In the last decade, the efficacy of therapy for chronic hepatitis C has been improved continuously. In patients infected with HCV-genotype 1, and having a high viral load, the rate of sustained virological response has gone from approx. 10% with standard IFN (interferon) to approx. 50% with a combination of pegylated interferon and ribavirin, which is the current standard therapy.

Efficacy of treatment is determined by a number of factors associated with the virus, the host, and IFN. Genetic host factors with a significant impact on antiviral therapy had not been identified so far, however. Therefore, mainly viral factors (genotype, kinetic behaviour, etc.) determined the decision to treat.

Recently, several research groups independently identified a genetic polymorphism in the human interleukin 28B gene region (C/T rs12979860) as closely associated with response to antiviral treatment (1) and also spontaneous clearance (2) among individuals infected with HCV genotype 1.

In these studies, patients showed an association of the CC genotype with a two- to three fold greater rate of sustained virological response to standard therapy when compared with patients carrying the CT or the TT genotype. This correlation between the IL28B genotype and therapy response was observed among HCV infected individuals of European, African (fig. 1), and Asian ancestry (not shown).

Fig. 1:
Percentage of sustained virological response (SVR) to HCV therapy (IFN/ribavirin; 48 wks) in carriers of different IL28B genotypes (rs12979860).
(Taken from Ge et al.)
**Triple therapy (including protease inhibitor)**

Recently, a new strategy was introduced in the treatment of chronic hepatitis C by means of inhibiting the virus-specific protease encoded by the NS3 gene region. In their clinical trial, Akuta et al. (3) investigated the influence of the IL28B polymorphism on hepatitis C patients receiving triple therapy of telaprevir (protease inhibitor) with PEG-IFN plus ribavirin.

According to the genetic variation in rs12979860, sustained virological response was achieved by 84% and 32% with genotype CC, and CT + TT, respectively.

Thus, a significantly higher proportion of patients with genotype CC showed sustained virological response than that of patients with non-CC genotypes.

**HCV genotypes 2 and 3**

While the investigation of the IL28B genotype had been restricted to HCV genotype 1-infected patients in the studies described above, Sarrazin et Zeuzem (4) extended their studies to patients infected with HCV genotypes 2 and 3. Carriers of the IL28B C/T and T/T genotypes showed 14% and 21% of non-responders, respectively. In homozygous carriers of the C allele (CC-genotype) the rate of non-responders was significantly lower (3.5%) demonstrating the striking influence of the IL28B genotype on HCV genotype 2/3 infected patients.

**Spontaneous clearance**

Approximately 30% of individuals spontaneously clear acute HCV infection. Host genetic factors, particularly variations in genes involved in the immune response, have been assumed to explain the heterogeneity in HCV clearance among individuals and ethnic groups. Recently, the direct role of the IL28B SNP (rs12979860) in HCV clearance in both individuals of European and African ancestry has been demonstrated (2). Patients with the C/C genotype were three times more likely to clear HCV relative to patients with the C/T and T/T genotypes combined, indicating a strong protective effect of the C/C genotype in both ethnic groups.

**SNP description and allele frequency**

The single nucleotide polymorphism rs12979860 (rs: reference snp identity), which is associated with spontaneous clearance and therapy success of hepatitis C infection maps 3 kilobases upstream of the IL28B gene on chromosome 19, which encodes the type III interferon IFN-λ3. The SNP comprises a C or T allele on the individual chromosomes (“dimorphism”). The presence of the unfavourable genotypes (C/T or T/T) was reported to be associated with lower expression of IL28B mRNA in peripheral blood cells.

Analysis of the C- and T-allele in more than 50 populations worldwide showed a striking global pattern of allele frequencies. Highest frequency (>90%) in East Asia and Oceania, lowest frequency (<50%) in Africa, and intermediate frequency in Europe (fig. 2). This global difference might explain the different frequency in viral clearance and treatment response among these populations.
Conclusion:

The IL28B gene polymorphism has been demonstrated to be in close association with the natural course and treatment response of chronic hepatitis C in different populations. It has been described to be an important predictive pre-treatment factor. Its differential global distribution explains much of observed clinical differences between ethnic groups. Genotyping of this polymorphism will aid clinical decision making for both current standard care and potentially for the integration of other agents in future, providing an opportunity for clinicians to individualize treatment regimens for hepatitis C patients.

IL28B specimen requirement: 3 ml EDTA blood in a monovette or vacutainer

TAT: approx. 3 days from receipt.

References:


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