Efficacy of sofosbuvir/daclatasvir in moderate and severe COVID-19 infection: the DISCOVER trial.

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Background: Sofosbuvir/daclatasvir has shown preliminary efficacy for patients with COVID-19 in five open-label studies. However, these trials were open-label, one was not properly randomised and the sample sizes were small. The aim of this larger trial was to assess if the addition of sofosbuvir (SOF) and daclatasvir (DCV) to standard care improved clinical outcomes in patients with moderate or severe COVID-19.

Methods: This was a placebo-controlled, double-blind, multicentre, randomised controlled clinical trial in adults with moderate or severe COVID-19 admitted to hospitals in Iran. Patients were randomised in a 1:1 ratio to SOF/DCV 400/60mg once-daily plus standard care or matching placebo alone. Patients were included if they were ≥18 years old; O_2 saturation <95%; PCR or diagnostic chest CT scan and had any one of: fever (oral temperature ≥ 37.8 °C), dry cough, severe fatigue or dyspnoea. The primary efficacy endpoint was discharge from hospital within 10 days of first treatment; secondary endpoint was survival (Intent To Treat population). The trial is registered on the Iran Registry of Clinical Trials https://www.irct.ir/trial/49198.

Results: Between July and October 2020, 1082 patients were recruited and allocated to either the SOF/DCV treatment arm (n=541) or matching placebo (n=541). At baseline, 54% of patients were male with median age 58 (Range 46-69). Co-morbidities included diabetes (28%) and hypertension (34%). Hospital discharge within 10 days was achieved by 475/541 (88%) in the SOF/DCV arm and 479/541 (89%) in the placebo control arm (relative risk = 0.99, 95% CI = 0.95-1.04). Overall the death rates were 67/541 (12%) in the SOF/DCV group versus 57/541 (11%) in the placebo group (relative risk = 1.18, 95% CI = 0.85-1.60).

Conclusions: In this randomised placebo-controlled trial of 1082 patients with moderate or severe COVID-19 infection, there was no significant effect of SOF/DCV versus placebo on the rate of hospital discharge or survival. However, the patient population were moderate to severe cases who had reported symptoms a median of 7 days prior to dosing, which may be too advanced and too late for antiviral drugs to be effective. SOF/DCV should now be evaluated in earlier stages of infection, at higher doses, and in combination with other antiviral drugs.

	SOF/DCV n=541	Control n=541	p-value
Baseline Characteristics			
Age, median (IQR)	57 (45,69)	59 (46,69)	
Male, n(%)	291 (54%)	293 (54%)	
O_2 Saturation %, median (IQR)	90 (88,93)	90 (87,93)	
Diabetes, n(%)	153 (28%)	146 (27%)	
Hypertension, n(%)	187 (35%)	181 (34%)	
Days since onset of symptoms	7 (5,8)	7 (5,9)	
Outcomes			
10-day discharge, n(%)	475 (88%)	479 (89%)	0.707[1]
Time to hospital discharge, days median	7 (5,11)	7 (5,11)	0.708[2]
Overall mortality, n(%)	67 (12%)	57 (11%)	0.318[1]
Time to death, days median	10 (6,16)	10 (6,14)	

[1]p-value for relative risk calculated using Pearson's Chi-squared test.
[2]Estimated from the cumulative incidence function, accounting for death as a competing risk; p-value is for Fine and Gray competing risk regression.