Side effect profile of hepatitis C treatment with peginterferon alpha-2b and ribavarin

Syed Mubashir¹, Irfan Gul²*, Abid Rasool¹, Shujat Gul², G. M. Gulzar¹, Muzamil Ahmad Wani²

INTRODUCTION

Chronic hepatitis C infection is a very common disease globally affecting over 180 million people. It is a leading cause of chronic hepatitis, cirrhosis, and liver cancer and a primary indication for liver transplantation. The major types of side effects include fatigue, influenza-like symptoms, gastrointestinal disturbances, neuropsychiatric symptoms and hematologic abnormalities.¹ ² These side effects may be treatment limiting and require dose reduction or drug discontinuation.³ ⁴ Numerous other side effects occur with lower frequencies but may still have an impact on the tolerability of antiviral therapy.² Pegylated interferons (peginterferon alfa-2a and peginterferon alfa-2b) have significantly improved pharmacokinetics resulting in improved antiviral efficacy, which also has

ABSTRACT

Background: The major types of side effects include fatigue, influenza-like symptoms, gastrointestinal disturbances, neuropsychiatric symptoms and hematologic abnormalities. These side effects may be treatment limiting and require dose reduction or drug discontinuation objectives of the study was to assess the side effect profile of hepatitis C treatment (peginterferon alpha-2b and ribavarin) in Kashmiri patients attending the Department of Gastroenterology skims.

Methods: In this study, all consecutive patients of hepatitis C infection on peginterferon and ribavarin treatment were enrolled after written consent. The patients underwent intervention treatment taking pegylated interferon α-2b (Viraferon, Schering Plough Corp., Kenilworth, NJ) and ribavirin in accordance with the standard protocol. Patients were monitored through weekly referrals while taking the medications. A detailed history was taken and complete physical examination done each time the patient presented to the hospital necessary blood sampling was taken.

Results: During the study period of 2 years, 105 Patients were enrolled 55 (52.4%) were males with a male:female ratio of 1.1:1.0. and mean age 37.6 years with a range of 13-75 years 7 patients (6.6) had a history of needle pricks, 4 patients (2.2%) of sharing same razors at barber’s shop, 4 (3.8%) patients of drug abuse; out of which 3 (2.8%) were intravenous drug abusers, Anemia occurred in 17 (16.2%) patients with requirement of dose modification w in 11 (10.4%) patients and dose stoppage in 1 (0.95%) patient in whom Hb dropped to less than 7, thrombocytopenia occurred in 27 (25.7%) patients with requirement of dose modification in 13 (12.3%) patients and dose stoppage in 1 (0.95%) patients due to platelet count decreasing to less than 30,000. Neutropenia as defined by ANC less than 1500 occurred in 22 (20.9%) patients.

Conclusions: Dose modification was required in 48 (45.7%) patients, 30 (28.5%) patients required dose modifications due to labortory abnormalities and 18 (17.1%) due to other side effects. In 8 (7.6%) patients dose was discontinued due to adverse events (including psychosis in 1, severe flu like symptoms in 3, dermatitis in 1, depression in 3).

Keywords: Hepatitis C, Neuropsychiatric, Pegylated interferon α-2b, Ribavirin
the potential to alter the side effect profile.5-8 Among the infrequently reported (1%) prominent serious adverse events associated with standard interferon therapy are retinopathy, retinal hemorrhage, visual loss, tinnitus, hearing loss, cardiac arrhythmias, congestive heart failure, interstitial pneumonia, acute renal failure, bacterial infections (particularly in patients with cirrhosis), and induction or exacerbation of autoimmune diseases, hyperthyroidism, hypothyroidism, acute psychosis, panic attacks, severe depression, and suicide.29,18

Certain adverse events associated with antiviral therapy have been responsible for most dose reductions and discontinuations and also have the greatest potential for altering the quality of life of individuals on antiviral therapy. Specific interventions may be available and deserve further discussion.

**Anemia**

Hemolytic anemia is a universal event associated with ribavirin combination therapy during therapy with standard interferon and ribavirin, hemoglobin levels decreased within the first 2-4 weeks of therapy with a mean maximal decrease of approximately 3g/dl. 9% of participants treated with peginterferon and ribavirin required dose reductions due to decreased hemoglobin levels less than 10g/dl.7

Hemoglobin levels promptly return to normal once therapy is discontinued. Significant anemia associated with ribavirin therapy can increase fatigue, has a demonstrable effect on quality of life, and is a frequent indication for dose reduction of ribavirin.7,8,19

**Neutropenia**

Peginterferon induce neutropenia to a greater degree than standard interferons. Rapid decreases in neutrophil counts may be seen within the first 2 weeks of initiation of therapy and usually stabilize over the next 4 weeks as steady-state concentrations of peginterferon are achieved. Neutrophil counts rapidly return to baseline after therapy is discontinued. Recommendations for dose reduction of peginterferon alfa-2b at neutrophil counts of less than 750 cells/mm.20 Neutropenia is the most common reason for dose reduction of peginterferon and, thus, significantly interferes with adherence.7,8

**Thrombocytopenia**

Decreases in platelet counts also occur with therapy but have been infrequently associated with dose reduction or discontinuation. Rare instances of autoimmune thrombocytopenic purpura have been reported with peginterferon therapy, and marked decreases in platelet counts should be investigated for the role autoimmunity.

**Depression**

Approximately 20% to 30% of patients treated with peginterferon and ribavirin report depression during therapy, making this a frequent cause of decreased quality of life and an indication for dose reduction and discontinuation. The relationship of depression and interferon therapy has recently been reviewed.21 In addition to depression, other manifestations such as irritability, anxiety, emotional lability, aggressive behaviors, mood disorders, and panic reactions have been reported.22 Evaluation of treatment-emergent side effects may be complicated by recently described subtle cognitive impairment before therapy pretreatment functional status and overlap with other side effects of interferon, such as fatigue and insomnia, which could exacerbate neuropsychiatric symptoms.23,27

Aims and objectives of the study was to assess the side effect profile of hepatitis C treatment (peginterferon alpha-2b and ribavirin) in Kashmiri patients attending the department of Gastroenterology, skims Soura.

**METHODS**

The present study was a prospective study conducted in the Department of Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir, India. Our department is a referral center which receives patients from whole of the Kashmir. The study was carried from June 2013 to June 2015.

All consecutive patients of hepatitis C infection who were on treatment on peginterferon and ribavirin were enrolled. Written informed consent was obtained from all patients. The patients underwent intervention treatment taking Pegylated interferon α-2b (Viraferon, Schering Plough Corp., Kenilworth, NJ) and ribavirin in accordance with the standard protocol. This protocol consisted of 1.5µg/kilogram of body weight of Pegylated interferon α-2b administered subcutaneously once per week. In genotype 1 and 4 patients, who weighed less than 75kg, they were given ribavirin administered orally in 1000 mg daily doses, and in patients who weighed over 75kg the medication was administered orally in 1200 mg daily doses. In genotype 2 and 3 patients, ribavirin was administered orally in 800mg daily doses.

The treatment length in genotype 1 and 4 patients was 48 weeks and it was 24 weeks in genotype 2 and 3 patients. Patients were monitored through weekly referrals while taking the medications. A detailed history was taken and complete physical examination done each time the patient presented to the hospital. Blood samples were drawn by venipuncture every week for first four weeks and then monthly till the completion of treatment. Blood samples were analysed for Hb, TLC, DLC, ANC, Platelets. Thyroid profile was done at months 0, 1, 3 and 6. Mild to moderate complications were countered through a decrease in medication dosage or through the prescription.
of appropriate drugs. Lab criteria for dose reduction of peginterferon α-2b included 500-750/mm³ neutrophils, 30000-50000/mm³ platelets or Hb less than 10g/dl. Peginterferon-α was discontinued in cases of neutrophils less than 500/mm³, platelets less than 30000/mm³ and hemoglobin levels dropping below 7g/dl. In addition, the ribavirin dosage was reduced in cases of hemoglobin levels falling below 10g/dl and it was stopped if hemoglobin dropped below 8.5g/dl. G-CSF was prescribed when prolonged dose reduction was required because of neutropenia. Thrombopoietin analogue eltrombopag 50mg was given when platelets dropped below 50,000/mm³.

RESULTS

During the study period of 2 years,105 Patients were enrolled of which 55 (52.4%) were males and 50 (47.6%) were females with a male:female ratio of 1.1:1.0. The mean age was 37.6 years with a range of 13-75 years. Majority of the patients were young (age ≤50yrs) n=88 (83.81%) while 17 (16.19%) were older than 50.

About 34 patients (32.38%) were smokers and 79 (75.2%) had a previous history of dental instrumentation, about 7 patients (6.6%) had a history of needle pricks. 4 patients (2.2%) had a history of sharing same razors at barber’s shop. 4 (3.8%) patients had a history of drug abuse; out of which 3 (2.8%) were intravenous drug abusers. Other risk factors were history of alcohol consumption (N=6 [5.7%]); promiscuous sexual activity in form of multiple partners (N=2 [1.9%]); past history of surgery (N=39 [37.1%]) Majority of the patients (83.8%) were in the age group of <50 years.

The general characteristics of these 105 patients of chronic hepatitis C are depicted in Table 1.

Table 1: The general characteristics of 105 patients of chronic hepatitis C.

| Parameters                           | Values                  |
|--------------------------------------|-------------------------|
| Total cases                          | 105                     |
| Age, mean (range) in years           | 37.6(13-75) years       |
| Sex, male: female                    | 55:50                   |
| Smoking                              | 34(32.38%)              |
| Dental extraction                    | 79(75.2%)               |
| Needle prick                         | 7(6.6%)                 |
| Sharing razor                        | 4(2.2%)                 |
| Sharing needles for injections       | 3(2.8%)                 |
| Blood products                       | 33(31.4%)               |
| Drug abuse                           | 4(3.8%)                 |
| *History of alcohol ingestion       | 6(5.7%)                 |
| Promiscuous sexual activity          | 2(1.9%)                 |
| Past surgery                         | 39(37.1%)               |

Hematopoietic side effects

Anemia

In our study group, anemia occurred in 17 (16.2%) patients. The maximum drop in Hb occurred after 4 weeks with Hb dropped from a median of 13.5g/dl at baseline to 12.2g/dl, there after remaining almost constant throughout treatment period.

Table 2: Frequency of side effects in 105 cases.

| Adverse effect of treatment | % affected (n=105) |
|-----------------------------|-------------------|
| Fatigue                     | 66.6              |
| Myalgias                    | 62.8              |
| Headache                    | 60.9              |
| Fever                       | 42.8              |
| Insomnia                    | 38.1              |
| Nausea                      | 34.3              |
| Anorexia                    | 34.1              |
| Pruritis                    | 26.6              |
| Thrombocytopenia            | 25.7              |
| Alopecia                    | 24.7              |
| Irritability                | 24.7              |
| Depression                  | 24.7              |
| Psychosis                   | 1.9               |
| Neutropenia                 | 20.9              |
| Cough                       | 17.1              |
| Diarrhea                    | 17.1              |
| Dermatitis                  | 16.2              |
| Anemia                      | 16.2              |
| Hypothyroidism              | 1.9               |

Dose modification was required in 11 (10.4%) patients in whom Hb dropped to less than 10g/dl. Dose was stopped in 1 (0.95%) patient in whom Hb dropped to less than 7.

Figure 1: Change in median Hb during the 24 week course of peginterferon alpha-2b and ribavirin in 105 patients.
Thrombocytopenia

In the 105 patients included in our study, thrombocytopenia occurred in 27 (25.7%) patients. The maximum drop in platelets occurred in the first 4 weeks when median platelet count dropped from 1.35 lac to 1.11 lac and remained constant thereafter. Dose modification was required in 13 (12.3%) patients due to platelet count dropping to less than 30,000. Dose was stopped in 1 (0.95%) patients due to platelet count decreasing to less than 30,000. 10 of our patients received the thrombopoetin analogue eltrombopag for thrombocytopenia.

Figure 2: Change in median platelet count during a 24 week course of peginterferon alpha-2b and ribavirin.

Neutropenia

Neutropenia as defined by ANC less than 1500 occurred in 22 (20.9%) patients in our study group. The maximum drop in leucocyte count occurred at the eighth week of therapy when median leucocyte count dropped to a value of 3300 from an initial value of 6400. 14 (13.3%) patients required dose modification due to neutropenia with ANC <750 and out of them 10 (9.5%) patients received G-CSF. 2(1.9%) patients required discontinuation of therapy due to neutropenia (ANC<500).

Figure 3: Line diagram showing change in median leucocyte count over a period of 24 weeks in 105 cases.

Dose modifications during therapy

Dose modification was required in a total of 48 (45.7%) patients. 30 (28.5%) patients required dose modifications due to labortory abnormalities and 18 (17.1%) patients required dose modification for adverse events. The cause of modification was neutropenia only in 8 (7.6%) patients, neutropenia plus thrombocytopenia in 5 (4.7%) patients, neutropenia plus anemia in 1 (0.95%) patient, anemia only in 8 (7.6%) patients, anemia plus thrombocytopenia in 2 (1.9%) patients and thrombocytopenia only in 6 (5.71%) patients. Thus out of all 30 patients who required dose modification due to laboratory abnormalities, neutropenia was present in 14 (13.3%) patients, anemia in 11 (10.4%) and thrombocytopenia in 13 (12.3%) patients. Of the adverse events requiring dose modification 9 patients had severe flu like symptoms, 3 had dermatitis, 2 had diarrhea, 3 had depression and 1 had pruritis.

Dose discontinuation during therapy

Of all the 105 patients included in our study, dose discontinuation was required in 13 (12.3%) patients. Of these 1 (0.95%) had thrombocytopenia, 1 (0.95%) had anemia, 2 (1.9%) had neutropenia, 1 had hypothyroidism and in 8 (7.6%) patients dose was discontinued due to adverse events (including psychosis in 1, severe flu like symptoms in 3, dermatitis in 1, depression in 3).

Table 3: Various factors causing dose discontinuation in our study.

| Abnormality           | Number (%) |
|-----------------------|------------|
| Adverse event         | 8(7.6%)    |
| Anemia                | 1(0.95%)   |
| Thrombocytopenia      | 1(0.95%)   |
| Neutropenia           | 2(1.9%)    |
| Hypothyroidism        | 1(0.95%)   |

DISCUSSION

The present study was conceived to assess the side effect profile of hepatitis C treatment in kashmiri patients on antiviral therapy with a combination of pegylated interferon-alfa2b and ribavirin. During this study period due to the non availability of oral antivirals in India, standard of care (SOC) for all HCV genotypes continued to be antiviral therapy consisting of combination of pegylated interferon alfa 2a or 2b and ribavirin (Peg-IFN-a/R) for 24 weeks for genotypes 2 and 3 or 48 weeks for genotypes 1. In our study Amongst the various adverse events observed fatigue was most common (n=70;66.6%) followed by myalgias (n=66;62.8%), headache (n=64;60.9%), fever (n=45;42.8%), insomnia (n=40;38.1%), nausea (n=36;34.3%), anorexia (n=35;34.1%), pruritic (n=28;26.6%), alopecia (n=26;24.7%), Irritability (n=26;24.7) depression (n=26;24.7), cough (18;17.1%), diarrhea (n=18;17.1%).
Table 4: Comparison of various studies with our study.

| Study (Author and year) | Country       | Males | Females | Mean Age |
|------------------------|---------------|-------|---------|----------|
| Our study              | India         | 55 (52.4%) | 50 (47.6%) | 37.6 (13-75) |
| Hazari et al²⁸         | India         | 45 (69.2%) | 20 (30.8%) | 39±12 (22-64) |
| Hissar et al²⁹         | India         | 279 (70.1%) | 119 (29.9%) | 41±13.5 (2-88) |
| Davis et al³⁰         | USA and Germany | 723 (60%) | 481 (40%) | 42.8±8.7 |
| Yu et al³¹           | China         | 56 (53.3%) | 49 (46.7%) | 41±7 |
| Kuboki et al³²       | Japan         | 198 (66%) | 102 (34%) | 51.5 |
| Kim et al³³         | S. Korea      | 33 (51.5%) | 31 (49.5%) | 50.1±9.8 |
| Alfaleh et al³⁴      | Saudi Arabia  | 54 (56.2%) | 42 (43.8%) | 47.4±10.4 |
| Borroni et al³⁵      | Italy         | 230 (58%) | 167 (42%) | 47.7±12.7 (18-70) |
| Hadziyannis et al³⁶  | Multicentre European | 288 (66%) | 148 (34%) | 43±10.1 |
| Fried et al³⁷        | Multicentre European | 326 (72%) | 127 (28%) | 48.2±10.1 |
| Manns et al³⁸       | Multicentre European | 322 (63%) | 189 (37%) | 43 |

Hematopoietic side effects: In our study group, anemia occurred in 17 (16.2%) patients. Dose modification was required in 11 (10.4%) patients. This is consistent with previous studies done in other parts of the world. Manns et al reported that a decrease in haemoglobin to less than 100g/L, the protocol requirement for dose modification occurred in 9% of patients.⁷ Stefan Zeuzem Maria Buti, reported a decrease in haemoglobin to less than 10g/dl in 12% patients Montserrat Laguno, Javier Murillas et al, reported that a decrease in haemoglobin to, 100g/l, the protocol requirement for dose modification, occurred in 13% of patients and discontinuation for anaemia was rare (one patient).³⁷ The maximum drop in Hb occurred after 4 weeks of treatment when Hb dropped from a median of 13.5g/dl at baseline to 12.2g/dl, there after remaining almost constant throughout treatment period. In previous other studies the maximum drop in average hemoglobin has been more but like in our study average Hb stabilised after first few weeks of treatment. Manns et al, reported a maximum drop in Hb of 2.5g/dl after first 4-8 weeks of treatment and remained constant thereafter.⁷ M. S. Sulkowski, R. Wasserman et al, reported a maximum drop in average Hb of 2mg/dl occurring after 4 weeks of treatment.³⁸ The lower absolute drop in average Hb in our study group may be explained by lower value of Hb at baseline as also found by M. S. Sulkowski.³⁸

**Thrombocytopenia**

In our study of 105 patients thrombocytopenia occurred in 27 (25.7%) patients. Dose modification was required in 13 (12.3%) patients due to platelet count dropping to less than 50,000 and stopped in 1 (0.95%) patients due to platelet count decreasing to less than 30,000. Thrombocytopenia and dose modification due to thrombocytopenia was higher than reported previously. MANNS et al reported that 3% of patients had a platelet decrease that reached the protocol defined criterion for dose reduction. No patient discontinued therapy owing to thrombocytopenia M. S. Sulkowski, R. Wasserman et al reported thrombocytopenia in 8% patients with 2% requiring dose modification and <1% requiring dose discontinuation due to thrombocytopenia Antonio Ascione et al. reported dose modification due to thrombocytopenia in 3% patients Robert Roemer, Bettina E. Hansen et al, reported dose modification in 3.7% patients due to thrombocytopenia on peginterferon alpha-2b and ribavirin treatments.³⁹-⁴⁰ The maximum drop in platelets occurred in the first 4 weeks of treatment. This was consistent with previous studies. M Schmid et al reported a maximum drop in platelets after 4 weeks which remained constant thereafter. Karen L et al, reported that platelet counts decreased from baseline during the first few weeks of treatment and stabilized during the remainder of treatment.³¹ Neutropenia: Neutropenia as defined by ANC less than 1500 occurred in 22 (20.9%) patients in our study group. 14 (13.3%) patients required dose modification due to neutropenia with ANC <750 and 2 (1.9%) patients required discontinuation of therapy due to neutropenia (ANC<500). This is consistent with studies done previously. Manns et al, reported that the frequency of dose reduction for neutropenia was 18% for the peginterferon alfa-2b plus ribavirin regimen and 1% or less of patients discontinued treatment for neutropenia.³⁷ Their ypoynard et al, reported neutropenia in 20% patients with 8% requiring dose modifications because of neutropenia. Andrew J et al, reported dose modification due to neutropenia in 14% patients and 3% patients requiring dose discontinuation due to neutropenia.³² In our study the maximum drop in median neutrophil count occurred after 8 weeks of therapy remaining constant thereafter till the completion of treatment. Similar findings have been made previously. M Schmid, et al reported a maximum drop in neutrophil count after 8 weeks of treatment after which it stabilised Andrew J. et al noticed a maximum drop in ANC after 4 weeks of treatment, stabilizing around this value thereafter.³³ Neuropsychiatric side effects: Out of all the neuropsychiatric side effects depression was reported by 24.7% patients and equal number of patients (24.7%) developed irritability. Similar findings have been made previously by Michael P Manns, John G mchutchion who reported depression in 31% patients and irritability.
CONCLUSION

Of all the 105 patients included in our study, dose discontinuation was required in 13 (12.3%) patients. Of these 1 (0.95%) had thrombocytopenia, 1 (0.95%) had anemia, 2 (1.9%) had neutropenia, 1 had hypothyroidism and in 8 (7.6%) patients dose was discontinued due to adverse events (including psychosis in 1, severe flu like symptoms in 3, dermatitis in 1, depression in 3). Thus, all the adverse events requiring dose discontinuation, neuropsychiatric symptoms accounted for the majority. Neuropsychiatric side effects were the most common adverse events requiring dose discontinuation (3.8%). Neutropenia was the most common lab. abnormality requiring dose discontinuation [n=2(1.9%)].

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Syed M, Gul I, Rasool A, Gul S, Gulzar GM, Wani MA. Side effect profile of hepatitis C treatment with peginterferon alpha-2b and ribavirin. Int J Basic Clin Pharmacol 2017;6:1577-84.