HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Pegylated Interferon-Associated Retinopathy Is Frequent in Hepatitis C Virus Patients With Hypertension and Justifies Ophthalmologic Screening

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Treatment with pegylated interferon alpha (PegIFNα) and ribavirin is still regarded as the standard of care for chronic hepatitis C virus (HCV). Retinopathy has been occasionally described but prospective, longitudinal data are lacking. We investigated the frequency and clinical significance of retinopathy during therapy with PegIFNα and ribavirin in 97 consecutive HCV patients. In all, 54 (55.7%) and 43 (44.3%) patients were treated with PegIFNα 2a and PegIFNα 2b, respectively. Ophthalmologic examination was performed before therapy (baseline), at 3 and 6 months (3T and 6T, respectively) of therapy, and 3 months after the end of therapy (3ET). All patients underwent the baseline and 3T examination, 95.9% and 90.7% of patients underwent 6T and 3ET examination, respectively. Overall, 30.9% of patients developed retinopathy, as defined by the presence of cotton wool spots and/or retinal hemorrhages. Variables significantly associated with retinopathy during treatment were age ($P = 0.004$), metabolic syndrome ($P = 0.05$), hypertension ($P < 0.0001$), cryoglobulinemia ($P = 0.05$), and preexisting intraocular lesions at baseline ($P = 0.01$). By multivariate analysis, the only variable independently associated with PegIFNα-associated retinopathy was hypertension (hazard ratio [HR] = 4.99, 95% confidence interval [CI] 2.29-10.89). The frequency of retinopathy was significantly higher in hypertensive patients versus those without hypertension at all timepoints (18.5% versus 5.7% at baseline, $P = 0.05$; 48.1% versus 15.7% at 3T, $P = 0.0009$; 68.0% versus 19.1% at 6T, $P < 0.0001$; 32.0% versus 6.2%, $P = 0.0005$ at 3ET). In one (1.1%) hypertensive patient, who developed bilateral branch retinal vein occlusion at 6T, the therapy was discontinued. A cost analysis showed that screening for PegIFNα-associated retinopathy was cost-effective as compared with thyroid-stimulating hormone screening. *Conclusion*: Retinopathy is frequent during treatment with PegIFNα and ribavirin, especially in hypertensive patients, who may develop serious complications. Screening for PegIFNα-associated retinopathy should be recommended for HCV patients with hypertension. (HEPATOLOGY 2012;56:455-463)

According to recent guidelines, the combination of pegylated interferon alpha (PegIFNα) and ribavirin is still regarded as the standard of care for the treatment of chronic hepatitis C (CHC).[1] Even though two direct antiviral agents (DAAs) have been recently approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of infection due to genotype 1 of hepatitis C virus (HCV), PegIFNα plus ribavirin will remain the backbone in any future combinations for several years.[2,3] Indeed, the recent practice guidelines of the American Association for the Study of Liver Diseases on treatment of CHC due to HCV genotype 1 state that PegIFNα and ribavirin remain vital components of the therapy. Moreover, DAAs should not be used without PegIFNα and weight-based ribavirin.[3] Thus, the clinician still has to manage side effects related to treatment with PegIFNα and ribavirin.

Abbreviations: BMI, body mass index; CHC, chronic hepatitis C; CI, confidence interval; DAAs, direct antiviral agents; DVR, delayed virological response; ETR, end-of-treatment response; EVR, early virological response; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard risk; PegIFNα, pegylated interferon alpha; RR, relative risk; RVR, rapid virological response; SVR, sustained virological response.

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Received December 8, 2011; accepted February 3, 2012.

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Complications associated with the use of PegIFNα include flu-like symptoms, neutropenia, thrombocytopenia, psychiatric side effects, fatigue, and thyroid dysfunction.[1,2] Ophthalmologic complications, including retinopathy, reduced visual acuity, and optic nerve neuropathy have been observed during treatment with standard interferon.[4-6] However, discordant data have been reported about their frequency and clinical significance during PegIFNα-based therapy. Several studies have reported that retinopathy and other optical syndromes are present with low incidence and are not clinically significant.[7-9] However, a few case series suggested that retinopathy in the course of PegIFNα-based therapy may be more frequent and serious.[10,11] Moreover, whether some conditions that are clinically associated with retinopathy, such as diabetes and hypertension, may aggravate the course of intraocular lesions during antiviral therapy is debated.[4,5,7] Therefore, the need of screening for retinopathy in patients with CHC before, during, and after treatment is controversial.[2,4,8-10]

The aim of this study was to investigate the frequency, clinical significance, and possible associated conditions of retinopathy during antiviral therapy with PegIFNα and ribavirin. To our knowledge, this is the first prospective, longitudinal study specifically designed to provide insight into this understudied side effect of current treatment for CHC.

Patients and Methods

Study Design. This was a prospective, longitudinal study conducted at a single center (Dell'Angelo Hospital, Venice), which included consecutive patients with CHC who were eligible for antiviral therapy between January 2008 and April 2009. The monitoring period ended in September 2010. Patients were enrolled according to inclusion and exclusion criteria. The aim was to investigate retinopathy during treatment with PegIFNα and ribavirin in CHC. The study was approved by the local Ethics Committee and was conducted according to the Declaration of Helsinki.

Inclusion and Exclusion Criteria. The inclusion criteria were: (1) a diagnosis of well-compensated CHC, and (2) indication to antiviral therapy, as defined by guidelines.[1] Exclusion criteria were: (1) decompensated liver cirrhosis; (2) coinfection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV); (3) history or evidence at entry of hepatocellular carcinoma (HCC); (4) liver transplantation. All cases gave informed written consent to be included in the study. Out of 125 consecutive patients with CHC, we included 97 monoinfected patients with CHC. Fifteen cases were excluded for decompensated liver cirrhosis, four for coinfection with HBV or HIV, six for HCC, and three for liver transplantation (Fig. 1).

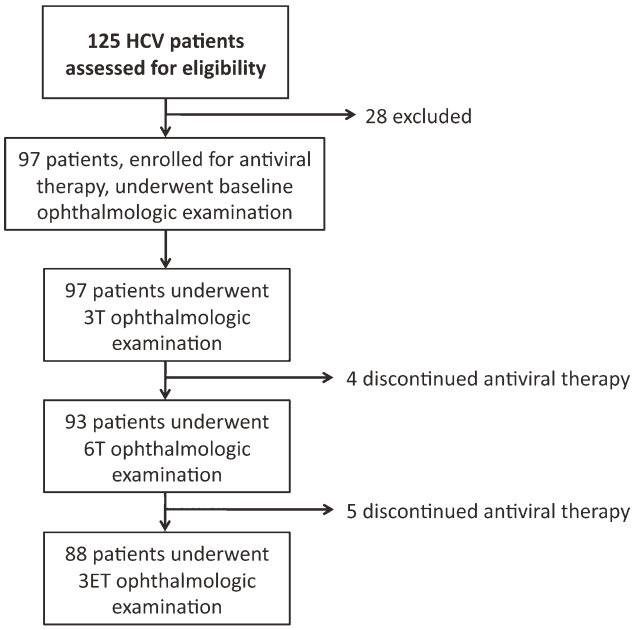

Fig. 1. Flow chart of the study. Overall, 28 patients did not meet the inclusion criteria and were excluded from the study. Treatment was discontinued in nine cases.

Patients. All patients were positive for HCV-RNA by polymerase chain reaction (Amplicor HCV Monitor Test, Roche Diagnostics, Indianapolis, IN). Information relating to patient demographics (gender, age, body mass index [BMI]), anamnestic features (history of hypertension, diabetes, metabolic syndrome, smoking, any alcohol consumption), biochemical parameters (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma glutamyl transpeptidase [γGT], cholesterol, tryglicerides, fasting glucose, presence of cryoglobulinemia), virological characteristics (HCV-RNA, HCV genotype) were prospectively recorded at baseline. The presence of metabolic syndrome was defined according to the criteria of the International Diabetes Federation.[12] As part of routine evaluation, in all patients the measurement of liver stiffness by Fibroscan was performed according to the manufacturer's recommendations within 3 months before the beginning of treatment.[13]

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DOI 10.1002/hep.25654
Potential conflict of interest: Nothing to report.
Additional Supporting Information may be found in the online version of this article.

Antiviral Treatment. Patients were randomly assigned to treatment with PegIFNα 2a or PegIFNα 2b. The dosage of PegIFNα 2a was 180 μg injected subcutaneously once weekly. The PegIFNα 2b dosage was weight-based.[1] All patients were treated with oral ribavirin (15 mg/kg/day for HCV-1 and HCV-4; 800 mg/day for HCV-2 and HCV-3) in addition to PegIFNα. Treatment duration was 48 weeks in patients infected with HCV-1 and HCV-4 (with a stopping rule at week 12 if the HCV-RNA decline was less than 2 $\log_{10}$ international units [IU]/mL), and 24 weeks in patients infected with HCV-2 and HCV-3. Virological responses were defined according to guidelines (Supporting Table S1).[1] Patients who achieved a sustained virological response (SVR) were considered responders. A nonresponder was defined by the presence of viremia (less than 2 $\log_{10}$ reduction) at 12 weeks, or by the failure to achieve undetectable HCV-RNA at 24 weeks. Patients with an end-of-treatment response (ETR) who tested HCV-RNA positive during follow-up were classified as relapsers.[1] The decision to stop therapy was based on the degree of retinopathy, as determined by the eye specialist, or on the guidelines with regard to other adverse events.[1]

Ophthalmologic Examination. Ophthalmologic examination, including visual acuity, slit-lamp anterior segment examination, slit-lamp fundus examination with 90D lens, and fluorescein angiography (if necessary) was performed by a single ophthalmologist (S.V.) at the University of Padova. When retinal abnormalities were detected, color fundus photographs were taken. Retinopathy was defined as the presence of any of the following lesions: cotton wool spots, microaneurysms, or retinal hemorrhages. In each patient an ophthalmologic visit was performed before therapy (baseline), at 3 and 6 months (3T and 6T, respectively) of therapy, and 3 months after the end of therapy (3ET).

Statistical Analysis. Descriptive results were expressed as mean ± standard deviation (SD) or number (percentage) of patients with a condition. The *t* test or nonparametric Mann-Whitney test was used to compare quantitative data and the chi-square test was applied for comparison of frequency data. The hypotheses were two-tailed and $P < 0.05$ was considered significant. To assess univariate associations between PegIFNα-associated retinopathy and tested variables, relative risks (RR) or hazard risk (HR) and their corresponding 95% confidence intervals (CI) were calculated using simple logistic-regression analysis. Cox's product-limit regression analysis was used for the multivariate analysis.

Table 1. Demographic, Biochemical, Virological, and Ophthalmologic Characteristics in 97 Patients with CHC at Baseline

Variable	Total Population (97)
Age (mean yrs±SD)	52.1 ± 11.0
Male gender (%)	62 (63.9)
Smoking (%)	33 (34.0)
Alcohol (%)	43 (44.3)
BMI (mean kg/m^2±SD)	24.3 ± 2.8
BMI > 28 kg/m^2 (%)	8 (8.2)
Hypertension (%)	27 (27.8)
Diabetes (%)	5 (5.2)
Metabolic syndrome (%)	13 (13.4)
Platelet count (mean 10^9/L±SD)	210.5 ± 65.8
AST (mean IU/L±SD)	62.9 ± 36.1
ALT (mean IU/L±SD)	93.3 ± 62.5
γGT (mean IU/L±SD)	65.8 ± 69.5
Cholesterol (mean mg/dL±SD)	167.8 ± 32.9
Tryglicerides (mean mg/dL±SD)	127.4 ± 41.1
Cryoglobulinemia (%)	29 (29.9%)
HCV-RNA (mean log IU/mL±SD)	3.6 ± 1.3
HCV genotype (%)	
1	60 (61.9)
2a/2c	24 (24.7)
3a	9 (9.3)
4c/4d	4 (4.1)
Treatment naïve (%)	67 (69.1)
Preexisting retinopathy (%)	9 (9.3%)
Fibroscan (mean kPa ± SD)	10.7 ± 7.7

Abbreviations: CHC, chronic hepatitis C; SD, standard deviation; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, gamma-glutamyltranspeptidase. Reference values: ALT 10-45, AST 10-45, γGT 5-55.

Results

The demographic, biochemical, and virological features of the study population at baseline are summarized in Table 1. There were 62 (63.9%) males, 27 (27.8%) cases were hypertensive, and five (5.2%) cases were diabetic. Overall, 67 (69.1%) patients were treatment-naïve, 64 (66%) cases were infected with HCV-1 or HCV-4. A failure or unreliable result of Fibroscan was obtained in five (5.2%) patients.

Variables Associated With Preexisting Retinopathy at Baseline. Nine (9.3%) patients had preexisting lesions referable to retinopathy at baseline. As shown in Table 2, variables associated with the presence of retinopathy at baseline by univariate analysis were age ($P = 0.01$), hypertension ($P = 0.05$), diabetes ($P = 0.01$), metabolic syndrome ($P = 0.004$), and low platelet count ($P = 0.05$).

Variables Associated With Retinopathy During Antiviral Therapy by Univariate Analysis. Overall, 30 (30.9%) patients exhibited signs of retinopathy during antiviral therapy. One (3.3%) of these cases developed bilateral branch retinal vein occlusion. As reported in Table 3, variables significantly associated

Table 2. Variables Associated With Retinopathy at Baseline by Univariate Analysis

Variable	Retinopathy + (n=9) (%)	Retinopathy – (n=88) (%)	Relative Risk (95% CI)	P
Age (mean yrs±SD)	59.4 ± 7.8	51.0 ± 11.0	3.81 (0.87-16.7)	0.01*
Hypertension (n)	5 (55.6)	22 (25.0)	3.24 (0.94-11.17)	0.05**
Diabetes (n)	2 (25.2)	3 (3.4)	5.26 (1.45-19.06)	0.01**
Metabolic syndrome (n)	4 (44.4)	9 (9.1)	5.17 (1.59-16.79)	0.004**
Platelet count (mean 10^9/L±SD)	165.9 ± 61.8	213.4 ± 63.0	3.25 (0.95-11.07)	0.05*

Abbreviations: CI, confidence interval; SD, standard deviation; n, number.
*Calculated by Student *t* test.
**Calculated by chi-square analysis.

with retinopathy during antiviral therapy were age ($P = 0.004$), hypertension ($P < 0.0001$), metabolic syndrome ($P = 0.05$), cryoglobulinemia ($P = 0.05$), and preexisting intraocular lesions at baseline ($P = 0.01$). No significant difference in the frequency of retinopathy between PegIFNα 2a and PegIFNα 2b was observed (29.6% versus 32.6%, respectively, $P = 0.7$).

Variables Associated With Retinopathy During Antiviral Therapy by Multivariate Analysis. By multivariate analysis, the only parameter independently associated with retinopathy during antiviral therapy was hypertension (HR = 4.99, 95% CI 2.29-10.89). On the basis of the multivariate analysis, patients were divided into two subgroups for the purpose of subsequent analysis: hypertensive subgroup (n = 27) and subgroup without hypertension (n = 70). The main demographic, biochemical and virological features of the two subgroups are summarized in Table 4. Overall, the hypertensive subgroup presented with older age ($P = 0.0009$), higher BMI ($P = 0.05$), higher prevalence of females ($P = 0.02$), and of metabolic syndrome ($P < 0.0001$). There was also a tendency for a higher prevalence of diabetes in the hypertensive subgroup, but this difference was not significant ($P = 0.09$).

Frequency of Retinopathy at Treatment Timepoints in Hypertensive Subgroup Versus Subgroup Without Hypertension. All patients underwent the baseline and 3T examination; 95.9% and 90.7% of patients underwent 6T and 3ET examination, respectively, because of the cases that discontinued the antiviral therapy. Frequency of retinopathy was significantly higher in the hypertensive subgroup versus subgroup without hypertension at all analyzed timepoints (Table 5). There was a progressive increase in the frequency of retinopathy during treatment in both subgroups, with a peak at 6T (68.0% and 19.1% in the hypertensive group and in the group without hypertension, respectively). Even though the difference was not significant, in the hypertensive subgroup there was a tendency for a higher frequency of retinopathy at 3ET versus baseline (32.0% versus 18.5%, $P = 0.19$), thus implying that in a number of patients the intraocular event persisted after cessation of treatment. Supporting Table S2 reports the descriptive ophthalmologic findings in the 30 cases with retinopathy during treatment. Nine (30.0%) patients complained of visual disturbances. In all cases retinopathy developed by 6T. In 12 out of 21 (57.1%) patients with normal optic fundi at baseline, retinopathy was initially diagnosed by the appearance of cotton wool spots. In 3 of these 12 cases, retinal hemorrhages were also observed simultaneously or sequentially. Nine of the 21 (42.9%) patients who developed retinopathy had only retinal hemorrhage without a cotton wool spot. Retinopathy disappeared in 18 of the 30 (60.0%) patients after the cessation of treatment. However, it continued in seven patients with retinal hemorrhage, in four with cotton wool spots, and in one case with bilateral branch retinal vein occlusion. All nine patients with preexisting retinopathy at baseline exhibited a worsening during therapy, as shown by the appearance of new retinal lesions.

Results of Antiviral Treatment. Overall, 54 (55.7%) and 43 (44.3%) of patients were treated with PegIFNα 2a plus ribavirin and PegIFNα 2b plus

Table 3. Variables Associated With Retinopathy During Antiviral Therapy by Univariate Analysis

Variable	Retinopathy + (n=30) (%)	Retinopathy – (n=67) (%)	Relative Risk (95% CI)	P
Age (mean yrs±SD)	56.5 ± 10.4	48.8 ± 10.5	2.56 (0.98-6.7)	0.004*
Hypertension (n)	17 (56.7)	10 (14.9)	3.39 (1.92-5.99)	<0.0001**
Metabolic syndrome (n)	7 (23.3)	6 (9.0)	1.97 (1.07-3.63)	0.05**
Cryoglobulinaemia (n)	13 (43.3)	16 (23.9)	1.79 (1.01-3.19)	0.05**
Intraocular lesions at baseline (n)	6 (20.0)	3 (4.5)	2.44 (1.38-4.34)	0.01**

Abbreviations: CI, confidence interval; SD, standard deviation; n, number.
*Calculated by Student *t* test.
**Calculated by chi-square analysis.

Table 4. Comparison of Demographic Findings, Laboratory Data, and Fibroscan Result Between the Hypertensive Subgroup vs. the Subgroup Without Hypertension

Variable	Hypertensive Subgroup (n=27)	Subgroup Without Hypertension (n=70)	P
Age (mean yrs±SD)	60.4 ± 9.8	50.3 ± 10.5	0.0009*
Male gender (%)	12 (46.2)	48 (68.6)	0.02**
Smoking (%)	10 (37.0)	24 (34.3)	0.8**
Alcohol (%)	11 (40.7)	32 (45.7)	0.6**
BMI (mean kg/m^2±SD)	24.9 ± 2.7	23.5 ± 2.8	0.05*
Diabetes (%)	3 (11.1)	2 (2.9)	0.09**
Metabolic syndrome (%)	13 (48.1)	0	<0.0001**
Platelet count (mean 10^9/L±SD)	217.2 ± 80.1	209.2 ± 61.4	0.8*
AST (mean IU/L±SD)	70.5 ± 45.3	61.6 ± 37.8	0.5*
ALT (mean IU/L±SD)	98.9 ± 66.7	88.0 ± 64.8	0.6*
γGT (mean IU/L±SD)	61.3 ± 49.6	67.0 ± 74.4	0.8*
Cholesterol (mean mg/dL±SD)	168.5 ± 54.4	164.2 ± 30.7	0.8*
Tryglicerides (mean mg/dL±SD)	133.3 ± 56.2	126.7 ± 37.8	0.5*
HCV-RNA (mean log IU/mL±SD)	2.9 ± 0.9	4.2 ± 1.6	0.5*
HCV genotype (%)			
1	15 (55.6)	45 (64.3)	0.4**
2a/2c	8 (29.6)	16 (22.8)	
3a	3 (11.1)	6 (8.6)	
4c/4d	1 (3.7)	3 (4.3)	
Treatment naïve (%)	21 (77.8)	46 (65.7)	0.2**
Fibroscan (mean kPa ± SD)	11.3 ± 7.5	9.7 ± 5.1	0.1*

Abbreviations: CHC, chronic hepatitis C; SD, standard deviation; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, gamma-glutamyltranspeptidase. Reference values: ALT 10-45, AST 10-45, γGT 5-55.

*Calculated by Student *t* test.

**Calculated by chi-square analysis.

ribavirin, respectively. Rapid virological response (RVR) was achieved in 54 (55.7%) patients. SVR was achieved in 53 out of 88 (60.3%) patients who terminated the antiviral therapy. There were 23 (26.1%) nonresponders and 12 (13.6%) relapsers. A dose modification was necessary in 40 (41.2%) cases. Treatment was discontinued in nine (9.3%) patients due to adverse events. The reasons for discontinuation were hematopoietic dysfunction (44.5%), severe patient intolerance (33.3%), uncontrolled hyperthyroidism (11.1%), and bilateral branch retinal vein occlusion (11.1%). The variables significantly associated with SVR were higher prevalence of HCV-2 and HCV-3 (56.6% versus 8.6% in responders versus nonresponders/relapsers, respectively, $P < 0.0001$) and lower Fibroscan values at baseline (9.4 ± 6.0 versus 12.3 ± 8.8 in responders versus nonresponders/relapsers, respectively, $P = 0.05$).

Discontinuation of Antiviral Therapy Due to Intraocular Complications. In one (1.1% of the whole study population, 3.7% of the hypertensive subgroup, 11.1% of the discontinued cases) patient belonging to the hypertensive subgroup, who developed bilateral branch retinal vein occlusion at 6T, the therapy was discontinued. This was a male patient age 68 years who did not smoke or drink any alcohol, with a BMI of 24.4 kg/m^2. The patient was infected with HCV-1 and was treatment-experienced. His Fibroscan result was 6.7 kPa (interquartile range [IQR] = 1.3). His baseline ophthalmologic examination showed preexisting retinopathy (retinal hemorrhage). The patient underwent treatment with PegIFNα 2a 180 μg once weekly plus ribavirin 1,000 mg/day. He achieved a delayed virological response (DVR) and HCV-RNA was undetectable at 24 weeks of therapy. Because of the serious intraocular adverse event diagnosed at 6T,

Table 5. Frequency of Retinopathy at Baseline and at Treatment Timepoints in the Hypertensive Subgroup vs. the Subgroup Without Hypertension

	Baseline	3T	6T	3ET
Hypertensive subgroup (n=27)	5 (18.5%)	13 (48.1%)	17/25 (68.0%)	8/23 (32.0%)
Subgroup without hypertension (n=70)	4 (5.7%)	11 (15.7%)	13/68 (19.1%)	4/65 (6.2%)
P	0.05	0.0009	<0.0001	0.0005

Abbreviations: 3T, 3 months of therapy; 6T, 6 months of therapy; 3ET, 3 months end of therapy. *P* was calculated by chi-square analysis. At 6T, there were 93 patients remaining because 4 patients had discontinued the treatment; at 3ET, there were 88 patients remaining because 5 patients had discontinued the treatment.

therapy was discontinued and the patient subsequently relapsed. At that time the patient complained of marked vision loss at the left eye. The patient has been followed up for 2 years with regular ophthalmologic examination, fluorescein angiography, and optical coherence tomography. He was treated with retinal laser photocoagulation over the ischemic areas. In the right eye visual acuity was preserved, with best corrected visual acuity of 20/20. In the left eye the patient developed macular edema that was treated with intravitreal corticosteroids and subthreshold micropulse laser treatment. Currently, macular edema has been completely resolved, and visual acuity remained 20/200 due to the foveal pigmentary changes and macular atrophy that do not require further treatment. He is scheduled for regular ophthalmologic follow-up every 6 months.

Cost Analysis of Ophthalmologic Screening and Comparison With Thyroid Screening. On the basis of the results of our study, an ophthalmologic screening should be recommended in HCV patients with hypertension who undergo antiviral therapy. Because all cases of retinopathy developed by 6T, we suggest that HCV patients with hypertension undergo an ophthalmologic examination at baseline, 3T, and 6T and continue after treatment cessation if intraocular lesions are documented at any of the previous timepoints (Fig. 2). We conducted a cost analysis of the proposed ophthalmologic screening and we compared it with thyroid screening, which is already recommended by guidelines.[1] Costs were valued in 2012 Euros (1 Euro = 1.28 USD = 0.83 UK Pounds). For the purpose of the cost analysis, we estimated the cost of an ophthalmologic examination to be 30.9 Euros and of thyroid-stimulating hormone (TSH) to be 12.5 Euros. According to guidelines, TSH should be performed every 12 weeks during therapy.[1] We considered two timepoints (12 and 24 weeks of therapy) for HCV-2 and HCV-3 cases, and for HCV-1 and HCV-4 cases not responding to treatment. For HCV-1 and HCV-4 responders we considered four timepoints (12, 24, 36, and 48 weeks of therapy).

In our study population, 27 HCV hypertensive patients should undergo the ophthalmologic screening (Fig. 3A). With regard to 10 cases with a negative ophthalmologic examination at baseline, 3T and 6T, the screening cost would be 927 Euros (Cost A). For the remaining 17 cases, there would be an additional ophthalmologic examination at 3ET, and the screening cost would be 2,101.2 Euros (Cost B). The total cost of the ophthalmologic screening for 27 HCV patients with hypertension would be 3,028.2 Euros.

In the same study population, all 97 patients should undergo thyroid screening (Fig. 3B). Forty-one responder/relapser HCV-1 or HCV-4 patients would undergo TSH at four timepoints and 23 nonresponders would undergo TSH at two timepoints. The screening cost would be 2,625 Euros (Cost 1). For the remaining 33 cases infected with HCV-2 and HCV-3, the screening cost would be 825 Euros (Cost 2). Thus, the total cost of the thyroid screening for 97 HCV patients would be 3,450 Euros. For simplicity, we did not consider the patients who discontinued the treatment in any of the cost analyses.

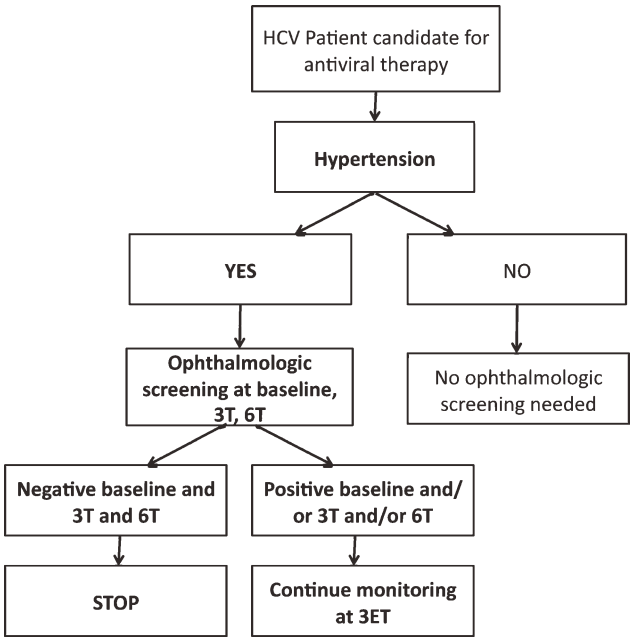

Fig. 2. Proposed decisional algorithm for the screening of PegIFNα-associated retinopathy in HCV patients.

Discussion

We here report the results of a prospective, longitudinal study specifically designed to provide insight into retinal complications of treatment with PegIFNα plus ribavirin. This is an understudied side effect of the current standard of care for treatment of CHC. Our data indicate that retinopathy is frequent during treatment with PegIFNα and ribavirin, especially in hypertensive patients, who may develop serious complications. On the basis of our results, ophthalmologic screening for PegIFNα-associated retinopathy should be recommended when hypertension coexists.

According to recent guidelines, the combination of PegIFNα and ribavirin is still regarded as the standard of care for the treatment of CHC.[1] Two DAAs have been recently approved by the FDA and EMA for the treatment of CHC due to HCV genotype 1, but they should not be used without a PegIFNα plus ribavirin

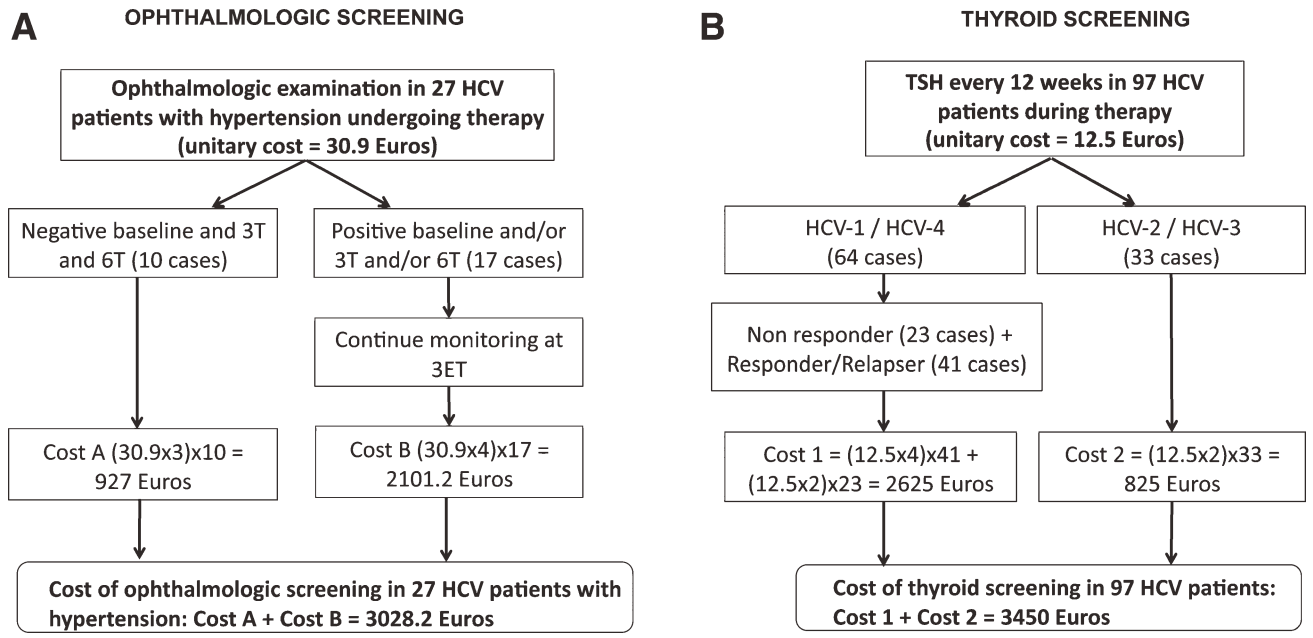

Fig. 3. (A) Flow chart showing cost analysis of the ophthalmologic screening in 27 HCV patients with hypertension undergoing antiviral therapy. A unitary cost of 30.9 Euros for the ophthalmologic examination was applied. (B) Flow chart showing cost analysis of thyroid screening in 97 HCV patients undergoing antiviral therapy. A unitary cost of 12.5 Euros for TSH was applied.

backbone.[2,3] Thus, the clinician has to deal with side effects related to treatment with PegIFNα and ribavirin. Various adverse effects have been reported due to use of interferon, including an influenza-like syndrome and toxicities of the central nervous, hematopoietic, gastrointestinal, urinary, cardiovascular, musculoskeletal, and endocrine systems.[1,2] Ocular toxicity has been occasionally reported, with somewhat discordant results. For this reason, there is a lack of consensus on whether ophthalmologic screening should be recommended in patients with CHC undergoing treatment with PegIFNα plus ribavirin.[4,5,7,8]

In the past, the frequency of retinopathy as a side effect of standard interferon varied widely in the literature, with values between 16% and 64%, which could be presumably attributed to the differences in the treatment regimen, background of patients, and to the retrospective design of most of the studies.[4,6] Moreover, discordant results have been reported about the influence of hypertension and diabetes mellitus on the development of interferon-associated retinopathy.[4-6]

Information about frequency, associated conditions, and severity of retinopathy during treatment with PegIFNα are scarce. In a case series of 52 patients, Malik et al.[9] found that 7.8% of cases treated with PegIFNα plus ribavirin developed retinopathy. Due to the low incidence, the study did not support routine screening for retinopathy during treatment for CHC. A more recent study by Panetta and Gilani[7] reported a very low incidence (3.8%) of symptomatic retinopathy among 183 patients with CHC treated with PegIFNα 2a or 2b and ribavirin. Moreover, patients with hypertension and diabetes were not at higher risk for interferon-associated retinopathy. The authors concluded that pretreatment and subsequent eye examinations while on treatment was not necessary in asymptomatic patients, even in the presence of hypertension and diabetes mellitus. However, that study had several limitations, being retrospective and including also patients treated with consensus interferon. Moreover, ophthalmologic examination was not performed at specific timepoints during therapy, but only in case of on-treatment visual complaint by the patient.[7]

In our experience, the frequency of PegIFNα-associated retinopathy was 30.9%. We did not observe any significant difference in the frequency of retinal complications between PegIFNα 2a and PegIFNα 2b.

Variables significantly associated with PegIFNα-associated retinopathy were age, hypertension, metabolic syndrome, cryoglobulinemia, and preexisting intraocular lesions at baseline. The strongest predictor of retinopathy was hypertension, which was the only variable to remain independently associated by multivariate analysis. Among the other factors, age and metabolic syndrome were associated with the presence of hypertension and they were in fact significantly higher and more frequent in the hypertensive subgroup. Patients belonging to the hypertensive subgroup also exhibited

significantly higher BMI and higher prevalence of female gender. This last finding could be explained by the fact that before age 50 women have a lower prevalence of hypertension than men, but after age 55 they have a higher prevalence.[14] With regard to cryoglobulinemia, it is known that it may be responsible for serious vasculitis syndromes with organ damage.[15] Association of cryoglobulinemia with retinopathy in CHC has been occasionally described in case reports.[16]

In our series, hypertension was also a risk factor for preexisting retinopathy at baseline. Other associated variables were age, diabetes, metabolic syndrome, which are associated with hypertension, and platelet count. Hypertension and diabetes mellitus are recognized causes of retinopathy *per se*, and this fact explains their highest prevalence in patients with preexisting intraocular lesions.[17] Interestingly, it has been suggested that retinopathy may be a frequent finding in thrombocytopenic patients.[18,19]

The underlying mechanism of interferon-associated retinopathy is not completely understood. It has been proposed that it may be related to an immune complex deposition causing occlusion of retinal capillaries leading to cotton wool spots formation.[20] On the other hand, it may be also related to disturbances in retinal microcirculation.[4] Preexisting arteriosclerosis that affects microcirculation may promote interferon-associated retinopathy. Chronic hypertension is associated with the thickening of the walls of the arteries and small arterioles.[21] In this view, the fact that hypertensive patients with CHC are more prone to develop interferon-associated retinopathy is pathophysiologically consistent. Indeed, the evidence that hypertensive retinopathy induces the formation of retinal hemorrhages and cotton wool spots, which are also seen in interferon-associated retinopathy, implies that they may share a similar pathogenesis and may exacerbate each other.

Thanks to serial ophthalmologic examinations at four timepoints, we were able to accurately evaluate the timeline of the retinopathy during antiviral treatment. PegIFNα-associated retinopathy was significantly more prevalent in the hypertensive subgroup versus the subgroup without hypertension at all analyzed timepoints. Retinopathy peaked at 6T, with 68.0% affected cases in the hypertensive subgroup, and disappeared in many patients after the cessation of treatment. However, retinal hemorrhages and/or cotton wool spots persisted in 32.0% of patients of the hypertensive subgroup. Importantly, in one patient belonging to the hypertensive subgroup, who developed bilateral branch retinal vein occlusion, treatment was discontinued.

The frequency of serious ophthalmologic adverse events requiring discontinuation of antiviral therapy with PegIFNα plus ribavirin has not been investigated before in a prospective, dedicated study. Severe ophthalmologic complications of interferon-based therapy have been reported, mostly as case series. These include retinal vein occlusion, retinal artery occlusion, severe hypertensive retinopathy, and bilateral ischemic optic neuropathy.[11] In our experience, the prevalence of severe intraocular complications requiring treatment discontinuation was 1.1% in the whole population study and 3.7% when the calculation was limited to the hypertensive subgroup. Even though treatment was continued in most patients, our data indicate that the extremely high frequency of retinopathy during treatment and the possibility of a serious ophthalmologic complication should orient toward a screening for retinopathy in HCV patients with hypertension. Moreover, the fact that retinal lesions worsened in all patients with preexisting retinopathy at baseline and persisted after treatment cessation in a significant number of hypertensive patients additionally supports the screening. The screening for retinopathy seems even more justified if we consider that hypertension is highly prevalent in the general population.[14] Finally, in our experience intraocular complications were as frequent as interferon-associated subclinical thyroiditis (30.9% versus 24.7%, data not shown), for which guidelines recommend monitoring during treatment.[1] The frequency of interferon-associated subclinical thyroiditis in our study is in line with previous reports.[22] Notably, we reported the same rate of treatment discontinuation (11.1%) attributable to intraocular complications and uncontrolled thyroid disease, and this figure is in line with other studies that reported that treatment discontinuation was due to thyroid disease in 4%-14% of cases.[23,24] We also showed that our selective ophthalmologic screening of HCV patients with hypertension undergoing treatment may have similar costs as compared with the recommended thyroid screening of HCV patients during therapy.

This study has several strengths. The prospective, longitudinal design allows exclusion of selection biases and monitoring the timeline of PegIFNα-associated retinopathy in a consecutive cohort of well-characterized patients with CHC.

Our study has some limits. The study population was relatively small. However, it was a prospective study conducted at a single center, allowing obtaining a homogeneous cohort with a similar management, considering that all patients were treated by only two experienced hepatologists and screened by the same single ophthalmologist. Moreover, we did not follow the patients for a longer period after treatment cessation to

better characterize the dynamics of persisting intraocular complications.

In conclusion, PegIFNα-associated retinopathy is frequent during antiviral treatment for CHC, especially in hypertensive patients, who may develop serious complications. Screening for PegIFNα-associated retinopathy should be recommended when hypertension coexists.

Acknowledgment: S.V. contributed to the study design, data, and interpretation of the data. D.T. and E.M. contributed data. F.N. contributed to statistical analysis of the data. G.S. contributed to the conception, study design, data, interpretation of the data, and first draft of the article. All authors approved the final version of the article. G.S. is the guarantor.

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