中文題目:宿主介白素 28B 基因多形性於感染慢性 C 型肝炎病毒基因型第一型患者接受長效型干擾素合併雷巴威靈快速停止治療的角色

英文題目:Sequential rapid stopping rule for hepatitis C genotype 1 patients with peginterferon plus ribavirin combination therapy-role of host interleukin-28B genetic polymorphisms

作者:黃釧峰 [1,2],戴嘉言 [1,3],黃志富 [1,3],莊萬龍 [1],余明隆 [1,4]

服務單位:[1]高醫肝膽內科 [2]高雄市立大同醫院職業病科 [3]高雄市立小港醫院內科 4 高雄市立大同醫院內科

Background

Recent advancement have demonstrated that host single nucleotide polymorphisms (SNPs) at and/or near the interleukin 28B (IL-28B) gene determine treatment outcome in HCV-1 infection. Current stopping rule for treatment of hepatitis C virus genotype-1 (HCV-1) patients with peginterferon/ribavirin is based on early virological response (EVR, defined as >2 $\log_{10}$ viral reduction at week 12). However, the HCV RNA data at week 12 were unavailable until week 14 in clinical practice. Actions of either stopping treatment or adjusting strategies as early as possible are an unmet need. It has been suggested poor viral kinetics at week 4 of treatment was predictive of detectable HCV RNA at week 12 and treatment failure. In the current study we aimed to set up a rapid stopping rule at week 4 on the basis of high negative predictive value (NPV) by combing both viral and host factors.

Methods

Patients who achieved 80/80/80 adherence of assigned 48-week treatment duration were selected retrospectively and consecutively. Forty-three patients who terminated early due to the classical 12-week stopping rule, < 2 logs drop of HCV viral loads after 12 weeks of treatment, were also included and classified as nonresponders. IL-28B rs8099917 genotype, a key genetic determinant in the treatment of HCV-1 infection, and on-treatment virological responses were determined in 528 HCV-1 patients with standard-of-care and were randomly divided into training and validation set with 1:2 ratios.

Results

In the training set, patients with higher HCV RNA levels at treatment week 4 (viral loads > 50 IU/mL, >1000 IU/mL or >10,000 IU/mL, and at least 1- $\log_{10}$, 2- $\log_{10}$, or 3-$\log_{10}$ decrease in HCV RNA levels from baseline) had significantly lower SVR rates compared with their counterparts (all P<0.001). Adding the unfavorable host factor, rs8099917 non-TT genotype, to week 4 viral loads, whatever the cut-off values,

greatly improved the NPV. The NPV of poor week 4 responses (W4R), defined as HCV RNA decline < 1 $\log_{10}$ IU/ mL (group A) or > 10,000 IU/mL/non-TT genotype (group B) was 92% and 94%, respectively. In the validation set, the NPV was 100 % and 94% in group A and group B, respectively. In the combined set, NPV was 98%, 94% and 95% in group A, group B and patients with poor W4R, respectively, among the 528 patients. Using the criteria of poor W4R as an earlier stopping rule only lost 0.8% (3/396) of potential responders. Multivariate analysis revealed that poor W4R was the most important factor predictive of treatment failure (odds ratio/ 95% confidence intervals [OR/CI]: 49.01/13.70-175.37, P<0.001), followed by failing to achieve an EVR, female gender, older age and increased body weight. Of the 62 patients with poor W4R, 85.7% (18/21) of the patients with an EVR and all (41/41) of the patients without an EVR ended in treatment failure. 80% (32/40) of the group A and 68.1% (32/47) of the group B patients failed to achieve an EVR. In addition to group A, using the criteria of group B helped identifying 32.2% (19/59) more non-responders and 52.6% (10/19) of them were with an EVR. With the strategy of sequential stopping rules, 53.7 % (73/136) of the non-responders could be identified (43.4% at W4, and 11.3% more at W12), compared to that of 40.4 % by using classical 12-week stopping rule.

Conclusion

We demonstrated that IL28B genotype combined with viral loads at treatment week 4 could predict treatment failure to 48-week peginterferon/ribavirin with NPV of as high as 95%. With the strategy of sequential stopping rules for HCV-1 patients, including 4-week stopping rule (IL-28B rs8099917 non-TT genotype plus viral loads > 10,000 IU/mL or decline < 1 $\log_{10}$ IU/mL at treatment week 4) and 12-week stopping rule (HCV RNA decline < 2 $\log s_{10}$ at treatment week 12), 53.7% non-responders could be early identified after 12 weeks of treatment. Of the early identifiable non-responders, 81% could be rapidly identified as early as 4 weeks of treatment. Beyond the factor of viral decline < 1 $\log_{10}$ IU/mL, the application of host IL-28B SNP helped identifying additional one-third patients who should stop treatment at week 4 with current standard-of-care.