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Interleukin 28B Genetic Polymorphism Testing – Is There Any Role In The Era Of Direct Acting Antivirals?

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Abstract

Background: Interleukin (IL) 28B is a member of type III interferons also termed interferon-lambda (IFN-λ). The predictive role of IL28B SNP polymorphism for cure was significant when the standard of care for HCV infection was therapy with PEG-IFN and ribavirin. IL28B CC genotype was considered to have favorable response as compared to Non-CC genotype. As newer therapies have shifted toward interferon-free regimens that offer very high-sustained virological response rates, the usefulness of IL28B polymorphism as a clinical test to predict the response rate to antiviral therapy has minimized substantially.

Aim: To review the current role IL28B genetic testing in patients with HCV beyond its role in predicting treatment response.

Methods: A structured search in PubMed was performed using defined keywords (Interleukin (IL) 28B, chronic hepatitis, and hepatitis C virus), including full text articles and abstracts in English language.

Results: Along with other members like IL29 and IL28A, IL28B exhibit a strong antiviral function and induction of interferon-stimulated genes. Various studies in recent years have shown that host IL28B genetic polymorphisms is also associated with occurrence of insulin resistance and diabetes mellitus, in predicting fibrosis, HCC and recurrence of HCV post-transplant in patients with chronic hepatitis C virus (HCV) infection, association with other infections like Hepatitis B, Helicobacter Pylori thus indicating its role beyond predicting treatment response.

Conclusions: If these early observations on expanding role of IL28B genetic testing for various roles beyond treatment response prediction get validation in future studies, new avenues will be opened in near future for using IL28B genetic test in patients with HCV.

Keywords: IL28B, Chronic hepatitis C; hepatitis C virus; Peginterferon; Cirrhosis

Abbreviations: IL: Interleukin; HCV: Hepatitis C Virus; IFN: Interferon; GWAS: Genome Wide Associated Study; SNP: Single Nucleotide Polymorphism; DC: Dendritic Cells; SOC: Standard-of-Care; LDL: Low-Density Lipoprotein; SNP: Single Nucleotide Polymorphisms

Introduction

Interleukin (IL) 28B is a member of type III interferons also termed interferon-lambda (IFN-λ). IL28B resides on the short arm of chromosome 19 (19q13.13) and encodes for interferon (IFN)-λ3. Along with other members like IL29 and IL28A, IL28B exhibit a strong antiviral function and induction of interferon-stimulated genes [1,2]. It was in the year 2009 when Ge et al. [3] for the first time found rs12979860 single nucleotide polymorphism (SNP) 3 kilobases upstream of the IL28B region, by genome wide associated study (GWAS). They observed that this SNP could be the strongest host genetic predictor of SVR in hepatitis C patients. Patients homozygous for the beneficial C allele had a two- to three-fold higher chance to eradicate the virus under treatment with PEG-IFN/RBV than patients carrying the T allele. Over the next 5-6 years substantial number of publications came on IL28B SNP and these findings were confirmed [4,5]. Different GWAS identified additional SNPs (rs8099917 and rs12980275) and were also compared with rs12979860 for their usefulness in predicting SVR in HCV [6,7,8].

Other SNP's were also identified but three SNPs related to IL28B gene, rs8099917, rs12980275, and rs12979860, are

important. The mechanism underlying the association between the IL28B polymorphism and response to hepatitis C treatment is not well understood. Possible explanation in accordance to in vivo models of chronic hepatitis C virus (HCV) infection is that exogenous IFN-α would increase IFN-λ production by HCV-infected hepatocytes during IFN-α therapy [9]. The amounts of IFN-λs produced on HCV-infected human hepatocytes were larger in liver with a favorable IL28B genotype. Dendritic cells (DCs) also produce large amounts of IFN-λ, following an immune response against HCV infection in the liver environment. The ability of IFN-λ3 production by DCs was also superior in subjects with a favorable IL28B genotype [10,11]. The current thought till now is that in hepatitis C virus infection, people born with the nucleotide cytosine (C) at location rs12979860 in both alleles of the gene that codes for interleukin 28B (the IL28B CC genotype) can count themselves luckier than those born with thymine (T) in this location in one of their alleles (the CT genotype) or both of their alleles (the TT genotype).

The predictive role of IL28B SNP polymorphism for cure was significant when the standard of care for HCV infection was therapy with PEG-IFN and ribavirin. Drugs with virus-specific targets (HCV-encoded proteins required for viral replication) have now become the major focus of new therapies in the treatment of chronic HCV and have heralded the era of the direct-acting antivirals (DAAs) [12,13,14]. These innovations in antiviral therapy for HCV have resulted in remarkable improvement in sustained virological response rates, better tolerability, and decreased duration of treatment compared to interferon and ribavirin-based therapy used till now. We are now able to achieve more than 90% of SVR with these drugs. It is uncertain if doing IL28B genetic testing still holds any role in HCV patients, as we have entered into the era of high cure rates for hepatitis C virus infective patients across all genotypes, ethnicity, sex and age group with the help of DAA's. Various studies in recent years have shown that host IL28B genetic polymorphisms is also associated with occurrence of insulin resistance and diabetes mellitus, in predicting fibrosis, HCC and recurrence of HCV post-transplant in patients with chronic hepatitis C virus (HCV) infection, association with other infections like Hepatitis B, Helicobacter Pylori thus indicating its role beyond predicting treatment response. In this article we will try to review if there is any utility left for performing this genetic test in HCV patients.

Il28b Polymorphism for Predicting Response of Direct Acting Antivirals

The standard-of-care (SOC) treatment for CHC during the last decade has been the combination therapy of pegylated-interferon-α (PEG-IFN) with ribavirin (RBV) [15]. Studies have found that HCV genotype other than 1, low baseline viral level, white race, Interleukin-28B genotype CC, absence of fibrosis, body weight <85 kg, age<40 year, female sex are predictors of favorable response to treatment with PEG- IFN and ribavirin therapy [16,17]. Interleukin-28B (IL28B) gene was found to be strongly associated with response to PEG-IFN/RBV therapy for chronic HCV genotype 1 infection and subsequently with other genotypes [7,18]. Antiviral therapy have consistently changed over last few years and various direct acting antiviral drugs (DAAs) have been developed, which are directed against essential components of viral replication [12,13]. Initially when first-generation protease inhibitors, telaprevir and boceprevir got approved and clinical trials in treatment-naïve patients with boceprevir and telaprevir, respectively, showed that the IL28B SNP: rs12979860 affected treatment outcome. The SVR rates were higher in patients with CC (80%, 90%) compared with CT (71%, 71%) or TT (59%, 73%) genotypes [19,20]. Boceprevir therapy was associated with high SVR improvement in non-CC patients also with response rates of 55–71% in the boceprevir arm compared to 27–28% in the PEG/RBV control arm [21]. Overall, logistic regression modelling found the IL28B genotype was independently associated with SVR in boceprevir based therapy, but the effect was attenuated in comparison to PEG/RBV alone. In treatment-experienced patients, IL28B was less informative for the outcome of boceprevir and telaprevir based therapy. Retrospective analysis of the RESPOND-2 and the REALIZE study showed no significant association between IL28B and treatment response [19,22].

In the Neutrino study [13] nucleoside NS5B polymerase inhibitor sofosbuvir (SOF) plus PEG/RBV in 327 treatment-naive genotype 1, 4, 5 and 6 patients, identified SNP rs12979860 in IL28B as independent pre-treatment predictor for SVR. Response rates were 98% (n = 93/95) in patients with CC compared to 87% (n = 202/232) in patients carrying the T allele (P = 0.006). When the second wave NS3 protease inhibitor simeprevir and PEG/RBV was studied in genotype 1 treatment naïve (QUEST-1 and QUEST-2) [23,24] and treatment experienced patients (PROMISE) [25] it was observed that IL28B genotype significantly impacted treatment response. Although there were statistical associations between IL28B genotype on SVR in the setting of triple therapy with NS3 protease, NS5A or NS5B polymerase inhibitors, these effects were markedly attenuated. IL28B genotype testing in the setting of triple therapy including interferon and DAA could still be a useful tool in pre-treatment counseling and for identifying patients eligible for shorter treatment duration with triple therapy. It is important to know whether IL28B genetic polymorphism had any effect when antiviral regime got interferon free. In SOUND-C2 [26] combination therapy of the protease inhibitor faldaprevir and the nonnucleoside NS5B polymerase inhibitor deleobuvir with or without RBV was studied in patients with CHC GT 1 and in multivariate analysis GT1b, female sex, normal baseline c-glutamyl transferase levels and the IL28B CC genotype were associated with a higher rate of SVR12. These data preliminary suggested that innate immunity and endogenous interferon release might still be important in interferon-free treatment regimes.

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Sofosbuvir (SOF), a pan-genotypic nucleotide analog, is the most important of all the available DAA's. This drug is being used in combinations with other DAA's in various interferon free regimes. In the phase III studies on the combination of sofosbuvir with ribavirin (POSITRON, FUSION and FISSION) in patients with CHC GT2 and 3 treated with SOF/RBV, no differences in response rates according to the IL28B genotype were observed [27,13]. In an all-oral combination of sofosbuvir with daclatasvir (NS5A-inhibitor) high SVR12 rates were achieved in GT1 patients (treatment-naive or experienced) and in GT2/3 patients across all IL28B genotypes [28]. In the ION-1 trial including sofosbuvir and ledipasvir in CHC GT1, it was observed that patients with non-CC genotype achieved a high SVR of 97-99%, thus blunting the utility of IL28B as a prognostic marker [29]. Table 1 compares the rates of response to hepatitis C treatment by interleukin-28B rs12979860 genotype after treating with PEG-IFN/RBV or combining DAA's with interferon and with interferon free regimes. The latest guidance from EASL and AASLD in 2018 and 2015 have incorporated newer DAAs in the management of patients with HCV [30,31]. As the new clinical guidelines are moving rapidly away from interferon-based combinations the clinical utility of IL28 testing is limited, particularly with more potent, all-DAA regimens. EASL and AASLD guidelines did not mentioned any role of IL28B genotyping in Hepatitis C management Further prospective studies can also be done to evaluate the impact of IL28B as a predictive factor in IFN-free treatments, which may allow shortening of treatment further and thus can help in reducing the cost burden of these drugs.

Table 1: Comparison of sustained virological response (SVR) prediction by interleukin-28B rs12979860 genotype [source references [3,19,13,29]].

Genotype	Pegylated interferon + ribavirin	Protease inhibitor+ pegylated interferon + ribavirin	Sofosbuvir + pegylated interferon + ribavirin	Sofosbuvir + ledipasvir
IL28 CC	78%	80-90%	98%	100%
IL28 CT	38%	72%	(87%) combining TT	100%
IL28 TT	26%	57%	(87%) combining CT	98%

Il28b Polymorphism and Spontaneous Clearance of Virus

It is believed that at least 70% to 80% of acute hepatitis C virus infections persist and become chronic, while 20% to 30% spontaneously get resolved [32]. According to AASLD guidelines, predictors of spontaneous clearance of virus include jaundice, elevated ALT level, hepatitis B virus surface antigen (HBsAg) positivity, female sex, younger age, HCV genotype 1, and host genetic polymorphisms near IL28B gene [31,33]. It is believed that variations in the genes involved in the immune response may contribute to one's ability to clear the virus. Thomas et al. [34] in 2009 showed that the SNP rs12979860 upstream of IL28B and the CC genotype were associated with spontaneous clearance of HCV. Consistent with these observations, various recent studies have shown that the polymorphism in the IL28B gene region encoding interferon lambda 3 strongly predicts spontaneous resolution of acute hepatitis C virus infection [35,36]. People who have the IL28B CC genotype are three times more likely to spontaneously clear the virus than those with the CT or TT genotype. Interestingly, jaundice during acute infection was more common in patients with the CC genotype than non-CC genotype [36,33]. An analysis of nine prospective international cohorts evaluating outcomes following acute HCV infection reported that spontaneous clearance occurred in 173 (25%) of 632 acute HCV infections during 1 year follow-up and that female gender, favorable IL28B genotype and HCV genotype 1 were independent predictors of viral clearance [37]. Thus, there is strong evidence to believe that genetic variations play an important role in spontaneous resolution or persistence of HCV infection. With these evidences it can be recommended that early therapeutic intervention in non-jaundiced patients with an unfavorable IL28B genotype should be considered because of their low likelihood of spontaneous HCV clearance.

Il28b and Natural History of Hepatitis C Virus

In the natural history in people in whom hepatitis C virus infection persists, up to 20% develop progressive liver fibrosis and eventually cirrhosis develops over 10 to 20 years(32)(38). The speed at which fibrosis develops in these patients is variable and unpredictable. Abe et al. [39] analyzed the effect of IL28B genotype on histological findings and found that inflammation was more active and fibrotic progression was more severe in patients with a favorable IL28B genotype. On the contrary Fabris et al. [40] reported that patients with an unfavorable IL28B genotype were at increased risk of severe liver fibrosis. In another study done by Marabita et al. [41], the authors reported that the IL28B genotype was not associated with progression of fibrosis in patients whose dates of infection were known. In a recent study done by Noureddin et al, the authors tried to study any association between IL28B with fibrosis progression and clinical outcome in HCV. At baseline biopsy, patients with IL28B CC genotype had significantly higher portal inflammation and alanine aminotransferase (ALT) levels. In longitudinal analysis, there was no difference in fibrosis progression (defined as an increase in Ishak score in two paired liver biopsy of at least 2) between CC and T allele carriers. Patients with IL28B CC were twice as likely to develop adverse clinical outcomes compared to non-CC. The authors finally concluded by suggesting that IL28B CC is associated with a state of enhanced immunity that, on the one hand, can promote viral clearance, but alternately can increase necroinflammation and hepatic decompensation without enhancing fibrosis progression. Thus, the relationship between IL28B polymorphisms and hepatic

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fibrosis in patients with chronic hepatitis C virus infection has not been clearly established. The reason could be difficulties to determine accurately when the patient contracted the virus, and that serial liver biopsies are needed to investigate the progression of hepatic fibrosis.

At present IL28B testing cannot be recommended to predict fibrosis progression in hepatitis C patients. Similarly, the impact of IL28B geno https://www.chictr.org.cn/searchprojEN.html?sourceofspends=self-funded&country=&createyear= type on higher risk of hepatocellular carcinoma is controversial. An earlier study demonstrated that patients with hepatitis C associated hepatocellular carcinoma carried the T allele more frequently(40). Recently, Asahina et al. [42] showed the association between IL28B genotype and HCC risk in a large-scale including 792 patients, indicating that rs8099917 non-TT is significantly associated with HCC development particularly in patients infected with HCV genotype 1. In contrast many investigators have also failed to find any association between IL28B genotype and the development of HCC [43,44]. An important implication of these relationships is that IL28B genetic testing might eventually help identify patients at greater risk of developing HCC, who therefore need earlier intervention. Further studies with validation of this association can justify doing testing of IL28B polymorphism for risk stratification of HCC.

Il28b and Liver Transplantation

Recurrence of Hepatitis C virus infection after liver transplantation results in serious consequences that include cirrhosis and liver failure. IL28B genotype of the recipient may determine the severity of histologic recurrence of hepatitis C. In the study by Charlton et al. [45] the authors found that recipient IL28B TT genotype was associated with more severe histological recurrence of HCV. Another study was done by Graziadei et al. [46] where they found that HCV viremia at week 2 and a non-C/C recipient IL-28B genotype were independent risk factors for recurrent HCV infection after transplantation. The IL28B genotypes of both the recipient and the donor are strongly and independently associated with response to interferon-based treatment in patients with hepatitis C after liver transplantation, similar to the way IL28B polymorphism influenced treatment response in non-transplant patients with HCV. Different authors in recent years have concluded The IL28B favorable genotype in either the recipient or the donor is associated with a higher rate of response to pegylated interferon and ribavirin combination therapy after liver transplantation [47-50]. In a met analysis done by Zhang et al. [51] including eleven studies, the authors concluded that rs12979860 genotype CC and rs8099917 genotype TT in both donor and recipient contribute to a high SVR in the recipient after antiviral treatment. IL28B genotype testing for prediction of HCV recurrence cannot be justified with this preliminary data. But, it is safe to conclude that the unfavorable allele in recipients is associated with a worse response to antiviral therapy as in the pre-transplant setting. As with non-transplant patients the management of reinfection with HCV in transplant recipients is taking a paradigm shift towards DAA's [30,31]. The utility of IL28B in predicting treatment response lies with PEG-IFN and RBV based regimes. The promise of direct acting antiviral therapy will minimize the impact of IL28B genotype in post-transplant settings as well.

Il28b and Metabolic Changes in HCV

Though the primary role of IL28B genotype SNP was to predict treatment response with interferon and ribavirin in HCV patients, it could be possible that these SNP on IL28B gene could influence other non-treatment related parameters also. An association between chronic hepatitis C infection and increased incidence of diabetes mellitus has been observed in comparison to other causes of liver disease [52]. The mechanism by which HCV causes an increased insulin resistance and diabetes are not well understood but studies have shown that HCV proteins may directly induce insulin resistance by impairing the insulin signaling pathway through several possible effectors such as suppressor of cytokine signaling and mammalian target of rapamycin [53,54]. If the duo (hepatitis C and diabetes) comes together, than there is rapid occurrence of fibrosis, decompensation and incidence of HCC increases [55,56]. Recently IL28B polymorphism has been linked to increased incidence of diabetes mellitus in patients with HCV. Stratemeyer et al. [57], in 2012 published their observation in which they found IL28B SNPs rs12979860 non-CC genotype as an independent risk factor for insulin resistance. Compared to CC homozygotes, T allele carriers had a higher frequency of insulin resistance (IR) irrespective of the degree of fibrosis or steatosis. In another recent study done by Kanwal et al. [58], rs12980275 SNP favorable AA IL28B alleles have a lower prevalence of diabetes and related complications compared with patients with unfavorable alleles. Even in post-transplant patients with chronic hepatitis C, it has been observed that the risk of developing DM is significantly increased in recipients carrying the TT polymorphism of the IL28B gene [59,60].

The specific mechanism by which IL28B SNP genetic variations cause insulin resistance and diabetes are poorly understood. It has been suggested that unfavorable genotypes (TT) may manifest higher interferon gene intensity. The interferon further suppresses insulin signaling via expression of suppressor of cytokine signaling (SOCS) 1 & 3. Suppressor of cytokine signaling (SOCS-1) and (SOCS-3) cause insulin resistance through inhibition of tyrosine phosphorylation of insulin receptor substrate proteins by discrete mechanisms [61]. Thus, a mechanistic link between IL28B unfavorable genotypes (CT and TT) and insulin resistance can be postulated. Lipid metabolism in HCV infected patients may also be influenced by the IL28B genotype. In a study done by Li et al they showed that patients who were carrying the favorable CC allele had significantly higher levels of total cholesterol, apo-lipoprotein B and low-density lipoprotein (LDL) cholesterol than those carrying the T allele [62]. Thus, there is scarce and preliminary literature in concordance with these association and

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further studies are needed to validate these observations. Larger population studies including HCV patients are needed and findings should be compared with other chronic viral diseases and normal population. If such kinds of associations are present, then IL28B genetic polymorphism may improve the ability to counsel patients regarding their individualized risk of diabetes, lipid metabolism diabetes-related complications and ultimately increased risk of cirrhosis and decompensation of liver disease in HCV patients.

Il28b and Hepatitis B

Genome-wide association studies (GWAS) in Asian population concluded that IL28B gene is not correlated with HBV infection or viral clearance [63, 64]. However, the single nucleotide polymorphisms (SNPs) constructed by SNPs in the IL28B gene can influence the HBV infection, HBV surface antigen Sero clearance, or treatment of HBV-infected individuals in special cohorts [65, 66]. SNPs rs12979860 and rs8099917 were mostly studied and identified to be associated with HBV-infection in Chinese [67]. There was no previous data whether SNPs in the IL28B gene influence the HBV infection and biochemical characteristics of HBV-infected individuals in Yunnan, China but Yuzhu Song et al. recently published a study [68]. In this study they screened genotypes of three single nucleotide polymorphisms (SNPs, rs12979860, rs8099917, and rs12980275) in HBV-infected individuals and general controls by using Snapshot and sequencing. Results of this study showed no significant difference in genotypes, alleles, and haplotypes frequency between the HBV-infected individuals and controls. After dividing the HBV-infected individuals into patients in acute infection, chronic HBV patients, and patients undergoing convalescence, the genotype GT (P D 0:033) and allele G (P D0:038) of rs8099917 showed statistically higher frequency in the acutely infectious individuals than in the HBV patients undergoing convalescence. HBV viral load was higher in the acutely infectious patients than in the chronic infection group. They also found that leukomonocyte (LYM) level was associated with SNPs in the IL28B gene. In addition, the LYM levels were lower in the HBV-infected individuals with genotype CC of rs12979860 and AA of rs12980275 than in the patients with other genotypes of these two SNPs. They concluded that genetic polymorphisms of the IL28B gene were associated with LYM level of HBV-infected individuals.

Il28b and Helicobacter Pylori

Association between H. pylori infection and HCC is published in literature. Xuan et al. calculated odds ratio of 13.6 for the association of H. pylori infection with the risk for HCC [69]. A close relative of H. pylori, H. hepaticus led to the development of HCC in an experimental infection model in mice [70]. In a meta-analysis, Wang et al. evaluated 12 studies looking for H. pylori (serological or PCR) in HCV-infected patients with a total 1449 patients and 2377 control cases [71]. Compared to the controls, they found an odds ratio (OR) of 2.93 having a positive test for H. pylori in chronically infected HCV patients, no matter which state of HCV-related liver disease was present. In a subgroup analysis, the ORs were 4.48 for HCV-related cirrhosis and 5.45 for hepatocellular carcinoma suggesting H. pylori infection as a risk factor for the progression of chronic HCV infection to liver cirrhosis and HCC. In a recent study conducted by Alexander Gutwerk, to evaluate the serological rate of Helicobacter pylori (H. pylori) infection in patients with chronic hepatitis C virus (HCV) infection and determine any correlations with liver damage and IL28B single-nucleotide polymorphism (SNP) [72].

One hundred eighty-nine patients with chronic HCV infection were included in the study, and H. pylori status was defined based on anti-H. pylori-IgG or anti-CagA-IgG antibodies using enzyme-linked immunosorbent assay (ELISA). Liver damage was assessed using histology or transient elastography. IL28B C/T polymorphism (rs12979860) was evaluated in circulating blood cells using a PCR-based restriction fragment length polymorphism assay. Overall H. pylori serology was positive in 38.1% of our HCV-infected subjects. Among those, the anti-CagA-IgG positivity rate was 43.1% and was within the range of previously described populations of the same region. Highest prevalence of H. pylori was found in patients between 31 and 40 years compared to other age subgroups. The seropositivity rate was higher in the non-cirrhotic group than the cirrhotic one (45.4% vs. 20.0%, $p < 0.05$). No difference was found in IL28B genotype between H. pylori-positive and -negative cohorts. However, they observed a trend for the lower anti-CagA-IgG expression level in relation to the IL28B T-allele. Though this study does not support an association between HCV and H. pylori infection, but whether IL28B SNP has a functional role in modulation of serological response to H. pylori CagA, needs further investigation.

Conclusion

In recent years IL28B genotype testing became readily available for clinical use. The IL28B polymorphism proved to be a strong predictor of spontaneous clearance of hepatitis C virus and responsiveness to interferon-based therapy. As newer therapies have shifted toward interferon-free regimens that offer very high-sustained virologic response rates, the usefulness of IL28B polymorphism as a clinical test to predict the response rate to antiviral therapy has minimized substantially. It may remain clinically relevant to identify candidates who are more likely to respond to pegylated interferon and ribavirin, particularly in resource-poor settings and in developing countries where prices of DAA's is enormously high and for patients in whom these treatments are contraindicated. A decline in clinical utility does not minimize the lesson we learned from the discovery of the IL28B gene and the impact on our understanding of the pathogenesis of hepatitis C virus infection. In recent years IL28B genetic testing has also found new roles by predicting fibrosis and hepatocellular carcinoma, predicting HCV recurrence in post-transplant patients and can even predict occurrence of insulin resistance and diabetes both in pre and post-transplant HCV patients. If these early observations get validation than new avenues might get opened in future for using this genetic test in patients with HCV.

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