Research Article

Impact of antiviral therapy on quality of life in hepatitis C patients measured using short form-36 questionnaire: A prospective observational study

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ABSTRACT

Aim: Even in the absence of cirrhosis, health-related quality of life (HRQOL) of hepatitis C virus (HCV) infected patients is low compared to healthy adults. HCV replication leads to various hepatic and extrahepatic manifestations and virological response to therapy can bring improvements in HRQOL. The present study was aimed to assess the effect of directly acting antivirals (DAA) on HRQOL in chronic HCV patients in a community hospital in North India. **Methods:** A total of 492 consecutive newly diagnosed non-cirrhotic hepatitis C patients and 500 matched controls were enrolled in this prospective observational study. Counseling regarding the disease and treatment was done monthly by a counselor. Available generic DAAs were given to the patients. HRQOL before initiation and after completion of treatment was measured using the short form-36 questionnaire. **Results:** HRQOL of cases was lower compared to controls before initiation of therapy. Of 492 cases, 460 (93.49%) patients completed the therapy and 400 (84.56%) patients achieved sustained virological response (SVR). Treatment success group showed significant improvement in all eight domains of HRQOL. In cases that did not achieve SVR (treatment failure), HRQOL did not improve in six out of eight parameters. SVR rates achieved using generic DAAs were comparable to those with branded DAAs. **Conclusion:** HCV infection has a substantial impact on the HRQOL. Significant improvements in HRQOL are associated with treatment success measured as SVR. Generic DAAs are effective and should be used in resource-limited settings. Rigorous counseling and regular follow-up can increase treatment adherence.

Keywords: Antiviral therapy, quality of life in Hepatitis C

Introduction

The global prevalence of viremic hepatitis C virus (HCV) is estimated to be 1.0%, whereas the reported prevalence in India is 0.9–1.9%.[1,2] Early detection of cases occurs during routine investigations, screening camps, and blood donation but 60–90% of HCV infection in India remains undiagnosed until the late stages of the disease.[3,4] Directly acting antivirals (DAA) have revolutionized the treatment of HCV due to their ease of administration, shorter duration of therapy, fewer side effects, and higher cure rates.

Besides liver, HCV infection affects a variety of organs and induces diverse extrahepatic manifestations. The extrahepatic manifestations further add to the burden of the disease and affect the health-related quality of life (HRQOL).[5,6] The health-related quality of life can be assessed by a simple standard short form-36 (SF-36) questionnaire.[7,8] The validity and reliability of SF-36 questionnaire have been established after translation in regional languages in India.[9]

Most of the patients in India do not have insurance coverage, and they have to pay for the treatment costs by themselves.[10] Branded DAAs are costly and hence out of reach of most patients in developing countries. Several companies in India have acquired voluntary manufacturing licenses for the generic production of oral DAA. Although the generic production of DAAs has reduced the cost of 12-week treatment to ~ $500 USD, there is limited data on their efficacy. One study by Gupta *et al.* comparable high virological response rates using generic DAA could be achieved.[11]

The present study was aimed to assess the effect of DAA on HRQOL in chronic HCV patients in a community hospital in North India.

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Materials and Methods

This prospective observational study was done in the hepatology department from January 2016 to December 2017, in consecutive, newly diagnosed HCV patients ($n = 492$), who were ≥ 18 years old. The detection of HCV patients was done during screening camps or during blood donation. Baseline liver function tests, HCV RNA viral load and genotypic evaluation, were done. All HCV positive cases without evidence of cirrhosis (as assessed by ultrasound abdomen, fibroscan, and biochemical investigations) were enrolled. Other exclusion criteria were: Coinfection with hepatitis B, HIV; coexistence of other hepatic diseases (Wilson's disease, autoimmune hepatitis), chronic kidney disease, known case of psychiatric illness taking antipsychotics, pregnancy, lactation, chronic cardiorespiratory disease, inability to buy medicines for 3 months, and extremely low cognitive status precluding reliable participation. For comparison purposes, a group of healthy control subjects ($n = 500$) was selected from volunteers who accompanied the HCV patients during the hospital visit and was negative for the presence of HCV antibody and any other chronic disease. Patients were treated with recently introduced DAA's in Indian market, which included generic sofosbuvir, ribavirin (RBV), Daclatasvir, and Ledipasvir in different combinations as per the genotype. Sofosbuvir was common to all combination therapies. In the initial phases of the study, sofosbuvir alone was available. It was given with RBV. Later on, sofosbuvir was used in combination with daclatasvir (for genotypes 2, 3) and ledipasvir (for genotype 1 and 4).

Data collection

The enrolled cases were counseled by the clinician and the counsellor. Health-related quality of life (HRQOL) assessment was done before and after therapy using a SF-36 questionnaire translated into the local language (Hindi).[9] The measured values included eight health concepts: Physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning energy/fatigue, and general health perception. The scores ranged from 0 (lowest) to 100 (highest), with higher scores indicating better quality of life. The questionnaire was self-administered in educated patients. The counselor filled the questionnaire with uneducated patients. The completion of the questionnaires took an estimated response time of 10–30 minutes. The patients were evaluated and counseled by a counselor on a monthly basis through telephone or in clinics. The follow-up clinical evaluation was done at the end of therapy (12 weeks). Quantitative measurement of Hepatitis C RNA and repeat assessment of HRQOL was done after completion of the therapy at 12 weeks. The final HRQOL assessment was done before disclosing the most recent HCV RNA levels result to the patients. The participants signed an informed consent before being enrolled in the study.

Statistical analysis

The SF-36 scores were calculated before initiation and after completion of DAA therapy. Eight patient-related outcomes domains were transformed from their original scales to a universal 0 to 100 scale with greater scores representing better well-being. The method of transforming the scale has been described for the evaluation and marking of the SF-36 score.[12,13]

All demographic and clinical parameters, patient-related outcomes in eight domains and changes in those, were summarized as mean ± standard deviation or frequency (percentage). The comparison was done using Wilcoxon rank sum nonparametric test (continuous parameters) or Pearson Chi-square test (categorical parameters). The decrements or improvements in patient-related outcomes at the study time points from patients' own baseline were tested for significance using Wilcoxon signed-rank test for matched pairs; $P = 0.05$ considered a threshold for significance.

RESULTS

Consecutive 492 HCV positive patients and 500 matched controls were enrolled in the study. Baseline demographic and clinical parameters between the two groups were comparable and are shown in Table 1.

Genotype 3 was the most commonly observed in the study population with 265 (53.08%) patients harboring HCV GT 3. In the study population, 153 (31.09%) were HCV genotype 1 patients and 74 (15.04%) had genotype 2.

In the chronic hepatitis C patients group, 492 patients completed the HRQOL survey before the initiation of therapy. Oral DAAs were given, and 473 (96.13%) patients completed the therapy. Out of 473 patients, 460 (97.25%) patients completed the 2nd part of the questionnaire, and 400 (84.56%) patients achieved sustained virological response (SVR) [Figure 1].

A total of 32 patients were excluded from the study. The reasons being no phone contact available ($n = 5$), stopped medications due to adverse events ($n = 5$), continues/started alternative medications ($n = 5$), drug defaulter ($n = 4$), and lost to follow-up ($n = 7$) and did not fill the questionnaire on follow-up ($n = 6$). Pre-treatment values of HRQOL in patients and controls groups are given in Table 2. HCV patients had significantly lower HRQOL in all of the eight domains of the SF-36 ($P < 0.001$).

Table 1: Baseline demographics and clinical presentation

Parameter	HCV± ve (n=492)	Control (n=500)	P value
Age (years)	44.6±5.1	45.3±4.8	0.02
Sex male/female (%)	59/41	54/46	0.11
Rural/urban (%)	64/36	64/36	1.00
Literate/illiterate (%)	45.5/54.5	41/59	0.15
HR (per min), mean±SD	77.1±8.0	76.0±10.6	0.06
MAP (mmHg), mean±SD	81.9±14.6	83.1±11.8	0.15
Hb (g/dl), mean±SD	10.8±1.1	11.2±1.4	0.08

SD: Standard deviation, HCV: Hepatitis C virus, HR: Health-related, MAP: Mean arterial pressure

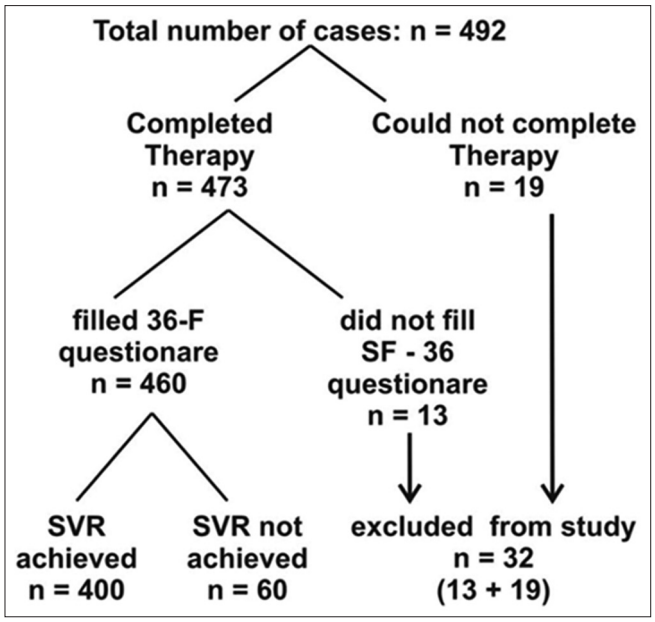

Figure 1: Study outline

Table 2: SF-36 physical and mental health parameters comparison (HCV vs. controls)

Parameter	HCV patients (mean±SD), *n*=492	Control (mean±SD), *n*=500	*P* value
Physical function	78.2±18.8	90.7±12	<0.001
Role physical	68.4±30.2	94.4±23.1	<0.001
Bodily pain	76.1±18.4	88.8±17.8	<0.001
General health	66.2±24.4	84.2±16.6	<0.001
Vitality	50.1±19.5	64.2±18.2	<0.001
Social function	74.7±22.1	84.1±18.2	<0.001
Role emotional	78.9±28.1	86.2±26.6	<0.001
Mental health	75.2±17.7	80.5±16.1	<0.001

SD: Standard deviation, HCV: Hepatitis C virus, SF-36: Short form-36

At the beginning of the study, sofosbuvir ± RBV was given to 86 patients, sofosbuvir ± daclatasvir was given to 336 patients, and sofosbuvir ± ledipasvir was given to 70 patients. In the final analysis, the response rate was 63% with sofosbuvir ± RBV, 95% with sofosbuvir ± daclatasvir, and 92% with sofosbuvir ± ledipasvir [Table 3].

The comparison of eight health-related quality of life domains according to the SF-36 questionnaire before and after therapy in patients who achieved SVR at 12 weeks (treatment success; $n = 400$) are given in Table 4. This table shows that the HRQOL improved in all eight domains.

The comparison of health-related quality of life domains of patients who did not achieve SVR (treatment failure group; $n = 60$) is given in Table 5. Barring general health perception and mental health parameters, other measures of HRQOL showed no significant improvement in HRQOL before and after therapy.

Discussion

The effects of chronic HCV infection are not limited solely to the liver and a number of recent publications have presented the prevalence, morbidity, mortality, and burden of extrahepatic manifestations.[14,15] The comprehensive benefit of HCV treatment is assessed by "HCV cure" and sustained virological response (SVR) along with an improvement in health-related quality of life.[14-17] In the present study, there was a significant reduction in HRQOL in patients with HCV as compared to the control population even in the absence of cirrhosis. The difference was noted in all eight domains of HRQOL. Two Japanese studies found no characteristic subjective symptoms in patients with HCV compared to healthy controls. In these studies, subjects in an earlier phase of disease or with low viral loads may have been included.[18,19] Majority of studies have shown an association of poor HRQOL with HCV infection, and this can occur due to reasons such as the proliferation of virus within the liver, extrahepatic manifestations, and psychological impact of the knowledge of chronic disease.[20-22]

The deterioration in HRQOL in HCV infection and subsequent improvement after successful treatment has been mentioned in many studies.[23-25] The proposed reasons for improvement are (1) suppression of the direct effect of HCV replication in the brain and central nervous system affecting cognitive function; (2) an indirect effect on HCV-related inflammation.[26] There is strong evidence that the inflammatory response to HCV infection (in particular, the production of proinflammatory cytokines) plays a major role in cognitive dysfunction.[27] Patients who achieve SVR report improvements in fatigue, in their mood, or in performing their daily activities.[28] Improvement in HRQOL was related directly to SVR to treatment in the present study. Further, the improvement was significant in all eight domains of the SF-36. Recent studies suggested a comprehensive benefit after achieving SVR using DAAs.[29,30] Benefits in HRQOL are also noted after viral eradication with Pegylated-interferon (PEG-IFN) ± RBV based antiviral therapy in HCV-infected patients. This indicates that successful antiviral therapy provides a comprehensive benefit on all the pertinent hepatic and extrahepatic manifestations of HCV infection.

A concern generally expressed when considering patient-related outcomes in chronic hepatitis C patients is that improvements in patients who attain SVR may be due to the "euphoria" of being cured and may not reflect actual underlying improvements in the disease. However, in the present study, virological treatment outcomes were not informed to the patient before filling up the post-treatment SF-36 questionnaire.

The present study comprised predominant (64%) rural population. Successful follow-up until completion of therapy was possible in 96.1% (473/492) patients. Follow-ups in rural Indian population are practically very demanding due to socioeconomic issues such as casual attitude toward chronic disease, illiteracy, poverty, and poor compliance with therapy. Improved compliance to therapy and appropriate follow-up in the present study can be attributed to:

Table 3: DAAs used and response rates

HRQOL in HCV after DAA	Included in study (*n*=492)	Completed follow-up (*n*=460)	SVR±at 12 weeks (*n*=400)	Response rate (%)
Sofosbuvir±RBV	86	81	50	63
Sofosbuvir±daclatasvir	336	312	290	95
Sofosbuvir±ledipasvir	70	67	60	92

DAA: Directly acting antivirals, SVR: Sustained virologic response, RBV: Ribavirin

Table 4: SF-36 HRQOL comparison pre- and post-treatment in treatment success group (SVR attained; *n*=400)

Parameter	Pre-treatment (mean±SD)	Post-treatment (mean±SD)	*P* value
Physical function	76.4±17.6	86.7±14	<0.001
Role physical	69.4±28.2	84.4±20.2	<0.001
Bodily pain	74.6±19.4	82.5±14.4	<0.001
General health	67.8±23.6	78.2±18.6	<0.001
Vitality	52.2±21.2	60.2±14.4	<0.001
Social function	76.8±22.6	82.6±20.8	<0.001
Role emotional	77.7±25.4	84±22.4	<0.001
Mental health	75.7±15.7	79.4±19.2	<0.001

SD: Standard deviation, HRQOL: Health-related quality of life, SVR: Sustained virological response, SF-36: Short form-36

Table 5: SF-36 HRQOL comparison pre- and post-treatment in treatment failure group (SVR not attained; *n*=60)

Parameter	Pre treatment (mean±SD)	Post treatment (mean±SD)	*P* value
Physical function	77.6±16.8	79±12.2	>0.05
Role physical	66.6±31.2	68.8±26.2	>0.05
Bodily pain	78.1±17.6	77.5±16.4	>0.05
General health	68.6±22.3	60.4±20.4	<0.001
Vitality	49.2±20.4	52.4±16.6	>0.05
Social function	77.5±21.2	74.4±16.6	>0.05
Role emotional	79.5±24.2	79.2±24.2	>0.05
Mental health	76.4±16.7	72.5±20.2	<0.05

SD: Standard deviation, HRQOL: Health-related quality of life, SVR: Sustained virologic response, SF-36: Short form-36

Table 6: Salient features of the study

Salient features of study
Predominantly rural population
Use of generic DAA
Improved follow-up due to various socioeconomic reasons
HRQOL improves after achievement of SVR
Treatment failure does not improve HRQOL

DAA: Directly acting antivirals, HRQOL: Health-related quality of life, SVR: Sustained virological response

1. Increased awareness of hepatitis in health care workers
2. Large scale publicity of hepatitis C - *"Kala Pelia"* by newspapers ("Kala - black, Pelia - jaundice") which is perceived by the general population as a serious and dreaded liver infection
3. Active participation of health care workers in the screening of hepatitis infection
4. Improving attitude toward the treatment of chronic diseases
5. Cheaper oral DAA drugs for HCV
6. Free follow-up investigations for the patients
7. Regular efforts by counselor
8. Availability of phone numbers of contact
9. Improvements in rates of literacy.

In a current study 473 treatment, naïve patients underwent treatment with generic DAA and overall SVR was 87% (412/473). Low overall response rate may be due to the inclusion of sofosbuvir ± RBV cases with an SVR of merely 63%. Subsequently, daclatasvir and ledipasvir were used achieving overall >90% SVR. With the availability of velpatasvir and other newer DAAs higher rates of SVRs could be attained. However, the management of decompensated GT 3 and treatment failures still remains challenging.

The effectiveness of generic DAA may be questionable as branded drugs go through extensive evaluation for quality, safety, and efficacy before distribution in the market. In interferon-free clinical trials, branded DAAs were associated with high SVR at 12 weeks after completion of treatment (SVR12). A recent study from north India has shown comparable response rates using generic DAA.[11]

In the present study, the direct medical costs of therapy to the patient were on average 25,000 INR ($450) which included drugs, outpatient visits, and investigations. Indirect costs caused by the disease (e.g., absenteeism and early retirement) are not considered and are variable. Achieving SVR provides substantial cost benefits to health-care systems, avoids the long-term expensive sequelae of untreated chronic hepatitis C. Drug defaulters were 3.8% (n = 19) in this study. Drug defaulters can develop antiviral drug resistance and may hamper the community efforts of HCV control by spreading the disease.

HCV elimination faces numerous challenges. The initial challenge is the detection of undiagnosed population. Procuring the resources to treat the diagnosed population is the next challenge. Generic oral DAA are associated with > 90% cure and their use appears an essential step toward "HCV elimination" in the society. Drug defaulters and financial restraints will be limiting factors and despite a progressive reduction of the cost of HCV cure. It does not seem possible without free treatment or large-scale insurance to the community.

Study limitations

Many new DAAs are now available with better SVR rates. However, the aim of the study was to evaluate the HRQOL in HCV patients and effect of treatment on HRQOL [Table 6]. Hence, patients who

received the previous generation of DAAs were also included in the study. The study population in the present study does not represent a true population data and excludes a large number of the female population in the screened group. The data are from a single tertiary care center, which may be associated with a referral bias.

Conclusion

HCV infection has a substantial impact on the HRQOL. This study shows that significant improvements in HRQOL are associated with successful clinical outcomes measured as SVR. Generic DAAs are effective and should be used in resource-limited settings. Rigorous counseling and regular follow-up can increase treatment adherence.

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