Predicting Therapeutic Results of Interferon Based Treatment by Modeling the First Week Viral Kinetics in Patients with Chronic Hepatitis C

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age, sex, body mass index (BMI), baseline aspartate transaminase (AST), baseline alanine aminotransferase (ALT), genotypes, and history of diabetes mellitus was collected from each patient. Serum biochemistry was measured before treatment and after 1, 4, 8, 12, 24, 36, 48, and 72 weeks of treatment.

Eligible patients were treated with PEG-IFN-α plus RBV therapy over a period of 24 or 48 weeks. HCV-RNA levels were measured using the Amplicor HCV test (Roche Molecular Systems, Branchburg, NJ) before treatment and after 1, 4, 12, 24, and 48 weeks of treatment and HCV genotypes were determined using a reverse hybridization assay (Innolipa HCV, Innogenetics, Ghent, Belgium). The primary outcome variable was SVR, defined as negative HCV RNA test 24 weeks after completion of antiviral therapy. Nonresponse was defined as a positive HCV RNA test 24 weeks after completion of antiviral therapy.

Informed consent was obtained from each patient and the study protocol conformed to the 1975 Declaration of Helsinki. During therapy, safety was evaluated by biochemical and hematologic tests at each visit. Patients were observed closely for signs of unusual side effects. The dose of PEG-IFN and/or ribavirin was reduced or discontinued if the side effects were severe or intolerable. The Institutional Review Board approved the study protocol before the investigation began.

Five HCV kinetic parameters were measured including (a) the logarithm of the HCV RNA level at week 0, indicating baseline HCV viremia; (b) δ, the logarithm of the decline in HCV RNA level (Figure 1) between week 0 and week 1. (Antiviral treatment can interrupt viral infection. Thus, viral clearance causes serum virus level to fall. The degree of the decline in HCV RNA level is a reliable indicator of treatment effectiveness); (c) ε, the logarithm of the HCV RNA level at week 1 divided by the baseline level (Figure 1) and representing the rate of HCV clearance; (d) α, the trapezoidal area [the algebraic sum of areas] under the graph of the viral load between week 0 and week 1 (Figure 2). (In the current model, frequent viral load measurements must be made between week 0 and week 1. In our study, the trapezoidal area was an approximation to the integral of the function over the given interval. However, α was regarded as inversely related to SVR); (e) π, denoting the ratio 1: α and representing an SVR rate.

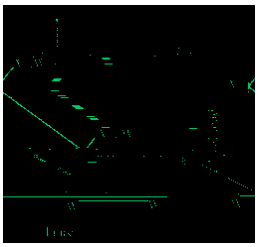

Figure 1: The graph shows the HCV RNA kinetics one week after PEG-IFN + RBV treatment of chronic hepatitis C. The viral decay slope, δ, indicating the decline of HCV at week 1, is (V0 – V1)/(W1 – W0). The viral load at baseline and week 1 is V0 and V1, respectively. W1=week 1. W0=week 0. The effectiveness in blocking virion production or the rate of HCV clearance at W1, ε, is (V0 – V1)/V0.

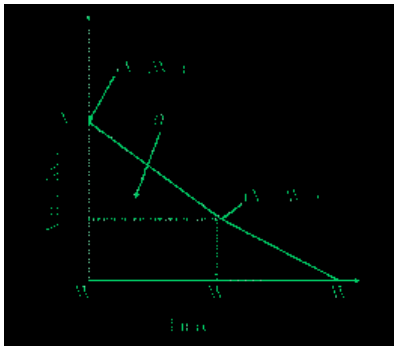

Figure 2: The graph shows the HCV RNA kinetics one week after PEG-IFN + RBV treatment of chronic hepatitis C. The viral load at week 0 and week 1 is V0 and V1, respectively. W1=week 1. W0=week 0. α is the trapezoidal area under the line connecting (V0, W0) and (V1, W1), which is equal to {[(V0 – V1)(W1 – W0)]/2}+ V1(W1 – W0). π is the ratio 1: α.

Statistical analysis

Continuous variables are expressed as means ± SD. Between-group differences in continuous variables were analyzed with the use of the Student's t-test (with 95% confidence intervals) or the Mann-Whitney U test. A p-value of less than 0.05 was considered to be statistically significant. Stepwise logistic regression was used to identify predictors of SVR that might be confounders. Receiver operating curve (ROC) statistics

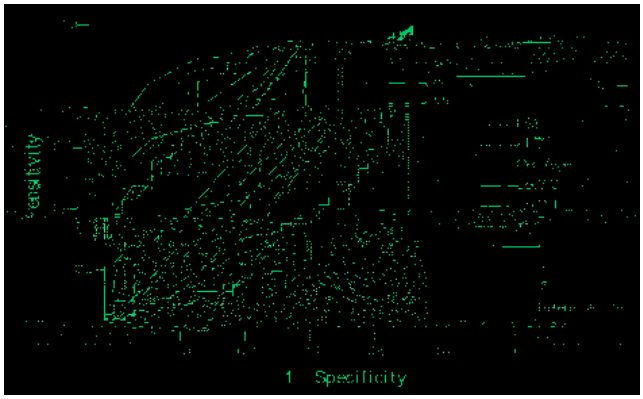

Figure 3: Comparing ROC curves of different clinical factors and HCV kinetic parameters for predicting SVR. π is the best predictor. BMI, body mass index; DM, diabetes mellitus; ALT, alanine aminotransferase; Log W0, logarithm of the baseline HCV RNA level; Log W1, logarithm of the HCV RNA level at week 1; Log W4, logarithm of the HCV RNA level at week 4; ε, logarithm of the HCV RNA level at week 1 divided by the baseline level, δ, logarithmic decline of the HCV RNA level; π, the ratio 1: α; α, trapezoidal area under the line between week 0 and week 1.

SVR. Therefore, HCV RNA level might be not the only factor that determines a therapeutic response. Furthermore, HCV viremia neither correlates with the severity of liver disease nor predicts the therapeutic outcome of HCV infection. Therefore, viral kinetics after initiating antiviral treatment might be a predictor of the real world therapeutic response in most situations. Based on the extrapolation of kinetic data demonstrating HCV decline, we were able not only to measure HCV RNA level earlier (i.e., one week after initiating antiviral treatment) but also to test five determinants of HCV RNA decay right after initiating treatment. Theoretically, models of the dynamic response to HCV therapeutic strategies can be used to individualize and optimize

20. Layden-Almer JE, Ribeiro RM, Wiley T, Perelson AS, Layden TJ (2003) Viral dynamics and response differences in HCV-infected African American and white patients treated with IFN and ribavirin. Hepatology 37: 1343-1350.