INTRODUCTION
Currently, there are several Food and Drug Administration-approved treatments for chronic hepatitis C virus (HCV). Prior to the release of direct-acting antiviral therapy, therapy was limited to administering ribavirin and pegylated interferon (PEG INF) to induce viral suppression and limit progression to cirrhosis. However, this combination has been associated with multiple side effects in all organ systems, including the hematopoietic system and the eye. Ribavirin, a guanosine analog which inhibits viral messenger RNA formation, has been associated with the development of anemia, whereas INF-associated retinopathy is a syndrome characterized by cotton wool spots, retinal hemorrhages, macular edema, and rarely, branch vein occlusions. Although not first-line therapy, ribavirin and PEG INF can be used with direct-acting antiviral therapy depending on the genotype of HCV.

INF-induced retinopathy generally develops within 2–6 months after the initiation of treatment, although early onset of the retinopathy has been observed in as little as 2 weeks. Multiple studies have found an increased risk in those with hypertension and diabetes and those receiving higher doses of INF. However, no known racial, age, or gender predilection exists. This condition is often reversible with patients returning to their baseline vision following modification of the PEG INF regimen.

The pathophysiology of INF-induced retinopathy is poorly understood, but several hypotheses exist. Most center around...
the idea of a decreased perfusion of the retinal microcirculation leading to local hypoxia, although there exist multiple proposals regarding the etiology of this dysfunction. Some have proposed increased leukocyte adherence to endothelial cells, while others posit a dysfunction caused directly either by the PEG INF or immune complex deposition in the endothelial cell walls. It has also been postulated that retinopathy may be caused directly by HCV, but no molecular basis for this has been offered.

A widely accepted classification system for screening and treatment also remains elusive. There is still controversy regarding the necessity of a baseline ophthalmic screening examination in addition to the timing of interval follow-up during the treatment course. The presence of early cotton wool spots, hemorrhages, branch arterial or central venous occlusions, or macular edema mandates increased ophthalmic follow-up and a decrease or discontinuation of the PEG INF or change in ribavirin dose. Here, we report a subset of patients observed to develop INF-induced retinopathy shortly after the diagnosis of anemia during the treatment with PEG INF and ribavirin. We found that patients who experience a significant percentage decrease in their hemoglobin and hematocrit from their baseline were at greater risk for developing retinopathy.

**Methods**

This study was approved by the Drexel College of Medicine Institutional Review Board and followed the tenets of the Declaration of Helsinki. In this retrospective cohort study, we examined the electronic medical records of all patients presenting from September 1, 2011, to September 30, 2013, with HCV as an ICD-9 diagnosis code. We subsequently narrowed the cohort to include only those who received PEG INF and identified 202 patients. Five patients presented for ocular examination during the course of INF treatment but were excluded due to a lack of a baseline examination. Only 23 of the remaining 197 patients presented for both baseline and follow-up examinations. However, 11 patients presented over 3 months after therapy initiation and were excluded due to the absence of ocular examination during the active treatment period. This resulted in the 12 patients included in this study who had both baseline examinations and examinations during treatment with PEG INF.

Patients were on a standardized regimen of Pegasys ProClick 180 mcg ([PEG INF] [Genentech, San Francisco, CA, USA]), a protease inhibitor – Incivek 375 mg – two tablets three times a day for the first 12 weeks ([Telaprevir] [Vertex Pharmaceuticals, Boston, MA, USA]), and ribavirin 1200 mg daily. Ribavirin doses were decreased to 400 mg/day if anemia was detected on twice monthly complete blood counts at the discretion of the managing physician. Similarly, the addition of PROCRIT® or Neupogen to the regimen was made at the discretion of the managing physician. All patients had a dilated fundus examination and photographic documentation with the Zeiss Meditec Visucam NM/FA 1851-800 (Dublin, CA, USA). All patients were seen for monthly follow-up from the baseline until discontinuation of the therapy.

Of the 12 patients who had both baseline examinations and returned for follow-up during their treatment regimen, we identified six patients who developed INF-induced retinopathy. The six patients without retinopathy concurrently receiving treatment and under ophthalmic screening were evaluated as a control group. Starting 1 month prior to the initiation of therapy through the treatment course, serial hemoglobin values for both the groups were recorded. Specifically, hemoglobin levels were noted at the time of the retinopathy diagnosis in affected patients and the nadir in those without retinopathy. Other clinically relevant data such as the alteration of treatment doses (ribavirin or PEG INF) or the addition of hematopoietic stimulating medications (PROCRIT® and Neupogen) were noted. The change in hemoglobin concentration from the baseline to follow-up ophthalmic examination and total percent reduction of hemoglobin were calculated.

Using one-tailed, unpaired t-tests, two comparisons were made. First, the total drop in hemoglobin between retinopathy patients and controls was calculated, and second, the total percentage drop in hemoglobin between retinopathy patients and controls was calculated. Patients’ demographics including baseline and best corrected visual acuities (BCVAs) are listed in Table 1. Control patient 6 had two treatment courses. The BCVAs at the initiation of courses 1 and 2 and posttreatment are recorded separately.

**Results**

Twelve patients were enrolled: six with and without retinopathy. The mean age was 57.58 ± 9.77 years. Hemoglobin concentration levels between control and INF retinopathy patients tended to be slightly lower in the group that developed retinopathy [Table 1]. However, there was no threshold hemoglobin concentration, under which the rate of developing retinopathy increased in a statistically significant manner (P > 0.10). Interestingly, we found that a >25% drop in hemoglobin conferred a statistically significant risk in the development of INF-associated retinopathy (P < 0.001).

Hemoglobin levels were recorded at the time of retinopathy presentation in affected patients, the nadir of hemoglobin levels was recorded for controls [Table 1]. Control patient 5 had his dose reduced by half and then discontinued due to an ANC 247 and platelet count of 16,000. Likewise, control 6 had two treatment courses of INF. It was discontinued after a 50% reduction of the dose 7 months into treatment due to a platelet count of 33,000. One year later, it was restarted due to the above drops in hemoglobin levels.

All the six patients with INF retinopathy had a complete resolution of retinal hemorrhages and cotton wool spots during follow-up. One patient developed a non-occlusive branch retinal vein occlusion. Without cessation of treatment, the
branch vein occlusion resolved and the BCVA returned to 20/20 without treatment. The final BCVAs in all patients with and without retinopathy were within one line of the baseline BCVA [Table 1].

**DISCUSSION**

Through comparison of the absolute reduction in hemoglobin values between the control and treatment groups during treatment with ribavirin and PEG INF, our data indicate that patients with a >25% reduction are at significantly increased risk for the development of retinopathy. Thus, these patients should receive an increased ophthalmic screening. We posit that the mechanism for this finding is the total percentage decrease of the hemoglobin level leading to an inadequate time frame to develop compensatory mechanisms in the retinal microcirculation. Patients with chronic anemia, even those with a lower hemoglobin and hematocrit at presentation than those who developed retinopathy, have a longer time frame to compensate for the relative hypoxia. Thus, it is not the absolute hemoglobin level that is indicative for retinopathy development but rather the drop from a given patient’s baseline. Given our relatively small patient population, a larger cohort study is needed to delineate if a causal relationship between anemia leading to the development of INF-induced retinopathy exists.

We also considered that our findings may have been a result of retinopathy due to anemia rather than INF. Retinopathy due to anemia has not been associated with a percentage decrease in hemoglobin but rather occurs when the levels decrease <8 g/dL.9 While phenotypically similar, it differs clinically from INF retinopathy by the predominance of hemorrhages and exudates with less cotton wool spots. The patients in this study had findings on ophthalmic evaluation consistent with only INF-induced retinopathy.

Confounding variables in the data analysis were the use of PROCRIT® to increase erythrocyte production and decreases in ribavirin doses per the discretion of the treating physician. All of the patients with retinopathy were started on PROCRIT® to increase their hemoglobin concentration, and the amount of ribavirin dose adjustment varied based on the managing physician’s preference from 200 to 800 mg prior to ophthalmic re-examination. None of the control patients received PROCRIT® and the ribavirin dose remained constant through treatment, also at the discretion of the managing physician. Control patient 2 had the dose of PEG INF that decreased due to the intolerance of systemic side effects, which were unrelated to laboratory values. This is in contrast to the patients who developed retinopathy, as the PEG INF was decreased by one-half given the abnormalities on their complete blood counts.

Another concern was patients’ follow-up during the treatment course, as not every patient had a dilated fundus examination coinciding with the nadir in hemoglobin levels. Since cotton wool spots and hemorrhages can remain visible for an average of 6 weeks, the hemoglobin concentration may have been lower at the onset of the retinopathy. This would cause us to underestimate the drop in hemoglobin levels associated with retinopathy development.

Finally, while the patients’ clinical diagnosis of anemia immediately preceded the identification of INF-induced retinopathy, a causal relationship cannot be determined. Studies with more patients and shorter follow-up are needed. Although not first-line therapy, ribavirin and PEG INF continue to be used clinically in patients with HCV. This requires ophthalmologists to have continued knowledge of the potential ocular side effects of these medications. Patients with a total drop in hemoglobin >25% while on PEG INF and ribavirin therapy are at a higher risk for the development of INF retinopathy and require monthly dilated fundus examination. Monthly examinations would allow for identification of the transient capsular warning

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**Table 1: Best corrected visual acuities, change in hemoglobin level, and medications in patients on peglated interferon therapy with and without retinopathy**

| Subject | Age | Sex | HIV status | Baseline BCVA (OD, OS) | Final BCVA (OD, OS) | Hemoglobin level at diagnosis or at follow-up (g/dL) | Overall hemoglobin from baseline (g/dL) | Percentage drop in hemoglobin | Procrit started | Ribavrin dose decreased | PEG INF dose decreased by 1/2 |
|---------|-----|-----|------------|------------------------|---------------------|------------------------------------------|------------------------------------|-------------------------------|----------------|-----------------------------|-----------------------------|
| Patient 1 | 60  | Female | Negative | 20/20, 20/20 | 20/20, 20/20 | 7.5 | 6.9 | 48 | Yes | Yes | Yes |
| Patient 2 | 54  | Male | Positive | 20/20, 20/20 | 20/20, 20/20 | 11.2 | 2.4 | 27 | Yes | Yes | Yes |
| Patient 3 | 59  | Male | Negative | 20/20, 20/20 | 20/20, 20/20 | 12.4 | 3.1 | 21 | No | Yes | Yes |
| Patient 4 | 51  | Male | Negative | 20/20, 20/20 | 20/20, 20/20 | 9.8 | 5.6 | 37 | Yes | Yes | Yes |
| Patient 5 | 57  | Male | Negative | 20/20, 20/20 | 20/20, 20/25 | 10.1 | 6.3 | 37 | No | Yes | Yes |
| Patient 6 | 60  | Female | Negative | 20/30, 20/40 | 20/40, 20/40 | 9.0 | 6.0 | 40 | Yes | Yes | Yes |
| Control 1 | 59  | Male | Negative | 20/25, 20/20 | 20/20, 20/25 | 14.2 | 2.9 | 16 | No | No | No |
| Control 2 | 56  | Female | Negative | 20/20, 20/20 | 20/20, 20/20 | 14.4 | 5.7 | 10 | No | No | Yes |
| Control 3 | 73  | Male | Negative | 20/20, 20/20 | 20/20, 20/25 | 10.7 | 2.4 | 14 | No | No | No |
| Control 4 | 57  | Male | Negative | 20/20, 20/20 | 20/20, 20/20 | 12.5 | 5.4 | 24 | No | No | No |
| Control 5 | 34  | Male | Negative | 20/20, 20/20 | 20/25, 20/30 | 11.5 | 1.4 | 24 | No | No | Yes |
| Control 6 | 71  | Male | Negative | 20/30, 30/30 | 20/25, 20/30 | 11.6, 11.4, 10.8 | 3.3 | 22, 23, 27 | No | No | Yes |

HIV: Human immunodeficiency virus, BCVA: Best corrected visual acuity, PEG INF: Pegylated interferon, OD: Right eye, OS: Left eye
syndrome and hemorrhages. Close coordination between the ophthalmologist and the gastroenterologist is needed for dose adjustments based on laboratory monitoring and ophthalmic findings.

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**Conflicts of interest**
There are no conflicts of interest.

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