

# Weight loss in HCV patients can be used as a surrogate marker for evaluation of interferon (IFN- $\alpha$ ) treatment efficacy – A prospective pilot study

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**Abstract:** The aim of the study was to investigate whether weight loss followed the same pattern in HCV patients ('responders' and 'non-responders') after interferon (IFN- $\alpha$ ) treatment. A total of 20 male HCV positive patients (mean age 33.1 $\pm$ 9.9) in Peshawar, Pakistan participated in this study. They were initially tested as HCV positive, and were given IFN/Ribavirin treatment for 6 months. Changes in body weight (BW), lean body mass (LBM) and body fat (BF) were monitored on monthly basis. End to treatment response (ETR) was established by a final undetectable HCV RNA in serum at the end of therapy and the patients were categorized as either 'responders' or 'non-responders'. The results show a total of 12 out of 20 patients as 'responders' (60%). All patients lost weight and the mean weight loss in 'responders' and 'non-responders' was 6.2 ( $\pm$ 1.5) and 5.8 ( $\pm$ 1.4) Kg, respectively. There was a significant difference in the mean change in BW, LBM, and BF between 'responders' and 'non-responders' during the last 3 month period only. This suggests that difference in drug response in HCV starts from month 4 and onwards (i.e. during the last 3 months). In conclusion, weight trends during treatment should be monitored as weight loss may be used as a surrogate marker for ETR to the current standard of care.

**Keywords:** HCV, interferon, weight loss, surrogate markers,

## INTRODUCTION

Recombinant interferon  $\alpha$  (IFN- $\alpha$ ) is used extensively in the treatment of hepatitis C infection. However, IFN therapy is not free of adverse effects and weight loss is one of its common side effects (Antaki *et al.*, 2008; Manns *et al.*, 2001). The possible mechanisms underlying weight loss or changes in other body composition have been reported that include suppressed appetite due to induction of TNF by IFN, a decrease in serum leptin level, lactic acidosis and mitochondrial damage induced by the therapy.

Despite the revolutionary findings of its beneficial effects in HCV treatment, ribavirin has some toxicity as it is eliminated slowly from non-plasma compartments of the body. The multiple-dose plasma half-life is reported to be approximately 298 hr (Physicians' Desk Reference, 2002), but the half-life in erythrocytes is 40 days (Physicians' Desk Reference, 2002; USP DI, 2002). The extensive accumulation of ribavirin in erythrocytes and other tissue compartments and its slow clearance from the body raise the theoretical possibility that ribavirin may accumulate in sperm in concentrations high enough to induce a defect; however, there is no evidence that ribavirin treatment actually affects human sperm.

Ribavirin did not induce chromosomal aberrations in rat or human leukocytes, however, and had no mutagenic effect in the Ames test (Narayana *et al.*, 2002). In addition, ribavirin was not found mutagenic in a dominant lethal study in rats (Hoffman *et al.*, 1987). Intraperitoneal administration of higher than recommended for human 24-hr dose of ribavirin to male rats altered sperm morphology and decreased sperm production, but it is not clear whether this was a toxic or mutagenic effect (Narayana *et al.*, 2002).

Some original studies (Fried, 2002; Anonymous, 2001; Manns *et al.*, 2001) were conducted to establish the safety of the treatment and to evaluate the IFN for its efficacy. These studies have reported weight loss in as much as 11-29% of the patients, while other studies have reported weight loss in up to 100% of the patients (Gottrand *et al.*, 1996; Seyam *et al.*, 2005).

Global prevalence of HCV has increased from 2.3% (>122 million) to 2.8% (>185 million) between 1990 and 2005 (Hanafiah *et al.*, 2012). In Pakistan, where HCV is highly prevalent (Ahmad *et al.*, 2012), the general concept is the use of standard interferon therapy. This is partly due to economic and relevant technical reasons. In addition, Pakistan Society of Gastroenterology and GI Endoscopy also favor the use of IFN in genotype-3 (Hamid *et al.*, 2004). The only product, which

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Government of Pakistan is providing on subsidized rates to the patients is IFN via a special Prime Minister's initiative program against hepatitis, thus pegylated IFN is out of reach for the majority of the patients.

Data on the pattern of changes in BW in HCV patients, particularly in developing countries, are however very fragmentary. Information on IFN associated changes in body fat (BF) and lean body mass (LBM) are necessarily absent. Whether IFN therapy associated changes in BW, LBM and BF follow a steady pattern and whether loss in BW is reflected proportionately in terms of loss in LBM and BF are poorly understood and reported. These are important questions of greater clinical significance as an earlier assessment of the drug efficacy is important and changes in BW, LBM, and BF can be used as simple and non-invasive tools for this purpose (Selivestрова *et al.*, 2011; Chau *et al.*, 2011). The present study was conducted to investigate changes and pattern of changes of body weight in HCV patients in order to establish whether changes in weight could be used as a possible marker for drug efficacy during treatment.

## **MATERIALS AND METHODS**

This was a cross-sectional prospective study, investigating changes in various parameters of body composition such as body weight (BW), body fat (BF), and lean body mass (LBM) as the out-comes and interferon (IFN) therapy as the factor responsible for changes in these out-comes. The present study was conducted in Khyber Teaching Hospital (KTH), Peshawar, Khyber Pakhtunkhwa (KP) of Pakistan. All the patients of the study visited the general OPD. Data on sero-positivity for HCV infection and other parameters of interest were collected. The procedures followed were:

### **Screening**

Initially all the subjects were tested for anti-HCV antibodies by immuno-chromatographic tests. After initial screening, PCR test was performed for each patient sample according to the instructions of the manufacturers (Roboscreen, Germany). Taken into account limited available resources, only 20 patients, whose PCR was positive among the confirmed anti-HCV patients, were selected for interferon therapy. The exclusive therapy criteria (Ahmad *et al.*, 2012), i.e. age of the selected personals (18-55 years), absence of associated co-infection, ALT level higher than normal, platelets and Hb levels within the accepted range and stage of cirrhosis were strictly observed.

### **Anthropometrics and dietary**

Anthropometric measurements (weight and height) were performed on digital scale/non-stretchable height tap using procedures as reported previously (Alam *et al.*, 2012b; Alam *et al.*, 2012c). These measurements were

recorded once in a month. Dietary intake was assessed during face-to-face interview using methods reported elsewhere (Alam *et al.*, 2012c; Alam *et al.*, 2012d; Alam *et al.*, 2012e).

### **Blood chemistry**

Selected biochemical and blood tests (albumin, hemoglobin, differential cell counts etc), were performed at baseline and at the end of therapy.

### **Body composition**

Body composition assessment was performed using the technique of Bio-electric Impedance. Quadsacn-4000 (Body stat, UK) was used for this purpose.

### **Treatment Protocol**

All HCV positive patients were given standard interferon therapy i.e. interferon alpha 2b (3MIU thrice a week) plus Ribavirin (1000 mg/day) continuously for 6 months with repeated testing of ALT level and HCV RNA during and after the interferon therapy as reported previously (Ahmad *et al.*, 2012). Re-testing for HCV RNA 4-6 months later is recommended to confirm the resolution of HCV infection (Polywka *et al.*, 2006). The primary measure of IFN efficacy was 'calculated end of treatment virologic response' (ETR) (Ahmad *et al.*, 2012), defined as 'undetectable HCV RNA in serum at the end of follow-up, i.e., 6 months after the treatment'. The secondary measure of IFN efficacy i.e. loss in weight and changes in other compartment of body was recorded on monthly basis in all patients.

The study was approved by the Board of Studies, Institute of Biotechnology & Genetic Engineering (IBGE), KP Agricultural University Peshawar, Pakistan. Written informed consents were obtained from all the participants before the start of study. All values were reported in means and SD. A student's t-test was used for comparison of means of the 'responders' and 'non-responders'. The analyses were made using JMP Version 14 Package of SAS, USA. A significant difference was defined at  $p \leq 0.05$ .

## **RESULTS**

The current study was conducted to investigate the changes in body composition as a result of interferon (IFN) therapy in HCV positive patients on IFN therapy. A total of 20 patients participated in the study. These patients were entered into two distinct groups i.e. 'responders' (N=12) and 'non-responders' (N=8). All patients used the IFN treatment and were followed for the initial 6 months of treatment.

### **Baseline Characteristics**

The age and other baseline characteristics of the patients are presented in table 1. The mean age, weight and BMI

of the two groups 'responders' and 'non-responders' at baseline did not differ significantly ( $p \geq 0.05$ ). All patients (either in 'responders' or 'non-responders') had normal BMI values (i.e. 17-25 Kg/m<sup>2</sup>), except one patient (patient ID 14, Age 21 yr), who had a BMI value of 16.1 (slightly underweight) in 'non-responders' group of HCV patients. Table 1 also shows the mean values of BF and LBM. These values also did not differ significantly for the two groups ( $p$ , for all trends  $> 0.05$ ).

### Response to IFN Therapy

After completion of the 6 months long therapy, the results on response to therapy were as: Out of total 20 patients, 12 (60%) were negative for HCV RNA and showing end of treatment response (ETR), while 8 (40%) were positive for HCV RNA and did not show ETR.

### Changes in Body Weight

Changes in body weight (BW), lean body mass (LBM) and body fat (BF) of HCV patients 'responders' and 'non-responders' over the therapy period of 6 months are shown in Figs. 1, 2 and 3, respectively. There was significant ( $p \leq 0.05$ ) loss in mean BW (61.04 $\pm$ 7.56 Kg at baseline vs. 54.83 $\pm$ 6.73 Kg at month 6), LBM (51.57 $\pm$ 8.43 at baseline vs. 47.88 $\pm$ 7.7 at month 6) and BF (9.51 $\pm$ 4.9 at baseline vs. 7.05 $\pm$ 2.28 at month 6) in HCV patients 'responders'. In 'non-responders' these parameters changed as: Significant reduction in BW (65.76 $\pm$ 8.96 Kg at baseline vs. 60.9 $\pm$ 8.6 Kg at month 6 ( $P \leq 0.05$ ), LBM (53.0 $\pm$ 10.24 at baseline vs. 49.51 $\pm$ 10.41 at month 6), and BF (10.3 $\pm$ 8.06 at baseline vs. 8.40 $\pm$ 7.76 at month 6).

In HCV patients 'responders', the total weight loss at month 6 varied in the range of 2.1–9.5 Kg compared with baseline with a mean weight loss of 6.2 ( $\pm$ 1.5) Kg, which was 10.5% of the pre-treatment weight. In addition, 58.3% (7 out of 12) patients had a weight loss  $\geq 10\%$  of the baseline body weight. In HCV patients 'non-responders', the total weight loss at month 6 varied in the

range of 2.4-9.6 Kg compared with baseline with a mean weight loss of 5.8 ( $\pm$ 1.4) Kg, which was 9.1% of the pre-treatment weight.

The difference in mean weight loss at the end of month 6 between 'responders' and 'non-responders' was not significant ( $p > 0.05$ ). In both 'responders and 'non-responders', the maximum weight loss occurred in the first 3 months of treatment i.e. 9.3 and 9.1% of the baseline weight, respectively. Similarly, the maximum loss in LBM and BF occurred in the first 3 months of the treatment, as also evident from the inclination of the graphs (Figs.1-3). In 'responders' the percent loss in LBM and BF was 7.2 and 36.4%, respectively at the end of month 6, while, in 'non-responders' these values were 7.7 and 18.7, respectively.

In the latter 3 month period, loss in weight followed the same pattern in 'responders' i.e. a steady but relatively lesser loss in BW (1.2% of the total loss in BW). However, in 'non-responders' there was a slight regain in weight during the last 3 months of treatment. Body fat and LBM also changed proportionately in the same way in 'responders' and 'non-responders'.

## DISCUSSION

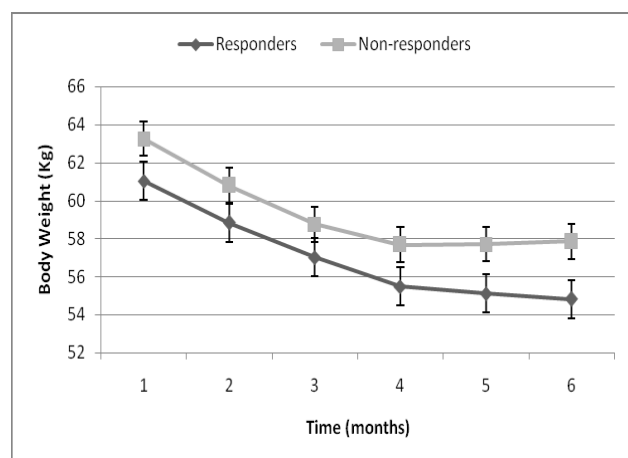
In this study we determined the End of Treatment Response (ETR), defined as the absence of HCV RNA at the end of 6 months of IFN therapy in HCV patients. The average calculated ETR was 60% (12 out of 20 patients) and resistance calculated was 40% (8 out of 20 patients). Although we used a relatively small sample in our study, nevertheless these figures are in close agreement with what have been reported by Ahmad *et al.*, (2012). i.e. 74.7 and 25.3%, respectively, for average calculated ETR and resistance. The figures for ETR reported in the current study are still very sub-optimal considering the sero-prevalence of HCV virus in Pakistan, reported in the

**Table 1:** Baseline Daily Nutrient intake and Blood Chemistry of the Patients

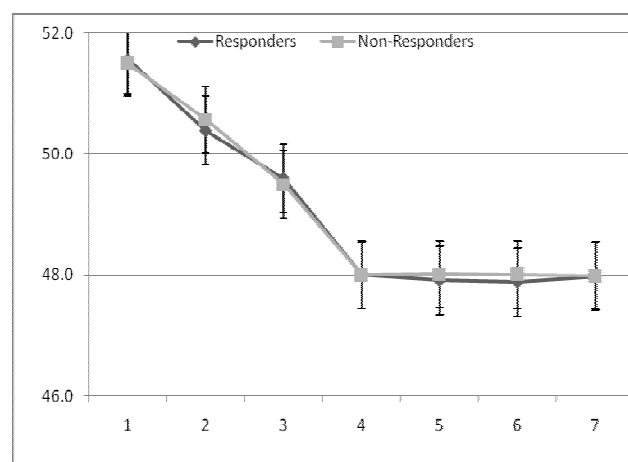
Characteristics	HCV Positive Patients		P-value
	Responders (N=12)	Non-Responders (N=8)	
Age (years)	33.2 $\pm$ 6.7	34.16 $\pm$ 5.1	0.322
BMI	20.62 $\pm$ 3.24	23.49 $\pm$ 3.73	0.076
Weight (Kg)	61.04 $\pm$ 7.57	65.76 $\pm$ 8.96	0.102
Lean Body Mass (Kg)	51.57 $\pm$ 8.44	51.66 $\pm$ 10.24	0.422
Body Fat (Kg)	9.51 $\pm$ 4.91	14.1 $\pm$ 8.06	0.064
Protein Intake (g)	71.3 $\pm$ 0.3	71.8 $\pm$ 2.13	0.211
Energy Intake (Kcal)	2110.1 $\pm$ 192	2117.4 $\pm$ 184	0.092
Albumin	2.8 $\pm$ 0.26	2.8 $\pm$ 0.74	0.332
ALT	54.1 $\pm$ 6.2	55.2 $\pm$ 4.6	0.078
Hemoglobin	13.1 $\pm$ 2.18	12.6 $\pm$ 3.11	0.097
White Blood Cell (10 <sup>3</sup> / $\mu$ L)	6.0 $\pm$ 1.41	5.7 $\pm$ 1.82	0.113

Significantly different if  $p < 0.05$

last 5 years, is from 2.2%-13.5% (Amin, 2004; Almani, 2002; Khan, 2006). Response rates of up to 80% have been extensively reported with similar treatment protocols in international (NIH, 1997; Manns *et al.*, 2001; CDC, 1998; Schalm *et al.*, 1997; Heathcote *et al.*, 2000; McHutchison *et al.*, 1998; Hadziyannis *et al.*, 2002; Mangia *et al.*, 2005) and some local studies (Ahmad *et al.*, 2012; Qureshi *et al.*, 2009; Shaikh *et al.*, 2002; Hussein *et al.*, 2002; Noor *et al.*, 2004).



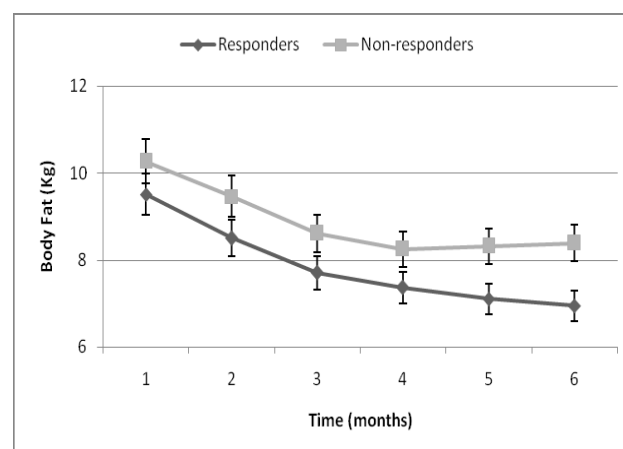
**Fig. 1:** Changes in Body Weight in HCV patients during the therapy period (from month 1 to month 6).



**Fig. 2:** Changes in lean body mass (LBM) in HCV patients during the therapy period (from month 1 to month 6).

The major findings of this research study are: significant loss in body weight as a result of IFN therapy during 6 months in both 'responders' and 'non-responders'. In our study, all patients (100%) receiving IFN therapy lost weight. Our figures for the percentage of patients who lost weight during treatment with IFN are much higher than the 11-29% reported by the original papers looking at the safety of these drugs (Fried, 2002; Anonymous, 2001; Manns *et al.*, 2001). However, what is more interesting and of clinical significance is the fact that changes in BW

were steady throughout the therapy period in 'responders', while in 'non-responders' changes in BW occurred in the first 3 months only and then there was a slight regain in BW during the last 3 months., although ending with a net loss of BW in overall. From these data, we may infer that loss in weight could be used as a surrogate indicator for evaluation of IFN treatment efficacy (Gottrand *et al.*, 1996; Seyam *et al.*, 2005). Furthermore, it is evident from the results that difference in drug response in HCV ('responders' and 'non-responders') starts from month 3 and onwards. In short, while monitoring weight changes during IFN therapy, a regain in weight may be the first signal of a break in the IFN efficacy. This is an important finding, since drug efficacy and response play important role in making drug-dosage and alternative therapy decision.



**Fig. 3:** Changes in body fat (BF) in HCV patients during the therapy period (from month 1 to month 6).

In addition to loss in BW, the percent mean loss in BF was significantly ( $p=0.021$ ) greater in 'responders' (36.4% of the baseline) compared to that of 'non-responders' (18.7% of the baseline). In 'responders', BF losses continued throughout the study (12.5, 11.6, 5.6, 2.1, 2.2, 2.3% of BF value at the previous month, respectively, from month 1-6). In 'non-responders', there was loss in BF observed in the first 3 months (i.e. 8.6, 9.1, 9.3% of BF value at the previous month, respectively, for month 1-6). However, there was a regain in BF in 'non-responders' in the last 3 months of the therapy. From these data, we may hypothesize that like BW, changes in percent BF may be used even as a better determinant for prognosis and hence a stronger indicator of IFN efficacy. These findings are further supported by many other studies. For example, Selivestрова *et al* (2011) conducted a study to assess prognostic value of body mass index (BMI), percent of body fat (PBF) and waist hip ratio (WHR) on to efficacy of therapy of chronic hepatitis C with pegylated interferon a2a plus ribavirin. The results showed no difference in mean BMI between patients achieved and non-achieved SVR. However, they had lower PBF and WHR. The authors concluded that PBF

and WHR demonstrate better prognostic value for pegylated interferon ribavirin combination therapy for HCV infection. Similarly, Chua *et al* (2011) investigated the relationship between weight loss and sustained virologic response in 194 patients. The authors concluded a relationship between weight loss and SVR and recommended weight loss as a surrogate indicator for IFN/ribavirin efficacy.

## CONCLUSIONS

The conclusion of the study is that (a) HCV patients on therapy experience loss in BW, LBM, and BF; (b) loss in BW, LBM, and BF occurred differently in responders' and 'non-responders' such that 'responders' lose BW, LBM, and BF throughout the treatment period, while 'non-responders' lose BW, LBM, and BF only in the first 3 months and regain BW, LBM, and BF in the last 3 months. This difference in change in BW, LBM, and BF may be used as prognostic marker and surrogate indicator earlier in the treatment for drug efficacy.

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## REFERENCES

- Ahmad B, Ali S, Ali I, Azam S and Bashir S (2012). Response rates of standard interferon therapy in chronic HCV patients of Khyber Pakhtunkhwa (KPK). *Virol J.*, **14**: 9:18.
- Alam I, Alam I, Paracha PI and Pawelec G (2012c). Higher estimates of daily dietary net endogenous acid production (NEAP) in the elderly as compared to the young in a healthy, free-living elderly population of Pakistan. *Clin. Interv. Aging*, **7**: 565-73.
- Alam I, Larbi A, Pawelec G, Paracha PI (2012b). A comparison of anthropometrics, biochemical variables and nutrient intake between young and elderly men. *J. Aging Res & Clin Prac.*, **1**(2): 116-124.
- Alam I, Larbi A and Pawelec G (2012d). Aging affects the number of T and B cells in a group of elderly in developing countries-a pilot study from Pakistan. *AGE.*, **35**(5): 1521-1530.
- Alam I, Larbi A and Pawelec G (2012e). Nutritional status influences peripheral immune cell phenotypes in healthy men in rural Pakistan. *Immun Ageing*, **9**: 16.
- Alam I and Pawelec G (2012a). Aging, nutrition and immunity -their relationship and interaction. *Nutr. and Aging*, **1**(3-4): 151-165
- Almani SA, Memon AS, Qureshi AF and Memon NM (2002). Hepatitis viral status in Sindh. *Professional Med. J.*, **9**(1): 36-43.
- Amin J, Yousf H, Mumtaz A, Iqbal M, Ahmed R and Adhami SZ (2004). Prevalence of Hepatitis B surface antigen and Anti Hepatitis C virus. *Professional Med. J.*, **11**(3): 334-337.
- Anonymous (2004). Hepatitis C: RKI-Ratgeber Infektionskrankheiten. *Epidemiologisches Bulletin*, **17**: 141.
- Antaki F, French MM, Moonka DK and Gordon SC (2008). Bioelectrical impedance analysis for the evaluation of hepatic fibrosis in patients with chronic hepatitis C infection. *Dig. Dis. Sci.*, **53**: 1957-1960.
- CDC, Centers for Disease Control (1998). Recommendations for prevention and control of Hepatitis C virus (HCV) infection and HCV related disease. *MMWR Morb. Wkly.*, **47**(RR-19): 1-40.
- Chua DL, Aden B, Jacobson I M and Gambarin-Gelwan M (2011). Is Weight Loss a Surrogate Marker of Response to Pegylated Interferon and Ribavirin Therapy in Patients with Chronic Hepatitis C Infection? *Gastroenterology-Orlando*, **14**: 1
- Fried MW (2002). Side effects of therapy of hepatitis C and their management. *Hepatology*, **36**: 237-244.
- Gottrand F, Michaud L, Guimber D, Ategbro S, Dubar G, Turck D and Farriaux JP (1996). Influence of recombinant interferon alpha on nutritional status and growth pattern in children with chronic viral hepatitis. *Eur. J. Pediatr.*, **155**: 1031-1034.
- Hadziyannis SJ, Cheinquet H, Morgan T, Diago M, Jensen DM and Sette H (2002). Peginterferon alfa-2a (40 kD) (PEGASYS) in combination with ribavirin (RBV): efficacy and safety results from a phase III, randomized, double-blind, multicentre study examining effect of duration of treatment and RBV dose. *J. Hepatol.*, **36**: 3A.
- Hamid S, Umar M, Alam A, Siddiqui A, Qureshi H and Butt J (2004). PSG consensus statement on management of hepatitis C virus infection-2003. *J. Pak. Med. Assoc.*, **54**:146-150.
- Hanafiah MK, Groeger J, Flaxman AD and Wiersma ST (2012). Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to HCV seroprevalence. *Hepatology*, **57**(4): 1333-1342.
- Heathcote EJ, Shiffman ML, Cooksley WG, Dusheiko GM, Lee SS and Balart L (2000). Peginterferon alfa-2a in patients with hepatitis C and cirrhosis. *N. Engl. J. Med.*, **343**: 1673-1680.
- Hussein AB, Hussein T, Anwar M, Shujaat H, Kazmi Y, Tariq WZ, and Karamat KA (2002). Treatment response in HCV related chronic hepatitis. *J. Coll. Physicians Surg. Pak.*, **12**: 609-612.
- Khan MSA, Khalid M, Ayub N and Javed M (2004). Seroprevalence and risk factors of Hepatitis C virus (HCV) in Mardan. *N.W.F.P. Rawal Med.*, **29**: 57-60.
- Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, and Persico M (2005). Peginterferon and Ribavirin for 12 vs. 24 weeks in Genotype 2 or 3. *N. Engl. J. Med.*, **352**: 2609-2617.

- Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M and Reindollar R (2001). Peginterferon alfa 2-b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: A randomized trial. *Lancet.*, **358**: 958-965.
- Manns MP, Wedemeyer H and Cornberg M (2006). Treating viral hepatitis C, efficacy, side- effects and complications. *Gut.*, **55**: 1350-1359.
- McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM and Rustgi VK (1998). Interferon aifa-2b alone or in combination with ribavirin as initial treatment of for chronic hepatitis C. *N. Engl. J. Med.*, **339**: 1485-1492.
- Narayana K, D'Souza UJA and Rao KPS (2002). Ribavirin-induced sperm shape abnormalities in Wistar rat. *Mutat. Res.*, **513**: 193-196.
- NIH Consensus Development Conference Panel Statement (1997). Management of Hepatitis C. *Hepatology*, **26**: 2-10.
- Noor M, Jan MA and Rahman N (2004). Treatment response of Hepatitis C patients to combination therapy of Interferon plus Ribavarin. *J. Postgrad. Med. Inst.*, **18**: 563-568.
- Physicians' Desk Reference (2002). 56<sup>th</sup> ed Montvale, Medical Economics Company, New Jersey, USA.
- Polywka S, Pembrey L, Tovo PA and Newell ML (2006). Accuracy of HCV-RNA PCR tests for diagnosis or exclusion of vertically acquired HCV infection. *J. Med. Virol.*, **78**: 305-310.
- Qureshi S, Batool U, Iqbal M, Qureshi O, Kaleem R, Aziz H and Azhar M (2009). Response rates to standard interferon treatment in HCV genotype 3a. *J. Ayub. Med. Coll. Abbottabad*, **21**(4): 10-14.
- Schalm SW, Fattovich G and Brouwe JT (1997). Therapy of hepatitis C: Patients with cirrhosis. *Hepatology*, **26**: 128-132.
- Selivestrova TR, Trufanova IuM, Morozov SV and Isakov VA (2011). Indicators of body composition as prognostic factors of efficiency of antiviral therapy for chronic hepatitis C. *Eksp. Klin. Gastroenterol.*, **1**: 54-58.
- Seyam MS, Freshwater DA, Odonnell K and Mutimer DJ (2005). Weight loss during pegylated interferon and ribavirin treatment of chronic hepatitis C. *J. Viral. Hepat.*, **12**: 531-535.
- Shaikh WM, Shaikh MA, Solangi GA and Zuberi BF (2002). Role of Interferon and Interferon plus Ribavarin in the management of Chronic Hepatitis C. *J. Coll. Physicians Surg. Pak.*, **12**: 609-612.
- USP DI (2002). Ribavirin and interferon -2b, recombinant. *In: USP Dispensing Information. Volume I. Drug Information for the Health Care Professional. 22nd ed. Greenwood Village, Co: Micromedex Thomson Healthcare, pp.2588-2592.*