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IL28B is An Irrelevant Prognostic Factor for HCV in the Era of Highly Effective DAAs

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Abstract

Direct-acting antivirals (DAAs) therapies have ushered in the beginning of new era for HCV treatment. Comparative studies to understand the efficacy, safety and factors associated with treatment non-response to DAAs therapies are much-needed. The present study was conducted primarily to evaluate the efficacy and safety of sofosbuvir based DDAs therapy and secondly to investigate the role of host and viral factors especially rs12979860 with treatment response. This study showed that sofosbuvir based therapy was safe and associated with high rates of sustained virological response in both treatment naive and experienced patients. IL28B rs12979860 was not associated with sofosbuvir based treatment hence an irrelevant prognostic factor in our population.

Key words: IL28B; IFNL4; DAAs; Sovaldi; Hepatitis C Virus; Genotype 3a

Introduction

Hepatitis C virus (HCV) affects approximately 71 million people worldwide. It is the main cause of chronic liver disease, cirrhosis, hepatocellular carcinoma (HCC), liver transplantation and about 500,000 deaths per year worldwide [1]. The virus was discovered in 1989 as a non-A, non-B hepatitis causative agent [2]. It is a blood-borne, ssRNA virus of family Flaviviradiae, spherical in shape, size of 55-65 nm in diameter and 9.6 kb long genome which encodes ten proteins [3,4]. It is highly divergent classified into seven genotypes and many subtypes which show huge geographic variations. Currently there is no preventive vaccine [5].

Since HCV discovery, for almost one decade (1989-1999), interferon alpha (IFN-a) alone and onwards combination of IFN-α plus ribavirin (IFN-a-RBV) and two years later combination of pegylated (peg-IFN-a-RBV) remained the standard of care therapy until the advent of DAAs in the beginning of second decade of 21st century. Efficacy of peg-IFN-α-RBV was poor against all genotypes in general, 1 and 4 in particular with severe side effects [6]. A number of factors associated with poor response to IFN-α over the years have been described [7,8]. However, in 2009, IL28B SNPs rs12979860 (now classified as IFNL4), became practically the litmus test prognostic biomarker for HCV peg-IFN-α-RBV treatment. The favorable allele C/C of rs12979860 was associated with two to three fold greater rate of SVR than the C/T or T/T alleles [9].

HCV treatment has entered into a new era with new DAAs therapies which have shown high sustained viral response (SVR) relatively for all genotypes with no or fewer side effects. DAAs therapies have increased SVR rates irrespective of host and viral factors i.e. age, gender, viral load, HCV genotype, IL28B genotype, co-infection and stage of liver disease [10,11]. Given the high efficacy of DAAs, understanding the factors associated with treatment non-response in relatively few patients are not only important but challenging as well. Factors that were associated with peg-IFN-α-RBV might affect DAAs therapies as well in patients who do not achieve SVR.

In Pakistan the rate of chronic hepatitis C is estimated to be up to 5 % of population (10 million). Genotype 3a is commonly found in Pakistan followed by 1, 2 and 4 [12]. Most recent price reduction of sofosbuvir (NS5B polymerase inhibitor) has led to a massive treatment uptake of by HCV patients in Pakistan. High SVR rate of sofosbuvir based therapy has been reported for genotype 3a in Pakistan [13-15]. The aim of this study was to understand the efficacy of sofosbuvir based regimens in HCV infected patients in Pakistan and the role of the epidemiological, viral and host factors in general and IL28B rs12979860 in particular.

Materials and Methods

A total of one hundred and ninety two (n=192) patients were recruited in the study from out-patient department of a tertiary care, General Teaching Hospital Islamabad, between March 2016 to March 2018 after taking informed consent. The study was approved by the institutional review board and was in accordance with the Helsinki declaration. Relevant demographic and clinical data including age, sex, baseline ALT levels, HCV genotype, ethnicity, co-morbidities, liver condition and IL28B genotype was collected. Some of the data of treatment experienced patient's was retrieved from the institute's medical record and only those patients who successfully completed the treatment and follow up were included in this study. The patients received oral combination of dual therapy of sofosbuvir (400 mg) plus weight-based ribavirin (1000 mg for <75 kg and 1200 mg for >75 kg) for 12 or 24 weeks daily or triple therapy with peg-IFN-α (180 µg weekly) for 12 weeks according to AASLD guidelines. The non-responders to above dual or triple therapy were treated with sofosbuvir plus daclatasvir (60 mg) for 24 weeks with ribavirin. The end point of the study was SVR12. Viral load estimation and HCV genotyping was carried out by ABI and Sansure Real Time PCR systems. Taqman-based genotyping assay (Applied Biosystems, Foster City, CA, USA; custom designed assay) was used to type the samples for 'CC', 'CT' and 'TT' genotypes for rs12979860 as described earlier [12].

Regimen	Duration	RVR no. (%)	EOTR no. (%)	SVR 12 no. (%)
SOF+RBV+Peg-IFN-α (n=72) (Naïve=37, experienced=35)	12 weeks	70 (97.2)	70 (97.2)	70 (97.2)
SOF+RBV (n=120) (Naïve=110, experienced=10)	24 weeks	118 (98.3)	118 (98.3)	118 (98.3)
SOF+DCV+RBV (Non-SVR to Sof regimens =4)	24 weeks	4 (100)	4 (100)	4 (100)

Table 1: Sofosbuvir based treatment regimens for treatment naïve (n=145), experienced (n=47) patients and SVR rate, RVR=Rapid Virological Response undetectable HCV RNA (<50I U/ml) (week 4); EOTR=End of Treatment Response undetectable HCV RNA (12/24); SVR=Sustained Virological Response undetectable HCV RNA after EOTR (12 weeks).

Characteristics of patients	Naive (n=145)	Experienced (n=47)
Male gender-no. (%)	75 (51.7)	21 (44.6)
Age (mean±SD)	41.5 ± 10.4	44 ± 11
ALTs (mean±SD)U/L	108 ± 55	122± 72
Baseline viral load (IU/ml)	2×10^3-1×10^7	1×10^3-2×10^7
Ethnicity-no. (%) Punjabi	141(97)Punjabi	45 (95.7) Punjabi
HCV genotypes-no. (%)	Gt1 3 (2)	2 (4.2)
	Gt2 2 (1.3)	1 (2.1)
	Gt3 138 (95.1)	41 (87.2)
	Gt4 2 (1.3)	2 (4.2)
IL28Brs12979860-frequencies	CC 75 (0.55)	19 (0.40)
	CT 39 (0.29)	15 (0.31)
	TT 22 (0.16)	14 (0.29)
	*11	0
Comorbid condition-no. (%)	HBV 2 (1.3)	1 (2.1)
	HIV 0	0
	T2DM 7 (4.7)	4 (10)
	CVD 7 (4.7)	04 (8.5)
Compensated cirrhosis-no. (%)	23 (15.8)	27 (57)
Liver transplant-no. (%)	0	01 (2.1)
SVR-no. (%)	RVR 143 (98)	45 (95.7)
Non-SVR. (%)	2 (1.3)	2 (4.2)

Table 2: Baseline characteristics, laboratory data of the patients with treatment outcomes, ALT=Alanine Transminase; race Punjabi and others, Gt=Genotype and * didn't opt for IL28B test, Non-SVR=Non-responder to Sofosbuvir based Regimens.

Results

Of the total (n=192), forty seven were (n=47) were treatment experienced over the years (2000-2017) and one hundred forty five were treatment naive (n=145). Of these 51.5% were male, mean age of treatment naïve was 41.5 ± 11.41 and experienced 44 ± 11 years, ALTs levels 108 ± 55 U/L and 122 ± 72, viral load 2×10^3-1×10^7 and 1×10^3-2×10^7 IU/ml respectively. Most of the patients had genotype 3 infection 94.5% (n=142). Only 5.5% patients (n=11) were infected with genotype 1, 2 and 4. Of the naïve 98% (n=143) achieved SVR and from treatment experienced 95.7% (n=45) achieved SVR. The treatment plan is given in the table 1. Patients with triple regimen (Sofosbuvir, Ribavirin, peg-IFN-α) were 72 (37.5%) among them 35 were treatment experienced. 120 (62.5%) patients were treated with double regimen (Sofosbuvir, Ribavirin). Forty eight (96%) cirrhotic patients responded to dual and triple therapy. Four (2%) genotype 3a patients showed no RVR and SVR to dual and triple regimen, two each from treatment naïve and experienced cirrhotic patients. These four non-responders achieved SVR with combination of sofosbuvir plus daclatasvir with ribavirin. There was one treatment experienced liver transplant patient. This patient successfully achieved SVR with dual therapy. There were only four non-responder patients, two with IL28B favorable genotype CC and one each with CT and TT genotypes. No adverse side-effects were observed in any of the patients. The demographic, clinical parameters and treatment outcomes are given in Table 2.

Discussion and Conclusion

This current study was primarily aimed at determining the efficacy and safety of sofosbuvir based therapy in HCV infected Pakistani patients and secondly to investigate if IL28B SNPs rs12979860 can be seen as a predictive marker for non-response to therapy. Our study showed a success rate of 98% (SVR12) achieved through sofosbuvir based therapy for genotype 1, 2, 3 and 4 both in treatment-naive and in treatment-experienced patients which was in agreement to other published studies and was higher than reported in clinical trials [10,11,14,15]. The treatment was generally well tolerated and the most commonly reported adverse events were fatigue, headache and nausea. The All the four (2%) non-responder patients had HCV genotype 3a infection, two had IL28B favorable genotype CC and one CT and one TT genotypes, two were cirrhotic but they achieved SVR when administered daclatasvir with sofosbuvir, a combination of NS5A and NS5B inhibitors as well as a classical approach of combining drugs with possible no cross-resistance. In addition, the treatment

experienced IL28B non-CC allele patients achieved SVR (98%) with sofosbuvir based regimens. Based on these results we can assume that treatment did not show association with any of the epidemiological, viral and host factors such as age, gender, viral load, HCV genotype, IL28B genotype, co-infection and stage of liver disease as previously reported [16-20].

Failure to eradicate HCV infection with a triple combination of pegylated IFN-a, ribav irin and a protease inhibitor, and the resulting outgrowth of protease inhibitors instant viral populations in these patients, raises two important questions: will treatment failure alter the natural history of HCV-related liver disease?

Moreover, IL28B rs12979860 acts via triggering JAK–STAT pathway by interferon stimulating genes (ISGs) at both the innate and humoral response levels while DAAs, as evident by their name, are directly attacking viral proteins and have no effect on ISGs, so association IL28B with DAAs is apparently out of question [21]. Strong association of CC with IFN treatment and spontaneous clearance in HCV patients has been found [8]. Also IL28B CC has a protective role in healthy individuals against HCV infection [12]. In fact the C allele is the major allele in most world populations i.e. 98% in East Asians, 92% Asians, 90% in Europeans, 84% in Hispanics, 75% in Caucasians, 73% in the Moroccans and 55% in African populations [http://www.1000genomes.org/]. In other words IL28B is affecting expression of ISGs and subsequently augmenting the treatment in case of IFN, suppressing the virus during spontaneous clearance and high expression levels acting as a protective immunity in healthy individuals.

This suggests that DAAS are equally effective against all populations due to their mechanism of action. Genotyping IL28B/IFNL4 SNPs was helpful for IFN therapy but not useful in DAA therapy [19,22-24]. We conclude that sofosbuvir based regimens are highly effective in treating all prevalent HCV genotypes in Pakistan and there is no benefit in additional testing for IL28B for treatment prediction for DAAs. This real-world result is highly encouraging and complete eradication of HCV is now becoming an achievable goal. However, for the few non-responders it would be meaningful to study the other host and viral factors that might contribute to the immune response in the patients and provide a better understanding of observed treatment responses.

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