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Sofosbuvir and daclatasvir for the treatment of COVID-19 outpatients: a double-blind, randomized controlled trial

Fatemeh Roozbeh[1], Majid Saeedi[2], Reza Alizadeh-Navaei[3], Akbar Hedayatizadeh-Omran[3], Shahin Merat [4], Hannah Wentzel[5], Jacob Levi[6], Andrew Hill[7] and Amir Shamshirian [3,8]*

[1]Mazandaran University of Medical Sciences, Sari, Iran; [2]Pharmaceutical Sciences Research Center, Mazandaran University of Medical Sciences, Sari, Iran; [3]Gastrointestinal Cancer Research Center, Non-Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran; [4]Liver and Pancreatobiliary Diseases Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran; [5]School of Public Health, Imperial College London, London, UK; [6]Department of Emergency Medicine, Homerton University Hospital, London, UK; [7]Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK; [8]Department of Medical Laboratory Sciences, School of Allied Medical Science, Mazandaran University of Medical Sciences, Sari, Iran

*Corresponding author. E-mail: shamshirian.amir@gmail.com

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Introduction: Effective treatments are urgently needed to tackle the novel coronavirus disease 2019 (COVID-19). This trial aims to evaluate sofosbuvir and daclatasvir versus standard care for outpatients with mild COVID-19 infection.

Methods: This was a randomized controlled clinical trial in outpatients with mild COVID-19. Patients were randomized into a treatment arm receiving sofosbuvir/daclatasvir plus hydroxychloroquine or a control arm receiving hydroxychloroquine alone. The primary endpoint of the trial was symptom alleviation after 7 days of follow-up. The secondary endpoint of the trial was hospital admission. Fatigue, dyspnoea and loss of appetite were investigated after 1 month of follow-up. This study is registered with the IRCT.ir under registration number IRCT20200403046926N1.

Results: Between 8 April 2020 and 19 May 2020, 55 patients were recruited and allocated to either the sofosbuvir/daclatasvir treatment arm ($n = 27$) or the control arm ($n = 28$). Baseline characteristics were similar across treatment arms. There was no significant difference in symptoms at Day 7. One patient was admitted to hospital in the sofosbuvir/daclatasvir arm and four in the control arm, but the difference was not significant. After 1 month of follow-up, two patients reported fatigue in the sofosbuvir/daclatasvir arm and 16 in the control arm; $P < 0.001$.

Conclusions: In this study, sofosbuvir/daclatasvir did not significantly alleviate symptoms after 7 days of treatment compared with control. Although fewer hospitalizations were observed in the sofosbuvir/daclatasvir arm, this was not statistically significant. Sofosbuvir/daclatasvir significantly reduced the number of patients with fatigue and dyspnoea after 1 month. Larger, well-designed trials are warranted.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and resulting coronavirus disease 2019 (COVID-19) continue to cause serious public health concern. Currently, there are millions of confirmed cases including hundreds of thousands of deaths.[1] However, no treatment so far has demonstrated clear efficacy against COVID-19; therefore, new treatments are urgently needed. Repurposing existing pharmaceuticals is an attractive short-term management strategy for the immediate pandemic. Repurposed pharmaceuticals may be used to treat mild or moderate disease to stop progression toward severe disease and reduce strain on healthcare systems.

SARS-CoV-2 is a positive-sense RNA virus that requires an RNA-dependent RNA polymerase (RdRp) during replication. Other viral families share similar replication mechanisms and therefore existing antivirals may be repurposed for treatment against SARS-CoV-2. Sofosbuvir and daclatasvir are direct-acting antiviral agents against hepatitis C.[2] Sofosbuvir and daclatasvir have predicted *in silico* activity against SARS-CoV-2[3,4] and therefore are attractive treatment options. In a recent study, sofosbuvir and daclatasvir

show *in vitro* activity against SARS-CoV-2-infected Huh-7 and Calu-3 cells.[5] In that study, daclatasvir also shows activity in Vero 6-infected cells; however, sofosbuvir does not. Reports of neurological complications associated with COVID-19 are increasing.[6,7] Sofosbuvir has also demonstrated protective activity against SARS-CoV-2-infected brain organoids.[8]

In Iran, sofosbuvir/daclatasvir is available as the fixed-dose combination, Sovodak (400/60 mg). Three recently published clinical trials investigating sofosbuvir/daclatasvir in moderate to severe hospitalized patients have shown improved clinical outcomes.[9–11] In addition to efficacy and safety, a potential treatment option for COVID-19 must be widely available and affordable—the estimated API production cost of generic sofosbuvir/daclatasvir is approximately $5 per 14 day treatment course.[12] The current guideline in Iran recommends conservative management with or without hydroxychloroquine, but sofosbuvir/daclatasvir has yet to be tested in an outpatient setting. We therefore conducted a randomized active-controlled trial to evaluate the effectiveness and safety of adding sofosbuvir/daclatasvir to the routine protocol of COVID-19 outpatients.

Methods

Study design and participants

This was a double-blind, randomized parallel-group, active-controlled clinical trial. Patients were recruited from 8 April 2020 to 19 May 2020 from Miandrood Outpatient Medical Clinic in Surak, Mazandaran, Iran. Adults with confirmed CT scan findings for COVID-19, typical COVID-19 clinical symptoms including fever, cough and fatigue, and positive C-reactive protein (CRP) test were evaluated to enter the trial. Exclusion criteria included: oxygen saturation less than 93%, pregnancy, amiodarone use, renal failure and cardiovascular diseases. All patients gave written informed consent for participation in the study.

Randomization and masking

Patients were randomly assigned to either sofosbuvir/daclatasvir and hydroxychloroquine or hydroxychloroquine groups through unstratified block randomization with a block size of four. A block randomization list was created using a computer-generated randomization plan. Physician and analyser were blinded and randomization with coding was done by a third person.

Procedure

All patients received standard care according to the national Iranian treatment guidelines. All patients received azithromycin capsules (500 mg for 6 days) with naproxen tablets (500 mg, twice daily for 7 days), as well as 40 mg pantoprazole tablets. The intervention group (sofosbuvir/daclatasvir group) received a single daily oral tablet containing 400 mg sofosbuvir and 60 mg daclatasvir (Sovodak, Rojan Pharma, Tehran, Iran) with hydroxychloroquine (200 mg twice daily) for 7 days, or until death/hospitalization. All patients required a diagnostic CT scan for COVID-19 infection, according to the definition by the Iranian Society of Radiology.[13] The percentage lung involvement by ground glass opacity was recorded. Patients were followed-up at Days 1, 3, 5 and 7 for symptoms such as fever, sore throat, headache, xerostomia, myalgia, cough and olfactory disorder. At Days 1, 3 and 5 patients were followed-up by phone call and at Day 7 by a personal visit. At 30 days from enrolment, patients were followed-up by phone call to monitor fatigue, shortness of breath and anorexia. Patients in both arms were given training regarding adequate rest, quarantine principles and increasing respiratory capacity.

Outcomes

The primary endpoint was symptom alleviation by Day 7. Secondary endpoints included hospital admission and alleviation of symptoms (fatigue, shortness of breath and loss of appetite) after 30 days of follow-up.

Statistical analysis

Categorical variables were analysed using Fisher's exact test and continuous variables were compared using Mann–Whitney *U*-test. A *P* value was considered statistically significant at the $P < 0.05$ threshold. Statistical analysis was performed using Stata version 16.0; StataCorp.

Ethics

This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences (approval number IR.MAZUMS.REC.1399.017) on 1 April 2020. This trial is registered with the Iranian Registry of Clinical Trials (IRCT20200403046926N1).

Results

From 8 April 2020 to 19 May 2020, 62 patients were assessed for eligibility and 55 patients were enrolled. Of those enrolled, 27 patients were randomized to the sofosbuvir/daclatasvir group and 28 patients to the control group (Figure 1). The median age of patients was 43 (IQR 37–53), 26 patients (47%) were men versus 29 (53%) women. Twenty-one patients (38%) had underlying conditions (diabetes, hypertension and pulmonary disease). Age, sex and baseline demographics were similar across treatment arms (Table 1).

In the primary endpoint of symptom alleviation, there was no significant difference between the sofosbuvir/daclatasvir group and control arm in symptom response for fever, cough, sore throat, headache, myalgia, xerostomia and olfactory loss (Figure 2). The number of patients experiencing any symptoms decreased by Day 7; however, this was not significant. One patient was admitted to hospital in the sofosbuvir/daclatasvir group (4%) versus four in the control (14%), but this difference was non-significant $P = 0.352$ (Table 2). After one month of follow-up, significantly fewer patients in the sofosbuvir/daclatasvir group reported fatigue compared with the control group (2 versus 16, respectively, $P < 0.001$). Furthermore, the number of patients with dyspnoea was significantly lower in the sofosbuvir/daclatasvir group compared with control (4 versus 11, respectively, $P = 0.035$). No patients experienced loss of appetite in the sofosbuvir/daclatasvir group compared with three (12%) patients in the control group, and this difference was non-significant, $P = 0.111$ (Table 2).

Discussion

In this randomized controlled trial of mild COVID-19 outpatients, we showed that sofosbuvir/daclatasvir with hydroxychloroquine may significantly reduce the number of patients experiencing fatigue and dyspnoea after 30 days of follow-up compared with hydroxychloroquine alone. However, sofosbuvir/daclatasvir did not show efficacy in reducing the number of patients who experienced symptoms at Day 7 of follow-up, or the number of hospital admissions compared with the control group.

It is reasonable to assume that any efficacy shown in the trial may be attributed to sofosbuvir or daclatasvir. Current evidence

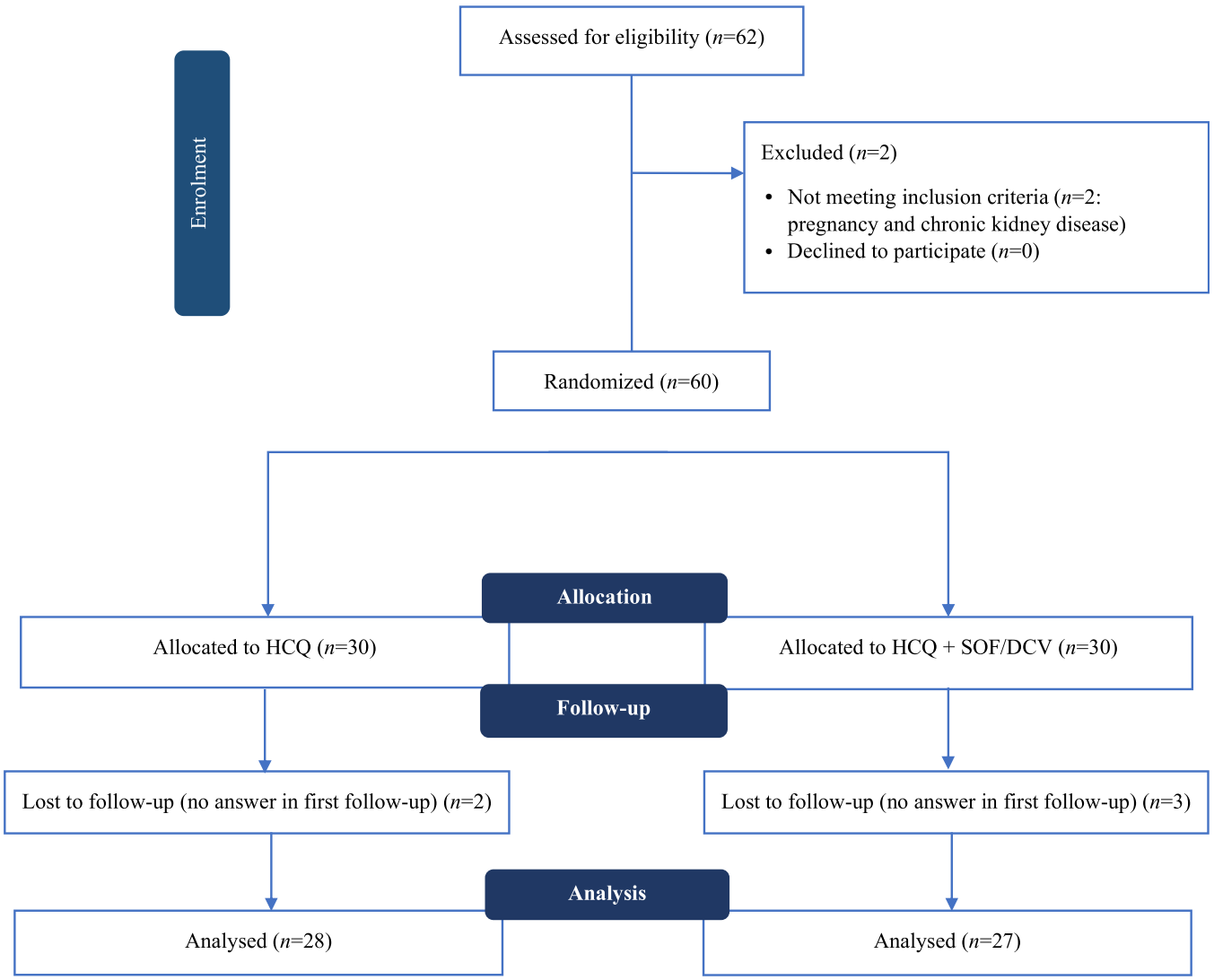

Figure 1. CONSORT 2010 flow diagram. HCQ, hydroxychloroquine; SOF/DCV, sofosbuvir/daclatasvir. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

suggests that hydroxychloroquine shows little efficacy against COVID-19, which has been removed from the UK RECOVERY Trial amidst potential cardiovascular adverse events.[14] Additionally, the hydroxychloroquine arm of the SOLIDARITY trial was halted and later resumed amidst this uncertainty.[15] Other candidate treatments such as favipiravir[16,17] and lopinavir/ritonavir[18] have not shown clear clinical benefit. Results from clinical trials investigating remdesivir have been mixed.[19–21] In a preliminary report, dexamethasone demonstrated improved survival for those who required oxygen or mechanical ventilation; however, no benefit was found in patients with milder disease.[22]

Currently, there is no medicine proven to be effective for treating COVID patients in an Outpatient Department (OPD) setting. Remdesivir and dexamethasone show potential benefit for hospitalized, severe patients. However, as an IV drug, remdesivir would be an impractical treatment for mild patients in an OPD setting. It stands to reason that if treatment is initiated earlier in the course of the disease, better results would be obtained. Having an oral treatment for COVID would allow this. There is already some evidence that sofosbuvir/daclatasvir is helpful in hospitalized patients.[9–11] Treating patients in an outpatient setting has the potential to reduce hospital admissions. It should also be noted that the combination of sofosbuvir/daclatasvir is remarkably safe as proven by years of experience in hepatitis C where patients with advanced cirrhosis and renal failure have been treated for 12 or 24 weeks without significant adverse events.[2,23,24]

This study has several key limitations. Primarily, assessment of symptom outcomes was not carried out using an objective grading system and therefore results are subject to information bias. More objective measures such as CRP status or lymphocyte count are required to measure the clinical effect of sofosbuvir/daclatasvir. However, viral load tests are restricted for diagnosis only by the Iranian government and cannot be used to measure treatment response. The small sample size of this study is another limitation and, therefore, future studies with larger sample sizes are warranted to reduce the risk of type II error.

Table 1. Baseline characteristics

	SOF/DCV ($n = 27$)	Control ($n = 28$)	*P* value
Age (years), median (IQR)	43 (37–52)	47.5 (37–53)	0.643
Male, *n* (%)	12 (44)	14 (50)	0.789
BMI (kg), median (IQR)	27 (25–33)	26 (23–30)	0.293
Comorbidities, *n* (%)	13 (48)	8 (27)	0.171
Oxygen saturation	98 (97–98)	98 (97–99)	0.834
SBP (mmHg), median (IQR)	120 (110–130)	120 (110–128)	0.572
DBP (mmHg), median (IQR)	80 (75–80)	80 (80–80)	0.821
Ground glass opacity, *n* (%)			
5%	3 (11)	6 (21)	0.646
25%	7 (26)	6 (21)	
50%	16 (59)	16 (57)	
75%	1 (4)	0 (0)	

SOF/DCV, sofosbuvir/daclatasvir; SBP, systolic blood pressure; DBP, diastolic blood pressure.
P values calculated using Fisher's exact test for categorical outcomes and Mann–Whitney *U*-test for continuous outcomes.

Table 2. Clinical outcomes

	SOF/DCV ($n = 27$)	Control ($n = 28$)	*P* value
Hospital admission, *n* (%)	1 (4)	4 (14)	0.352
Fatigue Day 30, *n* (%)	2 (7)	16 (62), $n = 26$	<0.001
Anosmia Day 30, *n* (%)	0 (0)	3 (12), $n = 26$	0.111
Dyspnoea Day 30, *n* (%)	4 (15)	11 (42), $n = 26$	0.035
Any symptoms, *n* (%)[a]			
Day 1	27 (100)	26 (93)	0.49
Day 3	16 (59)	15 (54)	0.79
Day 5	12 (44)	12 (43)	1.00
Day 7	7 (26)	7 (28)	1.00

SOF/DCV, sofosbuvir/daclatasvir.
P values calculated using Fisher's exact test for categorical outcomes and Mann–Whitney *U*-test for continuous outcomes.
Percentages calculated from non-missing values.
[a]Any of fever, sore throat, headache, stiff neck, myalgia, cough or olfactory loss.

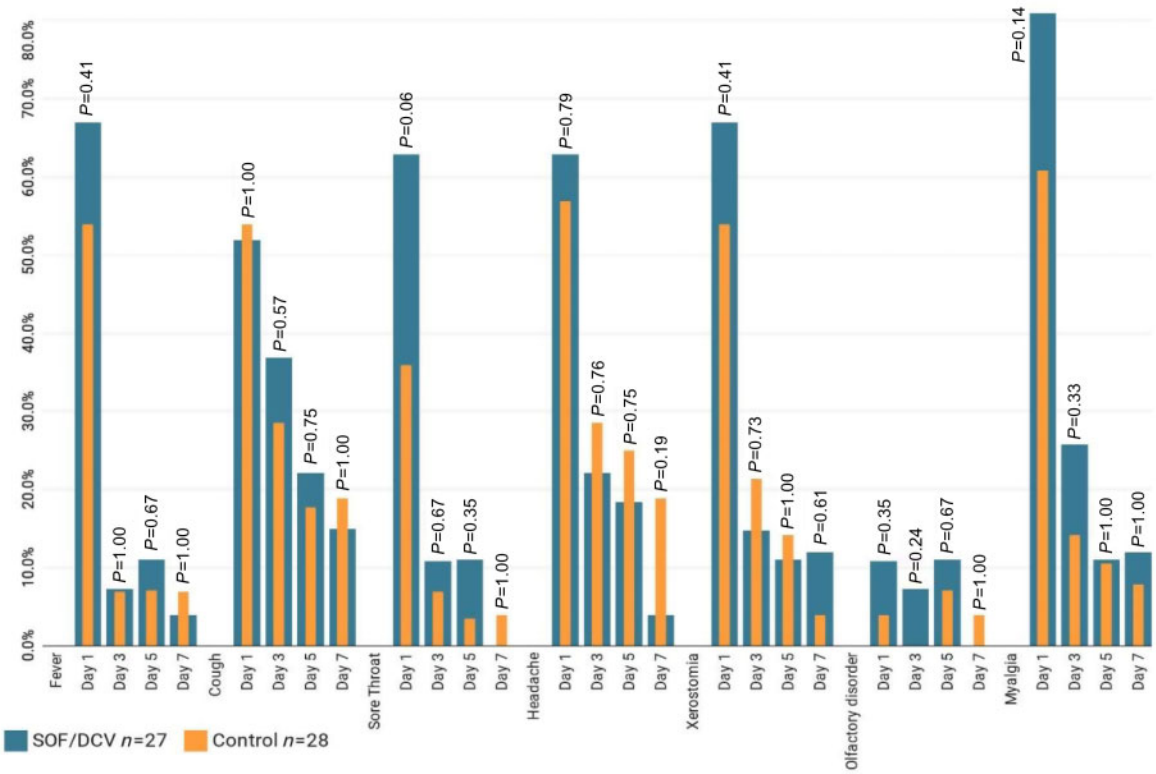

Figure 2. Treatment response monitoring. SOF/DCV, sofosbuvir/daclatasvir. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Overall, sofosbuvir/daclatasvir improves fatigue and dyspnoea after 30 days of follow-up. The long-term effects of COVID-19 remain unclear; emerging reports indicate that symptoms such as fatigue and dyspnoea may persist for longer than 2 weeks in mild patients.[25,26] Larger, well designed trials with longer follow-up times are needed to validate the efficacy of sofosbuvir/daclatasvir in an outpatient setting. Given the small number of outcomes in OPD patients, such a study would require a much larger sample size and should probably be multicentre.

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Transparency declarations

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

F.R., R.A.-N., M.S., A.H.-O. and A.S. designed the study. R.A.-N., H.W. and A.H. worked on the statistical analysis. A.S. wrote the first draft of the manuscript. J.L., S.M., H.W., M.S. and A.H.-O. helped with the preparation of the manuscript. All authors confirmed the final published version.

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