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Letter to the Editor

Sofosbuvir for the Treatment of COVID-19 Patients: Is It a Promising Therapeutic Medicine for the Inhibition of Severe Acute Respiratory Syndrome Coronavirus 2?

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Dear Editor,

The novel coronavirus disease 2019 (COVID-19), a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, first emerged in late 2019 with rapid global spread (1,2). Anti-inflammatory and antiviral treatments (e.g., tocilizumab and remdesivir) were found useful for ameliorating disease symptoms (2). Some days before the announcement of the World Health Organization (who) regarding the introduction of COVID-19, a pandemic disease, the first randomized controlled trial (RCT) study in Iran had been approved (https://www.irct.ir/trial/46790) on March 30, 2020. This study aimed to compare sofosbuvir (SOF) combined with velpatasvir or daclatasvir to the standard care in patients with COVID-19. Subsequently, up to the date of writing this letter, seven additional RCTs were approved in this regard by the Iranian Registry of Clinical Trials (Table 1). According to the WHO (3), the findings of clinical studies conducted in different cities of Iran showed that the effects of 14-day combined clinical improvements were merely effective in the treatment group but not in the control group (14%, 32%, and 82% better in the studies conducted in Sari, Tehran, and Abadan, respectively). However, SOF and daclatasvir were associated with more rapid discharge from the hospital and improved survival in these studies. The question is why some Iranian physicians focused on SOF and its usefulness for COVID-19 patients.

The story started on January 31, 2020, and a study proposed SOF as an antiviral for the SARS-CoV-2 due to some similarities between the mechanisms of replication in hepatitis C virus (HCV) and coronaviruses (4). Additionally, Elfiky (5) used sequence alignment based on the full genome sequence for the COVID-19 (NC_045512.2), and molecular docking demonstrated that SOF forms some interactions with SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which makes SOF a possibly effective treatment for COVID-19. Favipiravir and remdesivir bind to the RdRp active site justifying the treatment of other RNA viral diseases (6,7). Previous evidence indicated the antiviral activity of SOF against all Flaviviridae viruses (8). The RdRp structural conservation expands over the Flaviviridae family and contains all known RNA viruses (9). In addition, it was suggested that SOF combined with either velpatasvir or ledipasvir, or daclatasvir might be effective because they have dual inhibitory actions on two viral enzymes (10). The strand primer RNA in the active site of SARS-CoV-2 (nsp12) and HCV NS5B are alike. Their structural superposition causes their binding to SOF. This inhibitor can be modeled into the active site of nsp12 without any steric hindrances, and residuals participating in SOF binding are highly conserved in the SARS-coronavirus active site (11). Although there is no clinical evidence regarding SOF in the treatment of COVID-19 patients, it has some advantages including cost-effectiveness (~0.4$ for each SOF dosage 400 and $0.39/day for sofosbuvir/daclatasvir) and oral intake in a single daily dose manner (12). SARS-CoV-2 is a positive-sense single-stranded RNA virus with a conserved polymerase. SOF as well as other advantages such as offering fast-acting, high response rate, relatively safe profile, high efficacy, short administration period, and low rate of drug interaction, can effectively inhibit the SARS-CoV-2 RdRp could combat SARS-CoV-2?" Iranian physicians have a great experience regarding SOF for the treatment of HCV patients. The price of this drug is relatively low in Iran and is covered

Table 1. Summary of Ongoing RCTs Registered at IRCT.ir

Identifier	Treatment Arms	Target Sample Size	Inclusion Criteria	Phase	Outcome Variable(s)	Registration Date
IRCT20200324046850N2	A: Daclatasvir + Sofosbuvir B: Ribavirin	62	> 18-year-old confirmed patients	*2*	Consciousness level, blood pressure, respiratory rate, arterial oxygen saturation, and alterations in laboratory data, duration of hospitalization, gastrointestinal disorder, and the mortality rate	03.29.20
IRCT20100228003449N29	A: Sofosbuvir/ledipasvir 400/90 mg daily for 10 days B: Standard of care treatment	50	18-75-year-old patients with confirmed COVID-19 disease	2-3	The primary outcomes of the study are the rates of treatment response and adverse drug reactions. Secondary outcomes are the duration of hospitalization and patients' clinical outcomes	03.19.20
IRCT20130812014333N145	A: 400 mg of hydroxychloroquine + 100/400 mg of lopinavir/ritonavir + 100/400 mg sofosbuvir/Velpatasvir. B: 400 mg of hydroxychloroquine + 100/400 mg lopinavir/ritonavir	80	> 18 year-old confirmed, COVID 19; absolute lymphocyte count <1100/mL or SaO_2 < 93%	3	Clinical status	03.30.20
IRCT20200128046294N2	A: Standard of care treatment along with Sovodak (Daclatasvir 60 mg/sofosbuvir 400 mg) B: Standard of care treatment	70	> 18 year-old moderate to severe COVID-19 patients	3	Clinical recovery (composite) over 14 days from the start of study treatment until respiratory rate (≤24/min on room air), normalization of fever (≤37.2°C oral), and oxygen saturation (≥94% on room air), persistent for 24 h at least	03.14.20
IRCT20200328046882N1	A: Sofosbuvir 400 mg single dose + standard of care therapy each day for five days B: Standard of care therapy, along with sofosbuvir 400 mg single dose each day for ten days	60	> 18 year-old confirmed patients; positive and hospitalized with SpO2 < 94%, fever, pulmonary infiltrates radiographic evidence	*2*	Normalization of fever (≤37.2 °C oral, or ≤36.6°C armpits, or ≤37.8°C rectal and oxygen saturation (≥94% at room air), persistent for 72 h at least over 14 days from the start of treatment	04.05.20
IRCT20200328046886N1	A: Sovodak tablet (Daclatasvir 60 mg/sofosbuvir 400 mg) + Ribavirin. B: Standard of care treatment	48	18-65 year-old patients with mild-to-moderate COVID-19	*3*	Clinical recovery (composite) over 14 days from the start of treatment while not requiring for ICU, non-invasive and invasive mechanical ventilation, and the time for the virus eradication from the upper respiratory tract through RT-PCR examination	04.12.20
IRCT20130812014333N147	A: Standard of care treatment (200 mg hydroxychloroquine twice daily) B: 60 to 400 mg daily sofosbuvir/daclatasvir for ten days w/standard of care treatment C: 300 mg lithium for 10 days + standard of care treatment D: 5 mg trifluoperazine and 2 mg Trihexyphenidyl w/standard of care treatment	80	> 18 year-old confirmed patients with absolute lymphocyte count <1100/ML or SaO_2 < 93%	*3*	Hospitalization	04.22.20
IRCT20200403046926N1	A: Hydroxychloroquine + Sovodak B: Hydroxychloroquine	60	> 18 year-old confirmed patients	*3*	1- Symptoms ending 2- Lymphopenic condition 3- CRP status 4- SPO2	04.11.20

Note. COVID-19: Coronavirus disease 2019; ICU: Intensive care unit; RT-PCR: Real-time polymerase chain reaction.

by the health insurance companies (~ 0.4$ per day), and it is highly available. However, it is too early to speculate about the effectiveness of this drug. It is believed that it has a high potential to target viral replication without any severe adverse effects. Up to the date of writing this letter, no clinical data have been released in this regard. However, the results are critical even if being pessimistic.

Conflict of Interest Disclosures

None.

Ethical Issues

Not applicable.

References

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9. doi: 10.1001/jama.2020.1585.
2. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020;117(20):10970-5. doi: 10.1073/pnas.2005615117.
3. World Health Organization (WHO). R&D Blueprint and COVID-19. WHO; 2020. https://www.who.int/teams/blueprint/covid-19.
4. Ju J, Kumar S, Li X, Jockusch S, Russo JJ. Nucleotide analogues as inhibitors of viral polymerases. bioRxiv. 2020. doi: 10.1101/2020.01.30.927574.
5. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci. 2020;248:117477. doi: 10.1016/j.lfs.2020.117477.
6. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci. 2017;93(7):449-63. doi: 10.2183/pjab.93.027.
7. Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature. 2016;531(7594):381-5. doi: 10.1038/nature17180.
8. Gan CS, Lim SK, Chee CF, Yusof R, Heh CH. Sofosbuvir as treatment against dengue? Chem Biol Drug Des. 2018;91(2):448-55. doi: 10.1111/cbdd.13091.
9. Jácome R, Becerra A, Ponce de León S, Lazcano A. Structural analysis of monomeric RNA-dependent polymerases: evolutionary and therapeutic implications. PLoS One. 2015;10(9):e0139001. doi: 10.1371/journal.pone.0139001.
10. Chen YW, Yiu CB, Wong KY. Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CL (pro)) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates. F1000Res. 2020;9:129. doi: 10.12688/f1000research.22457.2.
11. 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(1):9294. doi: 10.1038/s41598-020-66440-9.
12. Hill A, Wang J, Levi J, Heath K, Fortunak J. Minimum costs to manufacture new treatments for COVID-19. J Virus Erad. 2020;6(2):61-9. doi: 10.1016/s2055-6640(20)30018-2.