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Assessment of Patient Compliance during treatment of chronic hepatitis C infection using Sofosbuvir and Daclatasvir with or without Ribavirin.

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Abstract

Background: Direct-acting antivirals (DAAs) are well-tolerated drugs for the treatment of chronic hepatitis C infection (CHC). We aimed to assess the patient compliance during DAAs treatment of CHC.

Materials and Methods: The study included 371 CHC patients commencing DAAs therapy. The socioeconomic status of patients was assessed at index time. Three questions were asked to all patients to determine their attitude towards DAAs. All patients were asked at each visit about drug adherence and side effects using a questionnaire. Adherence was measured using two equations; the first was Continuous, Single Interval Measure of Medication Gaps (CSG) = Number of days without any medication/total days in the interval and the second was, Pill count = (Number of dosage units dispensed-number of dosage units remained)/ (prescribed number of dosage unit per day× number of days between 2 visits).

Results: Out of 371 patients included in the study only, 368 patients continued the study divided into two groups; group (A) included 184 patients received (Sofosbuvir plus Daclatasvir) and group (B) included 184 received (Sofosbuvir plus Daclatasvir and Ribavirin). The adherence to DAAs was 99% in group A versus 100% in group B with no significant difference in CSG, pill count, and several days with improper timing of dosage between the two groups. The common side effects noticed in both groups were fatigue and headache.

Conclusions*:* Treatment of chronic hepatitis C infection, using Sofosbuvir plus Daclatasvir with or without Ribavirin, is well tolerated with very high adherence and few side effects.

Introduction

Chronic hepatitis C virus (HCV) infection is a universally prevalent pathogen leading to liver cirrhosis and liver cancer [1,2]. Hepatitis C viral infection is endemic in Egypt with the highest prevalence rate in the world [3, 4]. Until recently, the standard of care for treatment of chronic hepatitis Chas included a combination of pegylated interferon and ribavirin, administered to the patients for 24 to 48 weeks, according to HCV genotype with sustained virological response (SVR) rate nearly about 50% [5]. Approval of direct-acting antivirals (DAAs) substantial progress in the treatment of hepatitis C virus [6, 7].

The new interferon-free direct-acting antiviral-based regimens reportedly have a substantially higher efficacy rate with minimal side effects and excellent adherence [8-10]. Adherence is defined as; the extent to which the patient's behavior with drug administration matches the agreed recommendation from the prescriber. This refers to a process, in which the appropriate treatment is decided after a proper discussion with the patient [11]. Adherence to drugs is associated with high SVR rates.

In contrast, suboptimal exposure to therapy is associated with biological breakthrough or post-treatment relapse and the emergence of resistance-associated variants, especially during the early phase of treatment [9]. Evaluating adherence to DAAs regimens is vital to translating the high efficacy of these regimens. In particular, adherence is important to attaining the maximal rate of SVR from a treatment regimen, avoiding treatment failure and /or the development of DAAs resistance [12].

There are many factors affecting drug tolerability and adherence such as co-morbid depression, poor access to health care, limited or no insurance coverage, drug, and alcohol abuse [13]. This study aims to evaluate patient compliance during treatment of CHC using (Sofosbuvir plus Daclatasvir) with or without Ribavirin and to determine possible causes of non-compliance.

Materials and methods

This prospective observational cohort study included 371 patients with chronic hepatitis C. The patients aged more than 18 years from Mansoura Specialized Medical Hospital (Virology Outpatient Clinic) from April 2017 to March 2018. Patients were divided into two groups based on anti-viral therapy given according to the National treatment program in Egypt [14].

Inclusion criteria:

1. Patients with CHC eligible for DAAs treatment.
2. Child-Turcotte Pugh class (A).
3. Patients aged ≥ 18 years.

Keywords: Chronic hepatitis C infection; adherence; Sofosbuvir; Daclatasvir; Ribavirin.
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4. Patients who agreed to participate and signed informed written consent.

Exclusion criteria:

1. Patients not eligible for treatment, including malignancy, HBVcoinfection, and pregnancy.
2. Child-Turcotte Pugh class (B and C).
3. Patients aged < 18 years.
4. Patients who refused to participate.

Demographic data for enrolled cases were collected at the initial assessment visit to the Virology Unit.

Clinical and laboratory data for enrolled cases were collected at the initial assessment visit to the Virology Unit, then at 2, 4, 8, and 12-weeks of treatment.

Socioeconomic status (SES) was assessed by SES for health research in Egypt [15].

Pre-treatment attitude towards DAAs:

Three questions were asked to all patients to determine their attitude towards DAAs:

Q1- If he/she would be able to take medications as directed?

Q2- If the medication would have a positive effect on your health?

Q3- If he/she did not take the medication as instructed, HCV would not respond well to the medication? [16].

Adherence to drug schedule:

Every patient was asked if every dose of each drug was taken as prescribed, missed, or doubled, and if any side effect (s) occurred. This was adapted from Morisky Medication-Taking Adherence Scale (MMAS-8) [17].

Adherence was measured using two equations.

1. Continuous, Single Interval Measure of Medication Gaps (CSG) =Number of days without any medication/total days in the interval.
2. Pill counting = (Number of dosage units dispensed - number of dosage units remained)/ (prescribed number of dosage unit per day × number of days between 2 visits), [18] this means (as taken vs. as prescribed).

Sample size:

The sample size was calculated using PASS 2008 software (version 08.0.15), based on the results of a meta-analysis by [19] on genotype 1. We hypothesized that in our prevalent genotype 4 which behaves in a rather similar way to genotype 1 [20], adding ribavirin to Sofosbuvir plus Daclatasvir would increase drug discontinuation rate (DDR) from 0.9% to 9%.

Group sample sizes of 184 in group one (Sofosbuvir+Daclatasvir) and 184 in group two (Sofosbuvir+ Daclatasvir+Ribavirin) achieve 95% power to detect a difference between the group proportions of 0.0810. The DDR in group one (the dual treatment group) is assumed to be 0.090 under the null hypothesis and 0.00900 under the alternative hypothesis. The proportion in group two (the triple treatment group) is 0.090. The test statistic used is the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.0500. The dropout rate is expected to be very low.

Statistical analysis

Data were entered and analyzed using IBM-SPSS software (Version 25.0), and MedCalc Statistical Software (version 18.9.1). Qualitative data were expressed as absolute frequency (N) and percentage (%). Quantitative data were initially tested for normality using Shapiro-Wilk's test with data being normally distributed if p>0.050. The presence of significant outliers (extreme values) was tested by inspecting box plots.

Quantitative data were expressed as Mean ± standard deviation if normally distributed or Median (25th – 75th percentiles) if not normally distributed. Chi-Square or Fisher's exact test was used to compare categorical data. Quantitative data between two groups were compared by Independent-Samples t-Test if normally distributed or Mann-Whitney U-test if not.

Quantitative data between more than two groups were compared by Kruskal Wallis H-test (non-normally distributed data). For any of the used tests, results were considered statistically significant if p-value ≤ 0.050. Appropriate charts were used to graphically present the results whenever needed.

Results

The study included 371 CHC patients commencing DAAs therapy, three patients were missed from follow up and the remaining 368 patients completed the study to the end. The 368 patients were divided into; Group A included 184 patients who were treated by Sofosbuvir plus Daclatasvir and Group B, included 184 patients were treated by Sofosbuvir plus Daclatasvir plus Ribavirin.

(Table 1) shows, statistically significantly higher age of group B vs. group A with non-significant gender difference between both groups and a statistically significantly lower BMI in group A versus group B. Moreover, statistically, significantly higher TLC, platelet count, FBG, and albumin in group A Vs. group B. Statistically significantly higher INR, ALT, serum creatinine, and bilirubin in group B Vs. group A. No statistically significant difference in AST, AFP, and hemoglobin between the two groups.

Comparing the socioeconomic standard (SES), there was no statistically significant difference in SES in the two study groups (P = 0.201) **(Figure 1)**.

(Table 2) shows**,** a statistically significant difference in Q2 distribution between the two study groups, but not for Q1 and Q3. It, also, was found that, no statistically significant correlation between socioeconomic standard (SES) score and any of the three attitude questions (P = 0.831 for Q1, P = 0.923 for Q2 P = 0.261 for Q3).

(Table 3) shows no statistically significant difference in Medication adherence measures using Continuous, Single Interval Measure of Medication Gaps (CSG), (quantitative and qualitative) between the two groups. Compliance was very high (99% in group A vs. 100% in group B).

Table 1. Demographic and laboratory data of the studied blood donors.

Lab parameter	Group A (N = 184)	Group B (N = 184)	Z score	*P*-value
Age/years	51 (33- 65)	53 (43-66)	2.826	0.005
Sex: m/f	73 / 111	89 / 95	χ^2=2.823	0.093*
BMI (IQR)	28.7-33.7	29.3-35.1	2.421	0.015
Hemoglobin (gm/dl)	12 (11.6-12.9)	12 (11.8-12.5)	0.105	0.916
TLC (10^3/mm^3)	6.2 (5.3-7.8)	5.8 (4.9-6.5)	2.807	0.005
Platelet (10^3/mm^3)	225 (198-270)	122 (115-130)	16.595	<0.001
INR	1 (1.0-1.02)	1.45 (1.3-1.8)	16.909	<0.001
AST (IU/L)	60 (52-71)	62 (65-72)	1.803	0.071
ALT (IU/L)	50 (42-62)	52 (45-63)	2.449	0.014
Serum creatinine (mg/dl)	1 (0.8-1)	1 (0.9-1.03)	3.458	0.001
FBG	99 (96-106)	97 (95-102)	3.421	0.001
AFP (ng/ml)	7.5 (5.2-10)	6.7 (4.9-9.4)	1.679	0.093
Serum bilirubin (mg/dl)	0.9 (0.6-1.02)	1.5 (1.4-1.6)	16.632	<0.001
Serum albumin (gm/dl)	4.2 (3.9-4.3)	3 (2.9-3.2)	16.589	<0.001

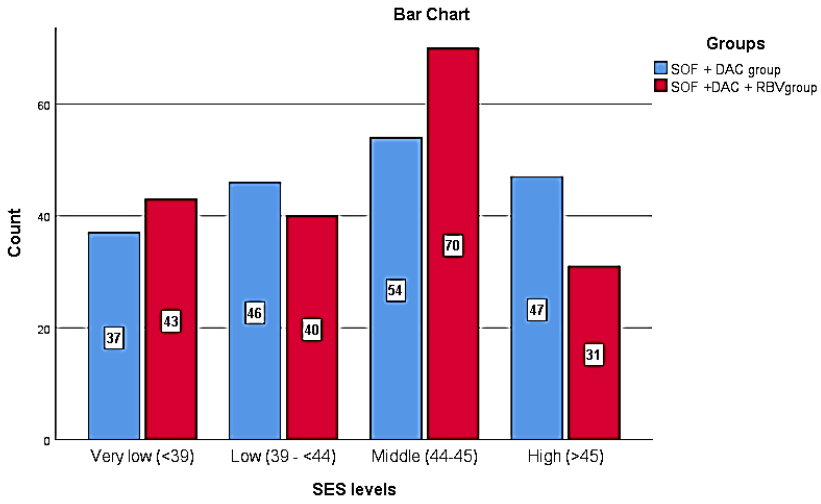

Figure 1. Socioeconomic standard in the two study groups.

Table 2. Pre-treatment patients' attitude towards DAAs in the two study groups:

Question	Group A (N = 184)	Group B (N = 184)	χ^2	*P*-value
Q1: You will be able to take medications as directed?				
Somewhat sure:	10 (5.4%)	10 (5.4%)	0.000	1.000
Definitely sure:	174 (94.6%)	174 (94.6%)		
Q2: The medication will have a positive effect on your health?				
Not sure:	11 (6%) a	11 (6%) a	FET	0.047**
Somewhat sure:	173 (94%) a	167 (90.8%) a		
Definitely sure:	0 (0%) a	6 (3.3%) b		
Q3: If you do not take the medication as instructed, HCV will not respond well to the medication?			2.823	0.093
Somewhat sure:	111 (60.3%)	95 (51.6%)		
Definitely sure:	73 (39.7%)	89 (48.4%)		

Table 3. Continuous Single Interval Measure of Medication Gaps (CSG) in the two study groups both quantitative and qualitative:

Statistic	Group A (N of patients = 184)	Group B (N of patients = 184)	Statistic	*P*-value
Quantitative[CSG (= Number of days without any medications/84)]				
Median	0.0	0.0		
IQR	0.0-0.0	0.0-0.0	Z = 1.416	0.157*
Range	0.0-0.4.0	0.0-0.0		
Qualitative[Number of patients having 0,2or 3 days without medications]				
0 days	182(99%)	184(100%)		
2 days	1(0.5%)	0.0	FET	0.504**
3 days	1(0.5%)	0.0		

Table 4. Pill count of Sofosbuvir and Daclatasvir in the two study groups.

Statistic	Group A (N = 184)	Group B (N = 184)	Statistic	*P*-value
Quantitative				
Median	1.0	1.0		
IQR	1.0-1.0	1.0-1.0	Z = 0.435	0.664*
Range	0.96-1.0	0.99-1.0		
Qualitative				
Frequency:				
0.96	1 (0.5%)	0 (0%)		
0.98	1 (0.5%)	0 (0%)	FET	0.251**
0.99	0 (0%)	3 (1.6%)		
1.00	182 (99%)	181 (98.4%)		

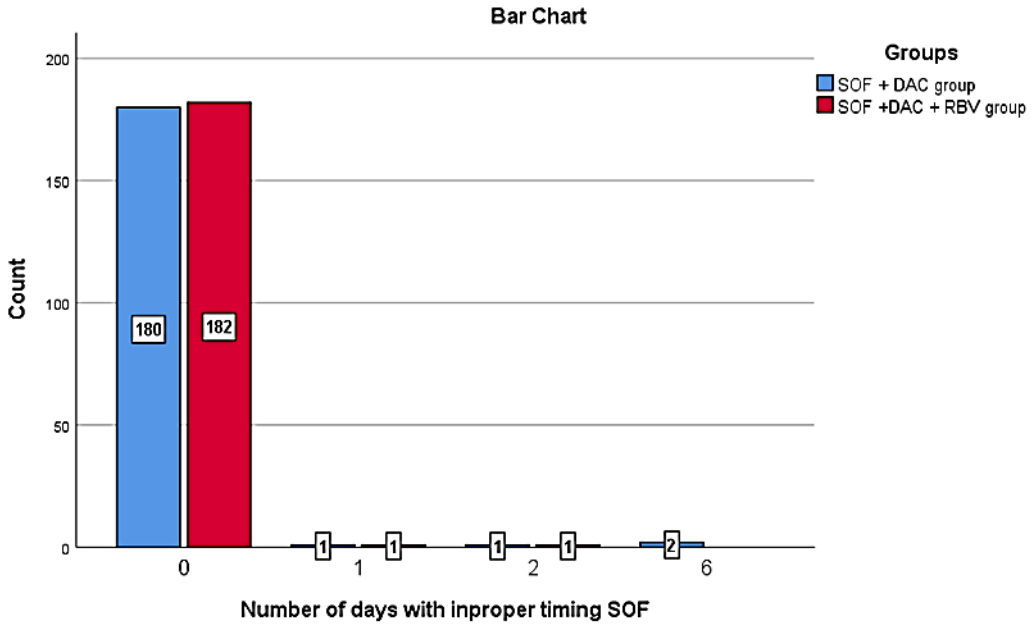

Figure 2. Improper timing of dosages (Sofosbuvir) same for (Daclatasvir)

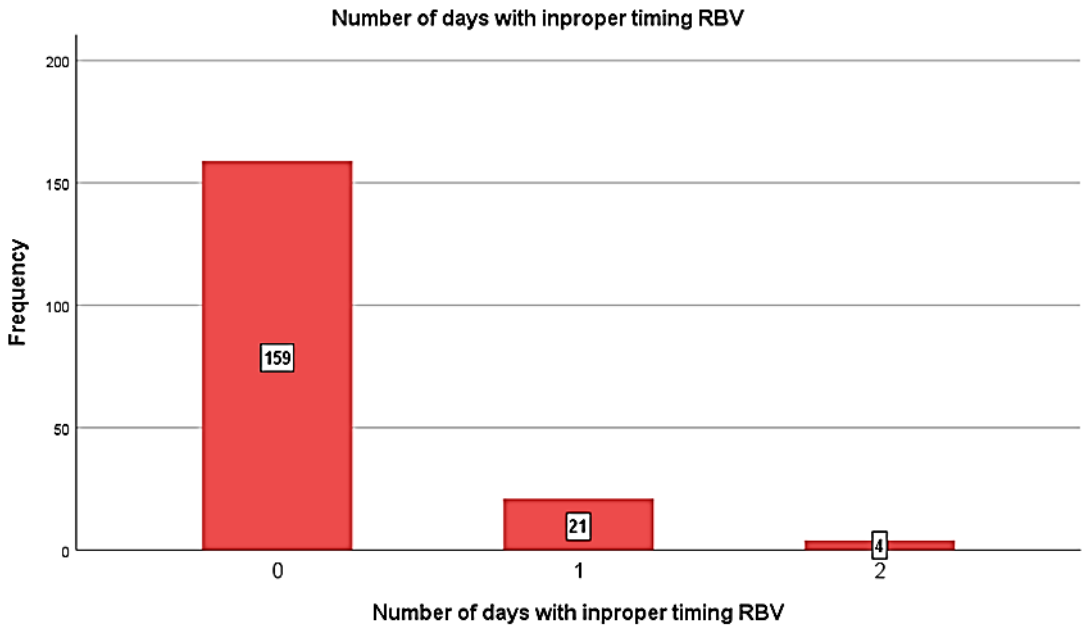

Figure 3. Improper timing of dosages (Ribavirin)

Table 5. Pill count of Ribavirin in the group (B).

Statistic	Group B (N of patients = 184)			Test of significance	
	(N = 63 patients) 252 doses (3 tablet*200mg)	(N = 60 patients) 336 doses (4 tablet*200mg)	(N = 61 patients) 420 doses (5 tablet*200mg)	**Statistic**	***P* value**
Quantitative assessment					
Median	1.0	1.0	1.0	KW = 0.379	0.827*
IQR	1.0-1.0	1.0-1.0	1.0-1.0		
Range	0.99-1.0	0.99-1.0	0.93-1.0		
Qualitative assessment					
Frequency:					
0.93	0 (0%)	0 (0%)	1 (1.6%)	FET	0.942**
0.99	2 (3.2%)	1 (1.7%)	1 (1.6%)		
1.00	61 (96.8)	59 (98.3%)	59 (96.7%)		

***P*-value*:** *KW=Kruskal Wallis H*, ***P* value**:** *Fisher's exact test (FET)*. **Patients received 252 doses:** *two patients missed 2 tablets (pill count=0.99)*. **Patients received 336 doses:** *one patients missed 2 tablets (pill count=0.99)*.**Patients received 420 doses:** *One patient missed 29 tablets (pill count =.093)*, one patient missed 5 tablets (pill count=0.99). **Pill count**= *1.00 means that no missed doses*

(Table 4) shows that, there was no statistically significant difference in SOF/DAC pill count between the two groups. Also, (Table 5) shows no statistically significant difference in ribavirn (RBV) pill count between the three dosages.

Moreover**,** no statistically significant difference in the number of days with improper timing of dosages of (SOF) and (DCV) between the two groups, quantitative [range=0-6 in group A and 0-2 in group B (*P* value = 0.406)], and qualitative (*P* = 0.875) (Figure 2). Also, (Figure 3) shows that, 159 patients (86.4%) in group B did not have any days of improper timing of dosages of RBV, 21 (11.4%) patients had only one day of improper timing of RBV doses and 4 (2.2%) patients had two days of improper timing of RBV doses.

As regards the side effects of the therapy, most of the patients complained of fatigue along the course of treatment. Some complained of headache and insomnia at two weeks of treatment (3 patients in group and 11 patients in group B). Few complained of musculoskeletal pain, flu-like symptoms at two weeks of treatment (3 patients in group A and 1 patient in group B). Only one patient in each

group complained of itching at two weeks of treatment. In group B, ten patients complained of anemia and jaundice at two weeks of treatment.

Discussion

By asking three pre-treatment questions regarding knowledge of patients about DAAs to determine their attitude towards DAAs, it showed a statistically significant difference in Q2 distribution between the two study groups but not for Q1 and Q3. Unpredictably, patients of group B were more optimistic about the medications. There was no statistically significant difference in SES between study groups which does not help us to find out association with compliance, and no statistically significant correlation between SES score and any of the three attitude questions. Although there was no significant difference as regards adherence to DAAs between the two studied groups (99% in group A versus 100% in group B), many factors could be explained the high adherence to DAAs in group B versus group A; The first is that a significant number of patients in group B were sure of that, the medication will have a positive effect on his health in comparison to patients in group A (question 2). This will give anticipation of high adherence of the patients to the therapy. The second was that two patients of group A had an improper timing of dosages of SOF and DCV for six days. The third was that the majority of patients in group B (86.4%) did not have any days of improper timing of dosages of RBV, which means good adherence to RBV that included a large number of capsules. The results of this paper as regards the high compliance of the patients to DAAs raising the importance of recommended pre-treatment questions regarding the attitude of the patients towards DAAs therapy. These questions made the patients more aware and more understanding of the value of the therapy and the importance of adherence to the DAAs. In our study, the compliance was very high (99% in group A vs. 100% in group B) using Continuous, Single Interval Measure of Medication Gaps (CSG) quantitative and qualitative. This is nearly similar to another study, which found a high compliance rate of 96% in 1483 patients treated with sofosbuvir + ledipasvir [21]. Another study comparing different drug regimen including 11 different DDAs medications, it found different compliance rates ranging from 31.43% up to 100 % [22]. Moreover, the high compliance rate may be due to treatment of all patients in structured HCV clinic, which optimize HCV therapy, this in concordance with other study comparing success rates of compliance and treatment of HCV in structured HCV clinic vs. general hepatology clinic [23]. Also, the high educational level of the patient himself or his relatives, regular follow-up visits, clear regimens, co-operative doctor, and pharmacist may be the causes of high compliance. The high cost of HCV treatment can affect patient's compliance, so cost-free regimens help achieve better compliance, our patients receive treatment cost-free which helps them to comply. Using pill count, the study showed no statistically significant difference in SOF/DAC pill count between the two groups. Dosage of Ribavirin differed among patients of Group B according to body weight, hemoglobin level, and tolerability. The study showed no statistically significant difference in RBV pill count between the three dosages. However, only one case in the 420 dosage group had a pill count of 0.93 and 4 cases had a pill count of 0.99 (2 in 252 doses group, 1 in 336 doses group, and 1 in 420 doses group). The majority of cases in all the three dosages had a pill count of 1.0. This is not agreed with Mathes et al, [24] who founded that higher RBV dose negatively affected compliance. Another aspect of adherence was improper timing of dosages. There was no statistically significant difference in the number of days with improper dosages of SOF and DCV between the two groups. One patient in group A and one in group B had an improper timing of dosages of SOF and DCV for one day. One patient in group A and one in group B had an improper timing of dosages of SOF and DCV for two days. Two patients of group A had an improper timing of dosages of SOF and DCV for six days. About RBV, 159 (86.4%) patients of group B did not have any days of improper timing of dosages of RBV, 21 (11.4%) patients had only one day of improper timing of RBV doses and 4 (2.2%) patients had two days of improper timing of RBV doses. One patient in the group (A) doubled the dosage of SOF/DAC for 7 days (the first week of treatment) due to an unclear regimen which was corrected in the next follow-up visit (two-week interval). One patient in the group (A) temporarily stopped treatment for 3 days to decrease pill burden and another patient in group (A) stopped treatment for 2 days due to side effects. Overall adherence was very high, with an average of 99% of DAA doses taken within the prescribed treatment period. In another study of 485 evaluable patients, 359 received DCV+SOF and 126 DCV+SOF+RBV, treatment was discontinued prematurely in 28 patients, including 10 who died in treatment. Sixteen DCV+SOF recipients (4%) discontinued treatment; the most common events leading to discontinuation were a multi-organs failure (n=4), sepsis (n=2), and hepatic encephalopathy (n=2). The discontinuation rate was higher (n=12, 10%) in DCV+SOF+RBV recipients; the most common events leading to discontinuation were general physical health deterioration (n=3), acute kidney injury (n=3), and hepatic failure (n=2) [25]. Regarding the adverse effects (AEs) of treatment in this study, data were classified as baseline symptoms and symptoms complained in each visit. As regards the side effects of the therapy, most of the patients complained of fatigue along the course of treatment. Some complained of headache and insomnia at two weeks of treatment (3 patients in the group and 11 patients in group B). Few complained of musculoskeletal pain, flu-like symptoms at two weeks of treatment (3 patients in group A

and 1 patient in group B). Only one patient in each group complained of itching at two weeks of treatment. In group B, ten patients complained of anemia and jaundice at two weeks of treatment. This came inconsistent with another study which showed that the most common side effects were non-specific, such as fatigue, headache, arthralgia, and gastrointestinal events [25]. Other colleagues showed that the most common AEs in both groups included in their study were fatigue, headache, anemia, cough, and sleeping disorders. Although most AEs were more common in patients treated with DCV + SOF + RBV for 24 weeks, these AEs cannot explain only by longer duration, since the differences between the groups were recorded during the first 12 weeks of treatment [26]. In another study, the most frequently reported AEs was fatigue followed by mild anemia. Overall, the rate of premature discontinuation because of adverse events was low. Most of the discontinued patients (7 out of 8 patients) were in the 60-65 age group while the single patient was in the older age group. All patients who stopped treatment, except one patient, did not achieve SVR12 [27]. The limitations of this study were, **e**nrolling only child patients who may be less susceptible to complications and single-center trials.

Conclusion

Adherence to DAAs (sofosbuvir + Daclatasvir with or without Ribavirin) is very high. However, follow-up is needed during treatment to encourage adherence. Recommended pre-treatment questions regarding the attitude of the patients towards DAAs therapy.

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