Research Article

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IFNL3 polymorphisms predict response to therapy in chronic hepatitis C genotype 2/3 infection

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Background & Aims: Single nucleotide polymorphisms (SNPs) near the interferon lambda 3 (*IFNL3*, previously known as *IL28B*) region are the strongest baseline predictors of sustained virologic response (SVR) to pegylated interferon and ribavirin therapy in hepatitis C virus (HCV) genotype 1 infection. Whether *IFNL3* SNPs influence treatment response in genotype 2 and 3 (HCV-2/3) infection remains controversial. This study sought to clarify in a large cohort, whether SNPs in the *IFNL3* region are associated with treatment response in HCV-2/3 patients.

Methods: The cohort comprised 1002 HCV-2/3 Caucasians patients treated with pegylated interferon-alpha and ribavirin who underwent genotyping for the SNPs *rs12979860* and *rs8099917*.

Results: Overall, 736 (73.5%) patients achieved SVR (81.9%, 67.9%, and 57.8% for *rs12979860* CC, CT, and TT [$p = 0.0001$]; 78%, 68.7%, and 46.3% for *rs8099917* TT, TG, and GG [$p = 0.0001$]). By logistic regression, both *rs12979860* CC and *rs8099917* TT were independent predictors of SVR with an odds ratio (OR) of 2.39 (1.19–3.81) $p = 0.0001$ and OR 1.85 (1.15–2.23) $p = 0.0001$, respectively. *IFNL3* responder genotypes were more frequent in relapsers than null-responders ($p = 0.0001$ for both SNPs). On-treatment rapid virological response (RVR) was predictive of SVR only in those individuals with *IFNL3* non-responder genotypes (*rs12979860* CT/TT and *rs8099917* TG/GG).

Conclusions: This adequately powered study in patients with HCV genotypes 2 or 3 infection clearly demonstrates that *IFNL3* genotypes are the strongest baseline predictor of SVR, in keeping with the known association for genotype 1 infection. *IFNL3* genotyping can aid in therapeutic decision making for these patients.
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Keywords: Chronic hepatitis C; *IFNL3* (*IL28B*); SVR; Genotype 2; Genotype 3; Response to therapy.

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Abbreviations: SNPs, Single nucleotide polymorphisms; *IFNL3*, interferon lambda 3; SVR, sustained virologic response; HCV-2/3, Hepatitis C virus genotype 2 and 3; RVR, rapid virological response; OR, odds ratio; PegIFNα/RBV, pegylated interferon-alpha and ribavirin; CHC, chronic hepatitis C; BMI, body mass index; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; γGT, gamma-glutamyl-transferase; SD, standard deviation.

Introduction

Hepatitis C virus (HCV) infects 170 million people worldwide [1] and is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma [2]. Treatment with pegylated interferon-alpha and ribavirin (PegIFNα/RBV) results in a sustained virologic response (SVR) in approximately 50% of people infected with HCV genotype 1 (HCV-1) and in ~75% of those infected with genotypes 2 or 3 (HCV-2/3) [3,4]. Although the addition of protease inhibitors such as telaprevir and boceprevir leads to a substantial improvement in the SVR rate for HCV-1 infection [5], PegIFNα/RBV remains the standard of care for non-1 genotypes [5]. In this context, there is growing interest in stratifying patients based on pre-treatment predictors of response, in order to have abbreviated treatment regimens both to minimize cost and more importantly, to reduce the adverse effects of interferon-based therapies.

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The discovery of polymorphisms near the *IFNL3* (formerly known as *IL28B*) gene, which codes for interferon lambda 3, represented a milestone in hepatitis C research [6–8]. Four years later, the value of polymorphisms in this region for predicting response to PegIFNα/RBV treatment in HCV-1 is well established [6–8]. In contrast, similar data for HCV-2/3 infection remains contentious [9–11], with results of two recent meta-analyses contradicting each other [12,13]. This controversy quite likely reflects the relatively small sample sizes of the previous studies and differences in ethnic stratification, which critically determines the frequencies of observed *IFNL3* genotypes [9–11].

The aims of this study were (1) to clarify the role of pretreatment *IFNL3* polymorphisms for predicting SVR in HCV-2/3 patients, (2) to explore the predictors of response in patients with the *IFNL3* responder genotype, and (3) to clarify the distribution of *IFNL3* in non-SVR patients. To address these questions, we analysed a large cohort of patients with genotype 2 or 3 chronic hepatitis C (CHC) infection and known treatment outcomes.

Patients and methods

Patient cohort

The cohort comprised 1002 Caucasians patients with CHC from Australia (N = 251), Spain (N = 261), Italy (N = 235), the United Kingdom (N = 199), and Germany (N = 56), fulfilling the following inclusion criteria: (a) adults aged 18 years or older with CHC based on the presence of anti-HCV and detectable serum HCV-RNA for >6 months, (b) infection with HCV-2 or 3, and (c) known outcome following PegIFNα/RBV based therapy. Patients were excluded if they were co-infected with either hepatitis B virus or HIV or had other liver diseases as assessed by standard tests. 89 of the patients from this study have been included in previous reports [14].

All patients were treated with PegIFNα/RBV; the duration of therapy and stopping rules employed were according to standard guidelines [5]. SVR was defined as undetectable HCV RNA 24 weeks after completion of therapy. Rapid virologic response (RVR) was defined as undetectable HCV RNA levels after 4 weeks of therapy. The non-SVR cohort included patients with either non-response or relapse. Virologic relapse was defined as HCV RNA undetectable at the end-of-treatment but positive thereafter, whereas virologic non-response was defined as HCV RNA detectable throughout the entire therapy of at least 24 weeks. Ethical approval was obtained from the Human Research Ethics Committees of the Sydney West Area Health Service and the University of Sydney. All other sites had ethical approval from their respective ethics committees. Written informed consent for genetic testing was obtained from all participants. The study was conducted in accordance with the international ethical guidelines of the International Conference on Harmonization Guidelines for Good Clinical Practice [15].

Clinical and laboratory assessment

The following data were collected at baseline: gender, age, ethnicity (Caucasian *vs.* non-Caucasian), recruitment center, body mass index (BMI), and routine laboratory tests. BMI was calculated as weight divided by the square of the height (kg/m^2). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl-transferase (γGT), bilirubin, hemoglobin, leukocyte and platelet count were determined by routine laboratory techniques.

Liver biopsy

Data on liver fibrosis at biopsy was available in 605 patients. Biopsies were interpreted according to the scoring schema developed by the METAVIR group [16] by a single expert liver pathologists in each center who was blinded to patient clinical characteristics and serum measurements. Thirty-five biopsies were scored independently by pathologists (DM, AZ, DG, and VA) from the various centers, and inter observer agreement was calculated by using the κ statistic. Fibrosis was scored on a 5-point scale: F0, no fibrosis; F1, portal fibrosis alone; F2, portal fibrosis with rare septae; F3, portal fibrosis with many septae; F4, cirrhosis. The presence of stage F2, F3, or F4 was termed "significant fibrosis", whereas the term "advanced fibrosis" was reserved for stage F3 or F4. Necro-inflammatory activity, based on assessment of piecemeal and lobular necrosis, was graded on a 4-point scale: A0, no activity; A1, mild; A2, moderate; A3, severe.

IFNL3 genotyping

Genotyping for *IFNL3* SNPs was undertaken using the TaqMan SNP genotyping allelic discrimination method (Applied Biosystems, Foster City, CA, USA). The *rs8099917* genotyping kit was supplied by Applied Biosystems and *rs12979860* genotyping was performed using a custom designed genotyping assay by Applied Biosystems. Detailed procedures have been described previously [17]. Genotyping was performed using the StepOne RT system and analyzed with StepOne software v.2.3.0 (Applied Biosystems, Foster City, CA, USA). All genotyping was blinded to treatment outcome.

Statistical analysis

Quantitative data are expressed as mean ± SD (standard deviation), and categorical data as number (percentage) of patients. Skewed variables are reported as median and range. The Student *t* test or non-parametric, i.e., Wilcoxon-Mann-Whitney U-test or Kruskal-Wallis tests were used to compare quantitative data, while appropriate. χ^2 and Fisher-exact tests were used for comparison of frequency data and to evaluate the relationships between groups. All tests were two-tailed and p values <0.05 were considered significant. Multiple regression models were used to assess for factors independently associated with RVR and SVR. *IFNL3* SNP comparisons were made using a dominant model, in which patients carrying one allele; or a recessive model (two copies of the minor allele), were compared with others unless otherwise indicated. Necroinflammation score was dichotomized as absent/mild necroinflammation or minimal changes (Metavir score A0-A1) or presence of moderate/severe necroinflammation (Metavir score A2–A3). Fibrosis stage was dichotomized into two groups; absent or mild fibrosis (Metavir score F0–1) and significant fibrosis (Metavir score F2–4).

To assess the cohort size required to detect significant differences, retrospective power analysis was performed, a power curve was plotted for power, sample size, and odds ratio. All analyses were carried out using the statistical software package SPSS for Windows, version 14 (SPSS, Chicago, IL) and SAS version 9.1 and SAS Enterprise 9.4.

Results

The characteristics of the study cohort are shown in Table 1. The median age was 43 (range: 19–69) years, with 560 (55.9%) patients being male. Of the cohort, 587 (58.6%) were infected with HCV-3, while the remaining had infection with HCV-2. The inter-observer agreement between pathologists was good (κ = 77.5) for METAVIR staging. An SVR was achieved in 736 (73.5%) patients; all others were classified as having a non-SVR. The latter included those with non-response (N = 139) and those with relapse (N = 127).

IFNL3 genotype distribution

Genotype distribution of the two *IFNL3* SNPs was in Hardy–Weinberg equilibrium (data not shown). The overall genotype distribution of *IFNL3 rs12979860* CC, CT, and TT was 46.9%, 42.9%, and 10.2%, and the distribution of *rs8099917* TT, TG, and GG was 63.1%, 32.4%, and 4.5%, respectively. 86 patients had no *rs8099917* genotype due to a lack of sufficient DNA for genotyping. The characteristics of those patients were matched to that of the whole cohort.

SVR rates were 81.9%, 67.9%, and 57.8% for *rs12979860* CC, CT, and TT ($p = 0.0001$) and 78%, 68.7%, and 46.3% for *rs8099917* TT, TG, and GG ($p = 0.0001$) (Fig. 1).

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