APRI as a predictor of early viral response in chronic hepatitis C patients

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Received: August 18, 2009 Revised: September 1, 2009 Accepted: September 8, 2009 Published online: October 21, 2009

Abstract

AIM: To evaluate the aspartate aminotransferase (AST) to platelet ratio index (APRI) as a predictive factor of early viral response in chronic hepatitis C naive patients.

METHODS: We performed an ambispective case-control study. We enrolled chronic hepatitis C naive patients who were evaluated to start therapy with PEGylated interferon α-2b (1.5 μg/kg per week) and ribavirin (> 75 kg: 1200 mg and < 75 kg: 1000 mg). Patients were allocated into two groups, group 1: Hepatitis C patients with early viral response (EVR), group 2: Patients without EVR. Odds ratio (OR) and 95% confidence interval (CI) were calculated to assess the relationship between each risk factor and the EVR in both groups.

RESULTS: During the study, 80 patients were analyzed, 45 retrospectively and 35 prospectively. The mean ± SD age of our subjects was 42.9 ± 12 years; weight 70 kg (± 11.19), AST 64.6 IU/mL (± 48.74), alanine aminotransferase (ALT) 76.3 IU/mL (± 63.08) and platelets 209 000 mill/mm$^3$ (± 84 429). Fifty-five (68.8%) were genotype 1 and 25 (31.3%) were genotype 2 or 3; the mean hepatitis C virus RNA viral load was 2269061 IU/mL (± 7220266). In the univariate analysis, APRI was not associated with EVR [OR 0.61 (95% CI 0.229-1.655, $P = 0.33$)], and the absence of EVR was only associated with genotype 1 [OR 0.28 (95% CI 0.08-0.94, $P = 0.034$)]. After adjustment in a logistic regression model, genotype 1 remains significant.

CONCLUSION: APRI was not a predictor of EVR in chronic hepatitis C; Genotype 1 was the only predictive factor associated with the absence of EVR in our patients.

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Key words: Hepatitis C virus viral load; Viral genotype; Hepatitis C; Aspartate aminotransferase to platelet ratio index; Early viral response

INTRODUCTION

According with the World Health Organization, 123 million individuals are infected with hepatitis C virus (HCV) worldwide, representing a prevalence of 2%[1]. HCV can result in progressive hepatic injury and fibrosis, culminating in cirrhosis and end-stage liver disease. Chronic hepatitis C is a major indication for liver transplantation and increases the incidence of hepatocellular carcinoma[2]. PEG-interferon and ribavirin...
therapy during 24 to 48 wk leads to a sustained viral response (SVR, a sustained loss of serum HCV RNA)\(^3\).

There are factors identified as predictors of SVR among patients who received PEG-interferon and ribavirin, including HCV genotype other than 1, viral load less than 600,000 IU/mL, age of 40 years or less, and body weight of 75 kg or less. Sixty five percent of patients with early viral response (EVR) subsequently have an SVR\(^4,5\). In addition, the absence of bridging fibrosis/cirrhosis has been significantly associated with SVR\(^6,7\). Infection with genotype 2 or 3, low viral load, and absence of advanced hepatic fibrosis have consistently been identified as independent predictors of SVR\(^8\).

Percutaneous liver biopsy has been the gold standard for grading and staging liver disease; recently however, non-invasive methods have been developed to determine hepatic fibrosis, such as transient elastography, fibrotest, and the aspartate aminotransferase (AST) to platelet ratio index (APRI)\(^9,10,11\). APRI is one of several markers that have been proposed to measure liver fibrosis. It is an inexpensive widely available tool\(^12\) that can predict accurately mild fibrosis in patients with a value < 0.42 and those with a value > 1.2 are diagnosed a significant grade of fibrosis. APRI establishes a 90% negative predictive value for the absence of fibrosis and a 91% of positive predictive value for its presence\(^12,13,14\). Previous studies have not explored the usefulness of noninvasive tests to assess liver fibrosis for the prediction of viral response in hepatitis C naive patients. The purpose of this study was to evaluate APRI as predictive factor of EVR in hepatitis C chronic naive patients.

**MATERIALS AND METHODS**

**Study design**

We performed an ambispective case-control study with enrollment of APRI as a predictor of EVR in chronic hepatitis C naive patients prospectively from July 2006 to February 2008. We also reviewed retrospectively medical records of chronic hepatitis C naive patients from January 2004 to June 2006 who were evaluated to start therapy with PEG-interferon \( \alpha-2b \) (1.5 \( \mu \)g/kg per week) and ribavirin (\( > 75 \) kg: 1200 mg and \( < 75 \) kg: 1000 mg) at Hospital de Infectología “La Raza” National Medical Center at Mexico City. After the subjects were treated for 12 wk, they were allocated into two groups: patients with EVR and patients without EVR.

**Study patients**

Patients were eligible for the study if they were between the ages of 18 and 75 years old, had chronic HCV infection, had no history of treatment of HCV infection and had HCV RNA positive serum (at least \( > 50 \) IU/mL) according to a Real Time RT-PCR (Cobas Amplicor HCV v2.0, Roche Molecular Systems), serum aminotransferase levels and platelets measures. Patients were excluded if they had poorly controlled psychiatric disease, a solid organ transplant, an autoimmune condition, thyroid disease, a hemoglobin level of 12 g/dL or lower, a neutrophils count of 1500 per cubic millimeter or lower, a platelet count of 75,000 per cubic millimeter or lower, drug abuse within the previous 12 mo, or alcohol abuse within the previous 6 mo, and an HBV or HIV coinfection.

The study was conducted in conformance with the principles of the Declaration of Helsinki. The institutional review board of the hospital approved the protocol and consent forms. All participants in the prospective way provided written informed consent.

**Clinical assessments**

Medical history was recorded for all patients (general attributes, medical problems, and medications), physical exam (height and weight), and laboratory results (blood cell count, liver function test, HCV RNA, and viral genotype).

We calculated the APRI using the following formula: APRI = AST levels (\( \times \) ULN)/platelet count (10\(^3\)/L) \( \times \) 100, where ULN means the upper limit of normal.

Fibrosis was established if the APRI was \( \geq 1.2 \). The primary efficacy end point was EVR, defined as \( \geq 2 \) log reduction of the HCV RNA level compared to the baseline HCV RNA level (partial EVR) or HCV RNA negative at treatment week 12 (complete EVR). To evaluate APRI as a predictor of EVR, we stratified between genotype 1 and genotype other than 1 (genotypes 2 or 3).

**Statistical analysis**

Statistical analysis was performed with SPSS for Windows (version 12.0; SPSS Inc., Chicago, Ill). Categorical variables were compared using the Pearson’s \( \chi^2 \) or Fisher’s exact test. Odds ratio (OR) and 95% confidence interval (CI) were calculated to assess the relationship between each risk factor. To adjust for the effects of potential confounders, we used logistic regression models. \( P \leq 0.05 \) were considered significant.

**Table 1 Patient’s baseline characteristics (\( n = 80 \))**

| Variable               | mean ± SD | Range          |
|------------------------|-----------|----------------|
| Age (yr)               | 42.9 ± 12 | 19-74          |
| Weight (kg)            | 70 ± 11.9 | 47-100         |
| Hemoglobin (g/dL)      | 14.8 ± 1.92 | 8.1-19       |
| Platelets (No/µL)      | 209,000 ± 84,429 | 37,300-444,000 |
| Leucocytes (cells/µL)  | 5.8 ± 1.87 | 2.9-13.2       |
| Glucose (mg/dL)        | 101 ± 18.94 | 73-172     |
| Creatinine (mg/dL)     | 0.96 ± 0.26 | 0.6-1.2       |
| Albumin (g/dL)         | 4.4 ± 0.51 | 2.9-5.5       |
| AST (IU/dL)            | 64.6 ± 48.74 | 17-253   |
| ALT (IU/dL)            | 76.3 ± 63.08 | 14-249      |
| LDH (IU/dL)            | 272.6 ± 90.96 | 116-704    |
| AP (IU/dL)             | 106.4 ± 40.37 | 51-240     |
| Baseline viral load (IU/mL) | 2,269,061 ± 7,220,266 | 1,200-56,000,000 |
| APRI                   | 1.61 ± 1.90 | 0.17-8.0      |

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; AP: Alkaline phosphatase; APRI: AST to platelet ratio index.

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Table 2  Clinical characteristics in EVR and non-EVR patients (n = 80)

| Variable                  | EVR patients (n = 54) | Non-EVR patients (n = 26) | P value |
|---------------------------|-----------------------|---------------------------|---------|
| Age (yr)                  | 43.61 ± 11.92         | 41.65 ± 12.90             | 0.505   |
| Weight (kg)               | 71.09 ± 11.77         | 68.69 ± 9.88              | 0.372   |
| WBC (cells/mm³)           | 5.824 ± 1.901         | 5.040 ± 1.850             | 0.820   |
| Hemoglobin (g/dL)         | 14.86 ± 2.05          | 14.77 ± 1.74              | 0.855   |
| Platelets (×10³/μL)       | 212,162 ± 79,956      | 207,815 ± 94,603          | 0.781   |
| Glucose (mg/dL)           | 101.16 ± 18.94        | 99.96 ± 17.13             | 0.697   |
| AST (IU/mL)               | 62.07 ± 46.52         | 69.84 ± 53.64             | 0.508   |
| ALT (IU/mL)               | 72.81 ± 62.15         | 83.61 ± 65.62             | 0.477   |
| Creatinine (mg/dL)        | 0.97 ± 0.31           | 0.93 ± 0.11               | 0.552   |
| LDH (IU/mL)               | 26.07 ± 9.977         | 263.65 ± 70.12            | 0.543   |
| HCV RNA viral load (copies/mL) | 2243191 ± 7664170 | 2322791 ± 6263297         | 0.964   |
| APRI                      | 1.47 ± 1.63           | 1.90 ± 2.37               | 0.333   |

EVR: Early viral response; HCV: Hepatitis C virus.

Table 3  Factors associated with EVR (Univariate analysis)

| Variable                  | OR         | 95% CI     | P value |
|---------------------------|------------|------------|---------|
| Sex                       | 1.079      | 0.797-1.491| 0.624   |
| Age > 40 years old        | 1.570      | 1.069-2.090| 0.346   |
| Weight > 75 kg            | 1.299      | 0.493-4.397| 0.798   |
| Platelets < 150 000/μL   | 0.776      | 0.264-2.870| 0.644   |
| Albumin < 3.5g/dL         | 1.471      | 1.144-14.863| 1.0     |
| ALT > 28 IU/dL            | 1.320      | 0.421-4.135| 0.633   |
| Viral load > 600 000 IU/mL| 0.944      | 0.352-2.533| 0.910   |
| Genotype 1 vs genotype other than 1 | 0.286 | 0.086-0.834| 0.034*  |
| APRI > 1.2                | 0.615      | 0.229-1.655| 0.334   |

Table 4  Factors associated with EVR (multivariate analysis)

| Variable                  | EVR         | 95% CI     | P value |
|---------------------------|-------------|------------|---------|
| Age > 40 years old        | 1.420       | 0.489-4.166| 0.515   |
| Weight > 75 kg            | 1.214       | 0.435-3.384| 0.711   |
| ALT > 28 IU/dL            | 1.645       | 0.469-5.773| 0.437   |
| Viral load > 600 000 IU/mL| 0.946       | 0.328-2.729| 0.919   |
| Genotype 1 vs genotype other than 1 | 0.304 | 0.087-0.946| 0.041   |
| APRI > 1.2                | 0.469       | 0.151-1.457| 0.190   |

Chi square. *P < 0.05.

RESULTS

Patients

During the study, 84 patients were assigned to treatment; 80 patients completed the first 12 wk of therapy, three patients withdrew because of adverse events related to PEG-interferon, and one patient was lost during this period. Forty-five (56%) were evaluated retrospectively and 35 (44%) prospectively. Forty-one (51%) were female and 35 (34%) were male. The mean ± SD age of our subjects was 42.9 ± 12 years. Fifty-five (68.8%) were patients who were treated with PEG-interferon α-2b and ribavirin.

Viorelogic response and APRI findings

Analysis revealed EVR in 54 (67.5%) patients; 40 of them reached a complete EVR and 14 showed a partial EVR.

The APRI was calculated in all patients; 25 (31%) patients were ≥ 1.2; the mean ± SD APRI was 1.61 ± 0.090.

Independent factors associated with EVR

To identify predictors of EVR, in an univariate analysis, we observed the following: sex (OR 1.079, 95% CI 0.797-1.491, P = 0.624), age > 40 years (OR 1.57, 95% CI 0.609-4.090, P = 0.346), body weight > 75 kg (OR 1.29, 95% CI 0.491-3.437, P = 0.598), viral load > 600 000 IU/mL (OR 0.944, 95% CI 0.352-2.533, P = 0.910), genotype 1 vs genotype other than 1 (genotype 2 or 3) (OR 0.286, 95% CI 0.086-0.834, P = 0.034) and APRI > 1.2 (OR 0.615, 95% CI 0.229-1.655, P = 0.334), (Table 3). Final multiple logistic-regression model, including the following factors, was entered in the final stepwise regression analysis: sex, age (< 40 years vs > 40 years), body weight (< 75 kg vs > 75 kg), pretreatment viral load (< 600 000 copies/mL vs > 600 000 IU/mL), pretreatment alanine aminotransferase quotient (> 3 vs < 3), pretreatment APRI score (< 1.2 vs > 1.2), and HCV genotype (1 vs non-1). Only one factor increased the odds of achieving an EVR independently and significantly: HCV genotype other than 1 (OR 0.304, 95% CI 0.087-0.946, P = 0.041, Table 4).

Among patients with genotype 1, APRI score (< 1.2 vs > 1.2) was evaluated and showed an OR of 0.65 (95% CI 0.20-2.09, P = 0.475). For patients with genotype other than 1 we found an OR of 0.40 (95% CI 0.045-3.57, P = 0.575).

DISCUSSION

Our results suggested that the APRI is not a predictor of EVR. We found no association when APRI was more than 1.2. In addition, when we stratified between genotype 1 and genotype other than 1 to evaluate APRI as a predictor of EVR, we found no association. Nevertheless, we found one predictor of absence of EVR (genotype 1 vs genotype other than 1) in patients who were treated with PEG-interferon α-2b and ribavirin.

A reasonable interpretation of these results is that, despite the possibility that biopsy could predict treatment response in HCV infected patients; an indirect measure of fibrosis with APRI is not an option to pre-
dict viral response.

We also found that in this Mexican population sex, age, weight, HCV viral load, and aminotransferase serum levels were not associated with viral response. One possible explanation for our results is that we adjusted ribavirin and Peg-interferon-α-2b doses according to patient’s weight.

Our findings are comparable with previous reports that evaluate predictors of sustained viral response.

Though our results might seem to differ with those of Fried et al., who found age and weight as predictors of viral response, most of the patients in their study were Caucasians, and race has been shown to be a factor in the response to therapy for hepatitis C virus infection.3,13

In their study, Akuta and colleagues concluded that hepatocyte steatosis is a factor associated with virological non-response, however they measured liver steatosis by obtaining liver biopsy percutaneously, and did not use a noninvasive assessment of liver fibrosis.4,16

Our results are consistent with those of Nagaki et al., who found no association among age, weight, and HCV viral load with sustained viral response in patients with chronic hepatitis C genotype 1b. Finally, similar to all prospective treatment studies, we found genotype as the strongest predictor of response.3,18-20

This was an ambispective study, and it has several limitations, more than half of patients were analyzed in a retrospectively way. In addition, rapid virological response was not measured in this group of patients, which now is a very important predictor of sustained viral response. In addition, these results could have been affected by the small sample size.

Another limitation in our study is that some of the patients are still undergoing treatment, for this reason, we still do not have the results for sustained viral response, which is the goal of treatment in patients with HCV infection. Thus, although EVR is a predictor of SVR in approximately 60%-80%, SVR is necessary to gain full results.

Previous studies have not explored the utility of noninvasive tests to assess liver fibrosis for the prediction of viral response in hepatitis C naive patients.

Despite the limitation of our study, we believe our results show that APRI is not a predictor of early viral response in HCV naive patients.

It is necessary to perform a study including sustained viral response as the final goal of treatment. In addition, other indirect liver damage measures (fibrotest or transient elastography) should be used to improve recognition, diagnosis, and management. Finally, future prospective research to study noninvasive assessment of liver fibrosis to predict sustained viral response should be developed.

COMMENTS

Background

Viral response in patients with chronic hepatitis C virus infection is more likely to be observed in some patients. The absence of bridging fibrosis/cirrhosis on biopsy has been significantly associated with sustained viral response (SVR). Despite its widespread use, performing a liver biopsy is not without due cautions and concern for physicians and patients alike. Significant complications, defined as requiring hospital admission or prolonging hospital stay, occurs in 1% to 5% of patients. AST to platelet ratio index (APRI) is an easy and non-invasive method to evaluate hepatic fibrosis. APRI as a predictive factor of early viral response in hepatitis C chronic naive patients has not been evaluated.

Research Frontiers

The APRI is one of several markers that have been proposed to measure liver fibrosis; it is an inexpensive widely available tool; however it has not been used as a predictive factor in chronic hepatitis C. Further studies across more diverse cohorts of liver disease will be necessary, and further refinement will likely enhance accuracy. In this study, the authors demonstrated that APRI is not a predictive factor for early viral response (EVR) in patients with chronic hepatitis C.

Innovations and Breakthroughs

Recent studies have shown the importance of this test to decrease the number of liver biopsies, particularly because patients with an APRI of less than 0.40 have very little chance of having significant fibrosis. This is the first study to evaluate the APRI as a predictive factor of early viral response in patients with chronic hepatitis C.

Applications

APRI is a good estimator of hepatic fibrosis. It could be used to decrease the number of liver biopsies; however it is not useful to predict EVR in chronic hepatitis C patients.

Terminology

The APRI is one of several markers that have been proposed to measure liver fibrosis; this index accurately predicts mild fibrosis in patients with a value < 0.42 and those with a value > 1.2 are diagnosed as a significant grade of fibrosis. APRI establishes a 90% negative predictive value for the absence of fibrosis and a 91% of positive predictive value for its presence. We calculated APRI with the following formula: APRI = AST levels (× ULN)/platelets counts (10%L) × 100.

Peer review

It is necessary to investigate the utility of APRI as a predictor of sustained viral response.

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