

## Pretreatment serum alpha fetoprotein and its relation to sustained virologic response in patients with chronic HCV infection treated with direct-acting antiviral therapy

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**Abstract:** *Background and study aim.* The introduction of directacting antiviral agents (DAAs) has increased sustained virologic response (SVR) rates in patients with chronic hepatitis C infection (CHC). The aim of this study is to evaluate the efficacy of DAAs in treatment of Egyptian patients with CHC, and to determine the parameters associated with non-response to DAAs. *Patients and methods.* This study included 200 treatment-naïve chronic hepatitis C patients who were divided into two groups and treated according to the Egyptian National Treatment Program for Hepatitis C Virus. Group 1 consisted of 100 easy-to-treat patients who were administered sofosbuvir 400 mg daily/daclatasvir 60 mg daily for 3 months, while group 2 included 100 difficult-to-treat patients treated by Sofosbuvir 400 mg/ daclatasvir 60 mg /ribavirin daily for 3 months. *Results.* The overall patient sustained virologic response (SVR) in the present study was 93.5% (187/200). SVR in group 1 was 100%, while group 2 showed SVR of 87% (87/100). Comparison between patients with and without SVR revealed no statistically significant differences regarding age and sex distribution, serum albumin, bilirubin, transaminases level, INR and platelets count. However, patients who were non-responders had significantly higher pre-treatment alpha fetoprotein (AFP) levels than responders. *Conclusions.* Treatment of CHC patients with DAAs is associated with higher sustained virologic response, particularly in easy-to-treat patients. AFP level may aid in prediction of non-responders to DAAs.

**Keywords:** Hepatitis C virus, Direct-acting antiviral agents, Sustained virologic response, Alpha fetoprotein.

### Introduction

Chronic infection with the hepatitis C virus often leads to progressive fibrosis and cirrhosis culminating in end-stage liver disease and hepatocellular carcinoma<sup>1</sup>. The primary objective of treatment of this infection is complete eradication of the virus. While interferon-based regimens had been the cornerstone of HCV therapy in the past, the recent introduction of direct acting antivirals (DAAs) with focused action on specific components of the virus has provided a

means of simple eradication of this virus<sup>2</sup>. Africa and the Middle East, including Egypt, have the highest rate of HCV genotype 4 infections<sup>3</sup>. Several real-world studies have shown high response rates of chronic HCV GT4 to therapy irrespective of the patients' cirrhotic state<sup>4</sup>. The most effective, and safe, being a combination Sofosbuvir / Daclatasvir with or without ribavirin for either 12 or 24 weeks. While patients without cirrhosis exhibited higher rates of SVR than cirrhotic patients, who demonstrated lower SVR12 rates in all treatment groups<sup>5</sup>, studies have concluded that this treatment regimen is the better option for chronic HCV GT4 patients with advanced liver fibrosis. The encouraging SVR rates achieved by Sofosbuvir/Daclatasvir have prompted HCV eradication campaigns in Egypt<sup>5,6</sup>. Virologic cure has been shown to universally decrease liver inflammation, mirrored by improved aminotransferase levels and decreased rates of liver fibrosis progression. In some patients, achieving SVR also leads to cirrhosis regression and improvement in clinical signs of portal hypertension and end-stage liver disease<sup>7</sup>. Several studies have demonstrated strong links between SVR and important reductions in the risk of HCC, liver-related mortality and liver transplantation<sup>8-10</sup>. The aim of this study is to evaluate the efficacy of DAAs in treatment of Egyptian patients with chronic hepatitis C, and to determine the parameters associated with non-response to DAAs.

### Patients and Methods

The present study was conducted at the Tropical Medicine and Internal Medicine Departments of Mansoura University Hospital, following approval of Mansoura Medical Research Ethics Committee. The study included 200 chronic hepatitis C patients treated according to National Treatment Program for Hepatitis C Virus in Egypt. Patients were divided into two groups. Group 1 included 100 easy-to-treat patients characterized by having total serum bilirubin  $\leq 1.2$  mg/dl, serum albumin  $\geq 3.5$  gm/dl, INR  $\geq 1.2$ , and only platelets count  $\geq 150,000$  m<sup>3</sup>. These patients were treated by sofosbuvir 400mg plus daclatasvir 60mg once daily for 3 months. Group 2 was comprised of



100 difficult-to- treat patients having serum bilirubin >1.2 mg/dl, serum albumin  $\leq$ 3.5 gm/dl, INR  $\leq$ 1.2, and/or platelets count <150000mm<sup>3</sup>. Treatment for these patients consisted of Sofosbuvir 400 mg plus Daclatasvir 60 mg once daily plus ribavirin for 3 months.

**Inclusion criteria**

The study included patients with chronic HCV infection diagnosed by positive PCR and eligible for treatment with direct acting antiviral therapy.

**Exclusion criteria**

Any other cause of chronic liver disease apart from HCV, such as chronic HBV infection, coinfection with HBV, hemochromatosis, alpha 1-antitrypsin deficiency, Wilson's disease, autoimmune disease, alcoholic liver disease, non-alcoholic fatty liver disease, hypersensitivity to ribavirin, as well as patients who were pregnant or breast-feeding. In addition, patients who had previously undergone anti-HCV therapy or those with decompensated cirrhosis or HCC were also excluded from the study. Patients with eGFR <30 ml/min or platelet count <50,000/mm<sup>3</sup> were referred for further pre-treatment assessment and were excluded from the current study.

**Laboratory and radiological investigation**

Patient work-up included liver function tests, e.g., serum albumin, serum bilirubin, alanine transaminase, aspartate transaminase, prothrombin time/international normalized ratio (INR), fasting blood sugar, serum creatinine, complete blood count, HBS antigen, HCV antibodies by ELISA, polymerase chain reaction for HCV, anti-nuclear antibodies, and alpha-fetoprotein. Ultrasound of liver was done in all patients and triphasic CT when indicated, such as to exclude malignancy.

**Study outcome**

The target outcome of the study was achievement of SVR at 12 weeks (SVR12) which was defined as undetectable HCV-RNA or that below the lower limit of quantification at 12 weeks after the last dose of treatment.

**Statistical analysis**

Data obtained from the present study were computed using SPSS Version 17 under the platform of Microsoft Windows 7. Continuous data were expressed in the form of mean  $\pm$  SD or median (IQR) while categorical data were expressed in the form of count and percent. Comparison of continuous data was performed utilizing student *t* test, while categorical data were done using the Chi - square test. A P value less than 0.05 was considered statistically significant.

**Results**

The present study included 200 chronic HCV patients treated by sofosbuvir 400 mg plus daclatasvir 60 mg once daily with or without ribavirin. **Table 1** shows the demographic data of patients revealing that, 122 patients were males and 78 patients were female with a mean age of 56 years. **Table 2** shows the laboratory data of the studied patients, who had a median viral load of  $3.59 \times 10^5$  and a median AFP of 3.42 ng/ml. The overall sustained virologic response in this study was 93.5% (187/200). The sustained virologic response in group 1 was 100%, while group 2 (difficult-to-treat) had SVR of 87% (87/100), **fig. (1)**. Comparison between patients with and without SVR revealed no statistically significant differences regarding age and sex distribution, serum albumin, bilirubin, transaminases level, INR, platelets count and baseline viral load. Moreover, patients who were non-responders had significantly higher baseline AFP levels when compared with responders, **tab. (3), fig. (2)**.

**Table 1.** Demographic data of studied patients (n=200)

Parameters		Value
Gender	Male	(122) 61%
	Female	(78) 39%
Age	Mean $\pm$ SD	56 $\pm$ 6.8

**Table 2.** Laboratory data of studied patients (n=200)

Parameter	Value
FBS (mg/dL)	(Mean $\pm$ SD) 105.23 $\pm$ 48.37
Creatinine (mg/dL)	(Mean $\pm$ SD) 0.95 $\pm$ 0.18
Albumin (g/dL)	(Mean $\pm$ SD) 3.82 $\pm$ 0.57
AST (IU/L)	(Mean $\pm$ SD) 41.69 $\pm$ 28.88
ALT (IU/L)	(Mean $\pm$ SD) 40.55 $\pm$ 26.03
Bilirubin (mg/dL)	(Mean $\pm$ SD) 1.18 $\pm$ 1.16
WBCs/cmm <sup>3</sup>	Median (Min-Max) 5.35 (2.60-54.00)
HB (g/dL)	(Mean $\pm$ SD) 12.29 $\pm$ 1.49
Platelets/cmm <sup>3</sup>	(Mean $\pm$ SD) 144.21 $\pm$ 58.62
INR	(Mean $\pm$ SD) 1.09 $\pm$ 0.09
Viral load log <sup>10</sup>	(Mean $\pm$ SD) 5.37 $\pm$ 0.86
AFP (ng/ml)	(Mean $\pm$ SD) 3.42 (0.23 - 26.59)

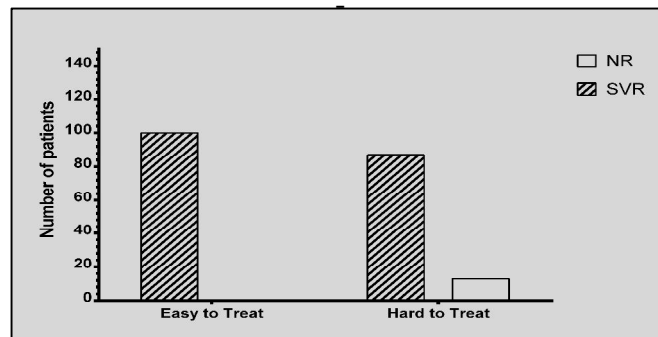


Figure 1. SVR in studied group

Table 3. Comparison between laboratory data of patients with and without SVR

Parameters	SVR (N=187)	NR (N=13)	P value
Sex (m/f)	112/75	10/3	0.22
Age/years	57 (38-68)	59 (42-68)	0.99
FBS (mg/dL)	105.01±35.96	106.39±93.15	0.47
Creatinine (mg/dL)	0.92±0.18	0.83±0.14	0.5
Albumin (g/dL)	3.81±0.57	3.85±0.57	0.40
AST (IU/L)	22 (3-125)	38 (4-94)	0.15
ALT (IU/L)	22 (11-24)	38 (14.5-63)	0.42
Bilirubin (mg/dL)	1.11±1.23	0.89±0.4	0.93
WBCs/cmm <sup>3</sup>	5.2 (3.3-5.4)	5.7 (2.6-11.8)	0.99
HB (g/dL)	13.32±1.46	13.06±1.78	0.69
Platelets /cmm <sup>3</sup>	144.43±55.91	142.77±77.07	0.52
INR	1.09±0.08	1.15±0.14	0.5
Baseline HCV (Viral load log 10IU/ml)	5.4±0.86	5.13 ±0.8	0.28
AFP (ng/ml)	3.23 (2.1-5.4)	6.50 (2.35-11.9)	0.023

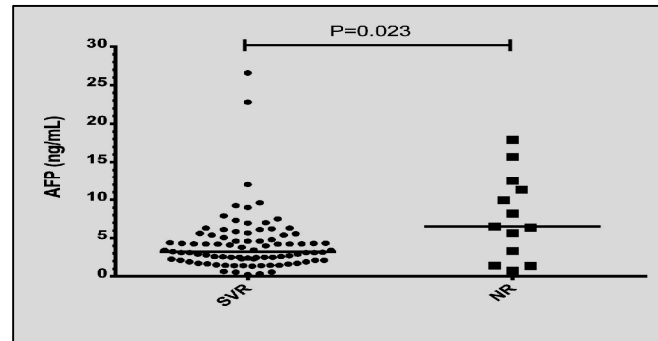


Figure 2. Difference in AFP between patients with SVR and those with NR.

**Discussion**

Hepatitis C virus (HCV) infection is a major public health problem worldwide, leading to the development of liver diseases ranging from fibrosis to cirrhosis and ultimately hepatocellular carcinoma<sup>11</sup>. In the past few years a short duration oral regimen of direct-acting antiviral drugs, with very high cure rates for all genotypes, have been developed<sup>12</sup>. In this study, the overall SVR12 was 93.5% (187/200). In easy-to-treat patients treated by Sofosbuvir/Daclatasvir, the sustained virologic response at 12 weeks was 100%, while hard-to-treat patients treated by Sofosbuvir/Daclatasvir plus ribavirin demonstrated SVR12 in 87 patients (87.0%). While these results are similar to

those from a study by Poordad et al who used a similar regimen where 100% of HCV genotype 4 patients achieved SVR12<sup>13</sup>, the rate of SVR12 in hard-to-treat patients in this study were lower than those reported by another Egyptian study where was 98.3% of 363 chronic HCV patients treated with Sofosbuvir/daclatasvir/ribavirin achieved SVR 12<sup>14</sup>. The efficacy and safety of sofosbuvir in treatment of GT4-infected patients was evaluated in a study by Babatin et al. where two groups of patients were given a 12-week treatment regimen, either sofosbuvir and semiprivir ± ribavirin (RBV) (group 1 = 56 patients) or sofosbuvir and DCV±RBV (group 2 = 40 patients). All patients in this study achieved (100%) sustained



virologic response at 12 weeks<sup>15</sup>. Other HCV genotypes having undergone the same treatment regimen demonstrated SVR12 rate of 90% and 86% in treatment-naïve and treatment-experienced genotype 4 patients, respectively<sup>16</sup>, while another study on a heterogeneous group (mainly genotype 1) of 72 patients showed SVR12 was achieved in 96.0% of cases<sup>17</sup>. A conclusive meta-analysis of studies investigating the use of direct-acting antiviral agents, including Sofosbuvir plus Daclatasvir without/with ribavirin in genotype 1 patients documented a SVR12 rate ranging from 93% to 100%<sup>18</sup>. A nearly identical treatment regimen as the current study was administered in a cohort of 946 Egyptian patients with chronic HCV who were administered sofosbuvir and daclatasvir with and without ribavirin. SVR12 was achieved in 95% of the easy-to-treat group receiving sofosbuvir and daclatasvir and 92% of the difficult-to-treat group receiving sofosbuvir, daclatasvir, and ribavirin, giving an overall SVR12 rate of 94%<sup>19</sup>. In the present study, the baseline AFP was found to be significantly elevated in non-responders when compared to SVR12 achievers. This is in accordance with another Egyptian study noting that the non-responder group had significantly higher frequency of cases with elevated AFP<sup>20</sup>. Other studies have similarly suggested various predictors for DAA success and failure. In a study on 256 HCV patients with genotypes 1 and 3, predictors of treatment failure were shown to be advanced liver disease and signs of portal hypertension, especially with platelets <100/nL<sup>21</sup>. Another study revealed that male gender, being a difficult-to-treat patient and previous interferon therapy were significant predictors of non-response in treatment groups<sup>22</sup>. A more recent study aimed to identify simple factors associated with non-response to DAAs using routine pretreatment patient work-up showed that non-responders had significantly higher AST, AFP and INR and a significantly lower albumin level and platelet count<sup>23</sup>.

### Conclusion

DAAs are an effective treatment in patients with chronic HCV with a high overall SVR rate, especially in easy-to-treat patients. AFP level can help in prediction of non-responders to DAAs.

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