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Evaluation of Macular and Choroidal Thickness by Optical Coherence Tomography with Direct Acting Antiviral Agents in Patients with Chronic Hepatitis C Virus Infection

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ABSTRACT

Background: One of the most significant threats to public health is hepatitis C virus infection (HCV). Pegylated interferon alpha (Peg-IFNα) and ribavirin (RBV) had been the main stay of treatment for hepatitis C until recently. This combination often causes systemic and ocular side effects. More effective and safer than IFN therapy is direct acting antiviral agents (DAAs). **Objective:** The objective of the current study was to assess the impact of sofosbuvir (SOF) and daclatasvir (DAC) on choroidal and macular thickness among HCV cases. **Patients and methods:** Between June 2018 and February 2019, 30 HCV cases were included and treated using RBV-free SOF/DAC regimen for 12 weeks. They were referred to the ophthalmology department where full ophthalmological assessment was done before and at the end of treatment. Furthermore, macular and choroidal thicknesses were assessed by optical coherence tomography (OCT). **Results:** 60 eyes of 30 HCV cases (aged from 24-56 years, males: 18 [60%], females: 12 [40%]) received RBV-free SOF/DAC regimen for 12 weeks. During the 3 months of follow-up, no ocular complications were reported. Best corrected visual acuity (BCVA) was not changed. OCT showed increase in macular thickness from baseline. Although there was an increase, it didn't show statistical significance (p=0.743). The choroidal thickness measurements showed no statistically significant difference. **Conclusion:** There are no observable ophthalmic sequelae among patients treated with DAAs, and this includes the RBV-free SOF/DAC regimen. There appears to be a decreased need for routine ophthalmic follow-up among patients treated with DAAs in comparison to INF.

Keywords: Hepatitis C, Ocular complications, Macula, Choroid, Optical Coherence Tomography, Direct Acting Antivirals, Sofosbuvir, Daclatasvir.

INTRODUCTION

Chronic hepatitis, liver cirrhosis, decompensation, as well as hepatocellular carcinoma are all caused by HCV, making it a global health problem. About 1.5 million new cases of HCV infection are reported annually, bringing the total number of people with the virus worldwide to 58 million [(1)]. Egypt has the world's highest prevalence, with 92.5% infected with genotype 4 [(2)].

IFN treatment remained for several years the treatment of choice for HCV. However, many side effects mainly affecting the retina have been linked to using IFN with or without ribavirin. IFN-associated retinopathy incidence is variable ranging from 18-86% [(3)]. Cotton-wool patches and retinal hemorrhage are two types of common retinal abnormalities [(4,5)]. In addition to retinopathies, other posterior pole disorders have been documented, including macular edema, bilateral anterior ischemic optic neuropathy, and optic nerve infarction [(3)].

With the advent of DAAs, treatment of chronic HCV has undergone dramatic revival, with sustained virological response (SVR) of >90%. DAAs are now the current standard of care for treating HCV because of their shorter treatment duration and fewer adverse effects [(6)].

Our objective was to evaluate the effect of sofosbuvir/daclatasvir regimen on macular and choroidal thickness in Egyptian patients with chronic HCV infection.

PATIENTS AND METHODS

Thirty chronic hepatitis C (CHC) patients who were presented to our institution between June 2018 and February 2019 to receive treatment with DAAs were invited to participate in this prospective study. Full ophthalmological examination was carried out in the outpatient clinic of the ophthalmology department of Ain Shams University Hospitals.

Participants were not included if they had any of the following conditions: retinopathy; diabetes mellitus; hypertension; autoimmune disease that could impact the retina; glaucoma; visual field abnormalities; or a single eye.

The sociodemographic data of the enrolled participants was recorded. Complete blood count (CBC), liver function tests, kidney functions, coagulation profile, and pelvi-abdominal ultrasound were performed at baseline. All patients received sofosbuvir 400mg and daclatasvir 60mg daily for 12 weeks. SVR12 was described as an undetectable HCV-

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RNA 12-weeks after the end of treatment (EOT).

Before and after treatment, all patients underwent the following ophthalmological evaluation: best corrected visual acuity (BCVA), slit lamp examination of the anterior segment, indirect ophthalmoscopy, and intraocular pressure (IOP) measurement by applanation tonometer. In addition, optical coherence tomography (OCT) was used to assess macular and choroidal thickness in all cases.

Ethical consent

An approval of the study was obtained from the Ethical Review Board of Ain Shams University. All participants applied an informed written consent before inclusion in this study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical analysis:

A computer programme was used to collect data, tabulate the data, and do statistical analysis (SPSS version 18). The collected data was described using descriptive statistical tests, including the frequency distribution, mean, and standard deviation (SD). When necessary, we used chi-square and t-test analyses. P value ≤ 0.05 was considered significant.

RESULTS

This study included 30 CHC patients who were recruited from our institution. There were 12 (40%) females and (60%) 18 males, with age ranging from 24 to 56 (mean ± SD: 39 ± 10.54 years). All patients were treatment naïve. Twenty-five (83.3%) patients were classified as child A, and 5 subjects (16.7%) as child B. Table 1 summarizes and compare between the results of the laboratory investigations of the enrolled patients at baseline and EOT.

Table (1): Comparison between the baseline and EOT laboratory investigations.

Variable	Mean ± SD				P-value
	BASELINE		EOT		
TLC (10^9/L)	6.79	1.68	5.49	1.00	0.000**
Hb (g/dl)	12.51	1.61	12.08	1.33	0.069
Platelets (10^9/L)	208.77	51.32	232.93	57.01	0.028*
ALT (IU/L)	29.13	7.60	22.23	5.01	0.000**
AST (IU/L)	32.83	7.15	17.80	4.31	0.000**
Total Bilirubin (mg/dl)	0.83	0.20	0.61	0.12	0.001**
Albumin (g/dl)	3.96	0.53	4.01	0.44	0.043*
INR	1.10	0.11	1.05	0.10	0.071
Serum creatinine (mg/dl)	0.90	0.28	0.81	0.20	0.063

P-value of Student's t test. *Significant, ** Highly significant.

Prior to treatment, the mean BCVA was 0.75 (SD 0.16) which decreased non-significantly to 0.74 (SD 0.17) at EOT (p=0.304). Regarding the IOP, it was not changed. Also, The EOT follow-up examination revealed no signs of uveitis or anterior segment changes.

Among the studied group, the follow up of macular (central foveal) thickness by OCT showed increase in the mean thickness from baseline (241.60 ± 20.20 vs. 244.65 ± 21.01 μm), however this increase showed statistical insignificance (p=0.743) (**Figure 1**).

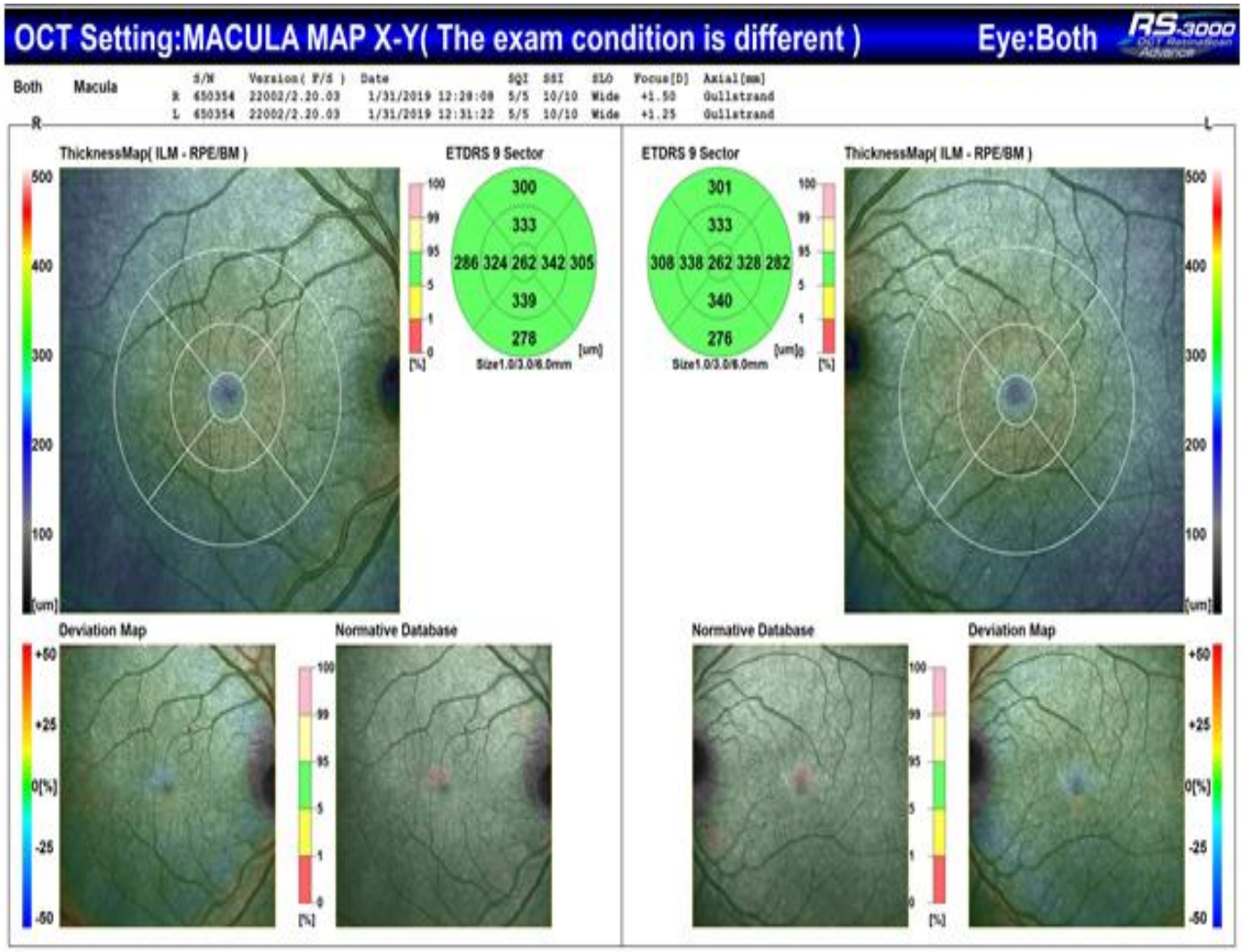

Figure (1): OCT macular map of one patient at EOT. Central foveal thickness was 262 µm in both eyes.

Moreover, choroidal thickness was evaluated by OCT at 3 points: subfoveal, 2 mm temporal and 2 mm nasal to the fovea. The mean subfoveal choroidal thickness (SFCT) did not differ significantly from baseline measurements (218.45 ± 28.50 vs. 220.73 ± 28.95 µm respectively, p=0.355) (Table 2) (**Figure 2**). Similarly, the choroidal thickness measurement 2 mm temporal and 2 mm nasal to the fovea did not change significantly at EOT (p=0.108 and p=0.356, respectively) (Table 2) (**Figures 3 and 4**).

Table (2): Comparison between choroidal thickness measurements before and after treatment.

Variable	Mean ± SD				P-value
	BASELINE		EOT		
SFCT (µm)	218.45	28.50	220.73	28.95	0.355
Choroidal thickness 2 mm temporal to fovea (µm)	172.65	30.13	184.58	41.72	0.108
Choroidal thickness 2 mm nasal to fovea (µm)	178.38	34.73	179.85	31.21	0.356

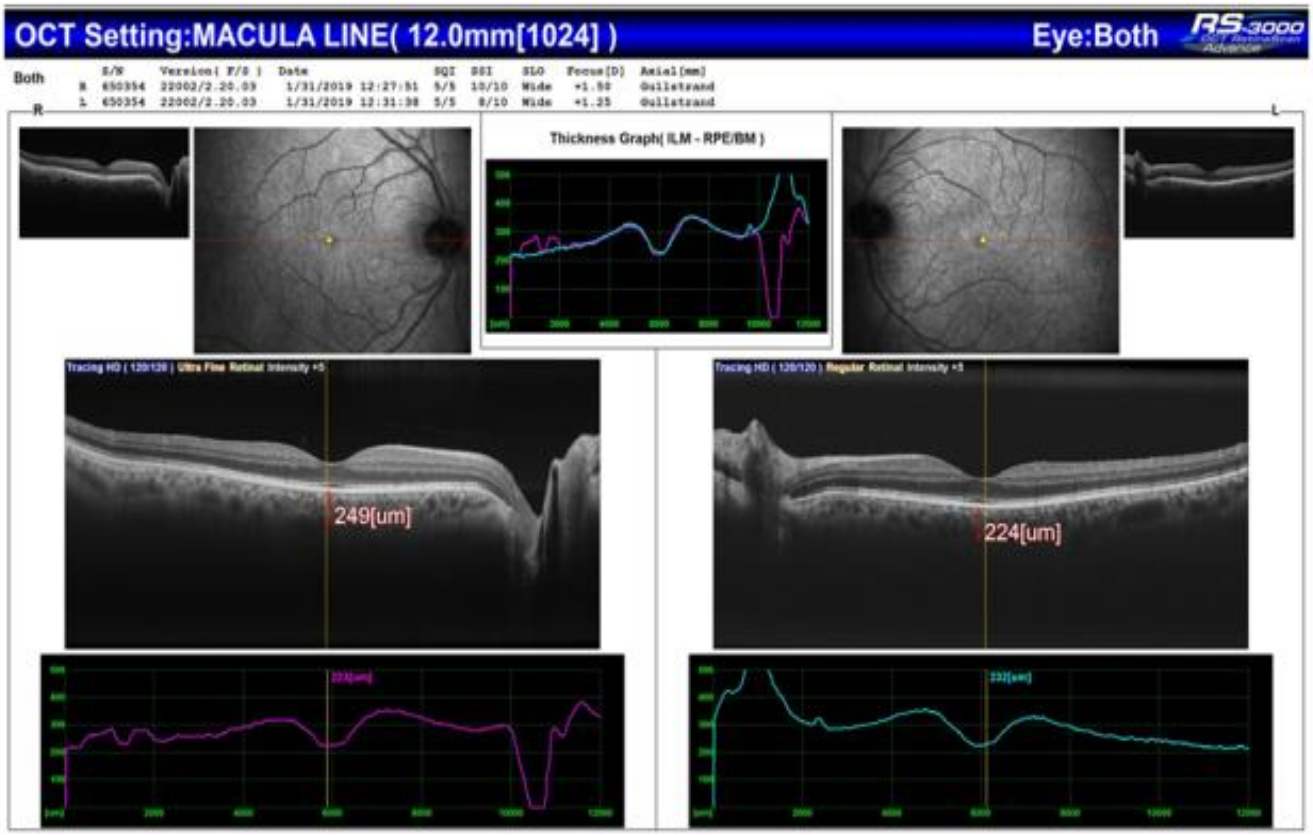

Figure (2): OCT macular line of one patient at EOT. SFCT was 249 µm in the right eye and 224 µm in the left eye.

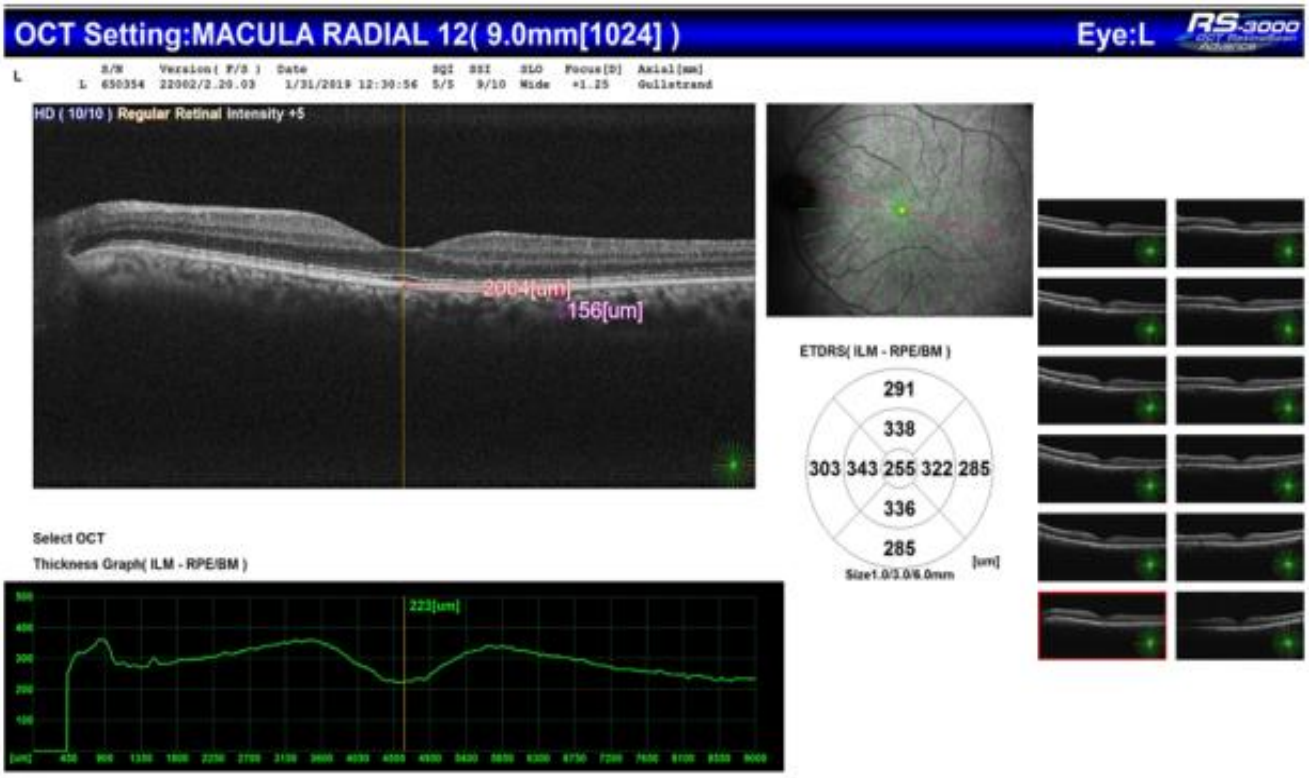

Figure (3): OCT macular radial image of one patient at EOT. Choroidal thickness temporal to fovea was 156 µm in the left eye.

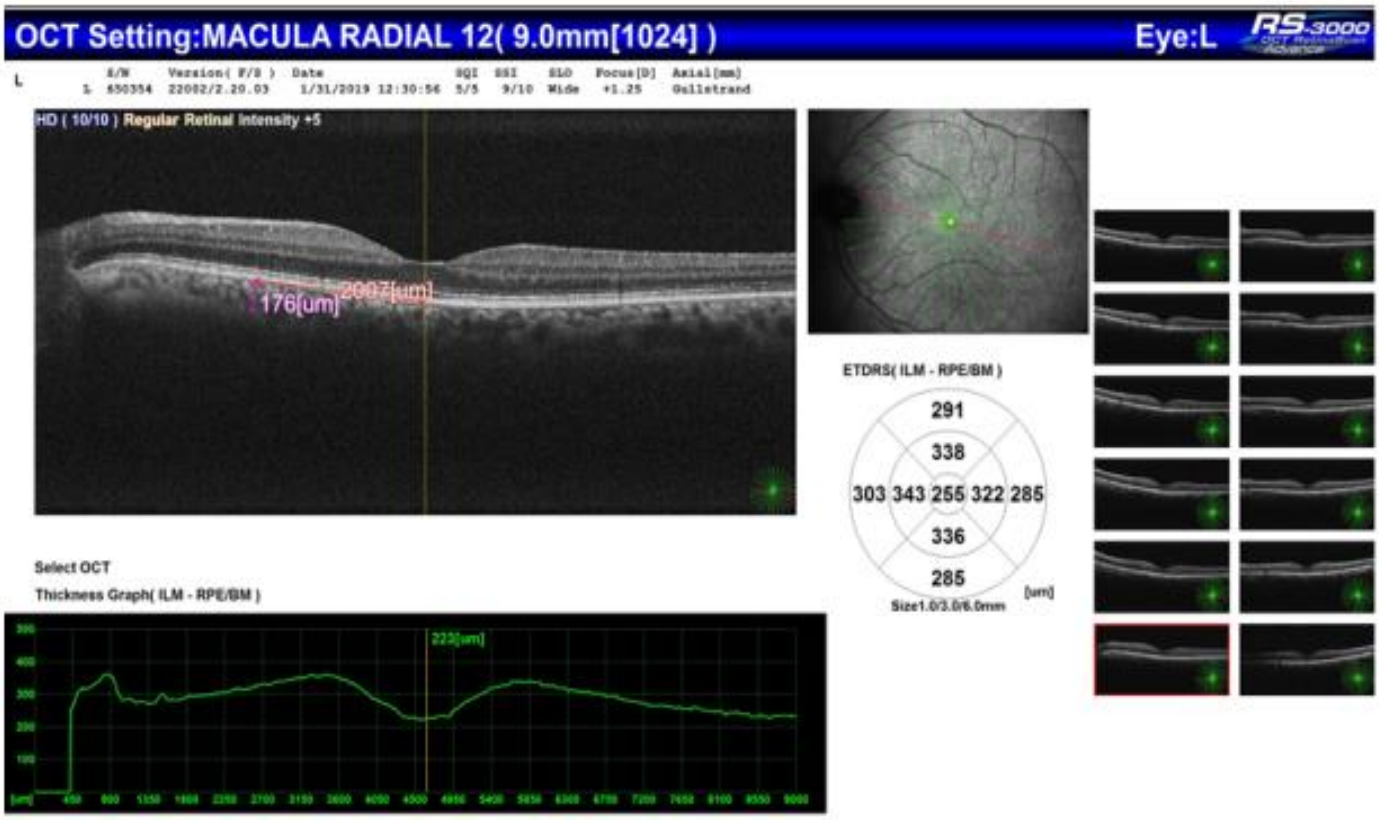

Figure (4): OCT macular radial image of one patient at EOT. Choroidal thickness nasal to fovea was 176 µm in the left eye.

DISCUSSION

Due to advances in diagnosis and improvements in treatment and prevention, clinical care for individuals with HCV-related liver disease has evolved in recent years. Primary objective of HCV treatment is viral eradication by achievement of SVR, which results in regression of liver necroinflammation and fibrosis, and restoration of liver function [(7)]. Additionally, HCV is linked to a number of extrahepatic manifestations, but viral elimination can result in a decrease in overall mortality [(8)].

For a long time, HCV was treated with IFN and RBV, but this combination was associated with many side effects, including fever, headache, and myalgia. Depression, pancytopenia, and autoimmune thyroiditis are major adverse events that may require a change in dosage or even treatment discontinuation [(9-10)].

Ocular alterations triggered by IFN are reported in many studies. Retinopathy, a well-recognized consequence of IFN therapy manifested by hemorrhages and cotton-wool patches, is caused by immune complex deposition and lymphocyte infiltration in the retinal microcirculation resulting in retinal ischemia [(3,11)]. Macular edema, optic disc edema, retinal vein occlusion, subconjunctival hemorrhage, vitreous hemorrhage, bilateral anterior ischemic optic neuropathy as well as pan ophthalmitis are all ocular complications linked to IFN [(5, 12)].

IFN have been replaced by the evolution of different generations of DAAs which have dramatically improved both response rates and the tolerability of treatment [(13)]. Sofosbuvir, a pan genotypic oral non-structural protein 5B (NS5B) inhibitor that incorporates into HCV RNA and functions as a chain terminator, is both effective and tolerable with once-daily dosing [(14)]. Daclatasvir is another pan genotypic NS5A inhibitor[(15)].

This research included 60 eyes of 30 CHC patients; all of them were registered for the oral dual therapy (SOF/ DAC) for 12 weeks. They were assessed before and at the EOT regarding macular and choroidal thickness by OCT. To our knowledge, there are few available studies regarding adverse effects of DAAs in the ophthalmologic context.

In consistence with previous results [(16-18)], our patients showed statistically insignificant change in BCVA from baseline (p=0.304), and no anterior segment changes or signs of uveitis were detected. In contrast, **Samy *et al.*** [(16)] detected anterior segment changes in two cases out of 200 patients. After finishing the course of triple therapy (SOF/DAC/RBV), they were presented with unilateral subconjunctival bleeding. These two patients had normal systemic blood pressure and coagulation profile.

The current study showed an increase in macular thickness compared to the initial measurements. This increase, however, did not reach statistical significance (241.60 ± 20.20 vs. 244.65 ± 21.01 µm, respectively [p=0.743]). This comes in accordance with other studies [(16, 19)] where there was no retinal ischemia by fluorescein fundus angiography (FFA) and no macular

edema.

Moreover, a prospective observational study was conducted to evaluate the incidence of retinal complications in patients treated with dual (SOF/RBV) versus triple (SOF/RBV/PEG-IFNα) therapy. After 3 months of treatment, 11 percent of patients receiving triple therapy experienced retinal hemorrhages and soft exudate. These retinal complications resolved after treatment was stopped. Retinal changes were not observed in patients receiving dual therapy. Therefore, PEG-IFN regimens may be the cause for these side effects [(17)].

In contrast, **Chin-Loy *et al.*** [(20)] found that sofosbuvir therapy for HCV has been linked to a case of retinopathy and uveitis. The male patient also presented with hearing loss, unstable gait, pain in the joints, and tremors. Eye drops containing prednisolone acetate and cyclopentolate were administered to him. Eleven weeks after discontinuing ribavirin and sofosbuvir and tapering off prednisolone, uveitis and cotton-wool spots resolve. This raised more concerns about the safety of IFN free DAAs, however these ophthalmic complications might be related to the autoimmunity associated with HCV itself [(21)].

On the other hand, our study showed that choroidal thickness did not change significantly from baseline at the measured 3 points: sub foveal, 2 mm nasal and 2 mm temporal to the fovea. To our knowledge, this is the first report on the effect of DAAs on choroidal thickness.

In conclusion, IFN-free-DAAs (SOF/DAC) are apparently safe with non-detectable ocular side effects. However, large-scale studies with longer follow-up duration using OCT angiography are needed for imaging the microvasculature of the retina and the choroid to determine if DAA-therapy affects retinal and choroidal vasculature.

Availability of Data and Materials: The datasets used and analyzed during the current study are available from corresponding author upon reasonable request.

Competing Interests: All authors declare that they have no competing interests.

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