Original Article

THE HEMATOLOGICAL SIDE EFFECTS ASSOCIATED WITH COMBINATION ANTIVIRAL THERAPY (CONVENTIONAL INTERFERON AND RIBAVARIN) IN PATIENTS WITH HEPATITIS "C" INFECTION

Khalid Amin[*], Dilshad Muhammad[**], Masood Javed[***], Sana Arshad[****], Irshad Ahmad[*****]
[*]Professor of Medicine, Punjab Medical College Faisalabad.
[**]Assistant Professor of Medicine, Punjab Medical College Faisalabad.
[***]Associate Professor of Medicine, Punjab Medical College Faisalabad.
[****]Senior Registrar, Punjab Medical College Faisalabad.
[*****]Assistant Professor, University Medical & Dental College Faisalabad.

ABSTRACT

INTRODUCTION: Hepatitis C virus infection is a major cause of chronic hepatic diseases. According to WHO statistics, the global prevalence of HCV is 3.1%. In East Mediterranean Region (including Pakistan), the prevalence is 4.6%. The most effective therapeutic regimen for infection with hepatitis C virus (HCV) is the combination of interferon alfa and ribavirin (combination therapy) and is effective in approximately 80% of patients infected with hepatitis C virus. The side effects of combination therapy predominantly include hematological abnormalities along with fatigue, influenza-like symptoms, gastrointestinal disturbances and neuropsychiatric symptoms.

OBJECTIVE: To evaluate the frequency of Haematological side effects with combination antiviral therapy (interferon and ribavarin) in patients with hepatitis 'C' Infection.

STUDY DESIGN: Descriptive case series

SETTING: Department of Medicine, DHQ Hospital, Faisalabad

STUDY DURATION: Six months from 29th November 2013 to 29th May 2014

MATERIALS AND METHODS: Total 150 patients with the diagnosis of Hepatitis C were included. Hemoglobin, Leukocyte count and Platelet count was sent before after 2 weeks and then after every four weeks of starting antiviral therapy in DHQ, hospital Laboratory. Informed consent was taken .The primary outcome measure was the frequency of hematological side effects associated with Interferon and Ribavirin in these patients.

RESULTS: A total of 150 patients in Medicine Department DHQ were included in the study. Out of these 150 patients, 66(44%) were male and 84(56%) were female. Mean age of the patients was 36.58$\pm$ 3.975 (range 20-45 years). Mean hemoglobin level before starting Antiviral therapy was 13.0g/dl (range 11.0-16.0g/dl). Clinically significant anemia (Hb< 9g/dl) occurred in 73% of the patients after starting the therapy. The mean drop in the hemoglobin concentration in the first two weeks of the treatment was 3 g/dl. Leucopenia (<3 x10^9 /L) occurred in 56 % of the patients and all patients recovered after antiviral therapy. Thrombocytopenia (<150 X 10^9/L) occurred in 63% of the patients which was insignificant clinically because platelet counts as low as 50 x 109/L was very well tolerated. Out of total 56 males, anemia was present in 47(71%), leucopenia in 38 (57%) and thrombocytopenia in 41 (62%). Out of 84 females, anemia was present in 63(75%), leucopenia in 46 (55%) and thrombocytopenia in 54 (64%).

CONCLUSION: Antiviral therapy is associated with hematological side effects. However, the side effects should be monitored regularly during the therapy to avoid complications and dose of the therapy should be adjusted.

KEY WORDS: Hepatitis C, Interferon, Hematological side effects.

INTRODUCTION:

Hepatitis C virus (HCV) infection is a major cause of chronic hepatic disease.[1] According to WHO statistics, the global prevalence of HCV is 3.1%. In East Mediterranean Region including Pakistan, the prevalence is 4.6%. Approximately 10 million people are infected with HCV in Pakistan.[2]

The natural history of HCV infection is characterized by acute asymptomatic or mildly symptomatic phase. More than half of these patients then become chronically infected with the virus Hepatitis C virus infection is an important etiological agent for chronic hepatitis, hepatic cirrhosis and hepatocellular carcinoma.

The most effective therapeutic regimen for infection with hepatitis C virus (HCV) today is the combination of interferon alpha and ribavirin (combination therapy), which increases the SUR (sustained viral response upto 60.5%.[3] The combined interferon and ribavirin antiviral treatment is effective in approximately 80% of patients infected with hepatitis C virus. Some older studies reported a 40–50% response to standard IFN/RBV combination therapy in genotype 1 CHC patients and a viral response of up to 70–80% in genotype 2/3 CHC patients; in acute HCV, response is close to 100%. The data regarding the SVR rate using conventional IFN/RBV are conflicting, even for genotypes 2a and 3a .Using PEG-IFN/RBV increases the convenience, but not the efficacy of therapy. In pivotal clinical trials, patients infected with HCV genotypes 2 and 3 achieved an SVR rate of 80% with PEG-IFN/RBV. However, an SVR rate of 30–50% has been reported in different regional studies.

The side effect profile of combination therapy include fatigue, influenza-like symptoms, gastrointestinal disturbances, neuropsychiatric symptoms, and predominantly hematologic abnormalities. These side effects may be treatment limiting and require dose reduction or drug discontinuation.[5] IFN exerts anti-proliferative effects on many cell types. These properties are used for treatment of chronic myelo-proliferative and lympho-proliferative diseases as well. Their use also accounts for several undesirable effects, such as thrombocytopenia and leukopenia and can interfere with the successful clinical application of full dose IFN in patients with chronic hepatitis C. Ribavirin treatment causes varying degrees of anaemia, presumably through haemolysis.

In a local study by Mahmood K, et al, carried out among 400 patients with hepatitis C infection, treated with combination therapy, the most common side effects observed in patients were hematological i.e 92.5%. In their study, the frequency of anemia (Hb< 11mg/dL) was 70%, leucopenia (TLC $<3X10^{9/}L$) was 64% and thrombocytopenia ($<150 X 10^{9}/L$) was 61%.[6]

Corresponding Author:
Dr. Khalid Amin
Professor of Medicine,
Punjab Medical College Faisalabad.
Email: drkamin2002@yahoo.com

PURPOSE OF THE STUDY:

Interferon plus ribavirin regimen is efficacious but associated with the hematological side effects. The presence of these side effects may limit the treatment. The previous studies show a great variability in results. The purpose of this study is to determine the actual frequency and pattern of hematological manifestation in our set up. Knowledge about the frequency of these side effects is essential to avoid the complications. I want to conduct this study so that the local policies could be established for early recognition, routine screening and management of the side effects. This will improve the outcome of treatment of Hepatitis C virus infection.

MATERIALS AND METHODS:

Study design
Descriptive case series
Setting
Department of Medicine, DHQ Hospital, Faisalabad
Sample size
The calculated sample size of 150 cases who under went interferon plus rebavirin therapy.
Sample technique
Non probability consecutive sampling
Study duration
Six months after approval of synopsis

Inclusion criteria

- Gender: both male and female
- Age: 20-45 years
- All the patients with the diagnosis of hepatitis C infection (as per operational definition) for a duration of last six months and going to start treatment of combination antiviral therapy (ribavarin and interferon)

Exclusion criteria

- Patients with Hepatitis B infection
- Patients with hepatocellular carcinoma or secondary liver metastasis
- Patients who have already taken treatment for Hepatitis C virus infection
- Decompensated HCV Disease.

DATA COLLECTION:

One hundred and fifty cases fulfilling inclusion criteria were registered through Department of Medicine, DHQ Hospital, Faisalabad. Demographic history [including age (in years) and sex (male or female) was taken. Informed consent was taken through patients. All the patients had the following investigations: Hb%, platelet count and leukocyte count before, after 2 weeks of starting therapy then every month. The patients were observed for the development of side effects (anemia, thrombocytopenia and leukopenia) (as per operational definition) and their presence or absence was labeled as yes /no. All the information was collected on a specially designed proforma (attached).

Data Analysis:

All the collected data was entered into SPSS version 10 and analyzed. The qualitative data like demographics (sex; male or female), presence of hematological side effects (anemia, leucopenia, and thrombocytopenia) associated with antiviral therapy (yes or no) were presented as frequency distribution. Quantitative data like age (in years)was presented as means and standard deviations. Effect modifier like age and sex were controlled by cross tabulation with side effects.

RESULTS:

A total of 150 patients in Medicine Department DHQ were included in the study. Out of 150 patients, 66(44%) were male and 84(56%) were female.(Table I) Mean age of the patients were 36.58$\pm$ 3.975. (Table II) Out of 66 males anemia was present in 47(71%), leucopenia in 38 (57%) and thrombocytopenia in 41 (62%). Out of 84 females anemia was present in 63 (75%), leucopenia in 46 (55%) and thrombocytopenia in 54 (64%) females. (Table III,IV,V) Mean hemoglobin level before starting Antiviral therapy was 13.0g/dl (range 11.0-16.0g/dl).Clinically significant anemia (Hb< 9g/dl) occurred in 110 (73%) of the patients after starting the therapy. The mean drop in the hemoglobin concentration in the first two weeks of the treatment was 3 g/dl. The leucopenia (<3 x10^9 /L) occurred in 84(56%) of the patients and all patients have recovered after antiviral therapy so there was transient decrease in total leukocyte count during this study. Thrombocytopenia (<150 X 10^9/L) occurred in 95(63%) of the patients. The thrombocytopenia was insignificant clinically because platelet counts as low as 50 x 109/L was very well tolerated.

Patients between age group (20-45 years) were taken.65 patients were between 30-34 years ,42 patients between 35-38 years and 43 patients had age > 38 years. There were 67 (44.7%) patients in age group $\leq$ 36 years who had anemia, 47 (31.3%) who had leucopenia and 54(36%) who had thrombocytopenia. (Table VI,VII). There were 43 (28.7%) patients in age group >36 years who had anemia, 37(24.7%) who had leucopenia and 41(27.3 %) who had thrombocytopenia. (Table VI,VII).

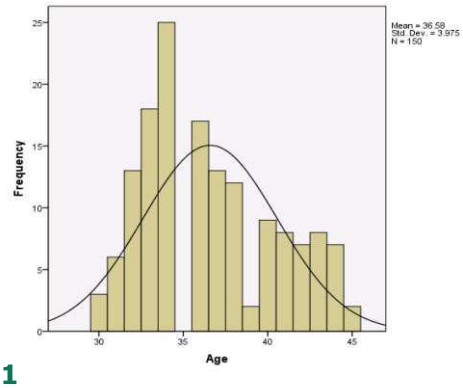

Figure 1
Normal Graph of Age distribution of the patients

DISCUSSION:

Table No. I
Association of Anemia with gender distribution

Gender	Anemia		Total
	No	Yes	
Male	19(12.7%)	47(31.3%)	66(44%)
Female	21(14%)	63(42%)	8456%)
Total	40(26.7%)	110(73.3%)	150(100%)

N=150
Chi-Square value=0.271, P value=0.603 Non-Significant

Table No. II
Descriptive statistics of age of the patients

	N	Range	Minimum	Maximum	Mean	SD	Median	Mode
Age in Years	150	15	30	45	36.58	3.975	36	34

N=150

Table No. III
Association of Leucopenia with gender distribution

Gender	Leucopenia		Total
	No	Yes	
Male	28(18.7%)	38(25.3%)	66(44%)
Female	38(25.3%)	46(30.7%)	8456%)
Total	66(44%)	84(56%)	150(100%)

N=150
Chi-Square value=0.119, P value=0.73 Non-Significant

Table No. IV
Association of Thrombocytopenia with gender distribution

Gender	Thrombocytopenia		Total
	No	Yes	
Male	25(16.7%)	41(27.3%)	66(44%)
Female	30(20%)	54(36%)	84(56%)
Total	40(26.7%)	110(73.3%)	150(100%)

N=150
Chi-Square value=0.075, P value=0.785 Non-Significant

Table No. V
Association of Anemia with Age Group distribution

Age Groups	Anemia		Total
	No	Yes	
Age ≤36 Years	15(10%)	67(44.7%)	82(54.7%)
Age >36 Years	25(16.7%)	43(28.7%)	68(45.3%)
Total	40(26.7%)	110(73.3%)	150(100%)

N=150
Chi-Square value=6.486, P value=0.011* Significant

Table No. VI
Association of Leucopenia with Age Groups distribution

Age Groups	Leucopenia		Total
	No	Yes	
Age ≤36 Years	35(23.3%)	47(31.3%)	66(54.7%)
Age >36 Years	31(20.7%)	37(24.7%)	84(45.3%)
Total	66(44%)	84(56%)	150(100%)

N=150
Chi-Square value=0.127, P value=0.721 Non-Significant

Table No. VII
Association of Thrombocytopenia with Age Groups distribution

Gender	Thrombocytopenia		Total
	No	Yes	
Age ≤36 Years	28(18.7%)	54(36%)	82(54.7%)
Age >36 Years	27(18%)	41(27.3%)	68(45.3%)
Total	55(36.7%)	95(63.3%)	150(100%)

N=150
Chi-Square value=0.495, P value=0.482 Non-Significant

Hepatitis C is an infectious disease affecting primarily the liver, caused by the Hepatitis C virus. A combination of harm reduction strategies, such as the provision of new needles and syringes and treatment of substance use, decrease the risk of hepatitis C in intravenous drug users by about 75%. The screening of blood donors is important at a national level, as is adhering to universal precautions within healthcare facilities. In countries where there is an insufficient supply of sterile syringes, medications should be given orally rather than via injection (when possible).IFN-R combination therapy for chronic HCV has a number of adverse events.[7] Majority of these side effects are due to interferon and a few due to ribavirin. [8]

The analysis of 150 showed that combination of interferon and ribavirin causes hematological side effects.Out of 150 patients, 66(44%) were male and 84(56%) were female. Mean age of patients in this study was 36.58± 3.975.Out of 66 males, anemia was present in 47(71%), leucopenia in 38 (57%) and thrombocytopenia in 41 (62%).

Out of 84 females anemia was present in 63 (75%), leucopenia in 46 (55%) andthrombocytopenia in 54 (64%) females. In my study , the frequency of anemia was 73%, leucopenia was 56 % and thrombocytopenia was 63 % as compared to the previous study Mahmood K, et al, carried out among 400 patients with hepatitis C infection treated with combination therapy, the frequency of anemia (Hb< 11mg/dL) was 70%, leucopenia (TLC <3X10$^{9/}$L) was 64% and thrombocytopenia (<150 X 10^{9}/L) was 61%. This shows that the frequency of hematological side effects in both studies have almost similar results.

In another study by Hayat AS, et al anemia occurred in 7.5% patients, leucopenia in8%and thrombocytopenia in 45% patients receiving combination therapy.[1] Haematologic adverse event are the commonest laboratory abnormalities leadingto dose modification or stoppage of therapy. The most common haematological side effect seen in my study was Anemia i.ein 73% of the patients, which is in corcordance to the previous studies done.The mean drop in the haemoglobin concentration in the first month of the treatment was 2.5g/dl.The haemoglobin level ranged between 8.5g/dl and11g/dl in majority of these patients(70%).The haemoglobin concentration returned to base line within four to eight weeks after the completion of treatment.Anaemia is caused both by interferon due to myelosupression and ribivirin causing haemolysis.

The leucopenia was seen in 56% of the patients.The lowest leucocytes count experienced was 2000/Ul. Neutropenia is one of the expected side effects of combination therapy.

Thrombocytopenia was seen in 63 %. Clinically, thrombocytopenia does not pose significant problem unless the patient is having pre-existing thrombocytopenia.

Patients between age group 20 -45 years were taken. Patients of age group ≤ 36years had

slightly more frequency of anemia (44.7 %), leucopenia (31.3 %) and thrombocytopenia as compared anemia (28.7 %), leucopenia (24.7 %) and thrombocytopenia (27.3) in age group >36 years.

This shows that therapy interferon and ribavirin causes hematological side effects that can be controlled by regular monitoring and patient education to prevent complications. The Recommended treatment for Hepatitis C after 2002 is PEG-IFN/RBV , but its high cost means that it is available only to a small, affluent proportion of the vast population of resource-constrained countries. The lack of a health-insurance system in our country (Pakistan) leads to unavailability of PEG—IFN/RBV to population because of the cost. So, we need to work to develop proper health care systems so PEG-IFN/RBV is available and better management is done.

There was no association of hematological effects with gender. My study shows anemia is more in age group ≤36years and shows significant p value. However, previous studies do not show any association of age with hematological side effects. [1,6]

CONCLUSION:

Combination therapy is not without harmful effects. Haematological abnormalities are one of the most common side effects seen in these patients. In our patients Anemia (73%) was the most common of all followed by thrombocytopenia(63%) and leucopenia (56%).Most of the unwanted effects were well tolerated by the patients. Thus using the appropriate management,early identification of unwanted side effects and effective strategies are required to overcome these adverse events and prevent complications.

REFERENCES:

1. Hayat AS, Khan RA, Shaikh N, Memon F, GhoriRA.Haematological side effects following antiviral therapy (conventional alpha – Interferon plus ribavarin) in patients with chronic hepatitis C. World ApplSci J. 2009;6:1020-2009.
2. World Health Organization.Hepatitis C [Internet]. Geneva: WHO. C2004 [cited 15.07.2008].Available from: http//www .who.int/mediacentre/fac tssheets/fs164 /en/)
3. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med.2009;361:580–93.)
4. Bochot E, Castelain S, Duverlie G, Capron D, Nguyen-Khac E, Catherine Francois. Ribavarin monitoring in chronic hepatitis C therapy: anemia versus efficacy. Antiviral ther 2010;15:687-95.)
5. Huang CF, Yang JF, Dai CY, Huang JF, Hou NJ, Hsieh MY, Efficacy and safety of pegylated interferon combined with ribavirin for the treatment of older patients with chronic hepatitis C. J Infect Dis. 2010;201:751-9
6. Mahmood K, Muhammad N. Side effects of combination of interferon plus ribavirin therapy in patients with chronic hepatitis C; an experience with 400 patients. JPMI 2007;21:187-91.
7. Barbaro G, Di Lorenzo G, Soldini M, Giancaspro G, Pellicelli A, Grisorio B, et al. Evaluation of long-term efficacy of interferon alpha-2b and ribavirin in combination in naive patients with chronic hepatitis C: an Italian multi center experience. Ribavirin-Interferon in Chronic Hepatitis Italian Group Investigators.J Hepatol. 2000 Sep;33(3):448-55
8. Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. Gut. 2006 Sep;55(9):1350-9.

Submitted for publication: 15.04.2015
Accepted for publication: 30.09.2015