Genotype 4 Hepatitis C Virus Responds Worse than Genotype 1 to 48-Week Combination Treatment with Pegylated Interferon Alpha Plus Ribavirin: a Greek Multi-Centered Study

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Abstract

Background: Prevalence of genotype 4 chronic hepatitis C is increasing in western countries, where response to current combination treatment is still in debate; reports from endemic areas of Middle East show favourable treatment outcomes, while European reports show the contrary. Aim of this retrospective study was to estimate sustained virological response (SVR) of genotype 4 HCV patients in Greece, and to examine possible differences in SVR determinants between genotypes 1 and 4, the two most difficult genotypes to treat.

Methods: Demographic, virological and histological data from 467 consecutive HCV patients from five centers of follow-up were recorded. All patients completed standard combination therapy with pegylated interferon alpha plus weight-based ribavirin, according to current guidelines.

Results: Genotype distribution was: 192(44.8%), 29(6.8%), 130(30.4%), 63(14.7%) and 14(3.3%) for 1, 2, 3, 4 and undefined genotypes, respectively. Baseline characteristics were: 245(57.2%) male, aged 44.8 ± 13.8 years-old, 422(98.6%) white Caucasians, 124(29%) former intravenous drug users, 49(12%) past alcohol abusers, 240(51.5%) overweight and 357(78.7%) naive. Liver biopsy revealed advanced fibrosis in 58(15.1%) and hepatic steatosis in 133(35.6%) patients. Age (OR 2.1, p=0.007), genotype (OR 3.4, p<0.001) and naïve status (OR 0.3, p=0.001) were independent prognostic factors for non-response. Comparison between genotype 4 and 1 revealed significant differences in SVR (39.7% vs. 62%, Fisher’s exact test, p=0.002). No difference related to any of the demographic, virological or histological variable was able to explain the difference in treatment response.

Conclusion: Genotype 4 chronic hepatitis C in Greece has the worst prognosis in achieving SVR using current combination treatment for 48 weeks. These results challenge the notion, mainly from non-european studies, of a favorable response of genotype 4 compared to genotype 1. Further studies addressing the efficacy of the newer antivirals on the “difficult to treat” genotype 4 should be investigated in the future.

Keywords: Hepatitis C virus; Genotype 4; Treatment outcome; Pegylated interferon alpha; Ribavirin

Abbreviations: HCV: Hepatitis C Virus; Peg-IFNa: Pegylated Interferon-α; SVR: Sustained Virological Response; HIV: Human Immunodeficiency Virus; HBV: Hepatitis B Virus; BMI: Body Mass Index; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ULN: Upper Limit of Normal; PCR: Polymerase Chain Reaction; HAI: Histology Activity Index; CI: Confidence Intervals; IVDU: Intravenous Drug Use

Introduction

Hepatitis C virus (HCV) is classified into six major genotypes and a series of subtypes, according to its nucleotide sequence [1,2]. Prevalence rates are attributable to the geographical distribution of genotypes, with genotype 4 predominating in Middle East and Africa [1-4]. Recent epidemiological studies report of an increasing prevalence of genotype 4 in western countries, mainly due to imported viral infection from endemic areas [5-7].

Data on the efficacy of current combination therapy with pegylated interferon-α (Peg-IFNa) plus weight-based ribavirin is limited and contradictory; sustained virological response (SVR) rates of more than 60% reported in endemic areas [8-14] are approximately two times higher than those encountered in Europe [15-17]. In Greece, genotype 4 accounts for about 15% of all HCV infections [18-22] and is generally considered as “difficult to treat” in everyday clinical practice.

Aim of this multi-centered study was i) to estimate genotype distribution in Greek consecutive HCV patients, ii) to examine retrospectively the efficacy of standard antiviral therapy, and iii) to compare genotype 1 to genotype 4 response to treatment and examine possible differences in SVR determinants.

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Patients and Methods

Patient selection

Databases from five major hepatology units were used to select demographic, virological and histological data from consecutive HCV patients from January 2004 to January 2010. According to inclusion criteria, patients had to be aged above 18 years old, and to have received and completed standard combination therapy by January 2010. Exclusion criteria included concurrent alcohol abuse, co-infection with Human Immunodeficiency (HIV) or Hepatitis B (HBV) virus, and severe comorbid conditions such as chronic kidney failure or thalassemia major. Subcutaneously Peg-IFNα (either Peg-IFNα-2a 180 μg/week or -2b 1.5 μg/kg/week) was administered to all included patients. Ribavirin was co-administered orally on a daily basis at a dose of 800-1200 mg according to patient’s baseline characteristics (body weight and genotype) and according to the specific regimen’s recommendations. Graph 1 represents a flow diagram demonstrating the selection of patients according to inclusion and exclusion criteria and their stratification according to genotype and treatment algorithm (Graph 1). Patients, who never received nor adhered to more than 80% of the recommended treatment duration, were excluded from the study. Thus, HCV patients who had received treatment totally for less than 20 weeks for genotypes 2 and 3 or less than 40 weeks for genotypes 1 and 4, were not included in final statistical analyses. Furthermore, patients who completed treatment but were lost to follow-up and their SVR had not been determined 24 weeks after the end of treatment, were also excluded from the study.

Demographic data

Databases were used to determine patients’ age, gender, origin, probable mode of HCV transmission, history of alcohol consumption, somatometric measurements, and history of previous interferon-based therapy. Past alcohol abuse was defined as a consumption of more than 120g alcohol per week, at least six months prior to the beginning of treatment. Weight and height measurements were used to calculate body mass index (BMI). Patients were defined as overweight if 25 ≤ BMI<30 kg/m², and obese if BMI ≥ 30 kg/m². Patients who had never received interferon-based therapy in the past were characterized as naïve.

Laboratory investigations including virology assessment

Baseline serum alanine (ALT) and aspartate aminotransferases (AST) were measured by standard biochemical analyzers. Abnormal values were considered as values just above the upper limit of normal (ULN).

All patients were HCV-RNA positive by qualitative polymerase chain reaction (PCR). HCV RNA was determined by reverse transcriptase-PCR using commercial kits (Amplicor HCV, Roche Diagnostics, Branchburg, NJ) [23]. Baseline high viral load was defined as HCV RNA greater than 800,000 IU/mL.

HCV genotyping was performed with a second-generation reverse hybridization line probe assay (Inno-LiPA HCV II; Belgium), while subtyping was available in only a small proportion of patients.

Liver histology

Inflammatory activity and fibrosis were assessed according to the
METAVIR scoring system (4 stages for activity: A0-A3 and 5 stages for fibrosis: F0-F4) or the modified Ishak score (Histology Activity Index (HAI) scale 0-18 and fibrosis scale 0-6) [24,25]. Severe inflammation was considered as having either A3 or HAI≥12. Advanced fibrosis was defined as METAVIR stage ≥ F3 or HAI fibrosis stage ≥ 4, while cirrhosis was defined as having METAVIR stage F4 or HAI stages ≥ 5.

Statistical analysis with multivariate logistic regression revealed that age above 40 years old (Odds Ratio=2.1, p=0.007, 95% CI:1.2-3.7), genotype 1 or 4 (Odds Ratio=3.4, p<0.001, 95% CI:1.9-6.1), advanced fibrosis (Odds Ratio=2.9, p=0.003, 95% CI:1.5-5.9) and naïve status (Odds Ratio=0.3, p<0.001, 95% CI:0.1-0.5) were independent factors for non-response to standard combination treatment (Hosmer-Lemeshow test 0.985>0.05). Naïve status was the only variable that was positively associated with SVR, while age older than 40 years, genotypes 1 or 4, advanced fibrosis and presence of hepatic steatosis were found to be associated with treatment failure.

Statistical comparison between different genotypes revealed no significant differences in gender (χ², df=4, p=0.974), history of past alcohol consumption (χ², df=4, p=0.078), BMI (one-way ANOVA, df=4, p=0.423), baseline viral load (χ², df=4, p=0.421), naïve status (χ², df=4, p=0.189) or histological features concerning fibrosis, necro-inflammatory activity and steatosis (Table 1). On the other hand, the observed statistically significant differences in age and mode of transmission were attributable to the fact that genotype 3 HCV patients were significantly younger and mostly former IVDUs. Furthermore, abnormal baseline ALT was seen more often in genotypes 1 and 3, while Peg-IFNα-2b had been preferred mostly for the longer treatments of genotype 1 and 4 patients.

SVR rates were 62.0%, 75.9%, 83.9% and 39.7% for genotypes 1, 2, 3 and 4, respectively. SVR was significantly lower for genotypes 1 and 4 compared to genotypes 2 and 3 (χ², df=4, p<0.001).

Determinants of treatment outcome

Factors associated with treatment outcome were analyzed statistically with univariate and multivariate logistic regression analysis (Table 2). In univariate analysis, history of IVDU and naïve status were positively associated with SVR, while age older than 40 years, genotypes 1 or 4, advanced fibrosis and presence of hepatic steatosis were found to be associated with treatment failure.

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Genotype 4 to genotype 1 comparison

Further statistical subgroup analysis included only genotype 4
In the multivariate logistic regression subgroup analysis, which included only genotype 4 and genotype 1 HCV patients, treatment failure was independently associated with genotype 4 (OR 4.28, 95%CI 2.03-8.99, p<0.001), older age than 40 years (OR 2.28, 95%CI 1.18-4.44, p=0.015), advanced fibrosis (OR 2.57, 95%CI 1.06-6.26, p=0.037) and previous interferon-based therapy (OR 5.77, 95%CI 2.27-14.71, p<0.001). Hosmer-Lemeshow goodness-of-fit test for this multivariate logistic regression model was 0.817 (>0.05).

**Discussion**

Recent epidemiological studies report that prevalence of genotype 4 chronic hepatitis C is increasing in western countries, and two major causes have been identified so far: first, a substantial population from endemic areas of Middle East immigrate across Europe every year and, secondly, genotype 4 has been found to widespread among IVDUs in several European countries [1,6,7]. In Greece, prevalence of genotype 4 is amongst the highest reported within Europe, estimated around 15% [18-22]. Similarly, a percentage of 14.7% was confirmed in our study cohort of consecutive HCV patients.

Data for the efficacy of standard combination therapy with Peg-IFNα plus ribavirin in genotype 4 comes mainly from endemic areas.
such as Egypt [8,9,12,14], Saudi Arabia [10], Kuwait [13] and Quatar [11]. The reported SVRs range between 59.7 and 67.8%. On the contrary, similar European studies report significantly lower SVRs, without being able to explain these observations by differences in patient baseline characteristics like age, naïve status or fibrosis stage [15-17]. In our study, genotype 4 HCV patients achieved SVR in 39.7%, similar to study, genotype 4 HCV patients achieved SVR in 39.7%, similar to those in other studies in the Middle East and Europe. In our study, the observed response of genotype 4 when compared to genotype 1 HCV patients could theoretically and partly been explained by differences in ethnicity, HCV subtype, the mode of transmission or the IL-28B polymorphism varies between different populations worldwide and could help explain the heterogeneity in response to treatment in different ethnic or racial groups, but this still needs to be confirmed in large epidemiological studies in the Middle East and Europe. In our study, the observed worse response of genotype 4 when compared to genotype 1 HCV patients could theoretically and partly been explained by differences in IL28B polymorphism. However, this identification could not have been performed retrospectively.

In conclusion, having in mind that major limitation of all retrospective studies is that they can easily be subjected to selection bias, and trying to interpret our observations with caution, the results of our study confirm that prevalence of genotype 4 has increased to 15% in southern Europe, and indicate that genotype 4 has a non-favorable response to standard combination treatment with Peg-IFNα plus ribavirin. This may be attributable to IL28B polymorphisms, but further studies have to address this hypothesis. The role of newer drugs like protease inhibitors and direct acting antivirals seem promising in genotype 4 as well [37,38] and should also be investigated in the future.

References


