

## 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

Firdevs Topal, Zeynep Zehra Gumus, Elif Saritas Yuksel, Cem Cekic, Fatih Aslan, Sezgin Vatanserver, Belkis Unsal

Firdevs Topal, Elif Saritas Yuksel, Cem Cekic, Fatih Aslan, Sezgin Vatanserver, Belkis Unsal, Department of Gastroenterology, Izmir Ataturk Education and Training Hospital, Turkey

Zehra Zehra Gumus, Department of Internal Medicine, Izmir Ataturk Education and Training Hospital, Turkey

Correspondence to: Zehra Zehra Gumus, Department of Internal Medicine, Izmir Ataturk Education and Training Hospital, Turkey

Email: [zeynepzehrag@gmail.com](mailto:zeynepzehrag@gmail.com)

Telephone: +90-232-244-4444

Received: November 5, 2014

Revised: December 17, 2014

Accepted: December 20, 2014

Published online: January 21, 2015

### 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- $\alpha$  and ribavirin, were enrolled in the study. P2/MS values were calculated before the treatment. HCV-RNA levels were measured at the initiation period, the 4<sup>th</sup> and 12<sup>th</sup> weeks.

**RESULTS:** Nine patients of 31 had detectable HCV-RNA in the 4<sup>th</sup> week. Among 6 of these 9 patients had P2/MS<45. HCV-RNA was undetectable in 22 patients at the 4<sup>th</sup> week of the treatment. Sixteen of them had P2/MS>45. Among 30 of 31 patients, HCV-RNA was undetectable at the 12<sup>th</sup> 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.

© 2015 ACT. All rights reserved.

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

Topal F, Gumus ZZ, Yuksel ES, Cekic C, Aslan F, Vatanserver S, Unsal B. 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. *Journal of Gastroenterology and Hepatology Research* 2015; 4(1): 1444-1446 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/879>

### INTRODUCTION

Hepatitis C virus (HCV) infection is a serious worldwide health problem causing an increased risk of cirrhosis and hepatocellular carcinoma<sup>[1,2]</sup>. 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<sup>[3]</sup>. When using the protease inhibitor telaprevir, the extended rapid virological response (eRVR) has an important role in response-guided therapy<sup>[4,5]</sup>. With eRVR which is associated about 90% with a sustained virologic response (SVR), the overall duration of treatment can be shortened in selected patients<sup>[6-8]</sup>. 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 diseases, 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 4<sup>th</sup> and the 12<sup>th</sup> weeks of the treatment were used for calculations.

### P2/MS calculation

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

### HCV-RNA test

HCV RNA levels were measured by PCR, at the beginning, the 4<sup>th</sup> and 12<sup>th</sup> 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)<sup>[10]</sup>.

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

### Statistical analysis

The analysis of the data was performed in SPSS for Windows 11.5 program. The appropriation of the distribution of the continuous 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. Sensivity, 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  $10^2$  IU/mL. Among these 9 patients, 6 of them were in group 2 ( $\text{P2/MS} < 45$ ) and 3 patients were in group 1 ( $\text{P2/MS} \geq 45$ ). 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  $10^3$  IU/mL and the

patient's P2/MS score was less than 45. The treatment of the patient was discontinued. Table 2 and figure 1 summarize the treatment response rates.

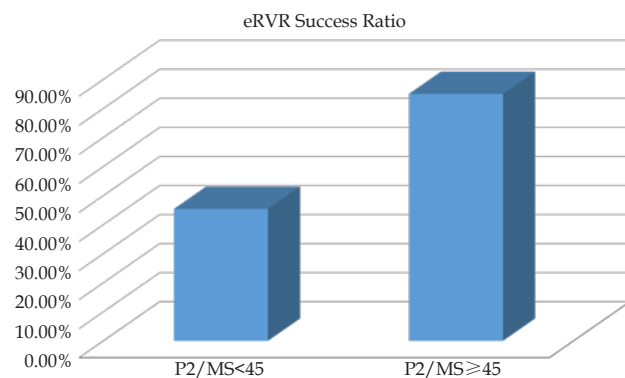
We believe that all P2/MS scores were related to degree of hepatic fibrosis. Because all possible confounding factors that may affect complete blood count and P2/MS calculation were excluded.

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

	P2/MS $\geq$ 45	P2/MS<45
Subject number	20	11
Female/Male	13F/7M	4F/7M
Mean HCV RAN leve (10*)	5.6	5.7
Mean age (year)	57.9	57.8

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

	P2/MS $\geq$ 45 (n=15)	P2/MS<45 (n=9)	<i>p</i> value
Undetectable HCV RNA (1. month)	12	4	0.9
Undetectable HCV RNA (3. month)	15	8	0.1
eRVR	12	4	0.9



**Figure 1:** eRVR success ratio.

## 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<sup>[12]</sup>. As a result, patients with SVR can be treated with shortening therapy. Hence, a marker which indicates eRVR and accordingly SVR will be cost-effective and time saving. 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.

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.

## REFERENCES

- 1 Feeney ER, Chung RT. Antiviral treatment of hepatitis C. *BMJ* 2014; **7**: 349: g3308
- 2 Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet* 2011; **378**(9791): 571-583
- 3 Pan Q, Peppelenbosch MP, Janssen HL, de Knegt RJ. Telaprevir/boceprvir era: from bench to bed and back. *World J Gastroenterol* 2012; **18**(43): 6183-6188
- 4 Wedemeyer H, Jensen DM, Godofsky E, Mani N, Pawlotsky JM, Miller V (HCV Drug Development Advisory Group). Under the auspices of the Forum for Collaborative HIV Research. Recommendations for standardized nomenclature and definitions of viral response in trials of HCV investigational agents. *Hepatology* 2012 Jun 18
- 5 Macartney MJ, Irish D, Bridge SH. Telaprevir or Boceprvir Based Therapy for Chronic Hepatitis C Infection: Development of Resistance Associated Variants in Treatment Failure. *Antiviral Res* 2014; **105**: 112-117
- 6 Ghany MG, Strader DB, Thomas DL, Seeff LB. American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; **49**: 1335-1374
- 7 Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. *Clin Infect Dis* 2011; **52**: 889-900
- 8 Petta S, Craxi A. How to optimize HCV therapy in genotype 1 patients: predictors of response: Review article. *Liver Int* 2013; **33**:1: 23-29
- 9 Kwak MS, Lee JH, Chung GE, Yu SJ, Jung EU. Low P2/MS value is an independent risk factor for early recurrence of hepatocellular carcinoma after radiofrequency ablation therapy. *Hepatogastroenterology* 2011; **58**(105): 147-152.
- 10 Alexopoulou A, Papatheodoridis GV. Current progress in the treatment of chronic hepatitis C. *World J Gastroenterol* 2012; **18**(42): 6060-6069
- 11 Berenguer J, Alvarez-Pellicer J, Martin PM, et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfecting with human immunodeficiency virus and hepatitis C virus. *Hepatology* 2009; **50**: 407-413
- 12 Swain MG, Lai MY, Shiffman ML, Cooksley WG, Zeuzem S, Dieterich DT, Aberger A. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. *Gastroenterology* 2010; **139**(5): 1593-1601

**Peer reviewers:** Noritaka Wakui, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Toho University Omori Medical Center, 6-11-1 Omori-nishi, Ota-ku, Tokyo, Japan; Luis Rodrigo, Gastroenterology Department, University Hospital Central of Asturias, c/ Celestino Villamil s. nº, 33.006. Oviedo. Spain; Seyed Mohsen Dehghani, MD, Associate Professor of Pediatric Gastroenterology, Gastroenterohepatology Research Center, Shiraz Transplant Research Center, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, 71937-11351, Iran; Saad A Noeman Professor of Immunology and Molecular biology, Department of Medical Biochemistry, Faculty of Medicine, Tanta University, Elgesh street, Egypt.