Tuesday, 15 August, 2019

Faculty of Medicine, Cairo University Postgraduate Research Program Template

1. Proposed Study Title

Role OF OCT-A TO Detect Possible Retinal Vascular Complications of Sofosbuvir (Sovaldi) in Patients With Hepatitis C Virus Infection.

Degree : M.Sc

2.Candidate Name:

Mohamed Saad Emam Ahmed .

(M.B.B.Ch October 6th University)

Date of Registration :January 2019

a. Occupation :

-Resident of ophthalmology at Giza Memorial Institute for Ophthalmic Research

-Visitor Resident of ophthalmology at Kasr Alainy medical school – Cairo university

b. Full mailing address :15 Hussein Darwish Building , Kornish Elnil St.

Hadayek Helwan ,

Cairo, The Arab Repuplic of Egypt

c. Phone number	+201007654385
f. E-mail addresses	Mohamedsaad2032@gmail.com

1. Investigators Contact Information

a. Principal Investigator	**Prof. Dr.Magda Salah** professor of Ophthalmology Faculty of medicine,Cairo university
c. Department name	Ophthalmology
e. Phone number	+
g. E-mail addresses	magdasalah@kasralainy.edu.eg
b. Other Investigators	**Dr. Hany El Mekawey** Assistant professor of Ophthalmology

	Faculty of medicine,Cairo university **Dr. Yomna Amr** Lecturer of Ophthalmlogy Faculty of medicine, Cairo university

2. Background and Rationale:

- Egypt − as an example of developing countries − has the highest prevalence rate of hepatitis C virus (HCV) infection that is suggested to be ∼14% in comparison with 2% in the developed countries. Among the 14% who carry the antibodies, there are ∼9% who have an active infection .**(1)**
- In chronic hepatitis C, the age of the patients is one of the considerable factors and has a significant role in determining the process of cirrhosis progression side by side with alcohol consumption, as − if there is no suitable antiviral treatment − cirrhosis develops at a faster rate from age 40 years onward than in young patients. So, on-time antiviral treatment is essential to reduce the risk of cirrhosis progression . **(2)**
- In early 2014, the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America published a recommendation for the management of hepatitis C. In this recommendation, Sofosbuvir (Sovaldi) and ribavirin, with or without pegylated interferon, formed a crucial part of all first-line treatments for HCV genotypes 1–6, and also contributed in some second-line treatments **.(3)**
- Sofosbuvir (Sovaldi) is a nucleotide analogue that inhibits the RNA polymerase enzyme, which is a necessary factor needed in hepatitis C virus replication .
- The recommended dose for Sofosbuvir (Sovaldi) is 400 mg/day. Dose

adjustment in renal or hepatic insufficiency is commonly unrequired .

- Sofosbuvir (Sovaldi) with ribavirin and interferon − as a triple-therapy strategy −was impressively appearing to be ∼90% effective in those with genotype 1, 4, 5, or 6 diseases. Sofosbuvir (Sovaldi) with just ribavirin − as a dual-therapy strategy appearing to be 70–95% effective in types 2 and 3 diseases . **(4,5,6)**
- It was reported that the Sofosbuvir (Sovaldi) treatment displays common side effects as chest pain, migraine, memory impairment, dyspnea, gastrointestinal reflux, alopecia, depression, muscle spasm and blurred vision , Moreover vision loss seems to be a growing side effect of Sovaldi . **(7)**
- In an experiment was held at the anatomy department, faculty of medicine, Menoufia University and Published at March 16, 2017 , Twenty adult male albino rats were used, each of them is weighting 170-200 grams were used in this experiment.
  The animals were divided in two groups: Group I (Control): included ten rats were kept without any treatment, Group II (Sovaldi treated): included ten rats that received 400 mg of Sofosbuvir (Sovaldi); these tablets were dissolved in distilled water and given for rats orally by gastric tube in a dose of 4 mg/kg per day for 5 weeks. **(8)**

  Corneal examination of the control group showed normal histological structure. Corneal examination of Sovaldi treated group showed focal areas of desquamation and separation of the epithelium. Some areas showed loss of corneal epithelium with apparent decrease in thickness of the epithelium. Corneal stromal collagen bundles were separated by multiple wide spaces, indicating corneal edema and showed cellular infiltration.

Immunohistochemical assaying showed that Sovaldi treatment significantly down-regulated the expression of E-cadherin. **(8)**

Examination of haematoxylin and eosin stained sections of the retina in the control group (group I) showed normal histological structure. The outer nuclear layer exhibited darkly stained nuclei whereas the inner nuclear layer and ganglion cell layer showed lightly stained vesicular nuclei. Sections of Sovaldi treated group showed denuded pigmented epithelium in the photoreceptor layer and fissures in the outer nuclear layer. Extravasated Red Blood Corpuscles (RBCs) were noted in the inner nuclear layer and ganglion cell layer. Vacuoles and wide clear areas were present around ganglion cells that showed irregular dark nuclei Sovaldi treatment significantly up-regulated the expression of fibronectin immunostaining.**(8)**

- A case report was published at May 2016 demonstrated A 57-year-old-male developed ocular inflammation and retinopathy four weeks after the administration of Sofosbuvir (Sovaldi) for a hepatitis C infection (vision of 20/40 and 20/50 in his right and left eyes, respectively. Anterior segment exam showed conjunctival injection, scattered, fine keratic precipitates, and 3+ cell and flare bilaterally. Dilated fundus exam revealed bilateral peripapillary cotton-wool spots) . The ophthalmic findings resolved with discontinuation of the drug (Eleven weeks after cessation of ribavirin and Sofosbuvir (Sovaldi), his vision was 20/20 and 20/25 with a resolution of the uveitis and cotton-wool spot) . **(9)**
- Another case report was published at June 2017 ,reported A 39-year-old Caucasian man presented with complaints of painless, progressive vision loss in his left eye over 24 hours. Past medical history was significant for hepatitis C secondary to blood transfusion. He completed

a six month course of 90 mg/400 mg Sofosbuvir (Sovaldi)) daily and 500 mg ribavirin twice daily three days prior to the onset of his visual symptoms.

Visual acuity was 20/20 right eye and 20/30 left eye. His color vision appeared. A 3 + afferent pupillary defect was noted in left eye. Fundus exam of the right eye revealed a 0.1 cup to disc with a “disc at risk” appearance. Left eye was remarkable for 360° hemorrhagic swelling of the optic disc with engorged venules

Initial labs were unremarkable with normal erythrocyte sedimentation rate and C-reactive protein (obtained because of the observed cotton wool spots). MRI brain/orbits and MR venography were unremarkable and showed no optic nerve enhancement or signs of demyelinating disease. Humphrey visual field examination was normal in the right eye and showed incomplete superior and inferior altitudinal defects in the left eye . Two months after cessation of treatment , central visual acuity, color vision, and perimetry were unchanged. Fundus exam showed resolution of left optic disc swelling with diffuse pallor. His overall health remained excellent **(10)**

- A study was performed on 300 eyes undergoing Sofosbuvir (Sovaldi) therapy with peginterferon and ribavirin and on 300 eyes undergoing treatment with only peginterferon and ribavirin. Patients were evaluated for dry eye subjectively (Ocular Surface Disease Index questionnaire) and objectively, Schirmer test, tear film breakup time, and conjunctival nucleus/cytoplasm ratio by impression cytology.
  it was noticed that that dryness significantly associated with sofosubuvir group **(11)**

References:

1. Cuadros DF, Branscum AJ, Miller FD, Abu-Raddad LJ. Spatial

epidemiology of hepatitis C virus infection in Egypt: analyses and implications. Hepatology 2014; 60:1150–1159.

2. **Sarrazin C, Berg T, Ross RS, Schirmacher P, Wedemeyer H, Neumann U, Peck-Radosavljevic M.** Prophylaxis, diagnosis and therapy of hepatitis C virus (HCV) infection: the German guidelines on the management of HCV infection. Z Gastroenterol 2010; 48:289.

3. **Hepatitis C Guidance:** AASLD-IDSA Recommendations for Testing, Managing, and Treating Adults Infected with Hepatitis C Virus." Hepatology 62, no. 3 (August 4, 2015): 932–954.

4. **Fung A, Jin Z, Dyatkina N, Wang G, Beigelman L, Deval J.** Efficiency of incorporation and chain termination determines the inhibition potency of 2′-modified nucleotide analogs against hepatitis C virus polymerase. Antimicrob Agents Chemother 2014; 58:3636–3645.

5. **Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Jacobson IM**. Sofosbuvir (Sovaldi) for previously untreated chronic hepatitis C infection. N Engl J Med 2013; 368:1878–1887.

6. **De Clercq E. Dancing with chemical formulae of antivirals**: a panoramic view (part 2). Biochem Pharmacol 2013; 86:1397–1410.

7. **"Food and Drug Administration (FDA).** Encyclopedia of Immunotoxicology (June 23, 2015): 333–333.

8. **El-Sherif NM.** Histological and Immunohistochemical Studies on the Cornea and Retina of Sofosbuvir Treated Rats. Austin Journal of Anatomy. 2017 March 16 4(2):1068.

9. **Chin-Loy K, Galaydh F, Shaikh S.** Retinopathy and uveitis associated with sofosbuvir therapy for chronic hepatitis C infection. Cureus. 2016 May;8(5): e597.

10. Manoharan N, Subramanian PS. A case of non-arteritic anterior ischemic optic neuropathy after completion of Harvoni therapy. American journal of ophthalmology case reports. 2017 Jun 1;6:55-57.

11. Salman AG. Ocular surface changes with Sofosbuvir in Egyptian patients with hepatitis C virus infection. Cornea. 2016 Mar 1;35(3):323-328.

12. Myers JP, Di Bisceglie AM, Mann ES. Cryoglobulinemia associated with Purtscher-like retinopathy. American journal of ophthalmology. 2001 Jun 1;131(6):802-804.

13. Chebil A, Mammouri R, Abdallah MB, El Matri L. Purtscher-like retinopathy as a rare presentation of cryoglobulinemia. Middle East African journal of ophthalmology. 2016 Apr;23(2):219.

11.Objectives:

The purpose of this study is to prospectively evaluate the value of Optical coherence tomography angiography (OCT-A) for the of detection of suspected retinal complications With Sofosbuvir (Sovaldi) in Patients With Hepatitis C Virus Infection.

12.Study Design :

Descriptive prospective cohort study (pilot study)

13.Study Methods

During 3 months duration (the treatment course duration) , Optical coherence tomography angiography (OCT-A) will be performed to 30 eyes of 30 patients with a documented diagnosis of chronic hepatitis C before and after receiving dual-therapy planning (Daclatasvir − Sofosbuvir (Sovaldi)). .

All OCT-A examinations will be performed at the Ophthalmology Department, Faculty of Medicine, Cairo University.

Inclusion criteria:

- Age between 20 and 80 years.
- Patients with chronic hepatitis C enrolled for (Daclatasvir – Sofosbuvir (Sovaldi)) .
- Patients who have normal ocular and fundoscopic examination before the onset of treatment.

Exclusion criteria:

- Relapsed cases who have formerly taken the antiviral therapy (depending on the basis of medical record and filing system), or treated with interferon for any other cause .
- Patients with elevated renal functions or positive Rheumatoid factor (as a clue to diagnose Purtscher like retinopathy which is a rare presentation of cryoglobuinemia , considered one of extra hepatic manifestations of HCV)

Methodology in details:

- the patients with a documented diagnosis of chronic hepatitis C , normal renal functions And Rheumatoid factor tests (to exclude Purtscher like retinopathy as a rare presentation of cryoglobuinemia which considered one of extra hepatic manifestations of HCV) will undergo a comprehensive ophthalmic examination including:
    - Manifest refraction
    - Corrected distance visual acuity
    - Anterior segment examination using slit lamp and tear film breakup time test
    - Fundus examination

- Recent OCT-A will be performed to all patients before Treatment Administration.
- Examination will be performed using Optovue AngioVue® (Optovue, Inc., Freemont, CA), which uses split-spectrum amplitude-decorrelation angiography algorithm, which minimizes motion noise. This system also allows quantitative analysis, since it provides numerical data about flow area and flow density maps.
- The patient will be examined before and after finishing the treatment course
- OCT-A image acquisition

OCT-A will be done for all patients who are instructed to focus on a fixation target. OCTA images are obtained using the RTVue XR Avanti (AngioVue; Optovue Inc, Fremont, California, USA) machine and the incorporated AngioVue OCT-A system. Algorithm used is Split-Spectrum Amplitude Decorrelation Algorithm (SSADA). The scans which will be included in the study are of high signal strength more than 0.7 and they will be carefully inspected for motion artifacts. Automatic segmentation of intraretinal layers will be done using the automated software of the machine (version 2016.2.0; Optovue Inc). Angio-retina scan sizes in this study will be 6 X 6 mm for all eyes. Assessment of the macular vessel density will be done for superficial vascular layer, capillary plexus, deep capillary plexus and all retinal plexuses). Assessment of the foveal avascular zone on both superficial vascular layer (SVL) and deep capillary plexuses DCP; including its size, perimeter and circularity (regularity) index. Circularity index is a measure of compactness of a shape relative to a circle. The circularity index of a circle is 1.0. Thus, a ratio closer to 0 indicates an irregular shape, and that closer to 1.0 indicates a circular shape.

All results will be in numerical values (percentage) to compare retinal vascularity before and after using the drug. Best corrected visual acuity (in values from o.o5 to 1.0) , dryness (in seconds) will be also measured before and after drug administration and it will be compared .

Possible Risk:

As a fast, safe and noninvasive procedure to assess the chorioretinal microvasculature, OCT-A has been increasingly used in retinal diseases

Primary outcomes:

- Evaluate the suspected retinal vascular complications With Sofosbuvir (Sovaldi)) in Patients With Hepatitis C Virus Infection, All results will be in numerical values (percentage) to compare retinal vascularity before and after using the drug..

- Comparing best corrected visual acuity (in values from o.o5 to 1.0) before and after drug administration .

Secondary outcome parameters (other outcomes to be assessed):

- Measuring amount of ocular dryness using Tear-up breaking test and Schirmer's test , dryness will be evaluated in seconds before and after drug administration and it will be compared .
- Confirm the advantages of OCT – A Detection retinopathy
- Assist in assessment of late ocular complications with Sofosbuvir (Sovaldi) in Patients With Hepatitis C Virus Infection (the research can be used as a guide for further researches) ..

Sample size (number of participants included):

Convenience sample
30 eyes of 30 patients with a documented diagnosis of chronic hepatitis C

Statistical analysis plan:

Data management and analysis will performed using Statistical Package for Social Sciences (SPSS). Median and range for non-parametric measures and ordinal (scores) data. Numerical data will be presented as means ± standard deviations (SD). Categorical data will be presented as number and percentages %. Pairwise comparisons between the two groups for normally distributed variables will be done using the Student's t-test; the Mann–Whitney test, a nonparametric test equivalent to the t-test, will be used in non-normally distributed variables. The Repeated measures ANOVA test will be used to compare the effect change within and between the study groups at different visits. The chi-square test or the Fisher's exact test will be used to compare between the groups with respect to categorical data. All p-values will be two-sided. P-values < 0.05 will be considered significant.

Source of funding:

No source of funding.

9.Cooperation with other departments:

10 Time Plan

Expected Finish date: after collecting and analyzing data (six months)