Doi: 10.4274/vhd.galenos.2021.2021-5-3
Viral Hepatitis Journal 2021;27(2):49-52

Long-term Kinetics of Alpha-fetoprotein in Chronic Hepatitis C Patients Treated with Direct-acting Antivirals and Possible Predictive Role of AFP Response to Treatment on Development of Hepatocellular Carcinoma

Direkt Etkili Antiviral Tedavisi Alan Kronik Hepatit C Hastalarında Uzun Süreli Alfa-fetoproteinin Kinetiği ve Tedaviye AFP Yanıtının Hepatoselüler Karsinom Gelişimini Öngörmedeki Muhtemel Rolü

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ABSTRACT

Objectives: To evaluate the post-treatment upto fourth-year kinetics of alpha-fetoprotein (AFP) in patients with chronic hepatitis C (CHC) treated with direct-acting antiviral (DAA) drugs.

Materials and Methods: In this retrospective, single-center study, 182 patients (124 female, 58 male) with CHC treated with DAA were included in the study. Biochemistry and AFP were recruited from the hospital database. The data at pre-treatment, 3rd and 48th month after the end of treatment were evaluated.

Results: Of the 182 patients, mean age was 58±12 (28-76), and forty-nine (27%) had cirrhosis. At month 3, the average decline of AFP was 35.6% (0.4-97.0). Early decline of AFP <8.7% was found to be a predictor for HCC development. Mean AFP was 7.7±9.2 ng/mL at pre-treatment and 3.8±2.7 at third month (p<0.001). The decline persisted at 48th month (3.6±2.4 ng/mL).

Conclusion: Early decline of AFP and persistence at fourth-year after DAA treatment was observed, except five cases developing HCC. Inadequate decline in AFP level found to be a possible predictor for HCC development. However, these results needs to be confirmed in large-scale multicenter cohorts. This study highlights the importance of AFP response to DAA treatment in identifying HCC risk, especially in patients with cirrhosis.

Keywords: Alpha-fetoprotein, chronic hepatitis C, direct-acting antivirals, hepatocellular carcinoma

ÖZ

Amaç: Doğrudan etkili antiviral (DAA) ilaçlarla tedavi edilen kronik hepatit C (KHC) hastalarında alfa-fetoproteinin (AFP) tedavi sonrası dördüncü yıl kinetiğini değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif, tek merkezli çalışmada DAA ile tedavi edilen KHC'li 182 hasta (124 kadın, 58 erkek) çalışmaya dahil edildi. Hastane veri tabanından serolojik, biyokimyasal veriler ve hepatoselüler karsinomaya ilerleme bilgileri kaydedildi. Tedavi öncesi, tedavi bitiminden sonraki 3. ve 48. aydaki veriler değerlendirildi.

Bulgular: AFP seviyesinde tedavi sonrası 3. ay ortalama düşüş %35,6 (%0,4-97 aralığında) idi. Olguların %4,4'ünde AFP düzeyinde değişiklik olmazken, %8,2'sinde AFP yükselmesi gözlendi. HCC olguları hariç ortalama AFP 3. ayda 3,8±2,7, 48. ayda 3,6±2,4 idi (p=0,119). AFP'nin tedavi sonrası 3. aydaki düşme oranı %8,7'den daha az olanlarda HCC gelişimi anlamlı bulundu.

Sonuç: AFP düzeyi, olguların çoğunda DAA tedavisi bitiminde belirgin düşme göstermiş ve bu durum tedavi bitiminden 48 ay sonra da sebat etmiştir. Daha geniş kapsamlı verilere ihtiyaç olmakla beraber, bu çalışmanın verileri DAA tedavisi sonrası AFP'deki düşmenin yetersiz olmasının, sirotik hepatit C hastalarında HCC açısından daha yakın takip için bir uyarı olabileceğini desteklemektedir.

Anahtar Kelimeler: Alfa-fetoprotein, hepatit C, direkt-etkili antiviraller, hepatoselüler karsinoma

Ulaşoğlu C, Erkalma Şenateş B, Yapalı S, Dumanoğlu B, Enc F, Çolak Y, Şenateş E. Long-term Kinetics of Alpha-fetoprotein in Chronic Hepatitis C Patients Treated with Direct-acting Antivirals and Possible Predictive Role of AFP Response to Treatment on Development of Hepatocellular Carcinoma. Viral Hepat J. 2021;27:49-52.

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Introduction

Chronic hepatitis C (CHC) is still a global cause of cirrhosis and hepatocellular carcinoma (HCC) (1). Alpha-fetoprotein (AFP), an onco-fetal glycoprotein with 59 amino acids and a half-life of five days may have mild elevations in CHC regardless of HCC (2). Early identification of HCC and early tumor stage determines the prognosis, thus close monitorization and evaluating AFP response are essential factors (3,4).

We aimed to examine the change in AFP levels following direct-acting antivirals (DAA) treatment and to determine the correlation of AFP change with biochemical parameters, aspartate aminotransferase-to-platelet ratio index (APRI), and fibrosis index based on four factors (FIB-4) scores.

Materials and Methods

We conducted a retrospective study of consecutive adult patients (older than 18 years) with CHC who received 12 or 24 weeks of DAA treatment between January 2015 and January 2017 in a tertiary hepatology clinic. Patients with CHC who received DAAs and under follow-up for at least 48 months. Patients with co-infection and who had HCC within 12 months of DAA treatment were excluded. Medical files were reviewed and the following data were recorded; 1) demographics, 2) co-morbidities, 3), underlying cirrhosis, 4) laboratory values including alanine aminotransferase (ALT), aspartate aminotransferase (AST), AFP, hepatitis C virus-RNA (HCV-RNA), HCV genotype (GT), and platelet (Plt) count, and hepato-biliary ultrasound. The treatment criteria were defined as CHC patients with Ishak fibrosis score ≥2 and /or hepatic activity score ≥2, patients with cirrhosis based on the reimbursement criteria of the Turkish Ministry of Health as of January 2015. The DAA treatment regimens included sofosbuvir + ledipasvi, ombitasvir + paritaprevir + ritonavir + dasabuvir, sofosbuvir and additional ribavirin in cirrhotic patients. The sustained viral response (SVR) was defined as the HCV-RNA negativity at the 3rd month of end-of-treatment (EOT). The SVR was defined as the HCV-RNA negativity at the 3rd month of EOT. The diagnosis of cirrhosis was based on biopsy, signs of portal hypertension, imaging and laboratory tests including ultrasound, transaminases, albumin, Plt, international normalized ratio and bilirubin.

The non-invasive fibrosis markers FIB4 score [(age x AST)/(Plt x √ALT)] and APRI score [(AST/upper limit of AST) X 100/Plt)] were calculated. FIB4 <1.45 indicates the absence of cirrhosis (with 90% negative predictive value for fibrosis), while the score between 1.45-3.25 is regarded as inconclusive and results >3.25 indicate cirrhosis (65% positive predictive value for advanced fibrosis). APRI <0.5 normal and ≥1.5 regarded likely as cirrhosis (5,6).

The study was approved by Ethics Committee İstanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 124, date: 17.05.2018).

Statistical Analysis

Statistical evaluation was done with SPSS v20 (IBM, Chicago). Numerical data are given as mean ± standard deviation (SD). The normality of distribution control was done by Kolmogorov-Smirnov. Categorical data were analyzed by chi-square or Fisher's exact tests. Student's t-test or Mann-Whitney U test was used for comparison of numeric values of two groups, and ANOVA or Kruskal-Wallis was used for more than 2 categories depending on normality of distribution. The cut-off point was calculated based on a receiver operator characteristic curve analysis. The results were given as mean ± SD. The $p<0.05$ was considered as the level of statistical significance.

Results

The study group consisted of 182 cases with HCV, mean age 58±12 (range: 28-76), 124 (68.1%) female, and all caucasian. SVR in the 12th week after the EOT was achieved in 98.4% of cases treated with DAAs. HCC developed in five patients with cirrhosis during a follow-up of 4 years. Pre-treatment (PreT) mean AFP level was 6.4±6.9 ng/mL in non-cirrhotic (n=133) and 11.1±13.1 ng/mL in cirrhotic cases (n=49) (p=0.021). Also, AFP level over 10 ng/mL was in 32.7% of the cirrhotic and 13.5% in non-cirrhotic patients. Initial, 3rd and 48th month AFP values were 7.5±9.2 ng/mL, 3.8±2.6 ng/mL, and 3.6±2.4 ng/mL, respectively (p=0.032).

The mean decline in AFP at the 3rd month compared to PreT was 33.3%±20.0% and 44.0%±22.0% for cirrhotic and non-cirrhotic cases, respectively (p=0.005). AFP level decreased in 159 (87.4%), increased in 15 (8.2%), and didn't change in 8 (4.4%) cases. The demographic and laboratory values are shown in Table 1.

Genotype distribution was as follows: GT1a 22 (12%), GT1b 148 (82%), GT2 4 (2%), GT3 4 (2%), GT4 4 (2%). Distribution of DAAs was sofosbuvir + ledipasvir (n=84), ombitasvir + paritaprevir + ritonavir + dasabuvir (PROD) (n=91), sofosbuvir (n=7), and additional ribavirin (n=67).

One non-cirrhotic case was non-responder and two cases relapsed (one cirrhotic). Five cirrhotic cases (4 responders and 1 relapser) developed HCC within 48 months of follow-up.

The cut-off for predicting HCC development in cirrhotic cases was 8.7% decline in AFP in our cohort (area under the curve 0.914, p=0.003, 0.818-1.000). Five cases developing HCC were female (n=3), GT1a (n=2), GT1b (n=3), non-responder (n=1), relapser (n=1), sofosbuvir based protocol (n=4), interferon-experienced (n=2), asthma (n=1), diabetes mellitus (n=3), hypertension (n=3), and chronic kidney disease (n=2).

Discussion

The pre-treatment level of AFP was found in a wide as 1-73 ng/mL in cirrhotic and 1-45 ng/mL in non-cirrhotic cases, with no evidence of HCC. The baseline AFP over 5.5 ng/mL was reported as 10%-48.2% of CHC patients in numerous studies (7). In our study AFP over 5.5 ng/mL was in 45.1% of cases. The AFP level was correlated with serum uric acid, steatosis, fibrosis, and low albumin levels (7).

In our study, the baseline AFP was not different between genotypes (p=0.110), CKD (p=0.149), diabetes mellitus (p=0.396), gender (p=0.343), but significantly higher in cirrhotic compared to non-cirrhotic (p=0.002). HCC cases had insignificantly higher baseline values of age, AFP, AST, ALT, HCV-RNA, Plt, APRI, and FIB-4 scores compared to the non-HCC group. In a study, males had lower post-treatment AFP, but still had the risk of HCC compared to females and the cut-off was reported lower as 3.5 ng/mL (8). Rapid decline of AFP in CHC during treatment may be due

Table 1. Demographic, clinical and laboratory data of chronic hepatitis C patients treated with direct acting antivirals

Variables	All cases	Cirrhotics	Non-cirrhotics	p*	HCC positive	HCC negative	p**
Total cases (n, %)	182	49 (27%)	133 (73%)	0.001*	5	177	0.001*
Gender F/M	124/58	35/14	89/44	0.162	3/2	121/56	0.692
Age	59±12	63±9	57±12	0.001*	70±5	59±12	0.041*
Baseline HCV-RNA**	6.4	7	6	0.508	11	6	0.158
HCV-RNA >6 mIU	78	23	55	0.499	4	74	0.089
SVR12	98.4%	98.0%	98.5%	0.801	80.0%	98.9%	0.001*
ΔAFP-0 vs 3rd m.	3.7±8.1	6.3±12.1	2.9±6.0	0.013*	-0.1±1.4	3.7±8.1	0.289
ΔAFP-3rd vs 48th m.	0.4±1.2	0.3±1.8	0.1±1.0	0.344	1010.0	0.14	0.000*
ΔAST-0 vs 3rd m.	31±36	51±48	24±29	0.001*	66±43	31±36	0.364
ΔAST-3rd vs 48th m.	0.2±1.2	0.3±12	0.1±10.0	0.945	-19±38	0.2±11	0.001*
ΔALT-0 vs 3rd m.	38±41	50±47	34±38	0.026*	25±32	38±41	0.640
ΔALT-3rd vs 48th m.	0.4±16	-2±15	1±16	0.233	22±49	0.4±16	0.001*
ΔAPRI-0 vs 3rd m.	0.6±1.1	1.5±1.8	0.3±0.5	0.001*	1.7±1.0	0.6±1.1	0.747
ΔAPRI-3rd vs 48th m	-0.5±0.8	0.1±0.5	-0.1±0.9	0.236	-0.5±1.2	-0.5±0.8	0.099
ΔFIB4-0 vs 3rd m.	2.9±3.1	6.5±4.2	1.8±1.1	0.001*	6.9±2.4	2.9±3.0	0.830
ΔFIB4-3rd vs 48th m	-0.5±1.0	-0.7±0.5	-0.3±1.1	0.122	-0.7±0.5	-0.5±1.0	0.968

*: Significant (p<0.05), **: Million IU, m: Months, F/M: Male/female, SVR12: Sustained viral response 12 weeks after treatment

to subsiding low-level inflammation in the liver, thus AFP may also be an acute phase reactant to ongoing liver inflammation.

In the recent decade, DAAs are increasingly efficacious in treating and raising the disease-related quality of life in CHC (9). One of the new emerging problems is the possible onset of post-treatment HCC, especially in patients with higher fibrosis (9,10). In our cohort, 2.74% of cases developed HCC. The HCC arising after DAA treatment is reported to have an aggressive prognosis (11). AFP normalization is found to be related to better prognosis (12,13). Even in patients without cirrhosis, Fib-4 scores ≥3.25 should be under follow-up for HCC (14). Older age is also another risk factor in SVR positive cases for HCC development (15). All five cases of HCC in our group were over 60 years old. The change of AFP in the 3rd month was 1.8% and 38.0% for cirrhotic with and without HCC, respectively (p=0.003). Serum AFP levels in pre-treatment and 48th month for each five HCC cases were changed 25 to 3,661 ng/mL, 9 to 917 ng/mL, 8 to 514 ng/mL, 18 to 21 ng/mL and 7 to 9 mg/dL.

In a study, AFP elevated 22.6% of cases and decreased in 77.4% after DAA treatment (16). A similar decline was also shown in interferon-alpha-based treatments (17,18). Lack of decrease in AFP was found to be a risk factor for HCC (19,20). Our study is compatible with this finding and additionally, a cut-off value for insufficient AFP decrease as 8.7% was a risk factor tor HCC development in cirrhotic and older patients.

In patients with CKD, AFP serum level was reported to have different kinetics (21). In our data, pre-treatment mean level (2.8±1.6 ng/mL) decreased to post-treatment (2.3±1.1 ng/mL) in CKD cases. AFP values were lower in CKD cases both pre- and post-treatment (p=0.000, p=0.032, respectively).

Study Limitations

The limitations of this study were the small number of HCC patients, retrospective pattern, lack of pre-treatment advanced imaging (22), genotype dominance of 1b, one ethnic group, the strength of the study was the availability of paired laboratory results of same laboratory standards and long-term surveillance for all cases.

Conclusion

In this CHC cohort DAAs resulted as 98,4% SVR at 12th week. The average change of AFP level was at 35% decline in all cases. In long-term surveillance, five cirrhotic cases with insufficient AFP response to treatment had developed HCC. Thus, despite to necessity for large-scale and multicenter data, insufficient AFP response to DAA treatment may be an alert for close monitorization of HCC.

Ethics Committee Approval: The study was approved by Ethics Committee İstanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 124, date: 17.05.2018).

Informed Consent: Since our study was retrospective, informed consent was waived.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: E.Ş., B.D., C.U., Design: E.Ş., B.D., C.U., F.E., Supervision: B.E.Ş., Y.Ç., Data Collection or Processing: B.D., C.U., B.E.Ş., Analysis or Interpretation: S.Y., Y.Ç., C.U., B.D., Literature Search: B.D., C.U., Writing: C.U., S.Y., B.D., Critical Review: S.Y., F.E., E.Ş., B.E.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial disclosure: The authors declare no financial support.

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