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The impact of sofosbuvir/daclatasvir or ribavirin in patients with severe COVID-19

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Objectives: Sofosbuvir and daclatasvir are direct-acting antivirals highly effective against hepatitis C virus. There is some *in silico* and *in vitro* evidence that suggests these agents may also be effective against SARS-CoV-2. This trial evaluated the effectiveness of sofosbuvir in combination with daclatasvir in treating patients with COVID-19.

Methods: Patients with a positive nasopharyngeal swab for SARS-CoV-2 on RT–PCR or bilateral multi-lobar ground-glass opacity on their chest CT and signs of severe COVID-19 were included. Subjects were divided into two arms with one arm receiving ribavirin and the other receiving sofosbuvir/daclatasvir. All participants also received the recommended national standard treatment which, at that time, was lopinavir/ritonavir and single-dose hydroxychloroquine. The primary endpoint was time from starting the medication until discharge from hospital with secondary endpoints of duration of ICU stay and mortality.

Results: Sixty-two subjects met the inclusion criteria, with 35 enrolled in the sofosbuvir/daclatasvir arm and 27 in the ribavirin arm. The median duration of stay was 5 days for the sofosbuvir/daclatasvir group and 9 days for the ribavirin group. The mortality in the sofosbuvir/daclatasvir group was 2/35 (6%) and 9/27 (33%) for the ribavirin group. The relative risk of death for patients treated with sofosbuvir/daclatasvir was 0.17 (95% CI 0.04–0.73, $P = 0.02$) and the number needed to treat for benefit was 3.6 (95% CI 2.1–12.1, $P < 0.01$).

Conclusions: Given these encouraging initial results, and the current lack of treatments proven to decrease mortality in COVID-19, further investigation in larger-scale trials seems warranted.

Introduction

The global pandemic caused by SARS-CoV-2 represents an unprecedented challenge to medical science. In our armamentarium of possible treatments, we have convalescent serum, repurposing existing approved drugs that may have a useful impact on this virus, and new developments such as vaccines or new small-molecule antivirals.[1,2]

We reasoned that with SARS-CoV-2, HCV and HIV all being positive-sense RNA viruses, antivirals that work for HCV and HIV might exhibit a spectrum that encompasses SARS-CoV-2. With the initial step in the duplication of HIV being reverse transcription, we further reasoned that there is substantially more lifecycle homology between SARS-CoV-2 and HCV as both use an RNA-dependent RNA polymerase.

In the realm of antivirals, we see two broad strategies: inhibition of duplication of the genetic material via nucleoside or nucleotide analogues (NUCs) or inhibition of the key viral proteins. With the genetic alphabet of RNA consisting of the letters CGAU, we reasoned NUCs targeting the need to incorporate these genetic letters into the elongating RNA strand had the highest probability

of success. Ribavirin is a weak NUC and a fake letter 'G'. Remdesivir is an NUC and a fake letter 'A'. Sofosbuvir is a strong NUC and a fake letter 'U'.

The SARS-CoV-2 replication and transcription cycle depends on several key enzymes, notably RNA-dependent RNA-polymerase (RdRp), main protease (Mpro) and helicase. The structures of SARS-CoV-2 RdRp and Mpro have been analysed and published in high resolution and are attractive targets to model antiviral drugs against.[3,4] Some *in silico*[5] and *in vitro*[6,7] studies of sofosbuvir have predicted that it and other nucleoside/nucleotide analogues will bind strongly to the SARS-CoV-2 RdRp enzyme and inhibit its function.[5,7] This is the same proposed mechanism of action as both remdesivir and favipiravir.

Sofosbuvir and remdesivir have chemical similarities including a molecular weight of 529.5 and 602.6 Da, respectively, and predicted SARS-CoV-2 RdRp binding strength of −4.41 and −5.16 kcal/mol, respectively; however, sofosbuvir is much more easily absorbed orally.[8] Results have not always been congruent because computer models use different formulae and make different assumptions, and *in vitro* analyses use different cell lines under different conditions.

One deep-learning model suggested that daclatasvir would have a binding strength to SARS-CoV-2 RdRp of 23.31 K_d, which is similar to remdesivir (20.17 K_d).[9] However, another modelling study compared the binding strength of 88 antiviral drugs with SARS-CoV-2 Mpro, and found daclatasvir to be one of the weakest binders to the enzyme (MolDock score −45.44)[10]

Sofosbuvir is available in Iran as a fixed-dose tablet where it is combined with daclatasvir (doses of 400 and 60 mg respectively). With molecular modelling predicting daclatasvir may also have activity against SARS-CoV-2, using this tablet was both pragmatic and offered the possibility of delivering a potential extra benefit from the daclatasvir.

Like interferon, ribavirin is known to have a broad spectrum of antiviral activity. Our research team differed in personal opinions about whether sofosbuvir/daclatasvir or ribavirin would be more effective. With the national standard COVID-19 treatment protocol at the time being lopinavir/ritonavir 200/50 mg two tablets every 12 h plus hydroxychloroquine 400 mg daily, it was decided to conduct a two-arm trial where both arms would receive the standard protocol in addition to either ribavirin or sofosbuvir/daclatasvir.

Materials and methods

This open-label parallel trial was conducted at the Abadan Faculty of Medical Sciences affiliated to Taleghani Hospital in Abadan city, the epicentre of the COVID-19 outbreak in Khuzestan Province located in south-western Iran. Patients were enrolled between 18 March 2020 and 16 April 2020 and their clinical course was followed for the 3 weeks immediately following commencement of trial medication.

Inclusion and exclusion criteria

Enrolment was only offered to hospitalized patients with a positive nasopharyngeal swab RT–PCR for SARS-CoV-2 or bilateral multi-lobar ground-glass opacity on their chest CT and signs of severe COVID-19, defined as oxygen saturation less than 94% or respiratory rate above 24 or decreased level of consciousness. The RT–PCR test used was qualitative, not quantitative. The exclusion criteria were subjects under 18 years, pregnant and breast-feeding women, those with severe anaemia (haemoglobin <7 mg/dL) or with prior use of medicine for COVID-19, and subjects not consenting to the study.

Study arms

Subjects were divided into two arms. One arm received a single daily pill containing 400 mg sofosbuvir and 60 mg daclatasvir (Sovodak, Fanavaran Rojan Mohaghegh Daru Co, Tehran, Iran) and the other received 600 mg ribavirin (Bakhtar Biochemistry Co, Kermanshah, Iran) every 12 h. Treatment was administered during admission for a maximum of 14 days. In addition, both arms received the national standard treatment protocol, which was at the time lopinavir/ritonavir 200/50 mg, two tablets every 12 h during admission for a maximum of 5 days, and hydroxychloroquine 400 mg single dose on admission. All study medication was discontinued at discharge.

Allocation

COVID subjects in Taleghani hospital are managed by six different specialists in infectious disease. Three of these specialists allocated all their patients to the ribavirin arm and the other three to the sofosbuvir/daclatasvir arm. As a result, subjects were allocated to study arms based on which specialist was on-call at the time of their admission, so the allocation was not blinded and pseudorandom rather than fully random. Subjects in either arm were admitted in the same dedicated COVID-19 wards with the same hospital staff.

Outcomes

The primary outcome measured was the time from starting the trial medications until discharge from hospital. Patients were discharged when clinical improvement was observed, defined as oxygen saturation 98% or higher, respiratory rate 18/min or less, and temperature under 37.5°C. The secondary outcomes measured were duration of stay in ICU, mortality, respiratory rate, laboratory values and adverse effects. Subjects were contacted daily after hospital discharge and asked about complications and re-admissions for 21 days.

Statistical analysis

Outcomes and baseline characteristics were summarized using descriptive statistics. The χ^2 test was used to compare categorical outcomes between groups and the independent *t*-test was used for continuous outcomes. The primary outcome, time to hospital discharge, was assessed considering all individuals who died as right censored at the maximum follow-up time. Time to hospital discharge was plotted and compared with a log-rank test. Cox proportional hazards models were used to adjust the primary outcome for baseline characteristics that may confound results. Relative risks of binary outcomes are presented with the corresponding 95% CI. The number needed to treat (NNT) was calculated as the reciprocal of the risk difference. A P value <0.05 was considered to be significant.

No sample size calculation was performed. All eligible patients admitted with COVID-19 over a 4 week period were enrolled.

The trial was approved by the Ethics Committee of Abadan Faculty of Medical Sciences (IR.ABADANUMS.REC.1398.113). Written informed consent was obtained from all patients or their legal representatives. Subjects were free to exit the study whenever they chose. The authors were involved in the design, data collection and analysis of the trial and approving the final version for publication. The study is registered in the Iranian Registry of Clinical Trials (IRCT ID: IRCT20200324046850N2, https://www.irct.ir/trial/46713).

Results

Eighty-two patients with severe COVID-19 were admitted to Taleghani Hospital during the enrolment period. Twenty patients were excluded (2 died before allocation, 7 had prior COVID medicine use, 11 refused consent). Sixty-two patients who met the eligibility criteria were included (27 in the ribavirin arm and 35 in the sofosbuvir/daclatasvir arm). All patients reached the study endpoints of death or discharge from hospital during the study period and none were lost to follow-up (Figure 1).

The median age was 62.5 years with an IQR between 46 and 71 years. The number of male and female patients enrolled was equal. There were no statistically significant differences between the two groups across a range of baseline observations (Table 1).

The minimum hospital stay for patients who survived was 3 days and the maximum 19 days. The median time to hospital discharge was 6 days in the sofosbuvir/daclatasvir arm and 11 days in the ribavirin arm (Table 2). Figure 2 presents the cumulative probability of being discharged from hospital alive for the two trial arms. This shows, rather clearly, the more rapid recovery of patients dosed with sofosbuvir/daclatasvir together with a significantly higher survival probability (log rank $P < 0.01$). Results remained significant after adjustment for baseline characteristics in the Cox proportional hazards model.

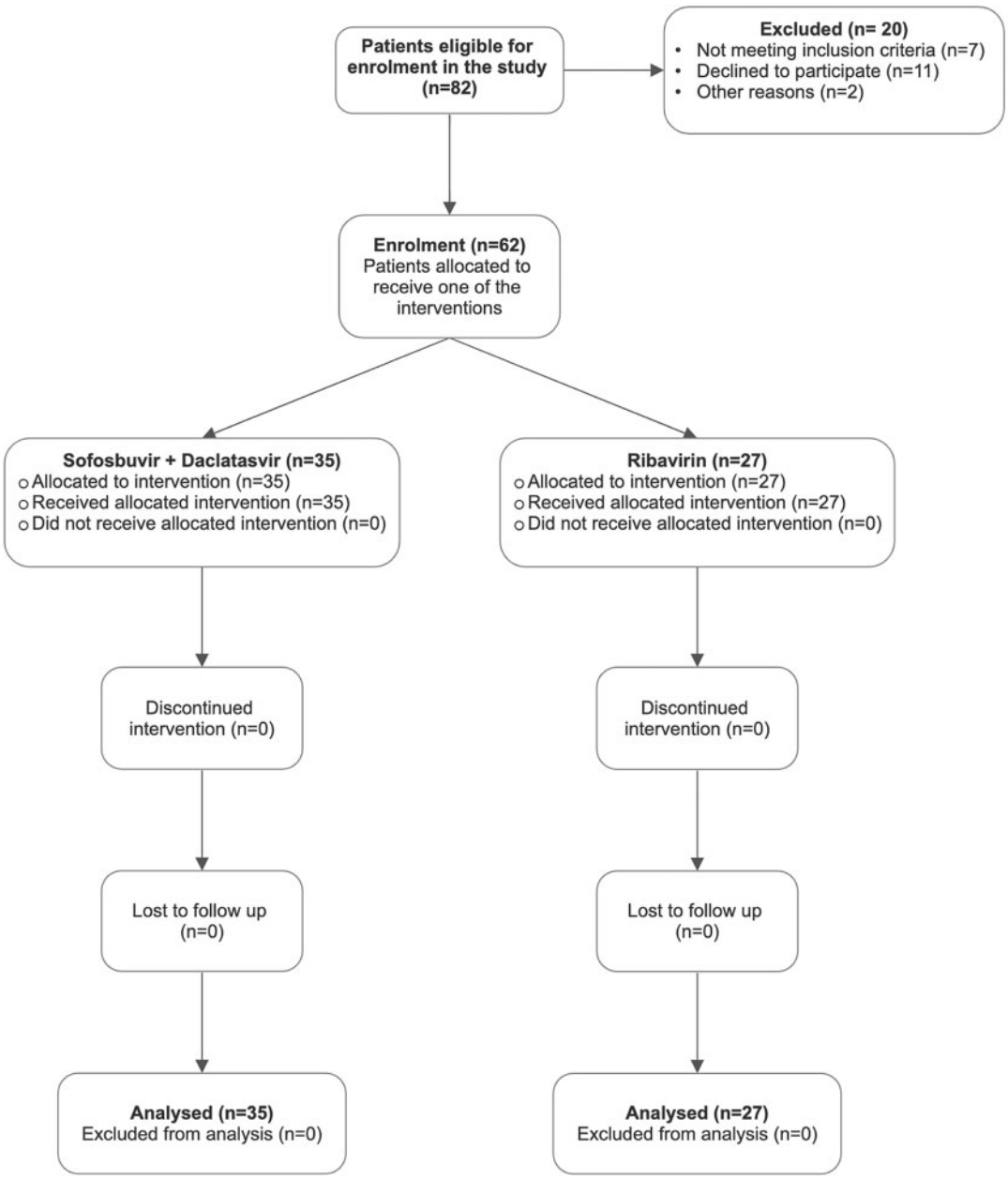

Figure 1. Patient enrolment process.

Table 1. Demographic and clinical characteristic of the patients at baseline

Characteristic	SOF/DCV ($n = 35$)	RBV ($n = 27$)	*P* value
General			
age, median (IQR)	62 (47–69)	60 (43–73)	0.69
gender: male, *n* (%)	17 (49)	14 (52)	0.80
BMI, median (IQR)	27 (24–29)	25 (23–28)	0.39
smoker, *n* (%)	6 (17%)	5 (19%)	1.00
Coexisting conditions, *n* (%)			
diabetes	10 (29%)	7 (26%)	0.82
chronic lung disease	1 (3%)	2 (7%)	0.41
COPD	3 (8%)	2 (7%)	1.00
asthma	2 (6%)	1 (3%)	1.00
chronic renal failure	1 (2.9%)	1 (3.7%)	0.85
cardiovascular disease	5 (14%)	7 (26%)	0.25
coinfection	1 (3%)	6 (22%)	0.037
other	3 (8.6%)	2 (7.4%)	0.87
Baseline observations			
Glasgow Coma Scale, median (IQR)	12 (11–14)	13 (12–15)	0.24
respiratory rate, median (IQR)	24 (21–26)	24 (20–26)	0.31
febrile, *n* (%)	35 (100%)	27 (100%)	1
arterial O_2 saturation (%), median (IQR)	92 (90–93)	92 (90–93)	0.23
systolic blood pressure, median (IQR)	120 (110–135)	125 (110–150)	0.32
white cell count ($\times 10^{-9}$/L), median (IQR)	7.4 (5.4–9.3)	7.9 (4.7–14.1)	0.65
lymphocyte count ($\times 10^{-9}$/L), median (IQR)	1.3 (0.9–1.7)	1.0 (0.7–1.8)	0.88
haemoglobin (g/dL), median (IQR)	12.6 (10.4–14.1)	11.8 (10.5–13.3)	0.28
platelet count ($\times 10^{-9}$/L), median (IQR)	204 (165–297)	239 (160–322)	0.82
serum creatinine (mg/dL), median (IQR)	1.1 (0.9–1.4)	1.2 (1.0–1.4)	0.58
AST (U/L), median (IQR)	26 (22–38)	36 (25–60)	0.04
ALT (U/L), median (IQR)	20 (15–30)	28 (14–43)	0.13

SOF/DCV, sofosbuvir/daclatasvir; RBV, ribavirin.

Table 2. Clinical outcomes in the intention to treat population

Outcome	SOF/DCV ($n = 35$)	RBV ($n = 27$)	*P* value
Duration of hospital stay, median days (IQR)	5 (5–7)	9 (6–11)	<0.01
Recovered, *n* (%)	33 (94%)	18 (67%)	0.01
time to recovery, median (IQR)	6 (5–8)	11 (9–?[a])	<0.01
Admitted to ICU, *n* (%)	6 (17%)	13 (48%)	0.01
days in ICU, median (IQR)	3.5 (2–4)	5 (2–10)	0.24
days in ICU, mean (SD)	3.5 (2.1)	5.6 (4.0)	0.24
relative risk of ICU admission (95% CI)	0.36 (0.16–0.81)	2.8 (1.2–6.4)	0.01
Deaths, *n* (%)	2 (5.7%)	9 (33%)	0.01
relative risk of death (95% CI)	0.17 (0.04–0.73)	5.8 (1.4–25)	0.02

SOF/DCV, sofosbuvir/daclatasvir; RBV, ribavirin.
[a]The 75th percentile was not evaluable.

The median duration of hospital stay for all patients was 5 days for the sofosbuvir/daclatasvir group and 9 days for the ribavirin group. The need to admit patients to the ICU was lower in the group taking sofosbuvir/daclatasvir (17%) than the group taking ribavirin (48%). The relative risk of ICU admission for the sofosbuvir/daclatasvir group versus the ribavirin group was 0.36 (95% CI 0.16–0.81, $P = 0.014$). The median duration for ICU stay was 3.5 days for the sofosbuvir/daclatasvir group and 5 days for the ribavirin group (Table 2).

The mortality in the sofosbuvir/daclatasvir group was 2/35 (5.7%) versus 9/27 (33%) for the ribavirin group with a relative risk of death of 0.17 (95% CI 0.04–0.73, $P = 0.02$) for patients treated

with sofosbuvir/daclatasvir versus ribavirin and an NNT for benefit of 3.6 (95% CI 2.1–12.1, $P < 0.01$).

Adverse effects

A total of 30 patients (86%) in the sofosbuvir/daclatasvir group and 27 (100%) in the ribavirin group reported at least one adverse effect (Table 3). The most frequent adverse effects in the ribavirin treatment group were anaemia and gastrointestinal (GI) disorders (including nausea, vomiting, diarrhoea, abdominal pain and discomfort, GI bleeding and decreased appetite). In addition, leucopenia was more frequent in the sofosbuvir/daclatasvir group.

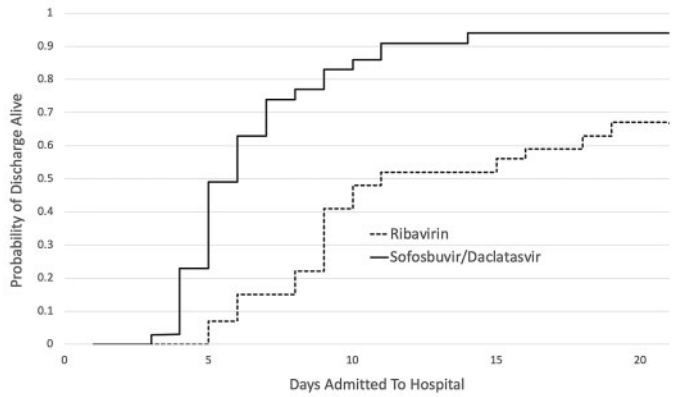

Figure 2. Cumulative probability of being discharged alive for the ribavirin and sofosbuvir/daclatasvir arms.

Even though thrombocytopenia was observed in the sofosbuvir/daclatasvir group, no patient in this group had GI bleeding. Notably, we observed no increase in liver enzymes in the sofosbuvir/daclatasvir group whereas five patients in the ribavirin group had mild increases.

Five patients in the ribavirin group developed sepsis, of whom three survived. One case of severe Stevens–Johnson syndrome was observed in the ribavirin group. The study medication was discontinued and the patient survived. Except for this case, none of the observed adverse effects demanded discontinuation of study medications.

Patients were followed daily by telephone for 21 days after hospital discharge. There was no report of COVID-related complications or re-admission.

Discussion

In this open-label trial, the effects of sofosbuvir/daclatasvir and ribavirin in patients with severe COVID-19 were measured. In the group receiving sofosbuvir/daclatasvir, duration in hospital, duration in ICU and mortality rate were significantly lower when compared with the ribavirin group. The time required before observing clinical improvement was significantly less in patients treated with sofosbuvir/daclatasvir, and the side effects of the medication, such as GI bleeding and anaemia, were lower than in the group receiving ribavirin.

Sofosbuvir as a monotherapy is no longer available in Iran so, due to the urgency of COVID-19 and the potential efficacy of daclatasvir,[9] it was decided to use the available fixed-dose

Table 3. Summary of adverse events

Event	SOF/DCV ($n = 35$)	RBV ($n = 27$)	All ($n = 62$)
Any adverse event	30 (86%)	27 (100%)	57 (92%)
Lymphopenia	5 (14%)	9 (33%)	14 (23%)
Thrombocytopenia	4 (11%)	4 (15%)	8 (13%)
Leucopenia	9 (25%)	3 (11%)	12 (19%)
Nausea and vomiting	13 (37%)	22 (82%)	35 (56%)
Increased AST or ALT	0 (0%)	5 (19%)	5 (8.1%)
Abdominal discomfort	9 (26%)	16 (59%)	25 (40%)
Diarrhoea	7 (20%)	18 (67%)	25 (40%)
Gastritis	5 (14%)	10 (37%)	15 (24%)
Anaemia	10 (29%)	14 (52%)	24 (38%)
Rash	0 (0%)	1 (3.7%)	1 (1.6%)
Leucocytosis	3 (8.5%)	7 (26%)	10 (16%)
Decreased appetite	13 (37%)	10 (37%)	23 (37%)
Prolonged QT interval	1 (2.8%)	0 (0%)	1 (1.6%)
Sleep disorders	7 (20%)	5 (19%)	12 (19%)
GI bleeding	0 (0%)	16 (59%)	16 (26%)
Acute kidney injury	2 (5.7%)	6 (22%)	8 (13%)
Shock	2 (5.7%)	9 (33%)	11 (17%)
Sepsis	0 (0%)	5 (19%)	5 (8.1%)
Stevens–Johnson syndrome	0 (0%)	1 (3.7%)	1 (1.6%)
Haematuria	1 (2.8%)	0 (0%)	1 (1.6%)
Diffuse intravascular coagulation	0 (0%)	2 (7.4%)	3 (4.8%)

SOF/DCV, sofosbuvir/daclatasvir; RBV, ribavirin.

formulation of sofosbuvir/daclatasvir. As a result, it was not possible to investigate whether sofosbuvir or daclatasvir was active alone. Our results may reflect the impact of one molecule only or both in combination, although according to the current literature we believe both could be responsible for the effects we have seen.[7,11] We are aware of other clinical trials in Iran using sofosbuvir/interferon, sofosbuvir/velpatasvir and sofosbuvir/ledipasvir and these may shed light on which molecule(s) appear to be active.

With any small trial, the outcome of a single patient can impact the results. For example, in the two deaths observed with sofosbuvir/daclatasvir one patient was 74 and the other 96 years old. It would not be unreasonable to argue that this 96-year-old patient might well have died, regardless of which treatment was offered. With so few deaths in the sofosbuvir/daclatasvir group, no reasonable comparisons can be made other than to note the youngest patient who died in the ribavirin group was 54, the oldest 84, and the median 71.

Since there is some evidence that ribavirin can help in COVID-19, one arm of our study received ribavirin.[5] It is well known that high doses of ribavirin have many adverse effects which might complicate an advanced case of COVID-19, especially in an ICU setting where impaired renal function is frequently an issue.[12] For instance, anaemia, a well-known adverse effect of ribavirin, was observed in 52% of our ribavirin group versus 29% in sofosbuvir/daclatasvir. On the other hand, the safety of sofosbuvir/daclatasvir is well proven, even in advanced cases of renal failure.[13,14] So both the possible effectiveness of ribavirin against SARS-CoV-2 and the potential increased mortality due to its side effects might have impacted on our results. In the case of benefit from ribavirin, the observed relative advantage of sofosbuvir/daclatasvir would have been diminished. Conversely, the putative success of sofosbuvir/daclatasvir may have been impacted by excess deaths due to adverse effects of ribavirin. The observation that the relative risk of ICU admission was 0.36 for the sofosbuvir/daclatasvir group versus ribavirin could be possibly explained by ribavirin conferring excess risk. That said, the long half-life of ribavirin (12 days), particularly with respect to the treatment duration and the knowledge that steady-state does not occur for five half-lives, suggests it could equally well be argued that the outcome occurred well before steady-state, and perhaps even before clinically relevant blood levels of ribavirin were reached.

Our study did not have an arm receiving only lopinavir/ritonavir. But the study by Cao *et al.*[15] reported a mortality of 19.2% among hospitalized adults treated with this combination. Although a direct comparison is not possible, the mortality in our sofosbuvir/daclatasvir group with roughly similar subjects was much lower at 5.7%. Hence, we recommend that sofosbuvir/daclatasvir should be compared with a placebo in a fully blinded and randomized study with a large sample size in order to accurately determine whether the benefits suggested by this pilot study can be duplicated elsewhere. It would also appear worthwhile to investigate if sofosbuvir or daclatasvir are both active, or if it is only one of these drugs that is active.

Several antiviral drugs are being evaluated for the treatment of COVID-19 infection. Remdesivir has shown clinical benefits in some randomized trials, but the results are not consistent.[16,17] In addition, remdesivir needs to be given by intravenous infusion and supplies are limited. Favipiravir has shown antiviral effects and trends for improved clinical recovery in pilot studies, but these results need to be confirmed in larger randomized trials.[18]

In a recent *in vitro* study daclatasvir consistently inhibited the production of infectious SARS-CoV-2 virus particles in Vero cells, in the hepatoma cell line HuH-7 and in type II pneumocytes, with EC_{50} of 0.8, 0.6 and 1.1 μM, respectively. The antiviral effects of sofosbuvir were seen only at high drug concentrations in this study. It is not clear whether these concentrations can be achieved during standard dosing.[11]

If sofosbuvir/daclatasvir was proven to be effective in larger randomized clinical trials, this treatment would be cheap to provide and the drug supplies are widely available in many countries for the treatment of hepatitis C. The safety profile of sofosbuvir/daclatasvir has been well described from 12 to 24 weeks of treatment for hepatitis C. In future studies, it would be worth checking whether the sofosbuvir needs to be included in this combination. It is possible that daclatasvir is the only active antiviral at standard doses. In addition, the antiviral effects of daclatasvir might be improved by more frequent dosing (for example three times per day).

The inability to perform a fully randomized and blinded study due to the urgency of the global situation was a significant shortcoming, although the baseline characteristics of the two groups (Table 1) indicate that patients were reasonably well distributed. Only having ribavirin-treated patients as controls leaves open the possibility that the higher mortality rate seen in this group was a function of ribavirin use, and that without its use the mortality in this group may have been lower. On the other hand, ribavirin might have had a positive effect on COVID-19 and thus have diminished the beneficial effect we observed with sofosbuvir/daclatasvir. In either case, a study with a non-ribavirin arm is required.

In this open-label study, treatment of patients with severe COVID-19 with sofosbuvir/daclatasvir was significantly more effective than ribavirin through improved clinical symptoms, lower mortality rates, a shorter duration of both ICU and hospital stays, and fewer side effects. These preliminary results need to be confirmed in larger double-blind, randomized trials for sofosbuvir/daclatasvir to be approved for the worldwide treatment of COVID-19 infection.

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Transparency declarations

None to declare.

Author contributions

S. Mobarak and A.S. designed the study. Recruitment and care of patients were done by S. Mobarak, S.S., G.E., A.H.J.K., Z.L., and S. Marjani. S.M.T. and M.H.F. interpreted radiologic data. S.J., H.E., S.B., S. Mousaviasl, B.S., A.F., and H.W. were involved in statistical analysis and data management. A.W., R.T.,

A.H., J.F., M. Momtazan, M. Mobarak, S. Mobarak, E.R., B.S., H.W. and A.H. drafted the paper. All authors were involved in critical revision of the manuscript and final approval of the published version.

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