Original Article

Treatment of HCV with Triple Therapy Drugs

Down Staging of Cirrhosis in All Cirrhotic Patients with HCV Genotype 3-a Infection, Treated with 12-Weeks Triple Therapy, Including Sofosbuvir, Daclatasvir and Ribavirin

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ABSTRACT

Objective: This study was mainly conducted to assess the improvement in the stages of cirrhosis in all treated patients with HCV genotype 3a infection, treated with triple therapy including daclatasvir, sofosbuvir and ribavirin in population of Khyber Pakhtunkhwa.

Study Design: Prospective longitudinal study.

Place and Duration of Study: This study was conducted at the Department of Pharmacology, Khyber Medical College and Khyber Teaching Hospital Peshawar from May 2017 to October 2017.

Materials and Methods: Total of 75 cirrhotic patients with HCV genotype-3a infection, were enrolled and were assigned into 02 groups including group-I as those having Child Pugh Turcott stage-C cirrhosis and group-II as those having Child Pugh Turcott stage-B cirrhosis. Daclatasvir, Sofosbuvir and ribavirin was given for 12-weeks. Child Pugh Turcotte (CPT) staging was done before and after the completion of 12-weeks treatment. The primary end point was end of treatment (EOT-12) response with 12-weeks therapy, which is defined as HCV RNA level<40IU/ml after 12-weeks of therapy and improvement in the stages of cirrhosis.

Results: Out of total 75 liver cirrhotic genotype 3a infected patients 44 (58.7%) were males while 31 (41.3%) were females. Their mean age is 50.95 ± 8.58 years. According to the CPT staging criteria, 40 (53.3%) patients with stage-C (group-I) while 35 (46.7%) patients with stage-B (group-II). At the end of therapy, 15% and 62.5% of the patient in group-I were down staged from C to A and C to B respectively. Similarly, in group-II, 57.1% of total patients were down staged from stage-B to stage-A.

Conclusion: Triple therapy including Daclatasvir, Sofosbuvir and ribavirin is not only effective in all cirrhotic patients with chronic hepatitis-C genotype-3a infections, but also improve the clinical parameters and stages of cirrhosis.

Key Words: Chronic hepatitis C, non-cirrhotic, Cirrhotic, triple therapy, down staging of cirrhosis**.**

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INTRODUCTION

Hepatitis-C is a chronic disease, which affects human in all seven continents of the worlds. Decompensated cirrhosis is a life-threatening complication of HCV infection, with 5-years survival in only 50% cases[1]. HCV is considered as one of the leading cause of post transfusion non-A and non-B hepatitis[2,3] and one of the most important causes of Chronic Liver disease. Hepatitis C is one of the most dangerous and rapidly increasing public health problem.

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This is one the most common cause of Liver Cirrhosis and Hepatoma and ultimately one of the common indications for liver transplantation. According to WHO, the global prevalence of CHC >3%, which affect almost 170 to 200 million people worldwide[4]. Along with hepatitis–B, it shares >75% cases of all chronic liver disease (CLD) worldwide[5]. Almost every patient, if not treated timely can develops Cirrhosis, which may lead into hepatocellular carcinoma and finally death. Chances of Cirrhosis and death usually increase with the severity of Cirrhosis.

There are many guidelines and scoring system to document the level of cirrhosis. These scoring systems basically categorize the level of cirrhosis and prognosis of individual patient[6]. One of the most important scoring systems is Child Pugh Turcotte (CPT) staging. It's have got five parameters, each having 3-points, which are based on its severity where 1 point means least severe while 3 as more severe. It is shown in the following table No 1.

This scoring system is used along with other scoring system like MELD etc. around the world to assess the severity of cirrhosis and possible future prognosis of that patient. It is also used for future treatment planning for that particular patient. Based on this scoring, cirrhosis can be staged into three stages, including stage A as less severe and Stage C as more severe cirrhosis. This is showing along with the possible one year and two years prognosis in the following table No 2.

In last decade, HCV remains the focus of research and new drugs, which are acting as direct antiviral drugs, are introduced. Previously, pegylated interferon was used along with Ribavirin. This treatment was only recommended in non-cirrhotic patients but the introduction of new DAAs (Direct Acting Anti-viral) have alter the therapy dramatically in both cirrhotic and non-cirrhotic patients. These can be safely used in both cirrhotic and non-cirrhotic patients. Some of them are specific to a single genotype, but other has pan genotyping activity and can be used in all genotype in different combination. The most recommended therapy for HCV genotype 3a infection by AASLD and EASL guidelines includes Sofosbuvir, Daclatasvir and Ribavirin. Sofosbuvir is NS5B HCV RNA dependent RNA polymerase inhibitor, and is one of the most combating drug against hepatitis C virus while Daclatasvir is a NS5A inhibitor. Sofosbuvir in a dose of 300mg OD and Daclatasvir in a dose of 60mg OD along with weight-based Ribavirin can be given for 12 weeks in all HCV genotype 3 infection including both cirrhotic and non-cirrhotic[7].

Liver cirrhosis and hepatocellular carcinoma (HCC) are the major complications of HCV and are the major cause of deaths in patients with Hepatitis-C infection. Therefore, all these patients must be treated aggressively to completely eradicate virus from the serum, and to improve the different parameters, which show the severity of cirrhosis and risk of HCC. By eradicating virus and improve the level of cirrhosis, HCC and risk of death can be decreased.

Many studies are published worldwide recording the efficacy of these drugs. But we have conducted this unique study in order to assess the level of HCV related cirrhosis improvement with this treatment combination in Pakistani community.

MATERIALS AND METHODS

This single centered prospective study was carried out in Khyber Teaching Hospital Peshawar Pakistan. The duration of the study was 6 months starting from May 2017 to OCT 2017 in which total 75 liver cirrhotic genotype 3a infected patients who responded to the therapy were included in the study after both ethical approval and informed consent from patients. They were divided in to two groups, group-I and group-II, based on their liver cirrhosis according to the Child Pugh Turcotte Staging. The group-I includes 40 stage C patients while the group-II includes 35 stage B patients. The demographics were obtained on structural proforma. All these patients were treated with oral antiviral drugs including sofosbuvir, Daclatasvir and Ribavirin for a period of 12 weeks. After the completion of therapy, the CPT Staging was repeated and the results were recorded.

Statistical analysis: All the data were entered in the excel sheet. The frequencies and percentages for both group-I and group-II were calculated. Difference of patients in group I that were reverted from liver cirrhosis stage C to A and C to B were calculated using SPSS version 16.0. Similar analysis was performed for group II using SPSS version 16.0 and the data were presented in tables. Similarly, the graph was constructed using Microsoft Excel 2013.

RESULTS

Out of total 75 liver cirrhotic genotype 3a infected patients 44 (58.7%) were males while 31 (41.3%) were females. Their mean age is 50.95 ± 8.58 years. All the data is summarized in table 3.

According to the Child Pugh Turcotte Staging criteria, 40 (53.3%) patients with stage C were grouped in group-I while 35 (46.7%) patients with stage B were placed in group-II as shown in table 4.

Table No.1: CPT Scoring

Measure	1-Point	2-points	3-Points
Total Bilirubin (mg/dl)	2	2-3	>3
Serum Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Prothrombine Time (seconds Prolongation)	<4	4-6	>6
Ascites	None	Mild	Moderate to Severe
Hepatic Encephalopathy	None	Grade 1-2	Grade 3-4

Table No. 2: Liver Cirrhosis staging

Points	Class	One-year Survival	Two-year Survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Table No.3: Demographics of study population

		Frequency	Mean	SD
Age		75	50.95	8.58
Gender	Males	44 (58.7%)	-	-
	Females	31 (41.3%)	-	-
Total		75	-	-

All the patients were given triple oral therapy including sofosbuvir, Daclatasvir and Ribavirin for 12 weeks and at the end of therapy, 15% and 62.5% of the patient in group I were down staged from C to A and C to B

respectively. Similarly, in group II, 57.1% of total patients were down staged from stage B to stage A as shown in table 5 and their difference is graphically shown in figure 1.

Table No.4: Child Pugh Turcotte Staging before therapy

Stage	Frequency	Percent
A	0	0
B	35	46.7%
C	40	53.3%
Total	75	100%

Table No.5. Child Pugh Turcot Staging after therapy

Stage	Frequency	Percent	Group I		Group II
			Conversion from C to A	Conversion from C to B	Conversion from B to A
A	26	34.7%	06 (15%)	25 (62.5%)	20 (57.1%)
B	40	53.3%			
C	09	12.0%			
Total	75	100%			

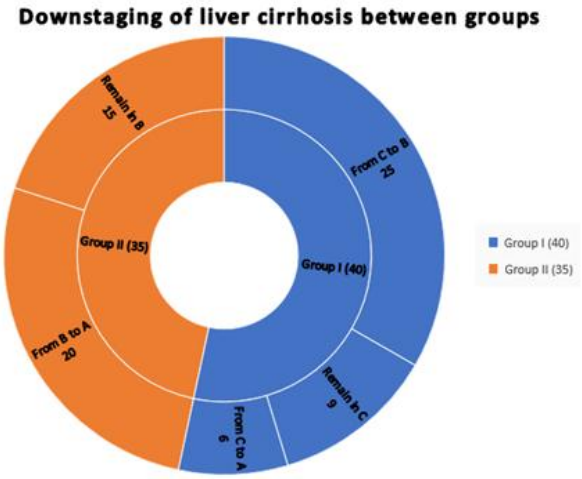

Figure No.1: Down staging of liver cirrhosis in group I and group II

DISCUSSION

The paradigm shift in the treatment combination from interferon-based therapy to direct acting anti-viral therapy has totally changed the direction of research in chronic hepatitis-C. Around the globe in the specialty of hepatology, hepatitis-C remains the main target of research. The new drugs, which are acting as direct Antiviral drugs (DAAs) have really revolutionized the treatment strategy in all HCV genotypes. Previously, only patient with healthy liver were treated with interferon but now one can give these drugs even in case of advanced cirrhosis[8]. In recent guidelines, adopted by AASLD (American Association for the Study of Liver Diseases), IDSA (Infectious Diseases Society of America)[9] and EASL (European Association for the Study of Liver)[7,10], Daclatasvir, sofosbuvir plus ribavirin can be given for 12 weeks for the optimal treatment of all Chronic HCV genotype-3 infection, including both cirrhotic and non-cirrhotic cases.

In our present study, all the patients were given triple oral therapy including sofosbuvir, Daclatasvir and Ribavirin for 12 weeks. At the end of therapy, 100%(n=75/75) response rate has been observed with triple therapy in both CPT stage-B and CPT stage-C cirrhotic cases with HCV-genotype-3a infection. The main target of our study was to analyze the improvement in the clinical parameters and stages of cirrhosis. In group-I with CPT stage–C cirrhosis, 15% and 62.5% of the patient were down staged from C to A and C to B respectively. Similarly, in group-II with CPT stage-B cirrhosis, 57.1% of total patients were down staged from stage-B to stage-A.

The finding of our study is closed to the finding of another study, conducted in Europe by Deterding K. et al. In that study, liver function parameters including albumin, bilirubin, cholinesterase and prothrombin time all improved in the majority of patients during antiviral therapy irrespectively of the underlying HCV genotype, however, with different kinetics. They used MELD scores instead of CPT score, which get improved by 44% of the patients[11].

This combination is not only effective but also absolutely safe in advanced cirrhosis. This association was confirmed by another study conducted by Poordad F. et al. In this study, "12 weeks of treatment with the pan-genotypic combination of daclatasvir with sofosbuvir and ribavirin achieved SVR12 rates of 83% and 94% in the advanced cirrhosis and post transplantation cohorts, respectively". It was also found that this regimen was absolutely safe in all stages of cirrhosis and there was significant improvement in the clinical parameters in all these patients[12].

Improvement was observed in clinical and biochemical parameters in the staging of cirrhosis in another study conducted by Ohkoshi S, et al, in 2015. It was found that new DAAs are safe and very effective to reverse the clinical and biochemical parameters in case of decompensated cirrhosis, improve the standard of life of these patients, decrease the urgency for liver transplantation and improve post-transplant outcomes[13].

Similar improvement was observed in the clinical and biochemical parameters in the staging of cirrhosis in another study conducted in 2016 by Van der Meer AJ et al. Significant improvement was observed in the clinical and biochemical stages in both compensated and decompensated cirrhotic patients[14].

Limited sample size, poor elaboration and investigation regarding all parameters of cirrhosis, lack of data on

some important potential confounders, effects of the level of cirrhosis on response rate and application of only one scoring system for the staging of cirrhosis are considered as the main limitations of this study.

Finally, it is now a documented fact worldwide with many trials, that DAAS are the safe and most effective drugs in the management of both cirrhotic and non-cirrhotic cases. These drugs not only have very good outcome in term of virologic response but also improve all the clinical and biochemical parameters of cirrhosis. These drugs can be considered as a blessing and can be safely recommended for patients with advanced cirrhosis due to HCV infection. However, large trial is needed to address role of some other factors like age, sex, initial viral load, concomitant disease and genotype 3-subgroup in the down staging of cirrhosis due to HCV genotype-3 infections.

CONCLUSION

It is now concluded from results of this study that triple therapy including Daclatasvir, Sofosbuvir and ribavirin is not only effective in all cirrhotic patients with chronic hepatitis-C genotype-3a infections, but also improve the clinical and biochemical parameters and stages of cirrhosis in Pakistani population. Further study is suggested, both at national and international level for further confirmation this outcome in term of improvement in the stages of cirrhosis in HCV patients.

Author's Contribution:

Concept & Design of Study:	Abid Shah, Niamat ullah khan
Drafting:	Abid Shah, Nizamuddin
Data Analysis:	Niamat ullah khan, Waheed Iqbal
Revisiting Critically:	Nizamuddin
Final Approval of version:	Abid Shah

Conflict of Interest: The study has no conflict of interest to declare by any author.

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