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Local Experience with Generic Sofosbuvir and Ribavirin With or Without Pegylated-IFN in Chronic Hepatitis C Predominantly Genotype 3 Patients

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Abstract

Objective: To study the efficacy and safety of generic Sofobuvir and ribavirin with or without pegylated IFN.

Material and Methods: This was a prospective observational multicenter study with non-probability convenient sampling procedure and duration of 1 year from 31 January 2016 till 1st February 2017.The study was conducted after ethical approval by Ethics Committee of the Gujranwala Liver foundation. The patients infected with Hepatitis C Virus, belonging to both genders, and willing for treatment with sofosbuvir, pegylated interferon and ribavirin were enrolled for the study. The written consent was taken from all the patients with complete confidentiality of the data. The genotype of the patient was categorized through polymerase chain reaction (PCR). HCV RNA by PCR was done before treatment and at 12weeks after completion of the treatment classified as Sustained Virological Response(SVR12). The goal of the treatment was classified as achieved and not achieved. The therapy was categorized into dual containing Sofosbuvir and Ribavirin, and triple containing Sofosbuvir, Ribavirin and Pegylated Interferon. The patients were classified as non-cirrhotic or cirrhotic based on findings of fibroscan or APRI score. Patients were treated with Sofosbuvir 400 mg daily, weight based ribavirin in 2 or 3 divided doses and Pegylated Interferon 180 µcg weekly. All data was entered and analyzed on SPSS version 20.

Results: Total 150 patients were selected with male to female ratio of 1:1. 97.4 % were GT3 and 3.4 % were non GT3. Overall SVR12 was achieved in 134 patients (89.3 %). 130 patients received dual therapy with sofosbuvir and ribavirin, of these 116 (89.2 %) achieved SVR12. 20 patients were treated with triple combination of pegylated interferon, sofosbuvir and ribavirin, 18 (90%) amongst these achieved SVR12. In the dual therapy group, Treatment naïve, non-cirrhotic patients showed 96 % (73/76) SVR12 while treatment experienced non-cirrhotic patients achieved 100 % (8/8) SVR12. Treatment naïve and treatment experienced cirrhotic patients in the same group achieved 87.5 % (35/40) and 100 % (6/6) SVR12 respectively. Amongst the 20 patients in the triple therapy category, SVR12 were 100 % (5/5) in treatment naïve non cirrhotic patients, 87.5 % (7/8) treatment experienced non-cirrhotic patients, 100 % (2/2) in treatment naïve cirrhotic group and 80 % (4/5) in treatment experienced cirrhotic category. The most frequently reported adverse events were fatigue followed by anemia, nausea, headache and insomnia with no report of serious adverse events.

Conclusion: Treatment with generic Sofosbuvir and Ribavirin with or without pegylated Interferon has shown excellent sustained virological response in HCV genotype 3 infected non-cirrhotic and cirrhotic patients. The results are at par with the International studies and the therapy was well tolerated.

Key words: Generic Sofosbuvir; Genotype 3; Sustained Virological Response

Abbreviation: Sofosbuvir; Genotype 3, (SVR)

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Introduction

WHO estimates that in 2015, 71 million persons were living with HCV infection in the world, accounting for 1% of the population. HCV infection is unevenly distributed, the Eastern Mediterranean Region had the highest prevalence (2.3%) followed by the European region (1.5%) [1]. Hepatitis C virus (HCV) infection is one of the most common causes of chronic hepatitis and liver transplant worldwide [2-4]. Pakistan is one of those countries with a very high prevalence rate of hepatitis C [5]. The reported cases of HCV infection in Pakistan ranges range from 2.2-14% [6]. It is estimated that about 10 million people in Pakistan are infected with HCV with the prevalence rate 6.7 %, 5 %, 1.5 %, 1.1 % in Punjab, Sindh, Baluchistan and Khyber Pakhtunkhwa respectively [7, 8].

For a long time, interferon has remained the mainstay of antiviral therapy for Chronic Hepatitis C virus infection. Sustained viral response (SVR) rates on IFN remained far from satisfactory and the combination did not go down well with the patients and treating physicians alike because of the number of associated side effects. Moreover, interferon remained contraindicated in advanced cirrhotic patients. The landscape changed completely with the arrival of directly acting antiviral drugs (DAA's). The DAA therapy is well tolerated and boasts excellent SVR rates. A number of DAA's namely sofosbuvir, daclatasvir, velpatasvir, grazoprevir, elbasvir, abbvie 3-D combination are now approved for used in Chronic Hepatitis C infection with and without ribavirin. The results have been excellent across all genotypes. Improvement in histology of liver and the quality of health with low risk of hepatocellular carcinoma and liver related mortality is associated with attainment of SVR [9]. SVR has also shown association with viral genotype, viral load, patient's age, BMI, race, environmental and other factors [10, 11].

Patients who received 12 weeks treatment with the nucleotide polymerase inhibitors Sofosbuvir and combined with Ribavirin and Peg Interferon demonstrated to have higher sustained virologic response rates for genotypes 1, 2, 3, 4 and 6 in comparison with treatments that include only Peg Interferon and ribavirin [12]. Sofosbuvir is administered daily with or without meal at dosage of 400mg, and is effective against all HCV genotypes. The intracellular metabolism of Sofosbuvir generates active uridine analog of triphosphate which acts as chain terminator [13].

Sofosbuvir was made available in Pakistan by Gilead Sciences in April 2014 through a special patients' access program. Its use remained limited because of high cost for the local population despite being available at substantially cheap rates as compared with the West. Sofosbuvir generics got approval by Drug Regulatory Authority of Pakistan (DRAP) in early 2016. These appealed a large number of patients because of ease of availability and fractional cost as compared to the brand leader. It is worth mentioning that daclatasvir and velpatasvir are not approved by DRAP in Pakistan to date.

Our study was intended to know the efficacy and safety of generic Sofobuvir and ribavirin with or without peg IFN in real life settings.

Material and Methods

This was a prospective observational multicenter study with the consumption of non-probability convenient sampling procedure. The duration of study was 1 year from January 2016 till February 2017.The study was conducted after ethics committee approval of the Gujranwala Liver foundation. The Gujranwala Liver foundation is an NGO running a specialized hepatology clinic in Gujranwala, Punjab, Pakistan. The clinic offers subsidized treatment options for poor patients and funding is also available for those who are unable to afford even the subsidized rates.

Patients of both genders aged 18 or more with detectable HCV RNA by PCR and willing for treatment were included. Exclusion criteria: co infection with HBV or HIV, CTP score > 9, known allergies to sofosbuvir or ribavirin, depressive illness not controlled on treatment, eGFR < 30 ml/min, pregnant or lactating females. Written consent was taken from all patients with complete confidentiality of the data. The demographic variables like age and gender were documented. Baseline investigations included complete blood picture, liver function tests, creatinine, blood sugar, thyroid stimulating hormone, alpha fetoprotein and abdominal ultrasound. The genotype of the patient was categorized through PCR. Patients were categorized as non-cirrhotic or cirrhotic based on liver stiffness measured by Fibroscan or APRI score. The patients were classified into treatment naïve and treatment experienced. A person is said to be treatment naïve who did not have any treatment before. All patients were offered all oral AVT with generic sofosbuvir and ribavirin except interferon tolerant treatment experienced cirrhotic patients. A few patients willingly opted triple combo because of short duration of therapy. CBC and LFT were checked at week 2 and then every 4 weeks depending upon the results. On treatment anemia was managed with ribavirin dose reduction with or without addition of erythropoeitin. HCV RNA by PCR was done at week 12 after the completion of treatment classified as Sustained Virological Response (SVR12). The goal of the treatment was classified as achieved and not achieved. The patient with undetectable viral load was categorized to achieve the objective of the treatment.

Data Analysis

All data was entered and analyzed on SPSS version 20. Frequencies and percentages were measured for the qualitative variables. Chi-square test was used to assess the difference and the P value less than or equal to 0.05 was taken as significant.

Results

Total 150 patients were selected for the study including 70(46.7 %) males and 80(53.3 %) females with the male to female ratio of 1:1. The frequency of genotypes of hepatitis C was found to be 146(97.6 %) as genotype 3 and the rest of them were non genotype 3. Patients were allocated on the basis of previously received treatment that is Naive group (who have not received any treatment previously for hepatitis C) and experienced group (who have received treatment previously) and their frequencies were 123(82 %) and 17(18 %) respectively. 130(86.7 %) patients received dual therapy (Sofosbuvir and Ribavirin) for the

Table 1: General analysis

Variable		n	%
Gender	Male	70	46.7
	Female	80	53.3
Genotype	3	146	97.3
	Others	4	3.6
Treatment Naive	Yes	123	82
	No	27	18
Therapy	Dual	130	86.7
	Triple	20	13.3
Duration of treatment	3 months	20	13.3
	6 months	130	86.7

duration of 6 months and 20(13.3 %) patients received triple therapy (Sofosbuvir, Ribavirin and Peg Interferon) for the duration of 3 months.97(64.7 %) were non-cirrhotic patients and 53(35.3 %) were found to have liver cirrhosis. Amongst patients with liver cirrhosis 48 were CTP class A and 5 were CTP class B.

Table 2: Showing the sustained virological response in cirrhotic and non-cirrhotic patients

Variables			SVR12	
			n	%
Sofosbuvir, Ribavirin (n=130)	Non-Cirrhotics (n=84)	Naïve (n=76)	73	96
		Experienced (n=8)	8	100
		Total	81	96.4
	Cirhhotics (n=46)	Naïve (n=40)	35	87.5
		Experienced (n=6)	6	100
		Total	41	89.1
	Overall		116	89.2
Sofosbuvir, Ribavirin and Peg Interferon (n=20)	Non-Cirrhotics (n=13)	Naïve (n=5)	5	100
		Experienced (n=8)	7	87.5
		Total	12	92.3
	Cirhhotics (n=7)	Naïve (n=2)	2	100
		Experienced (n=5)	4	80
		Total	6	85.7
	Overall		18	90

130 patients received dual therapy with sofosbuvir and ribavirin, of these 116 (89.2%) achieved SVR12. 20 patients were treated with triple therapy of pegylated interferon, sofosbuvir and ribavirin, 18 (90%) amongst these achieved SVR12. In the dual therapy group, treatment naïve, non-cirrhotic patients showed 96 % (73/76) SVR12 while treatment experienced non-cirrhotic patients achieved 100 % (8/8) SVR12. Treatment naïve and treatment experienced cirrhotic patients in the same group achieved 87.5 % (35/40) and 100 % (6/6) SVR12 respectively. Amongst the 20 patients in the triple therapy category, SVR12 was 100%(5/5) in treatment naïve non-cirrhotic patients, 87.5%(7/8) in treatment experienced non-cirrhotic patients, 100 % (2/2) in treatment naïve cirrhotic patients and 80%(4/5) in treatment experienced cirrhotic patients (Table: 2).

Discussion

The burden of viral hepatitis constitutes a public health threat in many areas of the world. In 2016, the World Health Assembly approved a global strategy to achieve elimination of this public health threat by 2030. To do this, and starting from the 2015 baseline, countries and regions need to reduce new infections (incidence) by 90 % and reduce deaths (mortality) by 65 % by 2030 [14]. To achieve this in a resource poor country like Pakistan where majority of the patients rely on out of pocket health care, the cost of treatment assumes a very crucial role.

The prime objective of the study was to study the SVR12 rate of generic sofosbuvir and ribavirin with or without pegylated interferon in real life setting. Secondary objective was the assessment of safety including serious adverse events and discontinuation of therapy with this formulation. The latest guidelines recommend sofosbuvir in combination with velpatasvir or daclatasvir with or without ribavirin for chronic hepatitis C patients infected having genotype 3. The duration of treatment varies between 12 to 24 weeks depending upon the stage of fibrosis and previous exposure to antiviral therapy [15].

As already mentioned velpatasvir and dacltasvir are still not approved by drug regulatory authority of Pakistan leaving sofosbuvir as the only DAA option. Generic sofosbuvir got approval in early 2016 drastically bringing down the cost of treatment significantly. In Valence Study, where Sofosbuvir and Ribavirin was used for 24 weeks the SVR12 rates in treatment naïve non-cirrhotic patients, treatment naive cirrhotic patients, treatment experienced non-cirrhotic patients and treatment experienced cirrhotic patients were 94 %, 92 %, 87 % and 60 % respectively [16]. The Lonestar-2 trial showed improvement in SVR12 of treatment experienced genotype 3 patients with overall SVR12 of 20/24 (83 %) including 10/12 who had liver cirrhosis [17]. In Boson trial, 86 % SVR12 is reported in treatment experienced genotype 3 patients [18]. Another study presented the SVR in patients with decompensated cirrhosis among patients taking triple therapy was 88.8 % [19]. In a meta-analysis of 757 patients, in which 411 were selected for study that were having HCV infection revealed SVR rate for triple regime as 88.54% [20].

In our study, the overall SVR 12 in 150 patients was 89.3 %. The compliance remained excellent at 100% in the study population. In treatment naïve non-cirrhotic group on dual therapy with sofosbuvir and ribavirin SVR 12 was 96% (73/76), while all 8 patients who were treatment experienced without cirrhosis achieved SVR12. In the case of cirrhotic patients treated with sofosbuvir and ribavirin, 35/40 (87.5 %) treatment naïve, and 8/8 (100 %) treatment experienced patients achieved SVR12. Similarly, treatment naïve patients regardless of liver cirrhosis achieved 100 % SVR12 with sofosbuvir, ribavirin and peg interferon in this study though the numbers were smaller.

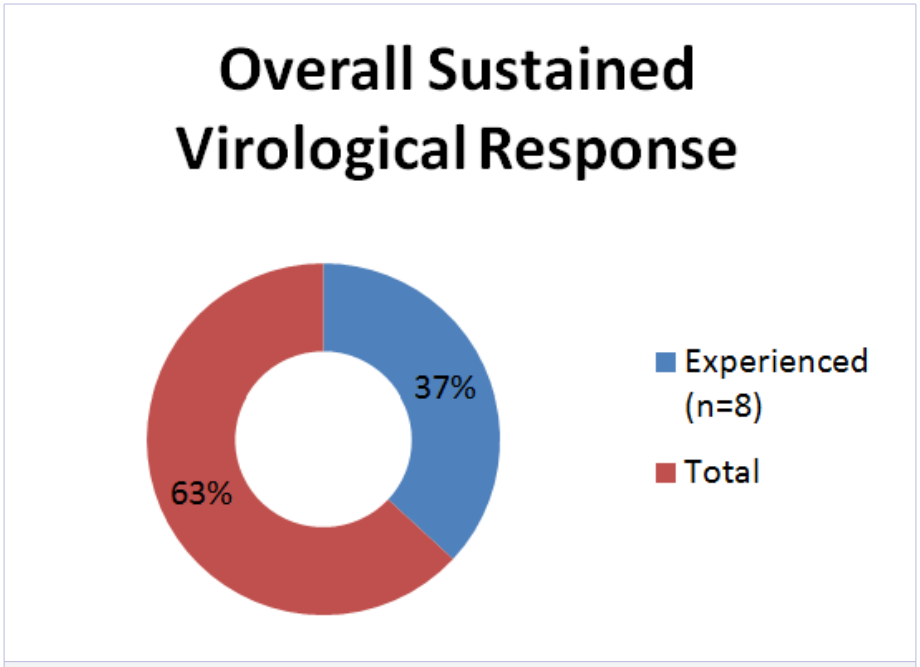

Figure 1: The overall attainment of the SVR regardless of the gender, treatment type and extend of liver damage was 134(89.3%) out of the total of 150 patients

The above results are comparable to international trials and the fact that they come in the real life setting is even more important. Sofosbuvir with Ribavirin has shown to be very effective for treatment naïve non-cirrhotic patients and despite omission as an option in the international guidelines remains a very useful option in resource poor settings. This also holds true as the alternatives, velpatasvir and daclatasvir are unavailable in Pakistan. The qualitative approach in this study has assured that we have evaluated wide perspective of the treatment with Generic Sofosbuvir in combination with Ribavirin and Peg Interferon. However, the study might not be immune from the selection and experimental bias.

Conclusion

Sofosbuvirand ribavirin with or without Pegylated Interferon has shown excellent SVR12 in genotype 3 non-cirrhotic and cirrhotic patients. We conclude that sofosbuvir and ribavirin should remain the mainstay of antiviral therapy especially in treatment naïve non-cirrhotic patients with genotype 3 in resource poor settings for the time being. The addition of Pegylated Interferon is especially useful in treatment experienced cirrhotic patients, a situation which will change after availability of daclatasvir and/or velpatasvir in Pakistan. Overall the treatment was well tolerated. Excellent SVR12 rates with low-cost generic sofosbuvir enhance the chances of eliminating viral hepatitis as a public health threat by 2030 in resource poor countries as approved by World Health Assembly in 2016.

Conflict Of Interest

Sofosbuvir, Ribavirin &pegylated-IFN to the patients for this study was provided by Hilton Pharma. The authors declare no other conflict of interest.

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