Pharmacoeconomic analysis of treatment of patients infected with hepatitis C virus

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Abstract: Hepatitis C infection imposes a high economic burden globally. It has been estimated that in 2012, the healthcare cost of Hepatitis C virus (HCV) was $6.5 billion. Furthermore, it has been projected that the cost will reach at $9.1 billion by the year 2024.Frequency of hepatitis C in Pakistan is significantly higher (4.5%) when compared to the populations like India (0.7%), Nepal (1.0), Myanmar (2.5%), Iran (0.8%), China (1%) and Afghanistan (1.1%). The current standard of care for chronic infection with hepatitis C virus is 24 or 48 weeks of therapy with Pegylated interferon-alfa-2a (Peg INF) +Ribavirin (RV) or Interferon alfa-2a (INF) + RV. The objective of this study was to determine that which combination is more effective and the gain in sustained virologic response (SVR) is worth the incremental cost. In total 84 patients were enrolled who received current standard treatment of care for chronic infection with HCV either 24 or 48 weeks of therapy with Peg INF + RV or INF + RV. A pharmacoeconomic analysis was done including fixed and variable cost (comprising concomitant therapies, emergency visits and hospital admissions) of both treatment regimens were calculated and compared with the SVR accomplished by the patients. It was concluded that the Peg INF + RV is cost effective as compared with conventional INF + RV for the treatment of adult patients infected with HCV genotype 3a under a varied array of possibilities regarding treatment costs and effectiveness.

Keywords: Hepatitis C, Sustained virologic response, cost effectiveness, genotype.

INTRODUCTION

Hepatitis C (HC) is one of the most common virus-induced liver diseases (Sobia *et al.,* 2011). Existing estimates point out that there were 54,000 deaths and 955,000 debility-adjusted life-years allied with acute Hepatitis C virus (HCV) infection. The major encumbrance from HCV infection is due to the side effects from chronic infection (Perz JF *et al.,* 2006). It is estimated that three to four million individuals are being infected with HCV each year, 170 million individuals are chronically infected and are at a risk of developing liver disease like cirrhosis and/ or hepatocellular carcinoma, and 350,000 deaths take place each year due to HCV-related causes (Khayriyyah *et al.,* 2006).

Hepatitis C infection is caused by HCV, which is a small, enveloped, single-stranded RNA virus and is a member of the Hepacivirus genus in the family Flaviviridae. Frequency of Hepatitis C in Pakistan is significantly higher (4.5%), when compared to the populations of same ethnicity like India, Nepal, Myanmar, Iran and China (Noureen and Raisa Gul, 2011). HCV infection is a silent disease and most of the times detected incidentally through the evaluation of liver function tests or at the time of blood donor screening. The time when the disease becomes apparent, the treatment becomes less effective in most of the cases. As a result of this latency of infection, various country specific scrutinizes acclaim that over the next 10 years HCV will cause an increased number of liver-related deaths.

The efficacy of the therapy can be evaluated on the basis of achievement of sustained viral response (SVR) also known as viral cure; it occurs when a person's hepatitis C remains undetectable six months after treatment ends (Ghany *et al.,* 2009). HCV can lessen life expectancy and impair quality of life, yet it is not for sure that all patients will develop decompensated liver disease. SVR decreases the rate of disease-related side effects including hepatic fibrosis, cirrhosis, and hepatocellular carcinoma and, in turn, upturns health-related quality of life (Zobair *et al.,* 2007). Moreover, it has been proved that the combination therapy has increased the chance to achieve sustained viral response (Zobair *et al.,* 2007). The treatment of HCV infection is expensive. Neither effectiveness nor development of complications is uniform. The current standard of care for chronic infection with HCV is 24 or 48 weeks of therapy with Pegylated interferon-alfa-2a (Peg IFN) and ribavirin (RV) (Sean *et al.,* 2004; Nezam *et al.,* 2011). Response to therapy is variable. Viral and host characteristics can influence whether patients achieve a sustained virological response (SVR) or not. Viral genotype is also a predictor of response (Zobair *et al.,* 2007). Pakistan belongs to a low socioeconomic area and a need was felt to find out the cost effectiveness of combination therapy. So, a study was designed to institute a Pharmacoeconomic analysis of the treatment regimens

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being used in Pakistani local population to treat Hepatitis C infected patients.

MATERIALS AND METHODS

This was a non-interventional prospective cohort study conducted on patients of public as well as private hospital visiting the outpatient department. Total duration of the study was 18 months. Sample size (n) was calculated on the basis of frequency of Hepatitis C infection in Pakistani population by using the following formula (Naing & Winn, 2006)

$$n = \frac{Z^2 \times P(1-P)}{m^2}$$

Where,
n = sample size i.e. required number of patient to be included in the study,
Z= Level of confidence which is conventionally taken as 1.96,
p=the estimated frequency of Hepatitis C infection,
m=precision or margin of error and its value can be 0.05, 0.01, 0.02.

Total 96 patients infected with hepatitis C 3a genotype were recruited in this study randomly. 12 of them lost follow up. Out of remaining 84 patients, 44 patients were treated with Interferon alpha-2a (INF) + RV therapy and 40 were treated with Peg INF + RV. All patients were provided with a written informed consent form. A data collection sheet was developed according to the requirement of the study for recording the relevant information. Adult male / female patients, seropositive for HCV RNA on testing with the polymerase chain reaction without decompensated liver disease infected with genotype 3a were included in the study. Patients with decompensated cirrhosis, anemia (hemoglobin concentration, less than 12g/dl in women and less than 13g/dl in men), pregnant women, men whose female partner is pregnant or those who were not willing to take contraceptive measures and with human immunodeficiency virus infection, psychiatric conditions, seizure disorders, cardiovascular disease, hemophilia, poorly controlled diabetes mellitus, or autoimmune diseases were excluded.

The content of the data collection sheet was validated in terms of simplicity, reliability, precision in the word, adequate for the problem intended to measure, relevancy to underlying theory and capable of measuring change as per European association for study of liver diseases (EASL) guideline. Data was collected by visiting the outpatient department of the selected hospital of public and private sector one each, on daily basis. Viral load was measured at the start of the therapy labeled as week 0, then at week 4, week 12, week 24 and week 48 by real time PCR.SVR was calculated by determining the viral load at week 12 after the completion of the therapy.

Pharmacoeconomic analysis

For Pharmacoeconomic analysis, we examined the cost relation of the combination of INF + RV and Peg INF + RV regimens. The cost analysis was based on fixed and variable cost of both therapies. Fixed cost was calculated through cost of total medicines administered to the study population and cost of standard laboratory profile ordered over a period of 24 and 48 weeks for both treatments. There was no difference in the cost of laboratory profile as it was done in all patients as per recommendations of the EASL. Variable cost was calculated through the cost of concomitant therapies initiated/ordered during treatment, emergency visits and hospital admissions (tables 2B&C). Following are the formulas for the estimation of cost of HCV therapy

Cost calculation

Step -1

Hepatitis C treatment Cost = Fixed cost (FC) + Variable cost (VC)

Step -2

Calculation of FC

FC = Cost of Medicines + Laboratory Test

Step -3

Calculation of VC

**VC = CT + EV + HA*

Where

CT = Cost of Concomitant therapies

EV= emergency visit

HA = Hospital Admission

*The variable costs are those costs that vary and depend upon 'number of patients' who experienced different adverse effects after hepatitis C treatment and resulted into emergency visit, rescue medicines ordered and hospital admission, which may increase or decrease in magnitude based upon patients clinical condition.

Furthermore, it is difficult to compare the additional cost (including emergency visit, hospital admission and medicines prescribed) of a single patient because of high variance of clinical requirements. So, a factor was created based upon the number of patient having uncontrolled clinical requirements with respect to the total number of patients on treatment (table 2 D). Net cost formula including factor cost calculated as follows

Step -4

Cost of Concomitant therapies:

A factor was calculated to see the net (estimated) cost per patient as follows

Cost Factor of CT (PRBC's + Screening)

= # of patient screened + # of patient received PRBC's / Total No of patient received Hepatitis C treatment regimen

Table 1: Pharmacoeconomic analysis of two different treatment regimens (Cost in PKR)

		Patient No*		Treatment Regimen		Diff.†	Var. (%)
		Peg INF+RV	INF + RV	Peg INF+RV	INF + RV		
Fixed Cost							
Cost of therapy	24 weeks treatment			171,960	58,008	-113,952	66
	48 weeks treatment			343,920	116,016	-227,904	66
Laboratory Profile	No difference			-	-	-	
Variable Cost**							
Concomitant therapies	PRBC,s	2	9	2,350	49,705	47,355	-2015
	Screening	2	9	-	-		
	Medicines	17	25	1,396	12,420	11,024	-790
Emergency Visit	Febrile Neutropenia	2	7	225	716	491	-218
Hospital Admissions	Febrile Neutropenia	0	4	0	909	909	NC
Total (Variable Cost)				3,971	63,750		
Grand Total	24 weeks treatment			175,931	121,758	-54,173	31
	48 weeks treatment			347,891	179,766	-168,125	48

* Total Number of Patients = (INF + RV = 44, Peg INF + RV = 40), ** Probability based cost, †Diff. = Difference = (INF + RV)– (Peg INF + RV), NC = Not computable, INF +R= Interferon alfa-2a + Ribavirin, Peg INF + RV= Pegylated interferon-alfa-2a + Ribavirin, PRBC's = Packed red blood cells

Table 2: Sub Calculation of table 1

A. Cost of hepatitis C virus drugs (Cost in PKR)

	Brand*	Selling price	24 weeks		48 weeks	
			Doses	Cost	Doses	Cost
Peg INF	Brand A (180mcg)	6,500	24	156,000	48	312,000
INF	Brand B (3miu)	584	72	42,048	144	84,096
RV	Brand C (600mg)	48	336	15,960	672	31,920

Prices - Current selling prices printed on the relevant brand packs as dated on 2nd Feb, 2015, *Brand names masked, INF= Interferon alfa-2a, Peg INF =Pegylated interferon-alfa-2a, RV = Ribavirin

B. Cost of concomitant therapy of INF + RV(Cost in PKR)

		Patient No.* (n)	Cost	Doses	Cost
			Average		
Medicines	Omeprazole Cap 20mg	13	9	56	504
	Omeprazole Infusion 40mg	8	230	14	3,220
	Paracetamol Tab 500mg	10	0.5	60	30
	Epoetin Alfa (Erythropoietin) 4000IU	12	2,000	10	20,000
	Hydroxyzine 25mg Tab	12	1	30	30
	Fluoxetine HCL 20mg	6	76	180	13,680
	Levofloxacin Tab 500	6	10	14	140
	Folic Acid 5mg Tab	6	0.3	60	18
	Filgrastim 300mcg	8	3,300	7	23,100
Others	PRBC,s	9	9,000	26	234,000
	Screening	9	1,000	9	9,000
			Total		60,722
	Per patient average cost	(60,722 / 44)			1,380

*Total Number of Patients (INF + RV) = 44, Prices - Current selling prices printed on the relevant brands packs as dated on 2nd Feb, 2015, PRBC's= packed red blood cells

Net Cost of CT (PRBC's + Screening)
= Cost Factor of CT ((PRBC's + Screening) / Total cost of PRBC's + Screening

Cost Factor of CT (Medicines)
= # of patient received medicines / Total No of patient received Hepatitis C treatment regimen

Net Cost of CT (Medicines)
= Cost Factor of CT (Medicines) / Total cost of medicines
A factor including net cost (estimated) was then calculated for EV and HA for both regimens as described above**.** The total cost calculated was then compared with the number of patients who attained SVR in both sub groups.

RESULTS

The total fixed cost of therapy of Peg INF + RV was PKR 171,960, while PKR 58,008 was constituted by INF + RV regimen for 24 weeks of treatment. When these two regimens were given for 48 weeks, the total fixed cost of therapy was PKR 343,920 and PKR 116,016 for Peg INF + RV and INF + RV respectively. Peg INF + RV treatment regimen was high in fixed cost as compared to the INF + RV (the difference in the fixed cost of therapy was PKR 113,952 for 24 weeks and PKR 227,904 for 48 weeks (table 1). In contrary, the total variable cost of Peg INF + RV and INF + RV was PKR 3,971 and 63,750 respectively. Variable cost was very high with INF + RV therapy in all selected variables (concomitant therapies, emergency visit and hospital admission) as compared to Peg INF + RV. In addition, the variances in percentage were also significantly very high (variance of PRBC's, medicines, and febrile neutropenia were -2015%, -790%, -218% respectively). 'Hospital admission' variable was non-computable because no admission recorded in Peg INF + RV therapy. The prices considered for calculation were those printed on the relevant brand packs as dated on 2nd of February, 2015 (table 2 A).

The total cost (fixed and variable cost) of two therapies was compared and it was observed that with INF + RV per patient cost was PKR 121,758 and 179,766 when treated for 24 weeks and 48 weeks respectively. For Peg INF + RV therapy it was PKR 175,931 and 347,891 when treated for 24 weeks and 48 weeks respectively. Major difference in the cost of two therapies was observed and it was found to be cheaper in the case of INF + RV therapy or in other words when patients are to be treated with Peg INF + RV they have to spend an extra amount of PKR 54,173 for the therapy when they are to be treated for 24 weeks, and they have to spend an extra amount of PKR 168,125 for the therapy when they are to be treated for 48 weeks. The variance in cost of 24 and 48 weeks treatment of Peg INF + RV and INF + RV was 31% and 48% respectively (table 1).

When comparison of SVR against different treatment regimens was assessed, we found that 90% of the patients were successfully treated with Peg INF+ RV treatment regimen, 2.5% patients were relapsers and 7.5% of the patients were non responders. Amongst those who were treated with INF+ RV treatment regimen only 20.5% of the patients were successfully treated, 65.9% of the patients had breakthrough infection when still were on treatment and 13.6% of the patients did not respond to the treatment at all (table 3).

DISCUSSION

This study allows patient, physician and health regulatory authorities to estimate the burden of HCV treatment in their population as well as contrast the drugs and medical costs between two drug regimens. Treatment with combination of INF + RV regimen was comparatively cheaper. The total cost of treatment for Hepatitis C patient treated with INF + RV regimen calculated was PKR 54,173 and PKR 168,125 (24 weeks and 48 weeks respectively). The three variables that had the most effect on per patient cost were: (a) concomitant therapies, (b) emergency visit and (c) hospital admissions. Increasing the length of therapy for the anticipated therapy resulted in a cost increase and vice versa. However, this scenario is very unlikely to occur in a group, who received Peg INF + RV therapy. The variable cost was high in INF + RV group as compared to Peg INF + RV (PKR 63,750 vs. 3,971 respectively). In addition, the estimated cost of diagnosed HCV with genotype 3a is based on data from both local and private sectors and can be generalizable to the general population in Pakistan.

The treatment success rate for INF+ RV regimen was 20.5%, and 65.90% of the patients treated with this therapy had breakthrough infection and the HCV reappeared, when the patients were still on treatment. The results of this study are in accordance with the study done in other populations infected with genotype 1 (John, 2006) while the patients treated with Peg INF + RV had a higher percentage to attained SVR (90%). These results were also in agreement with the findings of other studies done previously showing 76-84% SVR's when treated with Peg INF + RV (John G *et al*., 2009).

Moreover, in the case of INF + RV therapy, majority of the patients do not recover rather relapse, so these patients may end up with chronic infection with some other comorbidity during the time spent in the treatment which proved futile. The patients with comorbidities or decompensated liver are then difficult to treat or don't attain SVR at all. So treating HCV with Peg INF + RV is cost effective compared with conventional INF + RV. These findings of the study are in agreement with the findings of the previously done studies that IFN based therapy may be treatment-limiting because of not achieving SVR (Sean *et al.,* 2004).

Limitation of the study

It is difficult to compare the various additive costs of all patients' because of high variance of clinical situation including medical conditions and requirements. So, in order to balance the cost, a factor was created based upon the number of patient having uncontrolled clinical requirements with respect to the total number of patients on treatment. Furthermore, due to time limitationSVR12 was calculated in this study.

CONCLUSION

In hepatitis C adult patients, the combination of Peg INF + RV produces a higher rate of SVR when compared with

patients treated with INF + RV and this increase is cost-effective as well. However, future clinical trials of new treatment regimens should not only include the traditional clinical outcomes, but also a systematic assessment of health-related quality of life.

REFERENCES

Ghany MG, Strader DB, Thomas DL and Seeff LB (2009). Diagnosis, management and treatment of hepatitis C: An update. *J. Hepatol.,* **49**(4): 1335-1374.

John BW (2006). Hepatitis C. *Pharmaco. Economics*, **24**(7): 661-672.

John GM, Eric JL, Mitchell LS, Andrew JM, Greg WG, Jonathan M, Lisa MN, William ML, Reem HG, Eugene RS, Joseph SG, Bruce RB, Mitchell ND, Pabak M, Kenneth K, Stephanie N, Lisa DP, Clifford AB, Janice KA and Mark SS (2009). Peginterferon Alfa-2b or Alfa-2a with Ribavirin for Treatment of Hepatitis C Infection. *N. Engl. J. Med.,* **361**: 580-593.

Khayriyyah MH, Justina G, Abraham DF and Steven TW. (2013). Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to HCV seroprevalence. *J. Hepatol.,* **57**(4)*:* 1333-1342.

Naing L, Winn T and Rusli BN (2006). Practical issues in calculating the sample size for prevalence studies. *Arch. Orofac. Sci.*, **1**: 9-14.

Nezam HA, John GM, Stefan Z, Alessandra M, Jean MP, Jeffrey SM, Kevin VS, Yasuhito T, David LT, David RB and David BG. (2011). Hepatitis C pharmacogenetics: State of the art in 2010. *Hepatology,* **53**(1): 336-345.

Noureen J and Raisa G (2011). A Silent Storm: Hepatitis C in Pakistan. *JPMS,* **1**(3): 89-91.

Perz JF, Armstrong GL, Farrington LA, Hutin YJ and Bell BP (2006). The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J. Hepatol.,* **45**: 529-538.

Sean DS, Antonio C, Alfredo Al, Giovanni G, Claudio DC, Neil W, Kavita KP and Jesse G. (2004). Cost Effectiveness of Peginterferon α-2a Plus Ribavirin versus Interferon α-2b Plus Ribavirin as Initial Therapy for Treatment-Naive Chronic Hepatitis C. *Pharmaco. Economics,* **22**(4): 257-265.

Sobia A, Sanaullah K and Ijaz A (2011). Hepatitis C virus genotypes in Pakistan: A systemic review. *Virology Journal*, **8**: 433.

Zobair Y, Jillian K and John K (2007). The effects of HCV infection and management on health-related quality of life. *J. Hepatol.,* **45**(3): 806-816.