

Relation of IL28B Rs12979860 Polymorphism on Depression Symptoms in the Treatment of Chronic Hepatitis C

Elza Cristina Miranda da Cunha^{1,2}, Bruna Brandão Farias¹, Natalia Xavier Carvalho¹, William Silva Ribeiro¹, Indira Viegas¹, Andreia Santos¹, Christian Loret de Mola³, Rodrigo Proto-Siqueira⁴, Lysandro Alsina Nader², Gabrielle Ghisleni¹

1 Laboratório de Neurociências Clínicas, Programa de Pós-Graduação em Saúde e Comportamento, Universidade Católica de Pelotas, Rua Gonçalves Chaves 373, CEP 96015560, Pelotas, Brazil;

2 Faculdade de Medicina, Universidade Federal de Pelotas, Av. Duque de Caxias 250, CEP 96030000, Pelotas, Brazil;

3 Programa de Pós-Graduação em Epidemiologia, Universidade Federal de Pelotas, Rua Marechal Deodoro 1160, CEP 96020220, Pelotas, Brazil;

4 Laboratório Antonello, Molecular Biology Institute, Av. Ferreira Viana, 380 - Centro, Pelotas / RS - CEP: 96085-000, Brazil.

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Correspondence to: Elza Cristina Miranda da Cunha, Programa de Pós-Graduação em Saúde e Comportamento, Centro de Ciências da Vida e da Saúde, Universidade Católica de Pelotas, Pelotas, Brasil.

Email: ecmirandacunha@gmail.com

Telephone: +55 53 2128 8031

Fax: +55 53 2128 8229

Received: August 19, 2019

Revised: August 30, 2019

Accepted: September 2, 2019

Published online: October 21, 2019

ABSTRACT

AIM: The present study we aim to evaluate the relationship between the single nucleotide polymorphism (SNP) rs12979860 in the IL28B gene with the diagnosis of depression and its symptoms along the

treatment of HCV patients.

MATERIAL AND METHODS: Is a convenience cohort where patients were follow-up by 12 weeks during the antiviral therapy. A sociodemographic questionnaire, psychiatric diagnostic interview and laboratorial data were applied at the baseline, 4th week and 12th week of treatment. A sample of buccal cells was collected from each patient in the baseline and IL28B rs12979860 (C/T) polymorphism was genotyped by real-time PCR.

RESULTS: 90 patients were evaluated in relation to IL28B rs12979860 (C/T) polymorphism. The rs12979860 polymorphism were not significantly associated with the diagnoses of major depression ($p = 0.186$) in the baseline, but along the treatment the T allele present a risk factor for irritability OR 3.75 [CI (1.22-11.57); $p = 0.021$]. Past depression is associated with the diagnosis of current depression pré treatment ($p = 0.018$).

CONCLUSION: Our results suggest that patients carrying T-allele of rs12979860 have worst symptoms of depression related to those with CC genotype. These results indicate that genotypes of IL28B rs12979860 polymorphism should be better studied to be considered for further treatment.

Key words: Hepatitis C; Depression; IL28B; BDI; Treatment hepatitis; Depressive symptoms

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da Cunha ECM, Farias BB, Carvalho NX, Ribeiro WS, Viegas I, Santos A, de Mola CL, Proto-Siqueira R, Nader LA, Ghisleni G. Relation of IL28B Rs12979860 Polymorphism on Depression Symptoms in the Treatment of Chronic Hepatitis C. *Journal of Gastroenterology and Hepatology Research* 2019; **8(5)**: 2957-2961 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2658>

INTRODUCTION

Hepatitis C, like many chronic medical illnesses, is associated with an increased prevalence of psychiatric disorder, notably major depression. The presence of depressive symptoms in Hepatitis C patients, such as in other chronic medical illnesses, is an important

side effect on the course of illness with amplification of physical symptoms, functional impairment, reduced treatment compliance and reduced quality of life^[1].

The mechanisms by which Hepatitis C virus (HCV) induce systemic diseases seem to be multifactorial, correlated to its ability to penetrate and replicate within cells of the main body systems and to induce local and systemic inflammation, metabolic alterations, and immune-mediated phenomena. HCV can target the central nervous system (CNS) causing a wide range of neurologic and psychiatric manifestations, and around 50% of infected individuals reported neurologic and psychiatric disorders^[2].

Consistent with previous reports, Interferon (IFN) therapy was accompanied by a significant increase in neurovegetative and somatic symptoms of depression including changes in appetite, fatigue and irritability increasing within the first two weeks of treatment^[3]. Moreover, studies have shown that around 42% of patients who initiated IFN therapy develops an episode of major depression and most of patients show a significant increase in the severity of symptoms related to pre-treatment^[4].

Evidences hint at an association between depression and HCV infection by different aspects: (a) the stress to have a potentially life-threatening; (b) the stigmatizing nature of the diagnosis; (c) and the high proportion of persons at risk for psychiatric disorder in cohorts of HCV-infected people^[5]. In fact, depression has an important impact on patients live, since it decreases quality of life, can cause delays and interruptions in the treatment of HCV^[6,7]. In this context, early diagnosis and treatment of depression have been associated with better adherence to antiviral therapy.

In 2009, a series of genome-wide association studies (GWAS) identified polymorphisms (SNPs) in the IL28B gene, a gene coding for IFN-lambda-3 (IFN-l-3) as a predictor of sustained virologic response (SVR), as well as spontaneous clearance in chronic HCV genotype 1 patients treated with Interferon Pegylated (PegIFN) and Ribavirin (RBV)^[8,9]. Risk for side effects during IFN treatment may also be influenced by genetic polymorphisms, including those affecting the serotonin system^[10,11], other cytokines such as IL-6, the receptor for IFN- α ^[12], phospholipase A2^[13] and IL28B rs12979860 associated with less appetite, energy and sleep complaints^[14]. So, in the present study we aim to evaluate the relationship between the single nucleotide polymorphism (SNP) rs12979860 in the IL28B gene with the diagnosis of depression and its symptoms along the treatment of HCV patients.

METHODS

Study design

This study is a convenience cohort where patients were followed-up by 12 weeks during the antiviral therapy. The study was performed from February 2013 to August 2016, in the Gastroenterology Outpatient Clinic Center for the Application and Monitoring of Injectable Medicines (CAMMI) - in Medicine Faculty of Federal University of Pelotas (UFPel), Rio Grande do Sul, Brazil. The initial sample was composed of 90 HCV patients with treatment indication according to the Protocol Treatment of Viral Hepatitis of the Health Ministry^[15,16,17]. Health professionals from the service, weekly monitored the adherence to treatment through direct contact with the patients. Inclusion criteria: patients older than 18 years, mono-infected with HCV and treatment with PegIFN and RBV. Exclusion criteria: patients under 18 years of age, co-infected and using others medications to treatment of HCV (protease inhibitors and direct acting antiviral).

The treatment was based in drugs currently used for the HCV in Brazil. In our sample, patients used 180 mcg/kg of PegIFN- α 2a once a week. This treatment was associated with RBV (mean dose of 13 mg/kg/day) for 24 to 48 weeks depending on the virus genotype, viral load and fibrosis degree. The fibrosis degree was assessed by the METAVIR System in which F0 means absence of fibrosis and F4 means cirrhotic patient, advanced fibrosis was considered F3-F4 patients. High viral load was defined by values above 600,000 IU/mL and low viral load by less than 600,000 IU/mL.

Psychiatric history was considered if the patient had previous episodes of depression or psychiatric treatment. Before starting treatment for HCV, 20 (22.22%) of the patients used some type of psychiatric medication, and 19 (21.1%) used psychiatric medication during the antiviral treatment.

Instruments

A sociodemographic questionnaire was applied at the baseline, before the beginning of the antiviral therapy. The psychiatric diagnostic interview and laboratorial data of patients were collected at the baseline, in the 4th and 12th week of treatment.

Subjects were evaluated with a structured diagnostic interview - the Mini International Neuropsychiatric Interview - MINI, that uses the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* as criterion for psychiatric diagnostic. The diagnosis of major depression, risk of suicide and generalized anxiety disorder were used in the present work. The Beck Depression Inventory (BDI) Interview was also used in order to confirm the presence and severity of depressive symptoms in patients with HCV.

All ethical principles established by the National Health Council in Resolution No. 466/12 were respected. All patients who agree to participate in the research provided a written informed consent. University's Ethics Committee approved the study under protocol number 151.642 and 658.087. Any patient with a diagnosis of depression or suicide risk was referred to the CAPS (Psychosocial Support Center - psychiatric service support to patients with mental disorders) or to the Psychiatric Service of UFPel.

Laboratorial analysis

Laboratorial information such as the fibrosis degree, virus genotype and viral load values were obtained from the Laboratory of UFPel Hospital along the antiviral therapy.

DNA extraction

A sample of buccal cells was collected from each patient in the baseline. Each collection were made with help of a wooden tongue depressor using disposable special cytological brushes by twirl the cytobrush for 30s over the malar region to obtain exfoliated cells of the buccal mucosa. The first scraping was scorned. The DNA was processed following the manufacturer's instructions (PUREGENE™ DNA Buccal Cell Kit; Gentra Systems, Inc., Qiagen, Minneapolis, MN). After extraction total DNA was quantified by spectrophotometry and stored at -20 ° C until molecular analysis.

Polymorphism genotyping

IL28B SNP rs12979860 (C/T) was genotyped using primers and probes contained in the 40x Human Custom TaqMan Genotyping Assay (Life Technologies, Foster City, CA, USA). The reactions were conducted in a 96-well plate, in a total 5 μ l reaction volume using 2 ng of genomic DNA, TaqMan Genotyping Master Mix 1x (Applied Biosystems), and Custom TaqMan Genotyping Assay 1x, as determined by the manufacturer. Then plates were positioned in a

real-time PCR thermal cycler (7500 Fast Real PCR System; Applied Biosystems) and heated for 10 min at 95°C, followed by 45 cycles of 95°C for 15 s and 60°C for 1 min. Fluorescence data files from each plate were analyzed using automated allele-calling software (SDS 2.0.1; Applied Biosystems).

Statistical analysis

Sociodemographic and clinical characteristics of HCV patients were described by simple frequencies. Sociodemographic and clinical characteristics of patients according to clinical diagnosis of major depression were compared by unpaired Student's *t*-test or χ^2 as appropriate. To evaluate the association of IL28B SNP rs12979860 in depressive symptoms over time a multivariate mixed effect analysis was performed using the dominant model (CC vs CT/TT). Variables are presented as mean \pm standard deviation (SD), number and percentage, or Odds Ratio (95% CI). The analyses were performed in STATA and *p* values < 0.05 are considered statistically significant.

RESULTS

In a total of 90 patients, the mean age was 52.4 \pm 12.3 years, 39 (43.3%) were female, 56 (62.2%) married, 76 (84.45%) caucasian, the mean years of the study was 10.3 \pm 5.5 years, 16 (17.8%) had advanced fibrosis according to hepatic biopsy, and 43 (47.8%) had genotype 1. About 18 (20.2%) of patients were diagnosed with current depression, 24 (27%) had a history of depression, 11 (12.4%) were at risk of suicide, 33 (37.1%) had generalized anxiety disorder, and 38 (42.2%) have ever consulted with psychologist or psychiatrist (data not shown).

In relation to genotypes distribution of IL28B SNP rs12979860, 24 (26.7%) of the patients had CC genotype, 55 (61.1%) CT and 11 (12.2%) TT genotype. There was no statistically significant difference for ethnicity (*p* = 0.880), gender (*p* = 0.518) and age (*p* = 0.739) according to genotypes of IL28B rs12979860 polymorphism (data not shown). The influence of rs12979860 genotypes on SVR was evaluated showing no significant differences between genotypes (*p* = 0.323), as well no association was observed when the sample was stratified according to viral genotypes 1 (*p* = 0.686) and 2/3 (*p* = 0.679) (data not shown).

The SNP rs12979860 were not significantly associated with the diagnoses of major depression (*p* = 0.186), generalized anxiety disorder (*p* = 0.093), and suicide risk (*p* = 0.728) at baseline (data not shown). Table 1 depicted sociodemographic and clinical characteristics of patients according to diagnosis of current episode of major depression at baseline. Only a past episode of major depression (*p* = 0.018) was significantly associated with major depression in baseline (Table 1). Data presented in Table 2 showed the relation between depressive symptoms and genotypes of IL28B SNP rs12979860 along the HCV treatment. Using a dominant model we observed that T-allele confers risk for irritability [OR: 3.75; CI (1.22-11.57); *p* = 0.021].

DISCUSSION

In this study our results reveals that T-allele of IL28B rs12979860 SNP may confer risk for depressive symptoms in CHC patients during the treatment with IFN. IL28B SNPs have been extensively studied on the success rate of CHC therapy, although its mechanisms remain unknown and little investigation has been made for clinical outcome.

IL28B SNPs have been described for differences in immune response to HCV infection in the pre-treatment, which suggest higher

Table 1 Sociodemographic and clinical characteristics of Hepatitis C patients according to current depression.

Variable	Diagnosis of Current Depression		P value
	No	Yes	
Gender			
Female	29 (32.6%)	9 (10.11%)	0.33
Male	36 (75%)	12 (25%)	
Age	53.13 \pm 12.57	50.17 \pm 11.26	0.365
Years of study	10.68 \pm 5.80	9.39 \pm 4.40	0.382
Marital Status			
Married	46 (51.68%)	10 (11.23%)	0.59
Others	25 (28.08%)	8 (8.98%)	
Working			
Yes	40 (44.94%)	7 (7.86%)	0.305
No	30 (73.2%)	11(26.8%)	
Virus Genotype			
1	36 (40.45%)	6 (6.74%)	0.146
2/3	35 (39.32%)	12 (13.48%)	
Degree of fibrosis			
Low	32 (35.95%)	7 (7.86%)	0.458
High	14 (15.73%)	2 (2.25%)	
Viral load baseline			
High	23 (25.84%)	3 (3.37%)	0.154
Low	48 (53.93%)	15 (16.85%)	
IL28B Genotype			
CC	17 (19.10%)	6 (6.74%)	0.186
CT	43 (48.31%)	12 (13.48%)	
TT	11 (12.35%)	0 (0%)	
IL28B Dominant Model			
CC	17 (23.9%)	6 (33.3%)	0.609
CT/TT	54 (76.1%)	12 (66.7%)	
Past Depression	15 (16.85%)	9 (10.11%)	0.018
Total	72 (79.8%)	18 (20.2%)	

Displayed as mean \pm standard deviation or n and %. *p* values \leq 0.050 were considered significant. High fibrosis was considered F3-F4 and low F1-F2; High viral load > 600,000UI/ml and Low viral load <600,000UI/ml.

Table 2 Depressive symptoms evaluated by BDI in relation to IL28B rs12979860 genotypes.

Depressive Simptoms	Dominant Model	
	CT+TT	p-value
Sadness	1.86 (0.35-9.78)	0.459
Pessimism	0.99 (0.20-4.88)	0.998
Past Failure	1.96 (0.02-19.56)	0.563
Loss of pleasure	0.85 (0.22-3.24)	0.813
Guilt	2.30 (0.30-17.26)	0.415
Feelings of punishment	1.33 (0.16-10.45)	0.786
Self-esteem	1.93 (0.25-14.76)	0.523
Self-criticism	2.28 (0.56-9.22)	0.245
Suicidal thoughts	1.07 (0.08-13.80)	0.955
Crying	1.32 (0.31-5.57)	0.701
Agitation	2.22 (0.96-5.10)	0.060
Loss of interest	0.47 (0.10-2.07)	0.323
Indecision	0.51 (0.09-2.73)	0.439
Devaluation	0.67 (0.14-3.07)	0.608
Lack of energy	1.36 (0.47-3.90)	0.560
Sleepiness	2.19 (0.79-6.01)	0.127
Irritability	3.75 (1.22-11.57)	0.021
Appetite	3.04 (0.90-10.27)	0.072
Concentrating	1.57 (0.70-3.54)	0.271
Fatigue	1.71 (0.56-5.18)	0.338
Loss of interest in sex	0.60 (0.21-1.72)	0.350

Displayed as OR (CI 95%); Multivariate mixed effect analysis was performed using the dominant model (CC vs CT/TT). Reference group: CC; *p* values \leq 0.050 were considered significant. Beck Depression Inventory (BDI).

severity of liver disease^[18]. A number of studies have postulated that T-allele of rs12979860 was associated with worst SVR in CHC patients during the IFN treatment, although the mechanisms that

regulate the IL28B genotypes on the success rate of therapy remain unclear^[9,19,20,21,22]. In fact, this SNP had been claimed as the key predictor among IL28B SNPs for SVR in HCV infected patients^[19]. The underlying mechanisms by which IL28B could predict risk for depressive symptoms and SVR was suggested by recent in-vitro report had shown that IL28B can inhibit HCV replication through JAK-STAT pathway, with genotypes conferring differential expression of intrahepatic interferon-stimulated genes in CHC patients^[23]. In this study, our results do not shown an association between SVR and rs12979860 genotypes, but for the first time the T-allele of this SNP was associated with depressive symptoms, suggesting that this allele may be related to worst overall outcome of patients.

Neuropsychiatric disorders and neurocognitive dysfunction are reported in nearly 50% of patients with chronic HCV infection, which are independent of the severity of liver disease or HCV replication rates^[24]. Fatigue, sleep disturbance, depression and reduced quality of life are commonly associated with neurocognitive alterations in patients with non-cirrhotic chronic HCV infection^[24]. People with HCV infection also present higher risk for depression, anxiety, somatization, compulsiveness, insecurity, aggression/hostility, and phobic anxiety^[5]. In this study, the only variable associated with the diagnosis of current depression in pre-treatment was the past depression variable ($p = 0.018$) and no association was observed between the IL28B rs12979860 SNP and major depression, the T-allele of rs12979860 was suggested to confers risk for irritability. Controversial to our results, Lotrich et al showed that the C-allele of rs12979860 SNP was associated with specific somatic symptoms of major depression analyzed by BDI, namely loss of energy, worsened sleep, and change in appetite^[14]. Moreover, genetic variants in the IL28B gene (rs12979860, rs12980275, rs8099917) that otherwise are linked with more favorable therapeutic outcome were associated with more pronounced inflammation, steatosis, fibrosis, insulin resistance and depressive symptoms^[25,26,27].

Importantly, anger and irritability are underestimated side effects of INF treatment. In fact, irritability might be secondary to other mood disorders which often arise during antiviral treatment. The irritability ranged from mild to severe, being able to undertake almost half of patients on treatment reported symptoms of irritability and anger first developing within 2 months after initiating treatment^[28]. In the context of CHC patients, anger/irritability and fadigue during antiviral treatment were linked to TNF-alpha rs1800629 genotypes^[29]. Moreover, 5-HTTLPR rs25531 SNP was more specifically associated with depression and sleep^[11,30].

This study as well as that performed by Lotrich et al. ^[11], founded an association of IL28B with distinct depressive symptoms, pointing out to a relevant role for IL28B SNPs for HCV infected patients. The IL28B rs12979860 is of paramount importance for the follow-up and planning of the treatment of HCV, becoming another tool to help in the therapy for psychiatric disease of these patients. However, the small number of patients evaluated here represents an important limitation of this study, and point to necessity of further studies to better comprehend the involvement of IL28B in the mechanisms of psychiatric symptoms induced by IFN.

ACKNOWLEDGEMENTS

This study was supported by CNPq/CAPES Brazil, and Laboratory Antonello, Molecular Biology Institute (Polymorphism genotyping).

Funding: This study was supported by CAPES Brazil and the funder had no such involvement in the study design; data collection,

analysis and interpretation; in the report writing; and paper submission for publication.

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