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Long Term Sustained Virological Response with Generic Daas - An Important but Often Missed Perspective of Management of HCV

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Abstract

Background and Aims: Hepatitis C (HCV) infection is one of major causes of liver cirrhosis. Treatment of HCV has changed dramatically due to the availability of direct acting oral antivirals (DAAs) with good treatment response. Patented DAAs shows excellent sustained Viro logical response (SVR) at 12, 24 and 96 weeks. There is sparse evidence of long-term SVR maintenance to generic DAAs. This study will provide an excellent data on long-term SVR to generic DAAs in different liver disease states due to HCV and with different generic drug regimens available in Pakistan.

Aim: To assess the maintenance of sustained Virological response at 96 weeks in patients of HCV who were treated with generics direct acting antivirals.

Material and Methods: This study was conducted at Hepatology clinic in Madinah teaching hospital Faisala bad.

Inclusion Criteria: Patients with Chronic Hepatitis C (CHC) treated with different regimens of DAAs and achieved SVR 12 were enrolled and followed for 96 weeks.

Exclusion Criteria: Patients with chronic hepatitis C with other co-morbids like continuing Alcohol intake, NASH or auto immune disorder etc. were excluded.

Participants were classified according to: Their liver disease status (Chronic Hepatitis C, compensated chronic liver disease (cCLD) and decompensated liver disease (dCLD) group). Cohort was sub classified by different drug regimens of DAAs used by patients (Sofosbuvir + ribavirin, Sofosbuvir + Daclatasvir and ribavirin, Sofosbuvir + Daclatasvir, Sofosbuvir + Velpatsavir and Sofosbuvir + Velpatsavir and ribavirin groups respectively). Chi square test was used to find significance between these groups.

Results: 190 patients were enrolled in study. 96(50.5%) were males and 94(49.5%) were females. 96 (50.50%) had CHC, 72 (37.9%) had cCLD and 22(11.6%) had dCLD patients respectively. 159 (83.7%) patients maintained SVR at 96 weeks while 31 (16.3%) patients relapsed. In CHC group 88.5% patients maintained long term SVR, while in dCLD group 72.7% maintained SVR at 96weeks. The Pearson Chi Square test did not show statistically significant difference of SVR 96 between these groups (P= 0.128). SVR-96 was above 80% in all the drug regimens used, 86.7% on sofosbuvir plus daclatsavir and 85.7% in Sofosbuvir plus velpatsavir. P-value (0.933) is non-significant for drug regimens groups.

Conclusion: Long-term SVR in HCV treated patients with different generic regimens of DAA is good despite their low cost and it is better in non-cirrhotic as compared to dCLD patients.

Keywords: Sustained Virological Response (SVR), Hepatitis C Virus (HCV), Direct Acting Anti virals (DAAs), Chronic Liver disease (CLD)

Clinical Relevance

Eradication of hepatitis C in third world countries with high prevalence rate is a challenge because majority of the patients in our part of the world cannot afford costly patented DAAs. Can we use generic drugs confidently for the long term sustained Virological Response is a big question which strikes in the minds of every hepatologist. This study highlighted that every patient of hepatitis C should be treated if we want to eradicate hepatitis C from globe according to the goals of world health organization even with generic DAAs.

Introduction

Hepatitis C is a single stranded RNA virus, which was discovered in 1989 (1). According to WHO 2021 report, Hepatitis C virus(HCV) has affected 58(0.5%) million people globally with about 300 000 people die due to CHC related com plications.(2) (3). According to latest data Pakistan is 2nd most affected country after Egypt with chronic hepatitis C prevalence of 4.5% to 8.2% with increasing number of infected people every year. There are six main genotypes infecting humans and genotype 3a is prevalent in Pakistan with 78.96% infected individuals (4).

The treatment of HCV included interferons-based regimes in the past. The sustained Virological response (SVR) was achieved only in 40 to 80% of patients depending on genotype with highest response to genotype 2(5). In Pakistan interferons were used under government treatment program. According to an audit, 7752 patients were enrolled, while only 45.6% completed treatment and followed with PCR at 06-months. SVR was achieved in 67% of patients who completed treatment. The biggest hurdle in adherence to treatment was long duration of therapy and higher side effect profile.(6). Other big limitation with interferons based regimes was that it was contraindicated in dCLD patients(7).

The approval of sofosbuvir (NS5a inhibitor) a direct acting antiviral drug (DAA) in 2013 was a major breakthrough in the treatment of hepatitis C. Different classes of DAA are available now with majority of them being Pan genotypic (8).

The DAAs have SVR rates above 90% with some combinations achieving SVR up to 99%. They have fewer side effects with better tolerability and compliance (9).

But, the cost of patented DAAs in 2015 was between 11000 US$ to 90000 US$ for 03 months treatment. That limited the treatment option for developing countries like Pakistan where monthly income is 100 to 170usd. For that pur pose, generic DAAs were developed for

developing countries with reduced cost of around 72US$ for the 03months treatment (10).

The Patented DAAs have shown excellent (SVR) at 12 and 24 weeks and maintaining the excellent long term treatment response (11-13). The treatment of HCV with generic DAAs also showed good response achieving SVR 12 and 24 in 82% to 95% treated patients (14, 15). But there is very limited data about the durability of long-term treatment response in patients treated with generic DAAs in Pakistan whether they require further surveillance or these drugs could be trusted to be as good as there patented counterparts. This study will provide an excellent tool to shed light on this part of treatment by enrolling and maintaining follow up of these patients and checking SVR at 96 weeks.

Methods

It is a Quasi interventional, prospective study. A total of 190 patients with Chronic hepatitis C (CHC) were enrolled through non-probability consecutive sampling technique at hepatitis clinic in Madinah Teaching Hospital Faisalabad from Jan 2020 to December 2020. Madinah teaching Hospital is tertiary care teaching facility with a fully operational GI and liver department. We provide free of cost treatment for non-affording patients with viral hepatitis.

Inclusion Criteria

Patients aged 18 years or above who gave consent were enrolled. Patients with chronic hepatitis C (CHC) who have received treatment with any of the following drug regimens of DAAs: Sofosbuvir + ribavirin, Sofosbuvir + Daclatasvir and ribavirin, Sofosbuvir + Daclatasvir, Sofosbuvir + Velpatsavir and Sofosbuvir + Velpatsavir and ribavirin and achieved SVR 12 were included in to the study group.

Exclusion criteria

Patients aged under 18 years, Immuno compromised, pregnant females, patients who are co-infected with other viruses, Glomerular filtration rate (GFR) < 15 ml/ min/ 1.73 m. Patients who had liver cirrhosis due to other causes and patients who were HCV positive but has other conditions (like continuing Alcohol intake, NASH or auto immune disorder e. t .c).

Patients were labelled Cirrhotic if they had biochemical abnormalities fulfilling APRI score (16) and/or ultrasonography findings of cirrhosis (surface nodularity, coarse and heterogeneous liver texture, and segmental hypertrophy or atrophy) (17). These patients were divided into decompensated group on the basis of ascites, variceal bleed or portosystemic encephalopathy.

Patients were followed with HCV RNA Qualitative PCR at 96 weeks (SVR 96). Patients were divided into groups according to disease status and drugs used. Following are the groups a) Chronic Hepatitis C without cirrhosis, b) Chronic Hepatitis C with Compensated liver disease, and c) Chronic Hepatitis C with decompensated liver disease. Further assessed by regimes of generic DAAs: Sofosbuvir + ribavirin, Sofosbuvir + Daclatasvir and ribavirin, Sofosbuvir + Daclatsavir, Sofosbuvir + Velpatsavir and Sofosbuvir + Velpatsavir and ribavirin. This study was approved by the ethical review committee of our university.

Statistical Analysis

Data analyzed using IBM-SPSS version 24.0. Counts with percentages were reported for gender, Disease and SVR outcomes. Pearson Chi Square test was used to check the association of PCR with disease and Drug groups, P-values less than 0.05 were considered statistically significant. Bar charts was also used to give graphical presentation of data.

Results

A total of 190 HCV treatment experienced patients with DAAs were enrolled into the study who had either achieved SVR 12. Table-1 reports the baseline characteristics of studied samples. 96(50.05%) patients were male and 94(49.5%) were females. The mean age of the participants was 50.4 ± 8.63. Out of 190, 96 patients were non cirrhotic, 72 were with CHC related compensated liver disease and 22 were with decompensated liver disease. Majority of patients included in the study were treated with Sofosbuvir + Ribavirin, Sofosbuvir + Velpatsavir and Sofosbuvir + Daclatasvir + Ribavirin respectively.

Table 1: Baseline Characteristics of Studied Samples (n=190)

		Number of patients (Total n=190)	Percentage (%)
Gender	Female	94	49.5%
	Male	96	50.5%
Disease State	Chronic Hepatitis C (CHC)	96	50.5%
	Compensated liver disease (cCLD)	72	37.9%
	Decompensated liver disease (dCLD)	22	11.6%
Treatment regime	Sofosbuvir + Ribavirin	70	36.8%
	Sofosbuvir + Daclatasvir	30	15.8%
	Sofosbuvir + Ribavirin + Daclatasvir	40	21.1%
	Sofosbuvir + Velpatsavir	42	22.1%
	Sofosbuvir + Ribavirin + Velpatsavir	8	4.2%

Out of 190 enrolled patients, 159 (83.7%) patients had long term SVR at 96 weeks after treatment with generic DAAs. Only 31 (16.3%) patients relapsed at 96 weeks after treatment with DAAs and (Fig 1).

Figure 1: showing frequency of sustained virological response at 96 weeks.

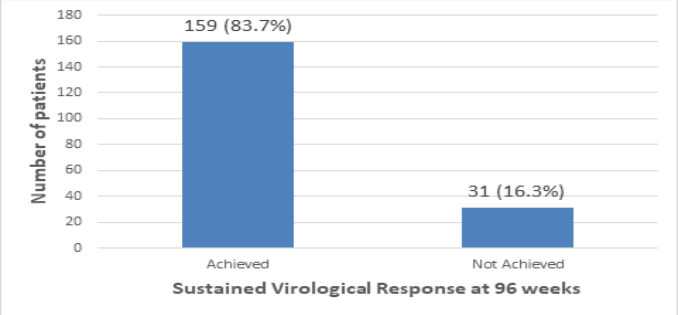

Table 2: Association of PCR with Disease and Drug.

		Sustained Virological Response at 96				
		Achieved		Not Achieved		P-Value
		Number	Percentage %	Number	Percentage %	
Disease State	Chronic Hepatitis C, non-cirrhotic	85	88.5%	11	11.5%	0.128
	Compensated Liver Disease	58	80.6%	14	19.4%	
	Decompensated liver disease	16	72.7%	6	27.3%	

Treatment regime	Sofosbuvir + Ribavarin	58	82.9%	12	17.1%	0.933
	Sofosbuvir + Daclatasvir	26	86.7%	4	13.3%	
	Sofosbuvir + Ribavarin + Daclatasvir	32	80.0%	8	20.0%	
	Sofosbuvir + Velpatsavir	36	85.7%	6	14.3%	
	Sofosbuvir + Ribavarin + Velpatsavir	7	87.5%	1	12.5%	

Patients without cirrhosis shows excellent response to treatment (88.5 %) achieving long term SVR at 96 weeks. While patients with cirrhosis and decompensated liver disease shows relapse rate of 27.3%. But Pearson Chi Square test did not show significant difference of SVR 96 with disease (P= 0.128). 58 (82.9%) patients treated with sofosbuvir plus ribavirin shows long term SVR at 96 weeks, 86.7% of sofosbuvir plus daclatasvir regime and 85.7% of sofosbuvir and Velpatsavir treated patients. Chi square test did not show any significant difference between treatment regimens used and SVR 96 (P= 0.933)

Discussion

The management of hepatitis C virus has evolved significantly over the period of time from 1991 to 2022, especially after development of direct acting antiviral agents (DAAs) in 2014. Initially treatment with interferons-based therapy was not good and many patients with cirrhosis couldn't be treated. But approval of DAAs changed all that with excellent treatment response and fewer side effects. Patients with cirrhosis, co-infections and with renal failure could also be treated with excellent results with DAAS. (5, 9) The biggest issue was their high cost. After availability of generics the treatment was available for everyone. Studies done previously had shown comparable results of the generic DAAs to their patented counterparts for short term follow-up at 12 and 24weeks. In a study conducted on 1913 patients in Pakistan, 92.6% patients achieved SVR at 24 weeks post treatment with DAAs, another study showed 82.4% SVR 12 post treatment with DAAs. (18, 19). Our study is the first long term follow-up study with generic DAAs.

Considering low-cost generic DAAs usage in our circumstances this study has demonstrated that patients treated with these drugs after achieving SVR 12, showed good long term virological response at 96 weeks (SVR 96= 83.68%) with relapse rate of 16.3% overall. This is comparable with international studies as demonstrated by Lin et all showing near 100% durability up to 4 years in patients who achieved SVR 24 with non-generic DAAs. (20) This shows reliability of these drugs with respect to treatment response by achieving and maintaining durability of sustained virological response in more than 80% of patients treated with these drugs.

The patients without cirrhosis showed excellent long term SVR at 96 weeks (88.5%) in this study, 14 (19.4%) patients out of 58 cirrhotic patients with compensated liver disease relapsed despite achieving the SVR after completion of treatment and 27.3% patients with decompensated liver disease relapsed. This is also demonstrated by other studies, stating that patients with cirrhosis show greater relapse rate than the patients without cirrhosis in the long-term follow up periods (20-22).

This study has shed an excellent light on long-term SVR with DAAs of CHC patients in different disease state scenarios and with different regimes. But it has few limitations.

It didn't identify the risk factors in the relapsed patients, that whether the relapse was due to external factors.

Conclusion

Long term SVR in HCV treated patients with different generic regimens of DAA is excellent despite their low cost and it is better in non-cirrhotic CHC patients as compared to patients with decompensated cirrhosis. So, these generic DAAs can be given to the patients with confidence of excellent long term SVR.

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