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Haematological Side Effects Following Antiviral Therapy (Conventional α-Interferon plus Ribavirin) in Patients with Chronic Hepatitis C

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Abstract: Treatment of chronic hepatitis C with interferon (IFN- α) and ribavirin lead to haemotoxic effects. We evaluated the side effects of IFN- α / ribavirin treatment on haematopoiesis. 50 patients admitted to Liaquat University Hospital Jamshoro Sind for treatment of chronic hepatitis C with IFN-α plus ribavirin were studied. Their haematological parameters including total leukocyte count (TLC), haemoglobin (Hb) and peripheral platelet counts (PPC) were recorded before starting antiviral therapy and then at 12 weekly intervals. All patients were given injection IFN-α plus capsule ribavirin as antiviral therapy. A total 50 patients with mean age of 35.5 years (range 15-50 years) were included in this study. There was a mean haemoglobin drop of 0.90 g/ dl at 12 weeks and 2.0 g / dl at 24 weeks of antiviral therapy. Clinically significant anaemia (i.e Hb < 11.0 g/ dl) occurred in 7.5% at 12 weeks and 10.5% at 24 weeks of antiviral therapy. Mean total leukocyte count (TLC) has fallen to 1.95×10^9/L at 12 weeks and 1.38×10^9/L at 24 weeks of antiviral therapy. Clinically significant leukopenia (i.e TLC < 3.0×10^9/L) was seen in 8% of the patients at 12 weeks of antiviral therapy. Clinically significant thrombocytopenia (i.e PPC < 150×10^9 /L) has occurred in 45% of the patients which maintained upto 24 weeks of antiviral therapy. IFN-α plus ribavirin therapies are associated with a decrease in all three haematopoietic lineages. Morbidities and mortalities associated with chronic hepatitis C has placed tremendous burden on health resources of developing countries. Potential uses of exogenous haematopoietic growth factors and their impact on the virological response need to be explored.

Key words: IFN-α · Ribavirin · Leukopenia · Anaemia · Thrombocytopenia · Chronic hepatitis C · Haematotoxicity · Growth factors

INTRODUCTION

Chronic hepatitis C is a major cause of cirrhosis, end-stage liver disease and hepatocellular carcinoma [1-3]. The current treatment of choice for chronic hepatitis C is combination therapy with interferon α (IFN- α) and ribavirin (RBV) [4, 5]. Unfortunately, both drugs have significant haematological toxic effects [6, 8].

IFN-α exerts anti-proliferative effects on many cell types. These properties are used for treatment of chronic myelo-proliferative and lympho-proliferative diseases [9, 10], but also account for several undesirable effects, such as thrombocytopenia and leukopenia and can interfere with the successful clinical application of full dose IFN-α in patients with chronic hepatitis C [9,11]. IFN-α induced thrombocytopenia and leukopenia is common, where as anaemia is more a sequel of combination therapy with ribavirin [4,5,8,12,13]. Thrombocytopenia is mild in most cases, amounting to decrease in peripheral platelet count of 10-50% but,when severe, can lead to bleeding complications [14,15] and discontinuation of IFN- α therapy [16]. Absolute neutrophil and lymphocyte counts typically decrease by 30-50% of baseline values during IFN-α therapy but this is usually not associated with infections [17,18].

The main mechanism leading to cytopenia during IFN-α therapy seems to be bone narrow suppression by IFN-α [19-21]. This suppressive action can be observed for pluripotent progenitor cells of all lineages [19, 20].

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Immune-mediated haematological toxicity [21] and capillary sequestration of platelets and white blood cells [22] have been proposed as additional causes for severe thrombocytopenia and leukopenia during IFN-α therapy.

Ribavirin treatment causes varying degrees of anaemia, presumably through haemolysis [12,13,23]. Discontinuation of IFN-α therapy usually leads to restitution of a normal complete blood count within several weeks [5, 8]. Dose reduction can improve haematological toxicities but carry the risk of a suboptimal treatment response [24].

This study has been carried out to evaluate the effects of antiviral therapy (IFN-α plus ribavirin) on the corpuscular elements of the blood in patients with chronic hepatitis C. Haematological parameters are peripheral indicators of bone narrow activity.

MATERIALS AND METHODS

This is a hospital based interventional descriptive study carried out at Medical unit 2 of Liaquat University Hospital Jamshoro Sind Pakistan from April to September 2008. A total 50 patients between age of 15-50 years who had chronic hepatitis C, were included in this study. Informed written consent was obtained from each patient before entry into the study. Those patients having pre-existing anaemia, other haematological disorders and taking concurrent medications were excluded from this study.

Patients were exposed to a battery of investigations including liver biopsy. The stage of chronic hepatitis C was determined and patients having minimal fibrosis with chronic inflammatory cells on liver biopsy were selected for anti-viral therapy.

The antiviral therapy was given to indoor patients. The conventional IFN-α (in dose of 3.0 million units thrice/week) plus oral ribavirin (in dose of 800-1000 mg per day according to body weight) were given for 24 weeks as standard antiviral therapy.

The study variables Hb estimation, total leukocyte count (TLC) and peripheral platelet counts (PPC) were noted on day 0 (before IFN-α therapy) and at 12, 24, 36 and 48 weeks after start of IFN-α therapy. All patients were followed up for 12 and 24 weeks after the end of IFN-α therapy.

Descriptive statistics were applied to the recorded data using SPSS version 10.0 for analysis.

Mean of the variables, Hb estimation, TLC and PPC were calculated and analysed for any fluctuation during antiviral therapy.

RESULTS

A total of 50 patients admitted at Medical unit 2 of Liaquat University Hospital Jamshoro Pakistan were included in this study. All patients were males. Mean age of the patients were 35.5 years (range 15-50 years). Mean Hb level at the time of admission before antiviral therapy was 13.0 g/dl (range 11.0-16.0 g/dl). Mean Hb level after 12 weeks of antiviral therapy was 12.10 g/dl. At 24 weeks, mean Hb value was 11.0 g/dl. There was a mean Hb drop of 0.90 g/dl at 12 weeks and 2.0 g/dl at 24 weeks of antiviral therapy. This change is statistically significant since ($P<0.05$). Clinically significant anaemia (Hb < 11.0 g/dl) occurred in 7.5 % of the patients at 12 weeks and it was raised to 10.5% at 24 weeks of antiviral therapy.

Clinically significant leukopenia (i.e TLC $<3.0\times10^9$/L) occurred in 8.0% of cases at 12 weeks and all patients have recovered at 24 weeks after antiviral therapy so there was transient decrease in total leukocyte count during this study. Clinically significant thrombocytopenia (i.e peripheral platelet counts $<150\times10^9$/L) occurred in 45% of the patients. This decrease in peripheral platelet counts has maintained upto 24 weeks of antiviral therapy. The thrombocytopenia was insignificant clinically because platelet counts as low as 50×10^9/L have been very well tolerated by the patients without bleeding tendencies.

DISCUSSION

Administration of conventional IFN-α in combination with ribavirin causes a significant decrease in all three lineages of the haematopoietic system, which cannot be completely counteracted by the endogenous production of haematopoietic growth factors [8,16,25]. The mechanisms responsible for induction of cytopenia during antiviral therapy have been studied in detail in vitro. Direct inhibition of progenitor cell proliferation in the bone narrow seems to be the dominant factor [19,20,26]. Haemoglobin levels were significantly decreased in those patients receiving combination therapy with ribavirin, which accumulate in red blood cells and causes alteration in the erythrocyte membrane known to be associated with erythrophagocytic extra-vascular destruction and haemolysis [7,23]. Although reticulocytes increase significantly following combination therapy, the increase was inadequate to overcome the effects of IFN-α/ribavirin combination therapy, despite significantly elevated erythropoietin levels. This confirms the suppressive action of IFN-α on erythroid progenitor cell proliferation [10,19,20].

Correction of anaemia could result in better adherence to antiviral therapy, which may lead to improved sustained virological response rates. Potential strategies include treatment with antiviral drugs that do not cause significant haemolysis, such as levovirin or viramidine, or support with haematopoietic growth factors. Recent data shows that treatment with super-physiological doses of recombinant erythropoietin can positively impact erythropoiesis, by correcting anaemia and thereby permitting maintenance of patients intended ribavirin dose [27-31]. The haemoglobin values usually reached to baseline 24 weeks after the end of IFN-α /ribavirin therapy.

According to Soza *et al.* [32] neutropenia is common during treatment of chronic hepatitis C with antiviral therapy (IFN-α plus ribavirin). Their results have compared to us, the neutropenia occurred in 8% of cases at 12 weeks of antiviral therapy. The neutrophil counts have returned to baseline 24 weeks after the end of IFN-α /ribavirin therapy.

Peripheral platelet counts were significantly reduced after 24 weeks of treatment in 45% of the patients. During this study, thrombocytopenia was so severe in 5% of cases that it sometimes leads to either dose reduction or discontinuation of the treatment. The decrease in peripheral platelet counts by IFN-α was caused by diminished production of platelets through suppression of megakaryocyte progenitor cell proliferation and differentiation in bone narrow [9,10,20].

There is evidence that patients with marked haematological toxicities will benefit from treatment with super-physiological doses of specific haematopoietic growth factors [7, 28, 31, 33-35], enabling them to receive full dose combination therapy. Whether this can ultimately improve sustained virological response rates remain to be established in prospective randomised trials. These trials should provide the answer to the important question of whether expensive growth factor therapy in addition to full dose antiviral therapy will become an accepted and worthwhile alternative to dose reduction of antiviral therapy.

Our study has revealed significant haematological toxic effects of antiviral therapy,therefore all patients should be followed up for at least 12 weeks for complete blood count. Timely intervention such as dose reduction or stoppage of treatment might be life saving.

CONCLUSION

The haematological toxic effects of antiviral therapy (i.e IFN-α / ribavirin) occur in association with a marked increase in endogenous growth factors, which are still insufficient to counteract the side effects to an extent that would allow all patients to receive full dose antiviral therapy.

A further detailed study needs to be carried out to determine cause of anaemia, leukopenia and thrombocytopenia in patients with chronic hepatitis C.

REFERENCES

1. Di Bisceglie A.M., Goodman Z.D., Ishak K.G., *et al.* Long-term clinical and histopathological follow-up of chronic post-transfusion hepatitis. Hepatology, 1991; 14: 969-974.
2. Tong M.J., el-Farra N.S., Reikes AR., *et al.* Clinical outcomes after transfusion-associated hepatitis C. N. Engl. J. Med., 1995; 332: 1463-1466.
3. Fattovich G., Giustina G., Degos F., *et al.* Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology, 1997; 112: 463-472.
4. Davis G.L., Esteban-Mur R., Rustgi V., *et al.* Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. International Hepatitis Interventional Therapy Group. N. Engl. J. Med., 1998; 339: 1493-1499.
5. McHutchison J.G., Gordon S.C., Schiff E.R., *et al.* Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N. Engl. J. Med., 1998; 339: 1485-1492.
6. Russo M.W., Fried M.W. Side effects of therapy for chronic hepatitis C. Gastroenterology 2003; 124: 1711-1719.
7. Fried M.W. Side effects of therapy of hepatitis C and their management. Hepatology, 2002; 36: (suppl 1): S237-44.
8. Peck-Radosavljevic M., Wichlas M., Homoncik-Kraml M., *et al.* Rapid suppression of haematopoiesis by standard or pegylated interferon-alpha. Gastroenterology, 2002; 123: 141-151.
9. Wang Q., Miyakawa Y., Fox N., *et al.* Interferon-alpha directly represses megakaryopoiesis by inhibiting thrombopoietin-induced signaling through induction of SOCS-1. Blood, 2000; 96: 2093-2099.
10. Lengfelder E., Berger U., Hehlmann R. Interferon alpha in the treatment of polycythemia vera. Ann. Hematol., 2000; 79: 103-109.
11. Fattovich G., Giustina G., Favarato S., *et al.* A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alfa interferon. J. Hepatol., 1996; 24: 38-47.

12. Bodenheimer H.C. Jr, Lindsay KL., Davis G.L., *et al.* Tolerance and efficacy of oral ribavirin treatment of chronic hepatitis C: a multicenter trial. Hepatology, 1997; 26: 473-477.
13. Dusheiko G., Main J., Thomas H., *et al.* Ribavirin treatment for patients with chronic hepatitis C: results of a placebo-controlled study. J. Hepatol., 1996; 25: 591-598.
14. Shrestha R., McKinley C., Bilir B.M., *et al.* Possible idiopathic thrombocytopenic purpura associated with natural alpha interferon therapy for chronic hepatitis C infection. Am. J. Gastroenterol., 1995; 90: 1146-1147.
15. Lopez Morante A.J., Saez-Royuela F., Casanova Valero F., *et al.* Immune thrombocytopenia after alpha-interferon therapy in a patient with chronic hepatitis C. Am. J. Gastroenterol., 1992; 87: 809-810.
16. Pardo M., Marriott E., Moliner M.C., *et al.* Risks and benefits of interferon-alpha in the treatment of hepatitis. Drug Saf., 1995; 13: 304-316.
17. Wong S., Kaita K., Gauthier T., *et al.* A comparative trial of recombinant interferon alpha 2A versus alpha 2 beta on myelosuppression in healthy adult volunteers. Hepatogastroenterology, 1996; 43: 301-305.
18. Soza A., Everhart J.E., Ghany M.G., *et al.* Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. Hepatology, 2002; 36: 1273-1279.
19. Ernstoff M.S., Kirkwood J.M. Changes in the bone marrow of cancer patients treated with recombinant interferon alpha-2. Am. J. Med., 1984; 76: 593-596.
20. Ganser A., Carlo-Stella C., Greher J., *et al.* Effect of recombinant interferons alpha and gamma on human bone marrow-derived megakaryocytic progenitor cells. Blood, 1987; 70: 1173-1179.
21. Hoofnagle J.H. Thrombocytopenia during interferon alfa therapy. JAMA 1991; 266: 849.
22. Dormann H., Krebs S., Muth-Selbach U., *et al.* Rapid onset of haematotoxic effects after interferon alpha in hepatitis C. J. Hepatol., 2000; 32: 1041-1042.
23. De Franceschi L., Fattovich G., Turrini F., *et al.* Haemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. Hepatology, 2000; 31: 997-1004.
24. Manns M.P., Mc Hutchison J.G., Gordon S.C., *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.
25. Peck-Radosavljevic M., Wichlas M., Pidlich J., *et al.* Blunted thrombopoietin response to interferon alfa-induced thrombocytopenia during treatment for hepatitis C. Hepatology, 1998; 28: 1424-1429.
26. Hoofnagle J.H., di Bisceglie A.M. The treatment of chronic viral hepatitis. N. Engl. J. Med. 1997; 336: 347-356.
27. Dieterich D.T., Pockros P.J., Schiff E.R., *et al.* Epoetin Alpha (Procrit) once weekly maintains ribavirin dose in hepatitis C virus (HCV)-infected patients treated with combination therapy: interim results of a randomized, double-blind, placebo-controlled study (abstr.). Hepatology, 2002; 36: 286A.
28. Dieterich D.T., Wasserman R., Brau N., *et al.* Once-weekly epoetin alfa improves anemia and facilitates maintenance of ribavirin dosing in hepatitis C virus-infected patients receiving ribavirin plus interferon alfa. Am. J. Gastroenterol., 2003; 98: 2491-2499.
29. Dieterich D.T., Wassermann R., Brau N., *et al.* Once-weekly recombinant human erythropoietin (Epoetin Alpha) facilitates optimal ribavirin (RBV) dosing in hepatitis C (HCV)-infected patients receiving IFN-alpha-2b (IFN)/RBV combination therapy. Gastroenterology, 2001; 120: 340.
30. Wasserman R., Brau N., Haasnein T.I., *et al.* Once weekly Epoetin alpha increases haemoglobin and decreases RBV discontinuation among HCV patients who develop anemia on RBV/INF therapy. Hepatology, 2000; 32: A368.
31. Afdahl N.H., Dieterich D.T., Pockros P.J., *et al.* Epoetin alfa treatment of anemic HCV-infected patients allows for maintenance of ribavirin dose, increases haemoglobin levels, and improves quality of life vs placebo: a randomized, double-blind, multicenter study. Gastroenterology, 2003; 124: (suppl 1): A714.
32. Soza A., Everhart J.E., Ghany M.G., Doo E. Neutropenia during combination therapy of interferon alfa and ribavirin for Chronic Hepatitis C. J. Hepatol., 2002; 36: 1273.
33. Burroughs A.K. Post-transplantation prevention and treatment of recurrent hepatitis C. Liver Transpl., 2000; 6: (suppl 2): S35-40.
34. Gopal D.V., Rabkin J.M., Berk B.S., *et al.* Treatment of progressive hepatitis C recurrence after liver transplantation with combination interferon plus ribavirin. Liver Transpl., 2001; 7: 181-190.
35. Golia P., Talal A.H., Jacobson I.M., *et al.* A preliminary study of growth factor versus dose reduction for peg interferon alfa-2b and ribavirin associated neutropenia and anemia in HIV/HCV co-infected patients. Gastroenterology, 2003; 124: (suppl 1): A766.