SIDE EFFECTS PROFILE OF THERAPY FOR CHRONIC HEPATITIS C AND THEIR MANAGEMENT

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ABSTRACT

Objectives: This study was conducted to assess the side effects of combination therapy of conventional interferon and ribavirin in chronic hepatitis C patients and their management.

Material and Methods: This prospective observational study was conducted at the Department of Medicine Khyber Teaching Hospital and Department of Pathology PGMI, HMC, Peshawar from March 2009 to June 2010. A total of 350 patients of chronic hepatitis C with reactive anti HCV (Hepatitis C virus) antibodies, elevated ALT, normal echo texture of liver on ultrasound and reactive HCV RNA by polymerase chain reaction (PCR) were enrolled in this study. Genotyping for HCV RNA was not done due to non availability of this test in the hospital and non affordability by patients. These patients received injection interferon alpha2b 3MIU subcutaneous(S/C) thrice weekly for 24 weeks. The prevalence of genotypes 2 and 3 is high in our community, but as we don’t know the exact genotyping of patients, so ribavirin therapy was started in high doses according to body weight. At each visit any side effects were recorded and graded according to modified WHO guidelines as mild, moderate, severe and life threatening.

Results: The most common side effects observed in our study were flu like symptoms in 330 (94.29%), hematological in 315 (90%), gastrointestinal in 269 (76.86%), dermatological in 256 (73.14%), neuropsychiatric in 244 (69.71%), respiratory symptoms in 29 (8.29%), thyroid function abnormalities in 11 (3.14%). Most of the adverse effects were mild to moderate. The severe adverse effects leading to dose reduction, use of hematopoietic growth factor, filgastrim or premature discontinuation of treatment were noted in 41 (11.71%) patients.

Conclusion: Interferon and ribavirin combination therapy for chronic hepatitis C is not without harmful effects. Early identification and strategies for controlling adverse effects can prevent moderate to severe complications.

Key Words: Chronic Hepatitis C, Interferon, Ribavirin therapy, Side effects.

INTRODUCTION

Hepatitis C is a disease with a significant global impact. The virus infects approximately 3% of the world total population corresponding to 170 million people worldwide. The natural history of Hepatitis C virus (HCV) infection is characterized by an acute asymptomatic or mildly symptomatic phase. Chronic disease occurs in approximately 85% of patients following HCV infection. HCV infection is an important etiological agent for chronic hepatitis, hepatic cirrhosis and hepatocellular carcinoma. In Pakistan HCV is emerging rapidly as an infection warranting attention as an important cause of chronic liver disease.

Therapy for chronic HCV infection has improved significantly over the last decade. An effective treatment is now available in the form of combination therapy with interferon and ribavirin leading to marked improvement in response rates. This combination therapy is cost effective but has a wide spectrum of side effects. The main hurdle to adherence in combination therapy for chronic HCV is treatment associated side effects, sometimes leading to dose reduction or even premature discontinuation. It is therefore essential to monitor the patients at regular intervals during treatment to detect the adverse events early and to manage them properly. This study was designed to evaluate the side effect profile of interferon and ribavirin (IFN-R) combination therapy in chronic HCV patients and their management.

MATERIAL AND METHODS

A total of 360 patients were enlisted in the study during the period from March 2009 to June 2010 as outpatient at Khyber Teaching Hospital, Peshawar. Out of these 360 patients, 350 completed follow up. The remaining 10 patients were either lost (08) or did not come for regular follow-up (02). These 10 patients were excluded from the final analysis.
Patients included in the study were 15 to 65 years old, of both genders, treatment naive with compensated liver disease had raised alanine aminotransferase (ALT), reactive HCV antibodies by 3rd generation ELISA and positive HCV RNA by PCR. None of these patients had significant psychiatric history or cardiovascular disease. Patients with evidence of decompensated liver disease, co-infected with hepatitis B virus, serious underlying illness and patients who had other contraindications to combination therapy were excluded from the study.

At each visit complete blood count (CBC), platelet count and ALT were checked. Thyroid functions were checked before the start of treatment and at 12 week treatment. At each visit the unwanted effects were graded according to modified WHO guidelines as mild (not requiring consultation and not affecting quality of life), moderate (requiring consultation, reassurance and symptomatic treatment) and severe (requiring dose reduction, hematopoietic growth factors, filgastrim or discontinuation of treatment). Ribavirin dose was decreased to 800 mg/day when Hb level dropped to between 10–12gm%. Erythropoietin was given to patients when Hb value dropped below 10 gm% and when despite giving three injections of erythropoietin, Hb value remained below 8.5gm%, Ribavirin was stopped. Filgastrim was administered to patients when their leukocyte count dropped below 2000 per cubic mm or neutrophils count to below 500 per cubic mm. IFN-R therapy was discontinued when despite giving three doses of Filgastrin, leukocyte count did not improve above 3500 per cubic mm. Thrombocytopenia was labeled as mild when platelet count dropped between 50,000 -150,000, moderate when platelet count is between 30,000-50,000 and severe when platelet count dropped below 30,000/mm\(^3\). Data was analyzed using SPSS version 13.

**RESULTS**

Patients demography and base line characteristics are given in Table 1. Flu like symptoms were observed in 330 (94.29%). These included fever (82.86%), fatigue (82.29%), myalgias (53.72%), headache (47.43%), rigors (35.71%) and arthralgia (27.43%). These features were mild to moderate and all these patients were managed with reassurance, adequate hydration and simple analgesics. Hematological side effects were noticed in (90%) 315 patients. Mild to moderate anemia Hb > 8.5 gm/dl was noted in 68.57% patients, mild to moderate leucopenia in 64.29% cases. The leucocytes count dropped during therapy by a mean value 2400 ± 680/mm\(^3\). Asymptomatic thrombocytopenia (platelet count > 50,000) was observed in 230 (65.72%).

Gastrointestinal symptoms were noted in 269 (76.86%) cases. These symptoms were nausea (70%), dyspepsia (37.43%), loss of appetite (35.71%) and altered bowel habits (6.29%). These manifestations were mild to moderate and were managed with reassurance, adequate hydration, proton pump inhibitors (PPIs) and prokinetics. Dermatological side effects were observed in 256 (73.14%) cases. These side effects included pruritis (25.43%), photosensitivity (25.42%), erythema (10.57%), skin rash (10%), hair loss (8%) and injection abscess (0.29%). These manifestations were mild to moderate and managed with reassurance, skin moisturizers, avoidance of excessive sunlight exposure and antihistamines.

Neuropsychiatric manifestations were noticed in 244 (69.71%) patients. These were insomnia (44.29%), irritability (28%), depression (21.71%), anxiety (16.57%), emotional lability (12.57%) and suicidal ideas (0.29%). These patients were suffering from moderate to severe disease and managed with reassurance, SSRIs, short term anxiolytics and psychiatrist consultation. Respiratory problems were observed in 8.29% (n=29) cases. These were pharyngitis (7.71%), rhinitis (6.29%) and tightness in the chest (4.57%). These manifestations were mild to moderate and managed with reassurance, avoidance of irritants and anti allergics.

Thyroid function abnormalities were encountered in 11 (3.14%) patients. These abnormalities were mild and asymptomatic and managed with reassurance and regular follow-up. Retinopathy was noted in 4 (1.14%) patients. Amongst them three were diabetics and one was hypertensive. The three diabetic patients had long standing diabetes and the medical record also documented retinopathy prior to initiation of IFN-R. Similar was the case with hypertensive patient. However further studies are needed to document the

| Table 1: Patients demography and baseline characteristics n=350 |
|-----------------|-----|
| Males           | 200 |
| Females         | 150 |
| Mean Age        | 38.0±9.5 years |
| Treatment status| Treatment naïve |
| HCV RNA         | Positive |
| Mean ALT (IU/L) | 96(SD±18.6) |
| Mean Hb(gm/dl) | 12.5(SD±0.6) |
| Mean Platelets count (mm\(^3\)) | 270, 000 (SD±30) |
| Mean Neutrophils (/mm\(^3\)) | 8300(SD±7) |
| Mean leukocyte drop during treatment | 2400±680/mm\(^3\) |
association of IFN-R therapy and retinopathy. The severe side effects leading to either dose reduction, withdrawal of treatment or use of hematopoietic growth factors and granulocyte colony stimulating factor (GCSF) were noticed in 41 (11.71%) patients. Amongst them, hematological side effects were 38 (10.86%) and included severe anemia (Hb < 8.5 gm/dl) 10.29%, severe neutropenia (cell count <500/mm³) 7.14% and severe thrombocytopenia (platelet count <30,000) in 0.57% cases.

Erythropoietin was used in a dose of 6,000 iu/wk in 24 (6.86%) patients which led to increase in hemoglobin level up to 3.8gm% in 22 (6.29%) patients. Filgastrim was used at the dose of 300 µg on alternate day in 22 (6.29%) patients leading to rise in TLC up to 3000 in 20 (5.71%) cases. Only 2 (0.57%) patients failed to respond effectively to EPO and filgastrim. Ribavirin dose was decreased to 800 mg/dl in 23 (6.57%) patients suffering from severe anemia. None of the patients with thrombocytopenia showed bleeding tendency. Only 1 (0.29%) with severe neutropenia had evidence of infection.

Major neuropsychiatric side effects were observed in 3 (0.86%) cases. These included major depression in 2 (0.57%) and suicidal tendencies in 1 (0.29%). All the patients with major depression except the one with suicidal ideas completed the IFN-R therapy in close consultation with psychiatrist. Premature discontinuation of IFN-R was evidenced in 6 (1.71%) cases. These included 1 (0.29%) patient having severe suicidal tendency and 5 (1.43%) patients with severe hematological adverse events. Amongst these 5 patients 3 couldn’t afford EPO and filgastrim while in 2 patients the response of filgastrim and EPO was poor.

**DISCUSSION**

IFN-R combination therapy for chronic HCV has a number of adverse events. Majority of these side effects are due to interferon and a few due to ribavirin. The side effects profile observed in our study was generally mild to moderate with the exception of a few patients in whom intervention had to be done. Flu like symptoms (94.29%) out numbered other symptoms in our study during the initial four weeks of treatment. The symptoms usually improved with explanation and simple analgesics like paracetamol and ibuprofen. McHutchison JG et al reported influenza like symptoms in 70% patients taking conventional interferon ribavirin therapy, Giuseppe B et al in 77.7% of patients with IFN-R combination therapy and 65% of patients with interferon alone while Manns MP documented flu like symptoms in 62% of patients receiving PEG-alpha 2b and ribavirin. Hematological side effects were the commonest laboratory abnormalities (90%) in our study. Mild to moderate anemia (Hb >8.5 gm/dl) was observed in 68.57% (n=240) of patients. The mean drop in hemoglobin concentration during the first 4 weeks of treatment was 2.8 gm/dl. The hemoglobin level ranged between 8.5 gm/dl and 12.0 gm/dl in majority of these patients. Ribavirin dose decreased in 6.57% (n=23) patients in whom the hemoglobin fell below 10gm/dl. In these patients, dose reduction resulted in rise in hemoglobin level which remained stable throughout treatment. Anemia is caused both by interferon due to myelosuppression and ribavirin induced hemolysis. The dose limiting toxicity of ribavirin is reversible, normocytic normochromic hemolytic anemia. Mechanism is still unclear but ribavirin gets accumulated to a much higher degree (60-70 folds) in non-nucleated red cells than in nucleated cells. McHutchison JG reported severe anemia in 8% and Hadziyannis SJ et al in 20% patients taking IFN-R therapy. Our study documented mild to moderate anemia in 225 (64.29%) and severe anemia in 25 (7.14%) patients on interferon ribavirin therapy. These figures are comparable with Khalid M and McHutchison JG utilizing conventional IFN-R therapy but much higher than Manns MP, Fried MW utilizing PEG-alpha 2b + Ribavirin therapy.

Asymptomatic thrombocytopenia (platelet count >50,000) was observed in 230 (65.72%) and severe thrombocytopenia (platelets count <30,000) in 2 (0.57%) patients only. However thrombocytopenia did not pose a significant clinical problem in our study. Gastrointestinal side effects in our study (76.86%) is comparable with Khalid M (88.5%) and Khalid SR treating patients with IFN-R therapy but much higher than that of Manns MP (43%), Fried MW (29%) and Dieperink E et al (n=40%) utilizing PEG-alpha 2b-RBV therapy.

Our study documented dermatological adverse events (73.14%). This figure is lower than that of Khalid M (81.5%) but higher than that of McHutchison JG (30%), Manns MP (36%), Fried MW (23%). There is limited data on the association of dermatologic side effects and IFN-R therapy. Neuropsychiatric manifestations of IFN-R were reported in 69.7% patients in our study. They are mostly attributed to interferon but the exact mechanism is unclear. These neuropsychiatric manifestations responded well to selective serotonin receptor inhibitors and regressed after discontinuing treatment in few weeks. This figure of 69.7% correlated with studies utilizing conventional interferon-ribavirin therapy but much higher than that of studies utilizing PEG IFN-R therapy.

Respiratory problems were documented in 8.29% patients in our study. Most of these symptoms are most probably due to edema of respiratory tract mucosa. Thyroid function abnormalities were noticed in 3.14% patients in our study. This figure is comparable with Bini EJ and Tran HA. Thyroid function abnormalities are most probably due to...
immunomodulatory properties of interferon resulting in autoimmune thyroiditis. Retinopathy was documented in 1.14% patients in our study and it compares with that of Khalid M. Retinopathy is a well documented side effect of interferon and ribavirin.

The side effects profile of our study is comparable with national studies. Discrepancy in few side effects is due to non specific nature of these manifestations which are common in the population at large. Most of the chronic hepatitis C patients without treatment have these constitutional symptoms and IFN-R therapy could not be attributed solely to these side effects. G-CSF (Filgastrim) increases neutrophils in patients treated with interferon based therapies. Similarly, erythropoietin can be effectively used to correct ribavirin induced anemia at least partially and to avoid ribavirin dose reduction or red blood cell transfusions. Both of these facts are favored by our study. However, further studies are needed to augment our findings.

CONCLUSION

Early identification of unwanted side effects with interferon, ribavirin combination and effective strategies to overcome these adverse events can prevent moderate to severe complications.

REFERENCES


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