

## Impact of Serum Alpha-fetoprotein Levels on the Response to Antiviral Therapy in Egyptian Patients with Chronic Hepatitis C

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Received: March 6, 2013

Revised: March 22, 2013

Accepted: March 25, 2013

Published online: May 21, 2013

### ABSTRACT

**AIM:** The changes in alpha-fetoprotein (AFP) levels and the response to anti-viral therapy among chronic HCV patients have become of great interest. This study was intended to investigate the potential use of AFP level as a predictor for end of treatment response (ETR) in chronic HCV patients and detect its changes with therapy.

**METHODS:** Retrospective data of 2378 biopsy-proven chronic HCV Egyptian patients who received anti-viral therapy at the National Hepatology and Tropical Medicine Research Institute, Egypt were analyzed. Detailed baseline and follow up data with special emphasis on the serial AFP levels were evaluated.

**RESULTS:** Early virological (EVR) and ETR were 58%, 42% respectively on an intention to-treat basis. Median baseline AFP at 3.5 ng/mL; was significantly correlated with amino-transferase levels, stages of fibrosis and grades of necro-inflammation. AFP levels decreased with IFN therapy regardless of virologic response with a significant decrease in patients with ETR. ETR was more evident among patients AFP < 3.5 ng/mL compared to those with higher values (91.3% vs 87.2 respectively; *p*-value, 0.03). There was a significant decrease between baseline AFP and levels at either 24 or 48 weeks of therapy; 2.1 ng/mL and 2.8 ng/mL respectively. ETR was significantly related to the difference at week 24; *p*-value 0.034 but not to the latter; *p*-value 0.11.

**CONCLUSIONS:** In chronic HCV patients; low baseline AFP level could be a potential predictor for ETR while the decrease in serial AFP levels was related to anti-viral therapy irrespective of treatment outcome.

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**Key words:** Alpha-fetoprotein; HCV; Egypt; Pegylated IFN/RBV; Virological response; EVR; ETR-Egypt

Mabrouk M, Doss W, Zayed N, Afify S, Esmat G. Impact of Serum Alpha-fetoprotein Levels on the Response to Antiviral Therapy in Egyptian Patients with Chronic Hepatitis C. *Journal of Gastroenterology and Hepatology Research* 2013; 2(5): 597-601 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/388>

### INTRODUCTION

Serum alpha-fetoprotein (AFP), a well known clinical serum marker for diagnosing hepatocellular carcinoma (HCC), was found to be elevated in patients with chronic liver disease in the absence of HCC, especially in those with viral etiology and with the development of cirrhosis<sup>[1,2]</sup>. Several studies have found the rate of HCV patients with elevated AFP between 10% and 43%<sup>[3-6]</sup>. This wide range may be due to the different patient populations, sample sizes, definitions of serum AFP elevation and the inclusion of patients at different stages of chronic hepatitis C.

Elevated AFP in patients with chronic HCV was associated with female gender, black race, advanced fibrosis, genotype 1b infection, elevated aspartate aminotransferase (AST), prolonged prothrombin time (PT), decreased platelet count, and lower serum albumin levels<sup>[1,6]</sup>. In addition, HCV genotype 1b, thrombocytopenia, AST elevation, and AFP level  $\geq 6$  ng/mL were associated with advanced fibrosis<sup>[7]</sup>. Moreover, a recent study reported that AFP and ALT values were correlated to each other in chronic HCV patients; however, such correlation was not evident among patients with HCC. Thus the prognostic and diagnostic value of AFP levels might be increased by adjusting for ALT values<sup>[8]</sup>. Few studies worldwide have been conducted on chronic HCV infection with reference to AFP levels and its effect on anti-viral therapy. Previous studies have demonstrated that AFP can be considered one of the serological predictors of response to antiviral therapy<sup>[9,10]</sup> and thus could be integrated in the pretreatment assessment of prognostic factors of a virologic response. Moreover, Changes in AFP levels were observed with interferon (IFN) therapy irrespective of the virological response<sup>[11]</sup>. The clinical significance of serum AFP is still under estimated in Egypt and needs further studies.

This retrospective study intended to investigate the potential use of baseline or changes in serial serum AFP levels with the administration of pegylated interferon (peg-IFN) plus ribavirin (RBV) therapy as a predictor for response in Egyptian patients with chronic HCV presumably genotype-4.

## PATIENTS AND METHODS

### Study Population

This study included retrospective data of 2378 Egyptian patients with chronic hepatitis C who attended the hepatology clinic at National Hepatology and Tropical Medicine Research Institute (NHTMRI), Ministry of Health and Population (MOHP), Egypt during 2007 who were scheduled for antiviral therapy. All participants had been previously consented for data retrieval for research purposes in the context of the national treatment of HCV.

Inclusion and exclusion criteria for the eligibility for pegylated interferon (peg-IFN) plus ribavirin (RBV) therapy were performed according to the guidelines of the National Committee for Control of Viral Hepatitis established by the Egyptian MOHP. Patients' data were retrieved from their medical records.

Inclusion criteria: adult (18-60 years old), IFN-naïve, non-obese; body mass index (BMI)  $\leq 35$  patients; of both sexes, who have evidence of serologic, virologic and histologic evidence of chronic HCV presumably genotype-4. Liver biopsy showing at least F1 stage of fibrosis (according to the Metavir score) in the presence of elevated ALT and AST levels above the upper limit of normal (ULN) or the presence of at least F2 stage of fibrosis in case of normal enzymes.

Patients with decompensated liver disease, positive for hepatitis B surface antigen (HBsAg), poorly controlled co-morbid conditions such as diabetes mellitus or the presence of contra-indications to receive IFN therapy were excluded. None had evidence of HCC by image study at enrollment and for during the follow-up period.

### Data Collection

Data cleansing: detecting and correcting corrupt or inaccurate record; was applied to our database resulting in almost complete valid data for 2378 patients with chronic HCV.

Baseline data retrieved from the patients' files included demographic, routine laboratory and histopathological data.

Liver biopsies were scored according to ISHAK score<sup>[12]</sup>. Histopathological interpretation of liver biopsy was grouped according to the presence of significant fibrosis (F3 i.e. bridging necrosis).

Both AST and ALT values were adjusted for their upper limit of normal (ULN). The ULN value for baseline AFP was 10 ng/mL<sup>[13]</sup>.

HCV-RNA values were transformed to IU/mL and patients were grouped according to median value.

Patients received either weekly subcutaneous pegylated interferon alpha 2a (180µg) or 2b (1.5 µg/kg) in addition to daily dose of weight-based RBV; 13-15 mg/kg.

Follow up data including serial AFP (ng/mL) measurements at weeks 24 and 48 and response to treatment at weeks 12, 24 and 48 of therapy were also retrieved.

Patients were classified by virologic response into three groups: end of treatment response (ETR) defined as negative HCV-RNA at week 48 of therapy, no response (NR) defined as positive HCV-RNA during IFN therapy at weeks 12, 24 or 48. Sustained virology response (SVR) at week 72 was not available in the medical records for most of the patients.

Baseline clinical, laboratory, histological variables were compared to AFP levels and changes of serial AFP levels between responders

and non responder were analyzed.

### Statistical Analysis

The descriptive statistics were presented with mean±standard deviation (SD) for parametric variables. Chi-square or Fischer's exact test (when appropriate) was used for categorical variables. Spearman correlation was used for correlating AFP level with other continuous variables. Student's *t*-test or Mann-Whitney test was used to compare difference of mean of AFP level before and after treatment. All analyses were performed with *p* value of <0.05 was considered significant and <0.01 highly significant. Most were categorized according to mean±SD or median values.

## RESULTS

Data was retrieved from patients' medical records of the 2378 patients who attended the outpatient clinic at NHTMRI from January-December 2007. Baseline clinical, biochemical, virological and histological characteristics of the 2378 chronic HCV participants are shown in table 1. There was a male predominance with male/female ratio was 4/1, median age within the 5<sup>th</sup> decade of life, 10% having history of controlled DM and 51.7% of the patients received Peg-IFN alpha 2a. Mean±SD values for AST were 44±33.69 with median 53 IU/L while mean±SD, median ALT were 62.49±42.89 and 51 IU/L respectively. Mean±SD values for AFP was 7.06±12.94 ng/mL. According to ISHAK score, significant fibrosis ( $\geq$ F3) was evident in 54.3% and 24% of patients had moderate-marked activity; histological activity index (HAI); 9-18.

**Table 1** Baseline clinical, laboratory, virological and histological characteristics of the total 2378 chronic HCV patients and according to median level of baseline serum AFP at 3.5 ng/mL.

Baseline Variables	Total 2378 chronic HCV	AFP median value		<i>p</i> value
		AFP $\leq$ 3.5	AFP> 3.5	
Age mean±SD	41.66±9.11	41.38±9	43±9.2	0.38
Gender				
Male	1978 (83.2%)	85.1%	81.6%	0.14
Female	400 (16.8%)	14.9%	18.4%	
ALT (U/L)				
Mean±SD	62.49±42.89	61.81±42.56	63.15±43.21	0.21
AST (U/L)				
Mean±SD	44±33.69	51.82±32.38	54.21±34.87	0.04
Baseline viral load ( $\times 10^3$ IU/mL)				
Median	75.00	90.40	67.76	0.15
Stage of fibrosis				
F <3	1086 (45.7%)	53.2 %	38.2%	<0.001
F $\geq$ 3	1292 (54.3%)	36.8%	61.8%	
HAI				
0-4	639 (26.9%)	33.4%	20.3%	<0.001
5-8	1166 (49%)	49.8%	48.1%	
9-12	519 (21.8%)	15.1%	28.4%	
13-18	54 (2.3%)	1.7%	3.2%	

Values are expressed in numbers and percentages in parentheses, median or mean  $\pm$  SD; AST: aspartate aminotransferase; AFP: alpha feto-protein; ALT: alanine aminotransferase; HAI: histologic activity index.

The median baseline AFP level of our study population was 3.5 ng/mL and the different baseline demographic, biochemical and histological data were analyzed with respect to the median level table 1. Patients' age, gender, baseline ALT levels and viral load were not statistically related to the median AFP levels; *p* value was 0.14 and 0.38, 0.21 and 0.15 respectively. On the other hand, median AFP levels were statistically correlated to the AST levels, *p* value 0.04, different stages of liver fibrosis  $r=0.134$ , *p* value <0.001 and grades of necro- inflammation;  $r=0.173$ , *p* value <0.001.

According to the data retrieved from patients' medical records; EVR was evident in 58%, 7% were non-responders while 854 (35%)

patients were lost to follow up either due to non compliance to treatment or due to side effects. On the other hand, ETR at week 48 was evident in 41.7% on an intention to treat basis.

The different baseline features related to either EVR or ETR were explored. Demographic parameters such as age, gender and biochemical parameters such as AST, ALT, viral load did not exhibit any significant relation neither with EVR nor ETR. On the contrary, stages of hepatic fibrosis and grades of necro-inflammation were significantly related with both EVR and ETR;  $p$  value 0.00. baseline median viral load was significantly correlated with the occurrence of EVR;  $p$  value 0.03 and median baseline AFP at 3.5 ng/mL was related to ETR;  $p$  value 0.03.

Serial AFP levels, their mean of difference and the likelihood of response to treatment are demonstrated in table 2 and 3. Baseline and serial AFP levels were categorized according to the median 3.5 ng/mL. Initial AFP levels, but not after 24 weeks or 48 weeks of IFN/RBV therapy were associated with ETR;  $p$  value 0.03, 0.08 and 0.55. There was a significant decrease in mean levels of AFP at week 24 and 48 as compared to baseline levels; 2.13 ng/mL and 2.84 ng/mL respectively;  $p$  value <0.001. The mean of difference at week 24, but not at week 48 was significantly correlated with ETR;  $p$  value 0.03 and  $r=0.09$ ,  $p$  value 0.11 respectively as demonstrated in table 3. Patients with low baseline AFP levels  $\leq 3.5$  ng/mL were able to maintain their low levels at both week 24 (75%) and week 48 of therapy (81%). On the other hand, half of patients with initial high AFP levels >3.5 ng/mL was able to express low values by the end of the treatment.

**Table 2** The relation between serial AFP levels and the likelihood of ETR after IFN/RBV therapy in chronic HCV patients.

Serial AFP measurements	ETR	Non-ETR	$P$ value
Baseline AFP			
$\leq 3.5$ (573)	523 (91.3%)	50 (8.7%)	0.03
>3.5 (540)	471 (87.2%)	69 (12.8%)	
AFP at week 24			
$\leq 3.5$ (332)	298 (89.8)	34 (10.2%)	0.08
>3.5 (180)	177 (84.7%)	32 (15.3%)	
AFP at week 48			
$\leq 3.5$ (741)	666 (89.8)	75 (10.2%)	0.55
>3.5 (372)	335 (89.9)	37 (10.1%)	

AFP: alpha feto-protein; ETR: end of treatment response.

**Table 3** The relation between the mean decrease in serial AFP levels and the likelihood of ETR among chronic HCV patients.

Decrease in AFP levels	ETR		$P$ value
	Non-ETR	ETR	
Baseline and week 24			
$\geq 2.13$	17.5%	82.5%	0.034
<2.13	10.3	89.7	
Baseline and week 48			
$\geq 2.84$	14.1	85.9	0.112
<2.84	9.1	90.9	

AFP: alpha feto-protein; ETR: end of treatment response.

## DISCUSSION

Alpha-fetoprotein (AFP) has been implicated in the development and growth of HCC in patients with chronic hepatitis or cirrhosis. However, elevated serum AFP is not uncommonly seen in patients with chronic hepatitis C without HCC<sup>[7]</sup>. There have been few previous reports concerning the relationship between AFP levels with the biochemical, histopathology, and virologic factors in chronic HCV patients in addition to the changes in AFP levels with IFN therapy. This study was designed to investigate the potential application of baseline and serial AFP levels as a predictor for

the clinical outcomes of response after Peg-IFN/RBV therapy in chronic HCV patients presumably genotype4. The sub-optimal response in subpopulations of chronic HCV patients i.e. genotype1 and genotype4 has advocated the exploration of simple biochemical markers that may help to predict the therapeutic outcome for the optimum management of these cases.

In the present series, we were able to demonstrate that 14.3% of our study population who represent a subset of adult Egyptian patients with chronic hepatitis C had elevated serum AFP. This findings was previously reported by several studies who observed a prevalence ranging from 10% to 42% among chronic HCV patients<sup>[3,14]</sup>. Moreover, the current study demonstrated that median baseline AFP level was 3.5 ng/mL, a figure which is rather identical to that observed in a previous study among Egyptian patients infected with HCV genotype-4 (median value 4.5 ng/mL)<sup>[9]</sup>. A rather higher median level (5 ng/mL) was set by another study which recruited chronic HCV patients with various genotypes, the majority being genotype 1, thus confirming that the initial observation was not genotype 4-specific<sup>[10]</sup>.

Furthermore, this study was able to express that pre-treatment AFP levels higher than the median value (>3.5 ng/mL) were significantly related to higher AST levels ( $p$  value 0.04), higher grades of necro-inflammation and advanced fibrosis ( $p$  value <0.001) in chronic HCV patients without HCC. This is in agreement with Chen *et al.*, who reported that elevated AFP was independently associated with stage of hepatic fibrosis  $\geq 2$ , AST  $\geq 40$ , and decreased level of albumin (< 3.5 g/dL), however, HCV-genotype 1b infection and viral load did not show such relation<sup>[15]</sup>.

Similar to our results, previous reports have expressed the association between AFP levels and a higher HAI inflammation score 4 and the advanced fibrosis stage in chronic HCV patients in the absence of HCC<sup>[6,16,17]</sup>. The correlation between the AFP levels and hepatic fibrosis have suggested that chronic HCV patients with even slightly elevated AFP levels, between 6 and 20 ng/mL, and moderately advanced liver fibrosis stages, were at an elevated risk for HCC<sup>[18]</sup>. These findings may indicate that hepatic fibrosis/cirrhosis is more important than necro-inflammation as a cause for the elevation of serum AFP in patients with chronic hepatitis C. Thus, AFP levels may be used as a non-invasive and predictive marker in place of the fibrosis stage.

After Peg-IFN/RBV combination therapy, EVR and ETR were evident in 58% and 42% respectively on an intention to-treat basis which represents a rather low un-favorable response rate. However, the fact that this retrospective data was collected during the year 2007 which represents the first year of implementation of anti-viral therapy under the supervision of the Egyptian National Committee for the Control of Viral Hepatitis and Ministry of Health and Population may explain these rates. Patients' compliance, adherence to treatment and complete awareness about the attendance of follow up visits were not optimal at such period.

Our study was able to express the predictive role of AFP with regard to treatment response in chronic hepatitis C. The likelihood of ETR (91.3%) was significantly related to the low baseline AFP ( $\leq 3.5$  ng/mL) vs 87% in those with high AFP (>3.5 ng/mL). The likelihood of SVR was not applicable in this study as there was no such data in the patients' medical record. This major drawback has halted the definite impact of AFP in the settings of SVR. Serial AFP levels decreased with treatment in a time-dependent manner irrespective of the treatment outcome. The significant decrease ( $\geq 2.13$  ng/mL) at week 24, but not that at week 48 ( $\geq 2.84$  ng/mL) was significantly associated with the achievement of ETR.

The present study was able to confirm previous reports that Peg-IFN/RBV therapy was associated with a decrease in serial AFP levels irrespective to the virological response to treatment<sup>[19-22]</sup>. A significant decrease in serum AFP level during IFN monotherapy was noted as well<sup>[23]</sup>. The decrease in serum AFP levels was more evident and prolonged in responders in contrast to a rather transient decrease in both partial responders and non-responders. A rather similar study revealed a significant decrease in serial serum AFP in 383 HIV-HCV co-infected patients ( $p < 0.002$  for all comparisons between baseline and week 48), but this decrease was not sustained in non-responders ( $p < 0.0001$  for comparisons between week 48 and week 72)<sup>[24]</sup>. These data support the finding that IFN, can possibly improve hepatic necrosis, hepatic regeneration and may ultimately affect AFP secretion<sup>[19]</sup>. The inhibitory role of IFN on AFP synthesis or secretion was also supported by previous reports<sup>[25]</sup>. A significant decrease in serum AFP level during and after IFN therapy was reported in an SVR group, whereas no significant decrease in serum AFP level was observed in the non-SVR<sup>[26]</sup>. Moreover the decrease in AFP pattern was secondary to a decline in aminotransferase levels and thus can be related to necrosis rather than with direct inhibitory effect of IFN on hepatocyte regeneration alone<sup>[11]</sup>. Decrease AFP levels with antiviral treatment despite the lack of antiviral effect in patients with advanced fibrosis/cirrhosis could be a potential useful marker for the regression of inflammatory changes and progression toward carcinogenesis, but this finding regarding needs to be elucidated. Previous reports have used AFP of 8 ng/mL (which represented the manufacturer's upper limit of normal)<sup>[27]</sup> or even an AFP level of 5 ng/mL at study entry<sup>[28]</sup> as a high risk of HCC development.

The marked decrease in the AFP levels is unlikely to be a spontaneous event, but is possibly due to the temporary suppression of viral replication and/or decreased inflammatory activity with the anti-viral therapy. This effect is far from negligible, and of the same magnitude than that of other well-accepted predictive factors of treatment response such as HCV genotype.

A major limitation in this study is that AFP was evaluated with the respect to ETR rather than SVR, however, the fact this study included retrospective data that was previously recorded in one of the national treatment centers affiliated to the MOHP in the beginning of the national program for the control of viral hepatitis may explain this limitation. In Egypt, it seems that patients' compliance after the end of the treatment course is not easy. They don't receive any follow up service at the treatment centers specially the testing for HCV-RNA at week 72 to define either SVR or relapse. The national program for HCV in Egypt does not support these follow up tests and patients consider themselves cured by the end of treatment and so they neglect week 72.

In conclusion, the dynamics of AFP levels in chronic HCV patients may be useful in identifying patients with advanced fibrosis to estimate the risk of developing HCC. Moreover, the addition of the serial pretreatment and follow-up AFP levels in the routine assessment of factors potentially predictive of the anti-HCV treatment outcome could be of high relevance.

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