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TREATMENT OF HEPATITIS C WITH DIRECT ACTING ANTIVIRAL DRUGS CAN PROTECT AGAINST SEVERE ACUTE RESPIRATORY SYNDROME CORONA VIRUS 2 INFECTION

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Abstract

Owing to the similarity between SARS-CoV-2 and hepatitis C virus (both SARS-CoV-2 Mpro protease and HCV NS3/4A protease are double B-barrel folded with similar orientation), and based on molecular docking models, many researchers suggested using hepatitis C direct acting antiviral drugs (DAAs) for the treatment of SARS-CoV-2 infection.

Aims & Methods:

This study aimed to estimate the prevalence of SARS-CoV-2 infection among chronic hepatitis C patients receiving treatment with sofosbuvir plus daclatasvir in comparison to chronic hepatitis C patients who finished treatment course one year before COVID-19 pandemic (control group). 500 chronic hepatitis C patients were included in our study who was receiving treatment with sofosbuvir plus daclatasvir (study group) during COVID-19 pandemic (March to September 2020) in comparison to matched 500 individuals who finished treatment course for hepatitis C one year (March to September 2019) before COVID-19 pandemic (control group). Both groups were followed up for 6 months starting from March 2020 up to September 2020. Baseline demographic data, comorbidities, history of confirmed diagnosis of with SARS-CoV-2 infection, or close contact with confirmed or suspected cases were compared in both groups.

Results:

Our study included 1000 participants (500 in each group), mean age ± SD was 48.45 ± 7.68 in the study group and 47.67 ± 10.56in the control group (p value=0.18). Most of participants in the study were males, 400 (80%) in the study group and 380 (76%) in the control group. No significant differences were present in baseline characteristics including area of residence (rural versus urban), level of education, work in medical field, smoking, presence of liver cirrhosis or other comorbidities (Diabetes mellitus, Hypertension, Chest diseases, Cardiac disease, Autoimmune disease or Obesity). In the study group 22 (4.4%) patients had contact with SARS-CoV-2 infected patient while in the control group 24 (4.8%) individuals had contact with SARS-CoV-2 infected patient (p value=0.88). Patient receiving chronic hepatitis C treatment with sofosbuvir plus daclatasvir had a lower rate of SARS-CoV-2 infection (2.2%, 11 SARS-CoV-2 infections) than individuals in the control group (6%, 30 SARS-CoV-2 infections) with p value =0.002.

Introduction

Coronaviruses are a single-stranded RNA viruses. Where RNA is translated into numerous proteins; structural proteins (S, N, M and E proteins) and non-structural proteins (nsp12, RdRp and proteases (PLpro and 3CLpro). COVID-19 is a member of Beta coronaviruses family which include; Severe Acute Respiratory Syndrome Human coronavirus (SARS HCoV) and Middle-East Respiratory Syndrome Human coronavirus (MERS HCoV) (1)

Six different strains are known for Human coronaviruses (HCoVs), in addition to newly emerged COVID-19. 229E and NL63 strains of HCoVs belong to Alphacoronaviruses meanwhile OC43, HKU1, SARS, MERS, and COVID-19 human coronaviruses belong to Beta coronaviruses. SARS and MERS HCoV are the most aggressive strains of coronaviruses. SARS has a 10% mortality rate, while MERS has a 36% mortality rate, according to the WHO statistics. (2)

In December 2019, several patients in Wuhan, Hubei, China were diagnosed with pneumonia secondary to an unknown virus. An epidemiological alert was placed with the World Health Organization (WHO) on December 31st, 2019. On January 7th,2020 Chinese scientists had isolated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Later, SARS-CoV-2, the cause of coronavirus disease 2019 (COVID-19), spread across the globe resulting in the current pandemic. (3)

Different clinical pictures were reported but most cases had fever, dyspnea, fatigue, generalized aches, myalgia and dry cough. Although most cases of Covid-19 have very satisfactory clinical

course, few cases require hospital admission and oxygen therapy, and fewer cases develop cytokine storm and other fatal complication. (4)

Despite efforts for quarantining and social distancing, avoiding contact among infected and uninfected individuals and trials to diminish transmission rates, it's evident that long-term control and prevention of COVID-19 dependents on effective antivirals and vaccination. (4-5).

Solidarity WHO's global clinical trial had selected four drug interventions: lopinavir (LPV)/ritonavir (RTV), together with interferon B (IFN-β) or alone, chloroquine (CQ) and remdesivir (RDV) as treatment options for COVID- 19. Very early treatment with RDV showed promising results in non-human primates and clinical studies (6). Neither Hydroxychloroquine nor lopinavir/ritonavir produced reduction in the mortality of hospitalized COVID-19 patients when compared to standard of care. (7)

Direct-acting antivirals (DAAs) against hepatitis C virus (HCV) are among the safest antiviral agents proposed as they were routinely used during the last five years. Drugs like daclatasvir and sofosbuvir (SOF) were not systematically tested against SARS-CoV or MERS-CoV.1,2

Many clinically approved drugs have been reused in treatment of patients with COVID-19, however lack of safety studies and limited efficiency risks clinical benefits. Daclatasvir and sofosbuvir (SOF) are clinically approved direct-acting antivirals (DAAs) against hepatitis C virus (HCV), with satisfactory safety profile. (8)3

In HCV replicative cycle, daclatasvir and Sofosbuvir target certain viral enzymes which are NS5A and NS5B, respectively. NS5A is endowed with pleotropic activities, overlapping with several proteins from SARS CoV-2. HCV NS5B and SARS-CoV-2 nsp12 are RNA polymerases that share homology in the nucleotide uptake channel. These characteristics of the HCV and SARS-CoV-2 gives hope for further studying the activity of daclatasvir and SOF against the new coronavirus. (9)

Many researchers suggested HCV antiviral medication for the treatment of Covid-19 supported by the recently published molecular docking models. The availability of direct acting antiviral "DAAs" in Egypt makes it feasible to investigate its efficacy in treatment of COVID-19 (5)

Egypt is currently undertaken by the global pandemic of COVID-19 and the fact that HCV represents an endemic disease where numerous patients are receiving DAAs simultaneously makes it an optimal time to study the effect of DAAs in the context of COVID-19 pandemic. (5) in this study we aimed to estimate the prevalence of SARS-CoV-2 infection among chronic hepatitis C patients receiving treatment with sofosbuvir plus daclatasvir in comparison to chronic hepatitis C patients who finished treatment course one year before COVID-19 pandemic.

Methodology

Chronic hepatitis C patients seeking treatment at National committee for Control of Viral Hepatitis (NCCVH) centers between March 2020 and September 2020 were prospectively enrolled (study group). Baseline demographic data, laboratory investigations and ultrasound abdomen results, history of confirmed diagnosis with SARS-CoV-2 infection, or close contact with confirmed or suspected cases were recorded. Patients were followed-up to report any emerging SARS- CoV-2 infection during or after DAAs therapy up to week 24 after completion of treatment course. SARS-CoV-2 infection was defined according to the Ministry of health and population definitions of suspected and confirmed cases. The following additional data were collected from confirmed cases of SARS-CoV-2: history of hospital admission, disease severity and clinical outcomes. A historical control group of chronic hepatitis C patients who have completed treatment course with DAAs one year before starting the study (before March 2019) were also recruited (control group). Baseline demographic data, laboratory investigations and ultrasound abdomen results, history of confirmed diagnosis with SARS-CoV-2 infection, or close contact with confirmed or suspected cases were recorded for the control group also. Comparison between the two study groups was done by Chi square test or fisher exact test as appropriate and independent t test; using SPSS vs.24 . Significance level was set at 0.05 to detect the prevalence of suspected or confirmed SARS-CoV-2 infection. Patients with previous confirmed diagnosis of SARS-CoV-2 before starting the study were excluded. Informed consent was obtained from all participants and confidentiality of data was maintained during the study. The study

was implemented after approval of NCCVH research ethics committee approval.
Statistical analysis

Results

Our study included 1000 chronic hepatitis C patients (500 in each group). Both groups had insignificant differences as regard baseline data (P> 0.05). Majority of both groups were males and came from rural areas. Liver cirrhosis was present in 110 (22%) and 81 (18.2%) patients of control and study group, respectively. Sixty-seven (13.4%) patient of the control group and 63 (12.6%) of the study group were health care workers. Other baseline data are summarized at table 1.

Table 1: Baseline data of enrolled groups

	Control group (n=500)	Study group (n= 500)	*P* value
Age (years)	47.7 ± 10.6	48.5 ± 7.7	0.18
Sex			0.14
Male	380 (76%)	400 (80%)	
Female	120 (24%)	100 (20%)	
Liver cirrhosis	110 (22%)	91 (18.2%)	0.15
Residence			0.87
Rural	400 (80%)	403 (81.6%)	
Urban	100 (20%)	97 (19.4%)	
Education level			0.09
Illiterate	285 (57%)	270 (54%)	
Read/write	80 (16%)	100 (20%)	
Below university	120 (24%)	115 (23%)	
University	15 (3%)	15 (3%)	
Working at medical field	67 (13.4%)	63 (12.6%)	0.77
Occupation			0.11
Skilled	205 (41%)	207 (41.4%)	
Employee	109 (21.8%)	112 (22.4%)	
Housewife	100 (20%)	95 (19%)	
Retired	35 (7%)	37 (7.4%)	
Others	51 (10.2%)	49 (9.8%)	
Smoking	49 (9.8%)	53 (10.6%)	0.75

Data expressed as frequency (percentage), mean ±SD. P value was significant if < 0.05

The most frequent comorbidities among the studied groups were hypertension and diabetes mellitus. Chest diseases included asthma and obstructive lung diseases were present in 17 (3.4%) patients of the control group and 21 (4.2%) patients of the study group. Different comorbidities showed no significant differences between both groups (P> 0.05).

Table 2: Comorbidities among enrolled groups

	Control group (n=500)	Study group (n= 500)	*P* value
Diabetes mellitus	92 (18.4%)	102 (20.4%)	0.47
Hypertension	112 (22.4%)	107 (21.4%)	0.75
Chest diseases	17 (3.4%)	21 (4.2%)	0.61
Cardiac disease	16 (3.2%)	17 (3.4%)	0.99
Autoimmune disease	5 (1%)	8 (1.6%)	0.57
Obesity	24 (4.8%)	28 (5.6%)	0.66

Data expressed as frequency (percentage). *P* value was significant if < 0.05

Both groups had insignificant differences as regard contact with infected person with COVID-19 24 (4.8%) vs. 22 (4.4%); P= 0.88) but the frequency of confirmed infection with COVID-19 was

significantly higher among the control group (30 (6%) vs. 11 (2.2%); P= 0.03), figure 1.

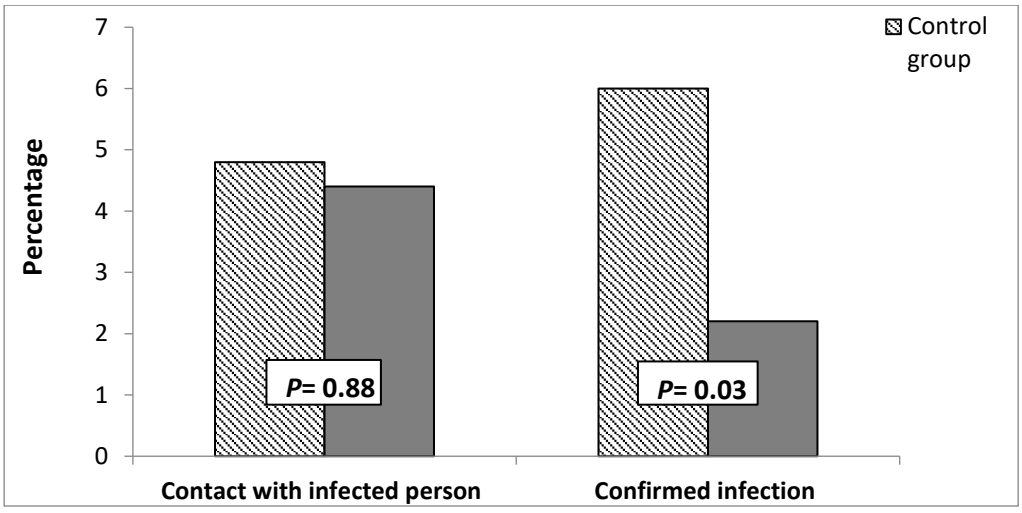

Figure 1: Confirmed Infection and contact with COVID-19 patient among the studied group

There were no significant differences between both groups as regard severity and outcome of the disease. It was found that two patients in the control group and one patient from the study group had severe disease and all of them were admitted to ICU, deteriorated, and died (Table 3).

Table 3: Severity and outcome among confirmed cases with COVID-19

	Control group (n=6)	Study group (n=11)	*P* value
Severity of disease			0.44
Mild	1 (16.7%)	3 (27.3%)	
Moderate	3 (50%)	7 (63.6%)	
Severe	2 (33.3%)	1 (9.1%)	
Outcome			0.21
Alive	4 (66.7%)	10 (90.9%)	
Dead	2 (33.3%)	1 (9.1%)	

Data expressed as frequency (percentage). *P* value was significant if < 0.05

Discussion

In Egypt, there has been an increasing number of cases of COVID-19 infection since March 2020. Several treatment protocols for treating coronavirus infection have been updated based on the evidence available at that time (10-13)4. Many researchers suggested HCV antiviral medication for the treatment of Covid-19 supported by the recently published molecular docking models. The availability of direct acting antiviral "DAAs" in Egypt makes it feasible to investigate its efficacy in treatment of COVID-19 (5)3. The current study aimed to estimate the prevalence of SARS-CoV-2 infections in chronic hepatitis C patients receiving DAAs in comparison to chronic hepatitis C patients who finished treatment course one year before COVID-19 pandemic. Both groups had insignificant differences as regard to baseline data and In different comorbidities.

In the current study, both groups had insignificant differences as regard contact with infected person with COVID-19. However, the frequency of confirmed infection with COVID-19 was significantly higher among the control group. These results may validate the value of sofosbuvir based regimens in preventing COVID-19 infection. Recently, 5 studies (14-17)3 investigated if sofosbuvir plus daclatasvir was effective in combination with mild to severe disease COVID-19 patients. All of them found a beneficial effect of Sofosbuvir-daclatasvir on the outcome of COVID-19 patients; however, most of the differences between sofosbuvir-daclatasvir and comparatives in terms of these clinical outcomes, such as clinical recovery and the length of hospital stay did not reach statistical

significance.only one Egypian study found that their use was associated with shorter hospital stay,faster PCR negativity and may be reduced mortality in COVID -19 patients with pneumonia. The insignificant differences can be attributed to the small case number in each study. Therefore, all four studies concluded the need for further study on a large scale. The promising results of these small samples encouraged further trials of the effectiveness of sofosbuvir and daclatasvir for treating COVID-19.

In the clinical study by Abbaspour Kasgari et al. 2020 (14), there was no significant difference in the number of deaths in patients who received Sofosbuvir based regimen (0 versus 3, $P = 0.234$). This was also postulated by Sadeghi et al. 2020 (16) study which included 66 COVID-19 patients, three patients died in the treatment arm and five in the control arm. However, in a study by Eslami et al. 2020 (15); the mortality in the sofosbuvir/daclatasvir group was 2/35 (6%) and 9/27 (33%) for the ribavirin group with a significant difference.

The main limitation of this study is being conducted only on Egyptian patients only which may need validation of its results in other populations before its results become generalizable.

Conclusion and recomendtaions

Patients treated with Sofosbuvir plus Daclatasvir had a lower rate of SARS-CoV-2 infection. This study may validate the value of sofosbuvir-based regimens in preventing COVID-19 infection. More international multicenter studies are needed to generalize these findings.

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