

Hepatitis C Viral Kinetics as a Determinant of Stopping Pegylated Interferon and Ribavirin in Genotype 1 Infection

Do Young Kim

Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

See "Prediction of a Null Response to Pegylated Interferon α -2b Plus Ribavirin in Patients with High Viral Load Genotype 1b Hepatitis C" by Yuki Wada, et al, on page 421, Vol. 8, No. 4, 2014

Despite a substantial progress in the management of hepatitis C virus (HCV) infection for the last decade, the probability of achieving sustained virologic response (SVR) in genotype 1 infection just ranges from 40% to 55% with pegylated interferon (PEG-IFN) and ribavirin (RBV) for 48 weeks which has been the standard-of-care.^{1,2} Furthermore, a variety of adverse events associated with PEG-IFN and RBV are major obstacles to complete the antiviral therapy, particularly in cirrhotic or elderly patients. The baseline predictors of achieving SVR in genotype 1 patients were extensively studied and include IL28B single nucleotide polymorphism, viral loads, body mass index, and so on. Currently, there are two stopping rules in genotype 1 HCV infected patients who receive PEG-IFN and RBV therapy. Failure to achieve early virologic response (EVR) defined by HCV RNA ≥ 2 logIU/mL at week 12 has been a strong indicator of stopping antiviral therapy with PEG-IFN and RBV. A high negative predictive value (97%) of EVR justifies universal assessment of viral loads at week 12 of PEG-IFN/RBV treatment in genotype 1 infection. Discontinuation of PEG-IFN and RBV is also recommended in patients who show detectable HCV RNA at week 24 if they achieve partial EVR (HCV RNA decrease ≥ 2 logIU/mL, but still detected).³ The clinical significance of rapid virologic response (RVR) defined by undetectable HCV RNA at week 4 is that the patient has a favorable response to interferon and it would be possible to shorten the treatment duration from 48 to 24 weeks.

During antiviral therapy with PEG-IFN and RBV, early identification of patients with genotype 1 infection who are going to fail to achieve SVR has clinical implications that appropriate discontinuation could prevent wasting of medical resources and

unnecessary adverse events which result in poor quality of life. With antiviral therapy using PEG-IFN and RBV, the kinetics of viral declines are characterized by a biphasic shape; the first phase of rapid viral decline for 24 to 48 hours and second phase of slower viral decline for weeks with significant variations among individuals.⁴ The slopes of the second phase determine the effectiveness of viral clearance and differ between patients with responding and nonresponding to therapy. Thus, it is important to figure out an optimal time point during the second phase of viral kinetics which predicts null response to therapy.

Would it be useful to assess viral response at earlier time point rather than week 4 or 12 in genotype 1 infection to decide whether to continue or stop antiviral therapy? The article by Wada *et al.*⁵ published in this issue tried to investigate whether HCV RNA measured at week 2 during antiviral therapy with PEG-IFN α -2b and RBV in genotype 1b patients could predict the null response indicated by HCV RNA decline < 2 logIU/mL at week 12. In 72 genotype 1 patients with high viral loads (> 5 logIU/mL), depletion of HCV RNA less than 0.8 log at week 2 had a similar accuracy with combined IL28B (rs8099917) minor allele (T/G or G/G) and core 70 mutation. The areas under receiver operating characteristics curve to predict null response were 0.983 for HCV depletion at week 2, which were higher than those of other variables such as HCV RNA at week 4, IL-28B mutation or core 70 substitution. The sensitivity, specificity, positive predictive value and negative predictive value (NPV) of HCV RNA depletion at week 2 less than 0.8 log was 82% (9/11), 96% (53/55), 82% (9/11), and 96% (53/55), respectively. In a previous study, the HCV RNA at week 4 as a predictor of nonresponse was studied in Western patients with genotype 1 infec-

Correspondence to: Do Young Kim

Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea

Tel: +82-2-2229-1992, Fax: +82-2-393-6884, E-mail: DYK1025@yuhs.ac

pISSN 1976-2283 eISSN 2005-1212 <http://dx.doi.org/10.5009/gnl.2014.8.4.335>

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

tion.⁶ Early nonresponse (eNR) was defined as HCV RNA decline at week 4 less than 1 logIU/mL. Among a total of 159 patients, 38 (24%) experienced eNR and of those, 19 patients (50%) failed to achieve EVR. Three patients (8%) with eNR achieved SVR, thus the NPV of eNR was 92%. Based on these results, HCV RNA decline at week 4 could potentially predict null response to PEG-IFN/RBV therapy in genotype 1 infection.

What is considered important in study of Wada *et al.*⁵ might be whether the accuracy of HCV RNA at week 2, especially in terms of NPV for null response, is not lower than that measured at week 4. Since RVR at week 4 tends to be routinely evaluated in genotype 1 infection, inaccurate interpretation at week 2 may let some patients unnecessarily stop antiviral therapy and lose the opportunity to achieve SVR. The performance of HCV RNA at week 2 was found to be superior compared with week 4 in Wada's study. However, a large-scale study and validation in other cohort with different races are necessary. In addition, the definition of high viral loads (>5 logIU/mL) in the study is not one generally accepted. The results would have been different if more strict definition (>6 or >7 logIU/mL) was applied.

In the era of direct acting antiviral for the management of chronic hepatitis C, the use of PEG-IFN and RBV is expected to be decreased in genotype 1 infection. Nevertheless, such 'extremely rapid' virologic assessment at week 2 in PEG-IFN/RBV therapy for patients with high viral loads can be helpful in screening very rapidly those who will not have a benefit by further treatment.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009;361:580-593.
2. Park SH, Park CK, Lee JW, et al. Efficacy and tolerability of peginterferon alpha plus ribavirin in the routine daily treatment of chronic hepatitis C patients in Korea: a multi-center, retrospective observational study. *Gut Liver* 2012;6:98-106.
3. European Association for Study of Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. *J Hepatol* 2014;60:392-420.
4. Herrmann E, Zeuzem S. The kinetics of hepatitis C virus. *Eur J Gastroenterol Hepatol* 2006;18:339-342.
5. Wada Y, Tamai H, Kawashima A, et al. Prediction of a null response to pegylated interferon alfa-2b plus ribavirin in patients with high viral load genotype 1b hepatitis C. *Gut Liver* 2014;8:421-427.
6. Reau N, Satoskar R, Te H, et al. Evaluation of early null response to pegylated interferon and ribavirin as a predictor of therapeutic nonresponse in patients undergoing treatment for chronic hepatitis C. *Am J Gastroenterol* 2011;106:452-458.