Interleukin 28b Single Nucleotide Polymorphism (rs8099917) as a Predictive Factor of Response to Pegylated-IFN/Ribavirintherapy in Chronic HCV Patients

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Abstract

Background: For Interleukin 28b Single nucleotide polymorphism (SNP) rs8099917, the favourable T allele is associated with a higher SVR after PEG-IFN alpha/RBV therapy while the G allele is a risk factor for non-response.

Aim of Study: To assess the value of Interleukin 28b (SNP) rs8099917 as a predictor of SVR.

Patients and Methods: This study is a retrospective controlled study and was performed on a total number of 240 patients who were treated by PEG-IFN alpha/RBV for 48 weeks and (SNP) rs8099917 was done for the all patients.

Results: TT genotype was more prevalent in SVR group than TG and GG genotypes.

Conclusion: IL-28b single nucleotide polymorphism (SNP) rs8099917 is a strong pretreatment predictor of response to pegylated interferon and ribavirin therapy in egyptian patients chronically infected with HCV genotype 4.

Key Words: *HCV-Pegylated Interferon – Interleukin 28b SNP rs8099917.*

Introduction

HEPATITIS C virus (HCV) infection is a major health problem throughout the world. Egypt has the highest prevalence of HCV (10-20%). More than 90% of HCV egyptian patients are of the genotype 4 variant [1].

The sustained virologic response (SVR) to PEG-IFN α and ribavirin therapy ranges from about 40 to 50% with genotype 1 to as high as 70 to 80% with genotypes 2 and 3, however, treatment is expensive and associated with adverse side effects [2].

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Due to the side-effects associated with PEG-IFN α and ribavirin therapy, assessing predictors of response prior to treatment initiation allows the physician to select those patients most likely to achieve SVR, and thus provides information about overall management [3]. Genotype is the strongest predictor of response to antiviral treatment. Patients infected with HCV genotype 2 or 3 are much more likely to achieve SVR to PEG-IFN α and ribavirin therapythan patients infected with HCV genotype 1 and 4 [4].

Four genome-wide association studies found associations of many single nucleotide polymorphisms (SNPs) in the IL28B gene on chromosome 19, which encodes type III IFN-γ, with the response to peg-IFN-α/RBV therapy [5,6].

The rs8099917 SNP was the only SNP in these studies that was strongly associated with response to peg-IFN-α/RBV therapy [7].

Determination of single nucleotide polymorphism (SNP) rs8099917 before starting antiviral therapy may serve as a tool to decide whether to undergo treatment or wait for other therapeutic options [8].

Even with the appearance of the new antiviral drugs, Peg IFN/RBV may remain the standard of care (SOC) in HCV therapy for the next few years. So every effort is made to improve the performance of the SOC [9]. The aim of this work is to assess the value of single nucleotide polymorphism (SNP) rs8099917 as a predictor of virological response to Pegylated interferon plus ribavirin in treatment of chronic hepatitis C virus patients.

Subjects and Methods

Patients:

This study was conducted on 240 Egyptian patients infected with HCV. Patients were selected from HCV patients who attended National Hepatology and Tropical Medicine Research Institute for receiving treatment for HCV from January 2012 up to October 2013. They were treated with Pegylated interferon a 2a or 2b (PEG-IFN) plus ribavirin. Duration of treatment was adjusted according to their response which was determined using quantitative PCR for HCV at the 12 th and 24th week from the start of treatment. Patients who had undetectable viraemia or decrease of viral load by more than two logs (by quantitative PCR) at 12th week from the start of treatment will continue treatment, while patients who didn't achieve that will discontinue treatment. Patients with any detected viraemia at 24 th week from the start of treatment will stop treatment. All patients signed an informed consent.

Inclusion criteria:

1- Chronically infected HCV patients aged 18 to 65 years old.

2- Serological, virological and histological diagnosis of chronic HCV.

3- Elevated ALT level above the upper limit of normal within 6 months prior to the study.

4- Patients had not been previously treated with interferon based therapy.

Exclusion criteria:

1- Decompensated liver disease.

2- Hemoglobin <13g/dL for men and <12g/dL for women, white blood cell count of $<3,000/mm^3$, absolute neutrophil count of $<1500/mm^3$, or platelet count of $<80,000/mm^3$.

3- Patients with hepatitis B surface antigen (HB-sAg) seropositivity or infected with the human immunodeficiency virus (HIV).

4- Active schistosomiasis.

5- Serum creatinine above the upper limit of normal.

6- Poorly controlled diabetes mellitus, hypertension, or psychiatric diseases.

7- Presence of ANA titre (antinuclear antibodies) >1/160.

8- Thyroid stimulating hormone (TSH) out of normal range (0.5-5 International Units/l).

Specimen collection:

Morning blood samples were collected; 6ml venous samples were withdrawn and divided into 2 tubes under aseptic conditions from patients and after obtaining their written consent as follows:

• Three milliliters (3ml) blood were left for 10 minutes to clot and then centrifuged for 5 minutes. The serum was then separated for determination of all serological tests as well as HCV-RNA Quantitation.

• Three milliliters (3ml) blood on EDTA using a sterile tube, the EDTA samples were stored at –80ºC to be used for molecular biology techniques.

Methods:

Laboratory Tests:

I- *Routine tests:*

1- Complete blood picture.

2- Liver biochemical profile: Serum bilirubin (total and direct), transaminases (ALT and AST), alkaline phosphatase, total protein, serum albumin and prothrombin time and concentration.

II- Serological tests for chronic hepatitis markers:

a- Anti-HCV EIA: The third generation Abbott HCV EIA 3.0 was used (Abbott Laboratories, Ludwigshafen, Germany).

b- HBsAg EIA: According to Abbott Monoclonal EIA (Abbott Laboratories, Ludwigshafen, Germany).

c- Anti-HBc EIA: The Abbott CORZYME commercial assay for qualitative detection of antibodies to HBV core protein (IgG and IgM) was used (Abbott Laboratory, Ludwigshafen, Germany and Abbott Park, II).

III- *HCV RNA using real time quantitative PCR Technique:*

It was done for all patients to detect the viral load. Pretreatment PCR assessment then at 12 th, 24th, 48 th and 72 th week from start of treatment.

IV- *Analysis of Interleukin 28B polymorphism by Real time PCR technique using TaqMan SNP genotyping assay:*

Extraction of genomic DNA from sterile EDTA anti-coagulated blood samples was done using QIAamp DNA blood Mini kit (Qiagen, Hilden, Germany) by silica-gel spin columns. Real-time PCR allelic discrimination was designed using TaqMan SNP Genotyping Assays (Applied Biosystems)and performed on Step OneTM Real Time PCR System (Applied Biosystems, Foster City, CA), using the fluorogenic 5`nuclease with TaqMan

minor groove binder (MGB) probes to define inter-leukin 28B gene SNP (rs8099917). The wild type TaqMan MGB probe was VIC labelled (Allele 1) and the mutant probe was FAM labelled (Allele 2).

The final volume of each reaction was 25ul, consisting of 12.5ul TaqMan Universal PCR Master Mix (2X) which contained AmpliTaq-Gold DNA polymerase, 1.25ul assay mix (20X) contained primers and probes, 5ul genomic DNA, and 6.25ul nuclease free water. Negative control (no DNA template) was run to ensure that there was no amplification of contaminating DNA. The amplification reactions were carried out with initial hold step at 95ºC for 10min for activation of AmpliTaq-Gold DNA polymerase followed by 40 cycles of three-step PCR: Denaturation at 92ºC for 15sec, annealing at 60ºC for 30sec and extension at 60ºC for 30sec. The fluorescence signal increases when the probe with the exact sequence match binds to the single stranded template DNA and is digested by the 5`nuclease activity of AmpliTaq-Gold DNA polymerase. Digestion of the probe releases the fluorescent reporter dye (either FAM or VIC) from the quencher dye.

V- *Liver biopsy for histological assessment:*

Trans-abdominal ultrasound guided liver biopsy was done for all patients prior to starting treatment for HCV to assess grade of inflammation (Activity) and stage of fibrosis according to METAVIR scoring system. The stage of liver fibrosis was scored according to the METAVIR scoring system: F0 (no fibrosis), F1 (mild fibrosis: portal fibrosis without septa), F2 (moderate fibrosis: few septa), F3 (severe fibrosis: Numerous septa without cirrhosis) and F4 (cirrhosis). Inflammation was graded A0 (no activity), A1 (mild activity), A2 (moderate activity), A3 (severe activity).

Statistical methods:

Data was analyzed using PASW statistics 18. Numerical data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data normally distributed, comparison between two groups was done using *t*-test. Comparison between 3 groups or more was done using ANOVA test. For quantitative and qualitative data not normally distributed, comparison was done using Kruskal-Wallis test. Logistic regression model was done for predictors' detection at 95% confidence level. A p-value <0.05 was considered significant.

Results

Table (1) shows all baseline demographic, histological and virological characteristics of the studied patients.

Table (1): Distribution of studied patients according to their baseline characteristics.

Variable	Studied patients	
	Number	Percent
Age:		
≤40	116	48.3
>40	124	51.7
Total	240	100
Mean ± SD	40.30±10.912	
Gender:		
Male	172	71.7
Female	68	28.3
Total	240	100
Degree of fibrosis:		
Mild (F1)	152	63.3
Moderate - severe (F2-F3)	88	36.7
Total	240	100
Degree of activity:		
Mild (A1)	152	63.3
Moderate - severe (A2-A3)	88	36.7
Total	240	100
IL 28:		
TG	100	41.7
TT	65	27.1
GG	75	31.3
Total	240	100

The rs8099917 allele frequency is 27.1% for TT (65 patients), 41.7% for TG (100 patients), and 31.3% for GG (75 patients). We defined the Inter-leukin 28b (IL28b) major allele as homozygous for the major sequence (TT) and the IL28b minor allele as homozygous (GG) or heterozygous (TG) for the minor sequence.

Statistically there was no significant correlation between response of chronic hepatitis C patients treated with peg-IFN/RBV and age or gender with p-value (0.653) and (0.403) respectively. The relation between the α feto protein and response to treatment was statistically non significant.

Table (2): Relation between response of chronic hepatitis C patients treated with Peg IFN/RBV and IL 28B SNP rs 8099917.

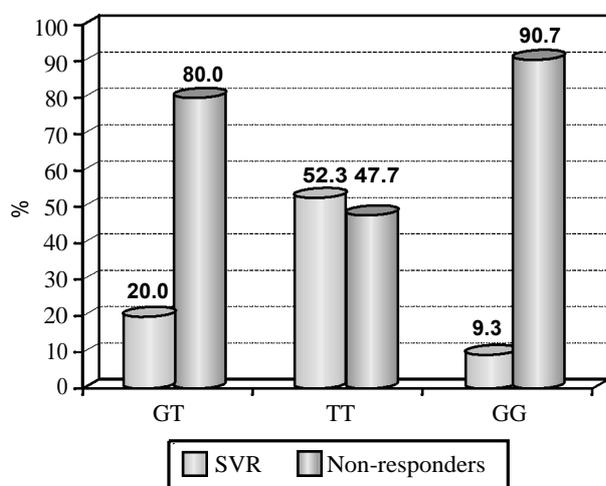|	TG		TT		GG		Significance
	N	%	N	%	N	%	
SVR	20	20	34	52.3	7	9.3	0.001
Non- responder	80	80	31	47.7	68	90.7	(HS)
Total	100	100	65	100	75	100	

Fig. (1): Relation between response of chronic hepatitis C patients treated with Peg IFN/RBV and IL 28b SNP rs 8099917.

Genetic polymorphism in one tagging SNP located 8 kb upstream of IL28b gene (rs8099917) was determined by OneTM Real Time PCR System (Applied Biosystems, Foster City, CA). Homozygosity (GG) or heterozygosity (TG) of the minor sequence was defined as having the IL28b minor allele (mutant type), whereas homozygosity for the major sequence (TT) was defined as having the IL28b major allele (wild type).

Patients with TT genotype have higher SVR to treatment with pegylated interferon plus ribavirin in chronic HCV patients than other patients with TG genotype and GG genotype (52.3% vs 20% & 9.3 %, p-value <0.001).

These findings suggest that IL 28b (rs8099917) has great impact on sustained virological response (SVR) to therapy with pegylated interferon plus ribavirin in chronic HCV patients.

Table (3): Predictive factors for response to peg-interferon by logistic regression model: Univariate analysis using a logistic regression model of predictive factors detection at 95% confidence level.

Predictor	95% CL	Significance
IL 28b SNP rs8099917	0.21 - 0.398	0.001 (HS)

A p-value <0.05 was considered significant.

The IL 28b SNP rs8099917 was highly significant as predictors of response to treatment of patients with chronic HCV with p-value <0.001.

Discussion

Host factors including age, body weight, insulin resistance, stage of fibrosis, and compliance influence the outcome of antiviral treatment in patients with chronic HCV. Moreover, chronic HCV European or Asian patients have a higher rate of SVR than African American or Hispanic patients [10,11] reinforcing the influence of genetic host factors.

Studies have identified single nucleotide polymorphisms (SNPs) in proximity to the interleukin-28b (IL-28b) gene as important predictors of treatment outcome. These findings have not only provided a new window into host responsiveness to IFN-based therapy but have also yielded insights into genetic susceptibility to chronic HCV infection, the molecular biology of host immunity against HCV, and the potential for discovery of new therapeutic agents [12].

In 2009 and 2010, four independent Genome-wide association studies (GWAS)on response to treatment of chronic hepatitis C with peg IFN- a and ribavirin were published [13-16]. Only SNPs around the IL28b gene reached significance for the association with treatment outcome. Consistently, rs12979860 C (good-response allele) versus T (poor-response allele) and rs8099917 T (good-response allele) versus G (poor-response allele) showed the strongest association with SVR of thus far characterized SNPs.

In the present study, the impact of rs8099917 genetic polymorphisms near the IL28b gene on response of chronic HCV patients to standard treatment was investigated by analyzing the association between genetic polymorphisms and sustained virological response (SVR) after administering Pegylated interferon and ribavirin.

We have demonstrated that carriers with the TT genotype of rs8099917, located 8 kb upstream of IL-28b, are more likely to achieve SVR with HCV infected egyptian patients after standard treatment.

It was found that the rate of SVR was significantly higher (52.3% vs. 20% and 9.3% with $p<0.001$) in patients with the IL28b major allele (TT, wild type) compared to those with the minor allele (non TT, mutant type).

Our study reconfirmed the previously reported findings in various populations around the world in a large cohort of HCV mono-infected patients with chronic hepatitis C genotype (GT) 1 [17-20] but our study included Egyptian patients who are mainly infected with HCV GT4.

Grebely J1 et al., (2010) observed that there was a difference in the impact of IL-28b polymorphism among viral genotypes (GTs). In contrast

to GT1 and GT4 patients, the rs12979860 SNP had no impact on SVR rates in GT2/3. They have reported associations of rs12979860 CC genotype and rs8099917 TT genotype with RVR but not SVR in patients with HCV genotype 2/3 infection, implying that the CC genotype may be associated with relapse in their population too [21].

This observation is in agreement with observations by others Kurosaki M1 et al., [22].

Studies of HCV genotype 2-infected European patients show that the CC genotype at rs12979860 can predict SVR, but this is largely driven by patients who do not achieve RVR [23].

Rauch et al., [6] have also shown no effect of rs8099917 in HCV genotype 2/3-infected patients in a smaller cohortstudy.

Similarly [6], AlsoMontes-Cano et al., [17] showed no association of rs12979860 with SVR in HCV genotype 2/3-infected patients.

Stättermayer et al., (2010) Studied 102 Egyptian patients infected with HCV (GT 4) and they found that the major allele T was associated with significant SVR (p=0.0036), also observed that low base line viral load (<800,000 IU/ml) had significant effects on the SVR (p=0.0085) [15]. Thompson et al., [18] found that genetic polymorphisms near the IL28b gene were associated strongly with early viral kinetics during the combination therapy with PEG-IFN and ribavirin.

Toyoda H., et al., [19] observed a difference in the decrease in HCV RNA levels 24 hours after administering Peg-IFN in patients with the TT genotype compared to those with the TG/GG genotype. The rs8099917 genetic polymorphisms near the IL28b gene was an only independent factor that was associated with a decrease in HCV RNA levels 24 hours after IFN administration.

Furthermore, it was suggested that IL-28b may play a role in determining whether acute HCV infection leads to spontaneous clearance or chronic infection. A large study of over 1000 individuals in which the prevalence of the rs 12979860 genotype was investigated in patients who achieved spontaneous resolution and those who developed chronic HCV infection [19,20]. These studies found that individuals with the C/C genotype had a 3-folds greater likelihood of spontaneous HCV clearance compared to patients who had the T/C or T/T genotype.

Similar findings have been found in association with the rs8099917 polymorphism, in which the favorable T/T genotype is associated with spontaneous resolution; this relationship was also found in HCV/HIV co-infected individuals [23-25].

Our findings suggested that the IL28b genotype SNP rs8099917 was a useful baseline predictor of virological response which should be used for selecting the treatment regimen: Whether to treat patients with peg-IFN and RBV or to wait for more effective therapy including direct acting antiviral drugs.

On the other hand, baseline IL28b SNP rs8099917 genotype might not be suitable for determining the treatment duration in patients who started PEG-IFN/RBV therapy and whose virological response is determined because the IL28b SNP rs8099917 genotype is not useful for the prediction of relapse. The duration of therapy should be determined based on the virologicalresponse [26].

Conclusion:

IL-28bsingle nucleotide polymorphism (SNP) rs8099917 is a strong pretreatment predictor of response to pegylated interferon and ribavirin in egyptian patients chronically infected with HCV genotype 4.

Author disclosure statement:

No conflict of interest.

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استخدام النمط الجينى للنيكوليوتيد الفردى متعدد الأشكال (رس 8099917) كوسيلة تنبؤية للاستجابة للانترفيرون طويل المفعول والريبافيرين فى علاج مرضى فيروس سى الكبدى المزمن

الخلفية: بالنسبة للنمط الجينى للنيكوليوتيد الفردى متعدد الأشكال (رس 8099917)، يرتبط النوع TT بالاستجابة الجيدة والعالية للعلاج بعقارى الانترفيرون طويل المفعول وكبسولات الريبافيرين لمرضى فيروس سى المزمن النشط.

الهدف من العمل: تقييم قيمة النمط الجينى للنيكو ليوتيد الفردى متعدد الأشكال (رس 8099917) كمتنبئ للاستجابة للعلاج بعقارى الانترفيرون طويل المفعول وكبسولات الريبافيرين لمرضى فيروس سى المزمن النشط.

المرضى والطرق: هذه الدراسة عبارة عن دراسة بأثر رجعى تم إجراؤها على إجمالى 240 مريضاً تم علاجهم بعقارى الانترفيرون طويل المفعول وكبسولات الريبافيرين لمرضى فيروس سى المزمن النشط لمدة 48 أسبوعياً وتم إجراء تحليل النمط الجينى للنيكوليوتيد الفردى متعدد الأشكال (رس 8099917) لجميع المرضى.

النتائج: كان النمط الجينى TT أكثر انتشاراً فى مجموعة المرضى المستجيبين أكثر من الأنماط الجينية الأخرى TG وGG.

الخلاصة: النمط الجينى للنيكوليوتيد الفردى متعدد الأشكال (رس 8099917) هو مؤشر قوى للتوقع المسبق لاستجابة للعلاج بالإنترفيرون والريبافيرين فى المرضى المصريين المصابين بفيروس سى المزمن النشط.