INTRODUCTION

Hepatitis C is a significant public health problem in Egypt where the highest prevalence (14.7%) of hepatitis C virus (HCV) exists **(Mousa, 2014).**

Egypt has higher rates of HCV than neighboring countries as well as other countries in the world with comparable socioeconomic conditions and hygienic standards for invasive medical, dental, or paramedical procedures. The strong homogeneity of HCV subtypes found in Egypt suggests an epidemic spread of HCV. Since a history of injection treatment has been implicated as a risk factor for HCV, a prime candidate to explain the high prevalence of HCV in Egypt is the past practice of parenteral therapy for schistosomiasis **(Lavanchy and McMahon, 2000).**

Clinical studies showed 70% to 90% of patients with chronic hepatitis, cirrhosis, or hepatocellular carcinoma had HCV infections **(Abdelwahab et al., 2013).**

Hepatitis C is treated with Interferon (IFN-α), often in combination with other antiviral drugs. Some of those treated with interferon have a sustained virological response and can eliminate hepatitis virus. The most harmful strain - hepatitis C genotype 1 virus - can only be treated around 50% of time by the standard of care treatment of interferon-α/ribavirin **(Ge et al., 2009).**

Combination therapy results in better treatment responses than monotherapy; the highest response rates have been achieved with pegylated interferon in combination with ribavirin **(Patrick, 1999).**

The rationales for treatment of chronic hepatitis are to reduce inflammation, to prevent progression to fibrosis, cirrhosis, and hepatocellular carcinoma {HCC} through the eradication of the virus in chronically infected patients, and to decrease infectivity and control the spread of the disease **(World Health Organization, 1999).**

After giving the treatment, biopsies show reductions in liver damage and cirrhosis. Control of chronic hepatitis C by interferon {IFN} is also associated with reduced hepatocellular carcinoma **(Ishikawa, 2008).**

A wide array of adverse effects of alpha interferon has been described. Several side effects such as fever, headache fatigue, arthralgias, and myalgias are common, especially with the initial injections. These early side effects of interferon are predictable and are encountered in the majority of patient **(Dusheiko, 1997).**

Many reports have discussed the ocular complications associated with interferon use as an antiviral or antiangiogenic agent. Ikebe first reported this condition in a 39-year-old gentleman who developed retinopathy after administration of intravenous interferon **(Ikebe et al. 1990).**

The incidence of retinopathy reported for patients undergoing interferon therapy for hepatitis viruses varies from 18-86% in different studies **(Hayasaka et al., 1998).**

Interferon-associated retinopathy often presents with cotton wool spots, retinal hemorrhages and other retinal microvascular irregularities **(Esmaeli et al., 2001).**

Several other atypical interferon-associated ocular complications reported, are neovascular glaucoma, periphlebitis, occulomotor nerve paralysis; optic disc edema; cystoid macular edema; subconjunctival, preretinal, vitreous hemorrhage; retinal vein occlusion and panophthalmitis **(Hayasaka et al., 1998).**

The exact pathophysiological mechanism due to which retinopathy develops is unknown. Similarities with some characteristics of diabetic and hypertensive retinopathy suggest an ischemic mechanism **(Cuthbertson et al., 2004).**

Other authors suggest that immune complex deposits in the vessels lead to retinal capillary perfusion failure and the formation of cotton wool spots **(Andrade et al., 2006).**

Risk factors for the development of interferon-associated retinopathy probably include age, diabetes mellitus, arterial hypertension, thrombocytopenia and hyper-trigyceridemia. Pretreatment evaluation and close monitoring are recommended, especially in patients with arterial

hypertension and/or diabetes mellitus **(d''Alteroche et al., 2006).**

Although it is assumed that fundus examination is most useful for determining the presence of cotton wool spots or retinal hemorrhages and perimetry for identifying and monitoring any visual field losses. **Schulman et al. (2003)** suggest the use of the focal electroretinogram (ERG) or the Humphrey visual field testing as more sensitive methods of testing for occult ischemic retinal damage.

The conventional ERG has been used to monitor the effects of systemically administered drugs on retinal nerve function in a number of conditions **(Scholl and Zrenner 2000 and Kuchenbeker et al., 2001).**

Electrophysiological studies (ERG and VEP) have previously been employed to study the impact of interferon on visual function in chronic hepatitis patients undergoing interferon therapy **(Manesis et al., 1998).**

Multiple logistic regression analysis showed that changes in wall shear rate (WSR) and patient age were independent risk factors for the development of IFN-induced retinopathy. A clinical study using visual-evoked responses and electroretinograms showed that patient age was associated with increased risk for subclinical neuro-visual impairment **(Manesis et al., 1998).**

More recently, the multifocal electroretinogram (mfERG) has been used to identify and monitor retinal pathology induced by vigabatrin therapy for epilepsy and to identify patients at risk from hydroxychloroquine retinal toxicity. The advantage of the mfERG is that it can differentiate localized from diffuse retinal damage **(Harding et al., 2000, McDonagh et al., 2003 and Penrose et al., 2003).**

AIM OF THE WORK

The aim of this study is to assess retinal function in patients being treated with pegylated interferon and ribavirin for chronic hepatitis C.

I. HEPATITIS C

Hepatitis is the Latin term for liver inflammation. Viral and toxic agents are the most common causes of hepatitis. Hepatitis is deemed chronic when present longer than 6 months **(Miriam and Harold, 1998).**

The World Health Organization has declared hepatitis C a global health problem, with approximately 3% of the world population (roughly 170-200 million people) infected with HCV. In the United States (US), approximately 3 million people are chronically infected, many of whom are still undiagnosed **(Mohamed, 2004).**

In Egypt the condition is quiet worse. The population in Egypt in 2009 was about 80 million. 14.7% of this population (0.147 X 80 million) is 11,760,000 persons who have been infected with this virus. This number is an underestimate because it does not include the number of people who have been infected that are under 15 years of age or over 60 years of age **(El-Zanaty et al., 2009).**

The histological hallmarks of hepatitis are hepatic necrosis and mononuclear infiltration. These parameters are assessed with liver biopsy. Specimens are graded according to portal and lobular inflammatory activity and are staged based on the degree of fibrosis or the presence of cirrhosis **(Saleem et al., 2004).**

Cirrhosis is the final stage of the fibrotic process with diffuse hepatocyte damage, nodular regeneration and extensive fibrosis with aberrant architecture accompanied by impaired hepatocyte function and impeded portal blood flow **(El-serag, 2002).**

Each year, 1% to 4% of people with HCV-related cirrhosis develop liver cancer **(El-serag, 2002).**

Previous research has suggested that the Egyptian HCV epidemic results from the use of unsterile injection equipment during mass treatment of the general population with parenteral anti-schistosomal therapy {PAT} **(Frank et al., 2000).**

There is a correlation between the level of exposure to parenteral anti-schistosomal therapy {PAT} and HCV prevalence among different age groups and geographic regions **(Habib et al., 2001).**

Jaundice occurs in 10% to 20% of patients with acute HCV infection, whereas 20% to 30% present with nonspecific symptoms such as fatigue, nausea, and vomiting **(Villano et al., 1999).**

HCV infection is self-limited in 10% to 50% of patients, in whom HCV RNA clears and serum alanine transaminase {ALT} levels normalize **(Villano et al., 1999).**

The rate of viral persistence varies, ranging from a low of 40% to 50% to a high of 90% to 100%, depending on factors

such as the patient age and gender; source of infection and size of inoculum; immune status of the host; and the patient's race **(Lehmann et al., 2004).**

Patients with chronic hepatitis C infection are most likely to complain of fatigue, although many patients are asymptomatic. Other frequent manifestations include arthralgia, paraesthesia, myalgia, and pruritus and sicca syndrome. Nonspecific symptoms include depression, nausea, anorexia, abdominal discomfort, and difficulty with concentration. The severity of these symptoms is not necessarily related to the severity of the underlying liver disease **(Fontana and Kronfol, 2004).**

In early 2009, the combined use of peg interferon-α and ribavirin still represents the standard of care for treatment of HCV infection **(Ghany et al., 2009).**

The primary aim of treatment is to prevent complications of chronic hepatitis C by eradication of infection. Treatment can permanently eradicate HCV infection such that hepatitis c virus ribonucleic acid {HCV RNA} is no longer detectable in blood or liver, titers of antibodies to HCV decline, and HCV-related liver pathology remits or improves **(Lau et al., 1998).**

II. INTERFERON AND RIBAVIRIN

1. Interferon:

Interferons (IFNs) are proteins made and released by the cells of most vertebrates in response to the presence of pathogens such as viruses, bacteria, parasites or tumor cells **(Liu, 2005).**

Types of interferon:

Based on the type of receptor through which they signal, human interferons have been classified into three major types:

I. Interferon type I:

All type I IFNs bind to a specific cell surface receptor complex known as the IFN-α receptor (IFNAR) that consists of IFNAR1 and IFNAR2 chains. The type I interferons present in humans are IFN-α, IFN-β and IFN-ω **(Liu, 2005).**

II. Interferon type II:

Binds to interferon-gamma receptor IFNGR. In humans this is IFN-γ **(Vilcek, 2003).**

III. Interferon type III:

Signal through a receptor complex consisting of Interleukin-10 receptor 2{IL10R2} (also called Cytokine Receptor Family 2 member4 **{**CRF2-4}) and IFNLR1 (also called

CRF2-12). Acceptance of this classification is less universal than that of type I and type II, and unlike the other two, it is not currently included in Medical Subject Headings **(Vilcek, 2003).**

Function:

All interferons share several common effects; they are antiviral agents and can fight tumors **(Fensterl and Sen, 2009).**

As an infected cell dies from a cytolytic virus, viral particles are released that can infect nearby cells. However, the infected cell can warn neighboring cells of a viral presence by releasing interferon **(Fensterl and Sen, 2009).**

The neighboring cells, in response to interferon, produce large amounts of an enzyme known as protein kinase R (PKR). This enzyme phosphorylates a protein known as eIF-2 in response to new viral infections; eIF-2 is a eukaryotic translation initiation factor that forms an inactive complex with another protein, called eIF2B, to reduce protein synthesis within the cell **(Fensterl and Sen, 2009).**

Another cellular enzyme, ribonuclease L {RNAse L}, also induced following protein kinase receptor {PKR} activation destroys RNA within the cells to further reduce protein synthesis of both viral and host genes. Inhibited protein synthesis destroys both the virus and infected host cells. In addition, interferons induce production of hundreds of other proteins; known collectively as interferon-stimulated genes

(ISGs) that have roles in combating viruses **(Fensterl and Sen, 2009).**

They also limit viral spread by increasing p53 activity, which kills virus-infected cells by promoting apoptosis **(Moiseeva et al., 2006).**

Interferon and hepatitis:

Both hepatitis B and hepatitis C are treated with IFN-α, often in combination with other antiviral drugs **(Shepherd et al., 2000).**

Some of those cases treated with interferon have a sustained virological response and can eliminate hepatitis virus. The most harmful strain - hepatitis C genotype I virus - can only be treated around 50% of time by the standard of care treatment of interferon-α/ribavirin **(Ge et al., 2009).**

After the treatment, biopsies show reductions in liver damage and cirrhosis. Some evidence shows giving interferon immediately following infection can prevent chronic hepatitis C, although diagnosis early in infection is difficult since physical symptoms are sparse in early hepatitis C infection. Control of chronic hepatitis C by IFN is associated with reduced hepatocellular carcinoma **(Ishikawa, 2008).**

Side Effects of interferon:

Side effects of treatment, however, are essentially universal. These led to modification of the dosage of interferon in 35-42% of patients treated with pegylated interferon in large, randomized clinical trials and discontinuation of therapy in 14-19% of these patients **(Manns et al., 2001).**

These side effects are usually fatigue, headache, fever myalgia, nausea, anorexia, diarrhea, insomnia, irritability, depression, hair loss, skin rash and dyspnea **(Manns et al., 2001, Fried et al., 2002 and Hauser, 2004).**

2. Ribavirin:

Ribavirin (1-beta-D-ribofuranosyl-1, 2, 4-triazole-3-carboxamide) is a synthetic guanosine analog with antiviral activity. It was originally synthesized in the 1970s and has been shown to be active against many DNA and RNA viruses **(Strader et al., 2004).**

Ribavirin mono-therapy is not effective in the treatment of chronic hepatitis C; however, in combination with interferon alfa, it has activity against this disease. Use of peg-interferon alfa with ribavirin is recommended in consensus guidelines for the treatment of chronic hepatitis C; the treatment goal is attainment of a sustained virologic response, which is defined as the achievement of undetectable HCV-RNA at the end of treatment and 24 weeks later **(Strader et al., 2004).**

III. OCULAR COMPLICATIONS OF INTERFERON

(A) Retinopathy:

The ocular manifestations of HCV infections best supported by the literature include a dry eye syndrome similar to Sjögren syndrome, and ischemic retinopathy caused by either an HCV-induced vasculitis or treatment with interferon **(Zegans et al., 2001).**

Interferon-induced changes include retinal hemorrhages, cotton wool spots, loss of color vision, cataracts, glaucoma, and occasionally retinal artery or vein occlusion. Although the incidence of ophthalmological disorders while on interferon therapy is low, this can result in loss of vision **(Saito et al., 2001).**

The postulated underlying mechanisms include vascular occlusion by micro-emboli formed from immune complexes tagged with complement **(Myers et al., 2001**) or an association with hypercoagulable states **(Viloi et al., 1995).**

It has also been reported that IFN-increased leukocyte adherence to the vascular endothelium and subsequent leukocyte trapping in the rat retinal microcirculation, suggesting that the impaired retinal circulation may be associated with IFN-induced retinopathy **(Nishiwaki et al., 1996).**

After leukocyte adherence to vascular endothelial cells, highly toxic substances such as oxygen-derived free radicals and proteolytic enzymes are produced by leukocytes and endothelial cells. Subsequently, these toxic substances cause vascular damage and adjacent tissue injury **(Tauber and Babior, 1985).**

Cotton wool spots are believed to develop secondary to obstruction of a retinal arteriole and resultant retinal ischemia. This focal hypoxia leads to a blockage of axoplasmic flow within the nerve fiber layer of the retina with the subsequent deposition of intra-axonal organelles **(Brown, 1994).**

Reported risk factors for interferon retinopathy include hypertension, diabetes mellitus, high interferon dosages, ribavirin, and pegylated interferon. Both hypertension and diabetes disrupt retinal microcirculation **(Okuse et al., 2006).**

Therefore, preexisting arteriosclerosis that affects microcirculation may promote interferon-induced retinopathy. Chronic hypertension is associated with the thickening of the walls of the arteries and small arterioles **(Sharrett et al., 1999).**

Retinopathy occurs between 2 weeks and 5 months from the beginning of treatment, but most frequently between 4 and 12 weeks, and is seen in 18–86% of patients **(Jain et al., 2001).**

From prospective observational studies, it is recognized that the incidence of visual symptoms is very low compared