

Ophthalmological side effects of interferon therapy of chronic hepatitis C

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Background: Egypt has one of the highest prevalence of hepatitis C virus (HCV) worldwide. Ophthalmological side effects are recognized complications of interferon (IFN) therapy. This study aimed to evaluate IFN-induced ophthalmological manifestations in patients receiving PEGylated interferon (PEG IFN) and ribavirin (RBV) and to assess the effect of IFN duration, response and systemic risk factors on the severity.

Methods: We retrospectively analyzed 100 patients with chronic HCV who were candidates for PEG-IFN and RBV therapy. All patients were subjected to clinical and ophthalmological examination, laboratory investigations, abdominal ultrasound, colored fundus photography and fundus fluorescein angiography, follow up was made at weeks 12, 24, and 48 of treatment.

Results: IFN-induced retinopathy had been found in (9/100; 9%), 5 (5/9; 55.5%) of them had bilateral lesions, (3/9; 33.3%) were treatment responders and (6/9; 66.6%) non responders. The time of retinopathy appearance was mainly at W12. Retinopathy was asymptomatic in most of the affected patients (7/9; 77.77%) and reversible, cotton wool spots was the major associated sign. Patients with older age, DM and or HTN, and non-responders to antiviral therapy were associated with more severe retinopathy.

Conclusions: Retinopathy is not a rare complication of IFN therapy for chronic HCV infection, but fortunately it's asymptomatic and reversible. Ophthalmological assessment at base-line and at follow up during IFN treatment is very important.

Keywords: Hepatitis C virus (HCV); interferon (IFN); retinopathy; fundus fluorescein angiography

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Introduction

Egypt has the highest prevalence of hepatitis C virus (HCV) in the world, estimated nationally at 14.7% (1). Combined therapy of PEGylated interferon alpha (PEG IFN- α) and ribavirin (RBV) is the base for HCV treatment (2). Ophthalmological complications are amongst many side effects of IFN based therapy for HCV infection (3). The exact mechanism of IFN induced retinopathy is not known, although some investigators have suggested, it may be related to a disrupted retinal microcirculation (4), others believe that

IFN impairs the vascular endothelial functions (5).

Methods

In this retrospective non-randomized study, IFN-induced ophthalmological complications were evaluated in 100 patients with chronic HCV who were candidates for IFN based therapy (PEG-IFN and RBV); All cases were selected consecutively from patients enrolled in the national program for treatment of HCV, they were examined and followed up

in EL-Kahera El-Fatemya Hospital, (one of the viral hepatitis treatment centers of the national committee for control of viral hepatitis, Ministry of health). They were 83 males and 17 females, their ages ranged between 21–60 years with a mean of 42 ± 10 years. All patients completed the course of therapy (48 weeks).

Exclusion criteria

Other causes of liver disease, decompensated liver disease, HCC, patients with (uncontrolled DM, uncontrolled HTN, or with other significant medical illness such as cardiovascular disease or renal failure) and patients with hypersensitivity to IFN or RBV.

Ocular exclusion criteria

Patients with moderate, severe or very severe non-proliferative diabetic retinopathy (NPDR), or with proliferative diabetic retinopathy (PDR), dense cataract or corneal opacity, iridocyclitis, grade 3 to 4 hypertensive vascular retinopathy, glaucoma, on medications of known ocular side effects, age-related macular degeneration, history of other retinal vascular disorders such as branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

This study was approved by the Department Ethics Committee and a signed written informed consent was taken from all participating patients before starting treatment.

All patients were subjected to: thorough history taking, clinical, and ophthalmological examinations including best corrected visual acuity and dilated fundus examination.

Investigations done

- (I) Complete blood picture (CBC);
- (II) Liver biochemical profile (LBP): transaminases; aspartate aminotransferase (AST), and alanine aminotransferase (ALT), alkaline phosphatase (ALP), serum albumin, total bilirubin, INR;
- (III) Kidney function tests (blood urea and serum creatinine);
- (IV) Fasting and 2 hours post prandial blood glucose;
- (V) Alpha fetoprotein (AFP), antinuclear antibody (ANA), thyroid stimulating hormone (TSH);
- (VI) Hepatitis seromarkers for HCV (anti HCV) and for hepatitis B virus (HBV); (HBsAg, anti HBc and anti

HBs) using ELISA technique;

- (VII) HCV RNA tested by PCR nested quantitative by IU/mL;
- (VIII) Rectal snip to diagnose active Schistosomiasis;
- (VIII) ECG (men over 40, women over 50). Patients were globally evaluated by Child Pugh score (6);
- (X) Abdominal ultrasonography by (Philips iU22 xMatrix ultrasound system). Splenomegaly is considered if >12 cm in females and >13 cm in males (7);
- (XI) Histopathological examination by ultrasound guided liver biopsy (in patients with INR <1.4 and platelet count $\geq 60.000/\text{mm}^3$) according to METAVIR scoring system (8).

Patients were followed up during antiviral therapy (for 48 weeks), clinically by regular symptoms checklist, and by laboratory testing: (I) CBC done every 4 weeks for 24 weeks then at the end of treatment; (II) PCR for HCV RNA at start of therapy, 12, 24, 48 and 72 weeks of therapy.

Follow up ophthalmological investigations

Colored Fundus photography, best corrected visual acuity, slit lamp microscopic examinations of the anterior segment, fundus fluorescence angiography (FFA) (if retinal involvement is suspected by fundus examination), visual evoked potential (VEP) (if optic nerve dysfunction is suspected by fundus examination) and color vision test (if optic nerve dysfunction is suspected by fundus examination). Ophthalmic examinations were done at start of therapy and at 4, 12, 24, 48 and 72 weeks of therapy.

Statistical analysis

Statistics were done by computer using Epi-Info. A word processing data base and statistics program.

- (I) X mean, SD standard deviation: to measure the central tendency of data and the distribution of data around their mean;
- (II) Independent sample test to compare between 2 groups;
- (III) F² analysis of variance (or ANOVA test) to test statistical significant difference between more than 2 means i.e., difference between 3 or more groups at the same time;
- (IV) Person correlation coefficient test ®: to test for linear relation between 2 numeric variables;
- (V) Fisher's exact test is used to calculate an exact P value for a 2x2 frequency table with small

Table 1 IFN-induced retinopathy in the studied patients (n=9)

Characteristics	n=9	%
Age	37–60 (mean: 47±8.05)	
Males	5	55.55
Females	4	44.44
Risk factors for retinopathy		
Diabetes mellitus (DM)	2	22.22
Hypertension (HTN)	1	11.11
Both (HTN and DM)	3	33.33
None	3	33.33
Retinopathy		
Bilateral	5	55.55
Unilateral	4	44.44
Type of PEG IFN		
PEG IFN- α 2a	5	55.55
PEG IFN- α 2b	4	44.44
Response to treatment		
Responders	3	33.33
Non-responders	6	66.66

PEG IFN, PEGylated interferon.

number of expected frequencies, for which the Chi-square test is not appropriate. Significant result is considered if P less than 0.05. Highly significant result is considered if P less than 0.005. Very high significant result is considered if P less than 0.001. (SPSS Inc., Chicago, IL, USA).

Results

The present study was conducted on one hundred HCV naïve patients. They presented to EL-Kahera El-Fatemeya Hospital, Cairo, seeking antiviral therapy according to the program supported by the national committee for control of viral Hepatitis C under supervision by Egyptian Ministry of health.

Demographic features of the studied patients showed that there was male predominance with eighty three males (83%), 36% of them were smokers. Their ages ranged from 21–60 years old with a mean of 42±10 years.

Five (5%) patients had controlled HTN, 7 (7%) patients had controlled DM, 6 (6%) patients had combined HTN and DM and only one (1%) patient with past history of mild bronchial asthma. Of the diabetic patients, 5 patients were on insulin, 6 on oral hypoglycemic drugs and 2 on diets

only. They had strict blood sugar monitoring and blood sugar levels were well controlled.

Baseline laboratory data of the studied patients showed that the mean Hb was (14.47±1.58 gm/dL), the mean platelets count was (212±54×10³/mm³) and the mean serum albumin was (4.3±0.36 gm/dL). Mean bilirubin was (0.7785±0.2779 mg/dL), AFP (6.0209±9.7493 ngms/dL) and HCV RNA by quantitative PCR (50,964,049±2,530,000,000 IU/mL). ALT and AST were mildly elevated (<2 folds rise).

Fifty two patients received PEG IFN- α 2a (pegasys) and 48 received PEG IFN- α 2b (peg-intron). The dose of PEG IFN- α 2a was 180 mcg (subcutaneously) every week. The mean dose of PEG IFN- α 2b was 1.5 mcg/kg (subcutaneously) every week. The mean starting dose of RBV was (800-1,600 mg) (orally divided dose—twice daily).

All Patients completed the course of 48 weeks of antiviral treatment, and the IFN dose was not reduced in all of them. The end of treatment response (ETR) was achieved in 37/100 (37%) patients and 63/100 (63%) patients failed to achieve ETR.

In the studied patients, IFN-induced retinopathy was diagnosed in 9 (9%) patients during the course of antiviral treatment, they included 5 (55.55%) males and 4 (44.44%) females, 5 (55.5%) of them had bilateral lesions, and 4 (44.4%) had unilateral lesions. Three (33.3%) patients were responders and 6 (66.6%) were non responders. Five Patients had received PEG IFN- α 2a and 4 had received PEG IFN- α 2b (*Table 1*).

Along the course of treatment, 7/9 (77.77%) patients were detected at week 12 and only 2/9 (22.22%) patients were detected at week 24. With no significant statistical difference (W12–W24, P=0.169 and W12–W48, P=0.114).

By studying the IFN induced retinopathy among different age groups in relation to the incidence rate within each age group, laterality, gender and the treatment response; it was revealed that incidence rate of retinopathy was marked in patients with advanced age, (4/9; 44.44%) among age range (40–50 years) followed by (3/9; 33.3%) among the age range (50–60 years). Also, the retinopathy signs were bilateral in (3/9; 33.33%) of cases with age range 50–60 years compared to (1/9; 11.11%) among patients aged <40 years and 40–50 years. Five males were affected, 3 of them in age group (40–50) years and it was statistically significant relative to age group (<40 years). Six patients with IFN-induced retinopathy were non-responders, all of them with advanced age (>40 years) and with statistically significant difference between different age groups (*Table 2*).

IFN induced retinopathy with associated systemic

Table 2 IFN induced retinopathy among age groups with associated systemic diseases in relation to the incidence, laterality, gender and response

Retinopathy cases	<40 y (n=44)	40–50 y (n=32)	50–60 y (n=24)	HTN (n=5)	DM (n=6)	HTN & DM (n=6)	P value
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
Incidence	2	4	3	1	2	3	NS
Related to age group	4.54	12.5	12.5	20	28.57	50	
Related to affected pt.	22.22	44.44	33.33	11.11	22.22	33.33	
Bilateral	1	1	3	1	1	2	NS
Related to age group	2.27	3.12	12.50	20	14.30	33.33	
Related to affected pt.	11.11	11.11	33.33	11.11	11.11	22.22	
Unilateral	1	3	0	0	1	1	NS
Related to age group	2.27	9.37			14.30	16.66	
Related to affected pt.	11.11	33.33			11.11	11.11	
Males	0 ^{*a}	3	2	0	0	3	
Related to age group		9.37	8.33			50.00	
Related to affected pt.		33.33	22.22			33.33	
Females	2	1	1	1	2	0	NS
Related to age group	4.54	3.12	4.17	20.00	28.57		
Related to affected pt.	22.22	11.11	11.11	11.11	22.22		
Responders	2	1	0	0	2	0	NS
Related to age group	4.54	3.12			28.57		
Related to affected pt.	22.22	11.11			22.22		
Non respond	0 ^{*a}	3	3 ^{*b}	1	0	3	
Related to age group		9.37	12.50	20.00		50.00	
Related to affected pt.		33.33	33.33	11.11		33.33	

^{*}, P<0.05 (statistically significant). a, P<0.05 relative to patients with age range (50–60 years); b, P<0.05 relative to patients with age range (<40 years). IFN, interferon; HTN, hypertension; DM, diabetes mellitus.

Table 3 Reported retinopathy associated symptoms

Symptoms	Affected patients (n=9)	
	No.	%
Asymptomatic lesions	7	77.77
Blurring of vision	1	11.11
Blurring of vision with variable degrees of impaired central vision	1	11.11
Visual floaters	0	0

diseases in relation to the incidence rate, laterality, gender and treatment response revealed that the patients associated with other systemic risk factors (DM and or HTN) had a higher incidence rate of retinopathy of (6/9; 66.66 %), among them 4 patients had bilateral lesions with equal

sex distribution. No significant statistical difference was detected between them (*Table 2*).

The retinopathy associated symptoms showed that most of the affected patients were asymptomatic (7/9; 77.77%) and the reported symptoms were reversible. The two symptomatic patients showed that one had periods of blurred vision (1/9; 11.11%), and the other patient suffered from various degrees of impairment of his central vision, so there was no need to discontinue or reduce the dose of IFN-RBV therapy. Just RBV dose was reduced in 6 patients in week 24 due to anemia (*Table 3*).

Retinopathy associated signs showed that six cases had single lesion (4 cotton wool spots, one flame shaped hemorrhage and one disc swelling), and 3 cases had multiple lesions (cotton wool spots with micro aneurysms, cotton wool spots with flame shaped hemorrhage and

Table 4 Pattern of IFN associated ophthalmological complications

Pattern	Affected patients (n=9)		
	Single lesion 6 (66.66%)	Multiple lesions 3 (33.33%)	Total
Cotton wool spots	4 (44.44)	3 (33.33)	7 (77.77)
Optic disc swelling	1 (11.11)	0	1 (11.11)
Retinal hemorrhage	1 (11.11)	2 (22.22)	3 (33.33)
Micro-aneurysms	0	1 (11.11)	1 (11.11)
Macular thickening or edema	0	1 (11.11)	1 (11.11)

IFN, interferon.

macular edema and the third case showed cotton wool spots with flame shaped hemorrhage). The retinopathy in the 9 patients were reversible by ophthalmologic examination during the course of therapy and at week 72, this proves that retinopathy was not related to DM or HTN (Table 4).

Discussion

HCV infection is one of the main causes of chronic liver disease worldwide (9). Egypt has the highest prevalence of HCV worldwide and is considered a major cause of chronic hepatitis, liver cirrhosis, HCC, and liver transplantation in the country (10).

IFN-induced retinopathy was first recognized in 1990 when Ikebe and associates (11) reported a 39-years-old patient with retinal hemorrhages and cotton wool spots following intravenous administration of IFN. Reported incidence of IFN-induced retinopathy varied from 18% to 86% according to the country, genotype, and study design. Higher frequencies are usually found in Japan where values of more than 50% are common (3).

The exact mechanism of IFN induced retinopathy is not known, although some investigators have suggested deposition of immune complex at the vessels and immunological dysfunction, others believe that it is related to IFN-induced neuro-visual toxicity (12).

This study was conducted to evaluate IFN-induced ophthalmological complications as regard the incidence, possible associated risk factors and to assess the need to screen for these complications.

The current study included one hundred patients with chronic HCV who received IFN based therapy (PEG IFN- α 2a or PEG IFN- α 2b) and RBV. The mean age of our patients was 42 \pm 10 years, our result was in agreement with Cuthbertson *et al.* (13) whose mean age was 44 \pm 10.5. In our study, a significant male predominance was reported;

this was also reported by Sherif *et al.* (14) and Mabrouk *et al.* (15), which may be due to more male patients attendance.

Few studies have evaluated the efficacy of IFN therapy in persons with persistently normal serum ALT (PNALT). ALT has been reported to increase during IFN therapy and this was apparently one major reason why the NIH consensus development conference recommended that such patients not to be treated with IFN (16). In our study, transaminases were mildly elevated (<2 folds rise). Transaminases are the first biochemical abnormality detected in patients with liver disease, its degree of elevation may correlate with extent of the liver injury but it is not of prognostic value (17). Treatment is widely recommended for patients with elevated ALT (18).

In this study, the incidence of IFN-induced retinopathy in the whole studied patients was found to be (9/100; 9%). Studies by Jain *et al.* (19), Cuthbertson *et al.* (13) and Okuse *et al.* (20) have shown a relatively higher incidence of retinopathy (symptomatic or asymptomatic) ranging from 19% to 64% during treatment with IFN; however Malik *et al.* (21) and Panetta *et al.* (22) showed relatively lower incidence of retinopathy (0% and 3.8%, respectively). Also, the estimated prevalence of diabetic retinopathy and vision-threatening diabetic retinopathy in USA was 28.5% and 4.4% respectively, among persons with diabetes aged 40 years and older. While the prevalence nationwide was 3.8% and 0.6% (23).

In our study, we found 5 (55.5%) patients with bilateral lesions and 4 patients had unilateral lesions, which is higher than that reported by d'Alteroche *et al.* (24) who showed that the lesions were bilateral in 26% of cases.

Also, we found that 6 patients of IFN-induced retinopathy were non-responders (failed to achieve ETR) which was similar to that reported by Fouad *et al.* (25).

Although Hauser *et al.* (26) showed that PEG INF- α

2a was associated with a higher sustained virological response in serum than with PEG IFN- α 2b, yet the clinical consequences of PEG IFN- α 2a versus PEG IFN- α 2b are unknown.

Bruno *et al.* (27) showed that the concentration of PEG IFN- α 2b did not remain stable over the week as a whole. At the end of the week, serum IFN could not be detected in most patients treated with PEG IFN- α 2b. When IFN was no longer detectable in the serum, the viral load increased until the next IFN injection. This phenomenon reduces the efficacy of the drug. While the reduced clearance of PEG IFN- α 2a, provides measurable therapeutic plasma levels even at the end of the weekly dosing period (28). These differences between the two types of PEG IFNs provide better compliance and more safety of PEG IFN- α 2a (29).

These results were in agreement with Wang *et al.* (30) as they reported that anterior ischemic optic neuropathy (AION) may occur with the use of combined PEG IFN- α 2b and RBV for chronic infection, and patients should be informed about its possible occurrence .

On the contrary, our study showed that IFN-induced retinopathy was reported in 5 patients treated with PEG IFN- α 2a and 4 patients with PEG IFN- α 2b with no detected significant difference.

During the course of IFN treatment, 7 patients developed retinopathy at W12 and only 2 experienced retinopathy at W24, which was similar to that reported by Sherif *et al.* (14) who stated that the time of appearance of retinopathy signs (between W4 and 16) in about 80% of cases.

Higher incidence of retinopathy was found, in our study, in patients above 40 years. Chronic hypertension predisposes patients to IFN-induced retinopathy through thickening of the walls of the arteries and small arterioles (31). The fact that hypertensive retinopathy induces the formation of flame-shaped hemorrhages and white cotton-wool spots, which are also seen in IFN-induced retinopathy, implies that systemic hypertension and IFN-induced retinopathy may be related to each other (32).

In this study, higher incidence of retinopathy was associated with other systemic risk factors (DM and/or HTN) with tendency to be bilateral. These findings were similar to previous results like Cuthbertson *et al.* (13), d'Alteroche *et al.* (24) and Sene *et al.* (33) who showed that hypertension, diabetes and older age were possible risk factors for IFN-induced retinopathy. On the contrary, Kawano *et al.* (34), Saito *et al.* (32) and Okuse *et al.* (20), reported no association between diabetes and IFN-RBV

induced retinopathy, this may be explained by the very low number of patients with DM in those studies.

In our retinopathy cases, six had single lesions and 3 had multiple lesions. The commonest finding was cotton wool spots, which appeared in 7/9 of the patients with retinopathy.

These findings were in agreement with Schulman *et al.* (35), Cuthbertson *et al.* (13) and Chuman *et al.* (36) who reported that the incidence of the cotton wool spots and retinal hemorrhages, retinal micro-aneurysms were reported as a complication of IFN therapy.

Nagaoka *et al.* (37) classified the IFN-induced retinopathy into two groups depending on the severity, the first group (mild retinopathy); patients with fewer than four hemorrhages, cotton wool spots, or both during treatment, and the second group (severe retinopathy); patients with more than five lesions. In our study, our affected patients were classified as having mild retinopathy

Most of the affected patients, in our study, were asymptomatic with reversible symptoms in the other two at the end of treatment. One patient had periods of blurred vision, and the other suffered from various degrees of impairment of his central vision, so there was no need to discontinue IFN-RBV therapy. This is in accordance with Mantel *et al.* (38) and Hayasaka *et al.* (39) who stated that in spite of the presence of retinopathy, the full course of treatment should be completed.

We excluded, in our study, the possibility that retinopathy observed in patients associated with systemic diseases (DM and or HTN) was caused only by these disorders by the following facts: we included only patients with tight control of blood sugar and ABP, the mean duration of DM was 3 years, and of HTN was 6.5 years, none of the patients had retinopathy signs at the base-line fundal examination before start of INF-RBV therapy, the appearance of retinopathy during the first few months after initiation of IFN therapy, the majority of reported signs have resolved spontaneously during the course of IFN therapy, the IFN retinopathy signs differed as regard their natural course from the classical courses of diabetic or hypertensive retinopathies.

We also excluded the possibility of retinopathy caused by INF-RBV associated anemia, as the mean Hb level of patients with retinopathy at W12 (most common point of retinopathy appearance) was 11.07 g/dL. Anemia can cause retinopathy when Hb decreases below 7 gm/dL (40).

Our results could not be applied to INF based therapy in multiple sclerosis or other conditions as the dose and duration of treatment differs and INF could be

combined with other immune modulators, so studying the ophthalmologic side effects in these cohorts of patients should be done. Also, studying retinopathy in INF plus DAA therapy in HCV should be pursued.

Finally, in the light of our results; we have reported that, close follow up of patients with retinopathy (in cooperation with the ophthalmologist) was very important, also, d'Alteroche *et al.* (24), Sene *et al.* (33) and Mousa *et al.* (41) recommended ophthalmological monitoring during IFN therapy.

Although our study had a relatively small sample size but conclusions can be applied generally as INF based therapy of HCV is globally standardized and the side effects of INF should be essentially similar. However, the differences in the incidence among studies could be due to differences in age, background diseases or cause of liver disease in participating patients. And although INF induced retinopathy is not rare but fortunately it's asymptomatic and reversible.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Department Ethics Committee and a signed written informed consent was taken from all participating patients before starting treatment.

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