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Changes in Health Related Quality of Life in Patients with Chronic Hepatitis C during the Clinical Course of Daclatasvir/ Velpatasvir Therapy: A Prospective Observational Study

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ABSTRACT

Background: Interferon-free direct-acting antiviral agent (DAA) therapy is preferred for the treatment of chronic hepatitis C (CHC) patients as it exhibits a higher rate of sustained virologic response (SVR), along with reduction in treatment related adverse drug reactions (ADR), which elevates the quality of life (QOL) of patients. The study aims to evaluate the health-related quality of life (HRQOL) in patients with CHC, receiving Daclatasvir or velpatasvir (DCV/VEL) therapy, using Short Form-36 (SF-36) as a tool. **Methods:** The study involves 50 CHC patients receiving DCV/VEL, who's HRQOL was measured using SF-36. Laboratory investigational data and SVR was recorded, and SF-36 was filled by the patient at baseline (prior to therapy), week 12 (post initiation of therapy), end of treatment (EOT), and week 24 (post initiation of therapy. HRQOL were analyzed at week 24. The association between laboratory data and HRQOL was also evaluated. **Results:** In regard to HRQOL, statistically significant changes were observed in physical functioning, general health, and emotional role functioning in the period between baseline to week 12 and week 24, respectively. A considerable change was observed in laboratory parameters such as aminotranferases, platelet count, and Fibrosis-4 (Fib-4) index at each time point of study as compared to baseline. **Conclusion:** It was found that HRQOL of patients with CHC improved significantly along with hepatic functions during the clinical course of interferon-free DAA therapy (DCV/VEL).

Keywords: Chronic Hepatitis C, Daclatasvir, Velpatasvir, Health-Related Quality of Life, Short Form-36.

INTRODUCTION

In 1989, Choo et al discovered the Hepatitis C virus (HCV) in United States.[1] It stated that more than 90% of previously diagnosed cases of non A and/or non B hepatitis have HCV as their etiology. Approximately 170 million patients are infected with HCV worldwide.[2-4] Nearly 15-30% of HCV patients develop major complications of this disease, such as end stage liver disease, liver cirrhosis, portal hypertension, encephalopathy, and hepatocellular carcinoma.[5] The mortality rate of HCV patients is as high as about 5.0 deaths/100,000 population in 2013.[6]

Recently, interferon-free direct-acting antiviral agent (DAA) therapy has been developed. It is preferred for the treatment of chronic hepatitis C (CHC) patients as it exhibits a higher rate of sustained virologic response (SVR) along with a reduction in treatment related adverse drug reactions (ADRs) by selective inhibition of HCV proteins like NS5A, nonstructural protein NS 3/4A protease, and NS5B polymerase.[7-8]

In India, combination of DAA therapies like Sofosbuvir with velpatasvir (VEL) or Daclatasvir (DCV) was approved for use in the year 2017 by CDSCO. As suggested by previous studies, treatment of CHC patients with interferon containing DAA agents significantly impairs the health related quality of life (HRQOL) by causing ADRs such as fatigue, flu like symptoms, and gastrointestinal disorders, majorly during the clinical course of therapy.[9-10] Alternatively, several studies have concluded that interferon-free DAA therapy has minimal effect on HRQOL and less incidence of ADRs during treatment.[11-14]

After extensive Medline research, it was found that very few number of studies have evaluated the HRQOL in CHC patients during the clinical course of DCV/VEL therapy. The study aims to evaluate the health related quality of life (HRQOL) in patients

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with chronic hepatitis C (CHC), receiving Daclatasvir or velpatasvir (DCV/VEL) therapy, using short form 36 (SF-36) as a tool. Specifically, we analysed laboratory data and HRQOL up to 12 weeks after the end of treatment (EOT).

MATERIALS AND METHODS

After obtaining written informed consent from patients, this prospective, observational study was conducted in Department of Gastroenterology, Teerthankar Mahaveer Medical College and Research Centre, Moradabad, from January to August 2018. The study enrolled 50 CHC patients with Genotype-3, aged between 20-70 years, receiving DCV/VEL therapy. Patients with comorbities such as Hepatocellular Carcinoma, HbsAG/ HIV Infection, Chronic Liver Disease, Chronic Alcoholic Disease, Severe Fatty Liver, Diabetes, Autoimmune Hepatitis, Primary Biliary Cirrhosis, Hemochromatosis, Wilson's disease, history of Congestive Heart Failure, alcohol consumption> 80 g/day, and those receiving hepatotoxic drugs were excluded from the study

Demographic data of all subjects was collected at baseline which included age, gender, alanine transaminase (ALT), aspartate transaminase (AST), hemoglobin (Hb), platelet count (Plt), fibrosis-4 index (FIB-4), serum albumin (Sr. Alb), α-fetoprotein (AFP), and estimated-glomerular filtration rate (eGFR).

At baseline, HCV infection was confirmed by both positive serum HCV antibody titers (ARCHITECT Anti-HCV; Abbott Laboratories, Abbott Park, Illinois, USA) and serum HCV RNA using a real-time PCR- based method (COBAS AmpliPrep/ COBAS TaqMan HCV Test; Roche Molecular Systems, Pleasanton, California, USA). Patients received a fixed dose combination of DCV (60 mg once daily) or VEL (100 mg once daily) with Sofosbuvir (400 mg once daily). The treatment regimen was scheduled for 12 weeks. Patients were asked to visit the clinic for the monitoring of treatment effects and adverse effects every 2 weeks throughout the treatment period. HRQOL, Laboratory data, and Serum HCV RNA levels were measured at baseline, week 12 (post initiation of therapy), EOT (end of treatmet), and week 24 (post initiation of therapy). HRQOL was measured using SF 36 as a tool.

The SF 36 comprised 36 questions, with 8 subscales related to physical and mental health: Physical functioning (PF), physical role functioning (RP), bodily pain (BP), general health (GH), vitality (VT), social role functioning (SF), emotional role functioning (RE), and mental health (MH). Each subscale is scored from 0 to 100, and higher scores indicate greater HRQOL.

Statistical analysis was performed using the SPSS (version 20.0; SPSS Inc, Chicago, IL). The data is represented as mean ± standard deviation (SD) or median (interquartile range). Categorical variables were compared by Fisher's exact test. Friedman test and Bonferroni's multiple comparison correction method were used to analyze differences among continuous variables at baseline, week 12, EOT, and week 24. The value of P< 0.05 was accepted as statistically significant.

RESULTS

Bodily pain at baseline and week 12 was found to be 51.2 ± 8.6 and 63.09 ± 31.45, respectively (P=0.01). However, other HRQOL parameters showed comparable results at baseline vs week 12. [Table 1, 2]

Table 1: Patient HRQOL parameters (SF-36 subscale)

Factor	Baseline (n=50)	Week 12 (n=50)	EOT (n=47)	Week 24 (n=47)
PF	56.8 ± 19. 4	61.00±17.75	67.82 ± 23.16	79.00 ± 29.61
RP	59.3 ± 9.7	65.00 ± 39.06	72.93 ± 43.79	73.62 ± 36.09
BP	51.2 ± 8.6	63.09 ± 31.45	64.27 ± 37.50	53.00 ± 29.58
GH	71.7 ± 14.5	75.00 ± 15.97	76.09 ± 12.80	77.31± 12.15
VT	50.6 ± 9.2	53.00 ± 23.79	57.95 ± 23.06	59.82 ± 25.69
SF	72.6 ± 15.2	79.55 ± 32.73	75.68 ± 33.71	74.55 ± 28.65
RE	71.6 ± 16.0	75.83 ± 39.49	84.03 ± 39.66	73.27 ± 40.84
MH	61.3 ± 9.6	65.57 ± 25.90	67.11 ± 24.22	68.30 ± 20.87

Data represented as mean ± SD.
EOT= End of Treatment, PF= Physical functioning, RP= Physical role functioning, BP= Bodily pain, GH= General health, VT= Vitality, SF= Social role functioning, RE= Emotional role functioning, MH= Mental health.

Table 2: P values for changes in HRQOL during and following DCV/ VEL therapy

Factor	Baseline Vs Week 12	Baseline Vs EOT	Baseline Vs Week 24
PF	0.27	0.01*	<0.001*
RP	0.32	0.03*	0.008*
BP	0.01*	0.02*	0.68
GH	0.29	0.11	0.04*
VT	0.5	0.04*	0.02*
SF	0.18	0.56	0.67
RE	0.48	0.04*	0.78
MH	0.28	0.12	0.03

EOT= End of Treatment, PF= Physical functioning, RP= Physical role functioning, BP= Bodily pain, GH= General health, VT= Vitality, SF= Social role functioning, RE= Emotional role functioning, MH= Mental health.
*Statistically significant difference between groups; (P < 0.05)

Physical functioning, physical role functioning, bodily pain, vitality, and emotional role functioning showed significant results on comparing baseline with EOT (P>0.05). [Table 2]

Statistically significant results were obtained on comparing physical functioning, physical role

functioning, general health, and vitality at baseline vs week 24 (P>0.05). [Table 2]

Furthermore, an overall intergroup comparison for aminotransferases, platelet count, fibrosis 4 score, serum albumin, α –fetoprotein, and estimate glomerular filtration rate revealed significant results (P<0.05). [Table 3]

Table 3: Differences in blood biochemistry during and following DCV/ VEL therapy

Factor	Baseline	Week 12	EOT	Week 24	P - value
AST (IU/l)	41.43±19.40	26.14±9.48	24.46±7.71	22.57±7.05	<0.01*
ALT (IU/l)	36.14±20.48	20.07±11.69	17.61±7.41	15.32±7.30	<0.01*
Hb (g/dl)	12.54±2.18	12.56±2.21	12.53±2.38	12.39±2.67	0.72
PLT (x104/µl)	15.26±8.55	15.47±7.70	15.49±7.67	17.14±9.25	<0.01*
Fib-4	5.28±5.19	3.79±2.77	3.63±2.62	3.40±2.33	<0.01*
ALB (mg/dl)	3.80±0.42	3.87±0.40	3.92±0.30	3.99±0.41	<0.01*
AFP (ng/ml)	4.90 (3.08, 8.93)	2.80 (2.38, 5.92)	2.85 (2.30, 5.43)	3.05 (2.40, 5.45)	<0.01*
eGFR (ml/m/1.73 m2)	70.54±23.95	66.12±22.22	66.35±21.98	66.43±21.77	<0.05*

Data represented as mean ± SD or median (interquartile range).

EOT= End of Treatment; AST= Aspartate Aminotransferase; ALT= Alanine Aminotransferase; Hb= Hemoglobin; PLT= Platelet Count; Fib 4= Fibrosis 4 Score; ALB= Serum Albumin; AFP= α -fetoprotein; eGFR= Estimate Glomerular Filtration Rate.

*Statistically significant difference between groups (P < 0.05).

DISCUSSION

Three of these fifty patients were excluded from analysis as they required treatments for hepatocellular carcinom and other malignant tumors during therapy. As a result, final analysis included 47 patients.

HCV patients have previously been reported to experience chronically decreased HRQOL due to fatigue, influenza-like symptoms, itchiness, and depression compared to non-infected individuals.[15,16] In recent years, treatment of HCV has been revolutionized with the development of highly effective all oral direct acting antiviral agents. Interferon free DAA result in increased SVR rates, shorter and simpler treatment regimens, with minimal ADRs. In the future, the significant factors in selecting treatment will include not only the efficacy of treatments that target a viremia or amelioration of Fibrosis, but also the improvement of patient QOL during and after treatment. In India, IFN- free combination therapy of Sofosbuvir with DCV and VEL for 12-24 weeks is approved as well tolerated and can achieve a high rate of SVR in patients with HCV genotype 3.

In the present study, HRQOL and biochemical parameters improved in most of the study patients. It may have led to an amelioration of liver function as well as improvements in nutritional status such as ALB. These findings are supported by Ohashi et al. who concluded that treatment of CHC patients with daclatasvir/ asunapavir improves HRQOL and biochemical parameters.[17]

Previous reports on DAA treatment containing IFN have indicated decreased HRQOL during treatment as well as an association between haemoglobin and HRQOL.[13] On the other hand, side effects such as loss of appetite and nausea are less likely to occur during DCV/VEL therapy.[18] This may have led to the amelioration of HRQOL and ALB through improved liver function. Previous studies have also reported an association between ALB and HRQOL in patients with haemodialysis or liver cirrhosis.[19,20] DCV/VEL therapy improves HRQOL, hepatic functional reserve, nutritional status, and liver Fibrosis during therapy, and could therefore prompt long-term improvements in HRQOL. Recently, DAA with treatment period of 12 weeks has appeared.[21-23] For example, Ledipasvir/ Sofosbuvir are one of the most common treatments in India, the achievement rate of SVR12 is reported as 98.8%. The discontinuation of treatment due to serious side effects is 0.6%.[24] In the future, further studies are needed in order to understand the influence of DAA with treatment period of 12 weeks on HRQOL.

The limitations of this study were that the sample size was small and that the data were representative of only a single institution covering a limited region. Future directions include expanding the study by increasing the number of patients from other institutions and region.

CONCLUSION

It was found that the Health- related Quality of Life in Chronic Hepatitis C improved significantly along with hepatic functional reserve and nutritional status during the clinical course of interferon- free Direct-acting Antiviral Agent therapy; Daclatasvir/ Velpatasvir.

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