The Role of Host Genetics in HCV Management

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Before the introduction of direct antiviral agents, standard of care (SOC) for treatment of chronic hepatitis C virus (HCV) infection is PegIFN plus RBV based on HCV genotype with a sustained virological response (SVR) rate of around 50% and 83% for HCV genotype-1/4 and HCV-2/3 patients, respectively, in Caucasian, and 70-75% and 85-90%, respectively, in Asian patients. Recently, response-guided therapy, based on on-treatment virological responses, has become the new era of care. A shorter 24-week regimen for HCV-1 with lower baseline viral loads and a rapid virological response (RVR, serum HCV RNA < 50 IU/ml at 4 weeks of treatment) and an abbreviated 16-week regimen with weight-based, standard dose of RBV for HCV-2/3 could provide equal efficacy to genotype-guided SOC. Extension of treatment to 72 weeks has improved the SVR rates among HCV-1 slow responders (HCV RNA > 2 log drop in HCV RNA but still detectable at week 12 and becomes negative at week 24.

Several host factors associated with treatment responses to IFN-based therapy may provide information for decision-making of individualized therapy for CHC patients, including age, BMI, insulin resistance, hepatic fibrosis and host genetic factors. Before the era of genome-wide association studies, single nucleotide polymorphism (SNP) of tumor necrosis factor alfa (TNF-α) promoter at position-308 could predicts response to combination therapy in CHC patients, in particular for patients with HCV-1 and high viral load. Both class I and II human leukocyte antigen (HLA) alleles have been associated with treatment outcome of chronic hepatitis C to IFN-based therapy. However, most of the results can not reach significance after adjustment with Bonferroni correction. A pharmacogenetic model consisted of 19 SNPs in five genes has been developed for improving and individualizing anti-HCV therapy in an Asian-specific, large-scale study. Further analysis demonstrated the prediction model could be used for tailoring treatment duration for HCV-1b patients. After introduction of IL28 genotype, the unfavorable IL28B genotpyes have been associated not only on-treatment virological responses, but also treatment success. It moght be applied for prediction of treatment failure in very early period of IFN-based therapy. Genetic variants on inosine triphosphatase (ITPA) gene leads to ITPA deficiency, a condition not thought to be clinically important, protect against haemolytic anaemia in hepatitis-C-infected patients receiving RBV. However, there is little role of the ITPA variants on treatment outcome.

Recently, studies on a liver-specific miRNA, miRNA-122, demonstrated that miRNA-122 is required for HCV replication in hepatocytes by its binding to the 5' UTR of HCV. Down-regulation of miRNA-122 in vitro and in vivo has led to significant inhibition of viral replication. Inhibition of miR-122 therefore presents a very attractive novel approach to treating HCV.

Several models of liver expression profile were developed to predict treatment out of interferon plus ribavirin combination therapy. However, the application of the prediction model is limited due to difficulty of tissue sampling in clinical practice.