Original Article

Impact of newer direct-acting antiviral drugs based on quality-adjusted life years: A prospective pharmacoeconomic study in hepatitis C patients

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Abstract

Context: The Indian government is dispensing newer direct-acting antiviral (DAA) drugs, which may have impact on hepatitis C virus (HCV) patients' quality of life (QoL).

Aims: To evaluate different DAA regimens and impact on QoL in terms of quality-adjusted life year (QALY) in HCV patients and to measure cost-effectiveness.

Methods: This prospective, observational study was carried out on patients who were diagnosed with HCV. Recruited patients were followed up until 12–24 weeks. Patients were recruited following the selection criteria. Along with demographic and drug details, the regimens used were analyzed and evaluated for cost minimization, cost-effectiveness, and cost–utility analysis. For health quality check, the Chronic Liver Disease questionnaire (CLDQ) was used which was also used for QALY assessment. Data were entered into MS Excel 2016. Difference in between the regimens for total cost was done using unpaired t-test and ANOVA test using SPSS 25.0. Overall cost-effectiveness, cost minimization, cost utility and cost of illness analysis was also calculated. $P < 0.05$ was considered statistically significant.

Results: A total of 31 patients were enrolled. A total of five drugs, namely, sofosbuvir, daclatasvir, ribavirin, velpatasvir, and ledipasvir were widely used. Sofosbuvir was most common (46.25%) component of drug combination in our study. A total of five types of regimen were used according to the genotype of patients. With 44,260.13 ± 15,884.92 INR of the total drug cost, 70.97% of patients spent around 30,000–40,000 INR for the whole pharmacotherapy. The total indirect cost was 2768.39 ± 3916.13 INR with the total direct cost of 48,660.90 ± 15,356.39 INR. The total cost including direct as well as indirect cost spent during 6-month therapy by 61.29% of patients was 40,000–50,000 INR. Based on the CLDQ score, QoL was 64.1 ± 25. Regimen 2 (sofosbuvir + velpatasvir) stood out with the lowest cost. Regimen 5 (ribavirin [200 mg] + sofosbuvir [400 mg] + velpatasvir [100 mg]) was found to be the most cost-effective. Considering 1 life year with good health after treatment, QALY was 0.31.

Conclusions: Ribavirin (200 mg) + sofosbuvir (400 mg) + velpatasvir (100 mg) was found to be the cost-effective and cost-saving regimen among DAAs.

Keywords: Hepatitis C, pharmacoeconomic, quality-adjusted life years, quality of life

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INTRODUCTION

Worldwide, the prevalence of hepatitis C virus (HCV) is 2.8%, with 1%–1.9% estimated prevalence in India,[1] causing a considerable global burden of morbidity and mortality.[2] HCV, being a silent killer, if left untreated leads to cirrhosis, hepatic carcinoma, etc., The American Association for the Study of Liver Diseases and Infectious Diseases Society of America framed guidelines on the basis of standard direct-acting antiviral (DAAs) regimen, but all these regimens include very costly drugs and some of them are yet not marketed in India, so few poor patients still stick to older regimens.[3] Now, with the arrival of new DAAs in the Indian market in March and December 2015, the recommendations for the management of HCV were accordingly revised in 2016.[4] Developing countries like India face the greatest challenges due to limited availability of testing and access to newer treatment. However, in India, several generic manufacturers provide newer DAAs at a price as low as 20,506 INR approx.[5] After the availability of DAAs, there is marked improvement in quality of life (QoL) and reduction in adverse effects.[6] There is dearth of Pharmacoeconomic and QOL studies of newer generic DAA in patients suffering from HCV infection. So ours being first of its kind of study in government setup.

Objective

The study objective was to evaluate different DAA regimens and their impact on QoL in terms of quality-adjusted life years (QALY) in HCV patients and to measure the cost-effectiveness of DAA regimens.

METHODS

This prospective, observational study was carried out on patients who visited the gastroenterology department of a tertiary care teaching hospital and were diagnosed with HCV. The recruited patients were followed up until treatment completion which extended for 12–24 weeks. The study began after obtaining permission from the Indian Council of Medical Research (ICMR) and the institutional ethics committee. Written consent of the patients was obtained in their vernacular language. Moreover, the confidentiality of the data was also maintained. Male and female patients were enrolled irrespective of their ethnicity. However, patients were recruited following the selection criteria. The patients were followed up until discharge.

Inclusion criteria

1. Patients of both gender and more than 18 years of age
2. All cases of diagnosed chronic HCV infection, along with cirrhosis complication and any complication due to HCV infection.

Exclusion criteria

1. Those who fit in the inclusion criteria, but are not consciously willing to contribute to the study
2. Any other type of viral hepatitis infections such as hepatitis B and hepatitis A infections and any concomitant disease
3. Hepatocellular carcinoma due to HCV.

Data were collected on a daily visit basis and were entered into a "Case Record Form." Data regarding demographic profile, clinical and medication data, diagnostic test, and relevant test were collected.

For pharmacoeconomic[7] evaluation, the following data were collected:

Cost of drug use per person per day and per person per month
- Direct cost: Cost of treatment, cost of investigation, etc.
- Indirect cost: Productivity losses, foregone leisure time, etc.

Cost of illness
Considering direct and indirect costs, the total cost of illness was calculated.

Cost minimization analysis
When two or more interventions are equal in terms of outcomes, the cost of each intervention was evaluated and compared. Different regimen-wise cost evaluations were done.

Cost-effectiveness analysis
Cost of treatment and resulting effect (outcome) ratio was evaluated for this analysis. Average cost effectiveness ratio was calculated.

Cost–utility analysis
Utility value and average cost–utility ratio were also calculated.

Study tool
QoL analysis was done according to the Chronic Liver Disease Questionnaire (CLDQ).[8] There were a total of six domains such as abdominal symptoms (AS), fatigue (FA), systemic symptoms (SS), activity (AC), emotional function (EF), and Worry (WO). All patients were administered the 29 questionnaire before starting the treatment and after completion of the treatment, patients filled the form on their own.

Statistical analysis

Month-wise and regimen-wise cost evaluation was assessed with mean and standard deviation. Difference in between the regimens for total cost was done using unpaired *t*-test and ANOVA test using SPSS 25.0 (IBM corp., Armonk, New York, USA). Overall cost-effectiveness, cost minimization, cost utility and cost of illness analysis was also calculated. $P < 0.05$ was considered statistically significant.

RESULTS

We enrolled 31 patients who were infected with HCV infection, with a mean ± standard deviation (SD) age of 49.83 ± 13.81 years. The most common age group affected was between 51 and 60 years (38.71%). Predominantly, male (54.83%) cases were higher than female cases (45.16%). Majority of male patients were employed in service sector (22.58%), and majority of female patients were homemaker (41.94%). The patients presented with a wide range of symptoms. Loss of appetite, fatigue, and abdominal pain were the most common symptoms. Most of the patients (64.5%) were not having any habits like smoking, tobacco chewing or drug addiction. Among the total number of patients, nine patients had hypertension. Diabetes and hyperthyroidism were present in four patients and one patient, respectively, as comorbid illness.

Out of the 31 patients, three patients had a history of blood transfusion in the past. Complete blood count, liver function tests, ultrasonography, electrocardiogram, laparoscopy, and endoscopy were the common investigations done. Apart from these, HCV diagnostic tests were also performed. Among the total number of patients, 87.09% of the patients were diagnosed with HCV ELISA alone and 12.9% of the patients were diagnosed by performing additional immunofluorescence analysis as well. Out of 16 patients who went for genotyping, 2 patients had genotype 1 and 14 patients had genotype 3.

Drug use pattern

A total of five drugs, namely, sofosbuvir, daclatasvir, ribavirin, velpatasvir, and ledipasvir were widely used in our setup. Sofosbuvir was prescribed majorily at 46.25%, and the least prescribed drug was ledipasvir (1.25%) [Figure 1]. A standardized 3-month regimen was started in all patients, and patients who did not show virological improvement were given 6-month therapy. Out of the total 31 patients, 6 patients were given 6-month therapy and the other 25 needed only 3-month therapy.

Regimens used for the patients were as follows:
- Regimen 1: Sofosbuvir + daclatasvir
- Regimen 2: Sofosbuvir + velpatasvir
- Regimen 3: Sofosbuvir + ledipasvir
- Regimen 4: Ribavirin + sofosbuvir + daclatasvir
- Regimen 5: Ribavirin + sofosbuvir + velpatasvir.

Sofosbuvir (Hepcvir), daclatasvir (Hepcdac), and ribavirin were administered as a single-drug combination, whereas valptasvir and ledipasvir were administered in "fixed-drug combination" along with sofosbuvir under the brand name of Velasof and Ledihep, respectively. The total number of drugs administered during the 6-month period was 240. All drugs were administered by oral route. Frequency of majority of the drugs were once a day with an exception of ribavirin which was prescribed five tablets a day. Per-day dose of sofosbuvir, daclatasvir, velpatasvir, Ledipasvir, and ribavirin was 400 mg, 60 mg, 100 mg, 90 mg, and 1000 mg, respectively.

Monthly analysis of drug use pattern showed that during the first 3 months, a total of 62 drugs were administered per month irrespective of any regimen. The average of total drug cost for the 1st, 2nd, and 3rd months was 6120.92 ± 3053.42 INR, 6089.67 ± 2870.88 INR, and 5935.43 ± 2969.09 INR, respectively. Only six patients needed additional three months therapy as there was inadequate response of drugs in them. In these six patients, additional 18 number of drugs was prescribed per month. Average of total drug cost for 4th month was 1191.17 ± 2733.20 INR, for 5th month was 1208.95 ± 2749.86 INR, and for 6th month it was 1191.17 ± 2733.20 INR. The total drug cost was 44,260.13 ± 15,884.92 INR for the whole duration of treatment. Nearly 70.97% of the patients spent around 30,000–40,000 INR for the whole pharmacotherapy [Figure 2].

Considering regimen wise, the highest total drug cost was found in regimen 4, with 73,838.69 ± 8955.91 INR. The minimum total drug cost was observed in regimen 2, with 35,266 ± 1038.03 INR. All the other regimens are summarized in Table 1.

The difference between regimens and months in terms of total drug cost is summarized in Table 2 which also shows an additional 3-month therapy which added on drug cost burden on the patients.

The difference between regimens in terms of *P* value is summarized in Table 3. High statistical significance (*P* = 0.0001) was found between regimens 1 and 4. The combination regimens 4 and 2, 4 and 3, as well as 4 and 5 also showed statistical significance (*P* = 0.0012, 0.0013, and 0.0013, respectively) which shows that regimen 4 is costlier than the other regimens.
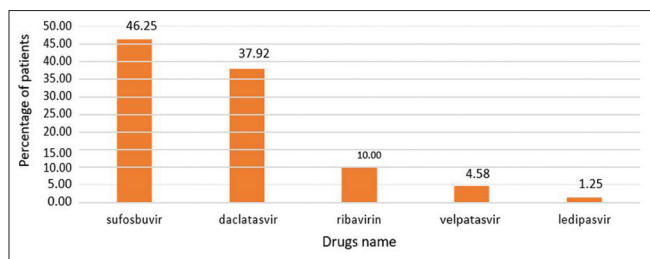
Figure 1: Drug use pattern in hepatitis C patients

Table 1: Regimen-wise distribution of total drug cost (INR)

Type of regimen	Total drug cost (INR), mean±SD
Regimen 1	37,452.38±5687.49
Regimen 2	35,266±1038.03
Regimen 3	36,000±0
Regimen 4	73,838.69±8955.91
Regimen 5	36,000±0

SD=Standard deviation

Total indirect cost

Indirect cost included transportation cost and loss of productivity cost, in which 64.52% of patients spent up to 1000 INR. The total indirect cost was 2768.39 ± 3916.13 INR.

Total direct cost

Direct cost included total drug cost for 6 months, investigational cost, and other expenses such as registration cost and case file cost. A majority of 61.29% of patients had spent 40,000–50,000 INR for the whole therapy, with 48,660.90 ± 15,356.39 INR.

Total cost

Total cost included direct and indirect cost spent during the 6-month therapy. Majority of the patients (61.29%) had spent 40,000–50,000 INR. The mean ± SD was 51,429.29 ± 17,093.17 INR.

Regimen wise, almost double cost was found with regimen 4 with 82,962.02 ±12,096.94 INR, and minimum cost was found with regimen 2; other values are tabulated in Table 4.

Quality-of-life analysis

QoL analysis was done according to the CLDQ score specifically formatted for chronic liver illness. A total of 29 questionnaires were filled up by the patients before the start of treatment and at the end of treatment. The QoL was 64.1 ± 25.00. Irrespective of the regimen, domain-wise mean ± SD for AS, fatigue, SS, activity, EF, and worry was 7.55 ± 3.49, 7.58 ± 4.87, 14.19 ± 9.62, 7.06 ± 3.26, 20.48 ± 8.36, and 7.26 ± 4.53, respectively. Table 5 shows the values of individual domain according to regimen. High statistical significance ($P = 0.0001$) was found in SS domain between regimens 1 and 4. Whereas, statistically significant was seen in FA domain between regimen 2 and 4.
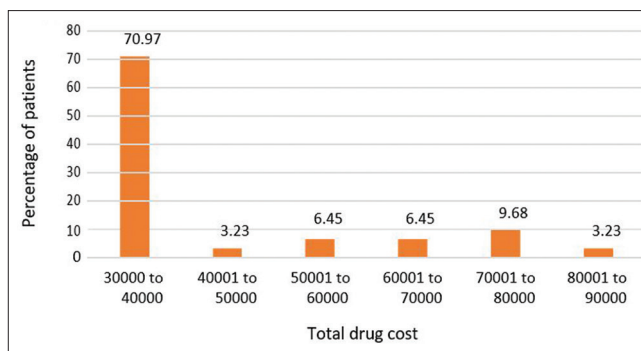

Figure 2: Frequency of total drug cost (INR)

Pharmacoeconomic analysis

All the regimens were equally clinically effective, but the cost of regimen 2 was low compared to other regimens, so it should be preferred over others. The maximum cost was found in regimen 4 [Table 6]. The average cost-effectiveness ratio of the regimens was in the following order: 5 > 2 > 3 > 1 > 4, which indicates that regimen 5 is most cost-effective [Table 7]. Transform utility value was calculated from before- and after-utility values according to the regimen. Utility value is an important parameter for the calculation of QALY; hence, regimen-wise utility value distribution is displayed in Figure 3. Considering 1 life year with good health after treatment, QALY was 0.31 [Figure 4].

DISCUSSION

Previously, pharmacotherapy for HCV is based on interferon regimen which has low efficacy and more adverse effects. From the year 2015 onward, the availability of newer DAAs has changed the HCV treatment paradigm, leading to hope of elimination of this viral infection. As such, cost of these newer drugs is a big debatable topic.

Demographic profile in HCV patients noticed similar kind of results as observed in a study done by Gupta *et al*.[9] The mean age of patients with HCV was 49 years, and males (69%) outnumbered females. Ours being a government setup, majority of the patients who came to the hospital were either driver or worker on daily wage basis by profession. The major risk factors for HCV are alcohol, intraveneous drug abuse, dialysis, any needle injury, and tattoos, which was significantly found in the study by Gupta *et al*.[9] In our setup, patients didn't reported history of alcohol addiction, only 3 patients reported positive history of blood transfusion.

In Gupta *et al*.'s[9] study, a majority of 21% of patients were found with the comorbidities of diabetes, whereas

Table 2: Total drug cost(INR) regimen-wise and month-wise

	Mean±SD				
	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Regimen 5
1st month	12,714.28±1927.24	11,250±1060.66	12,000±0	11,000±2683.28	12,000±0
2nd month	12,500±1870.82	12,016±22.62	12,000±0	11,172±2716.15	12,000±0
3rd month	12,238.09±2071.34	12,000±0	12,000±0	11,166.66±2714.16	12,000±0
4th month	0.00	0	0	13,500.02±1224.78	0.00
5th month	0.00	0	0	13,500±1224.74	0.00
6th month	0.00	0	0	13,500±1224.74	0.00

SD=Standard deviation

Table 3: Difference between regimens in terms of total drug cost (INR)

Regimen	1	2	3	4	5
1	1	0.6004	0.7272	0.0001[a]	0.7272
2	0.6004	1	0.4226	0.0012[b]	0.4226
3	0.7272	0.4226	1	0.0013[b]	1
4	0.0001[a]	0.0012[b]	0.0013[b]	1	0.0013[b]
5	0.7272	0.4226	1	0.0013[b]	1

P value [a]=statistically highly significant ($P<0.001$), [b]=statistically significant ($P<0.05$)

Table 4: Total cost in INR according to regimen

Type of regimen	Total cost, mean±SD
Regimen 1	44,154.95±5534.93
Regimen 2	40,726±376.18
Regimen 3	43,020±0
Regimen 4	82,962.02±12,096.94
Regimen 5	44,810±0

SD=Standard deviation

Table 5: Chronic Liver Disease Questionnaire score according to domain and regimen wise

Domain	Mean±SD				
	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Regimen 5
AS	7.85±3.2	10±4.2	9±0	5.5±4.4	7±0
FA	7.66±4.5	12.5±6.3	8±0	4.5±4.5	14±0
SS	15.43±3.2	14±2.8	15±0	9.17±3.2	18±0
AC	7.29±10.8	9±4.2	8±0	5±6.1	10±0
EF	20.76±8.6	24±4.2	21±0	17.5±10	25±0
WO	6.86±4.7	8±1.4	7±0	7.67±5	12±0
Total	65.86±24.1	77.5±20.5	68±0	49.34±29.9	86±0

AS=Abdominal symptoms, FA=Fatigue, SS=Systemic symptoms, AC=Activity, EF=Emotional function, WO=Worry, SD=Standard deviation

Table 6: Cost minimization analysis

Regimen	Average cost of regimen (INR)
Regimen 1	44,154.95
Regimen 2	40,726
Regimen 3	43,020
Regimen 4	82,962
Regimen 5	44,810

Table 7: Regimen wise QoL and ACER ratio

Regimen	Average cost of regimen	QoL	ACER
Regimen 1	44,154.95	65.86	670.43
Regimen 2	40,726	77.5	525.49
Regimen 3	43,020	68	632.64
Regimen 4	82,962	49.33	1681.77
Regimen 5	44,810	86	521.04

QOL=Quality of life, ACER=Average cost-effectiveness ratio

in our study, 29% of the patients had hypertension. All patients were diagnosed with HCV ELISA test in our government setup; among them, 12.9% of patients who were affordable referred for genotype testing at a private sector. A total of 16 patients had genotyping test, of which 14 patients (87.5%) came out with genotype 3 and 2 patients (12.5%) with genotype 1, which was found to be similar to the finding of Chakravarti *et al.*'s[10] study done in Delhi, India.

All patients were started on sofosbuvir + ribavirin regimen or sofosbuvir + daclatasvir, or sofosbuvir + velpatasvir regimen. Hence, sofosbuvir was the most commonly administered drug (46.25%), which correlated with a study done by Bhattacharya and Roy;[11] this finding emphasized that genotype 2 patients must be started on this regimen. For patients who failed to respond to this regimen, another add-on drug namely daclatasvir or velpatasvir or ribavirin was prescribed. Among the total number of patients, 25 patients had recovered with 3-month therapy and only 6 patients needed 6-month therapy, with one newer add-on DAA drug. The most commonly used drug combination was sofosbuvir + daclatasvir. Excellent viral eradication result was found with this regimen, as discussed in a review done by Zeuzem *et al.*[12]

Monthly analysis of total drug cost depicts that for the first 3 months patients expenditure was on an average 12,000 INR/month and for extended 3 months treatment additional 1500 INR per month must be spent. The total overall average cost for the whole pharmacotherapy was 30,000–40,000 INR. Regimen wise, the total drug cost was found to be maximum in regimen 4 with an average of 73,838 INR and lowest for regimen 2 with 37,453 INR, which was very less compared to the stated price mentioned in the "rights-based analysis" done by Grover *et al.*, which was 77,700 INR for previous regimen.[13] In our government setup, generic companies provided these regimens with discounted price, which may explain this discrepancy. *P* value for the total drug cost was found highly statistically significant between regimen 4 and regimen 1.
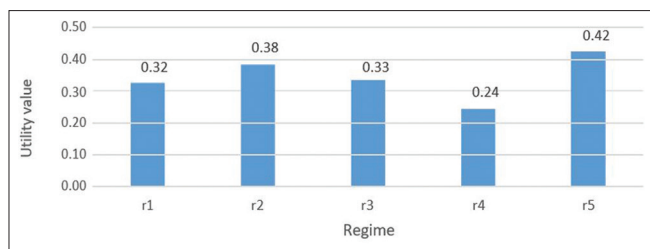
Figure 3: Utility value regimen wise

Figure 4: Quality-adjusted life years

Investigational cost was maximum i.e. 10, 000 INR for for genotype testing. In our study, 16.13% of patients spent zero INR as they avail government facility which is free of cost. Regime wise, the maximum investigational cost was spent in regimen 5. Transportation cost spent by majority of the patients was a maximum of 1000 INR, and regimen wise, regimen 3 costed the maximum.

The maximum total indirect cost expenditure was 15,000 INR. Nearly 64.52% of the patients spent only up to 1000 INR as majority of the patients were older and retired, so productivity loss is less. Transportation expenditure was also less as most of the patients were nearby locals. Indirect cost was highest for regimen 4 and lowest with regimen 2. In total direct cost, 61.29% of patients spent 40,000–50,000 INR. Total direct cost was maximum in regimen 4 and lowest with regimen 3. Total cost per patient was found 40,000–50,000 INR for treatment duration which was cheapest as compared to study done in Iran by Zare *et al*.[14] Regimen 4 was costlier and regimen 2 was cheapest among all.

QoL was evaluated with the CLDQ scale, which shows domain-wise difference in regimen in accordance with the study done by Chang *et al*.[15] Highly statistical significance ($P = 0.0001$) was found in SS domain between regimens 1 and 4.

Pharmacoeconomic analysis results emphasized that regimen 2 was cost-effective among all regimens, and the cost-effective regimen was regimen 5 in patients treated for 6-month therapy. Cost–utility analysis showed that the average maximum utility value was found with regimen 5 and lowest with regimen 4. Overall, QALY gained during the study period after treatment was 0.31, which correlated with the study done by Stein *et al*.[16]

This is first of its kind of pharmacoeconomic study in HCV patients in western Gujarat, specifically in a government setup. In future, when other newer DAAs arrive in the Indian market, this study can make one of the bases for economical analysis.
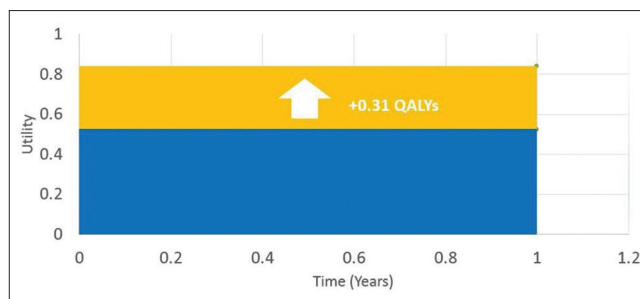
CONCLUSIONS

Newer DAAs such as sofosbuvir, velpatasvir, daclatasvir, and ledipasvir are now easily available in India. Hence, with these higher effective drugs, elimination of infection is hopeful. QoL by the CLDQ scale also showed drastical domain-wise improvement after treatment. Pharmacoeconomically, sofosbuvir + velpatasvir was cheapest using cost minimization analysis, whereas regimen sofosbuvir + velpatasvir + ribavirin was the cost-effective ones using cost- effectiveness analysis. Utility value was found higher with regimen sofosbuvir + velptasavir + ribavirin. Overall, a QALY of 0.31 was gained during the study period.

Conflicts of interest
There are no conflicts of interest.

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