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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

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Background: Currently no effective antiviral therapy has been found to treat COVID-19. The aim of this trial was to assess if the addition of sofosbuvir and daclatasvir improved clinical outcomes in patients with moderate or severe COVID-19.

Methods: This was an open-label, multicentre, randomized controlled clinical trial in adults with moderate or severe COVID-19 admitted to four university hospitals in Iran. Patients were randomized into a treatment arm receiving sofosbuvir and daclatasvir plus standard care, or a control arm receiving standard care alone. The primary endpoint was clinical recovery within 14 days of treatment. The study is registered with IRCT.ir under registration number IRCT20200128046294N2.

Results: Between 26 March and 26 April 2020, 66 patients were recruited and allocated to either the treatment arm ($n = 33$) or the control arm ($n = 33$). Clinical recovery within 14 days was achieved by 29/33 (88%) in the treatment arm and 22/33 (67%) in the control arm ($P = 0.076$). The treatment arm had a significantly shorter median duration of hospitalization [6 days (IQR 4–8)] than the control group [8 days (IQR 5–13)]; $P = 0.029$. Cumulative incidence of hospital discharge was significantly higher in the treatment arm versus the control (Gray's $P = 0.041$). Three patients died in the treatment arm and five in the control arm. No serious adverse events were reported.

Conclusions: The addition of sofosbuvir and daclatasvir to standard care significantly reduced the duration of hospital stay compared with standard care alone. Although fewer deaths were observed in the treatment arm, this was not statistically significant. Conducting larger scale trials seems prudent.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and subsequent coronavirus disease (COVID-19) continues to contribute to severe mortality and morbidity worldwide, affecting millions of people with over 100 000 deaths to date.[1] Observations of cases range from mild or asymptomatic to critical leading to

respiratory or multiorgan failure.[2] Vaccine development is unlikely to yield results before 2021. Therapeutic options are therefore urgently needed during this fast-moving pandemic. Repurposing existing pharmaceuticals is an attractive short-term management strategy. However, many promising treatments are yet to demonstrate clinically significant benefit in randomized trials.[3,4]

SARS-CoV-2 is a positive-sense single-stranded RNA virus whose replication mechanism requires a number of key enzymes, notably RNA-dependent RNA-polymerase (RdRp), main protease (Mpro) and helicase.[5] Other viruses share similar replication mechanisms using RdRps with well-conserved motifs. This has led to existing nucleotide/nucleoside analogues being investigated as potential COVID-19 therapies. Sofosbuvir and daclatasvir are clinically approved direct-acting antivirals (DAAs) that work by binding to HCV RdRp.[6] Some *in silico* and *in vitro* models suggest that sofosbuvir and daclatasvir may bind to SARS-CoV-2 RdRp with high affinity.[7–9] However, other studies have been less promising, predicting little effect of daclatasvir binding to SARS-CoV-2 RdRp,[9,10] and no effect of sofosbuvir or daclatasvir at preventing cellular death due to SARS-CoV-2 infection *in vitro*.[11] Sofosbuvir has a high bioavailability when taken orally, reaching maximum concentration 0.5–2 h post-dose administration.[12] Additionally, sofosbuvir has shown *in vitro* antiviral activity against other positive-strand RNA viruses, including Yellow Fever, Zika, Dengue and Chikungunya.[13–16] Evidence from these studies suggests that sofosbuvir may have broad potential antiviral activity.

Both sofosbuvir and daclatasvir have demonstrated favourable safety profiles with minimal drug interactions.[17,18] In a number of dose-ranging studies analysing sofosbuvir[19,20] and daclatasvir[21–25] individually or in combination with ribavirin and peginterferon alfa-2a compared with placebo, no progressive dose-related adverse events were observed. A recent review on sofosbuvir-containing regimens in pregnancy[26] concluded that DAAs have a favourable safety profile in pregnancy and suggests that a 12 week DAA course could be started at the end of the second or early third trimester. The safety of sofosbuvir and daclatasvir has even been proven in patients with severely impaired renal function.[27]

Sofosbuvir and daclatasvir are both widely available and affordable. Hill *et al.*[28] found that the weighted-mean active pharmaceutical ingredient (API) cost was US$700/kg and US$600/kg for sofosbuvir and daclatasvir, respectively. At a dose of 400/60 mg once daily, the corresponding API cost is, therefore, US$4.42 per 14 day treatment, which equates to US$0.39 per day. Sofosbuvir and daclatasvir are not approved for separate use in Iran, and the only available formulation is in combination. In the rush of the pandemic there was no time to go through the time-consuming regulations required to prepare and approve formulations of separate sofosbuvir and daclatasvir; therefore, we carried out this Phase III randomized trial to establish whether the combination of sofosbuvir and daclatasvir, which is available in Iran as a single pill, can improve clinical parameters in adults with moderate or severe COVID-19 compared with standard care.

Patients and methods

Study design and patients

This was a Phase III, multicentred, randomized, controlled trial. Subjects were recruited from Shariati, Baharloo, Sina (Tehran city) and Sayyad Shirazi (Gorgan city) hospitals. All adult patients aged at least 18 years admitted with suspected COVID-19 infection between 26 March and 26 April 2020 were evaluated for eligibility. Participants were enrolled into the study if they had both positive qualitative RT–PCR on nasopharyngeal swab and chest CT scan compatible with moderate or severe COVID-19 infection. In addition, participants were required to have signs of severity of disease defined as fever (oral temperature $\geq$37.8°C at any one time prior to enrolment) and at least one of respiratory rate >24/min, O_2 saturation <94% or PaO_2/FiO_2 ratio <300 mgHg. Only participants whose onset of symptoms was 8 days or less were included. Exclusion criteria included: a known allergic reaction to the intervention drugs, pregnant or breastfeeding, any prior experimental treatment for COVID-19, heart rate <60 bpm, taking amiodarone, evidence of multiorgan failure, requiring invasive mechanical ventilation at screening and estimated glomerular filtration rate (eGFR) <50 mL/1.73 m^2/min. All patients were required to provide written informed consent prior to participation in the study.

Randomization and masking

Once patients passed the inclusion and exclusion criteria and signed the consent form, they were randomly assigned to either the control arm or the treatment arm in a 1:1 ratio using a computer-generated randomization plan. Block randomization with a block size of 2 was used. The investigator, outcome assessor and data analyser were masked. Managing physicians and patients were not blinded.

Procedures

All patients received standard care according to the national Iranian COVID-19 treatment guidelines which at the time of the study was hydroxychloroquine 200 mg twice daily with or without lopinavir/ritonavir 200 mg/50 mg twice daily. The treatment arm received a single daily oral tablet containing 400 mg sofosbuvir and 60 mg daclatasvir (Sovodak, Rojan Pharma, Tehran, Iran) in addition to standard care for 14 days.

Standard care was started as soon as patients were admitted, but sofosbuvir/daclatasvir was started only after confirmation of COVID-19 by PCR and CT, randomization and consent, which was 24–48 h later.

Patients were contacted 1 month after hospital discharge and were asked about COVID-related complications or re-admissions.

Clinical and laboratory monitoring

All patients required both laboratory and radiological confirmation of SARS-CoV-2 infection by nasopharyngeal swab RT–PCR and chest CT scan, respectively. Other clinical details including history and laboratory findings were collected at baseline and at discharge. Liver and kidney function tests, white blood cell count, C-reactive protein, clotting screens and erythrocyte sedimentation rate were determined at baseline.

Reporting of CT images

All chest CT scans were reviewed by an experienced radiologist who was blind to the patients' allocation. Highly suggestive scans were defined according to the statement published by the Iranian Society of Radiology, which was released at the beginning of the outbreak and has been widely applied by radiologists in Iran.[29]

The pattern of parenchymal abnormality was recorded (ground-glass opacities, consolidation, reticular pattern, honeycomb formation) and, to calculate CT severity score (CSS), each lung was divided into three zones: (i) upper zone (above the level of the carina); (ii) middle zone (between the carina and inferior pulmonary vein); and (iii) lower zone (below the level of the inferior pulmonary vein). The percentage involvement for each zone for any of the mentioned parenchymal abnormalities was assessed and assigned a score from 0 to 4 (0, no involvement; 1, 1%–25% involved; 2, 26%–50% involved; 3, 51%–75% involved; 4, 76%–100% involved). CSS

was calculated by summing the scores from all six zones, resulting in a final score between 0 and 24 for each patient.

Outcomes

The primary endpoint of this trial was clinical recovery within 14 days of enrolment. Clinical recovery was defined as normalization of fever (≤37.2°C), respiratory rate (≤24/min) and oxygen saturation (≥94%) without supplementary oxygen therapy sustained for at least 24 h. If patients maintained these criteria for over 24 h they were safely discharged from hospital. Other secondary endpoints included all-cause mortality, requirement for mechanical ventilation, duration of hospital stay and time to hospital discharge. Safety endpoints were measured as frequencies of serious adverse events. Outcomes were extracted from patient files and medical progress notes by a researcher blinded to the allocation of patients.

Statistical analysis

Comparison of categorical variables was carried out using the Fisher's exact test, and continuous variables were compared using the Mann–Whitney *U*-test. The non-parametric cumulative incidence functions (CIFs) for hospital discharge were computed considering death as a competing risk and were presented graphically. Significant differences in CIFs between treatment groups were evaluated by Gray's test. A *P* value was considered statistically significant at the $P < 0.05$ threshold. Statistical analysis was performed using Stata (version 16.0; StataCorp) and R software (version 3.6.3; R Foundation).

No sample size calculation was performed. Because of the urgent situation, it was decided that all eligible patients admitted with COVID during a period of 1 month would be enrolled.

The study protocol was approved by the institutional review board and ethics committee of Tehran University of Medical Sciences (approval number: IR.TUMS.VCR.REC.1398.1035). The study is registered with IRCT.ir under registration number IRCT20200128046294N2 accessible at https://www.irct.ir/trial/46463.

Results

Between 26 March and 26 April 2020, 120 patients with moderate to severe COVID-19 were admitted and screened for eligibility and 70 patients were initially enrolled. After centralized review of patient files, it was discovered that four of these patients were not eligible for the study and had been enrolled in error. Two cases had eGFR <50 mL/min, one had multiorgan failure at enrolment and one had onset of symptoms >8 days before enrolment. Finally, 66 patients were enrolled in the study. Of the patients enrolled, 33 were randomized to the treatment arm and 33 to the control arm (Figure 1).

The median age of patients was 58 years (IQR 43–69); 34 patients were men (52%) versus 32 (48%) women (Table 1). The most frequent comorbidities observed were diabetes and hypertension; 28 patients (42%) had diabetes and 23 patients had hypertension (35%). Age, sex and baseline demographics were similar across study arms. The most common signs and symptoms at presentation were fever, dry cough and dyspnoea. Baseline laboratory findings were balanced across arms. CT findings were available from 47 individuals. All individuals showed an abnormal CT pattern, most frequently ground-glass opacities (89%) and consolidation (72%). The CSS was balanced between arms.

The primary endpoint of clinical recovery within 14 days was achieved in 29/33 (88%) in the treatment arm and 22/33 (67%) in the control arm ($P = 0.076$; Table 2). The effect was significant after adjustment for baseline characteristics. The duration of hospitalization was significantly shorter in the treatment arm compared with the controls [6 (IQR 4–8) versus 8 (IQR 5–13) days, $P = 0.029$]. Figure 2 shows the cause-specific cumulative incidence function over time. The median (IQR) time to hospital discharge was 6 days (4–10) in the treatment group and 11 days (6–17) in the control. The probability of hospital discharge was significantly higher for the treatment arm compared with the control arm (Gray's test $P = 0.041$; Figure 2).

For the secondary endpoints of all-cause mortality and requirement for invasive mechanical ventilation, there was no significant difference between treatment arms (Table 2). The number of deaths was three in the treatment arm and five in the control arm ($P = 0.708$). Of the three deaths in the treatment arm, two had sofosbuvir/daclatasvir discontinued by the physician after 1 and 2 days for respiratory failure and pulmonary thromboembolism, respectively. The number of patients that required invasive mechanical ventilation was three in the treatment arm and seven in the control arm ($P = 0.303$). All patients received hydroxychloroquine, but concomitant administration of lopinavir/ritonavir was less frequent in the treatment arm compared with the control arm (33% versus 64%; $P = 0.026$); however, the numbers of deaths in the treatment group were balanced across lopinavir/ritonavir administration (9% in both), and clinical recovery by 14 days was 82% with lopinavir/ritonavir compared with 91% without (Table 2). The use of corticosteroids and antibiotics was balanced between groups.

No drug-related serious adverse events were reported in any patients in either the treatment arm or the control arm. During the 1 month follow-up, no COVID-related complications or readmissions were reported.

Discussion

In this randomized controlled clinical trial in moderate and severe COVID-19 patients, we showed that a combination of sofosbuvir and daclatasvir with standard care (hydroxychloroquine ± lopinavir/ritonavir) may decrease the time to discharge and duration of hospitalization compared with standard care alone. It has been recently shown that hydroxychloroquine and lopinavir/ritonavir are unlikely to have any beneficial effects against COVID-19 and might even be harmful.[3,4,30] We have therefore assumed that any benefit we observed is most likely to be attributed to sofosbuvir and daclatasvir; however, we cannot rule out a synergistic effect. Sofosbuvir/daclatasvir showed no benefit in increasing survival of patients with COVID-19 in our study, and a larger study is definitely required. It should be noted that as the results of PCR took up to 2 days to become available, the treatment of the treatment arm was started later than controls. It is likely that if sofosbuvir/daclatasvir is started immediately on admission better results would be observed.

This study provides timely evidence of the benefit of sofosbuvir/daclatasvir against COVID-19 during a fast-moving pandemic. However, our study has several limitations. This study was not placebo controlled, instead an active comparator of hydroxychloroquine ± lopinavir/ritonavir was administered to participants in the control and treatment arms. Notably, fewer patients in the

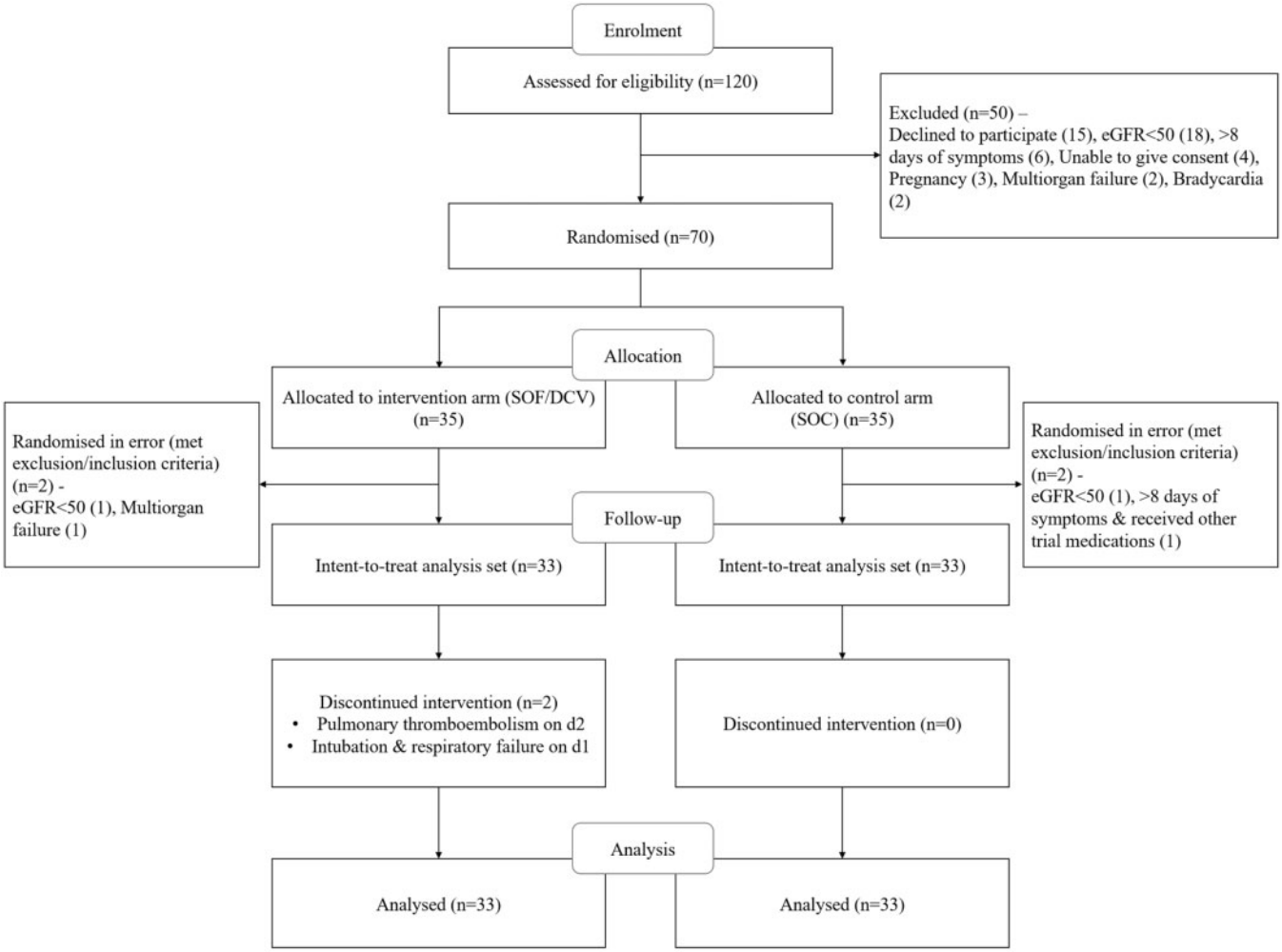

Figure 1. Patient flow.

treatment arm received lopinavir/ritonavir (33% versus 64% in controls) as the doctors managing the patients did not feel comfortable with prescribing an additional antiviral when one was already on the list. It is difficult to definitively comment on whether the different rates of lopinavir/ritonavir use in the two arms could have impacted outcomes. One study from China found little difference in any measurable outcome between lopinavir/ritonavir and standard care (which was no antiviral treatment).[4] As with HIV treatment, there may be a synergistic effect of combination antiviral therapies. This is a limitation to our study as any clinical benefits seen in either arm could be related to individual or synergistic effects of the combination of hydroxychloroquine and lopinavir/ritonavir with sofosbuvir/daclatasvir. Preliminary results of the RECOVERY trial show that dexamethasone significantly reduces deaths (by one-third) in patients receiving invasive mechanical ventilation.[31] In a univariable analysis of this study, concomitant treatment with corticosteroids was not a predictor of clinical recovery.

Our study was not blinded to patients or clinicians, therefore investigator bias is also a possibility; however, conducting a placebo-controlled trial during a pandemic remains a challenge. We partially compensated by masking the investigator, outcome assessor and data analyser. The small sample size of this study is another major limitation and so further studies with larger sample sizes are required in order to mitigate the risk of type II error.

Currently, the understanding of SARS-CoV-2 viral load kinetics and its relationship to disease severity is fragmentary.[32] The majority of patients with severe disease are found to have detectable viral loads in the respiratory samples for longer than those with milder disease.[33,34] However, the relationship between viral load and deterioration is unknown, and is limited by the inability to differentiate between infectious and non-infectious (dead or antibody-neutralized) virus with nucleic acid detection.[35] Some studies have shown that those who progress to severe disease have no detectable SARS-CoV-2 in sputum, and suggest an immune-mediated reaction as a cause for the deterioration.[36] In Iran, patients are encouraged to stay at home if they develop symptoms, and should only present to the hospital if they are breathless. This cohort of patients are therefore more likely to be at a later stage in their disease. To be able to attribute a positive clinical effect to an antiviral, it is important that in future studies, clinical progress is correlated with viral loads and days into

Table 1. Baseline characteristics of the study population

Characteristics	SOF/DCV ($n = 33$)	Control ($n = 33$)	*P* value
General			
Age, median (IQR)	58 (38–65)	62 (49–70)	0.211
Male, *n* (%)	20 (61)	14 (42)	0.218
Days from admission to enrolment, median (IQR)	1 (1–2)	1 (1–1)	0.062
Comorbidities, *n* (%)			
Chronic pulmonary disease	6 (18)	9 (27)	0.558
Asthma	1 (3)	1 (3)	1.000
Diabetes	17 (52)	11 (33)	0.213
Heart failure	3 (9)	7 (21)	0.303
Hypertension	12 (36)	11 (33)	1.000
Malignancy	1 (3)	2 (6)	1.000
Obesity (BMI $\geq$30 kg/m^2)	7 (23)	10 (33)	0.567
Concomitant medications, *n* (%)			
Angiotensin-converting enzyme inhibitors	1 (3)	1 (3)	1.000
Angiotensin receptor blockers	7 (21)	9 (27)	0.775
Symptoms and signs, *n* (%)			
Fever	21 (64)	20 (61)	1.000
Cough (with or without sputum)	22 (67)	23 (70)	1.000
Sore throat	5 (15)	3 (9)	0.708
Dyspnoea	26 (79)	28 (85)	0.751
Fatigue/malaise	15 (45)	12 (36)	0.617
Myalgia	15 (45)	11 (33)	0.450
Drowsiness	4 (12)	8 (24)	0.339
Nausea/vomiting	8 (24)	5 (15)	0.537
Diarrhoea	5 (15)	3 (9)	0.708
Rhinorrhoea	1 (3)	0 (0)	1.000
Headache	5 (15)	2 (6)	0.427
Chest pain	5 (15)	1 (3)	0.197
Vitals on admission, median (IQR)			
O_2 saturation (%)	91 (89–92)	90 (88–92)	0.225
Respiratory rate (breaths/min)	20 (18–22)	20 (19–24)	0.107
Temperature (°C)	38 (37–38)	38 (37–38)	0.866
Laboratory findings on admission, median (IQR)			
Haemoglobin (g/dL)	12 (11–14)	12 (11–14)	0.923
White blood cells ($\times 10^9$ per L)	6.9 (5.6–12.3)	10 (6–12)	0.174
Lymphocyte count ($\times 10^9$ per L)	1.4 (1.0–1.8)	1.2 (0.9–1.8)	0.597
AST (IU/L)	35 (27–44)	35 (25–54)	0.808
ALT (IU/L)	31 (26–38)	33 (23–58)	0.671
International normalized ratio (INR)	1.2 (1.0–1.3)	1.1 (1.0–1.2)	0.141
Creatinine (mg/dL)	1.0 (0.8–1.1)	1.0 (0.9–1.2)	0.613
Blood urea nitrogen (mg/dL)	16 (13–26)	17 (12–27)	0.893
C-reactive protein (mg/L)	45 (15–64)	30 (13–55)	0.405
Erythrocyte sedimentation rate (mm/h)	60 (35–99)	53 (37–92)	0.544
CT findings ($n = 47$)			
Any abnormal pattern, *n*/*N* (%)	21/21 (100)	26/26 (100)	
Ground glass opacities	19 (90)	23 (88)	1.000
Consolidation	16 (76)	18 (69)	0.746
Reticular pattern	4 (19)	5 (19)	1.000
Honeycomb formation	1 (5)	1 (4)	1.000
CT score severity (0–24), median (IQR)	9 (6–16)	10 (4–12)	0.255

Percentages are calculated from non-missing values. *P* values are calculated using the Fisher's exact test for categorical outcomes and Mann–Whitney *U*-test for continuous outcomes.
SOF/DCV, sofosbuvir/daclatasvir.

Table 2. Clinical outcomes

Characteristic	SOF/DCV ($n = 33$)	Control ($n = 33$)	*P* value
Clinical recovery $\leq$14 days, *n* (%)	29 (88)	22 (67)	0.076
Time to clinical recovery (days), median (IQR)[a]	6 (4–10)	11 (6–17)	0.041
Invasive mechanical ventilation	3 (9)	7 (21)	0.303
Death, *n* (%)	3 (9)	5 (15)	0.708
Concomitant treatments, *n* (%)			
Lopinavir/ritonavir	11 (33)	21 (64)	0.026
Corticosteroids	12 (36)	8 (24)	0.422
Antibiotics	29 (88)	30 (91)	1.000

P values are calculated using the Fisher's exact test for categorical outcomes and Mann–Whitney *U*-test for continuous outcomes unless otherwise stated.
SOF/DCV, sofosbuvir/daclatasvir.
[a]Estimated from the cumulative incidence function, accounting for death as a competing risk; *P* value is for Gray's test.

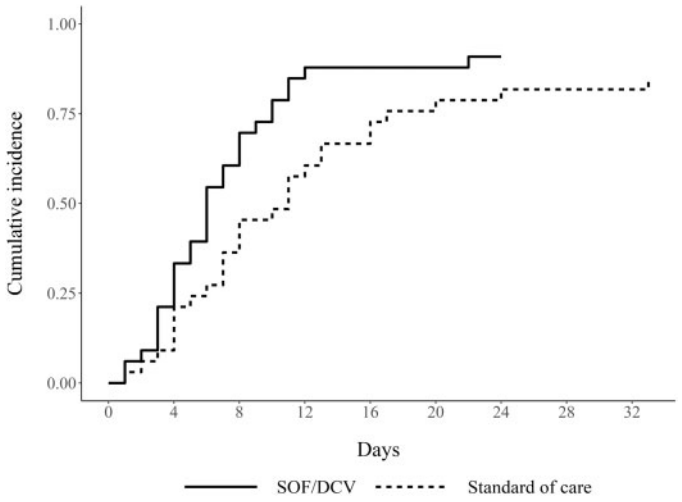

Figure 2. Cause-specific cumulative incidence function by treatment arm. SOF/DCV, sofosbuvir/daclatasvir.

COVID-19 illness. Due to the shortage of tests at the time of the study, we were not able to obtain follow-up SARS-CoV-2 PCR on our subjects.

A number of clinical trials in Iran have been registered investigating the efficacy of sofosbuvir alone or in combination with daclatasvir and other antivirals such as ledipasvir and velpatasvir for the treatment of COVID-19 (https://www.irct.ir/). In light of this, there is scope for a meta-analysis of results from these trials to investigate the efficacy of sofosbuvir-based regimens against SARS-CoV-2 in a larger number of participants. Additionally, results from trials investigating sofosbuvir in combination with alternative drugs could indicate whether sofosbuvir has greater efficacy compared with daclatasvir against COVID-19.

The combination of sofosbuvir and daclatasvir with standard care shows efficacy in reducing the median duration of hospital stay. If confirmed in an analysis of other similar studies, these results would justify the integration of sofosbuvir/daclatasvir into large pivotal trials leading to regulatory approval for treatment of coronavirus infection.

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Transparency declarations

A.S., A.A.A., Z.K., A.A., M.M., H.H., S.A., R.A., E.A. and A.R.R. are employees of Tehran University of Medical Sciences. S.M. has received travel grants from and is a stockholder of Fanavaran Rojan Mohaghegh Daru Co. All other authors: none to declare.

Author contributions

A.S, A.A.A., S.A. and S.M. designed the study. A.S., A.A.A., A.N., Z.K., A.A., M.M., H.H., S.A. and R.A. were involved in recruitment and care of patients. A.R.R. and A.H.D. interpreted radiological data. A.A.A., H.W., A.Q., B.S. and A.H. were involved in data management and analysis. A.S., A.H., J.L., A.G., E.A. and S.M. drafted the manuscript. All authors critically revised and approved the final published version.

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