Vol 5 | Issue 1 | Pages 161-165

Journal of Gastroenterology Research
ISSN: 2578-6210

Research Article

DOI: 10.36959/621/613

Serum Alpha-Fetoprotein, Albumin and Previous Antiviral Treatment, Can Predict Non-Response to Direct Antiviral Therapy in Egyptian Patients with Chronic Hepatitis-C

Hend Ibrahim Shousha[1], Yasmin Saad[1], Doa'a A Saleh[2], Hosam Dabes[3] and Mohamed Said[1]

[1]*Department of Endemic Medicine and Hepato-gastroenterology, Faculty of Medicine, Cairo University, Cairo, Egypt*

[2]*Department of Public Health and Community Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt*

[3]*National Medical Institute of Damnhour, Damnhour, Egypt*

Abstract

Background & Aims: Direct acting antiviral therapies (DAAs), are currently the state of the art therapy of chronic Hepatitis C (CHC) giving hope particularly to patients with liver cirrhosis. The aim of the study was to investigate the ability to use baseline data as predictors of non-response to DAAs in patients with CHC.

Methods: Baseline demographic and laboratory characteristics were collected for patients with CHC eligible for DAAs therapy. Patients were collected from March 2016 to October 2016 from Damanhur Viral Hepatitis Center (Boheira Governorate, Egypt). Monthly follow up was done during treatment to confirm safety, then at week 12 after the end of treatment to confirm sustained virological response (SVR) using routine laboratory data, ultrasonography, and quantitative HCV-PCR.

Results: This observational study included 2446 patients with CHC who received DAAs (combined sofosbuvir and daclatasvir with or without ribavirin). Their mean age was 50 ± 9.5 year and 57.3% were females. About 47.4% were cirrhotic and 299 (12.2%) patients were treatment experienced. 96.24% patients achieved SVR-12. Baseline AFP was significantly higher in non-responders (14.3 ng/ml versus 9.5 ng/ml respectively, P-value < 0.001). Multivariate logistic regression analysis revealed that SVR-12 was significantly associated with being treatment naïve, having higher Albumin levels and having AFP level ≤ 10.

Conclusions: The independent factors affecting SVR-12 were AFP level ≤ 10 ng, being treatment naïve, and serum albumin levels.

Keywords

HCV, Predictors, Sustained virological response, DAAs, AFP

Abbreviations

AFP: Alpha-Fetoprotein; DAAs: Direct-Acting Antivirals; HCV: Hepatitis C Virus; CHC: Chronic Hepatitis C; SVR: Sustained Virological Response; NCCVH: The National Committee for Control of Viral Hepatitis; ALT: Alanine Transaminase; AST: Aspartate Transaminases; INR: International Normalized Ratio; PCR: Polymerase Chain Reaction

Introduction

Chronic hepatitis C (CHC) is considered a major etiology of chronic hepatitis and cirrhosis around the world particularly in Egypt [1,2]. Egypt previously had the highest Hepatitis C virus (HCV) burden worldwide as reported in 2008, with 90% of patients infected with genotype-4 [3,4]. During 2015, the sero-prevalence of HCV infection declined to 6.3% [5] with an overall estimated 30% reduction [2,6].

Serum alpha-fetoprotein (AFP) is a fetal glycoprotein secreted by the yolk sac and liver of the fetus [7]. Following birth, AFP levels normalize but it increases significantly in certain pathologic conditions such as acute and chronic viral

***Corresponding author:** Hend Ibrahim Shousha, Department of Endemic Medicine and Hepato-gastroenterology, Faculty of Medicine, Cairo University, Postal code: 11562, Egypt, Tel: +201005738455, Facsimile: 0225326543

Accepted: February 13, 2021

Published online: February 15, 2021

Citation: Shousha HI, Saad Y, Saleh DA, et al. (2021) Serum Alpha-Fetoprotein, Albumin and Previous Antiviral Treatment, Can Predict Non-Response to Direct Antiviral Therapy in Egyptian Patients with Chronic Hepatitis-C. J Gastroenterol Res 5(1):161-165

hepatitis. Elevated serum AFP is a marker for hepatocellular carcinoma (HCC) in patients with chronic liver disease [8,9]. CHC may lead to fluctuations in AFP that makes it difficult to differentiate from the development of HCC [10]. AFP was found to normalize after antiviral treatment with interferon (IFN) [11].

Over the past several years, DAAs have replaced IFN for the treatment of CHC that improved safety, tolerability and utility [12-15]. The goal of HCV treatment is the achievement of SVR with undetectable HCV-RNA by highly sensitive quantitative assays 12 weeks after treatment (SVR12) which is highly concordant with the previous SVR24 in the interferon era [16,17].

Non-response is often related to relapse, a rebound in HCV-RNA once therapy is terminated after being undetectable at end of therapy, and less frequent to viral breakthrough while on treatment. Non-response to treatment has been related to combinations of host, viral, and treatment-related factors [18]. This study aims to investigate the relation between baseline AFP and the response to treatment in 2446 chronic HCV patients treated with DAAs (combined sofosbuvir and daclatasvir with or without RBV) using routine pre-treatment workup.

Patients and Methods

This study included 2446 Egyptian patients with treatment naive and treatment-experienced CHC who completed their combined antiviral treatment regimens. All patients were candidates for anti-viral therapy according to the guidelines of The National Committee for Control of Viral Hepatitis (NCCVH). The patients were recruited from Damanhur Viral Hepatitis Center (Boheira Governorate) affiliated to the NCCVH within the period from March 2016 and October 2016. HCV infection in all patients was confirmed by positive quantitative PCR for HCV infection.

The study was performed in compliance with the ethics principles of the 1975 Declaration of Helsinki and its later amendments with good clinical practice (GCP) guidelines. All patients signed a written informed consent. The study was approved by the ethical committee of The National Committee for Control of Viral Hepatitis (NCCVH).

Inclusion criteria

Adults > 18 years, All stages of fibrosis as assessed using FIB-4 score. All participants were subjected to baseline: History taking, clinical examination, electrocardiography (ECG) and abdominal ultrasound. Laboratory investigations included: Complete blood picture, alanine transaminase (ALT), aspartate transaminase (AST), international normalized ratio (INR), serum bilirubin, alfa fetoprotein (AFP), Quantitative polymerase chain reaction (PCR) for HCV RNA (CobasAmplicor, HCV Roche, Branchburg, NJ, USA, v 2.0, detection limit 15 IU/mL).

Exclusion criteria

Hepatic decompensation e.g. encephalopathy and/or ascites, calculated creatinine clearance ≤ 30 mL/min, extrahepatic malignancy (except after 2 years of disease-free interval), pregnancy and refusal to comply with adequate contraception and HBV or HIV coinfection.

FIB-4 score

FIB-4 score was calculated for all patients using Sterling's formula = [age (years) × AST (IU/L)]/ [platelet count (10^9/L) x ALT (IU/L) 1/2] [19].

Patients received a single daily dose of sofosbuvir (400 mg/day) and daclatasvir (60 mg/day). RBV recommended dose was 1200 mg daily if the patient's weight was above 75 kg, and 1000 mg daily if the patient weight was less than 75 kg, given in two divided doses. It was added if patient is treatment experienced or one of criteria for difficult to treat is present; total bilirubin > 1.2, serum albumin < 3.5, INR > 1.2 or Platelets < 150000. Liver cirrhosis was diagnosed on clinical basis according to laboratory tests and findings of abdominal ultrasound and transient Elastography above 14 Kpa.

AFP assay

Quantitative assessment of serum AFP was done using the CanAg AFPEIA enzyme immunometric assay kit (Fujirebio Diagnostics AB, Göteborg, Sweden).

Follow up

Follow up was done every month during treatment to confirm safety, then at week 12 after the end of treatment to confirm sustained virological response (SVR). Follow up was performed using routine laboratory data, ultrasonography, and quantitative HCV-PCR to confirm SVR.

Statistical analysis

Data were summarized using descriptive statistics (mean and standard deviation). Number and percentage were used for qualitative data. Statistical difference between groups were done using chi square test for qualitative data, independent t-test for quantitative normally distributed data and Mann-Whitney for quantitative non-normally distributed data. Value 0.05 was selected as a significant level for the test. Those factors demonstrating significant association in bivariate analysis and any others believed to be important regardless of these results were included in a multivariate logistic regression model. Analyses were performed using SPSS V. 23 (SPSS Inc. Released 2015. IBM SPSS statistics for windows, version 23.0, Armnok, NY: IBM Corp.).

Results

The demographic features of the patients are shown in Table 1 with no significant difference among responders and non-responders.The age of the included patients ranged between 20-74 years with a mean of 50 ± 9.5 years. Females represented 57.3% of patients. A total of 299 (12.2%) patients had received previous antiviral therapy (treatment experienced), and a total of 1160 (47.4%) patients were cirrhotic.

Comparison of baseline lab results revealed no significant difference between responders and non-responders except for Albumin, AFP, WBC count, Platelet count and Prothrom-

bin concentration ($p < 0.05$). Treatment responders had significantly higher Albumin level, WBC count, Platelet count and Prothrombin concentration and significantly lower AFP level ($p < 0.05$) (Table 2). The mean baseline serum AFP value was 9.7 ng/ml for all patients. Patients who did not achieve SVR showed significantly higher baseline AFP levels (14.3 ng/ml versus 9.5 ng/ml, P value- < 0.001). SVR12 rate among these patients was 96.24%.

Higher levels of AFP were significantly associated with lower odds of being a responder at week 24. Patients with AFP ≤ 10 had 5.7 times higher odds to be responder compared to those who had AFP > 100. Patients with AFP ≤ 10 had two times higher odds to be responder compared to those who had AFP > 10 (Table 3).

Table 4 shows the multivariate logistic regression analysis which revealed that responders who achieved SVR-12 were significantly associated with being treatment naïve, having higher Albumin levels and having AFP level ≤ 10 ($p < 0.05$).

Discussion

This study included 2446 patients with chronic hepatitis C infection who received direct acting antiviral therapy. SVR-12 rate among these patients was 96.24%. We aimed to study the role of baseline serum AFP and other baseline patients factors as a predictor of response to treatment with DAAs.

The normal adult serum AFP concentration does not exceed 6 ng/ml. Elevations of serum AFP > 20 ng/ml were present in patients with HCV-related cirrhosis but without HCC with a prevalence ranging from 10% to 43%. AFP levels are influenced by non-tumoral factors such as etiology of chronic liver disease and progression of cirrhosis [20-22]. AFP is also

Table 1: Comparison of baseline characteristics of responders and non-responders.

		Total (2446 patients)	Non-responder (92 patients)	Responder (2354 patients)	P value
Gender	**Female**	1402 (57.32%)	44 (47.8%)	1358 (57.7%)	
	Male	1044 (42.68%)	48 (52.2%)	996 (42.3%)	0.67
Treatment Status	**Treatment Naïve**	2147 (87.8%)	62 (67.4%)	2085 (88.6%)	
	Treatment Experienced	299 (12.2%)	30 (32.6%)	269 (11.4%)	0.27
Tobacco Consumption		531 (21.7%)	0	531 (22.55%)	1
Hypertension		186 (7.6%)	0	186 (7.93%)	1
Diabetes		216 (8.8%)	2 (2.17%)	214 (9.09%)	0.15
Liver on ultrasonography	**Non-cirrhotic**	1286 (52.5%)	46 (50%)	1240 (52.67%)	0.365
	Cirrhotic	1160 (47.4%)	46 (50%)	1114 (47.33%)	

Table 2: Baseline laboratory results of responders and non-responders.

	Total Mean (SD)	Responders Mean (SD)	Non-responders Mean (SD)	P-value
Age	50.0 (10.0)	50.0 (9.6)	50.3 (8.0)	0.749
BMI	29.2 (5.3)	29.2 (5.3)	29.1 (4.8)	0.341
ALT	57.2 (38.3)	57.1 (38.1)	60.6 (42.6)	0.558
AST	61.9 (40.4)	61.7 (40.3)	67.3 (41.4)	0.211
AFP	**9.7 (25.1)**	**9.5 (25.2)**	**14.3 (20.4)**	**<0.001**
Albumin (g/dL)	**4.0 (0.5)**	**4.0 (0.5)**	**3.8 (0.5)**	**0.018**
Total BILIRUBIN (mg/dL)	0.9 (0.5)	0.9 (0.5)	1.0 (0.4)	0.082
HbA1c*(%)	6.4 (1.1)	6.4 (1.1)	5.6 (0.4)	0.301
WBC × 10^3/mm^3	6.1 (2.1)	6.1 (2.1)	5.6 (1.9)	0.018
Hemoglobin (gm/L)	13.5 (1.7)	13.5 (1.7)	13.4 (1.7)	0.533
Platelets × 10^3/mm^3	**169.5 (70.5)**	**170.1 (70.6)**	**153.7 (65.8)**	**0.015**
Prothrombin concentration (%)	**85.5 (11.4)**	**85.5 (11.4)**	**85.2 (10.7)**	**0.027**
INR	1.1 (0.2)	1.1 (0.2)	1.1 (0.1)	0.185
Creatinine (mg/dL)	0.9 (0.5)	0.9 (0.5)	0.9 (0.6)	0.941
Liver Stiffness measurements	15.7 (10.6)	15.7 (10.6)	17.8 (9.5)	0.492
Fib4 Calculation	3.7 (10.9)	3.7 (11.0)	3.5 (2.5)	0.849

BMI: Body Mass Index; ALT: Alanine Transaminases; AST: Aspartate Transaminases; AFP: Alpha-Fetoprotein, HbA1C: Glycosylated Hemoglobin; INR: International Normalized Ratio

Table 3: AFP levels among responders and non-responders.

		non responder		responder		Total		P value	Odds ratio	95% CI
		N	%	N	%	N	%			
AFP	**≤ 10**	**60**	**65.2**	**1872**	**79.5**	**1932**	**79.0**	**0.026***	**5.67**	**1.23; 26.16**
	< 10 and ≤ 100	30	32.6	471	20.0	501	20.5	0.185	2.86	0.61; 13.47
	> 100	2	2.2	11	0.5	13	0.5	Ref	1	
	Total	92	100.0	2354	100.0	2446	100.0			

Table 4: Multivariate logistic regression analysis.

	P value	Odds ratio	95% CI
Age	0.743	0.996	0.970; 1.022
Gender (female vs. female)	0.052	1.642	0.995; 2.711
Treatment Status (Naïve vs. Experienced)	**<0.001**	**3.487**	**2.131; 5.705**
ALT Result	0.726	1.002	0.992; 1.011
AST Result	0.692	0.998	0.988; 1.008
Albumin (g/dL)	**0.030**	**1.691**	**1.052; 2.718**
Total BILIRUBIN (mg/dL)	0.892	0.969	0.614; 1.529
WBC × 10^3/mm^3	0.104	1.105	0.980; 1.246
Hb (G/L)	0.893	1.011	0.864; 1.182
INR	0.234	2.643	0.533; 13.095
Fib4 Calculation	0.596	1.025	0.934; 1.125
AFP (≤ 10 vs. > 10)	**0.014**	**1.877**	**1.135; 3.102**

raised in non-hepatic malignancies such as pancreatic, gastric, biliary and germ cell tumors [19].

For chronic hepatitis C patients, the HCV-coding core protein is known to upregulate the transcription of several molecules that activate the cell cycle and induce proliferation in hepatocytes, and it may also upregulate AFP transcription [23]. Therefore, mild elevation of the serum AFP level is sometimes seen in patients with chronic active hepatitis C but without HCC [19,24]. The percentage of chronic hepatitis C patients with an elevated AFP level (≥ 10 ng/mL) ranges from 11.6% to 43% [22,25,26].

Previous studies on CHC Egyptian patients, where genotype 4 is the prevalent genotype, revealed that serum AFP levels were found to be elevated in 12.6% of patients with 10 ng/ml upper limit of normal (ULN). Other studies reported elevated serum AFP with levels ranging between 10 and 30 ng/mlULN, with variable prevalence [27,28]. AFP used to be a strong predictor of response to the old standard of care therapy of combined pegylated interferon and ribavirin [29].

Studies have concluded that the SVR rate was higher among patients with serum AFP levels below rather than above the median value 5.7 ng/ ml [19,23] and have confirmed the value of serum AFP levels in predicting treatment outcome in CHC patients, regardless of the infecting genotype [19].

Serial AFP assay during and after treatment was not performed due to financial limitations. In addition, this serial AFP assay is not routinely performed in real life practice during therapy and we cannot add an extra financial load over the patients. Unfortunately the findings of this study cannot be extrapolated outside the current study population.

In conclusion; high AFP more than 10ng, being a routine pretreatment laboratory assessment, is a predictor of non-response to DAAs in patients with chronic HCV genotype 4.

Conflict of Interest

All included authors declare absence of any financial or personal relationships with other people or organizations that could inappropriately influence and bias the work.

Submission Declaration

This work has not been published previously, is not under consideration for publication elsewhere, its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out and, if accepted, will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

Contributors and Authorship

All authors have contributed significantly to finish this work; all authors are in agreement with the content of the manuscript

Design of the study: Mohamed Said Abdelaziz, YasminSaad

Performance of management: Mohamed Said Abdelaziz, HosamDabes, KadriElSaeed, and YehiaElShazly

Acquisition of data: Mohamed Said Abdelaziz

Analysis of data: Doa'aASaleh

Interpretation of data and drafting the article: HendShousha, Doa'aASaleh

Article revision: YasminSaad, Doa'aASaleh, HosamDabes, KadriElSaeed, YehiaElShazly, Mohamed Said Abdelaziz

Final approval of the version: Mohamed Said Abdelaziz

Article submission: Hend Shousha.

References

1. Cavalcante LN, Lyra AC (2015) Predictive factors associated with hepatitis C antiviral therapy response. World J Hepatol 7: 1617-1631.
2. El-Akel W, El-Sayed MH, El Kassas M, et al. (2017) National treatment programme of hepatitis C in Egypt: Hepatitis C virus model of care. J Viral Hepat 24: 262-267.
3. El-Zenati F, Way A (2008) Egypt demographic and health survey 2008.
4. Blach S, Zeuzem S, Manns M, et al. (2017) Global prevalence and genotype distribution of hepatitis C virus infection in 2015: A modelling study. Lancet Gastroenterol Hepatol 2: 161-176.
5. Ministry of Health, Egypt, El-Zanaty and Associates, ICF International (2015) Egypt health issues survey 2015.
6. Kandeel A, Genedy M, El-Refai S, et al. (2016) The prevalence of hepatitis C virus infection in Egypt 2015: Implications for future policy on prevention and treatment. Liver Int 37: 45-53.
7. Halbrecht I, Klibanski C (1956) Identification of a new normal embryonic haemoglobin. Nature 178: 794-795.
8. Gupta S, Bent S, Kohlwes J (2003) Test characteristics of alpha-fetoprotein for detecting hepatocellular carcinoma in patients with hepatitis C. A systematic review and critical analysis. Ann Intern Med 139: 46-50.
9. Taketa K (1990) Alfa-fetoprotein: Reevaluation in hepatology. Hepatology 12: 1420-1432.
10. Di Bisceglie AM, Sterling RK, Chung RT, et al. (2005) Serumalpha-fetoprotein levels in patients with advanced hepatitis C: Results from the HALT-C Trial. J Hepatol 43: 434-441.
11. Chen TM, Huang PT, Tsai MH, et al. (2007) Predictors of alpha-fetoprotein elevation in patients with chronic hepatitis C, but not hepatocellular carcinoma, and its normalization after pegylated interferon alfa 2a-ribavirin combination therapy. J Gastroenterol Hepatol 22: 669-675.
12. El Kassas M, Elbaz T, Hafez E, et al. (2016) Safety of direct antiviral agents in the management of hepatitis C. Expert Opin Drug Saf 15: 1643-1652.
13. Pol S, Corouge M, Sogni P (2013) Oral antiviral therapies for chronic hepatitis C infection. Ther Adv Infect Dis 1: 107-116.
14. Feld JJ, Foster GR (2016) Second generation direct-acting antivirals - Do we expect major improvements? J Hepatol 65: S130-S142.
15. Papudesu C, Kottilil S, Bagchi S (2016) Elbasvir/grazoprevir for treatment of chronic hepatitis C virus infection. Hepatol Int 11: 152-160.
16. Bacon BR, Dieterich D, Flamm SL, et al. (2014) Efficacy of sofosbuvir and simeprevir-based regimens for 304 HCV treatment-experienced patients in a reallife setting; data from the TRIO network. Hepatology 60: S672.
17. Dieterich D, Bacon B, Flamm S, et al. (2015) Final evaluation of 955 HCV patients treated with 12 week regimens containing sofosbuvir +/- simeprevir in the TRIO network: Academic and community treatment of a real-world, heterogeneous population. J Hepatol 62: S621.
18. Buti M, Esteban R (2016) Management of direct antiviral agent failures. Clin Mol Hepatol 22: 432-438.
19. Sterling RK, Lissen E, Clumeck N, et al. (2006) Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV co-infection. Hepatology 43: 1317-1325.
20. Greenberg F, Rose E, Alpert E (1990) Hereditary persistence of alpha-fetoprotein. Gastroenterology 98: 1083-1085.
21. Trevisani F, D'Intino PE, Morselli-Labate AM, et al. (2001) Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: Influence of HBsAg and anti-HCV status. J Hepatol 34: 570-575.
22. Hu KQ, Kyulo NL, Lim N, et al. (2004) Clinical significance of elevated alpha-fetoprotein (AFP) in patients with chronic hepatitis C, but not hepatocellular carcinoma. Am J Gastroenterol 99: 860-865.
23. Murashima S, Tanaka M, Haramaki M, et al. (2006) A decrease in AFP level related to administration of interferon in patients with chronic hepatitis C and a high level of AFP. Dig Dis Sci 51: 808-812.
24. Asahina Y, Tsuchiya K, Nishimura T, et al. (2013) α-fetoprotein levels after interferon therapy and risk of hepatocarcinogenesis in chronic hepatitis C. Hepatology 58: 1253-1262.
25. Fattovich G, Giustina G, Degos F, et al. (1997) Morbidity and mortality in compensated cirrhosis type C: A retrospective follow-up study of 384 patients. Gastroenterology 112: 463-472.
26. Kobeisy MA, Morsy KH, Galal M, et al. (2012) Clinical significance of elevated alpha-foetoprotein (AFP) in patients with chronic hepatitis C without hepatocellular carcinoma in upper EGYPT. Arab J Gastroenterol 13: 49-53.
27. Chu CW, Hwang SJ, Luo JC, et al. (2001) Clinical, virologic, and pathologic significance of elevated serum alpha-fetoprotein levels in patients with chronic hepatitis C. J Clin Gastroenterol 32: 240-244.
28. Dienstag JL, McHutchison JG (2006) American gastroenterological association technical review on the management of hepatitis C. Gastroenterology 130: 231-264.
29. El Raziky M, Attia D, El Akel W, et al. (2013) Hepatic fibrosis and serum alpha-fetoprotein (AFP) as predictors of response to HCV treatment and factors associated with serum AFP normalisation after treatment. Arab J Gastroenterol 14: 94-98.

DOI: 10.36959/621/613

SCHOLARS.DIRECT