Validity of Aspartate aminotransferase to Platelet ratio index as Predictor of early Viral response in patients with Hepatitis C treated by Interferon-based therapy

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Abstract

Objective: To observe any change in value of aspartate aminotransferase to platelet ratio index from the baseline and to compare it with the Hepatitis C virus ribonucleic acid at 12 weeks after the start of interferon-based treatment in patients with Hepatitis C.

Methods: The prospective study, conducted at the Department of Medicine, Liaquat University of Medical and Health Sciences Hospital, Jamshoro, Pakistan, from September 2009 to March 2010, included 158 consecutive, chronic patients of Hepatitis C with grade $\geq$ 2 fibrosis on liver biopsy, or having aspartate aminotransferase/Platelet ratio index of > 1. The aspartate aminotransferase to platelet ratio index was determined as aspartate aminotransferase level (upper normal limit)/ platelets counts (10^9/L) x 100. Eligible patients were assigned to receive thrice weekly subcutaneous injection of 3MIU standard interferon $\geq$-2b and weight-base dosage of ribavirin. The early virological response was defined as undetectable Hepatitis C virus ribonucleic acid test at week 12 of the study. APRI <1 was considered to be the response to therapy. Paired sample t-test was applied to observe pre-and post-treatment mean ± SD of continuous variables, while Chi-square test was applied for comparing categorical variables. A p-value of 0.05 was considered statistically significant.

Results: Out of 158 patients enrolled, 90 fulfilled the inclusion criteria. The aspartate aminotransferase to platelet ratio index before treatment was 1.61 ± 1.00 and after treatment 1.10 ± 1.08. Hepatitis C virus ribonucleic acid after 12 weeks of treatment was non-detectable (early viral response achieved) in 72 (80%) patients. A strong relation was found between aspartate aminotransferase to platelet ratio index and Negative polymerase chain reaction with early virological response as only 2 (4.5%) patients with negative polymerase chain reaction at 12 weeks had aspartate aminotransferase to platelet ratio index > 1 (p=0.001).

Conclusions: APRI can act as a predictor of early viral response in patients with Hepatits C.

Keywords: APRI, Early viral response, Hepatitis C. (JPMA 62: 1008; 2012)

Introduction

Hepatitis C has acquired a status of global epidemic, affecting nearly 180 million people throughout the world.[1] Approximately 300,000 to 400,000 deaths/year occur as a result of decompensation of cirrhosis, end-stage liver disease, and hepatocellular carcinoma due to Hepatitis C.[2] In Pakistan more than 110 million people suffer from Hepatitis C, constituting 3.6% of the population.[3] Genotype3 is the most prevalent of the six genotypes in Pakistan.[4]

Fortunately, with advancement in treatment over the years, combination treatment with interferon and ribavirin for six months can cure more than 75% of patients with Hepatitis C genotype 3.[5] It is now proved that sustained virologic response defined as reduction of serum Hepatitis C virus ribonucleic acid (HCV RNA) to undetectable or by at least 2 logs reduction in viral load six months after completion of treatment will not only halt the disease progression, but reverses the fibrosis and thereby reduces the chances of developing long-term complications such as cirrhosis of liver and hepatocellular carcinoma.[6] The presence of early viral response (EVR) at week 12 was considered to be an important predictive factor of sustained viral response (SVR) by the National Institutes of Health (NIH) in 2002 and was a routine part of monitoring patients.[7] EVR can predict SVR with high precision (98-99% NPV(negative predictive value)) and it is now a common belief that it is highly unlikely that patient will achieve a sustained virologic response if he or she will not experience a 12-week reduction of serum HCV RNA to undetectable or by at least 2 logs reduction (EVR).[8]

Despite advances in treatment and better outcome, a lot of patients do not complete their course because of significant side effects of interferon-based treatment which require aggressive treatment by multi-disciplinary experts.[9]

Because of the tremendous number of patients and

limited resources in our country, it is very important to select the timing of anti-viral therapy by identifying significant fibrosis. Many researchers consider Metavir stage ≥2 or Ishak stage ≥3 as significant fibrosis stage by considering the stage of fibrosis as an important predictor of outcome.[10,11]

Liver biopsy is the gold standard for identifying the degree of fibrosis, but it is an invasive procedure and inter-observer variation as well as sampling error limit its usefulness.[12]

Over the years, non-invasive methods of detecting significant fibrosis are gaining popularity. Among such methods, aspartate aminotransferase (AST) to platelet ratio index (APRI)) has developed as validated and useful non-invasive and inexpensive tool to detect significant fibrosis. In one study, APRI value of ≤ 1 predicted mild fibrosis in 88% of patients, whereas APRI ≥ 2 predicted advanced fibrosis in 75% of patients. By using these values, the absence or presence of advanced fibrosis could be diagnosed, thereby avoiding the need of liver biopsy in 77% of the patients.[13] In another study, APRI value of ≤ 1 predicted mild fibrosis with a positive predictive value (PPV) of 67.7%, and APRI ≥ 1 excluded mild fibrosis with NPV of 95%.[14] In most of previous studies, APRI has been seen as a static parametre of predicting or excluding fibrosis, but only few studies have evaluated APRI as predictor of EVR in prospective manner by observing any change in value of APRI in response to treatment just like HCV RNA being done during EVR.[15]

The current study was planned to observe any change in the value of APRI from the baseline and to compare it with HCV RNA at 12 weeks (EVR) after the start of interferon-based treatment in patients with Hepatitis C. The rationale behind this hypothesis was that HCV RNA was monitored by polymerase chain reaction (PCR), 12 weeks after treatment to observe EVR which is very costly. If the value of APRI matched the PCR, it would be a cost-effective, inexpensive method of detecting EVR.

Patients and Methods

Conducted at the Department of Medicine, Liaquat University of Medical and Health Sciences, Jamshoro, between September 2009 and March 2010, this prospective study included consecutive anti-HCV, HCV RNA positive with grade ≥ 2 fibrosis on liver biopsy, having AST/Platelet ratio index of > 1 naive patients with chronic hepatitis C. Fibrosis < grade 2 on liver biopsy, and /or AST/Platelet ratio index <1 and clinical or radiological evidence of cirrhosis (gastroesophageal varices, ascites, and hepatic encephalopathy) and patients developing complications during interferon therapy were excluded from the study. After the exclusion, the initial study population of 158 patients decreased to 90. The study was conducted in conformity with the principles of the Declaration of Helsinki. The Institutional Review Board of the hospital approved the protocol and consent forms. Written informed consent was obtained from all the participants.

The upper limits of normal (ULN) alanine aminotransferase (ALT) was taken as 41 U/L for men and 31 U/L for women. For AST, the ULN was 38 U/L for men and 32 U/L for women. Each patients' liver biopsy was done, the details of which are explained elsewhere.[14] The fibrosis stage was determined according to a scoring system available in literature, and was classified as F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = few septa; F3 = numerous septa without cirrhosis; and F4 = cirrhosis.[16] The APRI was determined as AST level (UNL)/ platelets counts (10^9/L) x 100.[17] Patients were divided into APRI <0.5 to 1 and the other group with APRI > 1. Eligible patients were assigned to receive subcutaneous injection of 3MIU standard interferon α-2b thrice weekly and ribavirin 10.6 mg/kg/d mg/day in two or three divided dosages for 24 weeks from the Hepatitis Prevention and Control Programme, Sindh Chief Minster Initiative.[18] Laboratory tests including complete blood count and serum alanine aminotransferase levels were assessed at each outpatient visit. Serum HCV RNA was evaluated qualitatively at baseline, and at week 12 of the study (CobasAmplicor HCV monitor V2.0 Roche Molecular Systems Pleasanton CA; with detection cut-off level of 50 IU/ml). The EVR was defined as undetectable HCV RNA by a sensitive qualitative assay test at week 12 of the study.[19] APRI <1 was considered to be the response to therapy.

Continuous variables such as age were expressed as mean ± standard deviation. Paired sample t-test was applied to observe pre- and post-treatment mean ± SD of continuous variables, while categorical variables were computed as frequency with percentage. The chi-square test was applied for comparing categorical variables APRI and EVR with the grade of fibrosis. A p-value of 0.05 was considered as statistically significant. All calculations were done using SPSS version 16.

Results

Of the 158 patients initially enrolled, 68 (43%) were excluded because of insufficient fibrosis or APRI readings, or due to complications during the interferon-based treatment. The mean age of the patients was 37.86 ± 11.18 years. Of the total 56 (62.2%) were male and 34 (37.8%) female (Table). On applying the paired sample T-test the mean platelet count before treatment was $1.9\times 10^9 \pm 71.3$ and after treatment $3.32\times 10^9 \pm 73.11$ (p=0.001); mean SGOT level before treatment was 72.24 ± 44.51 and after

Table: Relation of EVR and APRI with the degree of fibrosis(n=90).

		Grade of Fibrosis			
		2	3	4	P value
EVR not achieved	Count	4	7	7	0.001
	% within Grade of Fibrosis	7.40%	26.90%	70.00%	
EVR achieved	Count	50	19	3	0.001
	% within Grade of Fibrosis	92.60%	73.10%	30.00%	
APRI <1 not achieved	Count	5	8	7	0.001
	% within Grade of Fibrosis	9.3%	30.80%	70.00%	
APRI< Achieved	Count	49	18	3	0.001
	% within Grade of Fibrosis	90.7%	69.20%	30%	

EVR: Early viral response. APRI: Aspartate aminotransferase to platelet ratio index.

treatment it was 31.80 ± 19.45 (p=0.001); APRI before treatment was 1.61± 1.00 and after treatment, 0.848 ± 0.47 (0.001). HCV RNA after 12-week treatment was non-detectable (Early viral response achieved) in 72 (80%) patients. Grade 2 fibrosis was present in 54 (60%); grade 3 in 26(28.8%) and grade 4 in 10 (11.1%) patients. APRI < 1 was achieved in 70 (75.5%) patients after the 12-week treatment. A strong relation was found between APRI and Negative PCR after the therapy, as only 2 (4.5%) patients with negative PCR at 12 weeks had APRI > 1 (p=0.001). A strong relation was also found between EVR and the degree of fibrosis as 50(92.6%) out of 54 patients who achieved EVR were in grade 2 fibrosis,19 out of 26 (73.1%) were in grade 3 fibrosis, and only 3(30%) were in grade 4 fibrosis (p=0.001) (Table).

Discussion

Treatment for chronic Hepatitis C has now become more effective because of the interferon-based treatment. This therapy, though effective, is not without side effects, needs frequent dosage adjustments and is expensive. It is therefore very important to know in the early stage of the treatment, whether the patient will benefit in the long term. The primary goal of this study was to predict EVR by different methods. In this study, HCV RNA was undetectable 12 weeks after the commencement of treatment (EVR achieved) in 80% patients. Our results coincide with those of a study which included 505 patients of genotype 2 or 3 on standard interferon-based treatment and observed 80% response rate.[5] Another study also recorded EVR in 80% of its patients.[19] Our results were relatively higher than a study which found EVR in 61% (88/145) patients of non-genotype 1 on standard interferon.[20] Others observed a better response in which 44 out of 64(69%) patients showed early viral response.[21] The importance of EVR in predicting the sustained viral response was highlighted in all these studies as 75% to 80% patients achieved SVR.

APRI, a simple, inexpensive, formula, calculated from the routinely done test, has rarely been seen as predictive of EVR. In our study, there was a marked reduction in the value of APRI after treatment as 68 out of 90 (75.5%) patients showed APRI <1 after 12 weeks of treatment, whereas 72/90 (80%) patients had unbeatable HCV RNA by PCR. In the remaining 8 patients, APRI was reduced but it was not below 1. APRI predicted EVR with a sensitivity of 88.89%, PPV of 97.06% and NPV of 72.73%. Researchers who studied 114 patients of Hepatitis C coinfected with HIV observed that there was a significant reduction in APRI along with improvement in the degree of fibrosis in patients who responded to treatment for Hepatitis C compared to those who were non-responders.[22] A study of 340 patients reported that those who responded to the treatment dropped APRI from 1.7 ± 1.6 to 0.49 ± 0.36 compared to the non-responders whose APRI was slightly changed from 1.7 ± 1.6 to 1.5±1.8.[13] In HALT-C (Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis) study, similar results were obtained using simple laboratory tests to predict outcomes in patients with advanced chronic hepatitis C.[23] In contrast to our and other studies, a case-controlled trial of 80 patients observed that APRI was not a predictor of EVR as no association was found between the change in APRI and EVR.[15]

A strong relation was also found between EVR and degree of fibrosis as 50(92.6%) out of 54 patients achieving EVR were in moderate (grade 2) fibrosis, and 19 out of 26 (73.1%) were in grade 3 fibrosis and only 3(30%) were in grade 4 fibrosis. Others found a response rate of 65% in patients with grade 2 or less compared to grade 3 or cirrhosis (grade 4) where the response rate was 41%.[24] Another study also strengthened the idea that more advanced disease will respond less by showing that patients with fibrosis grade 3 and cirrhosis will have 10 to 15% poor response compared to grade 2 or less.[25] The reason for this poor response to treatment is not understood properly. It could be that patients with advanced fibrosis and cirrhosis could have increased prevalence of other established predictors of poor response.

Conclusion

Results of the study suggest that APRI is an inexpensive and cost-effective method of predicting EVR in chronic patients of Hepatitis C. More studies on a large scale are needed to confirm APRI as a useful marker to assess the effects of antiviral therapy on hepatic fibrosis.

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