EFFECTIVENESS OF COMBINATION THERAPY WITH SOFOSBUVIR AND DACLATASVIR IN HCV INFECTED PATIENTS

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ABSTRACT

Objective: To determine the effectiveness of combination therapy with Sofosbuvir and Daclatasvir in HCV infected patients

Material and Methods: This quasi experimental study spanning over six months from January 2019 till June 2019 was conducted in three tertiary care teaching hospitals of Khyber Pakhtunkhwa. A total of 255 RT-PCR confirmed genotype HCV infected patients were included. Combination therapy including standard dose Sofosbuvir (400mg) and Daclatasvir (60mg) regimen for 12 weeks was administered after recording baseline data. The SVR12 (sustained virologic response after 12 weeks) in these patients was observed by repeating the RT-PCR for HCV at 12 weeks after the completion of treatment.

Results: This study included 108(42.35 %) male and 147 (57.64 %) female with male to female ratio of 1: 1.36 and Mean age 42.23 ± 11.9 years. Among them 200 (78.4%) were treatment naïve and 55 (21.6%) were treatment experienced. A total of 249 patients (97.6%) achieved SVR12 responders and 06 patients (2.4%) failed to achieve SVR12 non-responders. This response to DAA treatment for HCV was clinically and statistically significant.

Conclusion: The standard three-month DAA therapy with Sofosbuvir and Daclatasvir for the treatment of HCV has better SVR12 when compared with conventional treatment.

Key Words: Sofosbuvir, Daclatasvir, Direct Acting Antiviral drugs (DAAs), Sustained Virologic Response (SVR12)

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INTRODUCTION

In the management of HCV infection modern technology with advanced testing and screening as well as latest treatment protocols have made the prevention and treatment of HCV related decompensated cirrhosis of liver a real possibility. HCV contributes far greater than that due to HBV in the overall 1.45 million deaths per year attributed to Viral Hepatitis[1]. When compared with HBV, its clinical course is particularly more chronic, has more chances of complications and carries an overall bad prognosis[2]. The higher rates of cirrhosis liver due to HCV therefore makes it important that in addition to measure aimed at prevention of new cases, effective treatment protocols are devised and implemented at earlier stages in those patients who have already been infected with HCV. In this way the disease burden of Cirrhosis liver can be lessened and a healthy society ensured. Globally HCV is prevalent at a rate 2.5%, while in Pakistan the figures are worse marking up to 6.4%. Worldwide, genotype 1 is the most prevalent (49.1%) followed by genotype 3 (17.9%)[3]. The Genotype 3a remains the most common (61.3%) genotype in Pakistan. When compared with other hepato-trophic viruses especially HBV, the lack of vaccine against HCV and its cumbersome therapy involving conventional interferon further complicates the management[4]. Following the discovery of HCV as a distinct hepatotropic virus in 1990's and the subsequent attempts at its successful treatment, Interferon α both in conventional and PEGylated forms along with the Guanosine nucleotide analog Ribavirin remained the cornerstone of treatment of the chronic HCV infection although with lesser sensitivity and specificity. Moreover, the adverse effect profiles like skin pigmentation, bone marrow depression and suicidal ideations related to this regimen made this treatment far from ideal. All this led to more research and clinical trials aimed at better therapeutic options. Ultimately the advent of directly acting antivirals (DAAs) since 2011 led to a paradigm shift in the treatment of HCV. The sequence of RNA gene for

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HCV has now been identified and specific targets there in are identified for therapeutic applications with better results with more sensitivity and specificity in the treatment approaches. Sustained Virologic Response (SVR) defined as the absence of detectable HCV RNA with an assay as sensitive as to detect less than 50 IU/ml six month after the treatment has now been set as gold standard in the management of HCV hepatitis and its complications. A desired value for such therapeutic approaches is set at SVR12 of 95% with these new DAA agents[5,6]. In fact SVR is directly related to prognosis and long-term complications in patients infected with chronic HCV. Historically the maximum SVR attained with interferon based therapy in combination with ribavirin was 45%. A recent study, however, reported mortality reduction of 62-84% with DAAs compared to interferon based therapy[7]. Likewise the 5-years risk of hepatocellular carcinoma (HCC) accordingly has been reduced from 9.3 to 2.9% with these novel drugs. This has also resulted in exponential reduction in risk of liver transplantation from 7.3 to 0.2% in patients with cirrhosis[7,8].

The first DAA was a protease inhibitor (PI). When used in combination to interferon it improved SVR to 75% but adverse effects were troublesome. With the development of other DAAs, including NS5A and NS5B polymerase inhibitors, combination therapy of DAAs with or without ribavirin attained SVR of 95%. Further, these combinations were pan genotypic i.e. they were effective against all the genotypes of HCV and were better tolerated with fewer adverse effects[9-12]. Sofosbuvir which is basically a prodrug is a nucleotide analog inhibitor of Hepatitis C virus NS5B polymerase, the key enzyme mediating HCV RNA replication. In fact it is changed inside the hepatocytes into uridine analog 5'-triphosphate form (GS-461203) which mimics the natural cellular uridine nucleotide and is incorporated by the HCV RNA polymerase into the elongating RNA primer strand, resulting in chain termination. This active form of Sofosbuvir does not affect host DNA polymerase, RNA polymerase or mitochondrial DNA. Daclatasvir as compared was the first discovered inhibitor of the non-structural viral protein NS5A. It inhibits viral RNA replication and virion assembly. It may also inhibit phosphorylation of the NS4A and therefore prevents the formation and activation of the HCV replication complex. Since then, different combination therapies have been offered. One study showed the combination of two DAAs (NS5B inhibitor Sofosbuvir and NS5A inhibitor ledipasvir) curing more than 90% treatment-naïve HCV positive patients without cirrhosis[13,14]. In a study on combination therapy with Sofosbuvir and Daclatasvir by Ossama A, 96% patients of HCV infected with genotype 4 showed SVR after 12 weeks of treatment[15].

Limited studies have been done on the clinical outcomes of combination therapy of Sofosbuvir and Daclatasvir on genotype 3 of HCV in our country. This study is aimed to determine the efficacy of combination therapy of Sofosbuvir and Daclatasvir in HCV infected patients in term of SVR12 in the settings of Pakistan and especially the Khyber Pakhtunkhwa. Getting a local data about the efficacy of Sofosbuvir and Daclatasvir in HCV infected will help improve the therapeutic approaches and also in better counselling of HCV positive patients who are candidates for treatment.

MATERIAL AND METHODS

This Quasi experimental study was conducted at Departments of General Medicine, Lady Reading Hospital Peshawar, Khyber Teaching Hospital Peshawar and Mardan Medical Complex Mardan, from January 2019 to June 2019. Elaborative inclusion criteria were devised. Two fifty five (255) patients from a total of 270 patients in the age group of 18 to 70 years were enrolled. These patients already had third generation Enzyme Linked Immunosorbent Assay (ELISA) done which showed Anti HCV antibodies and their Liver Function Tests showed serum ALT levels higher than the upper limits. Quantitative RT-PCR was done to determine viral load which was followed by the Genotyping. The demographic data along with the addresses for the follow up as well as thorough clinical, laboratory and imaging assessment of all patients was recorded prior to the start of treatment.

At the initial inclusion into the study detailed medical history including history of any previous treatment for HCV was noted to ascertain whether they were treatment naïve or not. Patients showing clinical signs of decompensated liver cirrhosis were excluded. Baseline laboratory tests including Liver Function Tests (LFTs), Renal Function Tests (RFTs) with eGFR, Complete Blood Count, Alpha Fetoprotein were done routinely. Co infection with HBV was accordingly ruled out and pregnancy test in married female patients of child-bearing age was performed for exclusion from the study. Abdominal ultrasonography was done for determining echogenicity and nodularity of the liver with estimation of Portal vein diameter and any signs of splenomegaly. For the performance of HCV PCR blood samples were obtained from all patients, centrifuged, and then stored at - 20^{o}C. A quantitative measurement serum load of HCV was performed by real time PCR (Cobas Ampliprep/Taqman HCV Monitor version2.0, with a detection limit of 15 IU/ml; Roche Diagnostic Systems, USA), and it was repeated at the end of treatment, and 12 weeks after completion of treatment to detect SVR 12. The Genotyping was only done initially at the start of the study which confirmed HCV genotype 3 as it is the most prevalent genotype in the country[4].

Strict exclusion criteria was enforced including patients with hepatitis B virus co-infection, advanced liver disease (decompensated cirrhosis) or HCC (hepatocellular carcinoma), eGFR < 30ml/min, hemoglobin less than 8g/dl or platelet count less than 50,000/mm^3.

A written informed consent was obtained from the patient on a printed proforma and appropriate consultation and follow up incentives were provided to the patients including preferential checkup and laboratory facilitation.

Treatment eligible patients were given oral Sofosbuvir 400mg and oral Daclatasvir 60mg daily for 12 weeks. During treatment, they were closely monitored at regular follow up at week 2, week 4, week 8 and week12. This included both clinical evaluation and by needful laboratory studies including CBC, creatinine, AST, ALT and total bilirubin.

The end point of our study was detecting the percentage of patients with Hepatitis C (both treatment naıve patients and treatment experienced) who achieved Sustained Virologic Response (SVR) at follow up week 12 (SVR12). Viral load less than 50 IU/ml on RT PCR for HCV RNA after 12 weeks treatment was defined as SVR 12 responder. Values greater than this with signs of clinical deterioration were ascribed as failure to attain SVR12 and thus labelled as non-responders.

The subjective improvement in response to treatment was assessed using Likert scale for agreement to the sense of well-being (Qualitative) in addition to their reporting the major side effect. The data was collected and analyzed on SPSS version 22. P-value of less than 0.05 was set as statistically significant.

RESULTS

A total of 270 patients who presented with history of HCV Hepatitis, either self-presenting or cases of referral; 255 were included in the study and 15 were dropped out from the study based on exclusion criteria. Among these 15 patients, 12 were having decompensated liver cirrhosis, one lady was pregnant, one patient had HBV co-infection and one patient had eGFR less than 30ml/min.

Two patients lost during follow up were replaced with new cases based on inclusion criteria. This RT PCR confirmed HCV Hepatitis patients were enrolled from January 2019 to June 2019, hence with a sample size reduced to 255. Table 1 outlines the number and percentage of distribution of the gender in the study population. Among these 255 studied patients, 108 patients (42.35%) were male and 147 patients (57.64%) were female. Male to female ratio was thus 1: 1.36. Age of the patients ranged from 18 to 70 years. Mean age was 42.23±11.9 years. Based on the age, patients were divided into different age groups. Majority of the patients (80 patients, 31.4%) belonged to the age group 31-40 years, followed by 41-50 years age group (69 patients, 27.1%), 52 patients (20.4%) were in the age group 51-60 years, 32 patients (12.5%) in 21 to 30 years age group and 15 patients (5.9%) represented 61 to 70 year age group . Only 7 patients, (2.7%) were noted in the age group 18-20 years (Table 2).

Regarding the laboratory data, the study revealed a pre-treatment mean ALT of 47±3 U/L. On Abdominal ultrasonography 239 patients (93.7%) had normal liver echogenicity prior to treatment and 16 patients (6.3%) had hepatic fibrosis normal size liver and Grade 1 echogenicity. Among the study sample 200 patients (78.4%) were treatment naïve and 55 patients (21.6%) were treatment experienced with either Interferon or single DAAs or both but not in combination.

Table 3 presents the data regarding the main yield in this study i.e. the attainment of SVR12. It is evident from this table that at the conclusion of the study at 12 weeks among 255 patients who had received standard dose of Sofosbuvir and Daclatasvir for 12 weeks, 249 patients (97.6%) were responders i.e., attained SVR12, while 06 patients (2.4%) were non-responders i.e., didn't attain SVR12 Post-treatment mean ALT observed was 23±2 U/L. Among the six non-responders, 03 (50%) were male and 03(50%) were female. Only one non-responder patient was treatment naïve and rest (05 patients) had treatment experienced in the form of PEGylated interferons with Ribavirin for six months.

Using the Likert scale as the basis for Qualitative assessment for the sense of well-being after the completion of treatment it was found that a vast majority of patients; 225 (88%) patients were strongly agreeing to the benefit of treatment in that they were feeling better at the completion of treatment (Table 4)

Table 1: Gender distribution among the participants of the study

Participant's Gender	Representative Number	Percentage (%)
Male	108	42.35
Female	147	57.64
Total participants	255	100

Table 2: Age group distribution among the participants of the study

Age group (in years)	Total numbers in this group	Percentage (%)
18 to 20	07	2.7
21 to 30	32	12.5
31 to 40	80	31.4
41 to 50	69	27.1
51 to 60	52	20.4
61 to 70	15	5.9

Table 3: SVR12 status of the patients in the study at the conclusion of 3 month treatment

SVR12 status (n= 255)	Responders	Non Responders
Total number	249	06
Percentage (%)	97.6	2.4

Table 4: Likert scale for the sense of well-being after the completion of treatment

Likert scale	Number of patients	Percentage (%) (Approx.)
Strongly agree	225	88
Agree	19	7
Undecided	3	1.5
Disagree	3	1.5
Strongly disagree	5	2

DISCUSSION

Sofosbuvir in daily dose of 400 mg is a pan-genotype directly acting antiviral used for the treatment of HCV. It is a NS5B inhibitor that is taken once daily with fewer adverse effects and good compliance[16-18]. Daclatasvir is also effective against all HCV genotypes taken once daily. Unlike Interferons both are administered orally thus increasing their compliance by the patients and are easily tolerated with superior safety profile. There are very few drug interactions with concomitant medications via weak induction of cytochrome P450 enzymes. No dose adjustment is required for patients with compromised renal functions because of their hepatic metabolism; that's why high SVR rate has been observed for combination therapy of Sofosbuvir and Daclatasvir particularly against resistant cases of genotype 1 to 4[19, 20].

In our study 97.6% of patients achieved SVR12 (responders) with standard 12 weeks treatment with Sofosbuvir and Daclatasvir. All of them showed better tolerability and only 2.4 % patients did not attain SVR12 (non-responders). These results are significant comparing to similar results reported by Nelson DR in their ALLY-3 Phase III study for genotype 3 in which 90% treatment naïve and 86% treatment experienced patients with an overall 89% patients achieved SVR 12 with the standard regimen[21].

In our study both male and female patients showed equal response to treatment and no effect of gender on the outcome was observed (p-value = 0.703). In fact gender, age and baseline HCV RNA levels all had no effect on the SVR12. A significant association of response to treatment was observed with the underlying liver status (p value= 0.01). Patients with normal liver had better response to treatment compared to those who had features of fibrosis even without decompensation. On that account our study was confirmatory to similar association demonstrated by Nelson DR et al in their study[21]. Based on the results of our study better outcomes were also showed by patients who had received previous treatment with conventional interferon based therapy and then presented with relapse. This was consonant with the better response to standard regimen of Sofosbuvir plus Daclatasvir shown by Sulkowski MS[22]. Combination therapy with Sofosbuvir plus Daclatasvir for HCV was better tolerated vast majority of the patients in the study.

Based on this study the recommendation on this regimen for the treatment of HCV in Pakistan should be prioritized over the other treatment modalities available at the moment by the National Health authorities for the maximum benefit to the patients and public at large. A large multicentre national study is required to generalize the impact of outcome.

CONCLUSION

Combination therapy with Sofosbuvir and Daclatasvir for the treatment of HCV has better efficacy in term of SVR12. The regimen is equally effective for both treatment naïve and treatment experienced patients.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Uddin Z:	Conception of idea, overall supervision
Suleman S:	Data collection, drafting and data analysis
Shahzeb:	Compilation of data, manuscript writing.
Ullah I:	Questionnaire development and statistical analysis
Zia S:	Data interpretation and proofreading
Fida Z:	Data interpretation and proofreading

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.