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Comparison between sustained virological response in week 2 (SVR 2) and sustained virological response in week 12 (SVR 12) in patients receiving Sofosbuvir plus Daclatasvir for chronic hepatitis C virus

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ABSTRACT

Infection of hepatitis C virus (HCV) is a chief reason of liver diseases globally. The oral direct acting antivirals (DAAs) introduction has significantly increased the possibility of achieving SVR and preventing hepatic decompensation. We aimed to evaluate the role of viral load in week 2 after end of treatment (SVR 2) as a predictor to sustained virological response at week 12 (SVR 12). This study included 200 patients receiving Sofosbuvir plus Daclatasvir for chronic HCV treatment recruited from Kasr Alainy Viral hepatitis Centre (KVHC) and from police hospitals, recruited from March 2017- March 2018, patients of this study were further classified according to previous HCV treatments into naïve group (186 patients) and experienced group (14 patients). Hepatitis C virus RNA had been measured by polymerase chain reaction (PCR) (quantitative) two weeks after stoppage of treatment (SVR 2) and compared to that 3 months after stoppage of treatment (SVR 12). Of 200 patients with chronic HCV receiving Sofosbuvir plus Daclatasvir for treatment, two patients (1%) were not responded to treatment and were positive at SVR2, so, 198 patients (99%) achieved SVR 2. Another two patients didn't achieve SVR 12 (2%) (relapsers), so, 196 patients (98%) achieved SVR 12. SVR 2 can predict SVR 12, but can't replace it. SVR12 is more reliable in evaluation of virological response after treatment. Sofosbuvir and daclatasvir showed a highly safety profile in treating HCV patients and well tolerability.

1. INTRODUCTION

Infection of chronic hepatitis C virus (HCV) is projected to affect 70-100 million people about 1% of the world populace [1], [2]. A major proportion of populace in Egypt infected with genotype 4 [3]. Management of HCV turned out to be more efficient after the emergence of diverse classes of direct antiviral agents (DAA), throughout last few years as they elevated the sustained virological responses (SVR) ratios from about 40% with the regimen of pegylated interferon (PEG) together with ribavirin (RBV) [4] to above 90% with DAA [5], [6]. Combinations of different DAAs classes offered the option of interferon-free treatments with high

cure rates [7].

A sustained virological response (SVR) is stated as "untraceable HCV RNA after completing treatment by 12 weeks (SVR12) or 24 weeks (SVR24)''.

The eradication of HCV infection is occurred in about more than 99% of SVR achieved patients [8].

Daclatasvir (DCV) inhibits HCV NS5A replication complex which is effective in opposition to HCV genotype 4 [9], [10]. Sofosbuvir (SOF) inhibits NS5B polymerase which is effective in opposition all HCV genotypes that displayed a high safety rates in addition to a barrier to resistance [11]. The two drugs together achieved a considerable rates of cure [12- 15], incorporating different situations as patients with progressive liver diseases, HIV-coinfection, haemodialysis and post-transplant patients [16].

In Egypt, Beginning from November 2015, SOF and DCV (with or without RBV) turn out to be the major regimen of treatment in the nationwide program, owing to a low cost relative to 80% of the low-price of the brand medications that were used, aiming to eliminate HCV infection in the country by treating all infected patients [17].

The purpose of this study was to assess the viral load role after 2 weeks from the end of treatment (SVR 2) as a predictor to sustained virological response 12

(SVR 12) in chronic hepatitis C virus patients receiving Sofosbuvir plus Daclatasvir for treatment.

2. Patient and methods

2.1 Study population

This study was conducted on 200 patients recruited from Kasr Alainy Viral hepatitis Centre (KVHC), Cairo University and from police hospitals in the period between March 2017 and March 2018 who were receiving Sofosbuvir plus Daclatasvir for chronic HCV treatment. This study was approved by the ethical committee of faculty of medicine, Cairo university institutional review board number 79-2016. Each patient signed a consent form before admission to the study.

The national program of HCV treatment in Egypt involved all patients aged more than 18 years with infection of chronic HCV, also, all phases of liver cirrhosis (F0-F4) were included.

Patients with combined infection of HBV and HCV, completely ablated hepatocellular carcinoma (as checked by triphasic CT or dynamic MRI) and the relapsed patients with prior interferon treatment or DAA-based regime were also allowed.

All patients with liver decompensation (occurrence of ascites and/or encephalopathy), other malignancies (excluding 2 years after malignancy-free interval), pregnancy and rejection to fulfil with contraception were excluded. The patients were further subdivided according to history of previous HCV treatment into pair of groups: naïve group (n: 186 patients) and experienced group (n: 14 patients). The naïve group received Sofosbuvir plus Daclatasvir +/- Ribavirin for 3 months but the experienced group received Sofosbuvir plus Daclatasvir with or without RBV for 6 months.

Patients were subjected to liver functions tests, liver enzymes, complete blood picture and viral load tests

before, during and after treatment. Fibrosis stage was evaluated by Fibroscan.

2.2 Medications

SOF administered in a daily dose of 400 mg, DCV administered in a dose of 60 mg per day.
The recommended dose of RBV was 1200 or 1000 mg daily in the patients weighted more than 75 kg or less than 75 kg respectively, in two separated doses.
Drug-drug interactions with patients' prescriptions were checked by the application of Liverpool University on smart phones or the internet site (http://www.hep-druginteractions.org/checker).

At the treatment completion Hepatitis C virus RNA was measured:

- At the time of treatment end; to assess end of treatment response (ETR).
- Two weeks afterwards treatment stoppage to assess the sustained virological response 2 (SVR 2).
- Three months after stoppage of treatment to assess the sustained virological response 12 (SVR 12).

3. Results

The demographic features of the studied 200 chronic HCV patients are displayed in table (1). The mean age of the studied patients was 45 ± 8.49 years (range: 22-69), 55% males, the mean BMI was 26.28± 4.20 kg/m2 (range: 16.7- 45.4).

Patients of this study are further classified according to previous HCV treatments into naïve group (186 patients) and experienced group (14 patients).

Platelets were significantly higher among naïve patients, while age, AST and INR were significantly higher among experienced patients as shown in (table 2).

The adverse effects observed during the study were headache observed in 25 patients, anemia in 8 patients, fatigue in 17 patients, rash in 6 patients, hyperbilirubinemia in 4 patients, diarrhea in 5 patients, insomnia in 9 patients and dizziness in 2 patients. Adverse effects were significantly higher in the group of patients attained Sofosbuvir + Daclatasvin + Ribavirin than in the other group as shown in (figure 1).

There are two patients who has end of treatment positive PCR and SVR 2 positive PCR (non-responder). There is statistically significant association between ETR and SVR 2 (P- value < 0.01) as shown in (table 3).

Two patients have end of treatment PCR positive (non-responder), another two patient don’t achieve SVR 12 (relapser).

There is statistically significant association between ETR and SVR 12 (P- value <0.01) as shown in (table 4).

There are two patients don’t achieve SVR 12 while achieving SVR 2 i.e. relapsed after 2 weeks end of treatment but before 12 weeks from the end of treatment.

There is statistically significant association between SVR 2 and SVR 12 (P- value < 0.01) as shown in (table 5).

Table 1 Demographic features of the patients

Variables	Mean	Range

Age (years)		45	22.0–69.0
BMI (kg/m2)		26.28	16.7-45.4
		No.	**%**
Gender	**Female**	90	45.0
	Male	110	55.0
History of previous treatment	**Naïve**	86	93.0
	Experienced	14	7.0

Table 2 Comparison between naïve and experienced groups according to demographics and laboratory data

	Previous Treatment	**Median**	**P-value**
Age	Naïve	43	0.023
	Experienced	59	
Hemoglobin	Naïve	13.4	0.27
	Experienced	12.3	
Platelets	Naïve	219	< 0.01
	Experienced	120	
HbA1c	Naïve	5.7	0.174
	Experienced	6.4	
ALT	Naïve	38	0.073
	Experienced	67	
AST	Naïve	36	< 0.01
	Experienced	88	
	Naïve	3.9	

Albumin	Experienced	3.3	< 0.01
INR	Naïve	1.1	< 0.01
	Experienced	1.4	
Portal Vein diameter	Naïve	1	< 0.01
	Experienced	1.4	

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Hb A1c: Glycosylated haemoglobin; INR: International Randomized Ratio.

Table 3 Comparison between ETR and SVR 2

			ETR		Total
			Responder	**Non responder**	
SVR2	**Responder**	**No.**	198	0	198
		%	99.0%	0.0%	99.0%
	Non responder	**No.**	0	2	2
		%	0.0%	100.0%	1.0%
Total		**No.**	198	2	200
		%	100.0%	100.0%	100.0%

P- Value < 0.01

Table 4 Comparison between ETR and SVR 12

			ETR		Total
			Responder	**Non responder**	
		No.	196	0	196

SVR12	**Responder**	**%**	98.0%	0.0%	98.0%
	Non responder	**No.**	0	4	4
		%	0%	100.0%	2.0%
Total		**No.**	196	4	200
		%	100.0%	100.0%	100.0%

P- Value < 0.01

Table 5 Comparison between SVR 2 and SVR 12

			PCR.		**Total**
			Negative	**Positive**	
Groups	**SVR12**	**No.**	196	4	200
		%	98%	2%	100%
	SVR2	**No.**	198	2	200
		%	99%	1%	100%

P- Value < 0.01

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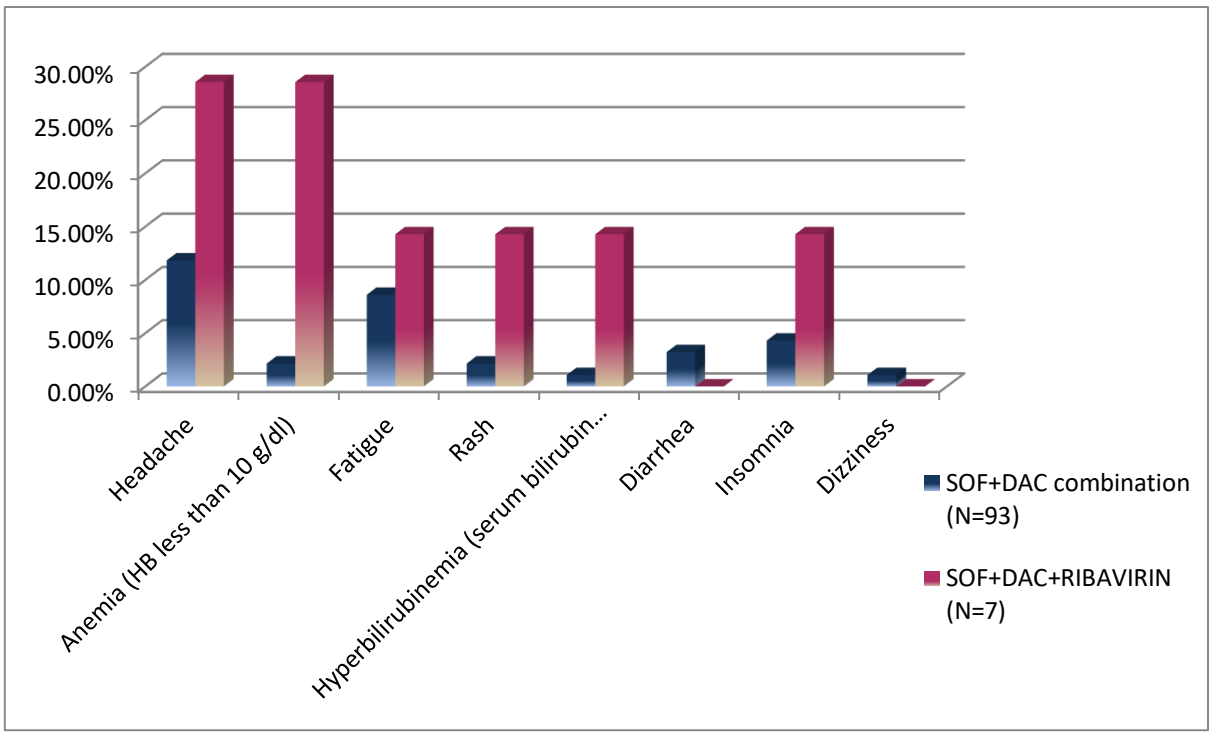

Figure 1 Side effects of SOF+DAC vs SOF+DAC+RIBA

4. Discussion

In this study, out of 200 patients received Sofosbuvir and Daclatasvir with or without ribavirin as a treatment for HCV, only two non-responded cases to treatment and two cases relapsed after 2 weeks from end of treatment, so, 98 (98%) patients achieved SVR 12. In study, SVR12 was accomplished in 88.9% of patients [18]. This could be clarified by the assessed group involved patients with treatment difficulty as prior treatment failure or progressive liver disease patients. An Egyptian study noted a high SVR12 in patients treated with Sofosbuvir and Daclatasvir in this large real-world 18378 patients. 95.1% accomplished SVR12 (95.4% in patients who treated without RBV and 94.7% in those received RBV [19].

In our study, out of 200 patients only two non-responder cases have positive SVR2 and there is another two positive cases appeared 2 weeks after end of treatment. So, 98.98% of patients that attained SVR 2 also reached SVR12.

These results are to be compared by studies comparing SVR4 with SVR12 i.e. who implemented a retrospective concordance study of SVR rates in 5 phase III clinical trials (NEU-TRINO, FISSION, POSITRON, FUSION, VALENCE) that evaluated the effectiveness of sofosbuvir-based regimes in patients with known virological outcomes, they concluded that Concordance of SVR rates, generally, 98% of patients who attained SVR4 also attained SVR12. Likewise, 99.7% of patients who attained SVR12 achieved SVR24 [20].

Observed that Sustained virological response adjusted after treatment by 12 weeks displays high rates of concordance to SVR at 24 weeks after treatment completion with DAAs regimes.

Hence, SVR12 is a proper valuable endpoint to estimate HCV eradication [21]. At this time, SVR4 is inappropriate because of the possibility of relapse post-treatment week 4.

Most relapses were noticed early after treatment, frequently in the earliest 4 weeks. Fortuitously, re-treatment is effective in utmost relapsed patients [22].

In this study, we tried to solve the problem of missing patients at follow up SVR 12 through prediction of response 2 weeks after treatment (SVR 2), SVR2 was achieved in 99% while, SVR12 was achieved in 98%, there is a significant association between SVR2 and SVR12, one patient only who relapsed after achieving SVR2, so SVR2 can predict SVR 12 but can`t replace it completely.

Lastly, we conclude that SVR12 is more reliable in evaluation of virological response after treatment and a proper valuable endpoint to estimate HCV eradication. Currently, SVR2 is inappropriate because of the possibility of relapse post-treatment week 4.

Abbreviations:
DAAs: direct-acting antivirals.
DAC: daclatasvir.
ETR: end of treatment response.
HCV: hepatitis C virus.
Peg-IFN: pegylated interferon.
PCR: polymerase chain reaction.
RBV: ribavirin.
RNA: ribonucleic acid.
SOF: sofosbuvir.
SVR: sustained virologic response.

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Declaration of Competing Interest
The authors declare that they have no known conflict of interest.

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