Original Article

Adverse Effects in HCV Treatment

Hematological Adverse Effects in HCV Patients Treated With Pegylated Interferon and Ribavirin in a Tertiary Care Hospital Peshawar

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ABSTRACT

Objective: To know the frequency of common hematological adverse effects during treatment of HCV.

Study Design: comparative study

Place and Duration of Study: This study was carried out OPD of gastroenterology unit HMC Peshawar from November 2013 to August 2014

Materials and Methods: This study comprising of 42 patients. Patient age more than 17 years, both genders, previously treatment experienced patients with normal hematologic and radiological parameters were included in the study. Patients age more than 70 years, patients with uncontrolled depressive illness, pregnant ladies, treatment naïve patients and decompensated cirrhotics were excluded from the study. Patients were evaluated for treatment with pegylated and ribavirin by history, clinical examination, routine laboratory investigations, ultrasound abdomen, HCV genotyping and upper GI endoscopy where considered necessary. Patient's who fulfilled the inclusion criteria were included in the study.

Results: Total of 42 patients, 24(57.14%) male and 18(42.85%) female were included in this study. The mean age was 39.05±8.54 with minimum age of 18 years and maximum age of 55 years. Genotype 3 was the most frequent genotype, present in 26 (61.90%) patients followed by untypeable genotype, present in 12(28.57%) patients. Anemia was present in 18(42.85%), thrombocytopenia in 10(23.80%) patients. Leucopenia was present in 6 (12.28%) patients.

Conclusion: Haematological abnormalities are common during treatment for HCV, so patients should be regularly followed to diagnose and treat the cytopenias in time.

Key Words: Pegylated interferon, SVR, Anemia, Leucopenia, Thrombocytopenia

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INTRODUCTION

Hepatitis C virus (HCV) infection is one of the main aetiologies of chronic liver disease, with a global prevalence of 3 %[1] and prevalence in Pakistan during 1999-2002 of 4.57%.[2] HCV is a positive strand RNA virus, characterized by high sequence heterogeneity. Seven HCV genotypes, numbered 1 to 7, and a large number of subtypes have been described.[3] Genotypes and subtypes differ among themselves by about 30% and 20% of their sequences, respectively. Genotype 1 is the most prevalent genotype worldwide, with a higher proportion of subtype 1b in Europe and 1a in the USA. Genotype 3a is highly prevalent in the European population of people who inject drugs. This group is currently experiencing an increasing incidence and prevalence of infections with HCV genotype 4. Genotype 2 is found in clusters in the Mediterranean region.[4] The novel genotype 7 was identified in patients from Canada and Belgium, possibly infected in Central Africa.[5]

It is estimated that approximately 85% of patients with a HCV infection go on to develop chronic disease and up to 20 % will eventually develop cirrhosis, which may lead to liver failure, hepatocellular carcinoma (HCC), and death.[6,7] The primary goal of HCV therapy is to cure the infection, which is generally associated with resolution of liver disease in patients without cirrhosis. Patients with cirrhosis remain at risk of life threatening complications, albeit at a lower rate, even after viral infection has been eradicated. The infection is cured in more than 99% of patients who achieve a sustained virological response (SVR), defined as undetectable HCV RNA 24 weeks after treatment. Completion until 2011, the combination of pegylated interferon-a and ribavirin was the approved and effective therapeutic regimen for infection with hepatitis C virus, which yields sustained virologic

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response (SVR) in up to 56% of patients in genotype 1.[8,9]

However, one of the main drawbacks of this combination therapy is the development of side effects, which can result in suboptimal dosing or discontinuation of therapy. That can limit the likelihood of SVR, since one of the determinants of SVR is adequate dose and duration of therapy. Among the side effects of combination therapy, haematologic abnormalities such as anaemia, neutropenia, and thrombocytopenia have been reported to result in dose reduction and discontinuation of therapy in up to 25% and 3% of patients, respectively.[10]

There are several mechanisms by which anaemia occur during combination therapy for HCV infection. Ribavirin causes a dose-dependent and reversible hemolytic anaemia. After entering red blood cells, ribavirin is phosphorylated into its active form, leading to depletion of adenosine triphosphate.[11] This leads to impaired antioxidant mechanisms, resulting in membrane oxidative damage and subsequent extravascular red blood cell removal by the reticulo-endothelial system.[11] Interferons also contribute to anaemia, mainly through bone marrow suppression.[12] Leucopenia occurs because bone marrow suppression or a reversible impairment in the release of neutrophils and lymphocytes[12]. Thrombocytopenia is caused primarily by reversible bone marrow suppression, although autoimmune- related thrombocytopenia may also occur.[13] The main aim of this study was to know the frequency of common haematological side effects of antiviral therapy in patients of chronic hepatitis C treated in the gastroenterology unit HMC Peshawar.

MATERIALS AND METHODS

This cross sectional descriptive study comprising of 42 patients was carried out in the Out-patients Department of Gastroenterology Unit Hayatabad Medical Complex Peshawar from November 2013 to August 2014. Patients of age more than 17 years, both male and female gender, previously treatment experienced patients either non-responders or relapsers and with normal haematologic and radiological parameters were included in the study. Patients age more than 70 years, patients with uncontrolled depressive illness, pregnant ladies, treatment naïve patients and decompensated cirrhotics were excluded from the study. Informed consent was taken from all patients and were evaluated for treatment with pegylated and ribavirin by taking detailed history, clinical examination, routine laboratory investigations including FBC, liver enzymes, liver synthetic function tests, renal function tests ,blood glucose level, ultrasound abdomen, HCV genotyping and upper GI endoscopy where considered necessary. All those patients who fulfil the inclusion criteria and gave consent were included in the study. Patients were started on pegylated interferon-alpha 2a 180ug subcutaneously once a week with oral ribavirin 800mg in two daily divided doses for genotype 2, 3 and untypeable and 1200mg in three daily divided for genotype 1. All patients were followed initially every 2 weeks for 2 month and thereafter 4 weekly by doing complete blood count and looked for any haematological adverse effects. All patients were followed for 6 months irrespective of the genotypes. All those patients who dropped Hb below 12gm/dl, leucocytes count below 3500 and platelets count below 150000 were labelled as having anaemia, leucopenia and thrombocytopenia respectively. All those patients who developed haematological adverse effects were treated. Patients who developed mild anaemia (Hb 12-10gm/dl) were treated with erythropoin injection 10000 IU SC weekly, patients with who developed moderate anaemia (Hb 10-8.5gm/dl) were by dose reduction and blood transfusion and in patients with severe anaemia (Hb less than 8.5Gm/dl) were treated with blood transfusion and antiviral treatment was discontinued. Patients with neutropenia and thrombocytopenia were observed infection and bleeding respectively and were treated supportively. After completion of the study, data was analyzed by using statistical software (SPSS version 10). Mean±SD was calculated for continuous variables like age and Frequencies were calculated for categorical variables.

RESULTS

Total of 42 patients were included in this study. Out of 42 patients 24 (57.14%) were male and 18 (42.85%) were female with a male to female ratio of 1.33 (Table 1). The mean age was 39.05±8.54.

Table No.1: Distribution of patients according to gender

Gender	No.	%age
Male	24	57.2
Female	18	42.8

Table No.2: Distribution of patients according to age

Age	No.	%age
18 – 30	8	19.1
31 - 45	28	66.6
46 - 55	6	14.3
Mean±SD	39.05±8.54	

Table No.3: Distribution of patients according to genotype

Genotype	No.	%age
Genotype 1	2	4.7
Genotype 2	2	4.7
Genotype 3	26	61.9
Genotype unbeatable	12	28.7

The minimum age in this study was 18 years and the maximum age was 55 years. Majority of the patients, 28 (66.66%) were in the age range 31-45 followed by

age range 18-30 having 8 (19.06%) patients (Table 2). Genotype 3 was the most frequently occurring genotype in our study which was present in 26 (61.90%) patients followed by untypeable genotype which was present in 12(28.57%) patients, while genotype 1 and 2 was the least frequent genotypes each of which was present in 2(4.76%) patients (Table 3). Anaemia was the most frequently occurring haematological adverse effect in this study and was present in 18 (42.85%) patients followed by thrombocytopenia which was present in 10 (23.80%) patients, while leucopenia was present only in 6 (12.28%) patients (Table 4).

Table No.4: Distribution of patients according to cytopenias

Cytopenia	No.	%age
Anaemia	18	42.8
Leucopenia	6	12.3
Thrombocytopenia	10	23.8

DISCUSSION

Infection with hepatitis C virus (HCV) is an increasing epidemic with over 180 million people infected worldwide.[14] Hepatitis C virus (HCV) infection is the leading cause of chronic liver-related diseases, including cirrhosis, liver failure, and hepatocellular carcinoma and currently, no effective vaccine is available for the prevention HCV infection.[15] Polyethylene glycol interferon-α (PegIFN-α) in combination with ribavirin (RBV) is the standard of care (SOC) for chronic hepatitis C. Both drugs have a significant effect on virological and histological responses and this combined therapy provides a SVR rate of 40% to 50% in patients with HCV genotype 1 and of 80% in patients with HCV genotypes 2 or 3 in randomised controlled trials.[16-17].

The primary aim of anti HCV therapy is permanent eradication of the virus or a sustained viral response thereby reducing the risk of progression to end-stage liver improving quality of life. A sustained viral response (SVR) is defined as undetectable plasma HCV RNA 6 months after the end of treatment, which lasts typically 6-12 months. This leads to a long term clearance of the virus in 98.3% of patients.[18] However this combination antiviral therapy is associated with many side effects like general malaise, fever, body aches, neuropsychiatric manifestation and haematological adverse effects.

In the present study out of 42 patients, 18 (42.85%) patients developed anaemia during the course of antiviral therapy. This occurrence of dropping Hb in our study is almost similar to other studies like the study done by JB Wong et al[19] in America and Lashin et al[20] in Egypt. However Majority of the patients in our study exercised severe dietary restriction despite counselling especially some to some specific meal like meat intake which was considered to be a major contributor to anaemia in this patient population which need further studies to clarify this association of dietary restriction and anaemia in these patients. So it is very necessary in our local set-up to counsel the patients before starting on antiviral therapy to avoid dietary restriction during the antiviral treatment especially meat intake.

In our study 6 (12.28%) patients developed leucopenia during the antiviral treatment and beside the antiviral therapy, no other cause for dropping leucocyte count was identified, however majority of the patients were asymptomatic, and leucopenia was an incidental finding during the routine follow up and no patient needed any granulocyte colony-stimulating factor, reduction in the dose or discontinuation of antiviral treatment. This suggests that neutropenia may be well tolerated by HCV-infected patients receiving combination therapy. This might be explained by a temporary enhanced innate immune cells activity. A recent study demonstrated that in patients with chronic hepatitis C neutrophil chemotaxis and oxidative burst significantly increased during treatment and returned to baseline at the end of therapy.[21]

Ten (23.80%) patients in our study developed varying degree of thrombocytopenia during the course of antiviral treatment, however no patient had serious consequences of thrombocytopenia like bleeding, discontinuation or reduction of the dose antiviral treatment. Other studies also gave the same result, meaning that beside antiviral treatment, other causes of thrombocytopenia should also be considered in HCV patients like Decreased platelet production occurs, due to decreased hepatic production of thrombopoietin[22], virus-induced bone-marrow suppression[23], an increased peripheral destruction of platelets, both immune-mediated[24] and due to portal hypertension and hypersplenism leading to increased splenic platelet sequestration.[25]

CONCLUSION

The antiviral treatment is without haematological side effects and it is extremely necessary to discuss all the pros and cons of antiviral treatment with the patient before starting antiviral, to do regular follow up of the patients, to check the compliance and to diagnose and treat any type of cytopenia in time, to avoid reduction or discontinuation of the antiviral dose and to increase the chances of achieving SVR.

REFERENCES

1. Lavanchy D. The global burden of hepatitis C. Liver Int 2009; 29(Suppl 1):74-81.
2. Theodor SY, Jamal MM. Epidemiology of HCV infection. Int J Med Sci 2006;3(2).

3. Rantala M, van de Laar M. Surveillance and epidemiology of hepatitis B and C in Europe – a review. Eur Surveill 2008;13(21).
4. Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, et al. Expanded classification of hepatitis C Virus into 7 genotypes and 67 Subtypes: updated criteria and assignment web resource. Hepatology 2013. http://dx.doi.org/ 10.1002/hep.26744 [Epub ahead of print, Pub Med PMID: 24115039.].
5. Antaki N, Craxi A, Kamal S, Moucari R, Van der Merwe S, Haffar S, et al. The neglected hepatitis C virus genotypes 4, 5, and 6: an international consensus report. Liver Int 2010;30:342–55.
6. Liang TJ, Rehermann B, Seeff LB, Hoofnagle JH. Pathogenesis, natural history, treatment, and prevention of hepatitis C. Ann Int Med 2000; 132(4):296-305.
7. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5(9):558-67.
8. 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; 358:958–965.2.
9. Fried MW, Shiffman ML, Reddy KR, et al.Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347:975–982. 3.
10. Fried MW. Side effects of therapy of hepatitis C and their management. Hepatol 2002; 36 (suppl 1): S237–S244.
11. De Franceschi L, Fattovich G, Turrini F, et al. Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. Hepatol 2000; 31:997–1004.
12. Peck-Radosavljevic M, Wichlas M, Homoncik-Kraml M, et al Rapid suppression of hematopoiesis by standard or pegylated interferon-alpha. Gastroenterol 2002; 123:141–151.
13. Janus. P, Zobair M. Younossi. Managing the hematologic side effects of antiviral therapy for chronic hepatitis C: anaemia, neutropenia, and thrombocytopenia. Cleveland Clin J Med 2004;71 (suppl 3): S17-S21.
14. World Health Organization (WHO). Weekly epidemiological record. World Health Organization 2007.
15. Yan Zhu, Song Chen. Antiviral treatment of hepatitis C virus infection and factors affecting efficacy. World J Gastroenterol. Dec 21, 2013; 19(47): 8963–8973.
16. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, 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; 358:958–965.
17. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975–982.
18. McHutchinson JG, Davis GL, Esteban-Mur R. Durability of sustained viral response in patients with chronic hepatitis C after treatment with interferon alfa-2b alone or in combination with ribavirin. Hepatol 2001; 34:244A.
19. Wong JB, Davis GL, McHutchison JG, Manns MP, Albrecht JK. Economic and clinical effects of evaluating rapid viral response to peginterferon alfa-2b plus ribavirin for the initial treatment of chronic hepatitis C. Peginterferon Alfa-2b +Ribavirin for Hepatitis C. Am J Gastroent 1998; 18: 2354-62.
20. Lashin 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 Gastroent 2013; 32(5):316-23.
21. Giorgini A, Capsoni F, Podda M, lleo A, Battezzati PM, Ongari AM, et al. Treatment with PEG-interferon and ribavirin for chronic hepatitis C increases neutrophil and monocyte chemotaxis. Ann NY Acad Sci 2009;1173:847–57.
22. Peck-Radosavljevic M, Wichlas M, Pidlich J, Sims P, Meng G, Zacherl J, et al. Blunted thrombopoietin response to interferon alfa-inducedthrombocytopenia during treatment for hepatitis C. Hepatol 1998; 28:1424–9.
23. Bordin G, Ballarè M, Zigrossi P, Bertoncelli MC, Paccagnino L, Baroli A, et al. A laboratory and thrombokinetic study of HCV associated thrombocytopenia: a direct role of HCV in bone marrow exhaustion? Clin Exp Rheumatol 1995; 13:S39-43.
24. Pockros PJ, Duchini A, McMillan R, Nyberg LM, McHutchison J, Viernes E. Immune thrombo-cytopenic purpura in patients with chronic hepatitis C virus infection. Am J Gastroentol 2002; 97: 2040–5.
25. McCormick PA, Murphy KM. Splenomegaly, hypersplenism and coagulation abnormalities in liver disease. Baillieres Best Pract Res Clin Gastroenterol 2000; 14:1009-31.