The Prevalence, Risk Factors and Outcome of Retinopathy Associated with Interferon Alfa-2a and Ribavirin Therapy in Patients with Chronic Hepatitis C

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Abstract

Background/Aim: In the treatment of chronic hepatitis C (HCV), by the use of a combination of interferon alfa-2a (IFN-a 2a) and ribavirin many side effects of this combination therapy have been described. Ocular complications are fairly common, retinopathy is a well recognized side effect of interferon therapy and is characterized by retinal hemorrhages, cotton wool spots, and macular edema. The aim of this study was to document the prevalence, risk factors and outcome of intraocular complications of IFN-a 2a and ribavirin therapy in patients with chronic HCV.

Patient and Methods: All patients started on treatment from May 2010 to August 2011 were invited to participate in the study according to the Egyptian national protocol for treatment of chronic HCV. The past medical and ocular history, visual symptoms, a full ophthalmological assessment were performed pre-treatment, any patient with retinal or optic diseases were excluded. Follow-up visits for full ophthalmological assessment were done at 1, 3, 6, 9 and 12 months.

Results: Out of the eligible 168 patients, received IFN-a 2a, 41 (24.4%) patients had diabetes, 24 (14.9%) patients had hypertension and 30 (17.9%) patients had both diabetes; and hypertension. Only 13 (7.73%) of 168 patients had evidence of retinopathy including deep retinal hemorrhage and cotton wool spots (4 had DM; 2 had hypertension; 4 had both hypertension and diabetes; and 3 patient without DM or hypertension). None had any visual symptoms and in all thirteen patients the retinopathy resolved completely while the patients completed their course of treatment. Multiple logistic regression analysis revealed that diabetic and hypertensive patients are at significant higher risk for development of IFN-associated retinopathy.

Conclusions: The incidence of retinopathy with IFN-a 2a and ribavirin is low. The retinal complications resolve, while treatment is continued and are asymptomatic. Routine frequent screening and followed-up for retinopathy in diabetic, hypertensive patients treated with pegylated interferon and ribavirin for chronic HCV is recommended because they are at significant higher risk for IFN-associated retinopathy (IAR).

Key Words: Chronic HCV — IFN-a — Ribavirin therapy — IFN-associated retinopathy.

Introduction

World Health Organization estimates that about 170 million people, 3% of the world's population are infected with hepatitis C virus which is responsible for 50-76% of liver cancer and two thirds of liver transplants in the developed world ill. Chronic hepatitis C virus infection is the leading cause of chronic liver disease worldwide [2]. Egypt has the highest prevalence of antibodies to hepatitis C virus in the world estimated nationally at 14.7% [3]. Standard therapy in chronic hepatitis C with a combination of interferon alfa and ribavirin for patients with moderate to severe hepatitis C infection is recommended [4-6]. Treatment is recommended for all adults who have not had previous interferon alfa monotherapy, as well as for those who have had previous treatment leading to an initial response and have then relapsed [4-7].

Interferon associated retinopathy was first described in 1990 by Ikebe, et al., [8] Features include hemorrhages and cotton wool spots around the disc and through the posterior pole, optic disc hypere mia, and macular edema [9-13]. The reported incidence of retinopathy as a side effect of interferon varies widely in the literatures (ranged from 18-33%) [19-111]. The reported incidence of retinopathy may be dose dependent [9,12]. Treatment regimens with subcutaneous doses of interferon varying from 3 million units three times a week to 9 million units six times a week.
have been used for the hepatitis viruses, with higher doses used in the treatment of various malignancies [13,14].

Case series and reports have shown an increased incidence of retinopathy in patients on higher and more frequent doses [15,16]. Pegylated interferon, this drug has slower absorption, a reduced volume of distribution, and lower elimination rates, as well as showing a more sustained virological response [4]. Plasma levels of the drug are kept more stable, with a lower peak level. The standard treatment protocol uses pegylated interferon alfa 2-a 180iu or encompasses a dose of 1.5mg/kg of pegylated interferon alfa 2-b, in combination with ribavirin, the dose of ribavirin used is also weight dependent with a total of 1000mg split over the day for patients weighing <75kg, and 1200mg for patients weighing ≥75kg [4,6]. However, IFN therapy often associated with ocular side effects, most resolve while treatment continues and are asymptomatic [16], severe ocular complications can occur, including brachial vein occlusion, [17,18] retinal rubeosis [19], and cystoid macular edema [20,21], which cause severe visual loss. Although the exact mechanism of IFN-induced retinopathy is unknown, it may be related to a disrupted retinal microcirculation, as reported in studies using fluorescein angiography, that showed poorly perfused retinal areas in patients with IFN retinopathy [9,22,23]. It has also been reported that IFN-increased leukocyte adherence to the vascular endothelium and subsequent leukocyte trapping in the retinal microcirculation, suggesting that the impaired retinal circulation may be associated with IFN-induced retinopathy [24]. In addition, one clinical study reported that flow-mediated vasodilation in the brachial artery decreased in patients with chronic hepatitis C treated with IFN, suggesting that IFN impairs endothelial function [25]. The impaired endothelium function may in turn impair the production of nitric oxide from the endothelium, which protects blood vessels from endogenous injury by mediating molecular signals that prevent platelet aggregation [26,27], and leukocyte interaction with the vascular wall [28]. In addition, other studies have reported high circulating level of plasma activated complement 5a (C5a), a potent intravascular aggregator of platelets, in patients with IFN-induced retinopathy [29,30]. Both impaired endothelial function and the increase in plasma C5 may cause abnormal platelet function, resulting in retinal capillary infarction, manifesting as capillary non perfusion, cotton-wool spots, and retinal hemorrhages, despite increased blood flow in the major retinal vessels. There is also the possibility that the retinopathy observed in patients with IFN-induced retinopathy was caused by systemic disorders including diabetes 131,32,1 hypertension 133,34, and anemia [35] because these diseases lead to impaired retinal circulation in those patients.

The aims of this study were to document the prevalence, risk factors of and outcome of intraocular complications of IFN-a-2a and ribavirin therapy in patients with chronic HCV.

Patients and Methods

This was a prospective, interventional, clinical trial study were conducted in Suez Canal University hospital. The study included 168 patients with chronic HCV who received treatment with pegylated IFN a-2a, and ribavirin according to the Egyptian national protocol during the study period between May 2010 to August 2011. The dosage of pegylated IFN-a-2a was 180mcg injected subcutaneously once weekly. The ribavirin was administered orally in divided doses at 1000mg/day and 1200/day in patient weighing <75kg and >75kg respectively.

Exclusion criteria included; decompensated liver cirrhosis (ascites, encephalopathy, bleeding varices), patient with FO and F4 on the Metavir scoring system, auto immune hepatitis, chronic hepatitis B, combined chronic hepatitis B and C, patients with diabetic, hypertensive, or any other retinopathy, or optic neuropathies, patients with uncontrolled psycatric disorders, cardiac diseases, advanced renal impairment, uncontrolled thyroid dysfunction, patients with uncontrolled diabetes mellitus (Fasting blood sugar >160mg/dl or Glycated hemoglobin >8%) and pregnant women.

All included patients were pretreatment assessed according to Egyptian national protocol for treatment of chronic HCV. Clinical assessment by history taking and clinical examination. Laboratory assessment included complete blood count (CBC), liver and kidney function tests, fasting blood sugar and Glycated hemoglobin (HbAlc), Viral markers for hepatitis B virus (HBV) and HCV using an ELISA technique, (ELISA Kit, Abbot Diagnostic). Thyroid stimulating hormone (TSH), alpha fetoprotein (AFP), auto-antibodies; anti-nuclear antibody (ANA) were studied with the ELISA method using Abbot laboratory reagents.

Viral load was assessed by using quantitative Reverse transcription polymerase chain reaction (RT-PCR) [36]. Abdominal Ultrasound was used to assess for liver and kidney condition, splenomegaly and ascites.
Liver biopsy was performed on all of patients for histopathological staging and grading according to the Metavir scoring system, grading of the Metavir is classified as (A0 to A3) and the stage of liver fibrosis (F0-F4) [37].

Patients were considered to have hypertension if systolic/diastolic blood pressure exceeded 140/90mm Hg or the patient was using antihypertensive drugs [38]. Patients were considered to have diabetes if they were being treated with insulin or oral hypoglycemic agents or if fasting blood glucose exceeded 126mg/dL or Glycated hemoglobin 7% [39].

Patients were referred for thorough ophthalmic examination comprising uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), Goldman applanation tonometry, and fundus examination. Fundus examination were done by direct and indirect ophthalmoscop and also, by slit lamp examination with +90 non contact lens. Fundus photographs were taken to document any abnormal findings. Ophthalmic examination assessed pre-treatment and on-treatment by a same observer. Scheduled on-treatment follow-up visits were at 1, 3, 6, 9, 12 months. Patients with new visual symptoms or signs were reported. No changes to the interferon and ribavirin treatment regimen were made for these patients.

Patients were educated on the potential complications, especially eye symptoms and were assessed for safety, tolerance and efficacy of the therapy, this occurred weekly for till the end of their treatment.

The study confirmed to ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from all patients.

Data analysis:

All data are expressed as the mean±SD. For statistical analysis, we used analysis of variance (ANOVA) for repeated measurements followed by post hoc comparison with the Dunnett procedure. To evaluate the relation between the change in different factors, simple and multiple regression analyses were performed. Variables predictive of IFN-induced retinopathy were analyzed by logistic regression analysis. p <0.05 was considered statistically significant. All analyses were conducted with statistical software (StatView 5.0); SAS Institute, Cary, NC).

Results

Between May 2010 to August 2011, 168 patients received pegylated IFN-a 2a and ribavirin for treatment of chronic HCV according to the national Protocol, and continue until the end of course of treatment (48 weeks). There were 98 (58.3%) men, with ages ranging from 20 to 60 years (Table 1).

Diabetes mellitus was present in 41 (24.4%) of the 168 patients, Systemic hypertension was present in 24 (14.3) of the patients and 30 (17.9%) patients had both diabetes; and hypertension (Table 1).

At the 3 month examination, 13 of the 168 patients (7.73%) had evidence of retinopathy consisting of cotton wool spots and/or hemorrhages. This was bilateral in eight (61.5%) patients and unilateral in other five (38.5%) patients. None of these patients had macular edema, disc changes or visual symptoms. Four of those patients had DM; 2 had hypertension; 4 had both hypertension and diabetes; and 3 patient without DM or hypertension. Multiple logistic regression analysis revealed that diabetic, hypertensive patients are at significant higher risk for development of IFN-associated retinopathy (p=0.003 & 0.004) (Table 2).

For the 13 patients with retinopathy at the 3 month visit, further visits were arranged, with strict control of hypertension, DM and medication to improve retinal vascularization and oxygenation. The retinopathy had disappeared in all patients at 6 month visit except three cases, whose retinopathy had disappeared at 9 months visit in two patients and at 12 months visit in one patient. All patients completed course of treatment (48 weeks) of treatment without any dosage alteration.

Table (1): Clinical and laboratory characteristics of patients at baseline.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Male: Female)</td>
<td>98: 70</td>
<td></td>
</tr>
<tr>
<td>Age Mean, y (range)</td>
<td>43 (21-60)</td>
<td>10.2</td>
</tr>
<tr>
<td>Viral Load (RT-HCV RNA): K IU/ml. (mean, range)</td>
<td>669 (53-2130)</td>
<td>579.6</td>
</tr>
<tr>
<td>ALT U/L (mean, range)</td>
<td>67 (22-234)</td>
<td>62.7</td>
</tr>
<tr>
<td>AST U/L (mean, range)</td>
<td>62 (20-438)</td>
<td>60.3</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.8</td>
<td>1.6</td>
</tr>
<tr>
<td>WBC (10^3/L)</td>
<td>4.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Platelet (10^3/L)</td>
<td>170.4</td>
<td>60.2</td>
</tr>
<tr>
<td>INR (sec.)</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>BMI (mean, range)</td>
<td>26.0 (17.3-36.3)</td>
<td>3.8</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>93.0</td>
<td>13.2</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>41 (56)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>24 (14.9)</td>
<td></td>
</tr>
<tr>
<td>Diabetes and Hypertension, n (%)</td>
<td>30 (17.9)</td>
<td></td>
</tr>
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</table>

Data are expressed as the mean±SD.
Table (2): Multiple logistic regression analysis of factors affecting the onset of IFN-induced retinopathy.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>RR</th>
<th>*95% CI</th>
<th>P</th>
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<tbody>
<tr>
<td>Age</td>
<td>1.26</td>
<td>1.01-1.57</td>
<td>0.07</td>
</tr>
<tr>
<td>Sex</td>
<td>2.93</td>
<td>1.04-7.29</td>
<td>0.35</td>
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<tr>
<td>Diabetes</td>
<td>0.03</td>
<td>0.01-4.61</td>
<td>0.03*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.20</td>
<td>0.14-11.61</td>
<td>0.04*</td>
</tr>
<tr>
<td>Viral load</td>
<td>2.82</td>
<td>0.16-10.6</td>
<td>0.89</td>
</tr>
<tr>
<td>BMI</td>
<td>3.12</td>
<td>0.27-4.99</td>
<td>0.78</td>
</tr>
</tbody>
</table>

RR = relative risk, BMI (Body Mass Index)
*p00.05 was considered statistically significant.

Discussion

Ocular side effects are well recognized complications of IFN-a and ribavirin therapy for hepatitis C, with the most common of these being an ischemic retinopathy characterized by hemorrhages and cotton wool spots [16,30]. Other features include optic disc hyperemia and macular edema [9,10].

The incidence of reported retinopathy in patients on treatment with interferon for hepatitis viruses in the literature is very variable, with figures from fairly small scale studies ranging from 18% to 86% [6-24]. Previous recommended treatment protocols have been based on the use of standard interferon alfa with ribavirin. The dose of interferon used in standard treatment is 3 million units subcutaneously three times a week. Following the recent availability of pegylated interferon. The advantages include less frequent injections, improved bioavailability and a lower total dose.

The prevalence of retinopathy in this study was 13 of 168 (7.73%), which is lower than any of the previously published studies [8,9,30]. None of the 13 patients with retinopathy were symptomatic. This finding may explained by: (1) Exclusion of patients who had retinopathy in pre-treatment assessment that may associated with increase risk of IFN associated retinopathy like diabetic or hypertensive retinopathy. (2) We also considered systemic disorders like DM [32,33] and hypertension [33,38] affected the retinal circulation and associated with significantly impaired retinal circulation, and to minimize this possibility, we included only patients with well-controlled glycemic and blood pressure levels with regular assessment of glycemic and blood pressure levels during IFN treatment. (3) Also exclusion of patients who had anemia in pre-treatment assessment, with rapid and proper correction of anemia that associated with IFN treatment (It is likely that anemia caused retinopathy in patients whose hemoglobin levels fall below 8g/dL during IFN treatment) [32].

In each case, the retinopathy resolved spontaneously without long term sequelae. No patient had premature termination or alteration of their treatment regimen, this finding agreed with previous reports that retinopathy is a temporary and asymptomatic complication of interferon therapy [23,24]. In this study. No convincing association of retinopathy with other socio-demographic criteria, clinical findings or laboratories investigations.

The presence of diabetes mellitus [31,32], and systemic hypertension [33,34] were significant risk factors for developing interferon associated retinopathy, and this finding is matched with other similar studies [22,34]. The similarity of the clinical features to diabetic and hypertensive retinopathy suggests an ischemic mechanism. Others have suggested that the deposition of immune complexes in the retinal vasculature leads to capillary non-perfusion and the formation of cotton wool spots [22,30].

By carrying out just one basic screening assessment at 3 months after starting the treatment it could be argued that there is potential to miss patients with retinal changes. Previous case series have commented on the time of onset of retinopathy in relation to the start of treatment. Most report onset of the retinopathy in the first 8-12 weeks following the start of treatment [6,7,20-22] with just a few noticing retinopathy later. There was sufficient evidence in previous studies to point to the most likely time for retinopathy to develop as being within the first 3 months, and that any earlier complications were unlikely to have resolved by then. It would theoretically be possible to miss earlier retinopathy that had remained asymptomatic and had resolved by the 3 month visit, but this is not likely to be of any clinical significance [20-22].

Conclusion and Recommendations:

The prevalence of intraocular complications of IFN-a-2a and ribavirin therapy in patients with chronic viral hepatitis C is low. The retinal complications resolve while treatment is continued and are asymptomatic, and treatment cessation is not necessary. This study supports routine ophthalmological screening diabetic, hypertensive patients treated with pegylated IFN-a-2a and ribavirin for HCV, because they are at significant higher risk for IFN-associated retinopathy (IAR).
References

1. WHO. 2009.


