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COMPARISON OF OPHTHALMOLOGICAL COMPLICATIONS OF ANTIVIRAL DRUGS FOR HCV INFECTION

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ABSTRACT
Purpose Of the Study.The study was conducted to compare the ophthalmological complications of Pegelated interferon, ribavirin combination with recently approved direct acting oral anti viral drugs sofosbuvir and daclatasvir. Material And Methods. 120 patients of HCV selected for the study were divided into four Groups .Group A (50) received pegelated interferon alpha (INF) and ribaveriin (RBV) for 24 weeks,Group B (25) INF,RBV and sofosbuvir (SOF) for 12weeks Group C (25) SOF and RBV for 24 weeks and Group D (20) SOF and Daclatasvir for 12 weeks. Retinal examination was done at baseline, 4,8,12 and 24 weeks during treatment and 4 weeks after completion of treatment. Results: Fifteen patients developed retinopathy in the form of cotton wool spots and hemorrhages, 12 in Group A,3 in Group B and none in Group C and D. Despite retinopathy treatment was completed and BCVA of 6/6 was maintained in all except in two patients ,one each in Group A and Group B. They lost vision due to cystoid macular edema and treatment was discontinued. One lost to followup and other recovered 6/6 vision. Conclusions: Retinopathy was detected only in those HCV patients who were taking INF as part of their treatment. With newer combinations tolerability and compliance has increased .Effective and safe treatment of all genotypes of HCV with interferon free, SOF based oral regimens is now becoming a reality and we can look forward to total eradication of HCV infection.

KEYWORDS: Hepatitis, Interferon, Ribavirin, Retinopathy.

INTRODUCTION
Hepatitis C viral (HCV) infection is prevalent globally and posses a serious worldwide health problem. It was first identified in 1989 as a major cause of chronic liver disease.[1] Nearly 3% of world's population (170 million) infected with HCV[2] if not treated can progress to cirrhosis and 20% of them are at risk of developing hepatocellular carcinoma.[3] The treatment of HCV has evolved over the past 20 years. It began with Interferon alpha (IFNα) alone but was soon combined with oral ribavirin (RBV). With it the rate of viral clearance increased by 2-3 times but due to inconvenience of three injections in a week and higher relapse rate this regime was subsequently replaced by pegylated interferon (Peg INF) and RBV. This not only increased the viral clearance but also decreased the frequency of dosing of interferon to once weekly injections. Most recently direct-acting antivirals (DAAs) have promised to open a new era in treating chronic HCV infection by providing shortened and simplified regimens,minimizing treatment related side effects and increasing SVR(sustained viral response) rates .First direct-acting antivirals boceprevir or telaprevir, were tried for Genotype 1 in 2011 but they were also soon discontinued due to their side effects.[4]

Sofosbuvir (SOF) (GS-7977), another recently approved nucleotide analog, a highly potent inhibitor of the NS5B polymerase in the Hepatitis C virus (HCV) is an oral drug .It has a pan-genotypic effect on HCV. It has shown high efficacy in combination with several other oral drugs with or without PEG-INF against HCV.[5] It is given with RBV for 24 weeks or with interferon and RBV for 12 weeks or with oral daclatasvir for 12weeks.

Interferon whether pegylated or not, can lead to a wide range of side effects including influenza like syndrome, central nervous, gastrointestinal, cardiovascular, endocrine, urinary and musculoskeletal system.[6] First ophthalmological complication was reported by Ikebe et al in 1990 in a 39 year old patient who developed retinal hemorrhages and cotton wool spots[7] Since then various ophthalmological adverse effects have been reported with the use of IFN but the most commonly documented ocular complication is retinopathy in the form of cotton wool spots and/ or retinal hemorrhages with or without

macular edema. Incidence of retinopathy is highly variable and may vary anything between 3% to 86% Interferon-associated retinopathy usually presents most notably around the optic nerve head and in the posterior pole .Most the time there is no visual impairment and patient remains asymptomatic but there can be severe visual impairment if it involves the macula. Retinopathy may develop as early as by 4-12 weeks after the start of treatment and disappear in about 4 weeks during the course of therapy[8-18]

Less than 1% of patients[20] receiving this treatment experience very uncommon ophthalmological side effects such as BRVO[15,19,21] ischemic optic neuropathy[22], neovascular glaucoma[23], B/L CRVO[24] cystoid macular edema,[25] sub conjunctival hemorrhage[8], transient visual loss[26] or pan ophthalmitis[27]

Diabetes mellitus[8,16,18,28] hypertension[6,16,18,28] which compromise the micro circulation are considered to be the possible risk factor for the development of retinopathy. Lesser significant risk factors include age of the patient[16] ESR, platelet count ,erythrocyte count,raised triglycerides AND total cholesterol.

With recent advances , the development and use of more effective and safer DAA like SOF and daclatasvir may help to eradicate HCV infection in near future .The only side effects reported in literature are headache, nausea, fatigue, dizziness insomnia and pruritis.[29-32]

Most of the patients on INF had no visual symptoms but had INF related retinopathy.None of the study mentions ophthalmological examination of patients on oral DDAs with or without interferon .Present study was taken up for detailed retinal examination of patients on oral drugs and comparing them with those on INF.

MATERIAL AND METHODS

After taking written informed consent, 120 patients (71males and 49 female) with mean age of 43 +/- 18 years of chronic HCV attending out patient department of Medicine in Government medical college, Amritsar between April 2015 and March 2016 were recruited in the study. In addition to the medical and laboratory examination, all patients were subjected to detailed retinal examination to evaluate the presence of retinopathy associated with drugs used for the treatment of HCV.

Patients were divided into four groups depending upon the drug administered for the treatment. Group A received Peg INF and RBV for 24weeks, Group B SOF, Peg INF and RBV for 12 weeks and Group C SOF and RBV for 24weeks and Group D SOF and Daclatasvir for 12 weeks for the treatment of chronic HCV. Pegylated interferon α-2a at a dose of 180 mcg was injected subcutaneously once weekly RBV was given twice orally 800–1200 mg/day according to the body weight, SOF 400mg tablet and daclatasvir 60mg tab were given orally per day.

Detailed history for any diminution of vision, any ocular disease or surgery of all enrolled patients of chronic HCV on treatment was taken. Their complete ophthalmological exam including comprehensive slit lamp examination, best corrected visual acuity, intra ocular pressure using Goldmann's applanation tonometer and fundus exam by slit lamp bimicroscopy using+90D lens and indirect ophthalmoscope after dilation of pupil with a combination of 1%tropicamide and 2.5% phenylephrine eye drops was done at baseline, 4,8,12 and 24 weeks of treatment .It was repeated 4 weeks after completion of therapy.

After complete medical examination ,laboratory investigations including polymerase chain reaction (PCR) for hepatitis C virus RNA, full blood count, fasting blood sugar,prothrombin time,serum glutamic oxaloacetic transaminase SGOT, serum glutamic pyruvic transaminase SGPT, blood urea and serum creatinine were recorded. Ocular fundus photograph and Optical coherence tomography (OCT) was done wherever indicated

Inclusion criteria was seropositivity for anti-HCV antibodies determined using ELISA
Patients (1) with history of co infection with human immunodeficiency virus or hepatitis B (2) with any other chronic liver disease (3) with renal failure (4) with any cardiovascular disease like IHD,CHF (5) with dense cataract, glaucoma or any preexisting retinopathy were excluded from the study.

RESULTS

The patients of mean age 43 ±18 (71 males and 49 females) had baseline BCVA of 6/6 and no retinopathy.All patients except for two, one each in Group A and group B maintained BCV OF 6/6 during the course of treatment. One of the affected patient in Group A had sudden painless loss of vision in both the eye after 6 weeks of treatment. This 72 years old male patient who was non diabetic but hypertensive developed cystoid macular edema (CME).Treatment was discontinued but he later lost to follow up. Visual acuity in the second affected patient in Group B fell to 6/24 in right eye after 6 injections due to CME. This male patient was 50 years old, diabetic as well as hypertensive. Treatment was discontinued and he regained his vision of 6/6 4 weeks after cessation of therapy.

Table 1 Demographic profile of patients on treatment for HCV infection

Groups	number of patients	Males	Females	Age	diabetic M/F	hypertensive	Duration of treatment
Group 1	50	32	18	43± 25	8/12	10/6	24 weeks
Group 2	25	15	10	42± 27	3/5	6/4	12 weeks
Group 3	25	14	11	45± 24	3/3	5/2	24 weeks
Group 4	20	10	10	49± 26	3/2	4/3	12 weeks
Total	120	71	49	43±18	17/22	25/15	

Total of 15 patients (12.5%) developed retinopathy, 12 in group A and 3 in group B and none in group C and Group D Table 1. Cotton wool spots were first to appear and were present in all the 15 patients, retinal hemorrhages were present in 13 patients. Table 2 All changes were limited to posterior pole around the disc. Cystoid macular edema was seen in two patients. Other side effects in patients included fatigue, headache and nausea, hair fall, seizures, myxoedema, influenza like symptoms of varying severity. They were more marked in Group A followed by Group B, Group C and least in Group D.

Table 2 Side effects with anti viral drugs against HCV infection

	Number of patientsn	retinopathy	fatigue, headache, insomnia,	Myxoedema	seizures	Hair fall	treatment stoppedn
Group 1	50	12(24%)	45	1	1	29	1
Group 2	25	3(12%)	21	0	0	10	1
Group 3	25	0(0%)	15	0	0	0	0
Group 4	20	0(0%)	2	0	0	0	0
Total	120	15(12.5%)	83	1	1	39	2

Table 3 Correlation of retinopathy with age, diabetes and hypertension

	retinopathy (n)	B/L - U/L	Mean age	Haemorrhage	Cotton wool spots	severe retinopathy	Diabetic	hypertensive	Both diabetic and hypertensive
Group 1	12	12/0	57±4	10	12	1	4	5	4
Group 2	3	2/1	60±2	3	3	1	3	3	3

Out of 120 patients , 39 patients had diabetes out of which 20 were in Group A ,8 in group B, 6 in Group C and 5 in group D .40 patients were hypertensive 16 were in group A, 10 in Group B,7 in Group C and 7 in Group D. None of these patients had any retinopathy at the baseline or 4 weeks after the cessation of therapy.

Retinopathy disappeared spontaneously in 10 patients (77%) despite continuation of full dose of therapy and even before the completion of therapy and in 3 patients (23%) in which it persisted disappeared during one month follow up.

DISCUSSION

Interferon-associated retinopathy (IAR) is well established. It was first recognized in 1990 when Ikebe et al reported a 39-year-old patient who developed retinal hemorrhages and cotton wool spots following intravenous administration of INF. Exact pathogenesis of retinopathy is not very well understood. Probable mechanism is the possibility of disturbance of microcirculation[6,33,34] Hepatitis C virus (HCV) induced vasculitis may augment ischemic retinopathy due to interferon.[35] IAR may also be triggered by microangiopathy of diabetes mellitus and arteriosclerosis in hypertension[6,13] Guyer et al. suggested that immune-complex deposition and leucocyte infiltration in the retinal vasculature would lead to ischemic episodes[36] Earlier studies have shown that the increase in plasma complement levels and plasma aggregation would cause capillary occlusion to facilitate ischemic alterations of retinopathy.[37]

Incidence of retinopathy is highly variable ranging between 16%-86%.[8-18] In our study the incidence of retinopathy in patients on treatment for HCV was 12.5%. It was highest in Group A (24%) followed by group B (12%) and then group C and D where none of the patient had retinopathy.

In a study conducted in Turkey, retinopathy was detected in only 1 (2.32%) patient out of 43 at the end of the treatment.[38] The fact that this was below the percentage shown in the literature could be due to the fact that the average age of the study subjects was 42.1, and systemic diseases such as hypertension or diabetes mellitus are less common in this age group, and hence the risk for retinopathy is decreased.Cuthbertson et al. reported evidence of retinopathy in16% after 3 months of treatment with PEG-IFN alfa and RBV. None had visual symptoms. Changes disappeared in all patients without any dosage alteration[12] Mousa et al. concluded that 8

patients (8.16%) out of 98 patients with HCV who underwent combination therapy of PEG-IFN alfa and RBV developed retinopathy.[28] Kim et al observed retinopathy in 34.4%[13] and Vujosevic S et al in 30.9% patients[19] of hepatitis C on Peg IFN and RBV. Kwano et al found retinal IAR in 36 (57.1%) of 63 patients, including retinal hemorrhage in 25 patients and cotton-wool spots in 28 patients.[39]

Most of the times interferon-treated patients have reversible retinopathy with no visual complaints or visual acuity changes. Retinopathy may resolve even before this treatment is discontinued[12] or can persist for several months after stopping treatment[6,16] In our study retinopathy in the form of cotton wool spots and hemorrhages was seen at the posterior pole and around the disc only in those patients who were receiving INF. Except for two patient who had macular edema none had any visual impairment . Visual symptoms improved 4 weeks after the treatment was discontinued in one patient in Group B with macular edema. Second patient lost to follow up. Hemorrhages and cotton wool spots disappeared in all the patients 4 weeks after stopping the treatment.

Visual impairement due to cystoid macular edema has been reported by Tkai R et al.[25] Shimura M, in 2005 observed macular edema in two patients. Both had hypoalbuminemia and thrombocytopenia at that time. After the remission of the hypoalbuminemia and thrombocytopenia, the macular edema observed by OCT disappeared and visual acuity returned to normal.[39]

Cases of severe, irreversible visual impairment due to ischemic optic neuropathy,[21] central retinal vein occlusion with macular edema[24], branch retinal occlusion[15,19,21] or both[40] are though rare but reported in literature. Yoshitoshi et al reported a 65 year old woman with type C chronic active hepatitis in whom panophthalmitis developed 6 days after Peg INF therapy and the eye had to be enucleated[27] None of such adverse effects were seen in our study.

Retinopathy associated with Peg INF α-2a and ribavirin combination therapy tends to develop more in patients with compromised microcirculation as in older age group[16] or patients with hypertension[6,16,18,28] and diabetes[8,16,18,28] In our study 39 patients were diabetic 40 were hypertensive and of mean age 43 +/-18. In Group A out of 12 patients with IAR, five were diabetic, four were hypertensive and five were both hypertensive and diabetic where as in Group B all three patients with IAR were diabetic as well as hypertensive.

Kawano et al observed retinopathy was higher among diabetic (11/12, 92%, $p < 0.05$) or hypertensive patients (4/5, 80%, not significant)[39] Kim ET et al also concluded hypertension to be the most significant risk factor.[17] Mausa et al found that eight patients out of 98 who developed IAR, 2 had diabetes, 1 had hypertension, 4 had both diabetes and hypertension[28] Similar observations were observed in other studies.[6,16,18,19] In contrast Panetta et al found no correlation of IAR with diabetes or hypertension.[14]

But now most recently oral DDAs have opened a new era to the treatment of HCV. They being more safe and effective have not only increased the SVR rate and shortened the duration of regime but also increased the compliance rate . Out of all, SOF marks the revolution in HCV treatment .In a dose of 400 mg once daily, the drug has been safe and generally well tolerated with most adverse reactions attributable to the concurrent use of RBV or Peg INF plus RBV . The most common adverse events other than retinopathy in our study were fatigue, headache, nausea and insomnia. They were worst and intolerable in Group A and decreased in frequency and intensity from Group B to Group D. Only two patients in Group D complained of mild headache and nausea. One patient in Group A developed myxedema, one generlized seizures. Hair fall was a common complaint in Group A patients. Bodyaches, infuenza like features,rash and anemia have been reported in other studies with oral drugs[41-45] Overall 0-1% of patients discontinued treatment with oral drugs due to adverse effects.[41,43] All patient in our study on oral drugs completed their treatment without any interference with their quality of life.

CONCLUSION

Ischemic retinopathy is frequent in older age group patients of HCV during treatment with PegIFNα and RBV especially if they are hypertensive or diabetic. Inspite of IAR, in most patients treatment is not discontinued as they have no visual complaints and retain normal visual acuity. Retinopathy disappears spontaneously during therapy or rapidly after stopping the therapy. Since significant irreversible ocular complications which impair visual acuity are also reported with Peg INF careful ophthalmologic monitoring before and during antiviral treatment of patients with hepatitis C is necessary. The efficacy and safety of SOF marks a revolution in HCV treatment. Successful treatment of all genotypes of HCV with interferon free, SOF based oral regimens has now become a reality.

Limitations: Sofosbuvir has been made available in India in April 2015 and Daclatasvir in December 2015. Sample size and time period of patients being treated only with oral DDAs is very small. Periodic retinal examination before starting and during treatment is be done especially in older patients with vascular risk factors for a longer time period and on larger sample size to conclude for sure the .Secondly we did not correlate our findings with hematological observations.

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