The Role of IL28B Genotype in HCV-RNA Baseline Levels

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Dear Editor,

The role of interleukin (IL)-28B has been described in the treatment response and the spontaneous clearance of hepatitis C virus (HCV) infection [1], but recently several studies have examined the effect of the IL28B genotype and the natural course of chronic hepatitis C (CHC), especially regarding the fibrosis progression and liver inflammation. In an interesting paper by Nouredin et al. [2] the IL28B rs12979860 CC genotype, already known for its higher response rate to pegylated interferon (PEG-IFN) treatment, was associated with hepatic inflammation and worse clinical outcomes; also the rs8099917 GG genotype was associated with slower fibrosis progression than the TT genotype in Caucasian patients [3]. Another important contribution by Grebely et al. [4] highlighted the role of the IL28B genotype in HCV-RNA levels as an important factor that can affect the progression of fibrosis in CHC; however, the role of IL28B in influencing the baseline viral load is still poorly understood and considered in clinical studies. Patients with CC or TT genotypes present a higher baseline viral load than CT/TT or TG/GG genotypes, despite a greater chance of viral clearance or response to PEG-IFN. Regarding this finding, in our previous published study we reported that the IL28B genotypes were related both to baseline viremia and to the presence or absence of mixed cryoglobulinemia [5]. Patients with the TT/CC ge-

notype for rs12979860/rs8099917 showed a significant correlation with higher HCV-RNA levels, the presence of mixed cryoglobulinemia and insulin resistance. Furthermore, in our cohort of 541 patients affected by CHC and treated with PEG-IFN/ribavirin we retrospectively evaluated baseline HCV-RNA according to the combined genotypes of IL28B rs8099917 and rs12979860. The results are as follows (fig. 1): 192 patients presented the TT/

CC genotype (35.5%) with median HCV-RNA = 6.0 log IU/ml (IQR 5.4–7.2); 118 had the TT/TC genotype (21.8%) with median HCV-RNA = 5.6 log IU/ml (IQR 4.7–6.1); 133 showed the TG/TC genotype (24.6%) with median HCV-RNA = 5.2 log IU/ml (IQR 4.5–5.8), and 35 patients had the GG/TT genotype (6.5%), with median HCV-RNA = 4.8 log IU/ml (IQR 3.4–5.3). All the differences among the *IL28B* combinations were statistically significant ($p <$

Fig. 1. Median baseline HCV-RNA levels according to different genotypes of IL28B rs8099917 and rs12979860 in 541 patients treated with PEG-IFN and ribavirin.

0.001). Surprisingly, the difference of HCV-RNA between the favorable TT/CC and the unfavorable GG/TT profile is 1.2 log IU/ml, despite the greater clinical response observed in patients with the TT/CC genotype; this difference is greater than reported by Nouredin et al. [2] considering only the rs12979860 (0.16 log IU/ml). In multivariate analysis, the most predictive factor as-

sociated with a higher baseline viral load (HCV-RNA >800,000 IU/ml) is precisely the TT/CC genotype (OR 6.05, 95% CI 2.33–11.09, $p < 0.001$), while the presence of the G allele at rs8099917 is an independent predictive factor of low viral load (OR 18.06, 95% CI 6.61–34.55, $p < 0.001$). We previously reported the same finding in HCV-4 patients, where the TT/CC geno-

type was associated with a sustained viral response and GG/TT with a null-responder despite the lower baseline HCV-RNA [6]. In conclusion, we confirm the role of IL28B as a determinant of baseline viremia, but both rs8099917 and rs12979860 polymorphisms should be determined to better assess clinical outcomes, treatment response and the progression of liver fibrosis.

References

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