INTERFERON RELATED OPHTHALMIC COMPLICATIONS IN PATIENTS OF HEPATITIS C

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ABSTRACT

Objectives: To determine the frequency of ophthalmic complications of interferon-α 2b and ribavirin combination therapy in patients of chronic hepatitis C.

Study Design: Quasi experimental study.

Place and Duration of the Study: Eye and Medical Department of Military Hospital Rawalpindi and Combined Military Hospital Peshawar, Pakistan from Jan 2010 to Jan 2011.

Patients and Methods: A total of 93 diagnosed and consenting cases of hepatitis C were recruited who were eligible for interferon therapy. They were administered 3 million units (mu) interferon (INF)-α 2b, subcutaneously thrice a week along with 800 mg of ribavirin orally daily for 6 months. Ocular examination of all the patients was performed before starting interferon and then monthly afterwards till the completion of interferon therapy. Their ocular complications were observed and recorded.

Results: The study included 54 (58%) males and 39 (42%) females. Mean age of the patients was 40.59 ± 8.68 years. Ocular complications developed in 24 (25.8%) out of 93 patients. Retinal microaneurysms were present in 5 (5.4%), cotton wool spots in 10 (10.8%), retinal haemorrhages in 8 (8.6%) and optic disc hyperaemia in 1 (1.1%) patient. These complications developed within 8-12 weeks after start of INF therapy.

Conclusion: Interferon alpha-2b and ribavirin combination therapy is characterized by its ophthalmic complications which are usually benign and self limiting. In our study, ocular complications which include retinal microaneurysms, cotton wool spots, retinal haemorrhages and optic disc hyperaemia developed in 25.8% of patients. In two third of these cases, these complications resolved before completion of INF therapy.

Keywords: Cotton wool spots, Interferon, Retinal haemorrhages, Ribavirin.

INTRODUCTION

Chronic hepatitis C is a tremendous health problem not only in Pakistan but also worldwide[1]. For patients of HCV infection, interferon-ribavirin combination therapy is advocated as a first-line treatment. A combination of 3-9 x 10^6 units of INF-alpha, given subcutaneously 3 times a week and 800-1200 mg of ribavirin given orally daily, for 6 months is usually administered in order to treat HCV infection[2]. But this therapy is not devoid of its complications. The commonest of these is an influenza-like syndrome characterized by fever, chills, arthralgias, myalgias and headache. Ocular complications of variable pathology and severity have also been reported in association with interferon-ribavirin combination therapy. Most of these side effects are benign, transient and are mainly represented by the INF-related retinopathy which is characterized by cotton wool spots and retinal haemorrhages especially around the optic nerve[3,4]. Other ophthalmic complications of INF-α and ribavirin therapy include transient blurred vision, increased intraocular pressure, inflammatory disorders like Vogt-Koyanagi-Harada like disease, subconjunctival haemorrhage[5], optic neuropathy[6], optic disc hyperaemia and oculomotor nerve palsy. Although visual loss is usually absent or limited but sometimes severe ocular complications occur like ischemic optic neuritis[7,8], occlusion of central or branched retinal vessels[9], Vogt-Koyanagi-Harada like disease, aggravation of diabetic and hypertensive retinopathy, panophthalmitis, vitreous and pre retinal haemorrhage. Old age,

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diabetes mellitus, hypertension, decreased platelet count and increased triglyceride levels are recognized risk factors for the development and progression of INF related retinopathy. The frequency of these complications is variable which is presumably attributed to the difference in the treatment regimen (dose and duration) and/or presence of co-morbid conditions. The frequency of interferon-ribavirin therapy related ocular complications is 16-64%[3]. However this value is quite variable and is published differently in different clinical settings and population groups.

While managing patients of hepatitis C and administering interferon, these ophthalmic complications are generally overlooked and very little clinical work has been done to document them in Pakistan. Therefore this study was carried out to determine the frequency of INF alpha-2b and ribavirin combination therapy related ophthalmic complications in patients of hepatitis C. This aspect merits even more attention in the presence of other co-morbid conditions like diabetes mellitus, hypertension and dyslipidemia.

PATIENTS AND METHODS

This quasi experimental study was carried out from Jan 2010 to Jan 2011 in the Eye and Medical Departments of Military Hospital Rawalpindi and Combined Military Hospital Peshawar. Diagnosed cases of chronic hepatitis C, whom medical specialist had prescribed interferon alpha-2b and ribavirin combination therapy, were selected by "non probability consecutive sampling" technique from medical OPD and ward. All the patients were between 20 to 60 years of age. Patients with past medical history or record of ocular trauma or surgery were excluded from the study. Visual acuity and detailed anterior and posterior segment examination of both eyes of these patients was carried out prior to the initiation of INF therapy and patients depicting any evidence of retinopathy, retinal dystrophies or optic neuropathy were also excluded from the study. A total of 93 patients, who were fulfilling the criteria, were registered for the study. Selected patients were admitted in the medical ward for the administration of each dose of interferon. Interferon alpha $3x10^6$ units, was administered subcutaneously three times a week by the medical specialist. As an adjunct, 800 mg ribavirin was also given orally daily. This combination therapy was continued for 6 months. Ophthalmic examination of these selected cases was performed in eye OPD monthly. Results of the study were analyzed by using computer software SPSS version 10.

Table-1: Frequency and percentage of co-morbid conditions.

Co-morbid conditions	n (%)
Diabetes mellitus (DM)	4 (4.3)
Hypertension (HTN)	8 (8.6)
DM & HTN	4 (4.3)
No co-morbid conditions	77

Table-2: Ocular complications 3 and 6 months after start of INF.

Ocular complications	Frequency	
	After three months	After six months
Retinal microaneurysms	5 (5.4%)	2 (2.2%)
Cotton wool spots	10 (10.8%)	3 (3.2%)
Retinal haemorrhages	8 (8.6%)	1 (1.1%)
Optic disc hyperaemia	1 (1.1%)	-

RESULTS

A total of 93 patients from 26 to 57 years of age were included in this study. Mean age of the patients was 40.59 ± 8.68 years. There were 54 (58%) males and 39 (42%) females. Mean age of males was 39.50 ± 8.47 years. Mean age of females was 42.10 ± 8.84 years. Frequency and percentage of patients with co-morbid conditions is shown in table-1. Three months after start of interferon therapy ophthalmic complications developed in 24 (25.8%) patients. Retinal microaneurysms were present in 5 (5.4%), cotton wool spots in 10

(10.8%), retinal haemorrhages in 8 (8.6%) and optic disc hyperaemia in 1 (1.1%) patient (table-2). But on completion of six months INF therapy, only 6 out of 24 (25%) patients were showing ophthalmic complications. Retinal micro-aneurysms were present in 2 (2.2%), cotton wool spots in 3 (3.2%) and retinal haemorrhages in 1 (1.1%) patient (table-2). No patient showed retinal vein occlusion, optic disc hyperaemia and oedema. Visual acuity of all the patients remained unaffected throughout the course of treatment.

DISCUSSION

Interferon alpha and ribavirin combination therapy is commonly used to treat chronic hepatitis C. But this therapy is not devoid of its side effects and affects hematopoietic, central nervous, gastrointestinal, urinary, cardiovascular, musculoskeletal and endocrine systems[2]. Its ophthalmic complications also need attention because few of them are sight threatening. The most common of interferon associated ophthalmic complications is retinopathy characterized by retinal microaneurysms, cotton wool spots and retinal haemorrhages[3]. Others include inflammatory disorders like optic neuropathy[6], optic disc hyperaemia, optic disc oedema, subconjunctival haemorrhage[5] and retinal vein occlusion[9]. Most of these ocular side effects are benign, transient and resolve by the end of treatment; however sometimes these persist for longer periods of time. In 1990, Ikebe and associates first reported a 39 year old patient with retinal haemorrhages and cotton wool spots following the administration of interferon[4]. These complications usually develop within three months following the start of treatment but these may occur even afterwards. The exact pathogenesis of INF related ocular complications is not well established. However, some proposed mechanisms include immune system dysfunction, deposition of immune complexes in the retinal vessels and increased adhesions of activated leukocytes to vascular walls[10].

Frequency of INF-ribavirin related ocular complications is published differently in various studies and there are wide variations due to different reasons. Dose and duration of interferon and ribavirin are directly proportional to frequency of ophthalmic complications. Secondly, presence of co-existing diseases like diabetes mellitus, hypertension and old age also enhance chances of developing these complications[11]. Okuse et al[12] reported that 19% of his patients on INF therapy developed retinopathy which was initially diagnosed by the presence of cotton wool spots in 16.4% of patients. Takikawa et al[13] reported this frequency as 18%, Chen et al[14] as 35.5%, Isaka et al[15] as 40%, Saida et al[16] as 40%, Kishinomoto et al[17] as 42%, Chuman et al[18] as 46%, Takamine et al[19] as 50%, Futami et al[20] as 61%, Abe et al[21] as 73.3% and Soushi et al[22] reported it as 86%. Gonçalves et al[23] and Fried[24] reported this frequency as low as less than 1%. In this study, ophthalmic complications developed in 24/93 (25.8%) patients. Out of these complications, retinal microaneurysms were present in 5 (5.4%), cotton wool spots in 10 (10.8%), retinal haemorrhages in 8 (8.6%) and optic disc hyperaemia in 1 (1.1%) patient. The frequency is comparatively less in this study. This is probably because patients in this study were relatively young (mean age 40.59 + 8.68). The most frequent age encountered in the study was 39 years. It supports this evidence that old age is a risk factor for INF related retinopathy. Another reason for lesser frequency of ocular complications is 82.8% of patients in our study were having no systemic risk factor like diabetes mellitus or hypertension.

In this study, retinopathy developed in first 3 months following the start of treatment and so in this aspect its results are similar to these of Cuthbertson et al[6] and Hayasaka et al[5]. On completion of six months INF therapy, only 6 out of 24 (25%) patients in this study were showing ophthalmic complications whereas in the rest, the complications had resolved. This finding is strongly supported by the results of Cuthbertson et al and Okuse et al. However some studies have

reported vision threatening complications occurring secondary to INF therapy. Sene et al[3] reported occurrence of Vogt-Koyanagi-Harada (VKH) like disease, central retinal vein occlusion, central retinal artery occlusion and bilateral ischemic optic neuropathy in patients receiving INF. Similar results are also reported by Bazarah et al[25] and Tu et al[26]. Khan et al[27] reported optic disc hyperaemia and optic neuritis secondary to INF therapy. However, there is a need that further studies on a larger scale should be performed in different clinical settings. More work should be done to determine pathogenesis of INF related retinopathy and its co-relation with other co-morbid conditions. Gender predisposition should also be explored.

CONCLUSION

Interferon alpha-2b and ribavirin combination therapy is characterized by its ophthalmic complications like retinal cotton wool spots, haemorrhages and microaneurysms. These ophthalmic complications are usually benign, self limiting and appear within 8-12 weeks following the start of treatment. In most of the patients, these complications resolve within 10-12 weeks. But sometimes these may persist even after completion of the six months INF therapy.

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