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

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Abstract:

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 population. Various treatment therapies are available for chronic hepatitis C patients. The most common regimen is combination of pegylated interferon and ribavirin therapy. The Aim of the current research to identify the frequency of hematological side effects of pegylated interferon and ribavirin combination therapy in chronic hepatitis C treated patients from February 2018 to February 2020 at Hayatabad Medical Complex Peshawar Pakistan. In the Present study 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 hemoglobin level, TLC, DLC and platelet count were checked. The data were entered in SPSS-11 and analyzed. In the Present study total 30 patients were studied among these, 20 were male and 10 were female. The drop of hemoglobin 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%).From the current study we conclude that Anemia, absolute neutropenia and thrombocytopenia were seen in few cases and these were managed with dose adjustment.

Keywords: Chronic hepatitis C, Pegylated Interferon, Ribavirin,

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 population (1).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 genotype (2). The duration of therapy is variable from 6 months to 1 year according to hepatitis C virus genotype.(3) 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, headache (4). Anorexia, weight loss, easy fatigability, generalized weakness and hair loss occur late. Depression, irritability and suicidal tendencies are more troublesome side effects (5). Neuro-retinitis is rare but once it occurs it becomes indication for stopping the therapy immediately (6). Hematological disturbances also occur commonly. Anemia, neutropenia and thrombocytopenia have been described as most frequent indication of dose reduction (7). Bone marrow suppression has been reported with interferon (8). The common side effects of ribavirin are hemolytic anemia, myalgias, hyperurecemia, GI upsets, skin rashes, and teratogenicity (9). These side effects are more marked in hepatitis C cirrhotic patients where discontinuation of therapy may be required in up to 14.5% of the patients (10). 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 therapy (11). Ribavirin accumulates in RBCs and produce relative deficiency of adenosine triphosphate this puts RBC's into oxidative stress and lead to extra vascular 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 up to 3.7g/dl in patients taking pegylated interferon and ribavirin (12).The anemia can be managed with dose adjustment, addition of folic acid and with erythropoietin therapy (13). Neutropenia is another side effect of pegylated interferon. It is defined as absolute neutrophilic count less than 1500/mm3. Overall dose 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 (14). 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 hyperspleenism. Interferon also reduces platelet count due to marrow suppression. Interferon related auto-immune thrombocytopenia has also been described (15). In a study 3-4% of the patients treated with pegylated interferon and ribavirin required dose adjustment due to thrombocytopenia (16). 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 Hayatabad Medical Complex Peshawar Pakistan. 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 February 2018 to July 2020 . The patients of chronic renal failure, decompansated 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 up to 1g/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%). 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 hemoglobinopathies (17).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 al (18).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 ribavirin (19). 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 cases (20). Significant thrombocytopenia less than 25000 mm may be treated with thrombopoietin receptor agonist eltrombopag but in present study it was not required in any case (22).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 cases (23).

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.

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