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Editorial

The effect of alanine aminotransferase dynamics on predicting sustained virological response in chronic hepatitis C virus infection

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The sustained virological response (SVR) of the combination of both pegylated interferon alfa (PegIFN) and ribavirin (RBV) in patients with chronic hepatitis C virus (HCV) infection is heterogeneous.[1] The therapeutic approach has been more individualized to obtain the better outcomes of patients with chronic HCV infection, and clinicians need to know the factors for predicting SVR.[2] The viral factors are HCV genotype and serum HCV RNA levels at baseline, and numerous host factors include age, sex, race, weight, liver fibrosis, and insulin resistance.[1] Recently, an interleukin-28 polymorphism has been acknowledged as powerful pretreatment predictor of SVR.[3,4]

Once treatment is initiated, the monitoring of on-treatment viral responses such as rapid virological response (RVR) and early virological response (EVR) can further aid in predicting treatment response.[5] However, there was little data evaluated the relationship between on-treatment ALT changes and therapeutic outcome of PegIFN and RBV in chronic HCV. Kim et al[6] reported interesting evidence showing that the rapid normalization of serum ALT after start of treatment may play an additional role on predicting SVR.

Serum ALT levels are usually elevated in patients with chronic HCV, but more than half of patients may have a normal ALT level at some point due to its fluctuation.[7] In patients with persistently normal ALT levels, the median ALT levels remains stable for prolonged period, but transient elevations occur about 50% of cases.[8] Sustained normal serum ALT levels were associated with female, lower serum HCV RNA titer, and less inflammation and fibrosis on biopsy.[8] During chronic infection, serum HCV RNA levels remain relatively constant without significant fluctuation in untreated individuals.[9] This suggests that the process of viral production and clearance has been relatively balanced.

To investigate the effect ALT dynamics on SVR, we need to know the relationship with viral kinetics. Viral kinetic profiles show that the appearance of HCV RNA after initiation of standard therapy can be biphasic in the first 4 weeks.[10,11] The final slope reflects the net loss of infected cells, and a rapid loss of infected cells is strongly associated with end treatment of response and SVR.[12,13] Serum ALT, a surrogate marker of hepatocyte damage or death, decreases during antiviral treatment, and shows the lowest activity at the end of treatment.[14] The mechanism of decline of ALT level is not clear, but it can be explained by a reduction in infected cells, a non-cytolytic cure, or cell removal

Keywords: Alanine aminotransferase; Hepatitis C, chronic; Sustained virological response

Abbreviations: ALT, alanine aminotransferase; EVR, early virological response; HCV, chronic hepatitis C; PegIFN, pegylated interferon alfa; RBV, ribavirin; RVR, rapid virological response; SVR, sustained virological response

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irrelevant ALT dynamics. However, a decreased ALT level at early phase of treatment is not related with apoptotic acitivity.[15] Theoretically, the rapid declines in ALT may reflect a rapid decrease of ongoing inflammation in the same manner as removal of the virus. The pattern of viral elimination shows a rapid decrease in the first month. Ribeiro et al[14] showed that the RVR was significantly correlated the decline of ALT level at week 4 of treatment. Also, the retrospective study of 111 patients with chronic HCV infection treated by conventional IFN and RBV demonstrated that larger decline rates of ALT within the first two and four weeks was predictors of SVR.[16] These correlations suggest that ALT dynamics can be presented a possibility to reflect rapid virological changes especially in patients with elevated baseline ALT levels.

Kim et al[6] retrospectively analyzed changes in ALT levels between baseline and week 4 of treatment in 168 patients with chronic HCV infection. Multivariate analysis in this study showed that genotype, baseline viral load, age and ALT changes during antiviral therapy were independent predictors of SVR. These factors are in good agreement with recent data. This study has three interesting points. First, rapid normalization of ALT within 1.5 times of normal range after treatment significantly was associated with improved SVR in genotype I HCV patients (34.1% versus 20.0%, P=0.01) and non-1 HCV patients (88.1% versus 66.7%, P=0.11) who had initially high ALT levels. Currently, the monitoring of on-treatment viral responses such as RVR or EVR is important in treatment of chronic HCV infection for predicting the therapeutic response and determining discontinuation of therapy.[1] As mentioned above, a rapid decreases of ALT may reflect declines of viral load, and this result suggests that rapid normalization of ALT at week 4 of treatment could be used as a strategy for predicting a response of early viral load quantification in patients with high baseline ALT levels.

Second, 37/113 (32.7%) of patients with elevated baseline ALT levels had remained high ALT levels and 15/55 (27.3%) of patients with normal range of baseline ALT levels experienced high ALT during treatment. These groups had a low probability of SVR. Similar to this result, recent report suggested that mild ALT elevations (peak ALT value 1-1.5 x baseline value) during treatment may reflect ongoing viral activity in non-responders, but more significant rise may reflect a good virological response due to an immune-modulating effect of interferon.[17] However, this data was difficult to analyze the reason of on-treatment ALT elevation and to elucidate the relationship between on-treatment ALT elevation and SVR.

Third, previous study showed that SVR rates of the standard therapy in patients with normal ALT had relatively high, and were comparable with those with elevated ALT.[18] In the present study, 55/168 (32.7%) of enrolled patients had baseline normal range of ALT, and 40/55(72.7%) of these patients with sustained normal range of ALT had a high SVR rates (77.5%). Again, this result confirmed that the therapeutic response of the interferon-based regimen was not different between patients with normal ALT and elevated ALT

This study has several limitations of retrospective design, smaller group, and absence of potential confounders. Rapid normalization of ALT was used for predicting SVR in patients with elevated baseline ALT levels, but its usefulness is limited because of the paucity of knowledge about RVR and the difficulty of application in normal ALT levels. Because RVR is the most important predictor of SVR in genotype 2 or 3 infection, it is unreasonable to apply this result for predicting SVR except for genotype 1 infection. Therefore, it is still unclear whether the use of serum ALT levels, instead of RVR, is helpful for predicting SVR in clinical practice.

In conclusion, this study showed that the rapid decline of ALT at week 4 of treatment is linked to SVR. To date, there is little data in relationship between ALT variability and SVR in chronic HCV infection. Therefore, such information predicting virological response may be useful to clinicians for designing a monitoring schedule, and counseling the future plan especially in patients with elevated baseline ALT levels and genotype 1 infection. Further well designed research is needed to test and confirm these concepts.

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