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LETTERS TO THE EDITOR

Predictive potential of *IL-28B* genetic testing for interferon based hepatitis C virus therapy in Pakistan: Current scenario and future perspective

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Abstract

In Pakistan which ranked second in terms of hepatitis C virus (HCV) infection, it is highly needed to have an established diagnostic test for antiviral therapy response prediction. Interleukin 28B (*IL-28B*) genetic testing is widely used throughout the world for interferon based therapy prediction for HCV patients and is quite helpful not only for health care workers but also for the patients. There is a strong relationship between single nucleotide polymorphisms at or near the *IL-28B* gene and the sustained virological response with pegylated interferon plus ribavirin treatment for chronic hepatitis C. Pakistan is a resource limited country, with very low per capita income and there is no proper social security (health insurance) system. The allocated health budget by the government is very low and is used on other health emergencies like polio virus and dengue virus infection. Therefore it is proposed that there should be a well established diagnostic test on the basis of *IL-28B* which can predict the antiviral therapy response to strengthen health care set-up of Pakistan. This test once established will help in better management of HCV infected patients.

Key words: Diagnostics; Hepatitis C virus; Interferon therapy; Polymorphisms; *IL-28B*; Genetic testing; Pakistan

Core tip: Pakistan has a very heavy burden of hepatitis C virus (HCV) infection with around 11 million positive cases; however, in spite of well established prognostic value, the data regarding the role of interleukin 28B (*IL-28B*) single nucleotide polymorphisms (SNPs) in HCV antiviral therapy response are very limited. There are only six reports on the topic and it can be concluded from this limited information that *IL-28B* could be a good prognosis marker for HCV patient management in Pakistan. The major prevalent HCV genotype in Pakistan is 3a and *IL-28B* SNP rs12979860 showed a good prediction for interferon based antiviral therapy response against this viral genotype. It can be predicted that inclusion of *IL-28B* genetic testing in

routine diagnostic set-up of Pakistan will help in better management of the disease. A well directed antiviral therapy based on personalized *IL-28B* genotyping along with virus genotyping will help in lessening of therapy cost and better management of the disease.

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TO THE EDITOR

Recent advancements in molecular biology techniques help in identification of various host and pathogenic factors influencing the disease prognosis and therapeutic outcomes. One example is identification of various genetic factors through genome wide analysis studies (GWAS). In the field of gastroenterology and hepatology, an example is the discovery of an association between single nucleotide polymorphisms (SNPs) at or near the interleukin 28B (*IL-28B*) gene and the sustained virological response (SVR) rate with pegylated interferon (IFN) plus ribavirin treatment for chronic hepatitis C (CH-C)[1-3]. IL-28B (IFN-λ3) is produced by many immune cells like neuronal cells, alveolar epithelial cells, and hepatocytes in response to viral infection. IFN-λ showed antiviral activity against many viruses. It not only inhibits viral replication but also has immune-modulatory functions[4]. It has been shown by four autonomous GWAS that SNPs of the *IL-28B* gene, which is located on chromosome 19q13, are strongly associated with treatment response to interferon based therapy and spontaneous viral clearance in chronic hepatitis C virus (HCV)-infected patients[4]. After these studies, the predictive potential of *IL-28B* genetic variations has been investigated and verified throughout the world in patients infected with HCV of all viral genotypes and currently IL-28B SNPs are in commercial use for antiviral therapy response prediction around the world.

In Pakistan, data regarding the role of IL-28B SNPs in HCV antiviral therapy response are very limited. To our knowledge, there are only six studies that investigated the role of IL-28B in HCV patients regarding interferon therapy response and disease prognosis (Table 1)[5-10]. These studies investigated the predictive potential of either IL-28B protein level or IL-28B SNPs (rs12979860, rs8099917, rs12980275). It can be concluded from existing limited data that IL-28B could be a good prognosis marker for HCV patient management. Recent studies by Shaikh *et al*[9] (2014) and Imran *et al*[8] (2015) reported significant existence (47.5% and 6.4%, respectively) of circulation of diagnostically untypable HCV variants in local populations of Sindh Province of Pakistan. We have lately highlighted the issue of diagnostically untypable HCV circulation in Pakistan and recommended immediate need to resolve this problem for the better management of HCV patients as course and fate of antiviral therapy are viral genotype dependent[11]. The resolution of this problem will also help in understanding the potential role of IL-28B SNPs in antiviral therapy response prediction against each viral genotype.

HCV is highly endemic in Pakistan with around 11 million infections[12-14]. The major prevalent viral genotype is 3a along with 2a, 3b, 1b, 2b, 2a and a large number of untypable ones[11,15,16]. It is observed that irrespective of the HCV genotype, SVR rate of interferon plus ribavirin is quite good (80%-97%) in Pakistan[7,8,17,18]. Pakistan is a resource limited country with much low per capita income in the general population. According to the World Health Organization, the total expenditure on health is only 2.8% of GDP, which means total expenditure on health per capita is only 126 $[19]. Other medical emergencies like polio virus and dengue virus endemics shift the government priorities and funds are becoming less available for HCV management. There is no health insurance for the general population in Pakistan, which also affect the patient's ability to bear therapy cost. *IL-28B* genetic test is an established diagnostic test for interferon based antiviral therapy response prediction across the world. In the current scenario of Pakistan, it is highly needed to have an established diagnostic test on the basis of IL-28B which can predict the antiviral therapy response.

The currently available literature on the role of IL-28B in HCV interferon therapy response in Pakistan shows that rs12979860 is a good predictor of therapy response against HCV 3a genotype. In the era of direct acting antivirals (DAAs), interferon based therapy against HCV will remain the major choice in Pakistan due to higher SVR and low cost compared with DAAs[20]. On the basis of the above discussion, we propose future studies across the country on different ethnic groups infected with all viral genotypes so that the results could be generalized for diagnostic purpose. It is also suggested that the forthcoming studies should include a comparatively larger number of patients so that the results could be applicable for commercial purpose. It is highly anticipated that inclusion of *IL-28B* genetic testing in routine diagnostic tests will help health care professionals in better management of the patients. Well directed antiviral therapy on the basis of personalized *IL-28B* genotyping along with viral genotyping will help in reduction of therapy cost and better management of the disease.

Table 1 Summary of interleukin 28B and interferon based therapy response in hepatitis C virus patients in Pakistan

Year	Viral genotype	Patients (*n*)	Objective/SNP investigated	Findings/conclusion	Ref.
2015	3a	66	IL-28B protein levels	IL-28B protein levels were significantly associated with therapy response	[5]
2015	3	105	rs8099917	TT genotype favors RVR	[6]
			rs12979860	CC genotype favors SVR	
2015	1a,1b, 3a	111	rs12979860	CC genotype favors SVR in HCV 3a genotype	[7]
2015	1a, 1b, 3a, 3b, 4, UT	140	rs8099917	No association was observed with therapy response	[8]
			rs12979860	CC genotype favors SVR	
2014	(2a, 3a, UT)	220	rs8099917	No association was observed with therapy response	[9]
			rs12979860	No association was observed with therapy response	
			rs12980275	AA genotype favors SVR	
2014	3a	200	rs12979860	TT genotype favors SVR	[10]

Genotyping performed only for non-responders patients. SVR: Sustained virological response; RVR: Rapid virological response; UT: Untypable; IL-28B: Interleukin 28B; HCV: Hepatitis C virus; SNP: Single nucleotide polymorphism.

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