Is P2/MS A New Pretreatment Predictor for eRVR and SVR in the Chronic Hepatitis C Patients Treated with Telaprevir Triple Therapy: A Retrospective Observational Study

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ABSTRACT

AIM: Extended rapid virologic response (eRVR) predicts sustained virologic response (SVR) and provides to determine shortening response guided treatment duration. P2/MS<45, an effective and noninvasive marker reflecting the degree of hepatic fibrosis, demonstrates serious hepatic fibrosis. In a retrospective observational study, we studied the relationship between P2/MS and eRVR among HCV genotype 1 (G1) infected patients who were treated with triple therapy patients. P2/MS was evaluated whether it is a predictor for treatment response by foreseeing eRVR.

METHOD: Thirty one patients infected with HCV-G1 and were treated with triple therapy involving telaprevir, pegylated interferon-α and ribavirin, were enrolled in the study. P2/MS values were evaluated before the treatment. HCV-RNA levels were measured at the initiation period, the 4th and 12th weeks.

RESULTS: Nine patients of 31 had detectable HCV-RNA in the 4th week. Among 6 of these 9 patients had P2/MS<45. HCV-RNA was undetectable in 22 patients at the 4th week of the treatment. Sixteen of them had P2/MS<45. Among 30 of 31 patients, HCV-RNA was undetectable at the 12th week of the treatment. We found that eRVR success was 85% in patients with P2/MS score>45 and 45.4% in patients with P2/MS<45.

CONCLUSION: P2/MS is a noninvasive marker for detecting hepatic fibrosis in HCV patients. A positive correlation between P2/MS score and eRVR is demonstrated. We suggest that P2/MS should be used as a pretreatment predictive marker for HCV-G1 infected patients, estimating SVR and the patients suitable for shortening therapy.

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Key words: Hepatitis C; P2/MS; Non-invasive hepatic fibrosis marker; eRVR; SVR

INTRODUCTION

Hepatitis C virus (HCV) infection is a serious worldwide health problem causing an increased risk of cirrhosis and hepatocellular carcinoma. Treatment of HCV infection is important to prevent the complications above. The use of triple-therapy, pegylated-interferon, ribavirin and one of the first generation HCV protease inhibitors (telaprevir or boceprevir), is the new standard care for treating genotype 1 chronic HCV infection. When using the protease inhibitor telaprevir, the extended rapid virological response (eRVR) has an important role in response-guided therapy. With eRVR which is associated about 90% with a sustained virologic response (SVR), the overall duration of treatment can be shortened in selected patients. Shortening treatment can help physicians to save time and to decrease the costs. However, a pretreatment predictor for eRVR, which is related with SVR and shortening treatment, has not been investigated before. Hence, in a retrospective
observational study, we aimed to analyze the relationship between P2/MS, a noninvasive hepatic fibrosis marker, and eRVR among HCV genotype 1 (G1) infected patients who were treated with triple therapy.

**METHODS**

We retrospectively searched the patients who were treated with triple treatment involving telaprevir, pegylated interferon alpha and ribavirin between January 2013 and November 2014. We excluded bocepravir patients due to the low number of patients. We recruited 31 patients who were previously naive, relapsers or nonresponders. All eligible patients were included in the study to avoid selection bias.

None of the subjects had the diseases or treatments that might affect leukocyte or platelet numbers, such as corticosteroid treatment, connective tissue disease, hematologic malignancies or idiopathic thrombocytopenic purpura. All patients were above 18 year-old.

Complete blood count before the triple treatment and HCV RNA levels at the beginning, the 4th and the 12th weeks of the treatment were used for calculations.

**P2/MS calculation**

P2/MS formula is as follows \( \left\{ \left[ \text{platelet count (10}^9/L) \right]^2 \left[ \text{monocyte fraction(%)} \times \text{segmented neutrophil fraction(%)} \right] \right\}^{1/2} \). We accepted that P2/MS<45 as severe fibrosis and P2/MS≥45 as mild or moderate fibrosis or no fibrosis. The patients were divided into two groups according to the P2/MS values (group 1=P2/MS≥45, group 2=P2/MS<45).

**HCV-RNA test**

HCV RNA levels were measured by PCR, at the beginning, the 4th and 12th weeks of the treatment. The linear interval of the test was between 15 IU/mL - 6.90.108 IU/mL.

Patients who have an undetectable HCV RNA levels at week 4 through week 12 are considered to have an extended rapid virologic response (eRVR)[10].

An undetectable HCV RNA level 24 weeks after treatment discontinuation is considered as sustained virologic response[11].

**Statistical analysis**

The analysis of the data was performed in SPSS for Windows 11.5 program. The appropriation of the distribution of the continous numeric variables to the normal distribution was checked with Shapiro Wilk test. The average value of the difference between the groups in terms of median value was measured with Mann Whitney U test. Nominal variables were evaluated with Fisher’s exact test. Sensitivity, specificity, positive and negative predictive values and the diagnostic accuracy rate were calculated to assess the diagnostic performance of P2/MS. P value <0.05 was considered statistically significant.

**RESULTS**

P2/MS scores were higher than 45 in 20 patients (group 1) and lower than 45 in 11 patients (group 2). The demographic data is summarized in table 1. At the 4th week of the treatment in 9 of 31 patients, HCV RNA was positive but below 10⁶ IU/mL. Among these 9 patients, 6 of them were in group 2 (P2/MS<45) and 3 patients were in group 1 (P2/MS≥45). HCV RNA was undetectable in 22 patients at the 4th week of the treatment. Seventeen of these patients were in group 1.

HCV RNA was undetectable in 30 of 31 patients at the 12th week of treatment. Only in one patient, HCV RNA was 10⁷ IU/mL and the patient’s P2/MS score was less than 45. The treatment of the patient was discontinued. Table 2 and figure1 summarize the treatment response rates.

We believe that all P2/MS scores were related to degree of hepatic fibrosis. Because all possible confounding factors that may affect complete blood count and P2/MS calculation were excluded.

**DISCUSSION**

As shown in tables and figure 1, the mean HCV RNA levels and the mean age of group 1 and group 2 were similar. eRVR success rate was 85% in group 1 and 45.4% in group 2. Although it seems that a disparity exists, the statistical analysis demonstrated that there was no significant differences between the groups and no relationship between P2/MS and eRVR (p=0.9).

eRVR provides to determine SVR, which means almost cure of chronic HCV infection. Because 99.1% of the patients who achieves a SVR, have undetectable levels of HCV RNA in serum samples throughout the follow-up period[12]. As a result, patients with SVR can be treated with shortening therapy. Hence, a marker which indicates SVR, have undetectable levels of HCV RNA in serum samples throughout the follow-up period[12]. This new method may provide the physician to skip triple treatment from the beginning. So, we investigated P2/MS, a noninvasive hepatic fibrosis marker, whether it is a predictor for eRVR or not. In this study, the statistical analysis demonstrated no significant difference. This might be a result of the small study population number (n=31). In a larger sample group, the same study may show a significant difference.

**Table 1** Demographic features of the patients.

| P2/MS ≥45 | P2/MS<45 |
|-----------|----------|
| Subject number | 20 | 11 |
| Female/Male | 13F/7M | 4F/7M |
| Mean HCV RNA leve (10⁶) | 5.6 | 5.7 |
| Mean age (year) | 57.9 | 57.8 |

**Table 2** Treatment responses of the patients.

| P2/MS ≥45 | P2/MS<45 | p value |
|-----------|----------|---------|
| Undetectable HCV RNA (1. month) | 12 | 4 | 0.9 |
| Undetectable HCV RNA (3. month) | 15 | 8 | 0.1 |

**Figure 1:** eRVR success ratio.
We suggest that P2/MS, a noninvasive and inexpensive hepatic fibrosis marker, can be used as a pretreatment predictive marker for HCV G1 infected patients, estimating SVR and the patients suitable for shortening therapy. Studies with larger sample sizes and with other hepatic fibrosis markers need to be done.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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