*Clinical & Refractive Optometry* is pleased to present this continuing education (CE) article by Dr. William J. Denton and Dr. W. Jeffrey McGill entitled **Co-management of a Patient with Hepatitis C on Interferon Combination Therapy.** In order to obtain a 1-hour Council of Optometric Practitioner Education (COPE) approved CE credit, please refer to page 210 for complete instructions.

# Co-management of a Patient with Hepatitis C on Interferon Combination Therapy

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## Abstract

**Worldwide, the hepatitis C virus (HCV) affects approximately 170 million people,[1] while the United States claims an estimated 3.5 million people.[2] The present, standard treatment is a combination of pegylated-interferon (PEG-IFN) and ribavirin (RBV). Unfortunately, this therapy is not without some very significant side effects, as noticed in this Case Report.** ***Case Report:*** **A 44-year-old Caucasian male presented to the eye clinic. Upon ocular examination, the left fundus showed an area of ischemic retinopathy later determined to be caused by the HCV. After the initiation of PEG-IFN/RBV treatment, a second form of retinopathy resulted.** ***Conclusion:*** **This is a case management example of providing maximum hepatic treatment without causing ocular devastation. According to our research, it also documents the only case reported of HCV retinopathy in a country other than Japan.[2-4]**

## Introduction

The hepatitis C virus (HCV) is very common. Worldwide, HCV affects approximately 170 million people,[1] while the United States claims an estimated 3.5 million people.[2] Treatment guidelines recommend pegylated-interferon (PEG-IFN) and ribavirin (RBV) combination therapy. Many systemic side effects are common, but it was first established in 1993 by Guyer that interferon treatment caused ischemic retinopathy.[5] Greater than 50% of treated patients develop retinopathy according to studies, which greatly depends upon the country in which the patient is located.[6] Upon discovering ischemic retinopathy as a side effect came the demand to closely monitor patients undergoing this treatment with a dilated funduscopic exam. It has been suggested that an initial screening for retinopathy be performed within 3 months of initiating treatment,[6] but no standardized guidelines have been established to date.[7]

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## Case Report

C.B. was a 44-year-old Caucasian male who first presented in conjunction with a consult sent to the VA eye clinic from his hepatologist, to follow his fundus changes during his 24-week interferon treatment for chronic, stage II, HCV (genotype 3a), which was scheduled to start two months later. His serum alanine aminotransferase (ALT) was 66 U/L (reference range 0 – 55 U/L). He had previously been on similar treatment a couple years prior, which necessitated discontinuance due to retinal changes. His ocular history was otherwise unremarkable with no complaints or symptoms. C.B. denied previous ocular injuries or surgeries. His family ocular history was negative.

C.B's medical health includes HCV (diagnosed 1999) and bursitis. The patient is taking etodolac 400 mg and admits taking the herbal remedy, silymarin (milk thistle). Previous notes from his primary care provider showed a negative depression screening, however, the patient admitted that his HCV made him feel down, depressed, and sometimes hopeless. He had been abstinent of alcohol for twelve years. He was a previous smoker (1.5 packs per day for 17 years) with cessation in 1991. He also had a history of IV cocaine use, which stopped in 1989.

Best-corrected visual acuities at distance were 6/6 (20/20) OD and OS with a moderate compound myopic prescription using glasses or soft contact lenses. No decrease in vision was found throughout our treatment period. Extraocular muscle testing showed full range of motion. Pupils were equal, round and reactive to light. Confrontational visual fields were full to two finger counting OU. Color testing (Ishihara) was normal OU.

Slit lamp biomicroscopy of the anterior segment revealed unremarkable findings OU. Goldmann applanation tonometry showed 15 mm Hg OU during the early morning.

Dilated funduscopic examination revealed a small cup to disc ratio of 0.2/0.2 OU in a round, centered and shallow formation. The maculae were clear and flat with a bright foveal light reflex OU. The vessels were of normal caliber and distribution. The mid-periphery of the right eye showed a small pin-point cotton wool spot inferonasal about 1.5 disc diameters away from the optic nerve head at 4:00. No appearance of neovascularization was observed on the disc or elsewhere in the fundus. The periphery was flat and intact 360° OU.

Combination PEG-IFN/RBV treatment was initiated two months prior to the follow-up in the eye clinic. After extensive laboratory testing and record review, it was determined that the initial retinopathy occurred from HCV.

During the following five months the patient was examined three times with as many as nine cotton wool spots (OS follow-up #1) to as few as none (OS follow-up #3), without any other retinopathy or posterior segment findings. Throughout the follow-up examinations, all anterior segment structures and appearances were viewed as normal, except for reduced mucosal tear prism and some inferior corneal staining in both eyes at the third follow-up visit. He had also experienced decreased wearing time with his contact lenses. He was advised to use non-preservative artificial tears as frequently as he needed for his symptoms.

At the last follow-up examination when the patient had been off the PEG-IFN/RBV treatment for seven weeks, the patient's fundus revealed to have posterior poles that were absent of hemorrhages and cotton wool spots. His HCV RNA was undetectable, showing that the treatment was a success. He was still not able to wear his soft contact lenses because of dry eye symptoms which were assessed to be caused from the treatment. The patient observed that the symptoms appeared to be getting better the further he was from his cessation of the PEG-IFN/RBV treatment. Preservative artificial tears were correcting the symptoms quite effectively.

## Discusion

Hepatitis C affects more than 170 million people in the world, and may lead to cirrhosis and/or hepatocellular carcinoma.[1] Approximately 20% of patients with chronic HCV will develop cirrhosis, and 20% of patients with cirrhosis will develop hepatocellular carcinoma (HCC). It is also the leading indicator for liver transplantation.[2]

Risk factors include intravenous drug use, blood transfusions or organ transplants prior to 1992, and high-risk sexual behavior.[8] Determining which HCV genotype also determines the success rate of any treatment. There are six genotypes with as many as eighty total subtypes.[2] The genotype gives an indication of the prognosis after treatment occurs. Genotype 1B is common in Japan. Genotype 6 is found mainly in Asia. Genotypes 1A and 1B are more prevalent in the United States and Northern Europe, with 2 and 3 also fairly prominent.[2,3]

It is important to realize that although the majority of infected people have no sign or symptoms of chronic HCV, there are a few ocular signs. Literature has mentioned the following: ischemic retinopathy, keratoconjunctivitis sicca, and Moorean ulcer (rare).[8]

Abe et al documented idiopathic retinopathy in 31.8% of untreated HCV patients in Japan.[2-4] After a thorough search of literature, the only other case documented was a patient with a dual causation for retinopathy having type II mixed cryoglobulinemia and HCV.[3] To the best of our knowledge, this is the first reported HCV patient with idiopathic retinopathy, despite being very mild, to be documented in any country other than Japan. It has been speculated previously that any untreated idiopathic retinopathy in patients with HCV might be explained by genomic variability.[9] Advanced age and female gender were considered as risk factors from the Abe et al study. However, this patient was not old (44 years of age) and was of the male gender.[4]

C.B.'s initial eye exam prior to PEG-IFN/RBV treatment showed a very small cotton wool spot. It is thought that this was caused by his stage II chronic HCV disease. However, it is important not to assume that the initial ischemic retinopathy was from his chronic HCV. Other systemic conditions that could cause the same retinal appearance should be ruled out. Cotton wool spots are found in many systemic diseases, such as anemia, HIV/AIDS, diabetes mellitus, and hypertension among others. The patient had normal blood tests (CBC, HIV, Hemoglobin A1c), and his blood pressure had always been in normal range. The cotton wool spot was not at an artery/vein bifurcation.

Most patients with chronic HCV are treated with PEG-IFN/RBV as long as there is not a contraindication, while many patients with stage I disease tend to proceed without treatment. In the past, the interferon was taken three times a week. A slow-release, long-acting "pegylated" formulation of interferon is now available for once-a-week administration. This allows for less frequent injections, better bioavailability and lower net dose.[10] The pharmaceutical class, interferons, comprises a group of pleiotropic proteins with anti-viral, anti-inflammatory, and anti-angiogenesis characteristics. They are also multifunctional immunoregulatory cytokines with effects at various points in the cytokine cascade, which most likely account for their immunostimulatory effects.[11]

When interferon-related retinopathy appears to be advanced, it is important to readdress treatment options with the hepatologist. The hepatologist may decide to reduce the dosage and extend the period of treatment, discontinue the treatment for a time and reintroduce it a few months later, or suggest that the eye care provider

monitor the retinopathy more frequently while undergoing full treatment. One study decided to reduce the dosage of PEG-IFN and extend the treatment time in more than two thirds of their cases with resultant retinopathy. In most patients, the retinopathy regressed when treatment was finished. Continuing treatment without reduction of dosage is generally preferred, but the choice should be made while weighing the risk factors for retinopathy, the evolution of the retinopathy and the severity of the liver disease.[6] Depending on the chronicity and viral genotype, treatment has shown to result in sustained virologic response rates of 46%-77%.[2,11] Therefore, each case of HCV must be taken individually in order to determine the proper treatment modality. PEG-IFN treatment is the typical choice by a hepatologist to manage advancing HCV. Treatment does not have to ever be initiated, however, without treatment in advancing disease there is an increased risk of liver cancer. Among studies examining IFN-based combinations, 7%-8% reported withdrawal due to adverse effects.[11]

In the past few years there has been a great appreciation for herbal remedies, with as many as 30-40% of all people with chronic viral hepatitis taking at least one herbal product. Some level of caution should be used as some herbal remedies have caused significant damage like hepatotoxicity. The most popular herbal remedies for viral hepatitis have been silymarin, glycyrrhizin, traditional Chinese medicine, and Japanese traditional medicine.[12] Silymarin, extracted from the milk thistle, is an alternative medicine that has been used to treat liver diseases since the 16th century[13] and has been shown to protect the liver from many toxic substances. The only reported side effect of significance has been reduced serum levels of bilirubin and enzyme levels.[12,14] Many theories have been postulated regarding the hepatoprotective effect of silymarin's mechanism of action. A few experimental studies state claims that include: antioxidant action,[12-14] prevention of glutathione depletion,[12-14] hepatocyte stabilization, promotion of liver regeneration, antifibrotic properties,[12-14] anti-neoplastic,[12,15] anti-diabetic,[15] anti-inflammatory, and cardioprotective effects.[14,15] Significant drug reactions have not been reported. It also appears to be safe for up to 41 months of use.[15] Silymarin and all other herbal remedies should be used with caution, although their pharmaceutical profile has been well defined, and hepatoprotective properties have been demonstrated both in vitro and in vivo.[13] With the increased incidence of their use, health care providers should regularly ask patients about their uses of various forms of complementary and alternative medicine (CAM).

As with many pharmaceutical drugs, there are side effects with PEG-IFN/RBV, sometimes necessitating cessation of treatment. It is imperative that retinal screenings occur within three months of treatment initiation.[6] Systemic side effects associated with the use of PEG-IFN include flu-like symptoms, rashes, hypotension, peripheral neuropathy, and thrombocytopenia.[2,16-18] Hemolytic anemia is the most common side effect of RBV.[2,19]

Reports have also documented ocular complications from using PEG-IFN, with onset between 8-12 weeks after treatment is initiated.[10] These include: ischemic optic neuropathy, subconjunctival hemorrhage, trichomegaly, ischemic retinopathy manifested as cotton-wool spots and retinal hemorrhage, combined choroidal and retinal perfusion deficits, and cystoid macular edema.[20] The incidence of these complications, according to literature, is 18-86%,[7,18,21,22] with no significant difference between PEG-IFN monotherapy (24-58%) and PEG-IFN/RBV combination therapy (16%-64%).[1] The retinopathy may depend on dosage or other risk factors.[10] However, the provider cannot depend on patient symptomatology, as less than 1% of the patient population has ocular symptoms.[6]

Studies have shown that certain factors have a tendency of increasing the patient's risk for retinopathy, which include: age,[6] hypertension,[1,6,23] diabetes,[6,23] dislipidemia and hypercoagulable states.[23] Resolution of retinopathy is thought to be delayed in patients with these factors after ending treatment.[6]

The exact mechanism of PEG-IFN retinopathy is unknown; however there are a few studies that may have some validity. It is generally accepted that cotton-wool spots are formed by obstruction of axoplasmic flow secondary to ischemia of the retinal vasculature. Retinal blood flow and wall shear rate have been shown to increase with PEG-IFN, which points at the possible blood vessel endothelial dysfunction as a possible reason for retinopathy.[24] Retinopathy could also be due to a disrupted retinal microcirculation, as proven through capillary nonperfused areas in patients with PEG-IFN retinopathy who have undergone fluorescein angiography as well as other retinal indicators of ischemic changes.[24]

## Conclusion

Pegylated-interferon alpha-2B/ribavirin combination treatment is generally very effective for chronic HCV. Its ocular side effects and signs are very similar to those for HCV.[8] The difference can be made through laboratory testing results and knowledge of the patient undergoing treatment. It is important for patients to receive co-management between their hepatologist and eye care provider to monitor for any ocular changes. The ultimate goal of treatment is to significantly reduce the HCV, which essentially eliminates the end-stage possibility of hepatocellular carcinoma or liver transplant.[19] This must be accomplished without putting other body organs at

risk, in this case the eyes, by preventing irreversible ocular damage. This Case Report shows an example of co-management between a hepatologist and an eye doctor to provide maximum hepatic treatment without causing ocular devastation. To the best of our knowledge, this is the first reported HCV patient with idiopathic retinopathy to be documented outside Japan.

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