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ORIGINAL ARTICLE

Safety of B-blockers in Patients with Chronic Hepatitis C under Treatment with sofosbuvir and Daclatasvir

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Abstract: Background: It's known that hepatitis C virus (HCV) one of the major health problems worldwide. Direct acting analogues (DAAs) are tolerable effective and safe agents for therapy of HCV. Till now, there are confirmed documentations about cardiovascular effects of DAAs. **Aim of the work:** this work was designed to determine safety of B-blockers use in chronic HCV patients under treatment with sofosbuvir. **Methodology:** A case control study was carried out on 60 patients with chronic HCV not hypertensive (control group) and 60 patients with chronic HCV and hypertensive on beta blockers therapy (study group). All patients were subjected to evaluation with electrocardiography at baseline before therapy and each month for three months of therapy. **Results**: There was no statistically significant difference between the studied groups as regard heart block. Only one patient in control group and 8 patients in study group developed heart block. **Conclusion**: Patients with underlying cardiovascular disease should be closely monitored if they receive sofosbuvir for HCV infection.

INTRODUCTION

HEpatitis C virus is known to be associated with an elevated risk of cardiovascular disease[1]. Direct antiviral drugs (DAA) ushered in a new era in HCV therapy. In clinical studies, these medicines demonstrated high sustained viral response (SVR) rates of around 90%, shorter treatments, reduced toxicity, and interferon-free regimens. Sofosbuvir (SOF) and daclatasvir (DCV) have been authorized for use in the treatment of HCV[2].

Clinical investigations on the combination of SOF and DCV show that it is one of the most promising antiviral treatments, with acceptable tolerability, low drug–drug interactions, and strong antiviral potency, with 90% SVR rates, among current HCV therapy regimens. Furthermore, the SOF/DCV combination shows potential because it is pangenotypic and easier to apply than other combinations[3].

The FDA approved a label update for SOF in March 2015, following a series of studies by Gilead Science, Inc. that documented symptomatic bradycardia occurrences in nine persons treated with SOF in combination with another DAA and amiodarone. This update said that bradycardia events frequently occur within hours to days, and a safety warning was issued to persons using amiodarone for cardiac testing[4].

There is no sufficient evidence regarding the interaction between SOF and B-blockers so, this study was designed to describe the effect of SOF treatment on ECG in chronic HCV patients. Also, assess safety of B-blocker use with SOF treatment in chronic HCV patients.

PATIENTS AND METHODS

Ethical consideration

Informed consent was obtained from all participants after being informed about the aims and process of the study as well as applicable objectives. The study was performed in accordance with the Declaration of Helsinki on medical protocol and ethics. It was approved by Institutional Review Board, Faculty of Medicine of Aswan University.

Study setting& design

A case control study was conducted in Outpatients Clinic in duration between 2019 and 2020.

Participants

The study enrolled 120 patients who were divided into; Group (A): Patients with chronic HCV not hypertensive, Group (B): Patients with chronic HCV and hypertensive on B-blocker treatment with confirmatory investigations for chronic HCV.

All recruited patients were eligible for therapy with SOF plus DCL either for three months (in case of absence of cirrhosis) and six months in presence of cirrhosis.

Any patient with one or more of the following was excluded; decompensated liver cirrhosis (encephalopathy, ascites, and bleeding varices); other aetiologies of liver disease as autoimmune hepatitis, chronic hepatitis B, or combined

chronic hepatitis B and C, advanced renal impairment, uncontrolled thyroid functions, previous history of cardiac diseases, severe psychiatric disorders, diabetes mellitus, patients on calcium channel blocker treatment, or patients on anti-arrhythmias treatment.

Methodology

All participants were subjected to through history taking with full clinical evaluation. The following data were gathered; age, sex, occupation, smoking, complaint, and previous history of antiviral or antibilharzial therapy.

Although baseline laboratory data were ordered; complete blood count, serum bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), creatinine, urea, coagulation profile, hepatitis B surface antigen, alpha feto protein (AFP) and quantitative HCV-RNA detection using real-time polymerase chain reaction (PCR). Abdominal ultrasonography (US) was done.

Electrocardiograph (ECG) was done for all patients at baseline and repeated monthly for 3 months till the end of treatment course. ECG was fully assessed particularly; prolonged QT interval, heart rate, P-R interval, QRS complex, presence of arrhythmias, supraventricular extrasystoles, ST-T wave changes, and corrected QT interval using the following formula: QTc = QT interval/√RR interval.

Statistical analysis

Analysis of data was done using Statistical Program for Social Science version 20 (SPSS Inc., Chicago, IL, USA). Quantitative variables expressed as mean and SD and compared by Student t test while qualitative variables expressed as frequency (percentage) and compared by chi-square (X2) test. Repeated ANOVA test was used to compare duration of PR, QRS and corrected QT interval at different times of follow up in each group. Level of confidence was kept at 95% and hence, *P* value was significant if < 0.05

RESULTS

Baseline data of studied groups (table 1):

Both groups had insignificant diffrences as regard baseline data (*P*> 0.5). It was found that majority of both groups was males and only three patients in each group were interferon experienced.

Baseline laboratory data of studied groups (table 2):

Both studied groups showed no significant diffrences as regard baseline laboratory data (*P*> 0.05). It

was found that 20 (33.3%) and 21 (35%) patient of group A and group B, respectively were cirrhotic based on ultrasound.

Frequency of heart block and baseline heat rate among studied groups (table 3):

As regard development of different degrees of heart block, both groups showed no significant difference while there was high significant difference between the two studied groups as regard mean heart rate. It was found that 52 years-old male patient experienced 1st degree heart block in the 3rd month of treatment in group A experienced.

In case of group B four patients experienced 1st degree heart block; 1) 62 years old male patient on bisoprolol 10 mg, occurred in the 2nd months of treatment course, 2) 58 years old male patient on bisoprolol 5 mg, occurred in the 3rd months of treatment course, 3) 54 years old female patient on bisoprolol 5 mg, occurred in the 3rd months of treatment course and 4) 62 years old female patient on propranolol 120 mg, occurred in the 1st month of treatment course

None of patients in group A experienced 2nd degree heart block, but in group B 3 patients experienced 2nd degree heart block as following: 1) 49 years old female patient on bisoprolol 5 mg, experienced 2nd degree heart block (Mobitz I), occurred in the 3rd month of treatment course, 2) 59 years old male patient on bisoprolol 5 mg, experienced 2nd degree heart block (Mobitz I), occurred in the 3rd month of treatment course, and 3) 48 years old female patient on propranolol 80 mg, experienced 2nd degree (Mobitz II) occurred in the 2nd month of treatment course.

There are no patients in group A experienced complete heart block, while in group B only 62 years old male patient on bisoprolol 5 mg, experienced complete heart block after the second month of treatment course. This patient was hemodynamically unstable, temporary peacing was done. The patient regained the sinus rhythm after 5 days of discontinuation of bisoprolol 5 mg.

Changes in PR duration in studied groups (table 4):

It was found that there was high statistically significant difference between studied groups as regard PR duration in each month but in each separate group there was no significant change in PR duration at different times of follow up in comparison to baseline data.

Changes in QRS complex duration in tudied groups (table 5):

It was found that there was no statistically significant difference between studied groups as regard QRS complex duration in each month. Also, in each separate group there was no significant change in QRS complex duration at different times of follow up in comparison to baseline data.

Changes in QTc duration in studied groups (table 6):

It was found that there was no statistically significant difference between studied groups as regards QTc complex duration in each month. Also, in each separate group there was no significant change in QTc complex duration at different times of follow up in comparison to baseline data.

DISCUSSION

Sofosbuvir is a novel direct-acting pyrimidine nucleotide analogue antiviral medication that has demonstrated outstanding effectiveness in clinical studies for the treatment of hepatitis C. However, anecdotal observational evidence recently showed an elevated risk of severe bradycardia in individuals receiving sofosbuvir with amiodarone[5].

In recent decades, hepatologists have prioritized the discovery of safe and effective therapies for hepatitis C virus (HCV) infection. The period of interferon (IFN)-based therapy regimens was plagued by frequent, severe adverse effects that need close monitoring and rapid care of problems, while sustained virologic response (SVR) rates were frequently poor. (**Zanetto et al., 2017)**[6].

With the development of all oral treatments in the last several years, the treatment of HCV has taken a significant stride forward. Direct-acting antiviral drugs (DAAs) have subsequently transformed HCV patient care, attaining high eradication rates while maintaining an outstanding safety profile[7].

The limitations imposed by IFN therapies have been abolished, and SVR rates have consistently surpassed 90%, independent of the antiviral regimen used. These surprising and stunning findings led to the notion that HCV might be practically eliminated and on a worldwide scale, disrupting the disease's natural course without causing any serious adverse effects[7].

The main objective of this study was the assessment of safety of B-blockers use in chronic HCV patients under treatment with sofosbuvir and daclatasvir. A Prospective follow-up study was carried out on 60 patients

with chronic HCV not hypertensive and 60 patients with chronic HCV and hypertensive. Majority of patients was males with no significant difference between both groups as regard baseline data.

In line with the current study **Villanueva et al. (2019)**[8] as they reported that there was no statistically significant difference between the studied groups regarding age and sex. The majority of both groups were males with mean of age 57 years.

The current study showed no significant diffrences as regard baseline laboratory data between both groups. In contrast, **Alkareemy et al. (2020)**[9] found that there is highly significant difference between the two studied groups as regard ALT. This discrepancy between the current study and this study may be due to different sample size and selection bias.

Also, the current study showed that there was no statistically significant difference between the studied groups as regard heart block, while there was high significant difference between the two studied groups as regard mean heart rate.

It has been demonstrated that up to 50% of individuals with severe liver cirrhosis may experience cardiac malfunction, a disease known as cirrhotic cardiomyopathy. At rest, such individuals have normal or enhanced cardiac output, but their reaction to stress is muted. In addition, they may have QT interval prolongation and chronotropic incompetence[10].

We found that there was high statistically significant difference between studied groups as regard PR duration in each month. There was no statistically significant difference between the studied groups or among the different periods in the same group as regard QRS duration. There was no statistically significant difference between the different periods as regard QTc duration.

Our results are supported by **Ibrahim et al. (2020)**[11] concluded that treatment had no effect on QTc interval, LV systolic and diastolic functions, and RV functions.

In 2017 **Durante-Mangoni et al**. **(2017)**[12] examined the ECG of 39 HCV infection patients treated with either a sofosbuvir- (n = 26) or a non-sofosbuvir-based treatment (n = 13). ECG tracings were obtained on the first day of treatment then after 7, 14, and 28 days. Their results showed that for the sofosbuvir group QTc interval significantly increased at 1 week (p = 0.013) then returned to baseline values

later during therapy till the end of treatment.

Lagrutta et al. (2016)[13] concluded drug–drug interactions between DAAs and b-blockers are not expected, but they of course may increase the risk of bradycardia by their mechanism of action itself.

The main limitation of the current study included; 1) relatively small sample size with short duration of follow up, 2) there was t weak cooperation of some of the of patients and their relatives, 3) patients with compensated cirrhosis on 6 months regimen monitored only for three months, so we recommend prolonged monitoring.

Based on the current study we recommended; 1) further studies on larger sample size and large geographical scale to emphasize our conclusion, 2) patients with cardiovascular disease (CVDs) are mostly victims of DDIs with DAAs. Therefore, when possible, monitoring of pharmacodynamics is recommended when co-administering these drugs with DAAs, and 3) prolonged monitoring for patients with compensated cirrhosis on 6 months regimen.

CONCLUSION

Using of sofosbuvir with B-blockers found to associate with decreasing in the heart rate and increasing in PR interval. While there was no strong evidence for heart block, increase in QRS complex width, no ST-T wave changes, or increase in QTC duration. So, patients on sofosbuvir and B-blockers treatment should be strictly monitored for ECG changes during the course of treatment.

Table (1): Baseline data of enrolled groups

	Group A (n = 60)		Group B (n = 60)		p
	No.	**%**	**No.**	**%**	
Gender					
Male	40	66.7	36	60.0	0.449
Female	20	33.3	24	40.0	
INF experienced	3	5.0	3	5.0	1.000
Age group (years)					
30 – < 40	9	15.0	8	13.3	0.081
40 – < 50	7	11.7	18	30.0	
50 – <60	27	45.0	18	30.0	
≥ 60	17	28.3	16	26.7	
Mean age	53.75 ± 10.15		51.78 ± 10.11		0.290

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. INF: interferon. **Group (A):** Patients with chronic HCV not hypertensive**, Group (B):** Patients with chronic HCV and hypertensive on B-blocker treatment.

Table (2): Baseline laboratory data and ultrasound findings of studied groups

	Group A (n = 60)	Group B (n = 60)	p
Log_{10} HCV RNA	4.99 ± 1.13	4.76 ± 1.13	0.261
AST (u/l)	71.68 ± 53.38	71.68 ± 53.38	0.102
ALT (u/l)	69.36 ± 50.86	69.36 ± 50.86	0.091
Bilirubin (mg/dl)	0.88 ± 0.28	0.86 ± 0.28	0.124
Direct bilirubin (mg/dl)	0.32 ± 0.18	0.31 ± 0.11	0.230
Albumin (mg/dl)	4.02 ± 0.47	4.05 ± 0.46	0.370
Hemoglobin (g/dl)	12.39 ± 1.36	13.37 ± 1.33	0.098
Leucocyte (10^3/ul)	6.43 ± 1.76	6.47 ± 1.71	0.390
Platelets (10^3/ul)	205.16 ± 62.78	238.82 ± 51.05	0.190
Creatinine (mg/dl)	1.10 ± 0.11	1.17 ± 0.17	0.770
Urea (mg/dl)	3.67 ± 1.90	4.11 ± 2.20	0.100
INR	1.03 ± 0.10	1.02 ± 0.10	0.090
AFP (ng/dl)	3.04 ± 1.23	3.33 ± 1.98	0.761
Liver cirrhosis by US	20 (33.3%)	21 (35%)	0.847

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. INF: interferon. Group (A): Patients with chronic HCV not hypertensive, Group (B): Patients with chronic HCV and hypertensive on B-blocker treatment. HCV RNA: hepatitis C viral ribonucleic acid; ALT: alanine transaminase; AST: aspartate transaminase; INR: international randomized ratio; US: ultrasound

Table (3): Frequency of heart block and baseline heat rate among studied groups

	Group A (n = 60)		Group B (n = 60)		p
	No.	**%**	**No.**	**%**	
1st degree Heart block	1	1.7	4	6.7	0.170
2nd degree Heart block	0	0.0	3	5.0	0.079
Complete heart block:	0	0.0	1	1.7	0.3174
ST-T wave change	0	0	0	0	
Heart rate (beat/minute)	67.99 ± 4.13		60.76 ± 2.13		<0.001

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. INF: interferon. **Group (A):** Patients with chronic HCV not hypertensive**, Group (B):** Patients with chronic HCV and hypertensive on B-blocker treatment.

Table (4): Changes in PR duration in studied groups

	Start (n =60)	1st month (n =60)	2nd month (n = 60)	3rd month (n =60)	p
Group A	147.66 ± 7.94	148.65 ± 7.98	149.68 ± 7.84	150.63 ± 7.69	0.18
Group B	162.31 ± 10.03	163.32 ± 10.02	164.21 ± 10.05	165.10 ± 10.03	0.466
p0		0.304	0.511	0.742	
p1	< 0.001	< 0.001	< 0.001	< 0.001	

Data expressed as mean (SD). *P* value was significant if < 0.05. INF: interferon. **Group (A):** Patients with chronic HCV not hypertensive**, Group (B):** Patients with chronic HCV and hypertensive on B-blocker treatment.

p: p value for association between different periods**, p_0: p value** for association between start with each other periods**, p_1: p value** for comparing between the studied groups in each period

Table (5): Changes in QRS complex duration in studied groups

	Start (n =60)	1st month (n =60)	2nd month (n = 60)	3rd month (n =60)	p
Group A	90.07 ± 6.11	90.98 ± 6.12	91.91 ± 6.07	92.75 ± 5.94	0.089
Group B	90.32 ± 7.89	91.26 ± 7.89	92.18 ± 7.85	93.20 ± 7.69	0.217
p0		0.624	0.353	0.170	
p1	0.722	0.837	0.826	0.848	

Data expressed as mean (SD). *P* value was significant if < 0.05. INF: interferon. **Group (A):** Patients with chronic HCV not hypertensive**, Group (B):** Patients with chronic HCV and hypertensive on B-blocker treatment.

p: p value for association between different periods**, p_0: p value** for association between start with each other periods**, p_1: p value** for comparing between the studied groups in each period

Table (6): Changes in QTc duration in studied groups

	Start (n =60)	1st month (n =60)	2nd month (n = 60)	3rd month (n =60)	p
Group A	419.05 ± 7.41	418.13 ± 8.33	417.67 ± 9.28	416.80 ± 8.32	0.211
Group B	421.71 ± 5.52	419.08 ± 5.95	416.34 ± 5.69	414.17 ± 5.86	0.074
p0		0.678	0.239	0.104	
p1	0.115	0.108	0.106	0.087	

Data expressed as mean (SD). *P* value was significant if < 0.05. INF: interferon. **Group (A):** Patients with chronic HCV not hypertensive**, Group (B):** Patients with chronic HCV and hypertensive on B-blocker treatment.

p: p value for association between different periods**, p_0: p value** for association between start with each other periods**, p_1: p value** for comparing between the studied groups in each period

Authors' contributions:

Mohamed Zain Eldin Hafez (study design and revising manuscript critically for important intellectual content)

Wael Abdelgwad Abdelaziz Elsayed (interpretation of data, and revising manuscript)

Ayman Maher Asham Ibrahim (interpretation of data, and revising manuscript)

Muhammad Nasser Muhammad Ajlan (acquisition of data, analysis and interpretation of data, and drafting the manuscript)

All authors have approved the final article for submission

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