ORIGINAL ARTICLE

Frequency of Retinopathy during Interferon and Ribavirin Therapy for Hepatitis C

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ABSTRACT

Background: Hepatitis C virus infection is fairly common in Pakistan and accounts for most of the cases of CLD. Therapy for Hepatitis C includes combination of Interferon and Ribavirin. Apart from well known side effects, studies have shown that retinopathy can occur during interferon therapy.
Aim: To determine the frequency of retinopathy during Interferon and Ribavirin combination therapy for Hepatitis C in normoglycemic and normotensive patients.
Methods: This was observational follow up study conducted in the Outpatient clinics of Mayo Hospital, King Edward Medical University Lahore, Pakistan from September 17, 2008 to April 16, 2009. 190 patients who were Polymerase chain reaction (PCR) positive for Hepatitis C virus Ribonucleic acid (RNA) were included in the study. The enrolled patients, while on combination therapy (Interferon alpha-2b 3 million units subcutaneous thrice a week and Ribavirin 400 mg orally thrice daily), had follow-up visits at 2, 4 and 6 months. On each visit their visual acuity was recorded and direct fundoscopic Examination was done, after pupil dilatation, for evidence of retinopathy and findings were confirmed by consultant ophthalmologist who had vast experience in dealing with such kind of patients.
Results: Retinopathy occurred in patients at 2, 4 and 6 months of therapy. Highest frequency was seen at 4 months when 53 (27.9%) of 190 patients developed retinopathy (soft exudates in 51(26.8%), retinal hemorrhages in 37(19.5%), and optic neuritis in 2(1.1%).
Conclusions: Retinopathy can occur with interferon therapy in normoglycemic and normotensive patients. Soft exudates and retinal hemorrhages may not cause visual deterioration but optic neuritis can be symptomatic. So regular follow up is required and fundoscopic examination should be the integral part of the examination of the hepatitis C patients before during and after the treatment that are on interferon and ribavirin therapy.
Keywords: Retinopathy, retinal haemorrhage, hepatitis C

INTRODUCTION

Hepatitis C virus (HCV) infection is fairly common in Pakistan and accounts for most of the cases of Chronic Liver Disease. The general sero-prevalence of Hepatitis C virus infection in Pakistan is increasing. 170 million people in the world are suffering from chronic hepatitis C out of which 10 million from Pakistan[1]. Punjab which is the largest province of Pakistan in terms of population has the highest prevalence of Hepatitis C infection that is 14.63%[2].

The risk of progression to Chronic Liver Disease after infection with hepatitis C virus is 85%[3]. HCV is also the leading cause of hepatocellular carcinoma in Pakistan[4]. In addition to this, several extra hepatic manifestations have been reported in the natural history of HCV. Up to 40-74% of patients infected with HCV might develop at least one extra hepatic manifestation during the course of their disease[5]. These include essential mixed cryoglobulins with skin, neurologic, renal, and rheumatologic complications, systemic vasculitis, splenic lymphoma, porphyria cutanea tarda, and the sicca syndromes[6]. As more and more people are getting infected with HCV, burden of chronic liver disease is also rising. Therefore it is important to recognize and treat the infection at an early stage so as to prevent the late complications. Once cirrhosis of liver takes place, it is irreversible and liver transplant becomes the only treatment option. There has been a tremendous increase in the awareness regarding Hepatitis and the turnover of patients seeking advice has increased as well. This has been facilitated by the availability of sophisticated tests like Polymerase chain reaction (PCR) for HCV ribonucleic acid (RNA), both in the government and the private sector. Standard therapy for Hepatitis C infection is combination therapy of pegylated Interferon and Ribavirin. In Pakistan, Interferon Alpha-2b (INF) and Ribavirin combination therapy is widely used, most often because of higher cost of pegylated Interferon. The common side

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effects of the treatment are flu-like symptoms, psychiatric symptoms such as irritability and depression, thyroid dysfunction and bone marrow suppression. Hemolysis has also been reported with the use of Ribavirin[3]. Retinopathy refers to various non-inflammatory disorders of the retina, which most commonly are caused by Diabetes Mellitus and Hypertension. Retinopathy includes microaneurysms, dot intraretinal hemorrhages, cotton-wool spots (soft exudates), dilated tortuous veins, generalized and focal arteriolar narrowing, arteriovenous nicking, flame-shaped and blot-shaped retinal hemorrhages and swelling of the optic disc[7,8]. HCV itself can cause a number of ocular conditions. The ocular manifestations of HCV infections include a keratoconjunctivitis sicca syndrome, macular edema, optic neuropathy and ischemic retinopathy[9,10]. Hepatitis C related vasculitis play a major role in development of ischemic retinopathy. However, there are several studies and case reports, which have shown ocular complications during Interferon therapy, which result from combination therapy. These range from mild retinopathy to more severe inflammatory and vascular intraocular manifestations. Retinopathy induced by INF includes soft exudates, retinal hemorrhages and optic neuropathy. While in severe cases Vogt-Koyanagi-Harada (VKH) like disease (an association of panuveitis, retinal detachment, ear and meningeal detachment and skin and hair changes), central retinal vein occlusion (CRVO) and central retinal artery occlusion (CRAO) has been reported[11,12]. In some studies, the retinopathy was asymptomatic and caused no deterioration in visual acuity[13]. On the contrary, some case reports showed that the affected patients complained of decrease in vision and their visual acuity was reduced. This was seen mostly with the optic neuropathy[14,15]. The retinopathy was transient and had a benign course in many patients and treatment was stopped only in a few cases who had severe changes[16,17]. Internationally, different studies have shown variable incidence of retinopathy associated with INF which ranges from 19% to as high as 64.2%[17,18]. Age, Systemic hypertension, Diabetes Mellitus, initial dose of INF and hemoglobin levels seem to be risk factors for development of this adverse effect[18,19].

Abundant data is available globally on this subject. However there is no prospective study in Pakistan regarding this side effect of combination therapy, though there are two case reports of interferon related optic neuropathy[20,21]. In this study, the frequency of retinopathy (soft exudates, hemorrhage and optic neuritis) was described in normotensive and normoglycemic patients of hepatitis C virus infection in our population, who received the combination therapy of INF and Ribavirin. We deliberately excluded diabetic and hypertensive patients which could have been the confounding factors in our study. This has helped us in better understanding of this potential adverse effect of combination therapy in our population.

MATERIALS & METHODS

This descriptive cross sectional study was conducted in Outpatient clinics of Mayo Hospital, King Edward Medical University, Lahore, Pakistan during a period of 7 months from September 17, 2008 to April 16, 2009. 190 patients receiving combination therapy for HCV were included in the study. This calculated sample size was taken with 7 % margin of error, 95% confidence interval and taking incidence of retinopathy associated with INF as 61%. Non-probability purposive sampling was used.

Data collection: 190 patients who were PCR positive for Hepatitis C virus RNA, presenting to outpatient departments of Mayo Hospital, Lahore for Interferon therapy were included in the study. Informed and written consent was taken from those who fulfilled the inclusion criteria. The enrolled patients, while on combination therapy (which included the standard dosage regimen of Interferon alpha-2b given 3 million units subcutaneous three times a week and Ribavarin 400mg orally three times daily), had follow-up visits at 2 months, 4 months and 6 months. On each visit their visual acuity was recorded using standard Snellen's Chart. And they were subjected to Direct Fundoscopic Examination after pupil dilatation at the start of therapy and then at 2,4 and 6 months for any evidence of retinopathy (soft exudates, hemorrhages and optic neuritis) and findings were confirmed by consultant ophthalmologist who had vast experience in dealing with such kind of patients and the findings were documented on a pre-designed Performa.

Data analysis: The data was entered in SPSS, version 19.0 and analyzed. The demographic variable like age was described as simple statistics giving mean and Standard Deviation. Data was stratified for age, gender and visual acuity (as measured using the Snellen's chart). The findings of retinopathy performed through fundoscope model number (HEINE BETA 200 LED) on direct Fundoscopy were classified as present or absent and were presented as frequencies and proportions at 2 months, 4 months and 6 months of combination therapy. Specific findings like soft exudates, retinal hemorrhages and optic neuritis were described as present unilateral, present bilateral or absent and were presented as frequencies at 2 months, 4 months and 6 months of combination therapy.

RESULTS

Table 1:

	Frequency	%age
Age in years		
18-25	22	11.57
26-35	76	40
36-45	63	33.15
46-55	28	14.73
56-65	1	0.5
Gender		
Male	121	63.7
Female	69	36.3

Table 2

	Frequency	%age
Visual acuity		
6-Jun-2008-09	181	95.3
9-Jun-2008-09	7	3.7
12-Jun-2008-09	2	1.1
Retinopathy		
Absent	148	77.9
Present	42	22.1

Table 3:

Soft exudates	Frequency	%age
Absent	148	77.9
Present unilateral	24	12.6
Present bilateral	18	9.5

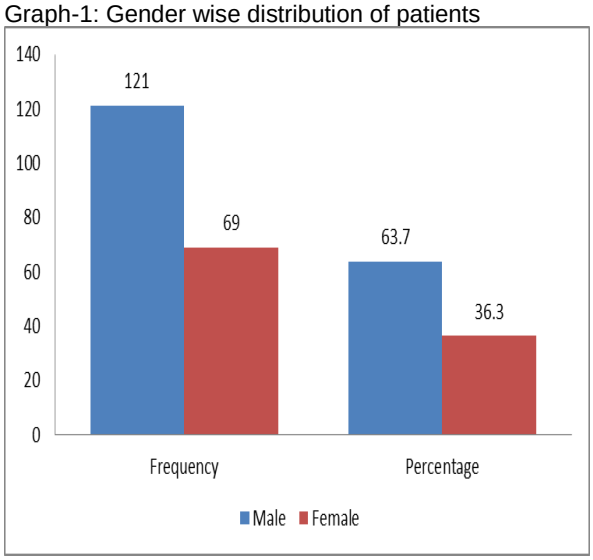
Table 4:

Retinal haemorrhages	Frequency	%age
Absent	164	86.3
Present unilateral	15	7.9
Present bilateral	11	5.8

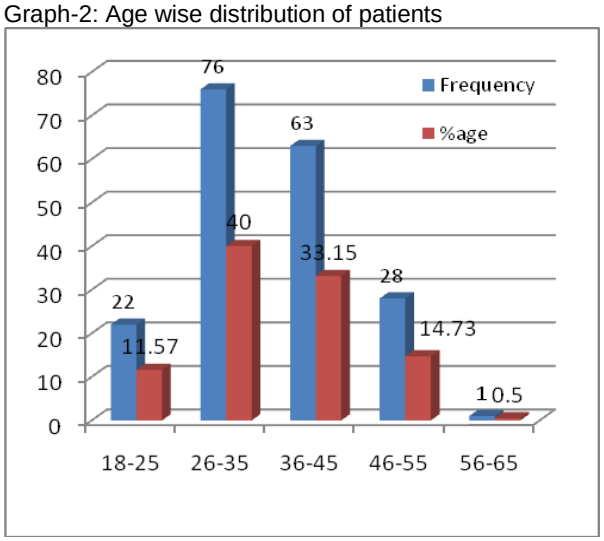
Table 5:

Optic neuritis	Frequency	%age
Absent	189	99.5
Present unilateral	1	0.5
Present bilateral	0	0

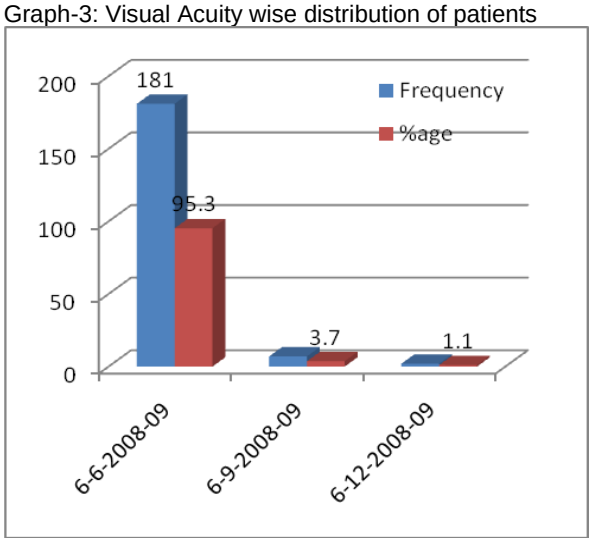
Graph-1: Gender wise distribution of patients



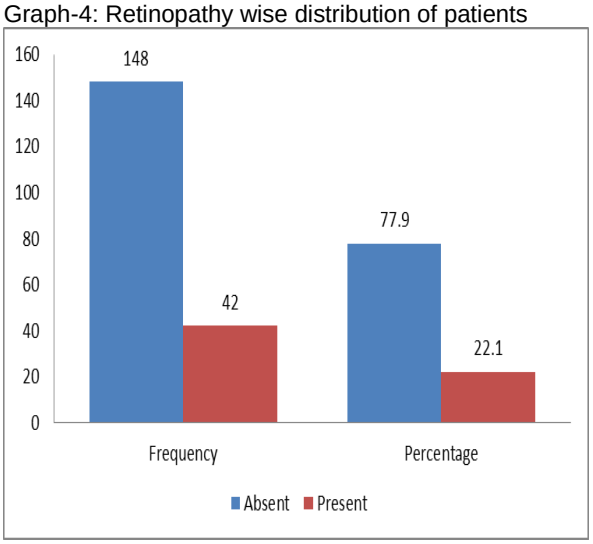
Graph-2: Age wise distribution of patients



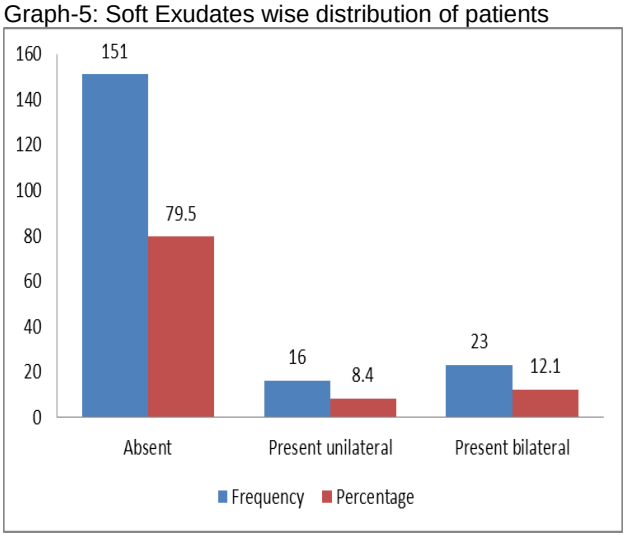
Graph-3: Visual Acuity wise distribution of patients



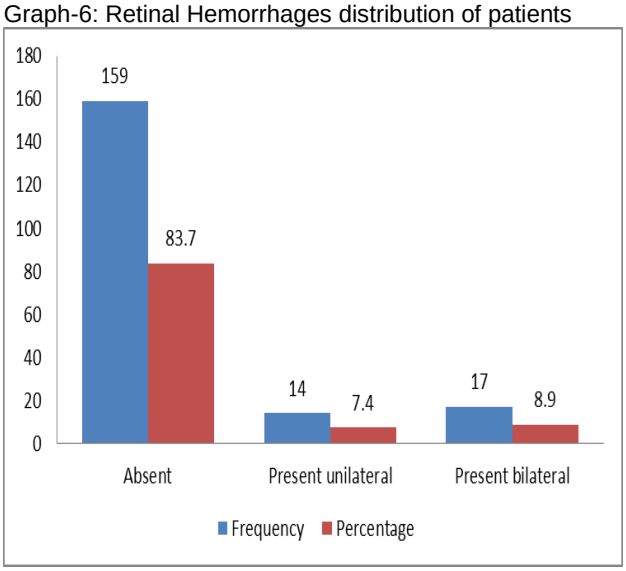
Graph-4: Retinopathy wise distribution of patients



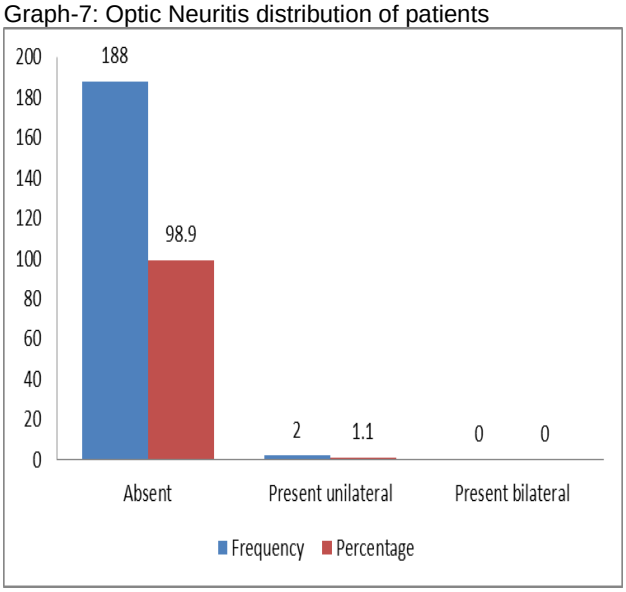
Graph-5: Soft Exudates wise distribution of patients



Graph-6: Retinal Hemorrhages distribution of patients



Graph-7: Optic Neuritis distribution of patients



The mean age of the patients was 36.74±9.10 years. The majority of the patients 76(40%) were in the age range of 26-35 years of age (Table 1).

In the sex distribution there were 121(63.7%) patients, who were male and 69 (36.3%) patients, who were female as described (Table 2).

At 2 months of combination therapy, 181(95.3%) patients had visual acuity of 6/6, 7(3.7%) patients of 6/9 and 2 (1.1%) patients had 6/12 (Table 3).

At 2 months of therapy, 42(22.1%) patients developed retinopathy (Table 4). Soft exudates occurred unilaterally in 24(12.6%) and bilaterally in 18(9.5%) patients (Table 5). Retinal hemorrhages occurred unilaterally in 15(7.9%) and bilaterally in 11(5.8%) patients. Optic neuritis was found unilaterally in 1(0.5%) patients. At 4 months of combination therapy, 181 (95.3%) patients had visual acuity of 6/6, 7(3.7%) patients of 6/9 and 2 (1.1%) patients had 6/12. At 4 months of therapy, 53(27.9%) patients developed retinopathy. Soft exudates occurred unilaterally in 27(14.2%) and bilaterally in 24(12.6%) patients. Retinal hemorrhages occurred unilaterally in 19(10%) and bilaterally in 18(9.5%) patients. Optic neuritis was found unilaterally in 2 (1.1%) patients.

At 6 months of combination therapy, 182 (95.8%) patients had visual acuity of 6/6, 7 (3.7%) patients of 6/9 and 1(0.5%) patients had 6/12.

At 6 months of therapy, 41(21.6%) patients developed retinopathy. Soft exudates occurred unilaterally in 16(8.4%) and bilaterally in 23(12.1%) patients. Retinal hemorrhages occurred unilaterally in 14(7.4%) and bilaterally in 17(8.9%) patients. Optic neuritis was found unilaterally in 2(1.1%) patients.

DISCUSSION

The general sero-prevalence of Hepatitis C virus (HCV) infection in Pakistan is increasing. Punjab has the highest prevalence of Hepatitis C infection that is 14.63%.[2] The risk of progression to Chronic Liver Disease after infection with hepatitis C virus is 85 %.[3] It accounts for most of the cases of Chronic Liver Disease and is also the leading cause of Hepatocellular carcinoma in Pakistan.[4] There has been a tremendous increase in the awareness regarding Hepatitis and the turnover of patients seeking advice has increased as well. Consequently more and more patients are getting the combination therapy which includes Interferon alpha 2-b and Ribavirin. Combination of pegylated interferon and ribavirin is standard of care in treating chronic hepatitis C.

Retinopathy refers to various non-inflammatory disorders of the retina which includes microaneurysms, dot intraretinal hemorrhages,

cotton-wool spots (soft exudates), dilated tortuous veins, generalized and focal arteriolar narrowing, arteriovenous nicking, flame-shaped and blot-shaped retinal hemorrhages and swelling of the optic disc. It is now well known that Interferon therapy can cause retinopathy.

In this study, 53 of 190 patients (27.9%) patients showed evidence of retinopathy and this was the proportion at 4 months of therapy. Our study group consisted mainly of young patients with majority of the patients i.e., 76(40%) in the range of 26-35 years of age. Mean age of the patients was 36.74±9.10 years.

Internationally, different studies have shown variable incidence of retinopathy associated with INF which ranges from 19% to as high as 64.2%[17,18]. This can well be explained by the sample size studied. Okuse C et al[18] showed in their study that 14 of their 73 patients (19%) patients developed retinopathy during INF therapy which is comparable with our study. It was asymptomatic and therapy was continued. In 9 patients, it disappeared during the course of treatment. Risk factor identified was hypertension. Nagaoka T et al[19] described retinopathy in 61% patients during INF therapy (21/36 patients) which is comparable with our study. The sample included diabetic and hypertensive patients, which were identified as risk factors. Similar risk factors were described by Stoffelns BM.[20] He also reported permanent visual loss in 3 out of 24 eyes.

Another study by Schulman JA[17] showed that 27 of 42 patients (64.2%) had retinopathy during INF therapy. In 3 patients treatment had to be discontinued because of severe posterior segment changes and visual deterioration.

Our study excluded diabetic and hypertensive patients, so we can comment that in Pakistani population, approximately one third of patients receiving INF therapy are at risk of developing changes consistent with retinopathy even in the absence of these risk factors.

Of note in this study is that the visual acuity of the affected patients remained same as the baseline throughout therapy. Retinopathy was noted as early as at 2 months of INF therapy. Maximum frequency was observed at 4 months. Majority had soft exudates and retinal hemorrhages present unilaterally and bilaterally. No hemorrhage or soft exudate was noted in the macular area to cause significant visual deterioration. Studies have shown that most patients remain asymptomatic for the retinopathy and therapy can be continued safely under close follow up. Our study data is consistent with these observations. In this study only 2 patients (1.1%) developed mild optic neuritis. In these patients visual acuity was deteriorated to a point below the baseline. Optic neuritis persisted throughout the therapy. However as it remained stable, therapy was continued. At 6 months of therapy (End of treatment) spontaneous resolution of retinopathy was noted in 12 of 53 patients while it persisted in the rest. Resolution of retinopathy during INF therapy has also been documented in International literature[18].

This is the first study of its kind in Pakistan. Large sample size as compared to International studies remains the strength of this study. This study highlights the high frequency of asymptomatic retinopathy in patients of HCV infection receiving INF and Ribavirin combination therapy, even in the absence of Diabetes and Hypertension. Clinicians must be made aware of this potential adverse effect which at times may need urgent referral to Ophthalmologist for review. Clinicians should also be advised to do routine fundoscopy of patients on INF therapy as most patients of retinopathy are asymptomatic for their changes. Patients should be advised to report any visual symptoms to detect retinopathy early so that close follow up can be done.

The limitation of this study was that patients were not followed up after the end of treatment to see whether complete resolution of retinopathy took place or not. Although our study showed retinopathy induced by INF only, excluding Diabetic and Hypertensive patients was an inadvertent limitation which otherwise may have detected higher frequency of retinopathy.

We therefore suggest further adequate sample size prospective studies comparing frequency of retinopathy induced by INF between Diabetic, Hypertensive and normoglycemic, normotensive patients. We further recommend that ophthalmologic examination by the treating physicians should be made integral part of the follow up of patients who are on INF therapy so that symptomatic or severe cases can be detected early and early referral to an ophthalmologist can be made for further management of the complication.

CONCLUSION

This study showed that retinopathy can occur during Interferon and Ribavirin combination therapy for Hepatitis C in normoglycemic and normotensive patients. Soft exudates and retinal hemorrhages usually do not cause visual deterioration but optic neuritis can be symptomatic. Retinopathy in some patients may resolve spontaneously during the course of therapy on the whole Interferon therapy can result into retinopathy therefore Periodic fundoscopic examinations help in early detection and prevent progression to permanent visual loss.

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