Int.J.Curr.Microbiol.App.Sci (2016) *5*(1): 350-363

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 5 Number 1(2016) pp. 350-363**
Journal homepage: http://www.ijcmas.com

Original Research Article http://dx.doi.org/10.20546/ijcmas.2016.501.033

Hematological Side Effects of Pegylated Interferon/ Ribavirin Therapy in Chronic HCV Egyptian Patients

Ehab F Mostafa[1], Mahmoud Saif-Al-Islam[2], Sahar M Hassany[1*], Yehya Rashad Abd-Alrhman[3] and Mohammed Abd Allah Mohammed[4]

[1]Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, Assiut University, Egypt
[2]Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, Sohag University, Egypt
[3]Sohag hospital of infecious diseases, Sohag University, Egypt
[4]Clinical Pathology Department, Faculty of Medicine, Sohag University, Egypt
**Corresponding author*

Keywords

Pegylated Interferon, Ribavirin Therapy, Hepatitis C virus (HCV), oral ribavirin

Article Info

Accepted:
16 December 2015
Available Online:
10 January 2016

A B S T R A C T

Hepatitis C virus (HCV) infection is a major health problem throughout the World. Egypt has the highest worldwide prevalence of HCV (10-20%). The combination of peginterferon and ribavirin can achieve sustained virologic response in over 50% of those treated**.** However, adherence to treatment is critical to maintain high rates of virologic clearance**.** Unfortunately, peginterferon plus ribavirin therapy can be associated with side effects, some of which may lead to dose reduction, premature discontinuation of the drug, and subsequent treatment failure. is to detect and to manage the hematological side effects of pegylated interferon/ribavirin therapy in chronic HCV in Egyptian patients. This study was done in Sohag city on 500 Egyptian patients who are candidates for pegylated interferon/ ribavirin therapy for chronic HCV**.** All patients were treated with peginterferon alfa 2a (180 mcg /week) or peginterferon alfa 2b (1.5 mcg/kg weekly) subcutaneously plus oral ribavirin in a dose ranging from 800-1200 mg/day for 48 weeks. Baseline pretreatment assessment included quantitative HCV-PCR, liver and kidney functions, complete blood picture, T3 and T4 levels, abdominal ultrasonography, liver biopsy, fundus examination and ECG. Liver functions and complete blood picture were done at the 4th, 12th, 24th, and 48th weeks. HCV- PCR was followed up at the 12th, 24th, and 48th weeks. During the period of our study, 153 (30.6%) of the studied patients had decrease in hemoglobin level to 10 g/dl, while severe anemia with hemoglobin level less than 8.5 g/dl was found in 33 (6.6%) patients. Reduction of total leucocytic count to 2000 cells/mm^3 was found in 49 (9.8%) patients, while severe neutropenia with neutrophils count less than 750 cells/mm^3 was found in 12 (2.4%) patients. Asymptomatic thrombocytopenia with platelets count from 50000 to 150000/mm^3 was found in 141 (28.2%) patients, while severe thrombocytopenia with platelets count less than 50000/mm^3 was found in 3 (0.6%) patients. the hematological side effects of pegylated interferon and ribavirin are anemia, leucopenia, and thrombocytopenia in 30.6%, 9.8% and 34% of the patients during the course of the treatment. These side effects can be managed by dose reduction or stoppage and by administration of erythropoietin and Granulocyte colony-stimulating factor (G-CSF).

Introduction

Hepatitis C virus (HCV) infection is a major health problem throughout the world. Recent estimates indicate that 175 million people are infected (1). Egypt has the highest worldwide prevalence of HCV (10-20%). More than 90% of HCV isolates from Egyptian patients are of the genotype 4 variant (2,3). In rural areas of Egypt the prevalence of HCV reaches 24%. Other countries where genotype 4 is prevalent include the equatorial and west-central African nations of Gabon, Tanzania, Libya, and Zaire, where seroprevalence can reach up to 8% (4).

Antiviral therapy for chronic hepatitis C has many goals; the primary goal is durable viral clearance as evidenced by the absence of HCV RNA in serum (virological response); the secondary goal is reduction of damage to the liver as determined by either persistently normal ALT levels (biochemical response) or improved liver biopsy, with the expectation that this will delay or prevent cirrhosis and HCC (5).

The combination of peginterferon and ribavirin can achieve sustained virologic response in over 50% of those treated. However, adherence to treatment is critical to maintain high rates of virologic clearance (6). Unfortunately, peginterferon plus ribavirin therapy can be associated with side effects, some of which may lead to dose reduction, premature discontinuation of the drug, and subsequent treatment failure (7).

Interferon (IFN) induced thrombocytopenia and leucopenia are common whereas anaemia is more a sequela of combination therapy with ribavirin (8). Thrombocytopenia is mild in most cases, amounting to a decrease in peripheral platelet count to 10-50% but, when severe, can lead to bleeding complications (9,10) and discontinuation of IFN therapy (6). Absolute neutrophil and lymphocyte counts typically decrease by 30-50% of baseline values during IFN therapy but this is usually not associated with infection (11).

The main mechanism leading to cytopenia during IFN therapy seems to be bone marrow suppression by IFN (8). Immune mediated hematological toxicity and capillary sequestration of platelets and white blood cells have been proposed as additional causes of severe thrombocytopenia and leucopenia during IFN therapy (10).

Ribavirin causes dose-dependent hemolytic anemia, and interferon can suppress bone marrow production of red blood cells. This result in anemia, which is likely in more than 20% of patients treated with pegylated interferon and ribavirin (12, 13). We aimed of this work is to detect and to manage the hematological side effects of pegylated interferon/ribavirin therapy in chronic HCV in Egyptian patients.

Materials and Methods

This study was done in Sohag city on 500 Egyptian patients who are candidates for pegylated interferon/ ribavirin therapy for chronic HCV (after a written consent). All patients were treated with peginterferon alfa 2a (180 mcg /week) or peginterferon alfa 2b (1.5 mcg/kg weekly) subcutaneously plus oral ribavirin in a dose ranging from 800-1200 mg/day for 48 weeks.

Pre-treatment Evaluation

I- Complete history taking and thorough clinical examination.

II- Laboratory investigations:

1- HCV Ab was carried out using fully automated ELISA (Axsym).

2- Quantitative HCV RNA level by PCR: for estimation of viral load, the test was carried out using the real time PCR system.

3- Liver functions and renal functions: including albumin, AST and ALT levels, which were carried out using the fully automated chemical analyzer (Bechman Caulter Alex 9).

4- Prothrombin time and INR using sysmex ca 1500 system.

5- Complete blood count (CBC) was carried out using the fully automated cell counter celldyn 3700. Pre-existing leucopenia or thrombocytopenia is a relative contraindication to treatment of HCV infection.

6- Thyroid profile: as a base line, as autoimmune thyroiditis can be caused or exacerbated by pegylated interferon. It was carried out using fully automated ELISA (Axsym).

III- Abdominal ultrasonography: to evaluate liver size and parenchyma and exclude ascites.

IV- Liver biopsy: to determine the grade of inflammation and the stage of fibrosis.

V- Upper GIT endoscopy: to exclude esophageal varices.

VI- Fundus examination.

VII- Electrocardiography (ECG).

Inclusion Criteria

Patients with chronic HCV who are candidates for interferon/ ribavirin therapy:

- Age is from 18 to 60 years.

Liver Biopsy

Minimal changes in the liver biopsy with Metavir score >A1 and >F0 with elevated liver enzymes.

Those with normal liver enzymes and Metavir score ≥ A2 and ≥ F2.

Quantitative HCV PCR was done before treatment and after 12 weeks of treatment. Therapy will continue only for responders and those with more than 2 log decrease in viral load after 12 weeks of treatment.

Qualitative HCV PCR was done after 24 weeks of treatment and therapy will continue only if PCR is negative.

Compensated liver cirrhosis (Child A) will be treated if there is no varix.

Exclusion Criteria

Body mass index (BMI) >35 will not be treated except after body weight reduction.

Patients with contraindication to interferon/ ribavirin therapy:

• Non-compliant or psychosocially unstable patient with active psychosis, major depression, active autoimmune disease, active bacterial infection (e.g. osteomyelitis).

• Pregnancy or lack of appropriate contraception (male and female, as ribavirin is teratogenic).

• Significant comorbidity such as renal failure, heart disease or uncontrolled diabetes mellitus.

• Decompensated liver disease.

• Males with hemoglobin less than 13g/dl and females with hemoglobin less than 12 g/dl.

• Platelets count less than 150000/mm^3 or white blood cells less than 4000/mm^3 or neutrophil count less than 1500/mm^3.

Monitoring and Follow up of Patients During the Course of Treatment (to Detect Possible Complications of Therapy)

I-Complete history taking and thorough clinical examination: with special stress on:

• Constitutional symptoms like fatigue, headache, myalgia and fever.

• Gastrointestinal symptoms like nausea, anorexia and diarrhea.

• Symptoms suggestive of psychiatric side effects like insomnia, irritability and depression.

• Symptoms suggestive of any visual changes.

• Skin examination to detect the presence of hair loss or skin rash.

II- Laboratory investigations with special stress on:

• CBC: to detect any possible hematological side effects.

• Liver profile including AST and ALT levels.

• Liver function tests and CBC were done regularly at 4^{th}, 12^{th}, 24^{th} and 48^{th} weeks.

• Renal profile including serum urea and creatinine.

• The level of HCV RNA post-treatment to determine the pattern of virological response. HCV PCR was fallowed up at 12^{th}, 24^{th} and 48^{th} weeks.

III- Abdominal ultrasonography.

IV- Psychiatric, hematological, dermatological or ophthalmological consultations were done when needed.

Treatment was Reduced to Half of the Dose in the Following

• Hemoglobin level ranging from 8.5 g/dl to 10 g/dl (reduce the dose of ribavirin to 600 mg)**.**

• Platelets count ranging from 25000/mm^3 to 50000/mm^3.

• White blood cells count less than 1500/mm^3**.**

• Neutrophiles count less than 750/mm^3**.**

Treatment was Discontinued in the Following

• Patients with positive HCV PCR after 12 weeks**.**

• Hemoglobin level less than 8.5g/dl (stop ribavirin).

• Platelets count less than 25000/mm^3**.**

• White blood count less than 1000/mm^3**.**

• Neutrophiles count less than 500/mm^3.

Results and Discussion

This study was conducted on 500 consecutive patients with proven chronic hepatitis C virus. The baseline demographic and laboratory characteristics of the studied patients were shown in Table 1. The mean age was 41.66±10.32 years. All patients had normal baseline blood indices as a prerequisite for initiating treatment.

Anemia with hemoglobin levels below 10 g/dl was detected in 3.2 % of cases at the 4th week, 11% of cases at the 12th week, 9% of cases at the 24th week and 3% of cases at the 48thweek. The highest frequency of anemia reaching 11% was found at the 12thweek. None of the patients developed anemia with hemoglobin below 6.4 g/dl (Table 2).

30.6% of the studied patients had decrease in hemoglobin to 10 g/dl, while 69.4% of the patients did not have anemia during the course of treatment. 19.4% of the cases had anemia at one time point, 9.2% of the cases had anemia at two time points, 1.2% of the cases had anemia at three time points and 0.8% of the cases had anemia at four time points during treatment (Figure 1).

Ribavirin dose was reduced when hemoglobin level reached below 10 g/dl and the patient received erythropoietin. In our study, 8.4% (42/500) discontinued INF and RBV combination therapy because of anemia.

There was highly significant difference in baseline characteristics between patients who developed anemia and those who did not. Patients who developed anemia had older age, male sex preponderance, higher body mass index, lower base line hemoglobin level, higher levels of ALT and higher viremia by PCR (Table 3).

Significant leucopenia with WBC count <2000 cell/mm^3 was detected in 0.6% of cases at the 4th week, 1.4 % of cases at the 12th week, 2.6 % of cases at the 24th week and 2% of cases at the 48th week (Table 4).

90.2% of the patients did not have significant leucopenia during the course of treatment. 5.8% of the cases had leucopenia at one time point, 1.6% of the cases had leucopenia at two time points, 1.4% of the cases had leucopenia at three time points and 1% of the cases had leucopenia at four time points during treatment (Figure 2).

There was highly significant difference in baseline characteristics between patients who developed significant leucopenia and those who did not. Patients who developed significant leucopenia had older age, male sex preponderance, higher body mass index, higher levels of ALT and higher viremia by PCR (Table 5).

Asymptomatic thrombocytopenia with platelets count ranging from 150000 to 50000/mm^3 was detect in 16% of the patients at the 4thweek, 17.4% at the 12th week, 20% at the 24th week and 14.8% at the 48th week (Table 6).

71.8 % of the patients did not have asymptomatic thrombocytopenia during the course of treatment. 10% of the cases had asymptomatic thrombocytopenia at one time point, 9.6% of the cases had asymptomatic thrombocytopenia at two time points, 5.2% of the cases had asymptomatic thrombocytopenia at three time points, and 3.4% of the cases had asymptomatic thrombocytopenia at four time points during treatment (Figure 3).

There was highly significant difference in

baseline characteristics between patients who developed asymptomatic thrombocytopenia and those who did not. Patients who developed asymptomatic thrombocytopenia were younger, had lower body mass index, had higher levels of ALT and lower levels of viremia by PCR. There is no significance difference between males and females regarding the development of thrombocytopenia (Table 7).

Severe anemia with hemoglobin level below 8.5 g/dl was present in 6.6% patients, severe neutropenia below 750 cells/mm^3 was present in 2.4% patients, severe thrombocytopenia below 50000/mm^3 was present in 0.6% patients, mild to moderate anemia with hemoglobin level between 8.5-10 g/dl was present in 30.6% patients, and asymptomatic thrombocytopenia with platelets count from 150000-50000/mm^3 was present in 34% patients. The lowest leucocytic count was 1.2 cells/ mm^3 and it was found in 0.6% patients (Table 8).

Figure (4) summarizes all the hematological side effects which had occurred all over the course of treatment. Anemia, leucopenia and asymptomatic thrombocytopenia, were found in 3.2%, 0.6% and 16% patients at the 4thweek; 11%, 1.4% and 17.4% patients at the 12thweek; 9%, 2.6% and 20% patients at the 24th week; 3%, 2% and 14.8% patients at the 48th week respectively.

Table.1 Baseline Demographic and Laboratory Characteristics of the 500 Studied Patients

	Mean	**Standard deviation**
Age	41.66	±10.32
Weight	73.48	±12.02
Height	169.63	±6.07
Body mass index	25.53	±3.88
ALT	38.79	± 39.79
Hemoglobin	14.81	±1.53
White blood cell	6.46	±2.06
Platelets	235900	±53.62
Ribavirin	1028.4	± 164.34
PCR	771979.38	±161966.0

ALT: alanine aminotransferase
PCR: polymerase chain reaction

Table.2 Anemia During the Course of Treatment among the 500 Studied Patients

Follow up time	**Hemoglobin<10 g/dl**	
	Number	**Percent**
4th week	16	3.2
12th week	55	11.0
24th week	45	9.0
48th week	15	

		3.0

Table.3 Comparison Between Patients with and without Anemia

	Patients with anemia (153)	**Patient without anemia (347)**	**P value**
Age	44.07±10.49	40.60±10.07	0.0001
Male:female	125:28	322:25	0.0001
Body mass index	25.83±3.48	25.40±4.04	0.0001
Base line hemoglobin level	13.9±1.45	15.07±1.44	0.0001
ALT	42.96±50.71	36.95±33.81	0.0001
PCR	871748.7±2285340.0	727988.9±1217617.0	0.0001

ALT: alanine aminotransferase
PCR: polymerase chain reaction

Table.4 Significant Leucopenia during the Course of Treatment among the 500 Studied Patients

Follow up time	**WBC <2000cell/mm^3**	
	Number	**Percent**
4th week	3	0.6
12th week	7	1.4
24th week	13	2.6
48th week	10	2.0

WBC: white blood cells

Table.5 Comparison between Patients with and without Significant Leucopenia during the Course of Treatment

	Patients with significant leucopenia (49)	**Patients without significant leucopenia (451)**	**P value**
Age	44.96±10.44	40.72±10.10	0.0001
Male:female	89:22	358:31	0.0001
Body mass index	25.82±3.83	25.57±3.89	0.0001
ALT	45.96±37.43	39.59±40.45	0.0001
PCR	1042740±2644491	694718.6±116798.7	0.0001

ALT: alanine aminotransferase
PCR: polymerase chain reaction

Table.6 Frequency of Asymptomatic Thrombocytopenia during the Course of Treatment Among the 500 Studied Patients

Follow up time	Asymptomatic thrombocytopenia <150000-50000cell/mm^3	
	Number	Percent
4th week	80	16.0
12th week	87	17.4
24th week	100	20.0
48th week	74	14.8

Table.7 Comparison between Patients with and without Asymptomatic Thrombocytopenia during the Course of Treatment

	Patients with asymptomatic thrombocytopenia (141)	Patients without thrombocytopenia (359)	P value
Age	38.68±10.3	43.2±10	0.0001
Male:female	153:17	294:36	0.754
Body mass indes	25.28±3.93	25.37±3.85	0.0001
ALT	47.45±39	34.33±39.51	0.0001
PCR	699553±2065266	809289.9±1335558	0.0001

ALT: alanine aminotransferase
PCR: polymerase chain reaction

Table.8 Severe Side Effects of Therapy

	Number	percent
Severe anemia (hemoglobin < 8.5 g/dl)	33	6.6
Severe neutropenia (neutophils < 750 cells/mm^3)	12	2.4
Severe thrombocytopenia (platelets < 50000/mm^3)	3	0.6
Mild to moderate anemia (hemoglobin = 8.5-10 g/dl)	153	30.6
Asympatomatic thrombocytopenia (platelets = 50000-150000/mm^3)	170	34
Lowest leucocytic count 1.2 cells/mm^3	3	0.6%

Figure.1 Frequency of Anemia among the Patients during the Course of Treatment

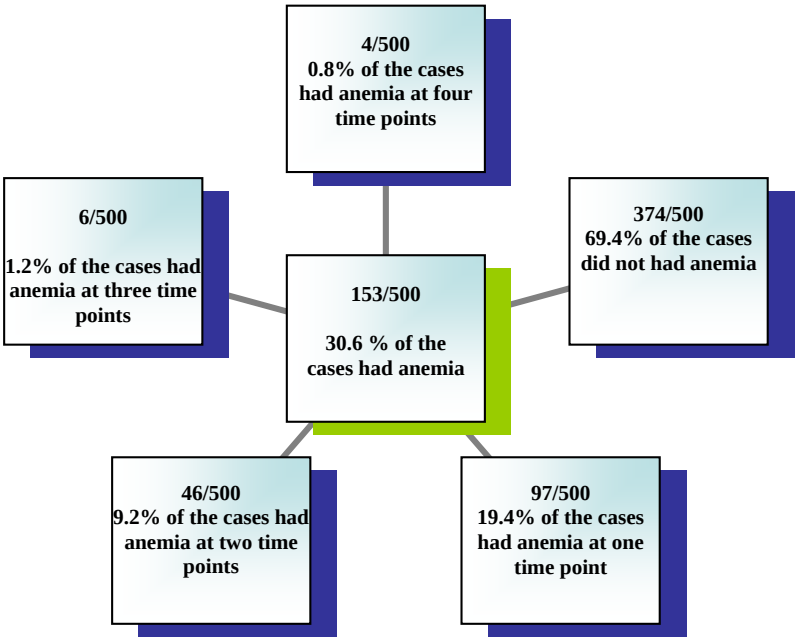


Figure.2 Frequency of Significant Leucopenia among the Patients during the Course of Treatment

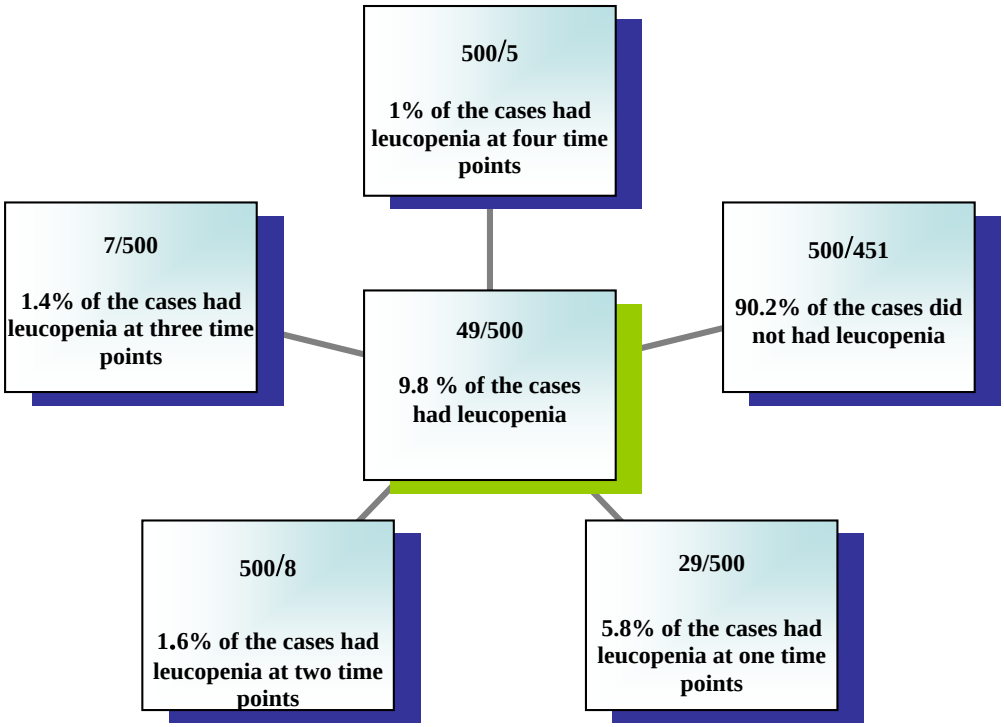


Figure.3 Frequency of Asymptomatic Thrombocytopenia among Patients during the Course of Treatment

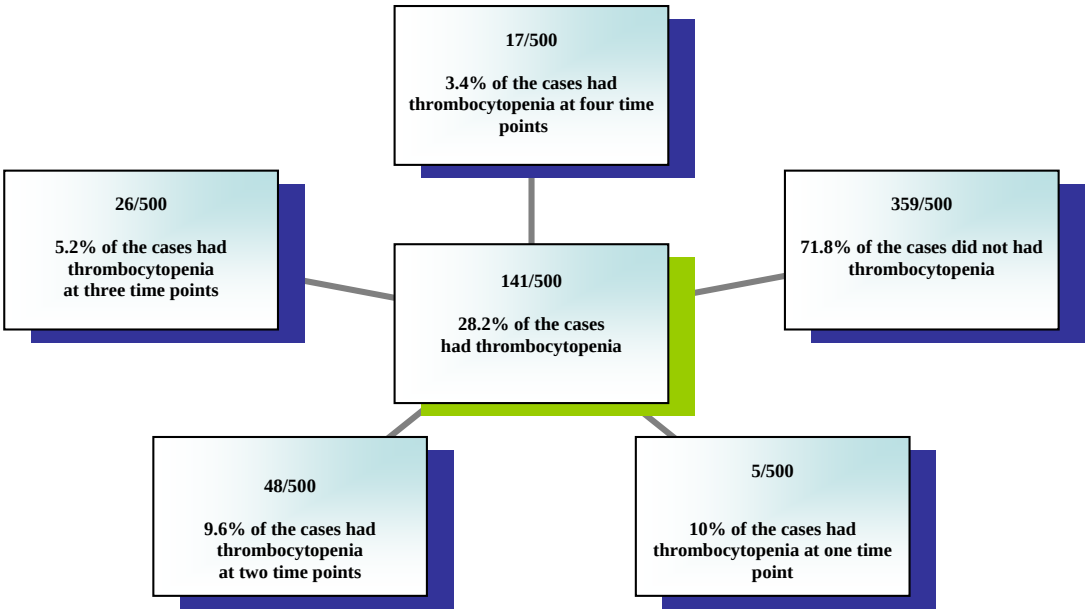
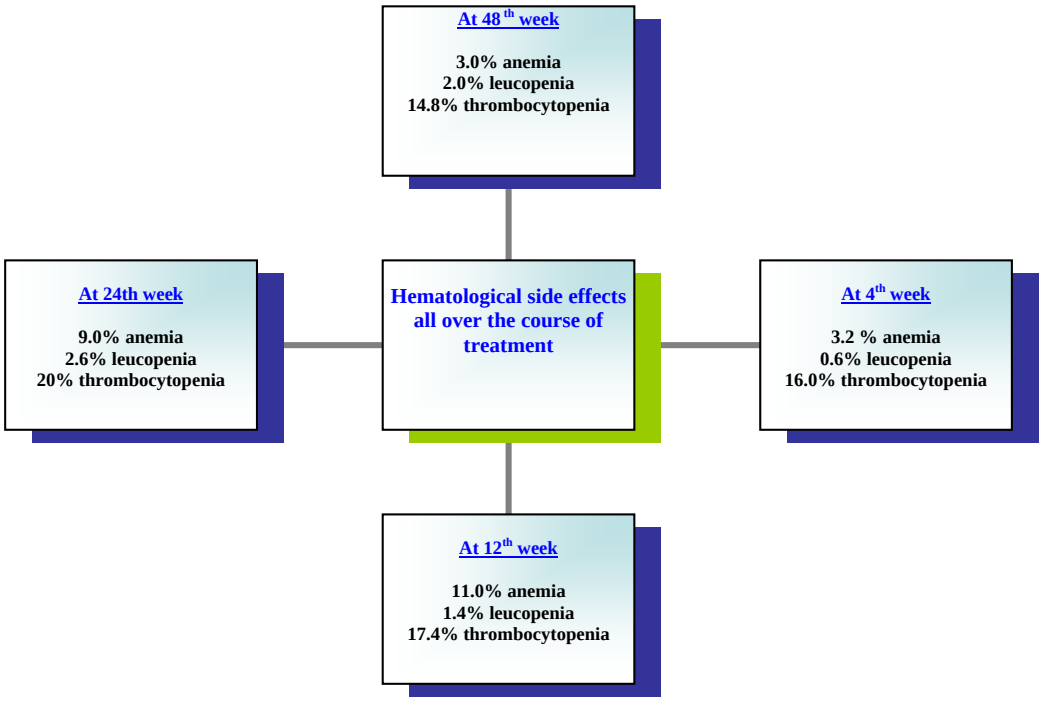


Figure.4 Summary of Hematological Side Effects during Treatment



The number of patients for whom ribavirin dose was reduced due to decrease of hemoglobin level to 10-8.5 g/dl and received erythropoietin was 111 (22.2%) patients, while the number of patient who stopped the treatment due to decrease of hemoglobin below 8.5 was 42 (8.4%) patients and also received erythropoietin.

The number of patients for whom interferon dose was reduced due to decrease neutrophil count below 750 cells/mm^3 was 12 (2.4) and received Granulocyte colony-stimulating factor (G-CSF).

In our study we followed 500 patients infected by chronic HCV receiving peginterferon alpha 2a (180 mcg /week) or peginterferon alfa-2b (1.5 mcg/kg weekly) subcutaneously plus oral ribavirin in a dose ranging from 800-1200 mg/day for 48 weeks. Our aim was to detect and to manage the hematological side effects of peginterferon alpha (2a or 2b) and ribavirin.

In our study, 30.6% of the studied patients had decrease in hemoglobin to 10 g/dl. The incidence of anemia in different weeks of treatment was 3.2% at 4^{th} week, 11% at 12^{th} week, 9% at 24^{th} week and 3% at 48^{th} week. Recent trials have demonstrated that higher starting doses of ribavirin can improve SVR rates in difficult-to-treat populations. Early indicators of subsequent considerable anemia should prompt the physician to consider early and small reductions in ribavirin dose (200 mg decrements) to reduce the risk of considerable anemia while maintaining adequate exposure to ribavirin (14,15). The use of recombinant human erythropoietin is not an easy option in Egypt where the therapy costs represent a major problem that limits adherence to therapy.

The results of the current study are in agreement with that of Fried who found that more than 20% of patients treated with pegylated interferon and ribavirin (in a dose of 1000-1200 mg/day) had anemia (16). We found that 8.4% of the patients discontinued IFN and RBV combination therapy because of anemia. However, Saito and coworkers found that 14.5% of the patients discontinued IFN and RBV combination therapy because of anemia (17).

The anemia is probably multifactorial in most cases. Some degree of hemolysis is virtually universal in patients receiving RBV. Erythrocytes selectively accumulate RBV metabolites, sustain oxidative membrane damage and become subject to increased extravascular hemolysis in the reticuloendothelial system. In addition, IFNs can directly suppress bone marrow erythropoiesis, thus impairing the response to RBV-induced hemolysis. Ribavirin itself has also been reported to have myelosuppressive properties (18).

In our study, we identified several independent factors, including older age, male sex, higher body mass index, lower base line hemoglobin level, higher ALT levels and higher viremia by PCR that were predictive of subsequent development of considerable decrease in hemoglobin, allowing the opportunity to identify patients at heightened risk of developing anemia even before starting therapy.

We found that, male gender, ages above forty years, body mass index more than 25, ALT above 42 and hepatitis C viremia more than 800000 were shown to be independent predictors of considerable decrease in hemoglobin in the multiple logistic regression analysis (both $p<0.0001$). Our results and those of others clearly show that anemia is a common and significant problem during treatment with interferon and ribavirin. A decline in hemoglobin begins shortly after initiation of treatment and generally reaches the lowest level after 4 to 8 weeks of therapy (19). Indeed, treatment-

induced anemia has been shown to be one of the most frequently reported adverse events and contributes to dose reductions and treatment discontinuations (7,19).

As regards total leucocytic count, we found that 9.8% had decreased WBCs count to less than 2000 cell/mm^3 during the treatment. The incidence of leucopenia in different weeks of treatment was 0.6% at the 4^{th} week, 1.4% at the 12^{th} week, 2.6% at the 24^{th} week and 2% at the 48^{th} week. Aspinall and Pockros found that patients receiving PEG-IFN alpha -2a combination or monotherapy experience significant neutropenia in approximately 20% of cases. Dose reductions occurred in monotherapy and combination therapy trials of PEG-IFN alpha -2a and RBV in 17-20% of individuals (18). Although anemia and leucopenia are reversible when therapy is discontinued, these hematological disorders have considerable impact on treatment outcome in relation to adequate ribavirin dosing (6).

Platelets counts were shown to drop during interferon and ribavirin therapy, due to interferon suppression of platelets production in the bone marrow. In our study 14.8% patients developed thrombocytopenia at the 48^{th} week of therapy, and only 0.6% developed severe thrombocytopenia below 50000/mm^3 during the course of treatment with subsequent dose reduction.

Aspinall and Pockros reported that interferon therapy frequently results in a 10-50% fall in the platelets count, although this is rarely of clinical significance. Possible mechanisms include a relative thrombopoietin deficiency, impaired thrombopoietin signal transduction in megakaryocytes, hypersplenism and in some cases increased immune-mediated sequestration of platelets (18).

In the trial reported by Fried only around 4-6% of patients receiving PEG-IFN alpha -2a and RBV required dose reduction for thrombocytopenia (16).

In conclusion the hematological side effects of pegylated interferon and ribavirin are anemia, leucopenia, and thrombocytopenia in 30.6%, 9.8% and 34% of the patients during the course of the treatment. These side effects can be managed by dose reduction or stoppage and by administration of erythropoietin and Granulocyte colony stimulating factor (G-CSF). Pegylated interferon and ribavirin proper doses are critical to the successful treatment of HCV and they should be initiated at the highest appropriate dose and maintained for as long as possible with appropriate management of the hematological side effects.

References

1.Hnatyszyn HJ (2005): Chronic hepatitis C and genotyping: The clinical significance of determining HCV genotypes. Antivir Ther; 10 (1):1-11.

2.Ray SC, Arthur RR, Carella A, Bukh J, Thomas DL (2000): Genetic epidemiology of hepatitis C virus throughout Egypt. J Infect Dis; 182 (3):698-707.

3.Kamal SM and Nasser IA (2008): Hepatitis C genotype 4: What we know and what we don't yet know. Hepatology; 47(4): 1371-83.

4.Abdel-Aziz F, Habib M, Mohamed MK, Abdel-Hamid M, Gamil F, Madkour S, Mikhail NN, Thomas D, Fix AD, Strickland GT, Anwar W, Sallam I (2000): Hepatitis C virus (HCV) infection in a community in the Nile Delta: population description and HCV prevalence. Hepatology; 32 (1):111-5.

5.Manns MP, Wedemeyer H, Cornberg M (2006): Treating viral hepatitis C: efficacy, side effects, and

complications. Gut; 55 (9): 1350-9.
6.McHutchison JG, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C, Dienstag J, Lee WM, Mak C, Garaud JJ, Albrecht JK (2002): Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology; 123 (4):1060-9.
7.Sulkowski MS, Wasserman R, Brooks L, Ball L, Gish R (2004): Changes in haemoglobin during interferon alpha-2b plus ribavirin combination therapy for chronic hepatitis C virus infection. J. Viral Hepat; 11 (3):243-50.
8.Russo MW and Fried MW (2003): Side effects of therapy for chronic hepatitis C. Gastroenterology; 124 (6):1711-9.
9.Soza A, Everhart JE, Ghany MG, Doo E, Heller T, Promrat K, Park Y, Liang TJ, Hoofnagle JH (2002): Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. Hepatology; 36 (5):1273-9.
10.Wang Q, Miyakawa Y, Fox N, Kaushansky K (2000): Interferon-alpha directly represses megakaryopoiesis by inhibiting thrombopoietin-induced signaling through induction of SOCS-1. Blood; 96 (6): 2093-9.
11.Schmid M, Kreil A, Jessner W, Homoncik M, Datz C, Gangl A, Ferenci P, Peck-Radosavljevic M (2005): Suppression of hematopoiesis during therapy of chronic hepatitis C with different interferon alpha mono and combination therapy regimens. Gut; 54 (7):1014-20.
12.Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK (2001): Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. Lancet; 358 (9286): 958-65.
13.Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garc□a J, Lazzarin A, Carosi G, Sasadeusz J, Katlama C, Montaner J, Sette H Jr, Passe S, De Pamphilis J, Duff F, Schrenk UM, Dieterich DT (2004): Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med; 351 (5):438-50.
14.Shiffman ML, Salvatore J, Hubbard S, Price A, Sterling RK, Stravitz RT, Luketic AV, Sanyal AJ (2007): Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alpha. Hepatology; 46 (2): 371-9.
15.Jacobson IM, Brown RS Jr, Freilich B, Afdhal N, Kwo PY, Santoro J, Becker S, Wakil AE, Pound D, Godofsky E, Strauss R, Bernstein D, Flamm S, Pauly MP, Mukhopadhyay P, Griffel LH, Brass CA (2007): Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. Hepatology; 46 (4): 971-81.
16.Fried MW (2002): Side effects of therapy of hepatitis C and their management. Hepatology; 36(5 Suppl 1):S237-44.
17.Saito H, Tada S, Ebinuma H, Ishii H, Kashiwazaki K, Takahashi M, Tsukada N, Nishida J, Tanaka S, Shiozaki H, Hibi T (2006): Role of Erythrocytes as a reservoir for ribavirin and relationship with adverse reactions in the early phase of interferon combination therapy for chronic hepatitis C virus infections. J Clin Microbiol; 44 (10): 3562-8.
18.Aspinall RJ and Pockros PJ (2004): The management of side effects during therapy for hepatitis C. Aliment

Pharmacol Ther; 20 (9):917-29.
19.Takaki S, Tsubota A, Hosaka T, Akuta N, Someya T, Kobayashi M, Suzuki F, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Kumada H (2004): Factors contributing to ribavirin dose reduction due to anemia during interferon alfa 2 b and ribavirin combination therapy for chronic hepatitis C. J Gastroentrol; 39 (7): 668-73.

How to cite this article:

Ehab F Mostafa, Mahmoud Saif-Al-Islam, Sahar M Hassany, Yehya Rashad Abd-Alrhman and Mohammed Abd Allah Mohammed. 2016. Hematological Side Effects of Pegylated Interferon/ Ribavirin Therapy in Chronic HCV Egyptian Patients. *Int.J.Curr.Microbiol.App.Sci.* 5(1): 350-363. http://dx.doi.org/10.20546/ijcmas.2016.501.033