Correlation between IL-28 Polymorphism and Spontaneous Clearance in HCV Patients: Systematic Review and Meta-Analysis

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Research Article

Keywords: Hepatitis C virus, IL28B gene, Polymorphisms, Spontaneous Clearance

Posted Date: April 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-203303/v1>

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Abstract

Hepatitis C virus (HCV) is a serious global health issue. Nearly 20% of HCV patients spontaneously clear the virus. While some studies have shown the association of spontaneous clearance (SC) of the virus with Interleukin (IL) 28B single nucleotide polymorphisms (SNPs), others didn't show such a relationship. Thus, the purpose of the present study was to investigate the association of IL28B polymorphisms (12979860 SNP) and SC of HCV infection. Upon initial screening of the databases, a total of 545 articles were retrieved, of which 22 studies that met predefined eligibility criteria were entered into the meta-analysis. Odds ratios (OR) with its confidence intervals (95% CI), heterogeneity, publication bias, and sensitivity analysis were assessed. According to the meta-analysis results, a significant association was observed between the rs12979860 SNP and SC of HCV infection. The results indicated that the ORs of SC from hepatitis C virus infection were 2.75 times higher in those with cytokine gene polymorphisms, 95% CI (2.23 to 3.38). Moreover, it was found that the prevalence of rs12979860 CC was 0.33 with 95% CI (0.28–0.38) in genotype one and was 0.40 with 95% CI (0.34–0.47) in other genotypes.

Our meta-analysis results suggest that IL28B rs12979860 CC is a strong predictor for SC of hepatitis C infection in PEG IFN- α /RBV-treated patients.

Introduction

Hepatitis C virus (HCV) is a serious public health problem worldwide affecting > 170 million persons globally and around 3–4 million people are newly infected each year [1–3]. Although HCV causes liver related morbidity and mortality and > 70% of patients will develop chronic HCV infection, 20% of patients show spontaneous clearance (SC) of the viral infection [4,5]. While the pathogenicity of HCV has not been completely determined, studies have shown that several viral and host factors have been connected to the differences in the viral persistence or clearance. Also, HCV patients respond differently to the treatment, indicating an important role of the host genetic context [6–8]. Several studies have shown that SC of virus and response to treatment might be related to interleukin (IL) 28B gene polymorphisms. There are three main single nucleotide polymorphisms (SNPs) for the IL28B gene including rs12979860, rs809917, and rs12980275. Several studies showed that there is a correlation between these SNPs and SC, treatment, and prediction of response [9,4,10]. Because these SNPs are located in the promoter and regulatory region of the IL28B gene on chromosome 19, they can affect IL28B cytokine gene expression and production. Besides, SC of HCV infections may be affected by these SNPs [7,11].

The antiviral properties of IL28B protein are mediated by stimulating the Janus kinase signal transducer and activator of transcription (JAK-STAT) protein, which controls interferon (IFN)-stimulated genes (ISGs) [12]. Many publications have reported the influence of IL28B polymorphisms on the clearance of HCV. One study conducted on the Asian population, patients with CC genotype at the rs12079860 SNP showed spontaneous clearance [13]. Furthermore, patients with rs12979860 SNP were associated with IFN-free treatment [14–16]. Besides, it has been shown that the C/C genotype at rs12979860 of IL28B is associated with sustained virologic response (SVR) in Asian, Caucasian, European, African-American and Hispanic populations [17,4]. To date, various meta-analyses have been released on the correlation between gene

polymorphisms of IL28B and SVR [17–21] but, few meta-analyses have been performed on the IL28B polymorphisms that are involved in SC. Furthermore, the studies have reached inconsistent conclusions and while some studies reported a significant association [22–39,19,40–42], some others didn't show such relation [43,44]. Accordingly, the objective of this paper was to clarify the association of IL28B polymorphisms with pegylated interferon (IFN) α and ribavirin (RBV) (PEG-IFN/RBV) treatment response and SC.

Methods

The present systematic review and meta-analysis was accomplished based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. (<http://www.prisma-statement.org/PRISMAStatement/PISMAStatement.aspx>).

Search strategy and data extraction

We identified relevant publications through a comprehensive and systematic search of databases of PubMed, MEDLINE/PubMed, Web of Science Scopus, and Google Scholar using keywords rs 12979860, IL-28 gene, Interferon lambda-3, Polymorphism, HCV, Spontaneous clearance, spontaneous resolution, spontaneous recovery (SR) and chronic hepatitis C. "AND" and "OR" Boolean operators were used for combining search keywords in the above-mentioned databases. The included papers were, first, screened based on their title, abstract, and keywords to select the eligible ones. Next, the full texts of the selected papers were evaluated by two independent reviewers. In the case of disagreement, the reviewers discussed until a consensus was reached. Through searching various databases, 545 articles were identified. Out of these, 515 were removed because they were irrelevant or duplicate articles. Then, the remaining 30 studies were assessed according to the title and abstract, and two publications did not qualify for assessing the full-text. Next, the full-text of the 28 eligible articles was evaluated of which, 6 papers were removed because of irrelevant and incomplete results, and finally, 22 studies were included in the meta-analysis (Fig. 1). Full or Entire searches were limited to English-language articles published between April 2011 and November 2019. The PRISMA flow diagram (<http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx>) illustrates the process of selection of included studies (Fig. 1).

Inclusion and exclusion criteria

Studies satisfying the below criteria were considered in our meta-analysis: 1) Case-control studies 2) published literature related to the association of cytokine gene polymorphisms (exposure) and spontaneous recovery (SR) from hepatitis C virus infection (outcome), 3) All cross-sectional, randomized controlled trials, case-series and cohort studies reporting on SC in HCV patients with at least 9 patients in two compared groups, 4) The original studies must provide the number of each group and the percentage of SC in each group. The papers with incomplete and non-relevant data were not noticed in this meta-analysis.

Assessment of study quality and risk of bias

The risk of bias of studies was evaluated using the Newcastle and Ottawa checklist by the two independent reviewers. In the case of disagreement, the two reviewers were further discussed in accompany with the third reviewer until reaching consensus (Table 1).

Table 1
Characteristics of 22 clinical trials included in study

First author, Year and Country	Design	No. of patient	Gender Male n(%)	IL – 28 SNP (s)	Event Exposure (n)	Non Exposure (n)	IDst
Mohamed Hashem [23] 2017 Pakistan	Prospective	54 a	0 (0%)*	rs 12979860	18/38	10/14	1
Sarvari, J [23] 2017 Iran	Cross-sectional	338	296 (87.5%)	rs 12979860	41/302	20/36	2
Edmondo Falletti [59] 2011 Italy	Retrospective	1057	671 (63.5%)	rs 12979860	205/629	201/428	3
Jason Grebely [25] 2014 Australia	Retrospective	632	404 (64%)	rs 12979860	168/459	98/173	4
R Carapito [60] 2015 Iran	Cross-sectional	283	187 (66%)	rs 12979860	85/176	69/107	5
Indolfi Giuseppe [61] 2014 Italy	Cross-sectional	177	96 (54.2%)	rs 12979860	48/147	17/30	6
Aldaco - Gonzalez, K [62] 2016 Mexico	Cross-sectional	234	90 (38.4%)	rs 12979860	35/149	39/85	7
Vincent Pedergrana [41] 2012 France	Cross-sectional	261	NR	rs 12979860	NR	NR	8
Susanne Knapp [63] 2011 UK	Cross-sectional	323	197 (61%)	rs 12979860	102/234	62/89	9
Sayeh Ezzikouri [29] 2013 Morocco	Cross-sectional	300	79 (26.3%)	rs 12979860	89/232	45/68	10
Indolfi Giuseppe [64] 2014 Italy	Cross-sectional	153	84(54.9%)	rs 12979860	43/130	14/23	11
Fuat Kurbanov [31] 2011 Egypt	Retrospective	162	66 (40.8%)	rs 12979860	25/82	48/80	12

Abbreviations : HCV, hepatitis C virus; SNP, single-nucleotide polymorphism; n, number; (%), (percentage); Event Exposure, the individuals with both chronic hepatitis C & favorable SNP (rs 12979860 CC); Non Exposure, the individuals with both spontaneous resolution & favorable SNP (rs 12979860 CC); IDst, ID study; NR, not reported; *, the whole of sample size in pregnant women; a, 2 cases of samples were missed; b, 1 case of samples was missed c, the analysis for 7 cases of samples was not applicable

First author,Year and Country	Design	No. of patient	Gender Male n(%)	IL – 28 SNP (s)	Event Exposure (n)	Non Exposure (n)	IDst
Susanne Knapp [65] 2015 UK	Cross-sectional	185	114 (61.6%)	rs 12979860	29/108	44/77	13
Silva- Fabrício, G.M [66] 2015 Brazil	Retrospective	286	147 (51.4%)	rs 12979860	61/245	24/41	14
Fatma M. Shebl [34] 2011 USA	Cross-sectional	1209	825 (68.8%)	rs 12979860	273/883	182/326	15
Heidar Sharafi [35] 2014 Iran	Cross-sectional	350	333 (95.1%)	rs 12979860	95/259	64/91	16
Laird, M.E [67] 2014 France	Cross-sectional	174	91 (52.3%)	rs 12979860	24/141	19/33	17
Jacob Nattermann [68] 2011 Germany	Cross-sectional	501	0 (0%) *	rs 12979860	140/396	42/105	18
Enea Spada [69] 2013 Italy	Cross-sectional	56	39 (69.6%)	rs 12979860	19/38	14/18	19
Rong-Rong Wu [70] 2014 China	Cross-sectional	427	215 (50.3%)	rs 12979860	243/277	122/150	20
Juliene Antonio Ramos [19] 2012 Brazil	Cross-sectional	179 b	91 (50.8%)	rs 12979860	36/161	16/17	21
Angeles Ruiz-Extremera [71] 2011 Spain	Retrospective	22 c	9 (40.1%)	rs 12979860	1/8	5/7	22
Abbreviations : HCV, hepatitis C virus; SNP, single-nucleotide polymorphism; n, number; (%), (percentage); Event Exposure, the individuals with both chronic hepatitis C & favorable SNP (rs 12979860 CC); Non Exposure, the individuals with both spontaneous resolution & & favorable SNP (rs 12979860 CC); IDst, ID study; NR, not reported; *, the whole of sample size in pregnant women; a, 2 cases of samples were missed; b, 1 case of samples was missed c, the analysis for 7 cases of samples was not applicable							

Statistical analysis

Meta-analysis was supposed to be performed on odds ratios for the association of cytokine gene polymorphisms (exposure) and spontaneous recovery (RS) from hepatitis c virus infection (outcome). Because in most of the included studies the reference group in calculation of OR was spontaneous recovery, the ORs and their 95% CI were reversed in the rest of the studies to make the reference group identical. Numerator of the reported prevalence were rs12979860 CC and its denominator were rs12979860 CC, CT and TT. (favorable homozygous versus heterozygous plus unfavorable homozygous). Then random effects model was used to combine ORs. Random effects model was preferred over fixed effect

model because it could be assumed that at least some of the variation among studies are real. This variation among studies, also called heterogeneity, was assessed using Cochran's Q test and the I squared statistic. To find out the study characteristics that could account for the possible heterogeneity, subgroup analysis was performed for country and study type and meta-regression was applied for mean of age and gender proportion. Publication bias was assessed statistically based on Egger's and Begg's tests and visually based on funnel plot. In order to find if one of the studies have a considerable effect on the summary effect influential analysis was performed. In this procedure each study is removed in turn and after which the summary effect is calculated providing the possibility to compare the summary effect with and without that study. All analysis was performed using packages for meta-analysis installed in Stata 14.1. significance level was set at 5%.

Results

The flowchart of the literature search procedure is illustrated in Fig. 1. According to the search strategy, 545 articles were retrieved from the related databases; and in the study selection step, 22 papers were considered in our meta-analysis (Fig. 1). From the twenty two articles, three studies were performed in Iran, three in Italy, two in Australia, two in France, two in the UK, two in Brazil, one in the USA, one in Mexico, one in Germany, one in Spain, one in Egypt, one in Morocco, one in China and one in Pakistan. All the included studies were English-language articles. The characteristics of each study included in the meta-analysis are shown in Table 1. The results of assessing the risk of bias in the included studies using the Cochrane checklist are presented in Fig. 2 and Table 2.

Figure 2 demonstrates the results of all the included studies based on REM. The summary effect (OR) as 2.75 with 95% CI from 2.23 to 3.38 (P -value < 0.000), shows that the odds of SC from hepatitis C virus infection is 2.75 times higher in those with cytokine gene polymorphisms. In terms of heterogeneity, I^2 was 66.5% (P = 0.00) that indicates the presence of some heterogeneity among the results of the included studies, and accordingly, REM was applied to account for this heterogeneity (Fig. 1). However, to deal with heterogeneity subgroup analysis was used for country and study type and meta-regression was applied for the mean of age and gender proportion. Nonetheless, none of them could persuasively account for the observed heterogeneity. Regarding publication bias, there is some asymmetry in the funnel plot presented in Fig. 3. Besides, Egger's test p -value was 0.001 showing the presence of publication bias (Fig. 3). In order to adjust for possible publication, bias trim and fill approach was used which resulted in OR of 2.09 but was not significantly different from 2.74. Besides, to assess the effect of individual studies on the summary effect influential analysis was performed and its output is indicated in Fig. 4. The three horizontal lines indicate the summary effect and its 95% CI. Each vertical line shows the summary effect and its 95% CI after elimination of the study specified by its ID in the x axis. The result of the influential analysis shows that the elimination of none of the studies could statistically or clinically change the summary effect. In other words, the summary effect was not sensitive to individual studies.

Association of IL-28 polymorphism and virus genotype In order to investigate the association of rs12979860 CC and genotype, we compared the prevalence of rs12979860 CC in genotype one versus

other genotypes all of which were restricted only to SC cases. This comparison was performed through a meta-analysis that pooled the prevalence of rs12979860 CC over two subgroups genotype one and other. It was found that there was some association between rs12979860 CC and genotype as the prevalence of rs12979860 CC was 0.33 with 95 CI (0.28–0.38) in genotype one and was 0.40 with 95 CI (0.34–0.47) in other genotypes.

Discussion

The results of numerous studies indicated that the analysis of genetic polymorphisms can help to understand the mechanism of disease and the differences in the complexity of the disease between individuals [45]. HCV is a serious reason for both acute and chronic hepatitis in infected individuals. It is estimated that the SC of the virus happens in 20% of patients with acute HCV infection, and liver cirrhosis and hepatocellular carcinoma (HCC) in chronic HCV patients could be an inevitable process [46]. An increasing body of experimental and clinical evidence since 2009 and genome-wide association studies (GWAS) have indicated that polymorphisms close to the IL-28B gene (interferon lambda) are associated with increased rates of SC in studied subjects with chronic HCV infection [47,48]. However, in some cases, there are contradictory conclusions, and while some studies have reported significant associations, others didn't find any associations [49–51]. IL-28B similar to other types III IFNs, such as IL-28A and IL-29, shows a strong antiviral activity and induces ISGs [52]. In the present work, we performed a systematic review and meta-analysis to examine the efficacy of a genetic variant (rs12979860) located in a gene (IFN- λ 3) involving in host innate immunity on the HCV SC. Based on our meta-analysis result, rs12979860 SNP exhibited a significant association with HCV SC and sustained virologic response (SVR). The Pooled result of all the included studies indicated a significant association between rs12979860 CC and SVR in HCV patients treated with PEG IFN- α /RBV. The result indicates that the ORs of SC from HCV infection is 2.75 times higher in those with cytokine gene polymorphisms, 95% CI (2.23 to 3.38). Although the molecular mechanism of the effect of IL-28B gene polymorphism on HCV clearance is unclear, several studies have shown that various factors including viral, host, epidemiological, and environmental factors can be accompanied with HCV clearance [53,54]. Preliminary reports evaluating the association between IL28B SNPs and the clearance of HCV have been reported in large groups of patients who are chronically infected with HCV and have been treated with standard antiviral drugs[55,56]. Thomas et al. [54] and Shi et al [21] showed that rs12979860 SNP firmly augments the probability of HCV clearance among patients from either African or European ancestry. Their result indicated that there was almost a 3-fold greater rate of virus clearance in patients with the rs12979860 genotype CC versus those with TT or CT. Although, T rs8099917 and C rs12979860, most strongly associated with HCV clearance, they might be affected by the HCV genotype, racial diversity, and population differences. It has been demonstrated that the polymorphism in IL-28B gene appears to be a weaker pretreatment predictor for anti-viral responses in individuals with HCV-2 and HCV-3 than in those with HCV-1 [20]. Hepatitis C treatment could be affected by several viral factors such as the genotype of the virus, quasi-species, primary load of the virus, and the kinetics of virus [6,57].

Regarding the existence of different HCV genotypes, patients with HCV that treated with PEG IFN- α /RBV produce a variable SVR and SVR for each genotype differs, so that individuals with genotype 2 have the highest rate of SVR and those with genotypes 1 and 4 have the lowest SVR rate [58]. In our work, virus genotype stratification analyses revealed that there was some association between rs12979860 CC and genotype as the prevalence of rs12979860 CC was 0.33 with 95 CI (0.28–0.38) in genotype one and was 0.40 with 95 CI (0.34–0.47) in other genotypes. However, the observed association, though consistent with the available literature, was not statistically significant as the two CIs overlapped each other. This could be explained by the low precision of the included studies or their low number. Our work may have some limitations that should be taken into consideration when interpreting the results. In the present study, only published studies have been used, and it is best to include all available individual patient data, such as previously unpublished data. Moreover, other factors besides genetic factors including viral load, patient's physiological and physical characteristics can affect the SC of infection in individuals with chronic HCV that treated with antiviral therapy. Also, due to the small size of the genotypes 2/3 and genotype 4, it may be argued that our conclusion cannot be generalized, and future researches with a larger number of patients per each group of genotypes 2/3 and genotype 4 and from different ethnic groups need to be studied to confirm the connection with the IL28B polymorphism. Nonetheless, our results suggest that IL28B rs12979860 CC is a robust predictor of SC in patients with chronic HCV.

Declarations

Ethics approval

1-This is an observational study. The Shiraz University of Medical Sciences Research Ethics Committee has confirmed that no ethical approval is required.

2- Compliance with ethical standards

Conflict of interest

All authors declare they have no conflicts of interest

Funding information

Shiraz University of Medical Sciences,

Grant/Award Number: 19569

Acknowledgment

This work was supported by a grant from Shiraz University of Medical Sciences

(No. 15969).

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Table

Table 2 is not available with this version

Figures

Figure 1

PRISMA Flowchart of the study selection process

Figure 2

Forest plot for Odds Ratio for association between cytokine gene polymorphisms and spontaneous recovery (RS) from hepatitis c virus infection. Each square (■) and its horizontal line, respectively, represent the OR and its 95% CI for each individual study (the size of the grey square corresponds to the weight of that study in the meta-analysis); the diamond and its horizontal diagonal (◇) show the combined overall OR and its 95% CI, respectively.

Figure 3

Funnel plot for Odds Ratio for association between cytokine gene polymorphisms and spontaneous recovery (RS) from hepatitis c virus infection.

Figure 4

Plot for assessing the effect of individual studies on the summary effect. The three horizontal lines indicate the summary effect and its 95% CI. Each vertical line shows the summary effect and its 95% CI after elimination of the study specified by its ID in the x axis. The scale is natural logarithm