Current standard of care for hepatitis C infection is treatment with interferon and ribavirin. Recent genome-wide association studies (GWAS) have shown that a genetic polymorphism at rs12979860 near IL28 gene on chromosome 19, encoding interferon-lambda-3, is associated with variable responses to the drugs. CC genotype of IL-28B is associated with two to three fold increases in sustained virologic response (SVR) as compared with either CT or TT genotype. These landmark studies have opened a new chapter in the field of host-viral interactions.

A study published in Nature analysed the data on more than 1,600 participants in a clinical trial IDEAL which compared the 2a and 2b forms of pegylated interferon in patients infected with HCV genotype 1. Genome-wide association studies were performed on tissue samples from these individuals, correlating their virologic responses to a large number of gene polymorphisms. SVR rates in patients with IL-28B genotype CC were 69% in Caucasians, 48% in African-Americans, and 56% in Hispanics. These response rates were two fold higher than genotypes TC and TT. IL-28B CC patients also responded more quickly to treatment within each ethnic group compared with the TC and TT genotypes. This genotype was seen in 77% of patients with rapid virologic response (RVR). Moreover, CC genotype predicted sustained responses in white patients who had not shown RVR. In such patients, 66% of those with the CC type eventually obtained a sustained response, compared with 31% of TC and 24% of TT genotypes.

Patients infected with viral genotype 2/3 already show good response to the treatment. Knowing IL-28B polymorphism in such cases may be of value only in those patients who do not achieve a RVR as shown by Mangia et al. Genetic variations in IL28B region may also predict who will have enough innate immune response to spontaneously clear virus after acute hepatitis C. Early therapeutic intervention could be recommended for individuals with unfavourable IL-28B genotypes.

IL28B genotype explains in part the racial differences in treatment response rates e.g. between Caucasians and African-Americans. The rs12979860 C variant is most frequently present in individuals from East Asia (allele frequency >0.9) and least common in individuals of African origin (allele frequency 0.2-0.5). In a US based study, the favourable CC genotype was observed in 37% of Caucasians, 29% Hispanics, and 14% of African Americans tested.

Suppiah et al and Tanaka et al identified a second polymorphism (rs8099917) in a similar region near the IL-28 gene which was strongly associated with response to combination treatment with interferon and ribavirin in Australian and Japanese patients, all infected with viral genotype 1. High rates of SVR are associated with rs8099917 TT genotype. Most recently, Rauch et al conducted a GWAS including all viral genotypes 1-4, and found that the rs8099917 minor allele was associated with both progression to chronic hepatitis C and failure to respond to treatment, with the strongest effects in patients infected with genotypes 1 or 4.

Interleukin-28A (IL-28A), IL-28B and IL-29, alternatively named as interferon lambda 2, 3 and 1 respectively are a family of class II cytokines that stimulate antiviral responses through a heterodimeric receptor that is distinct from the type I interferon. Unlike type I interferons, the target cell populations of interferon-lambda are restricted and mainly include epithelial cells and hepatocytes. Like interferon alpha, interferon lambda upregulates interferon stimulated genes (ISGs) by inducing JAK-STAT Pathway. However, interferon lambda binds to a receptor different from interferon alpha.

IL-28B genotype testing would become part of the standard of care once a test becomes clinically available. Genetic analysis of the host will be able to predict which patients are more likely to respond to treatment. IL-28B genotype is only one of many factors that can influence response rates to pegylated interferon and ribavirin therapy in HCV infection and should be interpreted in the context of other clinical factors predicting sustained response rates including HCV genotype, viral loads, ethnicity, baseline liver fibrosis, and fasting blood sugar etc. Association of single nucleotide polymorphism in IL-28B gene region with pegylated interferon treatment outcome raises the possibility of using IL-28B (interferon lambda) as a therapeutic agent against hepatitis C.

References


