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...
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<th>Identifier</th>
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| 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 SaO₂ < 93% | 3     | Clinical status                                                                     | 03.30.20         |
| IRCT202003128046294N2            | 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         |
| IRCT20200328046828N1             | 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 SaO₂ < 93% | 3     | Hospitalization                                                                     | 04.22.20         |
| IRCT2020040310406926N1           | 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         |

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**


