International Journal of Medical Sciences
2010; 7(1):36-42

Research Paper

Weight loss, leukopenia and thrombocytopenia associated with sustained virologic response to Hepatitis C treatment

Nuntra Suwantarat✉, Alan D. Tice✉, Thana Khawcharoenporn, Dominic C. Chow

Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii, USA 96813.

✉ Corresponding Author: Alan D. Tice, MD, FACP., Infections Limited Hawaii; 1286 Queen Emma Street, Honolulu, Hawaii 96813. E-mail: alantice@idlinks.com; Telephone: +1-808-373-3488; Fax: +1-808-536-2024. Co-Corresponding Author: Nuntra Suwantarat, MD., Department of Medicine, John A. Burns School of Medicine, University of Hawaii, 1356 Lusitana Street, 7th Floor, Honolulu, HI 96813. E-mail: nuntra@hawaii.edu; Telephone: +1-808- 586-2910; Fax: +1-808-586-7486

Received: 2009.10.19; Accepted: 2010.01.21; Published: 2010.01.22

Abstract

OBJECTIVE: To identify apparent adverse effects of treatment of chronic hepatitis C and their relationship to sustained virologic response (SVR).

METHODS: A retrospective study was conducted of all Hepatitis C virus (HCV)-infected patients treated with pegylated interferon and ribavirin in an academic ambulatory infectious disease practice. Clinical and laboratory characteristics were compared between patients with SVR and without SVR.

RESULTS: Fifty-four patients completed therapy with the overall SVR rate of 76%. SVR was associated with genotype non-1 (*P*=0.01), weight loss more than 5 kilograms (*P*=0.04), end of treatment leukopenia (*P*=0.02) and thrombocytopenia (*P*=0.05). In multivariate analysis, SVR was significant associated with HCV genotype non-1 (Adjusted Odd Ratio [AOR] 15.22; CI 1.55 to 149.72; *P*=0.02), weight loss more than 5 kilograms, (AOR 5.74; CI 1.24 to 26.32; *P*=0.04), and end of treatment white blood cell count level less than 3 X 10^3 cells/μl (AOR 9.09; CI 1.59 to 52.63; *P*=0.02). Thrombocytopenia was not significant after adjustment. Other factors including age, gender, ethnicity, injection drug use, viral load, anemia, alanine transaminase level, and liver histology did not reach statistical significance.

CONCLUSION: Besides non-1 genotype, SVR was found to be independently associated with weight loss during therapy, and leukopenia at the end of HCV treatment. These correlations suggest continuation of therapy despite adverse effects, may be of benefit.

Key words: Hepatitis C, pegylated interferon, ribavirin, weight loss, leukopenia, thrombocytopenia.

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of liver diseases and liver cancer (1-3). Among the six genotypes of HCV, the most common genotypes of HCV in the United States are genotype 1 (approximately 75%), genotype 2 (15%), and genotype 3 (7%) (2-5). At present, the standard treatment for chronic HCV genotype 1 infection is 48 weeks with a combination of pegylated (long-acting) interferon alfa-2a or alfa-2b plus ribavirin. Outcomes are measured by sustained viral response (SVR), defined as an undetectable viral load 24 weeks after the end of therapy. HCV genotype 1 has been reported to have a 54-56% SVR (2, 6-9). Prior studies have shown better response rates with genotype 2 or 3 with a 24 week-course of therapy (2, 8,9). Response rates have been found higher in Caucasians (52%) compared to

African-Americans (28%) (2). Response rates are reported lower with initial levels of HCV RNA >600,000 IU/ml, male gender, high body weight, and advanced liver fibrosis (11-17). Recent studies have also shown a poorer response to treatment associated independently with HCV genotype1 infection but a better response with weight loss (18). Limited knowledge exists regarding the influence of on-treatment factors during therapy. The purpose of our analysis was to identify clinical, biological, virological and histological predictive factors that may be helpful in guiding decisions during therapy, and for counseling patients about outcomes.

MATERIALS AND METHODS

Study population. We conducted a retrospective cohort study of 54 adults (age ≥ 18 years) patients who were diagnosed with HCV infection and completed treatment with pegylated interferon plus ribavirin through an academic ambulatory infectious disease practice from January 2004 to December 2007. The study was approved by the University of Hawaii Committee on Human Studies (CHS # 1541). Patients infected with HCV genotype 1 completed a 48 week-course with once weekly injections of pegylated interferon alfa-2a or alfa 2b (180 µg) plus ribavirin (1000 or 1200 mg/day in divided dose) for 48 weeks. Patients infected with HCV genotypes 2 or 3 completed a 24 week-course with once weekly injections of pegylated interferon alfa-2a (180 µg) plus ribavirin (800 mg/day in divided doses). SVR rates were measured at 24 weeks after the end of therapy. Interferon dosing was not adjusted but ribavirin occasionally was. Hematology growth factors were occasionally used but not consistently.

Study design and definitions. The study patients were identified from the clinic's medical records using the International Statistical Classification of Diseases and Related Health Problems (ICD) code of 070.44 and 070.54. During the period of study, 78 patients started on therapy. Twenty four patients were not included in the study analysis due to fail to complete treatment and evaluation. Of these, 13 failed to return for follow-up, 6 stopped because of adverse effects, 3 for poor response, and 2 because of death. Finally, a total of 54 charts were reviewed in the patients who completed therapy and returned for follow-up at 24 weeks after treatment. Information on demographic characteristics, co-morbid conditions, genotypes of HCV, laboratory data, treatment, and follow-up data were collected by using a study data collection form. SVR was indicated by undetectable HCV RNA at 24 weeks after therapy with combined pegylated interferon alfa-2a or alfa-2b plus ribavirin. Genotypes of HCV were defined using the Bayer TRUGENE HCV Genotyping Test. Serum concentration of HCV RNA was determined shortly before study and at 24 weeks after complete course of treatment (treatment duration: 48 weeks in genotype 1 and 24 weeks in genotype 2 or 3) by the COBAST (TaqMan) test, which has a limit of detection of 28 IU/mL. Body weight measurement and laboratory data were collected and compared at the beginning and at the end of therapy. The Knodell scoring system for liver biopsy (obtained at baseline) result was used as the indicator of histologic activity.

Statistical analysis. Descriptive statistics were produced comparing SVR versus non-SVR group. Categorical variables were compared using the Pearson's χ^2 or Fisher's exact test, as appropriate. The distribution of continuous data was evaluated by the O'Brien test for homogenicity of variances. When necessary, an appropriate normalizing or variance stabilizing transformation was applied. Analysis of variance was used to compare groups. Cut-offs of continuous data was determined by evaluating the median results of the groups and deciding among the investigators clinical importance. From the data, clinically relevant cut-offs determined by the investigators were as follows: for weight loss (more than 5 kilograms.), leukopenia (WBC less than $3x10^3$cells/µl) and thrombocytopenia (platelets less than $1x\ 10^5$ cells/µl). Logistic regression and multivariate analysis were performed to identify independent predictors for SVR. Statistical significance was considered with *P* value of 0.05. Odds ratio (OR) with 95% confidence interval (CI) was reported in categorical data. All statistical analyses were conducted using SPSS for Window software, version 15.0 (SPSS Inc, Chicago, IL).

RESULTS

A total of 54 medical records of patients who completed HCV therapy with follow-up viral load result at 24 weeks were reviewed. The majority of the study population was male (67%) and Caucasian (57%) with the mean age of 52.5 years (Table 1). Fifty six percent were infected with genotype 1, 16% with genotype 2 and 28% with genotype 3. Clinical characteristics, relevant laboratory data and liver biopsy results of all patients are shown in Table 1. The major risk factors for acquiring HCV infection were related to injection drug use and tattooing. Mild and moderate liver inflammation determined by Knodell score was presented in the majority of patients while cirrhosis was rarely observed. A total of 22 patients had liver fibrosis: portal fibrosis was the most common (n=11, 50%), followed by septal fibrosis (n=4, 18%),

bridging fibrosis (n=4, 18%), periportal fibrosis, and only one patient with cirrhosis pattern (n=1, 5%). Forty-one percent of the patient population had a history of alcohol abuse and 35% had underlying psychiatric problems. Concomitant psychiatric disorders among this patient population included depression (38%), anxiety (18%), schizophrenia (6%) and bipolar disorder (3%). Underlying medical problems included hypertension (15%) and diabetes mellitus (DM) (14%).

Demographics, clinical and laboratory data of patients (percent and means) were compared between patients with SVR and without SVR as shown in Table 2. All continuous variables were normally distributed and did not require log transformation. SVR was significantly affected by genotype non-1 (P=0.01) as well as low white blood cell (WBC) count (leukopenia) at the end of treatment (P=0.02) compared to patients without SVR. Moreover, low platelet count (thrombocytopenia) at the end of treatment was associated with SVR (P=0.05). Age, ethnicity, gender, drug abuse, and histology were not significantly associated with SVR. To allow for clinical applicability, logistic regression with clinical cut-offs in the significant relevant covariants, found in the linear regression models, were performed. Laboratory characteristics and categorical variables for the predictors of SVR were compared by using logistic regression and multivariate analysis (categorical data) as displayed in Table 3. In multivariate analysis, SVR was significant associated with HCV genotype non-1 (Adjusted Odd Ratio [AOR] 15.22; CI 1.55 to 149.72; P=0.02), weight loss more than 5 kilograms, (AOR 5.74; CI 1.24 to 26.32; P=0.04), and end of treatment white blood cell count level less than 3 X 10^3 cells/μl (AOR 9.09; CI 1.59 to 52.63; P=0.02). Thrombocytopenia was not significant after adjustment. Other factors including age, gender, ethnicity, injection drug use, viral load, anemia, alanine transaminase level, and liver histology and did not reach statistical significance.

Table 1: Baseline demographic, clinical characteristics and laboratory data of the study population

Characteristics	**Total, n = 54**
Male gender, n (%)	36 (67)
Ethnicity, n (%)	
Caucasian	31 (57)
Asian	10 (19)
Hispanic	7 (13)
Hawaiian	6 (11)
Others	3 (6)
Age, years, mean ± SD	52.5±5.8
HCV genotypes, n (%)	
Genotype 1	30 (56)
Genotype 2	9 (16)
Genotype 3	15 (28)
Weight, kilograms, mean ± SD	85.0± 19.1
BMI, kilograms/m², mean ± SD	28.2±5.5
Baseline HCV RNA (x 10^6 IU/mL ± SD)	6.45±13.4
HCV RNA > 600,000 IU/mL, n (%)	47 (87)
ALT >90 U/L, n (%)	45 (83)
Total bilirubin, mg/dlL, mean ± SD	1.0±0.5
Serum albumin, g/dl, mean ± SD	3.9±0.3
Liver biopsy results;	n = 38
Knodell score, mean ± SD	8.0 ± 3.2
Minimal inflammation (≤4), n (%)	4 (11)
Mild inflammation (5-8), n (%)	18 (47)
Moderate inflammation (9-12), n (%)	14 (37)
Marked inflammation (≥13), n (%)	2 (5)
Risk factors for acquiring HCV infection, n (%)	
Injection drug use	38 (70)
Tattooing	41 (76)
Sexual partners with HCV infection	10 (19)
Blood transfusion	5 (9)

History of cocaine use, n (%)	22 (41)
History of alcohol abuse, n (%)	22 (41)
History of methamphetamine use, n (%)	2 (4)
HIV co infection, n (%)	3 (6)
Underlying psychiatric disorders (depression, bipolar disorder, schizophrenia and anxiety), n (%)	19 (35)
Underlying medical conditions (diabetes mellitus, hypertension, others), n (%)	28 (52)

Abbreviations: ALT = alanine transminase; BMI = body mass index; HCV = hepatitis C virus; HIV = human immunodeficiency virus; RNA = ribonucleic acid; SD = standard deviation.

Table 2: Comparison of demographics, clinical characteristics and laboratory data between patients with and without sustained virological response (SVR).

Characteristics	**Patients with SVR (n=41)**	**Patients without SVR (n=13)**	***P*-Value**
Male gender, n, (%)	30 (73)	6 (46)	0.11
Caucasians, n (%)	23 (56)	8 (62)	0.94
Age <50 years, n (%)	25 (60)	10 (77)	0.24
Genotype 1, n (%)	18 (44)	12 (92)	**0.01***
Risk factors for acquiring HCV infection, n (%)			
Injection drug use	26 (63)	12 (92)	0.28
Blood transfusion	4 (10)	1 (8)	0.21
Baseline characteristic and risk factors			
Alcohol abuse, n (%)	14 (47)	8 (62)	0.22
Cocaine use, n (%)	13 (32)	7 (54)	0.15
Methamphetamine use, n (%)	0 (0)	2 (15)	0.15
HIV co-infection, n (%)	1 (3)	2 (15)	0.47
Psychiatric disorders, n (%)	14 (34)	5 (38)	0.75
Knodell score < 11, n (%)	16 (64)[a]	10 (77)[b]	0.07
HCV RNA (x10^6 IU/mL, mean ± SD)	4.6±5.6	8.3±15.6	0.22
Weight (kilograms, mean ± SD)	92.1±22.2	77.9±16.0	0.10
Baseline laboratory data			
WBC (X 10^3 cells/μl, mean ±SD)	6.6±3.1	6.8±2.8	0.97
Hemoglobin (g/dl, mean ± SD)	15.3±0.9	14.8±1.2	0.91
Platelet (X 10^5 cells/μl, mean ± SD)	184.0±93.8	239.7±99.7	0.14
ALT (U/L, mean ± SD)	78.5±70.5	63.6±28.8	0.31
Total bilirubin (g/dl, mean ± SD)	1.1±0.7	0.8±0.2	0.47
Albumin (g/dl, mean ± SD)	3.8±0.4	4.0±0.2	0.10
End of treatment laboratory data			
WBC (X 10^3 cells/μl, mean ± SD)	2.9 ±1.1	3.6±0.9	**0.02***
Hemoglobin (g/dl, mean ± SD)	11.8 ± 1.8	11.7±1.5	0.42
Platelet (X 10^6 cells/μl, mean ± SD)	122.4 ± 96.8	207.2±86.5	**0.05***
ALT (U/L, mean ± SD)	35.3 ± 26.8	36.6±28.1	0.60
Total bilirubin (g/dl,) mean ± SD)	1.4 ± 1.4	0.8± 0.3	0.13
Albumin (g/dl, mean ± SD)	3.8 ±0.3	3.8±0.5	0.95
Clinically significance relevantce characteristic and laboratory data			
Weight loss > 5 Kilograms, n (%)	29 (71)	5 (38)	**0.04***
End of treatment WBC count less than 3 X 10^3 cells/μl	34 (83)	3 (23)	**0.01***
End of treatment platelet count less than 1X 10^5 cells/μl	36 (88)	7(54)	0.06

Note: * Statistical significant. Biopsy results; [a] total n for SVR = 25; [b] total n for non SVR =13.

Abbreviations: ALT = alanine transminase; HCV = hepatitis C virus; RNA = ribonucleic acid; SD = standard deviation; SVR = sustained virological response; WBC = white blood cell count.

Table 3: Logistic regression and multivariate analysis for the predictors of SVR (Clinical significance relevance characteristic and laboratory data)

Variables	OR (95% CI)	*P*-value	Adjusted# OR (95% CI)	*P*-value
Age < 50 year	2.5 (0.57-10)	0.24	1.38 (0.23-8.33)	0.73
Genotype Non-1	15.33 (1.82-129.18)	**0.01***	15.22 (1.55-149.72)	**0.02***
Weight loss more than 5 kilograms	3.86 (1.05-14.82)	**0.04***	5.74 (1.24-26.32)	**0.04***
End of treatment WBC count less than 3 X 10^3 cells/μl	9.52 (1.86-50.00)	**0.01***	9.09 (1.59-52.63)	**0.02***
End of treatment platelet count less than 1X 10^5 cells/μl	6.9 (0.8-5.9)	0.06	2.43 (0.13-45.45)	0.51

Note: * Statistical significant. # Model adjusted with all table variables.

Abbreviation; CI = confidence interval; OR = odds ratio; SVR = sustained virological response; WBC = white blood cell.

DISCUSSION

The overall rate of response was 76% comparable with those reported in the previous US studies of 55%. Responses were better for both genotype 1 (56% vs 52%) and others (96% vs 81-84%).[2] Our study strongly indicated that being infected with HCV genotype 1 was associated with treatment failure. The higher treatment response in our study compared to the US literatures may have occurred from differences in our demographic population. Our study had less African Americans (only 1 patient), and a lower prevalence of HCV genotype 1 and HIV co –infection. Higher response rates among Asians have been noted before. This may be related to the *IL28B* gene polymorphism as it is apparently associated with higher response to treatment among Asian Americans patients compared to Caucasians, Hispanics and African Americans, respectively (19).

In our study, the patients with SVR had significant weight loss compared to those without SVR. The association between body weight, weight loss and SVR is controversial. Some previous studies showed that initial body weight is an independent risk factor for HCV treatment failure, and weight reduction was associated with treatment success (10, 20). However, other studies demonstrated that weight loss did not improve the treatment outcomes (15, 21). It is known that interferon therapy is associated with weight loss, but the mechanism and pathophysiology are still unclear. The reasons for weight loss among the study population are unclear. Many patients complained of loss of appetite or ate less related to the fatigue. Studies suggest that interferon decreases appetite via induction of tumor necrosis factors (TNF), the level of leptin, insulin and cytokines but findings are not consistent (21-24). Alternatively, several studies showed that TNF levels were not increased during interferon therapy and postulated other mechanisms of weight loss including changes in level of leptin and insulin which affect glucose metabolism (21, 22). In our studies, weight loss usually began within the first few dosages of interferon treatment. It was also associated with fatigue, nausea, vomiting. The weight loss was usually sustained during therapy or gradually progressed. On the follow-up after complete treatment, patients usually gained weight but did not achieve their baseline bodyweight.

In our study, patients with SVR had significantly lower WBC and platelet count at the end of treatment compared to those without SVR. These findings suggested that patients who developed leukopenia and/or thrombocytopenia during the interferon treatment responded well to the therapy and these side effects, if not severe, may not be indications for withholding or reducing the dose of the treatment. We hypothesized that the greater cytopenia is a marker for greater TNF activity in a specific treatment recipient which translates into greater SVR. Common side effects of interferon treatment that need to be monitored during the therapy are anemia, thrombocytopenia and leukopenia (25-29). These side effects may prevent physicians from continuing their patients on interferon therapy or reducing dosage (28, 29). A comparison of outcome by the approach of reducing interferon and/or ribavirin versus use of growth factors to stimulate promotion of white blood cell or red blood cell or platelet counts has not been done but is clearly needed. We believe that the differences in magnitude of interferon effects on individual pharmacokinetics, pharmocodynamics, and genetic determination of interferon susceptibility may play an important role in each patient's treatment response and side effect experience.

Our patients had a high rate of mental illnesses and social problems because of our open referral sys-

tem and the population at risk. However, the majority of patients tolerated HCV treatment which can be attributed to our supportive staff and follow-up system. The potential interaction between psychiatric illness and its treatment with HCV therapy could not be assessed with our limited study.

This study is limited in that it is retrospective and examined only subjects who completed HCV therapy. The association of SVR with factors reported by others, such as age, histological (fibrosis) score, viral load and alanine transminase level was not significant in our study. This may be related to the small sample size. Other factors such as adherence and insulin resistance were not assessed. The majority of patient with genotype 2 and 3 did not have liver biopsy reports. Further studies with larger sample size and molecular testing may enhance our understanding of the relationship between interferon and antiviral therapy in chronic hepatitis C infection.

In conclusion, the virological outcomes of the current HCV infection therapy in our study were comparable with the outcomes of the previous studies. The treatment failure was significantly associated with genotype 1. Side effects of interferon therapy including leukopenia, thrombocytopenia and weight loss were predictors of good treatment response. Giving these findings, a careful assessment is needed in regards to continuing therapy with interferon and ribavirin despite opposed adverse effects by laboratory parameters and weight loss.

ACKNOWLEDGEMENT

This work was supported by a Research Centers in Minority Institutions award, P20RR011091, from the National Center for Research Resources, National Institutes of Health. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCRR/NIH. The authors greatly appreciate Teera Chentanez, MD. for initial statistical analysis and Kathleen K. Baker Ph.D. M.S., research statistician, Hawaii Department of Health for recommendations regarding final statistic analysis.

CONFLICT OF INTEREST

Alan Tice has recently been a consultant or speaker or investigator for Roche, Schering, 3 Rivers, Human Genome Science, and Novartis.

REFERENCES

1. Lauer GM, Walker BD. Hepatitis C virus infection: Medical progress. N Engl J Med 2001; 345: 41-51.
2. Hoofnagle JH, Seeff LB. Peginterferon and ribavirin for chronic hepatitis C. N Engl J Med 2006; 355: 2444-51.
3. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C infection in the United States, 1999 through 2002. Ann Intern Med 2006; 1444: 705-14.
4. Simmonds P, Bukh J, Combet C, et al. Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. Hepatology 2002; 36: S21-9
5. Rifai MA, Moles JK, Short DD. Hepatitis C treatment eligibility and outcomes among patients with psychiatric illness. Psychiatr Serv 2006; 57: 570-2.
6. Sylvestre DL, Clements BJ. Adherence to hepatitis C treatment in recovering heroin users maintained on methadone. Eur J Gastroenterol Hepatol 2007; 19: 741-7.
7. Krook AL, Stokka D, Hegar B, et al. Hepatitis C treatment of opioid dependants receiving maintenance treatment: results of Norwegian pilot study. Eur Addict Res 2007; 13: 216-21.
8. Gheorghe L, Iacob S, Sporea I, et al. Efficacy, tolerability and predictive factors for early and sustained virologic response in patients treated with weight-based dosing regimen of PegIFN alpha-2b and ribavirin in real-life healthcare setting. J Gastrointestin Liver Dis 2007; 16: 23-9.
9. Shiffman ML, Suter F, Bacon BR, et al. Peginterferon alfa-2a and ribavirin for 16-24 weeks in HCV genotype 2 or 3. N Engl J Med 2007; 357: 124-34.
10. Wenger C, Bischof T, Gonvers JJ, et al. Interferon and ribavirin with or without amantadine for interferon non-responders with chronic hepatitis C. Swiss Med Wkly 2007; 137: 418-23.
11. Bressler BL, Guindi M, Tomlinson G, et al. High body mass index is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C. Hepatology 2003; 38: 639-44.
12. Males S, Gad RR, Esmat G, et al. Serum alpha-fetoprotein level predicts treatment outcome in chronic hepatitis C. Antivir Ther 2007; 1215: 797-803.
13. Yu JW, Wang GQ, Sun LJ, et al. Predictive value of rapid virological response and early virological response on sustained virological response in HCV patients treated with pegylated interferon alpha- 2a and ribavarin. J Gastroenterol Hepatol 2007; 22: 832-36.
14. Backus LI, Boothyroyd DB, Phillips BR, et al. Predictors of response of U.S. Veterans to treatment for Hepatitis C virus. Hepatology 2007; 46: 37-47.
15. Lo Re V 3rd, Kostman JR, Gross R, et al. Incidence and risk factors for weight loss during dual HIV/Hepatitis C virus therapy. J Acquir Immune Defic Syndr 2007; 44: 344-50.
16. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med 2007; 147: 677-84.
17. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975–82.
18. Lindsay KL, Morishima C, Wright EC, et al. Blunted cytopenias and weight loss: new correlates of virologic null response to re-treatment of chronic hepatitis C. Clin Gastroenterol Hepatol 2008; 6: 234-41.
19. Ge D, Fellay J, Thompson AJ, et al. Genetic Variation in *IL28B* predicts hepatitis C treatment-induced viral clearance. Nature 2009;461: 399-401.
20. Widjaja A, Wedemeyer H, Tillmann HL, et al. Hepatitis C and leptin system: bound leptin levels are elevated in patients with hepatitis C and decrease during antiviral therapy. Scand Gastroenterol 2001; 36: 426-31.
21. Tilg H, Vogel W, Dinarello CA. Interferon-alpha induces circulating tumor necrosis factor receptor p55 in humans. Blood 1995; 85: 433-5.
22. Seyam MS, Freshwater DA, O'Donnell K, et al. Weight loss during pegylated interferon and ribavirin treatment of chronic hepatitis C. J viral Hepat 2005; 12: 531-5.

23. Matarese G, La Cava A. The intricate interface between immune system and metabolism. Treds Immunol 2004; 25: 193-200.
24. Enjoji M, Nakamuta M, Iwao M, et al. Leptin response in patients undergoing interferon therapy. J Clin Gastroenterol 2002; 34: 287-8.
25. Sulkowski MS, Wasserman R, Brooks L, et al. Changes in haemoglobin during interferon alfa-2b plus ribavirin combination therapy for chronic hepatitis C virus infection. J Viral Hepat 2004; 11: 243-50.
26. Sulkoski M. Management of the hematologic complications of hepatitis C therapy. Clin Liver Dis 2005; 9: 601-16.
27. Soza A, Everhart JE, Ghany MG, et al. Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. Hepatology 2002; 36: 1273-9.
28. Perry CM, Wagstaff AJ. Interferon-alpha-n1: A review of its pharmacological properties and therapeutic efficacy in the management of chronic viral hepatitis. BioDrug 1998; 9: 125-54.
29. Turbide C, Soulellis C, Deschenes M, et al. Does a decline in the hematological and biological parameters induced by interferon and ribavirin combination therapy for the hepatitis C virus predict a sustained viral response? Can J Gastroenterol 2008; 22: 149-52.