Original Research Article

Efficacy of direct acting anti-viral agents in patients infected with chronic hepatitis C Virus: A Single center experience

Abstract

Background

Hepatitis virus C (HCV) infection is affecting millions of people globally with an estimated prevalence in Pakistan ranging from 4.5 to 8%. Advent of oral direct acting antiviral agents (DAAs) in combination therapy has made possible the treatment of decompensated cirrhosis secondary to hepatitis C (HCV) infection. Therefore, this study focused to evaluate safety and efficacy of direct antiviral agents (DAAs) in compensated and decompensated cirrhotic patients.

Materials and Methods

This cross sectional study was conducted in the Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation (SIUT) Karachi, from 1st September 2017 to 30th June 2018. Patients diagnosed with HCV, presenting in outpatient department were enrolled. All patients received Daclatasavir, Sofosbuvir and Ribavirin combination. Patient without cirrhosis and with cirrhosis received treatment for 12 and 24 weeks, respectively. End of treatment response was taken as primary end point. Statistical analysis was performed by SPSS version 20.0.

Results

Out of 180 patients, 88(48.9%) were male and 92(51.1%) were female, with mean age of 44.59±11.29 years. Majority had genotype 3 i.e., 145(80.6%). In this study population, 97(53.9%) patients were non-cirrhotic and received 3 months treatment while 83(46.1%) cirrhotic patient got 6 months treatment. Post- stratification observed that young patients have better treatment response rate than older individuals (p-=0.031) On the other hand, statistical insignificant association was observed between end of treatment response with regards to gender, duration of treatment, history of hepatic encephalopathy and ascites.

Conclusion

This study concluded that treatment with direct antiviral agents of Hepatitis C virus related chronic liver disease is effectual and has shown equivalent response in cirrhotic and non-cirrhotic patients. Age is an important factor affecting treatment response i.e, better response achieved in patient with less than 45 years.

Key word: Direct antiviral agents, cirrhosis, Sofobuvir, treatment response

INTRODUCTION

Globally, ribonucleic acid (RNA) virus is leading cause of Hepatitis C virus (HCV) infection that affects millions of people. In 2011 in Pakistan, it was predicted the prevalence rate of HCV ranges from 4.5 to 8%.[1] Most affected groups found in our local population are healthcare workers, blood donors and intravenous drug abusers.[1] The prevalence among high risk groups has already been found to reach 40%.[2] Data showed that the incidence of HCV is still insufficient. [3, 4, 5]Pakistan exhibits the second leading HCV encumbrance in the world, with current prediction proposing that Pakistan has a projected adult HCV sero-prevalence of 4.5–8.2%.[6,7] It is predicted that multiple factors are responsible for transmission of HCV in Pakistan for instance health care trainings (occurrence rate of 27–42.3% in health care experts and 7.8–68% in the overall population due to blood transfusion and injections), community-based happenings such as barbering, piercing of ear/nose, and use of injecting drug are also causative factor for the transmission of HCV.[7, 8, 9]

Previous studies performed in Pakistan demonstrated HCV genotype 3 to be the most common whereas other genotypes including 1, 2 and 4 were less commonly found.[3, 4] The determination of genotype in HCV infection is not only important for the choice of direct acting anti-viral agents (DAAs) but also guides the response to treatment. Historical data suggested that genotype 3 is more responsive to interferon therapy and requires short duration of treatment with early improvement, whereas other genotypes require prolonged treatment. [1]

Peg-interferon alfa and ribavirin therapy for chronic HCV infection is related to a sustained virologic response in about 40% of genotype 1 infected patients and 75% with genotype 2 or 3 infected patients. [10,11] The older drugs, boceprevir and telaprevir showed improved sustained viral response;[12,13] however, their effectiveness was restricted to HCV genotype 1 infection were

accompanied with side effects, complicated dose, and resistance. [13, 14, 15] Novel anti-viral agents that have been recently accepted for management of HCV infection include Sofosbuvir, Daclatasvir and Velpatasvir. Sofosbuvir is nucleotide analogue HCV NS5B polymerase inhibitor whereas Daclatasvir is HCV Serine protease 5A replication complex inhibitor. [16] They have potent antiviral activity, with End of Treatment Response (ETR) of more than 98% and provide pan genotypic coverage.[16, 17]

Sofosbuvir based twin or triple treatment has so far presented to be very effectual in genotype 3-infected patients, with a sustained virological response (SVR24) of 82.2–99.34%. Though, the outcomes are unsatisfactory, particularly in patients with decompensated cirrhosis and with or without considerable fibrosis.[18,19,20] Thus far, the biggest cohort study performed in Lahore included 1375 patients has also revealed a significant SVR rate of 97–99% in genotype 3 patients subsequent to administration of double or triple SOF therapy.[21]

As the data shows that these newer DAAs have better efficacy and less side effects in comparison to previous interferon based regimens [22], and scarce evidences are exists in our population to check the efficacy of DAAs. Therefore, this study was intended to assess the effectiveness of these innovative DAAs in Pakistani population.

MATERIAL AND METHODS

This cross-sectional study was conducted in Out-patient Department (OPD) of Hepatogastroenterology unit, Sindh Institute of Urology and Transplantation (SIUT) Karachi, after taking ethical approval from institutional ethical review board. The duration of the study was about 10 months from 1st September 2017 to 30th June 2018. A total of 180 patients of both genders aged between 18 and 70 years had chronic HCV infection were included in the study. Calculations of sample size done by WHO calculator, p=95 % , confidence level 95 %, margin of error 3.2 % . The Sample size of this study was 180. Patients who had liver transplantation, hepatocellular carcinoma (HCC), concomitant Hepatitis B virus infection and previous history of treatment of HCV infection were excluded from the study.

A structured Performa was used to collect data by non-probability consecutive sampling technique. Laboratory investigations including platelet count, serum albumin, qualitative HCV RNA polymerase chain reaction (PCR) and HCV genotype were performed. Ultrasound

abdomen had been carried out by consultant radiologist in the Radiology department for liver size, liver margins and spleen size. Treatment with Sofosbuvir, Daclatasavir and Ribavirin was started for all selected patients. Treatment duration was about 3 months for patients with no liver cirrhosis and 6 months for patients with liver cirrhosis. All patients had been followed till the treatment end and treatment efficacy was assessed in term of achievement of end of treatment response.

Statistical data was analyzed by SPSS Version 20. Categorical variables (gender, HCV genotype, previous history of hepatic encephalopathy, previous history of ascites, liver size, presence of splenomegaly, duration of treatment, achievement of ETR) were documented as frequencies and percentages and continuous variables (age, platelet count, serum albumin) were documented as mean and standard deviation. Effect modifiers such as age, gender, duration of treatment, history of ascites and encephalopathy had been controlled through stratification. Effect of modifiers on outcome was observed following the application of Chi square test. p value ≤ 0.05 was taken as statistically significant.

RESULTS

A Total of 180 patients of both genders aged 18 to 70 years were selected to determine the efficacy of direct acting anti-viral agents in chronic hepatitis C infected patients.

Baseline characteristics revealed that out of 180 patients, 88 (48.9%) were male and 92 (51.1%) were female, mean age of patients was 44.59 ± 11.29 years. Age was further stratified into two groups i.e., ≤ 45 and > 45 years. Mean serum albumin level was 3.33 ± 0.83 g/dL. Mean platelet count was 184086.11 ± 117544.15 per microliter. It was observed that 145 (80.6%) patients had genotype 3. History of ascites was present in 74 (41.11%), Liver margin was regular in 91 (50.6%) patients, Liver size was normal in 90 (50.0%) patients and increased in 19(10.6%) patients and decreased in 71(39.4%) patients. History of encephalopathy was present in 34 (18.9%) patients, while 46.7% patients had splenomegaly. In this cohort 97 (53.9%) patients had non-cirrhotic liver and received 3 months treatment and 83 (46.1%) patient had liver cirrhosis who were given 6 months treatment, as shown in Tab I.

End of treatment response was attained in 165 (91.7%) patients as depicted in Fig 1.

Pot-stratification results revealed significant association between End of treatment response with respect to age (p= 0.031), while there was statistical insignificant association in achievement of End of Treatment Response between males and females (p=0.15), duration of treatment (p=0.26), history of encephalopathy (p=0.13) and history of ascites (p=0.31), as shown in Tab II.

Table 1: Baseline characteristics and laboratory parameters of the study population. (n=180)

Variable		**Mean±SD n(%)**
Age (years)		44.59±11.29
Serum Albumin (g/dl)		3.33±0.83
Platelets count, per cubic millimeter		184086.11±117544.15
Gender	**Male**	88(48.9%)
	Female	92(51.1%)
Liver size	**Normal**	90(50%)
	Increased	19(10.6%)
	Decreased	71(39.4%)
Ascites	**Present**	74(41.1%)
	Absent	106(58.9%)
History of Encephalopathy	**Present**	34(18.90%)
	Absent	146(81.10%)
Splenomegaly	**Present**	83(46.10%)
	Absent	97(53.90%)
Duration of treatment	**Six months**	83(46.1%)
	Three months	97(53.9%)
Genotypes	**1a**	4(2.2%)
	1b	11(6.1%)

	2a	6(3.3%)
	2b	4(2.2%)
	3	145(80.6%)
	4	10(5.6%)

Table 2: Stratification of End of treatment response with respect to age, gender, ascites, encephalopathy and duration of treatment. (n=180)

Variables		**End of treatment response Achieved n(%)**	**End of treatment response not achieved n(%)**	**P-Value**
Age (years)	**≤45 years**	92(95.83%)	4(4.16%)	0.031
	>45 years	73(86.90%)	11(13.09%)	
Gender	**Male**	78(88.63%)	10(11.36%)	0.15
	Female	87(94.56%)	5(5.43%)	
Ascites	**Present**	66(89.18%)	8(10.81%)	0.31
	Absent	99(93.39%)	7(6.6%)	
Encephalopathy	**Present**	29(85.29%)	5(14.70%)	0.13
	Absent	136(93.15%)	10(6.84%)	
Duration of Treatment	**Six months**	74(89.15%)	9(10.84%)	0.26
	Three months	91(93.87%)	6(6.18%)	

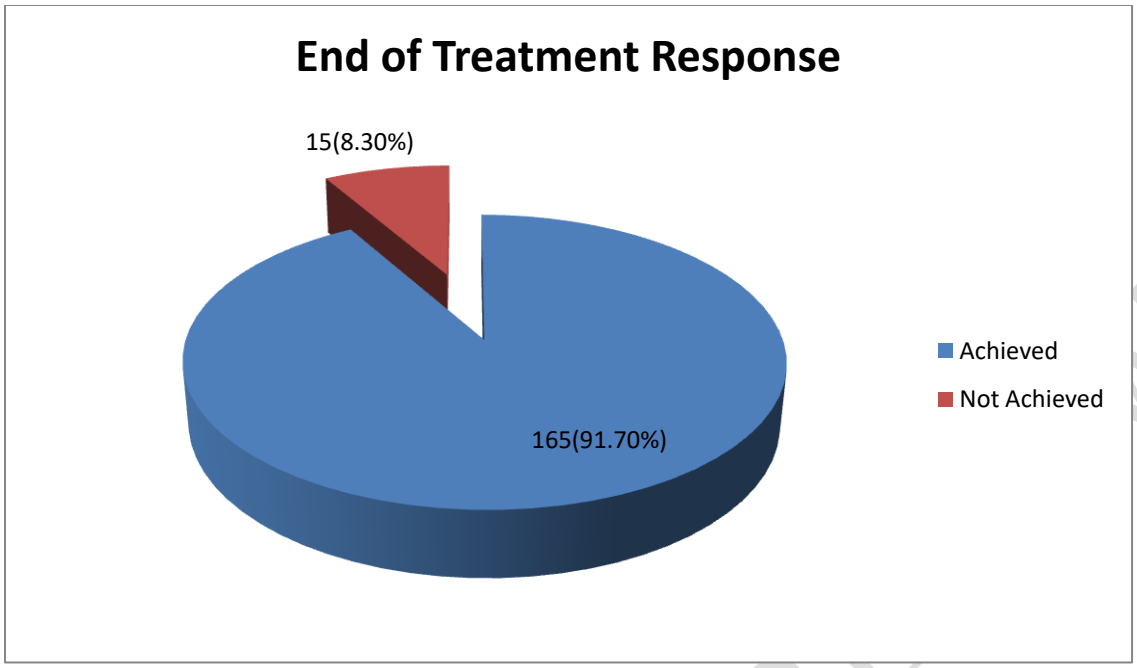

Fig 1: Frequency distribution of Achievement of End of treatment response

DISCUSSION

The present study demonstrated the effectiveness of direct acting anti-viral agents (DAAs) in patients with chronic hepatitis C infection of both genders having age between 18 to 70 years. It was revealed by many researches that acceptance of effectiveness of DAAs in the management of patients with HCV related chronic liver disease is now established.[23,24] The present study investigated those patients who were treated with newer DAAs, Sofosbuvir 400mg once daily, and Daclatasavir 60mg once daily along with Ribavirin 400mg twice daily. End of treatment Response (ETR) was achieved in 165(91.66%) patients and was not achieved in 15(8.33%) patients. While on the other hand, ETR was achieved in more than 99% of patient in the study conducted by David, et al. This difference is due to the fact that they included only those patients who were infected with HCV Genotype 3. [17]

SchmuckerDLet al, concluded that various changes related to age have been predicted in elderly population including reduced liver volume, raised hepatic compact body compartment (lipofuscin), moderate descent in the Phase I metabolism of certain drugs, alterations in the manifestation of a range of proteins and weakened hepatobiliary functions. [25] Further changes for instance reactions to oxidative stress, decreased expression of growth controlling genes,

gradually slower rates of DNA restoration, telomere shortening) may contribute to decreased hepatic recovering capability. Thus, it can be hypothesized that age related declining hepatic regeneration capacity, diminished rates of DNA repair as well as declines in drug metabolism can lead to poor response to DAAs. The present study revealed the better rate of End treatment response was achieved in 73(86.9%) patients above 45 years while 92(95.8 %) patients in less than 45 years with a significant association observed between them (p= 0.031).

European Association for the Study of the Liver (EASL) recommendations recommended that 6 and 3 months treatment to cirrhotic and non-cirrhotic patients, respectively. [26] These findings were similar to the present study. In contrary to Ahmed et al, our study found statistical insignificant association between the cirrhotic and non-cirrhotic patients (p=0.26). The variance in the result may be attributed to difference in population and HCV genotype.

Previously, interferon was not indicated for treatment of HCV related cirrhotic. With advent of DAAs, patients with compensated and decompensated cirrhosis can be offered treatment. Presence of ascites and hepatic encephalopathy is indicative of advance fibrosis and liver cirrhosis. AM Ippolitoet al. noted that presence of these factors does not affect treatment response to DAAs. [27] The present study observed that ascites and history of encephalopathy showed statistically insignificant impact on end of treatment response. (p= 0.13 and p=0.31 respectively). And this fact is in accordance with the recommendations issued by EASL that DAAs are equally effective in patients with or without signs of cirrhosis like encephalopathy or ascites. [26]

Similarly, one of the studies by Siddique MS et al investigated Rapid & End treatment response of patients managed with Sofosbuvir in Chronic Hepatitis C. They studied 201 patients with their reported mean age was 46.22± 14.41 years. Out of 201 patients, 131 (65.2%) were diagnosed by chronic hepatitis C, compensated cirrhosis diagnosed in 47(23.4%) cases, and with decompensated cirrhosis in 23(11.4%) patients. Most frequently genotype 3 was present in 180 (89.6%) patients subsequently genotype 1 in 9(4.5%), genotype 2 in 1(0.5%) and genotype 4 in 1(0.5%). It was proved that Sofosbuvir has revealed to be very efficacious with attainment of virological reaction with slight or no resistance in all genotypes mostly genotype 3 infected patients.[28] The present study was not in agreement with the above reported research and revealed

that mean age of studied patient was 44.59 ± 11.29 years with most of the patients 145 (80.6%) had genotype 3. It was also observed 97 (53.9%) patients were non-cirrhotic while 83 (46.1%) patient were cirrhotic. Antiviral drugs against chronic liver disease were efficacious and showed a better response.

CONCLUSION

This study concluded that treatment with direct antiviral agents of Hepatitis C virus related chronic liver disease is effectual and has shown equivalent response in cirrhotic and non-cirrhotic patients. Age is a significant factor affecting treatment response i.e, better response achieved in patient with less than 45 years of age.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected from Sindh Institute of Urology and Transplantation (SIUT), Karachi and preserved by the author(s).

Consent

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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