and Cytokines in COVID-19: A Comprehensive Pathophysiological Approach. 2020 Preprint [DOI: [10.20944/preprints202004.0023.v1](#)]
- 27 **Zhang L**, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. *J Med Virol* 2020; **92**: 479-490 [PMID: [32052466](#) DOI: [10.1002/jmv.25707](#)]
- 28 **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? *Arch Med Res* 2020; **51**: 577-581 [PMID: [32387040](#) DOI: [10.1016/j.arcmed.2020.04.018](#)]
- 29 **Jácome R**, Campillo-Balderas JA, Ponce de León S, Becerra A, Lazcano A. Sofosbuvir as a potential alternative to treat the SARS-CoV-2 epidemic. *Sci Rep* 2020; **10**: 9294 [PMID: [32518317](#) DOI: [10.1038/s41598-020-66440-9](#)]
- 30 **Elfiky AA**. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. *Life Sci* 2020; **248**: 117477 [PMID: [32119961](#) DOI: [10.1016/j.lfs.2020.117477](#)]
- 31 **Chien M**, Anderson TK, Jockusch S, Tao C, Li X, Kumar S, Russo JJ, Kirchdoerfer RN, Ju J. Nucleotide Analogues as Inhibitors of SARS-CoV-2 Polymerase, a Key Drug Target for COVID-19. *J Proteome Res* 2020; **19**: 4690-4697 [PMID: [32692185](#) DOI: [10.1021/acs.jproteome.0c00392](#)]
- 32 **Chien M**, Anderson TK, Jockusch S, Tao C, Kumar S, Li X, Russo JJ, Kirchdoerfer RN, Ju J. Nucleotide Analogues as Inhibitors of SARS-CoV-2 Polymerase. *bioRxiv* 2020 [PMID: [32511320](#) DOI: [10.1101/2020.03.18.997585](#)]
- 33 **Guedj J**, Pang PS, Denning J, Rodriguez-Torres M, Lawitz E, Symonds W, Perelson AS. Analysis of hepatitis C viral kinetics during administration of two nucleotide analogues: sofosbuvir (GS-7977) and GS-0938. *Antivir Ther* 2014; **19**: 211-220 [PMID: [24464551](#) DOI: [10.3851/IMP2733](#)]
- 34 **Gentile I**, Maraolo AE, Buonomo AR, Zappulo E, Borgia G. The discovery of sofosbuvir: a revolution for therapy of chronic hepatitis C. *Expert Opin Drug Discov* 2015; **10**: 1363-1377 [PMID: [26563720](#) DOI: [10.1517/17460441.2015.1094051](#)]
- 35 **Hebner C**, Lee Y-J, Han B, Chiu S, Tian Y, Pagratis N, Miller M, Mo H. In vitro pan-genotypic and combination activity of sofosbuvir (GS-7977) in stable replicon cell lines. *Hepatology* 2012; **56**: 1066A
- 36 **Lawitz E**, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, Kayali Z, Reddy KR, Jacobson IM, Kowdley KV, Nyberg L, Subramanian GM, Hyland RH, Arterburn S, Jiang D, McNally J, Brainard D, Symonds WT, McHutchison JG, Sheikh AM, Younossi Z, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; **368**: 1878-1887 [PMID: [23607594](#) DOI: [10.1056/NEJMoa1214853](#)]
- 37 **Jacobson IM**, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, Schiff E, Al-Assi MT, Subramanian GM, An D, Lin M, McNally J, Brainard D, Symonds WT, McHutchison JG, Patel K, Feld J, Panko S, Nelson DR; POSITRON Study; FUSION Study. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; **368**: 1867-1877 [PMID: [23607593](#) DOI: [10.1056/NEJMoa1214854](#)]

- 38 **Sulkowski M**, Rodriguez-Torres M, Lalezari J, Fessel W, Mounzer K, Shuhart M, Luetkemeyer A, Asmuth D, Gaggar A, Ni L, Svarovskaia E, Symonds B, McHutchison J, Naggie S, Dieterich D. All-oral therapy with sofosbuvir plus ribavirin for the treatment of HCV genotype 1, 2, and 3 infection in patients coinfecting with HIV (PHOTON-1). 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); Washington, DC. November 1-5, 2013. Available from: [https://natap.org/2013/AASLD/AASLD\\_34.htm](https://natap.org/2013/AASLD/AASLD_34.htm)
- 39 **Boissan M**, Schlattner U, Lacombe ML. The NDPK/NME superfamily: state of the art. *Lab Invest* 2018; **98**: 164-174 [PMID: 29451272 DOI: 10.1038/labinvest.2017.137]
- 40 **Muimo R**, Crawford RM, Mehta A. Nucleoside diphosphate kinase A as a controller of AMP-kinase in airway epithelia. *J Bioenerg Biomembr* 2006; **38**: 181-187 [PMID: 17039396 DOI: 10.1007/s10863-006-9033-2]
- 41 **Meier C**. Nucleoside diphosphate and triphosphate prodrugs - An unsolvable task? *Antivir Chem Chemother* 2017; **25**: 69-82 [PMID: 29096525 DOI: 10.1177/2040206617738656]
- 42 **Jockusch S**, Tao C, Li X, Chien M, Kumar S, Morozova I, Kalachikov S, Russo JJ, Ju J. Sofosbuvir terminated RNA is more resistant to SARS-CoV-2 proofreader than RNA terminated by Remdesivir. *Sci Rep* 2020; **10**: 16577 [PMID: 33024223 DOI: 10.1038/s41598-020-73641-9]
- 43 **Simmons B**, Wentzel H, Mobarak S, Eslami G, Sadeghi A, Ali Asgari A, Abbaspour Kasgari H, Tirgar Fakheri H, Merat S, Hill A. Sofosbuvir/daclatasvir regimens for the treatment of COVID-19: an individual patient data meta-analysis. *J Antimicrob Chemother* 2021; **76**: 286-291 [PMID: 33063117 DOI: 10.1093/jac/dkaa418]
- 44 **Abbaspour Kasgari H**, Moradi S, Shabani AM, Babamahmoodi F, Davoudi Badabi AR, Davoudi L, Alikhani A, Hedayatizadeh Omran A, Saeedi M, Merat S, Wentzel H, Garratt A, Levi J, Simmons B, Hill A, Tirgar Fakheri H. Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: a single-centre, randomized controlled trial. *J Antimicrob Chemother* 2020; **75**: 3373-3378 [PMID: 32812025 DOI: 10.1093/jac/dkaa332]
- 45 **Sadeghi A**, Ali Asgari A, Norouzi A, Kheiri Z, Anushirvani A, Montazeri M, Hosamirudisai H, Afhami S, Akbarpour E, Aliannejad R, Radmard AR, Davarpanah AH, Levi J, Wentzel H, Qavi A, Garratt A, Simmons B, Hill A, Merat S. Sofosbuvir and daclatasvir compared with standard of care in the treatment of patients admitted to hospital with moderate or severe coronavirus infection (COVID-19): a randomized controlled trial. *J Antimicrob Chemother* 2020; **75**: 3379-3385 [PMID: 32812039 DOI: 10.1093/jac/dkaa334]
- 46 **Eslami G**, Mousaviasl S, Radmanesh E, Jelvey S, Bitaraf S, Simmons B, Wentzel H, Hill A, Sadeghi A, Freeman J, Salmanzadeh S, Esmaeilian H, Mobarak M, Tabibi R, Jafari Kashi AH, Lotfi Z, Talebzadeh SM, Wickramatillake A, Momtazan M, Hajizadeh Farsani M, Marjani S, Mobarak S. The impact of sofosbuvir/daclatasvir or ribavirin in patients with severe COVID-19. *J Antimicrob Chemother* 2020; **75**: 3366-3372 [PMID: 32812051 DOI: 10.1093/jac/dkaa331]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

