Journal of Clinical Trials
ISSN: 2167-0870

Krasniqi and Farrag, J Clin Trials 2019, 9:5

Research Article Open Access

Ocular Surface Changes with Sofosbuvir in Egyptian Patients with Hepatitis C Virus Infection

Marsida Krasniqi[1*] **and Ahmed Abdel Kader Farrag**[2]

[1]Department of Medicine Sciences, University Aleksander Moisiu, International Eye Clinic, Durres, Albania

[2]Department of Ophthalmology, Matarya Teaching Hospital, Durres, Albania

[*]**Corresponding author:** Marsida Krasniqi, Department of Medicine Sciences, University Aleksander Moisiu, International Eye Clinic, Durres, Albania, Tel: 355 69 263 3061; E-mail: kmarsidayahoo.it

Received date: September 11, 2019; **Accepted date:** September 27, 2019; **Published date:** October 03, 2019

Abstract

Background: To detect any ocular surface changes with Sofosbuvir in Egyption patients with hepatitis C virus.

Design: Continuous audit over 3 months for patients enrolled for Sofosbuvir therapy

Participants: A total of 100 Egyptian Chronic hepatitis C patients enrolled for Sofosbuvir therapy, Egypt, from January 2018 to March 2018.

Methods: Ocular history.

Ocular examination including: Visual acuity measurement. Slit-lamp bio microscopy of the ocular surface.

Schirmer's test: To exclude dry eye, Break-up time test, Conjunctival impression cytology.

Main Outcome Measures: After the treatment, BUT and Schirmer test declined from 13.08 second and 14.47 mm to 6.4 second and 7.98 mm respectively. Regarding impression cytology, the mean N/C ratio decreased from 0.66 to 0.57 while squamous metablasia and keratinization was found in 16% of patients post treatment. It was also found that 44% were complaining of dry eye symptoms after the treatment

Conclusion: Our study detected ocular surface changes after three months of sofosbuvir treatment for HCV

Keywords: Audit; Chronic HCV; Ocular surface changes; Sofosbuvir

Introduction

Dry eye is considered a chronic inflammatory condition of the ocular surface, caused by tear hyperosmolarity and accompanied by ocular surface symptoms. The ocular surface includes the surface of the cornea and of the bulbar and tarsal conjunctiva, extending to the lid margin [1].

Dry eye is among the most commonly encountered ocular morbidities, affecting as many as 15%–25% of individuals over the age of 65 and up to 6% of adults over the age of 40. Inadequate lubrication results in ocular surface damage and discomfort. In addition to increasing the risk of ocular infection, dry eye can cause irreversible scarring and fibrosis due to unprotected corneal epithelial exposure [2].

Keratoconjunctivitis sicca (KCS), also called dry eye syndrome (DES), is an eye disease caused by eye dryness, which is caused in turn by either decreased tear production or increased tear film evaporation. Any abnormality of any one of the three layers of tears produces an unstable tear film, resulting in symptoms of keratitis sicca [3].

Many risk factors of dry eye were identified and discussed. Most common risk factors are: female sex, current contact lens use, allergies, arthritis, thyroid disease, antihistamine and steroid use [4].

The diagnosis of dry eye is based on clinical features and some diagnostic tests such as tear break-up time (TBUT), tear meniscus height, Schirmer I test (SIt) and impression cytology [5]. The tear break-up time measures the stability of the tear film. After instillation of fluorescein to the patient eye, TBUT is measured by the time interval after a patient blink to the first appearance of dryness in the tear film. The patient has dry eye if a dry area appears before 10 seconds [6]. Schirmer test also used to detect hyposecretion of tears, the Schirmer strips are inserted into the temporal lower conjunctival sac, and the length of wetting strips is recorded in millimeters after 5 minutes. Normal test values are greater than 10 mm [7]. Recently impression cytology is introduced in diagnosis of dry eye. It has a wide range of applications in ophthalmology in diagnosis and prognosis of ocular surface disorders such as keratoconjunctivitis sicca, ocular surface squamous neoplasia, and ocular surface infections. It is a minimally invasive method performed under topical anesthesia to obtain superficial cells by application of small membrane against conjunctival surface [8].

Hepatitis C is an infectious disease affecting primarily the liver, caused by the hepatitis C virus (HCV). Egypt has the highest hepatitis C virus (HCV) prevalence in the world (14.7%) [9]. the drivers of the HCV epidemic in Egypt are not well understood. HCV genotype 4 dominates the HCV epidemic in Egypt. The infection is often asymptomatic, but chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years. In some cases, those with cirrhosis will go on to develop liver failure, liver cancer, or life-threatening esophageal and gastric varices [10].

Recently in 2013 Sofosbuvir has been introduced to the market allows most patients to be treated successfully without the use of peginterferon providing a higher cure rate, fewer side effects, and a two- to four-fold reduced duration of therapy [11]. The Egyptian Ministry of Health has since proposed a new national strategy to control the HCV epidemic in Egypt with a greater capital fund and with support from the WHO as well as other institutes [12]. It has been reported that impairment of tear function and squamous metaplastic changes in the ocular surface occurred in patient with chronic hepatitis C treated by sofosbuvir [13].

Also, in July 2016, Katrina and her colleagues reported a case of a 59 year old male who was found to have retinopathy and uveitis associated with sofosbuvir therapy for chronic HCV infection. The condition started four weeks after administration of sofosbuvir, Hearing loss, rheumatologic disease, and essential tremor were also noted. The ophthalmic findings resolved with discontinuation of the drug [14].

Patients and Methods

Subjects

100 patients will be subjected to prospective study. All patients will be examined before and after three months from the start of sofosbuvir.

After the approval of the local ethical committee of Benha University, consent was obtained from all patients before participation.

At each visit patient will be subjected to the following: Full history taking including: personal history, medical history (at first visit only), and Ocular history.

Clinical examination including

Visual acuity measurement.

Slit-lamp bio microscopy of the ocular surface.

Schirmer's test: to exclude dry eye.

Break up time test.

Conjunctival impression cytology.

Inclusion criteria

Age between 20 and 60 years.

Chronic hepatitis C patient enrolled for Sofosbuvir therapy.

Patients who have normal ocular surface examination at the start of treatment.

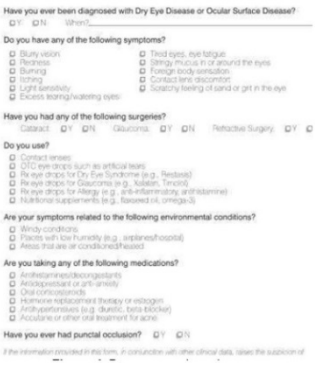
Exclusion criteria

Patient with dry eye based on symptoms, Schirmer and BUT tests.

Patient with any ocular surface disease such as (pterygium, Sjogren syndrome).

Any refractive surgery<12 months before enrollment.

Contact lens use, systemic diseases, and systemic medications inducing dry eye the presence of active ocular inflammation or allergy, eyelid changes, ocular trauma, any treatment of previous dry eye within the past 6 months Ocular history was taken by using a dry eye questionnaire (Figure 1).


Have you ever been diagnosed with Dry Eye Disease or Ocular Surface Disease?

Do you have any of the following symptoms?

Have you had any of the following surgeries?

Do you use?

Are your symptoms related to the following environmental conditions?

Are you taking any of the following medications?

Have you ever had punctal occlusion?

Figure 1: Dry eye questionnaire.

Instrumentation: Schirmer's test

Schirmer's test was performed by placing a single drop of Benox (Benoxinate Hydrochloride 0.4 mg) in each eye as topical anesthesia (Schirmer 2 test). This technique measures basic tear function. A standard Schirmer's strip was folded at the notch and placed in the inferolateral third of the lower lid, taking care not to touch the cornea in the process. After five minutes, the level of the strip wetting in millimeters was measured. Schirmer strips are filter papers 5 mm wide and 35 mm long. The test measures amount of moisture bathing the eye. More than 10 mm of moisture on the filter paper in 5 minutes is considered normal. Persons with Sjogren's syndrome moisten less than 5 mm in 5 minutes. Both eyes normally secrete the same amount of tears. Both eyes were tested at the same time (Figure 2) [15].

Normal values more than (10-15mm)

Mild dryness (6-10mm)

Moderate dryness (2-5mm)

Severe dryness (0-1mm)

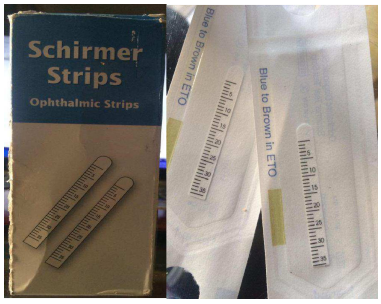


Figure 2: The above figure shows the schirmer strips.

TBUT test

TBUT test was performed as a functional measure of tear film stability. A fluorescein strip (Fluostrip, 1 mg fluorescein sodium, IP) was wetted with a single drop of Benox (Benoxinate Hydrochloride 0.4 mg) and applied to the lower bulbar conjunctiva. Participants were asked to blink several times and the ocular structures were viewed with a slit lamp bio microscope using a broad beam of the slit lamp with the cobalt blue filter. This should be done before any manipulation of the eyelids or instillation of other drops (fluorescein-anesthetic combination drops are not suitable for this purpose). The time lapse between the last blink and the appearance of the first randomly distributed dry spot on the cornea is the tear breakup time. The appearance of dry spots in less than 10 seconds is considered abnormal. This procedure was repeated three times and the average value in seconds was recorded in each eye (Figure 3) [16].

A TBUT value>10 sec. is considered normal.

Value 8-10 sec is considered mild dryness.

Value 5-7 sec is considered moderate dryness.

Value<5 sec is considered severe dryness.

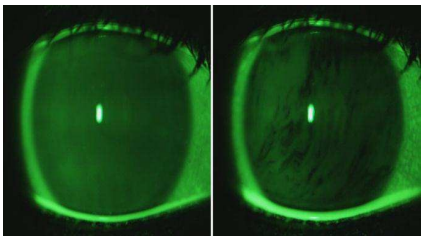


Figure 3: TBUT (Tear Break-Up Time Test).

Impression cytology

Impression cytology was performed by using 24-mm-diameter nitrocellulose membrane filter cut in half and trimmed into stips of approximately 4 × 6 mm. After instillation of 1 to 2 drops of topical anesthetic, the strip of the filter paper was gently pressed on the conjunctiva with a glass rod. After 5 to 10 seconds, the filter paper was peeled off and the cells were transferred by imprinting onto poly-l-lysine- coated glass slides. Specimens were collected from the inferior and temporal bulbar conjunctiva. The slides were air-dried and stained with modified periodic acid- Schiff and giemsa stain. Specimens were examined under a light microscope at *400 magnifications. Slides were prepared and examined under the microscope by professor of pathology: Abdel Latif El balshy at the pathology department in Benha University.

Impression cytology results

Photos were taken from the slides in the pathology department by Professor Dr: Abdel Latif Elbalshy. Before the start of the treatment, Slides showing normal stratified columnar epithelium (Figures 4-12).

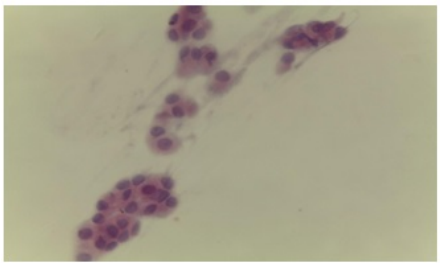


Figure 4: Conjunctival smears by impression cytology showing small sheets of bland looking stratified non-keratinized squamous epithelial cells H and Ex 400.

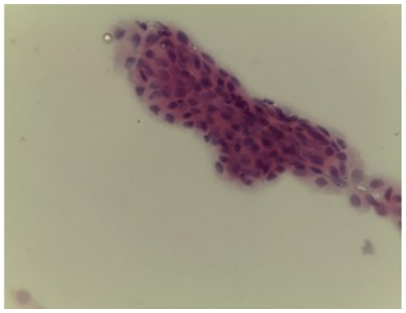


Figure 5: Conjunctival smears by impression cytology showing a large sheet of bland looking stratified non-keratinized squamous epithelial cells H and Ex 400.

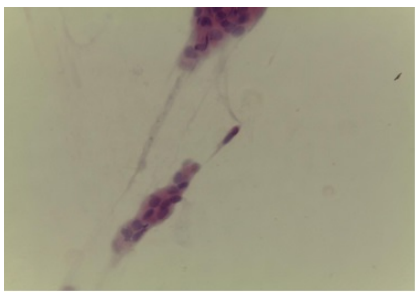


Figure 6: Conjunctival smears by impression cytology showing a large sheet of bland looking stratified nonkeratinized squamous epithelial cells H and Ex 200 (pre-treatment).

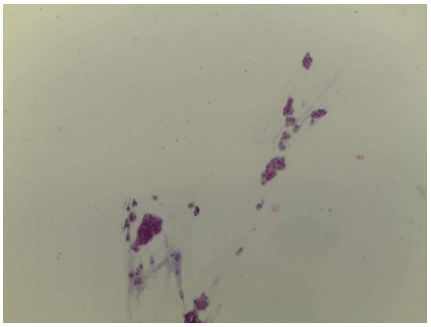


Figure 7: Conjunctival smears by impression cytology showing a large sheet of bland looking startified nonkeratinized squamous epithelial cells H and Ex 100 (pre-treatment).

After 3 months of the treatment: slides showing squamous metablasia and keratinization.

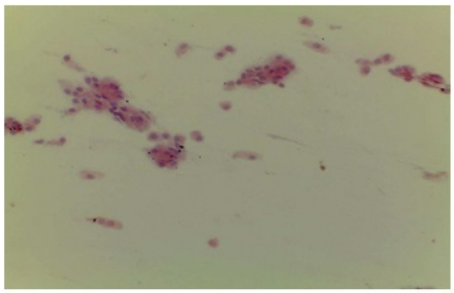


Figure 8: Conjunctival smears by impression cytology showing sheets of startified non-keratinized squamous epithelial cells entangling some cells having intracytoplasmic keratin. Some scattered (Metaplastic) spindles keratinized cells could also be seen. H and Ex 200 (post treatment).

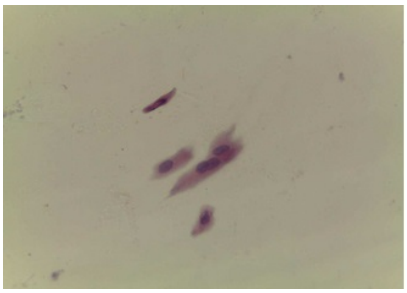


Figure 9: Conjunctival smears by impression cytology showing small sheets of startified keratinized squamous epithelial cells entangling. Some scattered (metaplastic) spindles keratinized cells could also be seen. H and Ex 400 (post treatment).

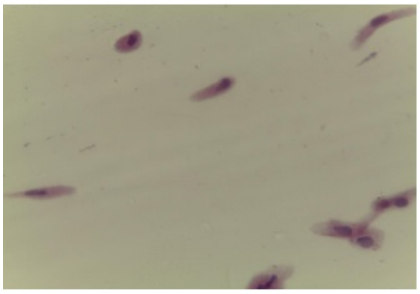


Figure 10: Conjunctival smears by impression cytology showing single scattered (metaplastic) spindles keratinized cells. H and Ex 400 (post treatment).

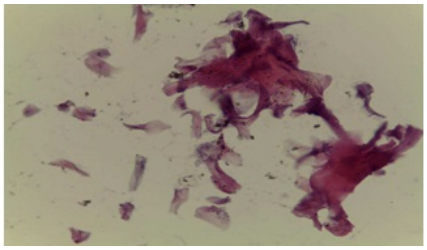


Figure 11: Conjunctival smears by impression cytology showing sheets of hyper keratinized startified squamous epithelial cells entangling. Some scattered (metaplastic) spindles hyper keratinized cells could also be seen. H and Ex 400(post treatment).

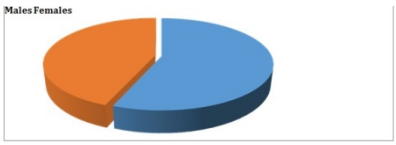


Figure 12: Description of personal data among cases.

Statistical Methods

Data management and statistical analysis were done using SPSS vs. 25. Numerical data was summarized as means and standard deviations. Categorical data was summarized as numbers and percentages. Breakup time and Shrimer test and nuclear cytoplasm ratio were compared pre and post treatment using paired t test. All P values were two sided. P values less than 0.05 were considered significant.

Results

The results are presented in tabular form below (Tables 1-7).

Age (years)	
Mean	45 ± 7
±SD	

Sex:	56 (56%)
Males (n, %)	
Females (n, %)	44 (44%)

Table 1: Description of personal data among cases.

Breakup time (sec)				
Pre treatment		Post treatment		
Mean	± SD	Mean	± SD	P value
13.08	1.13	6.4	2.09	<0.001

Table 2: Comparison between pretreatment and post treatment mean breakup time.

BCVA	N	%
18-Jun	16	16
12-Jun	20	20
09-Jun	36	36
06-Jun	28	28

Table 3: Description of the pre-treatment and post treatment BCVA.

BCVA did not change post treatment. Comparison between pretreatment and post treatment nuclear cytoplasmic ratio.

Schirmer test (mm/5min)				
Pretreatment		Post treatment		
Mean	± SD	Mean	± SD	P value
14.47	1.19	7.98	2.65	<0.001

Table 4: Comparison between pretreatment and post treatment Schirmer's test.

		N	%
Impression cytology Pre			
treatment	Normal	100	100 0.0
Impression cytology post treatment			
	Normal	84	84
	Squamous metaplasia		
		16	16

Table 5: Comparison between pretreatment and post treatment impression cytology results.

Nuclear cytoplasmic ratio		
Pre treatment	Post treatment	
Mean	± SD	Mean	± SD	p value
0.66	0.02	0.57	0.08	<0.001

Table 6: Comparison between pretreatment and post treatment dry eye symptoms.

		N	%
Dry eye symptoms pre treatment	No	100	100
Dry eye symptoms post treatment			
	Yes	44	44
	No	56	56

Table 7: According to nelson grading, pre-treatment impression cytology result was grade 0 in 100% of patients. While post treatment, 16% of patients, were grade 1 and grade 2.

Discussion

Dry eye is a common disorder, with an estimated 25% of patients in general ophthalmology. It is known that the incidence of dry eye increases with age and has a higher prevalence in women compared to men. Symptoms of dry eye have been standardized by use of questionnaires. The most common complaints described by patients include dryness or irritation, light sensitivity, foreign body sensation, red eyes and symptom fluctuation in different environmental conditions. However, it has also been noted that there is no strong correlation between signs and symptoms, particularly in mild dry eye. Therefore, the clinical diagnosis of dry eye needs to objective tests such as Schirmer's testing, fluorescein clearance and fluorescein breakup time (BUT)63.

There is no clinical test available that provides a direct measurement of lacrimal gland secretion. Schirmer's test is the most practical and most straightforward indirect test of lacrimal gland function. It measures basal and reflex tear secretion of the main and accessory lacrimal glands and the volume of the marginal tear film and tear lake. Tear BUT measurements assess the stability of the tear film. These tests lack sensitivity and specificity. Owing to the multifactorial nature of dry eye, there is a considerable confusion regarding the specificity of various diagnostic tests. Therefore, they should be used in combination with other tests to improve diagnostic accuracy as impression cytology which showed the highest sensitivity [17]. Also impression cytology plays an important role in diagnosis of dry eye and ocular surface changes. Ocular surface keratinization, squamous metaplasia prior to keratinization, and goblet cell density can be observed only by impression cytology, which therefore provides high sensitivity and gives reproducible index of severity of dry eyes. We believe as each test examines only part of the process, a more complete picture of tear film appears only when these tests are reviewed collectively.

Sofosbuvir is a newly introduced promising antiviral drug in combination with other antiviral treatment. In early 2014, the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America jointly published a recommendation for the management of hepatitis C. In this recommendation, sofosbuvir 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

[18]. Sofosbuvir is a nucleotide analogue that inhibits the RNA polymerase enzyme, which is a necessary factor needed in hepatitis C virus replication [19].

In our study, 100 patients were subjected to the study. The mean age of the patients was 45 year. There were 56 males and 44 females. After the treatment, BUT and Schirmer test declined from 13.08 second and 14.47 mm to 6.4 second and 7.98 mm respectively. Regarding impression cytology, the mean N/C ratio decreased from 0.66 to 0.57 while squamous metablasia and keratinization was found in 16% of patients post treatment. It was also found that 44% were complaining of dry eye symptoms after the treatment. In agreement with Salman study13 who enrolled 150 patients with chronic hepatitis C on treatment with sofosbuvir, he found that sofosbuvir affect ocular surface. He followed the patients during the three months of the treatment and for three months after stopping the treatment. In his study, there was no dry eye before sofosbuvir therapy.

His study showed that Schirmer test and BUT results changed significantly over the 6-month study period, which started to decrease at 1 month after the start of sofosbuvir antiviral drug therapy, decreased more after 3 months of treatment, and started to return to its normal value 1 month after the treatment was stopped. Mean Schirmer test values showed a significant change in the sofosbuvir group from 17.5 ± 2.7 mm at baseline to 10.8 ± 1.4 and 7.0 ± 2.5 mm after 1 and 3 months, respectively, and started returning to normal (11.0 ± 3.3 mm) after 1 month of stoppage of treatment and mean tear film breakup time varied from 11.0 ± 5.2 seconds at baseline to 9.2 ± 2.6 and 6.1 ± 1.2 seconds at 1 and 3 months, respectively. The mean nucleus/cytoplasm ratio was significantly different from 1/1.5 at baseline to 1/1.9 and 1/2.4 at 1 and 3 months, respectively.

Also, Thanaa, et al. [20] in their study at 2018, they did their research to find out the incidence of any ophthalmic adverse effects associated with sofosbuvir – ribavirin combination in patients having chronic hepatitis C. Their prospective nonrandomized comparative study was carried on 20 patients. All recorded patients were subjected to entire ophthalmic examination before the treatment strategy inauguration with periodic examination at 3 and 6 months during the treatment plan using Schirmer test and tear film breakup time test. There was no evidence of the enrolled patients to have dry eye before the start of antiviral drug therapy. It was found that Schirmer test and TBUT results changed significantly over the 6-month study period as they decreased at 3 months after the start of sofosbuvir antiviral drug therapy and continued to decrease throughout the period of follow-up. In this study, the baseline TBUT and Schirmer test decreased from 13.05 second and 18.02 mm to 11.85 second and 15.36 mm respectively. The results of Thanaa match that of Salman with reduction of Schirmer and TBUT over the course of antiviral treatment. We found some studies which link antiviral therapy with ocular surface changes. Huang, et al. [21] in 2005 evaluated ocular surface changes in patients with antiviral therapy for chronic hepatitis C. In this study, 19 patients with chronic hepatitis C undergoing a course of interferon alfa- 2b/ribavirin therapy participated in this prospective study. Patients were evaluated for dry eye subjectively (symptom assessment questionnaire) and objectively, including ophthalmologic examination, Schirmer test, tear clearance rate (TCR), tear function index (TFI), and nucleus/cytoplasm (N/C) ratio of conjunctival epithelial cell by impression cytology. All tests were performed before antiviral therapy (baseline); at 1, 3, and 6 months after initiation of therapy; and at 3 and 6 months after completing the 6-month course of treatment. The results showed that patients' mean score on the dry eye symptom assessment questionnaire was significantly higher than baseline after 1 and 3 months of therapy, peaked after 6 months of therapy, remained significantly elevated at 3 months after completion of therapy, but had decreased to almost baseline by 6 months after cessation of therapy. Compared with baseline, mean Schirmer test values showed a significant change only at 1 month after the start of treatment. In contrast, mean N/C ratio were significantly different from baseline at every examination, including 6 months after discontinuation of therapy. After 6 months of therapy, 4 patients (21%) had advanced squamous metaplasia. Although little is known about the pathogenesis of tear function changes in patients with chronic hepatitis C who were treated with a combination of sofosbuvir, IFN-alpha-2b, and ribavirin, the results of previous research showed that the mechanism for these changes could relate to changes in immune system function. Sofosbuvir is a nucleotide analog HCV polymerase inhibitor, which means that it blocks the polymerase enzyme that the virus uses to reproduce. There have been reports that patients receiving IFN, an immunomodulator, are more likely to develop new autoimmune diseases or experience exacerbations of preexisting ones, including systemic lupus erythematosus, rheumatoid arthritis, and Sjogren syndrome and that they are more likely to form autoantibodies in the absence of any clinically evident disease. Ribavirin also affects the immune system by promoting a change in the balance of T-helper cells (TH1/TH2) [22,23].

Also its was found that IFN combined with ribavirin promote the infiltration of lymphocytes, primarily T cells, into the lacrimal glands, and increase B cell activation factor secretion by epithelial cells24. This promote B-cell activation and maturation of plasma cells and the secretion of altered autoantibodies. IFN may be associated with the maturation of B cells into plasma cells and the production of altered antibodies. Alternatively, abnormally accumulated autoantibodies can form immune complexes with autoantigens, which participate in the local microenvironment of the lacrimal glands, as well as in the conjunctival mucosal membrane. These processes stimulate the activation of a chronic immune cascade, leading to dry eye caused by lacrimal gland and ocular surface dysfunction. In Yoshimoto et al. study, impression cytology showed pronounced signs of conjunctival epithelial metaplasia during and after combination treatment with sofosbuvir, IFN-a-2b, and ribavirin [23].

On the basis of these findings, it is presumed that IFN-a-2b and ribavirin promote the occurrence of dry eye by inducing inflammatory, autoimmune-like changes in the lacrimal gland and ocular surface, with subsequent alteration in the preocular tear film. Therefore, we believe that Sofosbuvir affect the ocular surface by the same mechanism and the effects of antiviral drugs were potentiated when they combined with sofosbuvir. However, further research is needed to conclude or to test this hypothesis. Our study confirmed the ocular surface changes that occur with sofosbuvir treatment. A related point to consider is that HCV is a chronic disease in Egypt and the government has a campaign to eliminate HCV in the whole country, therefore; our results should be taken in consideration to avoid any hazard from the treatment.

Drawbacks of our study were the absence of conjunctival biopsy and histopathology to confirm the pathological changes and its relation with changes in lacrimal function with these medications, another drawback is that there was no follow-up for the patients after cessation of therapy to detect if the dry eye is reversible. Follow-up is warranted to fully evaluate how the new antiviral agents alter the ocular surface in

patients with chronic hepatitis C on sofosbuvir and other antiviral treatments.

Summary and Conclusion

Egypt has the highest HCV prevalence in the world, 10%-20% of the general population is infected and HCV is the leading cause of chronic liver disease and hepatocellular carcinoma in the country.

The tear film overlays the ocular surface and provides the interface between the eye and the external environment. The tear film is essential for the nutrition and protection of the ocular surface and for clear vision as the tear film is the first refractive surface of the eye.

Dry eye is a disorder of the tear film which occurs due to tear deficiency or excessive tear evaporation. Dry eye is a common condition reported by patients who seek ophthalmologic care.

100 Egyptian subjects were enrolled in the study. All subjects were between 20 and 60 years old. Full ophthalmological examination was performed together with Schirmer 1test, TBUT test and impression cytology to all the cases.

Our study detected ocular surface changes after three months of sofosbuvir treatment for HCV. Many patients complained of dry eye symptoms. It was also observed that BUT increased while Schirmer test results were decreased. Also, squamous metablasia and keratinization was found in impression cytology.

These results indicate that a larger scale study with longer follow-up is warranted to fully evaluate how the new antiviral agents alter the physiology of tear production, tear dynamics, and the ocular surface in patients with chronic hepatitis C on sofosbuvir and other antivirals.

It may be recommended for the patients to be examined before starting sofosbuvir therapy to look for pre-existing ocular surface disease. If any is present, the patient should be monitored closely at monthly interval in addition to the use of artificial tears.

References

1. Anthony JB (2015) The definition and classification of dry eye disease. In: Colin Chan: Dry Eye A Practical Approach. pp:1-19.
2. Majid Moshirfar, Kasey Pierson, Kamalani Hanamaikai (2014) Artificial tears potpourri: A literature review. Clin Ophthalmol 8: 1419–1433.
3. Gary N Foulks, Michael AL, James VJ (2007) Report of the International Dry Eye Workshop (DEWS). J The Ocular Surface 5: 75-92.
4. Adam JP, Karen JC, Mary EF (2014) Dry eye in the beaver dam offspring study: Prevalence, risk factors, and health-related quality of life. Am J Ophthalmol 157: 799-806.
5. Saleh TA, McDermott B, Bates AK, Ewings P (2006) Phenol red thread test vs Schirmer's test: Comparative study. J Eye Lond 20: 913- 915.
6. Lemp MA (1973) Breakup of the tear film. Int Ophthalmol Clin:13: 97-102.
7. Shapiro A, Merin S (1979) Schirmer test and break-up time of tear film in normal subjects. Am J Ophthalmol 88: 752-757.
8. Lopin E, Deveney T, Asbell PA (2009) Impression cytology: Recent advances and applications in dry eye disease. Ocul Surf 7: 93-110.
9. El-Zanaty F, Way A (2008) Egypt demographic and health survey 2008. Cairo, Egypt: Ministry of Health, El-Zanaty and Associates, and Macro International. p: 431.
10. Elgharably Ahmed, Asmaa I Gomaa, Mary ME Crossey, Peter J Norsworthy (2016) Hepatitis C in Egypt-past, present, and future. Int J Gen Med 10: 1-6.
11. Cholongitas E, Papatheodoridis GV (2014) Sofosbuvir: A novel oral agent for chronic Hepatitis C. Ann Gastroenterol 27:331-337.
12. Yau AH, Yoshida EM (2014) Hepatitis C drugs: The end of the pegylated interferon era and the emergence of all-oral interferon-free antiviral regimens: A concise review. Can J Gastroenterol Hepatol 28: 445-51.
13. Salman AG (2016) Ocular surface changes with sofosbuvir in Egyptian patients with hepatitis C virus infection. J Cornea 35:323-328.
14. Chin Loy K, Farah Galaydh, Saad Shaikh (2016) Correction: Retinopathy and uveitis associated with sofosbuvir therapy for chronic Hepatitis C infection. J Cureus 8:3.
15. Na Li, Xin-Guo Deng, Mei-Feng He (2012) Comparison of the Schirmer I test with and without topical anesthesia for diagnosing dry eye. Int J Ophthalmol 5: 478-81.
16. Al Wadani FA, Rajshree Nambiar, Khalid M Abdul Wahhab (2016) Reliability and utility of impression cytology in the diagnosis of dry eye. Niger J Ophthalmol 24:51-6.
17. American Association for the Study of Liver Diseases (2014) Recommendations for testing, managing, and treating hepatitis C. Arlington: AASLD- IDSA
18. Fung A, Jin Z, Dyatkina N, Beigelman L, Deval J (2014) Efficiency of incorporation and chain termination determines the inhibition potency of modified nucleotide analogs against hepatitis C virus polymerase. Antimicrob Agents Chemother 58:3636-3645.
19. Mohammed Thana, Ali H Saad, Tarek M Yosef, Remon G Lamee (2018) Ocular effects of hepatitis c virus antiviral drugs. J Egyptian Ophthalmological Society 111: 1-6.
20. Huang FC, Shih MH, Chang TT, Lin SC, Tseng SH (2005) Tear function changes during interferon and ribavirin treatment in patients with chronic hepatitis C. J Cornea 24:561-566.
21. Chin-Loy K, Galaydh F, Shaikh S (2016) Retinopathy and Uveitis associated with sofosbuvir therapy for Chronic Hepatitis C infection. J Cureus 8:597.
22. Martin J, Navas S, Quiroga JA (1998) Effects of the ribavirin-interferon alpha combination on cultured peripheral blood mononuclear cells from chronic hepatitis C patients. Cytokine 10:635-644.
23. Yoshimoto, Tanaka M, Kojima M, Setoyama Y (2011) Regulatory mechanisms for the production of BAFF and IL-6 are impaired in monocytes of patients of primary Sjögren's syndrome. Arthritis Res Ther 13:170.