Original Article

Frequency of side Effects of Sofosbuvir and Daclatasvir in Patients of Chronic Hepatitis C

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[1] *Conception of study*
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Abstract

Background: Hepatitis is a common problem in Pakistan. Pakistan is the second most prevalent country regarding hepatitis C with a prevalence rate of 6.7%. Genotype 3 is the most commonly detected genotype in Pakistan. This study was conducting in Hepatitis Clinic, Medical Unit II, Jinnah Hospital Lahore and study duration was three months starting from 1st Dec 2018 to 28th Feb 2019. In our study we evaluate side effects of direct acting antivirals for hepatitis C patients by using descriptive case series.

Methods: Forty patients meeting the inclusion criteria were included in the study. All patients were then given direct anti-virals for a period of three months. Patients were called after every four weeks and observed for the presence of side effects like fever, fatigue, malaise, generalized weakness, myalgia, nausea and vomiting. Data was entered and analyzed in SPSS version ver.21.0. Frequency and percentages were calculated for demographic and clinical profile and side effects. Mean and Standard deviation was calculated for biochemical values at base line and end of therapy. Chi-square test was used to assess side effects among age, gender and duration of disease and paired t test for biochemical parameters with $p < .05$ as statistical significance.

Results: Mean age of the patients was 39 years + 11.6. Fever was recorded in 72.5% fatigue was seen in 52.5%, malaise was recorded in 37.5% and generalized weakness was noticed in 37.5. Myalgia was recorded in 12.5% and nausea and vomiting were reported in 2.5% of patients. . ($p> .05$). There was a statistically significant difference between mean baseline and at end treatment values for AST, ALT, AP and TLC. ($P< .05$).

Conclusion: Our study concluded that along with efficacy advantage of DAA therapy, their safety profile is acceptable in terms of adverse drug reaction of immediate or during treatment however long term follow up is needed to ascertain and apprehend the safety matters linked with the utilization of DAAs.

Key Words: Direct Acting Antivirals (DAAs), Side Effects, Chronic Hepatitis C.

Introduction

Hepatitis is a common problem in Pakistan. Pakistan is the second most prevalent country regarding hepatitis C with a prevalence rate of 6.7%. Genotype 3 is the most commonly detected genotype in Pakistan. Hepatitis C patients were conventionally treated with interferon and ribavirin which caused multiple side effects leading to non compliance and hence failure of

treatment .The newly developed direct anti virals DAAs have opened new horizons for the treatment of hepatitis C. Direct anti virals have proved safe and efficacious.

Sofosbuvir, a NS5B inhibitor was approved by FDA in 2013 is the leading direct anti viral followed by daclatasvir which is a NS5A inhibitor]. According to ALLY 3+ trial the combination of sofosbuvir and daclatasvir in genotype 3 patients has proved safe and efficacious with minimum side effects, less drug-drug interactions and has safely been tried in special circumstances such as in patients with liver transplantation, renal transplantation and HIV patients co-infected with hepatitis C.

Pakistan is developing nation with a population of 29.5% living below poverty line, the price of direct anti virals is a major issue. With the availability of generics, a combination of sofosbuvir and daclatasvir costs as low as US$75 for a 12-week course that makes it affordable for the majority of patients in the country. Scarce data are available to determine the safety and efficacy of these low-price generic drugs. Our study is one such effort to establish the efficacy and safety of these generics in Pakistani population.

Material and Methods

After approval from ethical committee and informed consent forty patients of either age or gender presenting to the outpatient medical department of Medical Unit II of Jinnah Hospital with hepatitis C were enrolled in the study after taking informed consent. All patients were then given direct anti-viral for a period of three months. Patients were called after every four weeks and observed for the presence of side effects like fever, fatigue, malaise, generalized weakness, myalgia, nausea and vomiting by researcher himself for controlled bias in the outpatient department. Data was entered and analyzed in SPSS version ver.21.0. Frequency and percentages were calculated for demographic and clinical profile and side effects. Mean and Standard deviation was calculated for biochemical values at base line and end of therapy. Chi-square test was used to assess side effects among age, gender and duration of disease and paired t test for biochemical parameters with $p < .05$ as statistical significance.

Result

Mean age of the patients was 39 years +11.6. Minimum age was 20 years and maximum age was 60 years. 67.5% patients were less than 40 years and 32.5% of patients were more than 40 years in age.90% of the patients were males and 10% of the patients were females. 82.5 % of the patients were single and 17.5% of the patients were married. 62.5% of the patients belonged to rural areas while 37.5% of patients were from urban areas. In 75% of patients the disease was present for less than 6 months while in 25% of patients the duration of disease was more than 6 months.(Table 1).

Fever was recorded in 72.5% of patients with a p value of 0.234.Fatigue was seen in 52.5% of patients with a p value of 0.906.Malaise was recorded in 37.5% of patients with a p value of 0.161. Generalized weakness was noticed in 37.5% with a p value of 0.433. Myalgia was recorded in 12.5% with a p value of 0.161.Nausea and vomiting were reported in 2.5% of patients. . (Table 1).

In gender cross tabulation fever was seen in 93.1% of males and 6.9% of females ($p > .05$).Fatigue was seen in 100% of males and 0% of ($p > .05$)..Malaise was seen in 86.7% of males and 13.3% of females with a p value of 0.586.Generalized weakness was noticed in 93.3% of males and 6.3% of females ($p > .05$).. Myalgia was noticed in 80% of males and 20 % of females with a p value of 0.426. Nausea and vomiting were recorded in100% of males and 0% of females ($p > .05$). (Table 3).

When results were recorded depending upon the duration of disease fever was recorded in 65.5% of patients with duration of infection less than 6 months and 34.5% of patients reported fever in whom the duration was more than 6 months ($p < .05$)..Fatigue was seen in 76.2% of patients with duration of disease less than 6 months and 23.8% of patients with duration of infection for more than 6 months ($p > .05$).. Malaise was recorded in 73.3% of patients with disease less than 6 months and 26.7% of patients with disease more than 6 months ($p > .05$)..Generalized weakness was recorded in 93.3% of patients with disease less than 6 months of duration and 6.7% of patients with disease more than 6 months in duration ($p > .05$).. Myalgia was reported in 60% of patients with duration less than 6 months of disease and in 40% of patients with duration more than 6 months. ($p > .05$). (Table 3).

There was a statistically significant difference between mean baseline and at end treatment values for AST, ALT, AP and TLC. ($P < .05$). (Table 4).

Table no: 1 Demographic and clinical profile of subjects

Variables	N	Percent
Age (Mean=39 ± 11)		
< 40 years	27	67.5
> 40 years	13	32.5
Gender		
Male	36	90.0

Female	4	10.0
Marital status		
Single	33	82.5
Married	7	17.5
Residential status		
Rural	25	62.5
Urban	15	37.5
Duration of disease (yrs) Mean=6.02 ± 5.56		
< 6 months	30	75.0
> 6 months	10	25.0

Table no: 2 Side effects experienced by subjects (multiple response frequencies)

	Responses		Percent of Cases
Side effect	**N**	**Percent**	
Side Effect:1 Fever	29	33.7%	72.5%
Side Effect: 2 Fatigue	21	24.4%	52.5%
Side Effect: 3 Malaise	15	17.4%	37.5%
Side Effect: 4 Generalized weakness	15	17.4%	37.5%
Side Effect: 5 Myalgia	5	5.8%	12.5%
Side Effect: 6 Nausea Vomiting	1	1.2%	2.5%
Total	86	100.0%	215.0%

Table no:3 Side effects experienced by subjects and age, gender and duration of disease cross tabulation

Side effects		**Fever**		**Fatigue**		**Malaise**		**Generalized weakness**		**Myalgia**		**Nausea Vomiting**	
		Freq	% age	Freq	% age	Freq	% age	Freq	% age	Freq	% age	Freq	% age
Age	**< 40**	18	62.10%	14	66.70%	12	80.00%	9	60.00 %	2	40.00%	1	100.00 %
	> 40	11	37.90%	7	33.30%	3	20.00%	6	40.00 %	3	60.00%	0	0.00%
P value		0.234		0.906		0.191		0.433		0.16		0.482	
Gender	**Male**	27	93.10%	21	100.00%	13	86.70%	14	93.30 %	4	80.00%	1	100.00 %
	Female	2	6.90%	0	0.00%	2	13.30%	1	6.70 %	1	20.00%	0	0.00%
P value		0.288		0.027		0.586		0.586		0.426		0.736	
Duration of disease (years)	**< 6 months**	19	65.50%	16	76.20%	11	73.30%	14	93.30 %	3	60.00%	1	100.00 %
	> 6 months	10	34.50%	5	23.80%	4	26.70%	1	6.70 %	2	40.00%	0	0.00%
P value		0.025		0.855		0.85		0.038		0.408		0.559	

Table no: 4 Base line and end point therapy comparison of liver biochemistry

Paired Samples Statistics					
		Mean	N	Std. Deviation	P value
Pair 1	Bilirubin total basline	1.04	40	0.74	.042
	Bilirubin total Endpoint	0.83	40	0.34	
Pair 2	PT baseline	13.00	3	0	.184
	PT Endpoint	13.66	3	0.57	
Pair 3	ALT baseline	68.72	40	42.69	.000
	ALT Endpoint	52.65	40	30.74	
Pair 4	AST baseline	90.12	40	68	.004
	AST Endpoint	61.55	40	40.30	

Pair 5	AP baseline	174.80	40	33.96	.012
	AP Endpoint	161.7	40	30.77	
Pair 6	TLC Baseline	5.71	40	1.02	.000
	TLC Endpoint	4.86	40	.97	
Pair 7	GT baseline	68	1	0	NA
	GT Endpoint	60	1	0	

Discussion

Hepatitis C virus (HCV) infection is a major health problem all over the world. Approximately, 170-200 million individuals are infected chronically worldwide and one fourth of these patients are at increased risk of developing complications such as liver cirrhosis, hepatocellular carcinoma and even liver failure. Complete eradication of the virus is the main aim in treatment of hepatitis C. In 2011, the first-generation protease inhibitors boceprevir (BOC) telaprevir (TVR) were approved by FDA as the direct-acting antiviral agents. New direct-acting antiviral agents (DAAs) have been developed in the past few years. Direct anti viral has shown increased efficacy, safety, and tolerability. Interferon-free oral therapies with DAAs are in use for patients with chronic HCV and cirrhosis patients.[6]

A greater understanding of the hepatitis C virus (HCV) genome and proteins has enabled efforts to improve efficacy and tolerability of HCV treatment. Notably, this has led to the development of multiple direct-acting antivirals (DAAs), which are medications targeted at specific steps within the HCV life cycle of DAAs are molecules that target specific non-structural proteins of the virus and results in disruption of viral replication and infection. There are four classes of DAAs, which are defined by their mechanism of action and therapeutic target. The four classes are non-structural proteins 3/4A (NS3/4A) protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors .[7]

In a study by Gonzales 78 patients who were co infected with hepatitis B or HIV treated with direct anti viral. 21 (26.9%) patients reported adverse effects that were secondary to direct anti viral. The most common adverse effects were fatigue (47.6%), gastrointestinal symptoms (38.1%), anaemia (14.3%), and headache (14.3%). In comparison with the rest of the study cohort, the patients who developed adverse effects were more often Caucasian (33.3% vs. 10.5%, p = 0.017) and were more frequently treated with PrOD/Ribavirin (9.5% vs. 0%, p = 0.018). In terms of antiretroviral therapy (ART), there was a trend towards a more frequent use of TDF/FTC + NNRTI (33.3% vs. 14%, p = 0.055).[8]

The overall rate of adverse effects in our study was 26.9%, which is much lower than those reported in other real-world studies. The study conducted by Hawkins et al. on HIV/HCV coinfected patients revealed that 48% of patients experienced at least one adverse event, which is similar to the findings reported by Bruno et al., who found a rate of 59.7%.

In our study most of the patients presenting in hepatitis clinic were of young age group less than 40 years comprising 2/3rd of total number of patients. The striking feature was that mostly male gender end up for treatment in my study that was composed of 90% of total patients. As mostly young ones were offered treatment so 82.5% were single. As the population of Pakistan is 62.5% based in rural area as also depicted by my study. Most of the patients ¾ had the disease for more than 6 months old.

Dyspnoea is reported in 4%, of the patients ,which is lower than the rate found in our patients (8.3%).[10] Headache was a common adverse effect seen in controlled studies, reported approximately in 20% of patients on Simeprevir / Sofosbuvir; however, none of our patients developed headaches during their treatment with this regimen].[9] Other clinically significant adverse effects that are reported in the literature are pruritus (14%), rash (16%), and photosensitivity (5%)][9,11]. None of these side effects was reported in other study cohort. [12,13]

In our study Fever was the most evident complaint described by the patient in three quarters in numbers. Half of the patients presented with fatigue. More than 1/3rd complaint of symptoms of malaise and general weakness. Just 12.5% had myalgia. Only minor 2.5% had symptoms of nausea and vomiting.

Conclusion

Our study concluded that along with efficacy advantage of DAA therapy, their safety profile is acceptable in terms of adverse drug reaction of immediate or during treatment however long term follow up is needed to ascertain and apprehend the safety matters linked with the utilization of DAAs.

Reference

1. Hessel, M. H., Cohen, A. F., & Rissmann, R. Sofosbuvir and daclatasvir. British journal of clinical pharmacology. 2016;82(3), 878-879.
2. Naranjo LM, Sanchez SV, Garre MS, et al CP-033 Evaluation of sofosbuvir plus daclatasvir combination for hepatitis C virus treatment Eur J Hosp Pharm . 2016;23:14-15.
3. Das D1, Pandya M. Recent Advancement of Direct-acting Antiviral Agents (DAAs) in Hepatitis C Therapy. Mini Rev Med Chem. 2018;18(7):584-596.
4. Poordad F, Dieterich D. Treating hepatitis C: current standard of care and emerging direct-acting antiviral agents. J Viral Hepat .2012;19:449.
5. Gonzales Zamora JA. Adverse Effects of Direct Acting Antivirals in HIV/HCV Coinfected Patients: A 4-Year Experience in Miami, Florida. Diseases. 2018;6(2):51.
6. Lawitz E., Matusow G., DeJesus E., Yoshida E.M., Felizarta F., Ghalib R., Godofsky E., Herring R.W., Poleynard G., Sheikh A., et al. Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: A phase 3 study (OPTIMIST-2) Hepatology. 2016;64:360–369.
7. Kutala B.K., Mouri F., Castelnau C., Bouton V., Giuily N., Boyer N., Asselah T., Marcellin P. Efficacy and safety of sofosbuvir-based therapies in patients with advanced liver disease in a real-life cohort. Hepat. Med. 2017;18:67–73.
8. Mariño Z., Pascasio-Acevedo J.M., Gallego A., Diago M., Baliellas C., Morillas R., Prieto M., Moreno J.M., Sánchez-Antolín G., Vergara M., et al. High efficacy of Sofosbuvir plus Simeprevir in a large cohort of Spanish cirrhotic patients infected with genotypes 1 and 4. Liver Int. 2017;37:1823–1832.
9. Hawkins C., Grant J., Ammerman L.R., Palella F., Mclaughlin M., Green R., Mcgregor D., Stosor V. High rates of hepatitis C virus (HCV) cure using direct-acting antivirals in HIV/HCV-coinfected patients: A real-world perspective. J. Antimicrob. Chemother.2016;71:2642–2645.
10. Bruno G., Saracino A., Scudeller L., Fabrizio C., Dell'Acqua R., Milano E., Milella M., Ladisa N., Monno L., Angarano G. HCV mono-infected and HIV/HCV co-infected individuals treated with direct-acting antivirals: To what extent do they differ? Int. J. Infect.. Dis. 2017;62:64–71.