

Hematological Side Effects of Pegylated Interferon Plus Ribavirin Combination Therapy In Chronic Hepatitis C Treated Patients

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ABSTRACT

Aim: To study the frequency of hematological side effects of pegylated interferon and ribavirin combination therapy in chronic hepatitis C treated patients.

Study design: Descriptive case series.

Settings: Al-Khaliq Patients care, Nishtar Road Multan.

Duration of study: Two years from July 2011 to July 2013.

Methods: The patients were explained about the objective of the study and informed written consent was taken. Convenient purposive sampling technique was used in this study. The patients were put on pegylated interferon (alpha-2a) 180ug subcutaneously once weekly and ribavirin 400mg twice a day. The patients were followed according to study protocol. At each follow up visit haemoglobin level, TLC, DLC and platelet count were checked. The data were entered in SPSS-11 and analyzed.

Results: Thirty patients were studied among these, 20 were male and 10 were female. The drop of haemoglobin upto 1 g/dl from the base line was noted in 5 (16.6%). A drop up to 2 g/dl from the base line was seen in 4(13.4%). Platelet count dropped to 90000/mm³ in 12 (39.99%) of cases. In 2(6.6%) it dropped up to 50000/mm³. Total leukocyte count dropped to 3000/mm³ in 4 (13.33%) of the cases and absolute neutrophilic count remained in the range of 1000/mm³ to 1500/mm³ in 2 (6.66%) of the cases. In 1 (3.33%) it dropped to 750/mm³. Serum uric acid was raised in 13 (43.33%).

Conclusion: Anemia, absolute neutropenia and thrombocytopenia were seen in few cases and these were managed with dose adjustment.

Keywords: Pegylated Interferon, Ribavirin, Chronic hepatitis C.

INTRODUCTION

Chronic hepatitis C infection is a global issue. In Pakistan prevalence of hepatitis C virus is 5% with pockets of high infection in different provinces and subsets of population¹. Various treatment therapies are available for chronic hepatitis C patients. The most common regimen is combination of pegylated interferon and ribavirin therapy. Pegylated interferon is given once weekly subcutaneously and dose of ribavirin varies from 800-1200 mg per day depending on body weight of the patients and hepatitis C virus geno type. The duration of therapy is variable from 6 months to 1 year according to hepatitis C virus genotype. The pegylated interferon and ribavirin therapy has many side effects. The common side effects related to pegylated interferon at early days of starting the therapy are influenza like symptoms, chills, fever, muscle aches and pains, headache²⁻⁶.

Anorexia, weight loss, easy fatigability, generalized weakness and hair loss occur late. Depression, irritability and suicidal tendencies are

more troublesome side effects. Thyroid dysfunctions can also occur. Neuro-retinitis is rare but once it occurs it becomes indication for stopping the therapy immediately⁶.

Hematological disturbances also occur commonly. Anemia, neutropenia and thrombocytopenia have been described as most frequent indication of dose reduction³. Bone marrow suppression has been reported with interferon^{4,6}. The common side effects of ribavirin are hemolytic anemia, myalgias, hyperurecemia, GI upsets, skin rashes, and teratogenicity⁶. These side effects are more marked in hepatitis C cirrhotic patients where discontinuation of therapy may be required in upto 14.5% of the patients⁷. Hematological side effects need special consideration. Anemia is common side effect in patients taking pegylated interferon plus ribavirin combination therapy. It is multi-factorial and is caused mainly by ribavirin which induces hemolysis. Ribavirin induced hemolytic anemia is dose dependent and usually subsides with dose adjustment and reverses with discontinuation of therapy⁸.

Ribavirin accumulates in RBCs and produce relative deficiency of adenosine triphosphate this puts RBC's into oxidative stress and lead to extra vascular

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hemolysis. Hemolysis correlates with ribavirin concentration in RBC's and usually achieves a steady level after 3-4 weeks of therapy. Ribavirin is excreted through kidneys and may accumulate to toxic level in RBC's in patients of renal insufficiency and results in severe hemolysis. So it is completely avoided in patients on dialysis and moderate to severe renal insufficiency. Animal studies with ribavirin also showed erythroid hypoplasia. Anemia is also caused by interferon which suppresses the normal compensatory response of bone marrow. Interferon is also associated with auto-immune hemolytic anemia. Special care is advised with reference to anemia in cardiac patients. A study showed that maximum decrease in hemoglobin was upto 3.7g/dl in patients taking pegylated interferon and ribavirin³. The anemia can be managed with dose adjustment, addition of folic acid and with erythropoietin therapy⁹. Neutropenia is another side effect of pegylated interferon. It is defined as absolute neutrophilic count less than 1500/mm³. Overall dose reduction of pegylated interferon is needed in 18-20% of the patients due to neutropenia. Severe neutropenia defined as absolute neutrophilic count to less than 500/mm³ has been described in 66% patients during the course of pegylated interferon therapy^{3,10}. Appropriate dose reduction of pegylated interferon is advised with reference to absolute neutrophilic count or filgrastim is added to control the neutropenia. Thrombocytopenia is common in patients of chronic liver disease mainly due to hypersplenism. Interferon also reduces platelet count due to marrow suppression. Interferon related auto-immune thrombocytopenia has also been described¹¹.

In a study 3-4% of the patients treated with pegylated interferon and ribavirin required dose adjustment due to thrombocytopenia^{3,10}. In 1 study platelet count less than 50000/mm³ was seen in 9% of the cases and less than 25000/mm³ was seen in 3% of patients who received pegylated interferon and ribavirin therapy. The present study was designed to see the side effects of these two drugs on hemoglobin, total leucocyte count, differential leucocyte and platelet counts.

MATERIAL AND METHODS

Thirty Chronic hepatitis C patients coming to Al-Khaliq patients' care, Multan for treatment were enrolled. The patients were explained about the objective of the study and informed written consent was taken. Convenient purposive sampling technique was used in this study. The study period was 2 years starting from July 2011 to July 2013. The patients of chronic renal failure, decompensated liver cirrhosis,

patients with depression, fits and eczema were excluded. The parameters like hemoglobin level, total leukocyte count, differential leukocyte count, platelet count, serum creatinine, serum albumin and thyroid profile were done as base line at the start of therapy. The therapy was started in patients who had acceptable baseline parameter for example haemoglobin >10g/dl in women and >13g/dl in men, TLC >4000/mm³, absolute neutrophilic count more than 1500/mm³ and platelet count >100000/mm³². The patients were put on pegylated interferon (alpha-2a) 180ug subcutaneously once weekly and ribavirin 400 mg twice a day. The patients were called initially for follow up fortnightly for 2 months, then once monthly for 4 months². Total duration of therapy was 6 months. At each follow up visit haemoglobin level, TLC, DLC and platelet count were checked. The data were entered in SPSS-11 and analyzed.

RESULTS

Thirty patients of chronic hepatitis C on pegylated interferon (alpha-2a) and ribavirin were followed for haematological side effects. Among these 20 were male and 10 were female. The age group was 20-60 years. Most of the disturbances in haematological parameters were seen in first two months of therapy. Decrease in haemoglobin level was the most common side effect noted. The drop of haemoglobin upto 1g/dl from the base line was noted in 5(16.6%). A drop upto 2 g/dl from the base line was seen in 4(13.4%). The drop of haemoglobin was more seen during first six weeks and then it attained steady level and remained in acceptable range with dose adjustment of ribavirin. Thrombocytopenia was next which was commonly observed. Platelet count was dropped to 90000/mm³ in 12(39.99%) of the cases. In 2(6.6%) it dropped up to 50000/mm³. Significant drop of platelet count was seen after 5 weeks of therapy.

Total leukocyte count was dropped to 3000/mm³ in 4(13.33%) of the cases and absolute neutrophilic count remained in the range of 1000/mm³ to 1500/mm³ in 2(6.66%) of the cases. In 1(3.33%) it was dropped to 750/mm³. Serum creatinine was not affected in our study cases. Serum uric acid was raised in 13(43.33%) of the cases. Hyperthyroidism was seen in only one case after 12 weeks of therapy.

DISCUSSION

The pegylated interferon and ribavirin combination therapy is the most common regimen used to treat chronic hepatitis C patients. Both these drugs have side effects which need to be monitored regularly. These side effects are commonly seen in first 12

weeks of therapy and need appropriate management. Special care is taken in cardiac patients if they develop anaemia during this therapy. Ribavirin is also avoided in patients of anemia and hemoglobinopathies⁹.

The drop in haemoglobin is most commonly seen in patients receiving this combination therapy. Drop in hemoglobin up to 2-3g/dl and hematocrit up to 5-10% can be anticipated⁹. In present study significant drop in haemoglobin level was seen in 5(16.68%) of the cases, while it has been reported in 33% of the cases by Qureshi et al².

The difference may be due to variation in sample size. Hemoglobin concentration decline by 2g/dl at week 2 is useful for predicting the probability of severe anemia and may help in deciding early dose adjustment of ribavirin¹². Anaemia was treated with dose adjustment of ribavirin and with addition of folic acid. In our study erythropoietin was not needed in any case. Thrombocytopenia has also been commonly described in many studies. Significant decrease in platelet count has been described by Qureshi et al in 20% of the cases. In present study platelet drop was seen only in 2(6.66%) of the cases as compared to other studies, where moderate thrombocytopenia was seen in 4 % of the cases¹³.

Significant thrombocytopenia less than 25000 mm³ may be treated with thrombopoietin receptor agonist eltrombopag but in present study it was not required in any case⁵. Disturbances in leukocyte count in patients receiving this combination therapy have also been described. Absolute neutrophilic count was decreased in 2(6.66%) of the cases and in only 1(3.33%) case dose adjustment was needed. While a study by Antonini et al has described neutropenia in 21% of the cases¹⁴ and a study from Egypt has reported moderate thrombocytopenia in 19.1% of the cases¹⁰.

CONCLUSION

In present study the effect of combination therapy on hematological parameters has not been so frequently observed. Anemia, absolute neutropenia and thrombocytopenia were seen in few cases and these were managed with dose adjustment. None of the cases required erythropoietin, filgrastim and

eltrombopag. Studies with large sample size are required to probe further in this issue.

REFERENCES

1. PMRC Report. National Survey on Prevalence of Hepatitis B and C in General Population of Pakistan [online] available from URL; <http://www.pmr.org.pk/hepatitisbc.html>.
2. Qureshi S, Batool U, Iqbal M, Omarah Q, Kaleem R, Aziz H, et al. Response rates to standard interferon treatment in HCV genotype 3-a. *JAMC Abbottabad* 2009; 21 (4): 10-14.
3. Fried MW. Side Effects of Therapy of Hepatitis C and Their Management. *Hepatology* 2002; 36: s237-s244.
4. Collier JD, Webster G. Liver and Biliary Tract Disease. In: Davidson's Principles & Practice of Medicine. 21st Ed. Elsevier India; p919-84.
5. Lawrence SF. Liver, Biliary Tract and Pancreas Disorders. In: Papadakis MA, McPhee SJ. Current Medical Diagnosis and Treatment. 52nd Ed. McGraw Hill 2013; p622-717.
6. Dusheiko G. Hepatitis C. In: Dooley JS, Lok ASF, Burroughs AK, Heathcote EJ. *Sherlock's Diseases of the Liver and Biliary System*. 12th Ed. Wiley Black-Well 2011; p406-26.
7. Bota S, Sporea I, Sirli R, Popescu A, Neghina AM, Danila M, et al. Severe adverse events during antiviral therapy in hepatitis C virus cirrhotic patients: A systematic review. *World J Hepatol* 2013; 5 (3): 120-6.
8. De-Franceschi L, Fattovich G, Turrini F, Ayi K, Brugnara C, Manzato F, et al. Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. *Hepatology* 2000; 31 (\$): 997-1004.
9. Dienstag JL. Chronic hepatitis. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J. *Harrison's Principles of Internal Medicine*. 17th Ed. McGraw Hill 2008; p1955- 69.
10. Manns MP, McHutchison, JG, Gordon, SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; 358:958.
11. Kawasaki, T, Takeshita, A, Souda, K, et al. Serum thrombopoietin levels in patients with chronic hepatitis and liver cirrhosis. *Am J Gastroenterol* 1999; 94:1918.
12. Hiramatsu N, Kurosaki M, Sakamoto N, Iwasaki Mm Sakamoto M, Suzuki Y, et al. Pretreatment prediction of anemia progression by pegylated interferon alpha-2b plus ribavirin combination therapy in chronic hepatitis C infection: decision-tree analysis. *J Gastroenterol* 2011; 46: 1111-9.
13. Lashi AH, Shaheen YA, Metwally MA, El-Feky HM, Hegab MF, Abbas SM. Incidence and predictors of hematological side effects in chronic HCV Egyptian patients treated with Pegylated interferon and ribavirin. *Ind J Gastroenterol* 2013; 32(5): 316-23.
14. Antonini MG, Babudieri S, Maida I, Baiguera C, Zanini B, Fenu L, et al. Incidence of neutropenia and infections during combination treatment of chronic hepatitis C with pegylated interferon alfa-2a or alfa-2b plus ribavirin. *Infection* 2008; 36(3): 250-5.