Muaed J.Alomar et al /J. Pharm. Sci. & Res. Vol. 10(3), 2018, 501-505

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Safety and Economic Evaluation of Patients Treated for Hepatitis with Antiviral Daclatasvir and Sofosbuvir Combined Vs. Ledipasvir/ Sofosbuvir 90mg/400mg in a medical institution in The U.A.E.

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Abstract

Aims: The pharmacoeconomic evaluation of Hepatitis C Virus (HCV) medications is necessary to assess the clinical benefits and cost-effectiveness of newer treatments for chronic (HCV) infection. This study determines the cost-effectiveness of Daclatasvir and Sofosbuvir compared with Harvoni (Ledipasvir/Sofosbuvir 90mg/400mg) which is a current treatment for Chronic Hepatitis C (CHC).

Methods: A retrospective quantitative comparative study was carried out by comparing patients' related health and economic status of HVC on two specific regimens; the first regimen is "Daclatasvir plus Sofosbuvir in patients infected with HCV. The second regimen is "Harvoni" once daily for 12 weeks. Data was collected anonymously from electronic patients' files.

Results: The use of Sovaldi 400mg and Daklinza 60mg compared to Harvoni alone was cost-effective due to the decreased frequency of concomitant disease progression and their associated costs. The clinical outcome of groups A & B, showed some differences in viral load in the first few weeks which was equalized by continued treatment for 8 weeks.

Conclusion: Sofosbuvir- and Ledipasvir-based treatments would significantly lessen the clinical burden of HCV. The new treatments are more cost-effective for patients who have HCV genotype 1, are newly infected, or are younger.

Key words: Cost, Effectiveness, Hepatitis, Virus, Harvoni, Sofosbuvir, Ledipasvir

INTRODUCTION

Hepatitis C Virus (HCV) infection is the main cause of cases of viral hepatitis; and current data suggests that there are approximately 130-170 million cases worldwide. While there are different estimates given by different countries, they have not changed much since the original estimates were given by WHO in 1997 [1]. Although HCV affects people of all age groups, it is most commonly seen in young adults, with the highest proportion of incident cases being among Caucasians; however, the highest incidence rates were among African-Americans and Hispanics [2,3,4]. Apart from causing continual liver infections, HCV is well-documented as a risk factor for liver cirrhosis and liver cancer [5].

The Arabian Gulf area consists of six nations: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates (UAE). These nations share common objectives, and together constitute the Gulf Cooperation Council (GCC) [6]. The Middle East and North Africa (MENA) area seem to have the highest reported prevalence of anti-HCV, compared to Western Europe, Australia and Northern America which have the lowest [7,8].

Economic evaluation in healthcare is the study of the economic value of pharacotherapuetic outcomes using a monetary value. There is an increasing pressure on healthcare providers to stop merely focusing on the clinical outcomes of a medication and instead focus on both clinical effectiveness and cost-effectiveness[9]. Cost-effectiveness ratios (CER) calculated for the use of peginterferon alpha 2b plus ribavirin (to treat heapatitis C) decreased per life year saved and per quality-adjusted life year gained, and increased the threshold age for which therapy was cost effective from 64 to 69 years[10,11]. Mortality and morbidity associated with HCV infection have increased in numbers since 1965. The reason for this increase may due to readily obtainable injectable therapies and the use of illegal injectable drugs [12, 13]. Improvements in the utilization of antiviral treatments may reduce mortality, improve renal and cardiovascular outcomes in diabetic patients, and may reduce the risk for hepatocellular cancer [14, 15].

There are currently six genotypes of HCV that have been identified [17]. The most common genotype in the United States is genotype 1 which accounts for 72% of cases; genotype 2 accounts for 16-19% of cases and genotype 3 accounts for 8% to 19%. The remaining 1-2% has other genotypes [18]. The incubation period for acute hepatitis is anywhere in the range of two weeks to six months, and most patients remain asymptomatic. Early detection of HCV is uncommon, and the disease may go unnoticed until patients have developed serious liver damage. If it is not dealt with promptly, the individual will develop the infection. In the United States, around 3.2 million individuals have persistent HCV disease[19]. Chronic hepatitis C is the main cause of cirrhosis and hepatocellular cancer [19, 20, 21]. In the last five years, treatment for HCV has developed rapidly, particularly for genotype 1. Previously, the suggested treatment was interferon (alfa-2a or alfa-2b) week by week infusions in addition to weight-based measurements of oral ribavirin, both for 48 weeks, which resulted in a sustained virological response (SVR) rate of 40-50% [22]. The first generation of direct acting antiviral (DAA) drugs followed, in the forms of protease inhibitors telaprevir and boceprevir[23]. In a 2011 study, after their approval for usage in the treatment of HCV, telaprevir, when compared to peginterferon–ribavirin showed a significant increase in the rates of sustained virologic response [24]. When treated with a combination of protease inhibitors with interferon alfa 2a and ribavirin, there was an increased probability of sustained virologic response relative to interferon and ribavirin alone from 40-50% to 67-75% [25,26]. Following the introduction of first generation DAAs, the second generation of DAA drugs "simeprevir" was approved for use in 2013. Also in 2013, Sofobuvir, (a nucleotide analogue inhibitor of the viral RNA-dependent RNA polymerase (NS5B)) was also approved for use in HCV genotypes 1-4 and Ledipasvir was given approval in 2014. The ledipasvir/sofobuvir combination (Harvoni) may be used alone without interferon or ribavirin [27, 28, 29,30].

In the previous decade; there have been numerous advances in the treatment of HCV. Harvoni is a once-daily, treatment that has been approved for use to treat HCV genotype 1. The medicine can be taken with or without food. It does not require the co-

administration of interferon and/or ribavirin and has shown improved SVR rates toward the end of post-treatment week 12 contrasted with verifiable controls. From March 2015, the cost of a four-week supply of Harvoni was $37,800 compared to the cost of Viekira Pak, which was $33,328 for treatment for the same period. For a 12-week course, the total cost for Harvoni would be $113,400 compared to $99,983 for 12 weeks of Viekira Pak. However, the price difference may be reduced if the patient receiving Viekira Pak also requires the addition of ribavirin if they also have cirrhosis [31].

Aim of the study:

To determine the cost-effectiveness of Daclatasvir and Sofosbuvir which are the current standard treatment in infected patients with chronic hepatitis C (CHC) compared with Harvoni (Ledipasvir/Sofosbuvir 90mg/400mg) which is a current treatment for the same disease. This study is based on Cost–Effectiveness Analysis (CEA) which is a type of economic analysis that compares the relative costs and outcomes of the different therapies.

Specific Aim(s):

A pharmacoeconomic evaluation of the use of "Daclatasvir (an HCV NS5A replication complex inhibitor) plus Sofosbuvir (a nucleotide analogue HCV NS5B polymerase inhibitor) both once daily, as regimen one, and "Harvoni" (Ledipasvir/Sofosbuvir 90mg/400mg) once daily, as regimen two, for patients infected with HCV genotype 1, & 4 for a period of 12 weeks in the management of hepatitis C infection. Quantitative comparative studies using cost effectiveness analysis "CEA" describes the risk factors for each group and makes comparisons between group 1 and group 2 and the specific regimen for each group.

MATERIALS AND METHODS

It is a retrospective quantitative comparative study which was carried out by comparing patients' related health status of HVC who are on two specific regimens; the first regimen is "Daclatasvir (an HCV NS5A replication complex inhibitor) plus Sofosbuvir (a nucleotide analogue HCV NS5B polymerase inhibitor) in patients infected with HCV. The second regimen is "Harvoni" (Ledipasvir/ Sofosbuvir 90mg/400mg) once daily for 12 weeks. Data collection forms will be used in order to collect data. The data includes: HVC patients who are on the aforementioned regimens, number of visits, all medical tests, co-morbidities, health outcomes, costs of treatment, age and gender. A detailed data collection form was used. Data was collected anonymously from the electronic records of patients' files.

The results of the study will be about the most cost-effective regimen for the treatment of hepatitis between the aforementioned two regimens. Either both will give the same pharmacotherapeuatic results, which means the less costly regimen will be suggested or one of the regimens will produce better pharmacotherapeuatic results which legitimize the costs.

Inclusion Criteria:

The following patients were included in the study:

1. Adult, male & female, with or without other medical conditions.
2. A background marked by chronic HCV
3. Inability to accomplish a virology or biochemical reaction amid past interferon treatment (with or without ribavirin)
4. Patients with high serum AST or ALT in the past 6 months
5. Aged 30 or over

Exclusion Criteria:

The following patients were excluded from the study:

1. Patients under 30 years of age
2. Patients with uncontrolled diabetes mellitus
3. Patients with psychiatric problems
4. Alcoholic patients
5. Patients using illegal drugs
6. Patients who failed to give educated consent
7. Patients who failed or were unwilling to undergo a liver biopsy.

A total of 100 patients were selected and started treatment during the study period. Genotype 1 HCV was the most widely recognized genotype.

Data was analyzed using SPSS version 22 & Minitab. Results were presented using absolute figures and percentages.

The target of treatment is to reduce the patient's HCV viral burden to imperceptible levels. An essential goal of this study was to evaluate the pharmacoeconomic value of using two different regimens for the treatment of hepatitis.

The study was carried out over six months, starting from 01 June, 2016 to 01 September, 2016. The study was conducted in two medical institutions (first one is called MI1 and the second one is called MI2). The total number patients required for the study was 100. Fifty patients were put on regimen one (group A) and fifty were given regimen two (group B) for genotypes 1 &4. Since it was a small scale study, population data was randomly collected from persons with the disease and various statistical methods were used to analyze the data namely: t-test, GLM Univariate test, cross tabs and the Median test. All the above processes were carried out using SPSS for Windows (version 22-evaluation version)

RESULTS

Two lots of data were obtained from the two groups: Group A (patients treated with Sofosbuvir 400mg + Daclatasvir 60mg) and Group B (patients treated with Harvoni). This was done in order to evaluate whether the response observed was as a result of the treatment or the difference in the regimen used. The mean age in the two groups was 49.6 for group A and 52.5 for group B. One hundred patients were involved in the study and randomly grouped into Group (A) and Group (B) groups in the ratio of 1:1. Most of the patients (59%) on average in the two groups were 30 to 40 years and only 4% were above 70 years. The ratio of women to men in the study for the two groups was 0.85:1.08 with more women than men.

In the two groups, most of the patients had viral rashes for 48-72hrs before the treatment began. The main variables that were taken into consideration were: the period taken for full crusting, complete healing and the reduction in the acute pain. This was summarized as shown in table 1.

The analysis of 100 patients included in this study revealed that most were female (74%) compared to male (26%). The majority of the participants were Emirati (95%), followed by Egyptians (4%), and Indians (1%). The most common genotype was 1a (68%), with. 67% of Emiratis having type 1a. Most participants (72%) were from MI2, and 28% were from MI1. Regarding the patients' ages, 84% of the participants were old and 16% were young. All patients were non-smokers who did not drink alcohol.

Liver cirrhosis was present in the following percentages: cirrhosis (54%), non-cirrhosis (45%), graft cirrhosis (1%). According to genotype, 37% of genotype 1a participants were non-cirrhosis patients, 30% were cirrhosis patients, and 1% had graft cirrhosis. Of the genotype 4 participants, 5% were non-cirrhosis patients, and 24% were cirrhosis patients).

Of the MI2 participants, 41% had cirrhosis, 1% has graft cirrhosis, and 30% were non-cirrhosis patients. Evidence of portal hypertension of splenomegaly, esophageal varices, and thrombocytopenia were present in 17%, of patients and absent in the rest. In MI1, 4% of the participants had evidence of portal hypertension, splenomegaly, esophageal varices, thrombocytopenia & 23% showed none. 13% of the participants in MI1 had cirrhosis, while the rest did not. Most Emirati

patients used Sofosbuvir (Sovaldi) 400mg once daily + Ledipasvir 90mg once daily (48%) & Sofosbuvir (Sovaldi) 400mg once daily + Daclatasvir (Daklinza) 60mg once daily (47%). Egyptian patients used Sofosbuvir (Sovaldi) 400mg once daily + Daclatasvir (Daklinza) 60mg once daily (2%) & Indian patients used Sofosbuvir (Sovaldi) 400mg once daily + Daclatasvir (Daklinza) 60mg once daily (1%).

The cost for each patient per day at MI2 of Sovaldi 400mg is (2029AED) + Daklinza 60 mg (1490 AED) = (3519 AED). Of the total cost, 35% is paid by the patient. The cost for each patient per day at MI1 of Sovaldi 400mg (2029 AED) + Daklinza 60 mg (1490 AED) = (3519 AED). Of the total cost, 15% is paid by the patient. The cost for each patient per day at MI2 of Harvoni is 2271 AED. Of the total cost, 37% is paid by the patient. At MI1, the cost for each patient per day of Harvoni is 2271 AED. Of the total cost, 13% is paid by the patient. The comparison between groups A & B can be seen in table (2).

Clinical Outcomes

The clinical outcome of groups A & B, showed some differences in viral load in the first few weeks. This was then equalized by continued treatment for 8 weeks. The statistical significant differences between viral load after every two weeks between the two groups is shown in table (3). Table (3) also shows the statistical significance of the differences between the outcome in the viral load after 12 weeks for each group compared with the baseline.

Adverse Drug Reactions

When the side effects & the ages of the two groups at the two different hospitals, using different DAAs (direct antiviral agents) were compared (using one way ANOVA test (p= 0.4)) there was no statistically significant difference. (For more details about side effects, see table 4).

The evidence of portal hypertension was 21%, but most of the patients had no portal hypertension (78%), only 1% showed evidence of splenomegaly, esophageal varices, and thrombocytopenia.

The outcome & the results of treatment of the two groups at the two different hospitals, using different DAAs were using T-test (p= 0.1). There was no statistically significant difference between males & females.

Table (1): Complete Treatment:

	Drug	Mean	SD	T	P
Full crusting	A	9.1	1.3439	-3.912	.000
	B	10.02	.9792		
Healing	A	20.46	3.5812	-1.071	.287
	B	21.12	2.4796		
Loss of pain	A	22.68	4.5957	-1.179	.241
		23.8	4.8990		

Table (2) : Cost comparison between two groups:

Cost comparison	S+D (group A)		S+L(Harvoni) (group B)	
	Cost	N	Cost	N
UP-AUH	2029+1490= 3519 AED	35 on MI2 15 on MI1	2271 AED	37 on MI2 13 on MI1
Total cost	170436+125160= 295596 AED		190764 AED	
Total W	12 W		12W	

D(OD): Daclatasvir 60mg once daily , S(OD): Sofosbuvir 400mg once daily , L(OD): Ledipasvir 90mg once daily, (N): Number of patients , UP: Unit Price per day, W: Weeks, MI2, MI1.

Table(3): Clinical Outcome Comparison (Detectable Virus):

WKS	Patients on S+D Mean VL	Patients on S+L(Harvoni) Mean VL	Statistical significant: (one – sample T test) (independent – samples T test)
VL (baseline by IU/ml)	3601084.36	3353956.26	p-value= 0.02 (one – sample T test)
VL (W2 by IU/ml)	82.17	54.27	p-value=0.051 (independent – samples T test)
VL (W4 by IU/ml)	20.80	4.27	p-value= 0.0001 (independent – samples T test)
VL (W8 by IU/ml)	1.02	1.06	p-value= 0.41 (independent – samples T test)
VL (W12 by IU/ml)	1.00	1.00	---
VL (PT4w by IU/ml)	1.00	1.00	---
VL (PT12wby IU/ml)	3.31	1.00	p-value= 0.44 (independent – samples T test)
Therapeutics Out Come For Each Group Compares With Baseline (12 W Vs. Base Line)	Baseline(3601084) W12(1.00)	Baseline(3353956) W12(1.00)	p-value= 0.02 (one – sample T test)

D(OD): Daclatasvir 60mg once daily , S(OD): Sofosbuvir 400mg once daily , L(OD): Ledipasvir 90mg once daily, (N): Number of patients , SVR: Sustained Virological Response , W: Weeks, VL: viral load.

Table (4): Adverse Drug Reactions:

Title of the event or side effect	Patients used S+D Group A	Patients used S+L (Harvoni) Group B	Statistical significance (No statistical significance between the two groups) (Pearson R of correlation p- value= 0.157) (spearman correlation p- value= .0157)
Anemia	16	8	(Pearson R of correlation p- value= 0.157) (Spearman correlation p- value= .0157)
Hyperbilirubinemia	7	8	(Pearson R of correlation p- value= 0.157) (Spearman correlation p- value= .0157)
Fatigue	2	1	(Pearson R of correlation p- value= 0.157) (Spearman correlation p- value= .0157)
Dizziness	4	0	(Pearson R of correlation p- value= 0.157) (Spearman correlation p- value= .0157)
Headache	2	1	(Pearson R of correlation p- value= 0.157) (Spearman correlation p- value= .0157)
Abdominal pain/mood swings	1	1	(Pearson R of correlation p- value= 0.157) (Spearman correlation p- value= .0157)
Weakness/itching	4	0	(Pearson R of correlation p- value= 0.157) (Spearman correlation p- value= .0157)
Skin bruises	1	0	(Pearson R of correlation p- value= 0.157) (Spearman correlation p- value= .0157)

D (OD): Daclatasvir 60mg once daily, S (OD): Sofosbuvir 400mg once daily, L (OD): Ledipasvir 90mg once daily. In general, group B had a lower incidence of adverse drug reactions than group A

DISCUSSION

Hepatitis C infection (HCV) is the most widely recognized chronic, blood-borne infection and the main cause of liver transplants in the United States [32]. There are currently around 3.2 million people who have an HCV infection in the United States [33]. In a study conducted on a population of 195 000 people, between September 2014 and September 2015, patients with chronic HCV who had completed treatment with the new DAAs (Sofosbuvir with Simeprevir; Sofosbuvir with Daclatasvir; Dasabuvir, Ombitasvir, Paritaprevir and Ritonavir) were chosen. At the end of treatment, 100% of patients had an undetectable viral load and 91.4% of them achieved SVR12 [34].

Some new medications including Harvoni, Olysio + Sovaldi, Viekira Pak and Sofosbuvir-based regimens have been approved by the United States Food and Drug Administration (FDA) giving more alternatives to chronic hepatitis C patients. Clinical trials have demonstrated that the new medicines expanded the SVR rate from 80 % to 95 %; however, with a significant increase in cost. Specifically, the current cost of a 12-week course of Sofosbuvir is almost US$84,000. Viekira Pak was shown to be cost-effective for the treatment of genotype 1 in patients without cirrhosis, while Harvoni was cost-effective for genotype 1 in patients with cirrhosis. When compared with Viekira Pak, Sofosbuvir-based treatments were not found to be cost-effective. It was suggested however, that a 30 % decrease in Sofosbuvir price would alter this result [35].

In a study reviewing the use of Ledipasvir/Sofosbuvir it was found that a sustained virological response after 12-weeks of treatment was observed in 99% of patients thus offering a significant advance in the treatment of chronic hepatitis C.

Oral Ledipasvir/Sofosbuvir was, generally, well-tolerated by patients with chronic hepatitis C, with the most frequently reported adverse reactions being nausea, anemia, upper respiratory tract infection, and headache [36, 37].

A study carried out on the cost-effectiveness of Boceprevir, in patients previously treated for chronic hepatitis C genotype 1 infection, showed Boceprevir was expected to improve the quality-adjusted life-years and decrease the risk of developing liver problems. Furthermore, Boceprevir-based treatment was found to be more cost-effective when compared to peginterferon-ribavirin alone. The use of Boceprevir and peginterferon-ribavirin resulted in less cases of hepatic disease at a lower associated cost, but greater total cost. This demonstrated that although the most expensive choice, a combination is the most effective treatment for patients with chronic HCV [38].

Generally, the main limiting factor against the use of antiviral therapies is the cost involved in the process. For instance, in the United States a three month supply of DAAs can cost anywhere from $83,000 - $ 153,000[39]. In the U.A.E., the cost of treatment ranges from $618 to $958 per day for Harvoni and Sovaldi respectively.

For this reason, even though these medications offer a cure to patients the related costs are still very high. According to various pharmaceutical firms, the high cost is due to the research & development expenses rather than the manufacturing cost.

A study was conducted to evaluate the efficacy of a combination tablet containing Ledipasvir (90mg) and Sofosbuvir (400 mg), administered orally for 12 weeks on patients with chronic HCV infection and HIV co-infection. Patients were expected to achieve SVR 12 weeks after treatment completion (SVR12). Those who did not, were offered additional treatment. The study resulted in high rates of SVR after treatment completion [40].

Treatment for HCV contamination is changing rapidly. Results from early studies demonstrated that Sofosbuvir or Simeprevir could be utilized in combination with interferon and Ribavirin for the treatment of HCV genotype 4 infection. In this way, Sofosbuvir and Ribavirin alone for 12–24 weeks appeared to bring about 59–100% SVR in patients with HCV genotype 4 who were previously untreated and patients who had previously received treatment, with comparative results in HIV/HCV genotype-4-co-contaminated patients.

CONCLUSION:

The utilization of Sofosbuvir- and Ledipasvir-based treatments would significantly lessen the clinical burden of HCV. The new treatments are more cost-effective for patients who have HCV genotype 1, are newly infected, or are younger. The utilization of Sofosbuvir-and Ledipasvir-based treatments will significantly decrease HCV-related complications and are cost-effective in the majority of patients. However, treating all HCV patients in tertiary clinics in the U.A.E. would place a huge financial burden on both private and government suppliers. Extra assets are needed to help HCV patients with these regimens.

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