

# Risk Factors for Ocular Surface Disease in Tunisian Users of Preserved Antiglaucomatous Eye Drops

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## Abstract

**Purpose:** To study the clinical and the functional findings in glaucomatous patients under preserved eye drops having ocular surface alterations and to analyze their risk factors.

**Methods:** A cross-sectional study of 155 glaucomatous patients was conducted. All of them answered the “Ocular Surface Disease Index” (OSDI) questionnaire and had a complete and precise evaluation of the ocular surface state including a Schirmer I test, a tear break-up time evaluation, eyelid, conjunctival, and corneal examination with a Fluorescein and a Lissamine green test. We studied factors that could influence the OSDI score and each type of ocular surface alteration (age, sex, glaucoma treatment duration, number and type of the active principle, and Benzalkonium Chloride [BAK] use).

**Results:** BAK was used in 80% of cases. The OSDI score was  $\geq 13$ , in 61.3% of cases. The biomicroscopic signs of ocular surface disease were at least minimal in 87.1% of cases. The main predictors of OSDI score increase were the glaucoma treatment duration ( $P = 0.01$ ,  $t = 2.618$ ), the number of molecules used ( $P = 0.018$ ,  $t = 2.391$ ), and the use of BAK ( $P = 0.011$ ,  $t = 2.58$ ). The severity of the biomicroscopic signs correlated with these same risk factors. Fixed combination was statistically associated with a lower incidence of superficial punctate keratitis (SPK) and corneal and conjunctival staining in the Lissamine green test ( $P < 0.001$ ). Beta-blockers were associated with a significantly higher risk of SPK and corneal or conjunctival staining in the Lissamine green test ( $P < 0.001$ ).

**Conclusions:** Preserved antiglaucomatous eye drops alter the patients’ ocular surface. The main risk factors were advanced age, duration of glaucoma treatment, multiple therapies, and the use of BAK.

**Keywords:** Benzalkonium chloride, Conjunctiva, Cornea, Glaucoma, Ocular surface, Treatment

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## INTRODUCTION

Eye drops are the first-line treatment of primary open-angle glaucoma (POAG).<sup>1,2</sup> This treatment generally involves poly therapies used with elderly patients who suffer from ocular surface alterations. Preserved multidoses containing quaternary ammoniums, especially Benzalkonium Chloride (BAK), are mostly prescribed. Their cumulative use over time is likely to cause a real ocular surface disease, leading to treatment intolerance, poor compliance to the treatment, and life quality alteration.<sup>2-4</sup>

The effects of antiglaucomatous eye drops on the ocular surface have long been neglected by ophthalmologists whose main concern is the achievement of intraocular pressure target. There has been a real awareness of these effects thanks to *in vivo* and *in vitro* studies. Many studies have demonstrated that different topical medications used to treat glaucoma can affect the ocular surface to varying degrees and that the preservative-free treatment has fewer side effects than the preserved one.<sup>4</sup> In Tunisia, despite the increasing importance given to the examination of the ocular surface,

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most antiglaucoma eye drops are preserved.<sup>5,6</sup> The evaluation of ocular surface disease in the glaucomatous patient should be exhaustive and precise. It must consider both the functional aspect, which reflects the patient's experience and the clinical aspect on which the therapeutic approach will focus. In this study, we provided the clinician with a complete assessment of the ocular surface disease in glaucomatous patients under preserved eye drops that we could achieve in daily practice. We highlighted the clinical and the functional findings using Ocular Surface Disease Index (OSDI) scores and a thorough clinical examination of the ocular surface components that permit us to classify the severity. We also analyzed the risk factors of each lesion, and we tried to identify the relation between the clinical and the functional findings.

## METHODS

We conducted a cross-sectional study of 155 glaucomatous patients between July 2017 and June 2018. Our work was completed under the Helsinki Declaration tenets and approved by the local Ethics Committee at Forces de Sécurité Intérieure Hospital.

We included patients of 35 years old or more, presenting a well-controlled POAG and treated with preserved antiglaucomatous eye drops for at least 3 months. We excluded patients treated with nonpreserved antiglaucomatous eye drops, patients having used other preserved eye drops in the last three months, patients wearing contact lenses, patients with a history of systemic diseases that modified tear production and chemotherapy or radiotherapy. We also excluded, patients who underwent ocular surgeries (cataract, glaucoma, retina, and eye lid surgeries), patients with ocular infections and chemical burns, patients with ocular pathologies that could impair their visual function and that could interfere with the results of the OSDI questionnaire (dense cataract), and finally patients with cognitive or sensory abnormalities making it impossible to carry out the interrogation. We obtained the consent of all subjects after informing them of the objectives of the study. An ophthalmological examination, emphasizing the ocular surface was conducted. We have chosen to classify the subjective symptoms and the clinical signs separately because of the lack of systematic correlation between these two parameters during ocular surface diseases.

### Ocular Surface Disease Index score

The patients responded to an Arabic version of the OSDI, translated by a Jordanian team but not yet validated, in order to assess the functional signs of the dry eye symptoms after starting the antiglaucomatous treatment.<sup>7</sup> OSDI questionnaire consisted of 12 questions divided into three sections: the frequency of the symptoms, the effects of the symptoms on daily tasks, and the effect of the environmental factors such as wind and air conditioning. Total scores were categorized for severity as follows: normal ( $\leq 12$ ), mild (13–22), moderate (23–32), or severe ( $>32$ –100). Patients reported the type and the number of current glaucoma eye drops.

Each patient underwent the following consecutive tests in the following order. These tests were performed by the same physician, (H.L.) who received a proper training to grade ocular surface disease.

### Tear film evaluation

Tear film state was assessed using the Schirmer I test then tear break-up time (TBUT) test. The Schirmer I test was performed with the patient's eyes closed, using a filter paper (Schirmer strips freedom), without local anesthesia and lasted 5 min. The Schirmer I test value was classified into normal ( $>10$  mm), minimal to moderate (6–10 mm), severe (3–5 mm), and very severe ( $<3$  mm).

### Eyelid examination

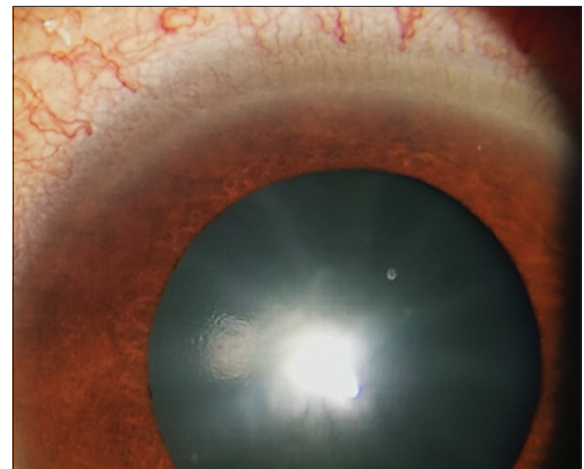
The presence of blepharitis, meibomian glands dysfunction, palpebral telangiectasia, palpebral mal position, or eczema was noted. To classify the meibomian glands dysfunction, we evaluated the inflammation of lid margin (thickening, vascularity, and telangiectasia), gland orifices, and character of secretion expressed (volume, quality, and expressibility) as well as gland dropout, lid margin notching, and tear film debris according to Bron *et al.*<sup>8</sup> Then, we estimated if these abnormalities were variably present or frequent to determine the severity of the ocular surface damage.<sup>9</sup>

### Conjunctival examination

The conjunctival hyperemia was classified into minimal, moderate, or severe.<sup>9</sup> Conjunctival folds (Lid-parallel conjunctival folds [LIPCOF] classification) were noted. They were observed without fluorescein instillation on the bulbar conjunctiva in the zone perpendicular to the temporal and nasal limbus above the lower eyelid (temporal and nasal LIPCOF), with high magnification  $\times 25$ .<sup>10</sup> Only the parallel and permanent conjunctival folds (LIPCOF, height of the folds = 0.08 mm) were retained.

### Corneal examination

Patients with corneal new vessels were classified as having a severe dry eye syndrome [Figure 1]. Hypoesthesia was



**Figure 1:** Corneal new vessels in the corneal upper sector

subjectively evaluated by a soft stimulation of the cornea with cotton because esthesiometer was not available in our department.

### **Lissamine green test**

A Lissamine green test with Van Bijsterveld score was performed to identify an abnormal corneal or conjunctival staining. This is a score varying between 0 and 9 (for each sector: nasal, temporal, and corneal conjunctiva were noted from 0 to 3).<sup>11</sup>

### **Fluorescein test**

The ocular surface was evaluated by instilling one drop of 0.5% sterile fluorescein (Fluoresceine Faure 0.5%) into the conjunctival sac to detect conjunctival and corneal lesions. We measured the status of the ocular surface using the Oxford Grading Scale, which quantifies the conjunctival and corneal alterations from 0 to 5.<sup>9</sup> The TBUT was also evaluated; it is the time (s) between a blink and the appearance of a dark spot in the fluorescein. The test should be repeated three times, and the average was used to obtain the most reliable result. The TBUT was classified into normal (>10 mm), minimal to moderate (6–10 mm), and severe (<5 mm).

### **Dry eye classification**

We categorized the biomicroscopic damage of the ocular surface according to its severity, based on the Dry Eye WorkShop (DEWS) classification 2007.<sup>9</sup> We have studied certain factors that could influence the OSDI score, the symptomatology, and the type of ocular surface alteration. These factors were the age of the patients and their sex, the glaucoma treatment duration, the number of molecules (we noted the fixed or the separate combination in case of multiple therapies), the types of molecules, and the presence of BAK.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22 (IBM Corp., Armonk, N.Y., USA).

Quantitative variables were expressed by means and standard deviation (SD). The qualitative variables were expressed by their numbers and their percentages. The associations between the OSDI scores and the qualitative variables were analyzed using the Chi-square test of Pearson and Fisher's exact test. Student's *t*-test, with the calculation of the Pearson correlation coefficient *r*, was used to study the correlations between the OSDI scores quantitative variables ( $P < 0.05$  was considered statistically significant). A correlation between the OSDI score and the severity of the ocular surface disease was searched by drawing up a contingency table with Kendall's tau calculation ( $\alpha < 0.4$  signifies the absence of concordance).

## **RESULTS**

Overall, 155 patients with a mean age of  $62.74 \pm 10.69$  years (from 36 to 84 years) were studied. Demographic features of our patients are summarized in Table 1. The patients were under treatment with either monotherapy or multiple therapies as fixed or separate combination [Tables 2 and 3] for a mean of

5.9 years (6 months to 26 years). The BAK was used in 67.7% of cases, polyquaternium was used in 20% of cases, and a combination of the two preserving agents was used in 12.3% of cases. Preservative-free artificial tears (Celluvisc® unidose, Lacrymed® unidoses) were used after starting the glaucoma treatments in 52.3% of patients.

The first treatment was changed in 20 cases (12.9%) because of the ocular surface-related side effects such as redness and or gritty eye feeling. BAK preserved eye drops were changed by polyquaternium preserved eye drops in 12 patients (7.7% of cases).

### **Ocular Surface Disease Index score**

Subjective symptoms were reported in 140 patients (90.3%). The most common functional sign was gritty eye feeling (reported by 65.8% of patients) followed by blurred vision (reported by 61.3% of patients). The OSDI score was categorized as normal in 38.7% of cases, mild in 22.6% of cases, moderate in 16.1% of cases, and severe in 22.6% of cases. In the multivariate study, the main predictors of OSDI score increase were the glaucoma treatment duration ( $P = 0.01$ ,  $t = 2.618$ ), the number of molecules used ( $P = 0.018$ ,  $t = 2.391$ ), and the use of BAK ( $P = 0.011$ ,  $t = 2.58$ ).

### **Clinical alteration of the ocular surface**

The correlation between the risk factors and the ocular surface alteration is summarized in Table 4.

### **Tear film alterations**

The TBUT and Schirmer I test value decrease was noted, in 131 patients (84.5%), and in 82 patients (52.9% of cases), respectively. On multivariate analysis, the main predictors of tear film changes were the glaucoma treatment duration ( $P = 0.006$  for the TBUT,  $P = 0.003$  for the Schirmer I test), the number of molecules used ( $P < 0.001$  for the TBUT,  $P < 0.001$  for the Schirmer I test), and the presence of BAK ( $P < 0.001$  for the TBUT,  $P < 0.001$  for the Schirmer I test).

### **Eyelid damages**

The meibomian glands dysfunction was the most common palpebral abnormality, as it was observed in 103 patients (66.5%). The multivariate analysis revealed that the main predictors of eyelids damage were the glaucoma treatment duration ( $P < 0.001$  for blepharitis,  $P < 0.001$  for meibomian glands dysfunction,  $P = 0.049$  for telangiectasia,  $P = 0.025$  for eczema,  $P = 0.034$  for keratinisation, and  $P = 0.01$  for symblepharon), and the number of molecules used ( $P = 0.049$  for blepharitis,  $P < 0.001$  for meibomian glands dysfunction,  $P < 0.001$  for telangiectasia,  $P = 0.03$  for eczema,  $P = 0.038$  for keratinization, and  $P = 0.031$  for symblepharon).

### **Conjunctival damages**

Conjunctival folds (LIPCOF) were observed in 128 patients (82.6%). Conjunctival hyperemia was noted in 72.3% of cases. On multivariate analysis, the main predictors of conjunctival folds (LIPCOF) and conjunctival hyperemia were the glaucoma treatment duration ( $P < 0.001$  for conjunctival

**Table 1: Demographic features of the glaucomatous patients**

Demographic features	Results
Average age	62.74±10.69 years (from 36 to 84 years).
Sex ratio (male/female)	1.5
Diabetes	36.8%
Average glaucoma treatment duration	5.9 years (6 months-26 years)

**Table 2: The distribution of preserved antiglaucomatous medications used**

Medications	Patients, n (%)	Total (%)
Prostaglandines		
Latanoprost (Xalatan®)	30 (19.4)	78 (50.3)
Travoprost (Travatan®)	26 (16.8)	
Bimatoprost (Lumigan®)	22 (14.2)	
Beta-blockers		
Timolol (Tunolol®)	4 (2.6)	25 (16.1)
Carteolol (Carteol Lp®)	20 (12.9)	
Bétaxolol (Betoptic®)	1 (0.6)	
Carbonic anhydrase inhibitors		
Dorzolamide (Alzor®)	25 (16.1)	29 (18.7)
Brinzolamide (Azopt®)	4 (2.6)	
Alpha-2-Agonists=brimonidine (a2) (Alphagan®)	16 (10.3)	16 (10.3)
Pg + Bb*		
Latanoprost + timolol (Xalacom®)	16 (10.3)	47 (30.3)
Travoprost + timolol (Duo trav®)	24 (15.5)	
Bimatoprost + timolol (Ganfort®)	7 (4.5)	
CAI + Bb <sup>†</sup> (dorzolamide + timolol) (Cosopt®, Zolol®)	17 (10.9)	17 (10.9)
a2 + Bb <sup>‡</sup> (brimonidine + timolol) (Combigan®)	2 (1.3)	2 (1.3)

\*Fixed combination of Pg and Bb; <sup>†</sup>Fixed combination of carbonic anhydrase inhibitor and Bp; <sup>‡</sup>Fixed combination of a2-adrenergic and Bb. a2: Alpha-2, Bp: Beta-blocker, Pg: Prostaglandin

**Table 3: Distribution of antiglaucomatous medication number**

Active principle number	Patients, n (%)	Total (%)
One active principle	74 (47.7)	74 (47.7)
Fixed combination	35 (22.6)	44 (28.4)
2 separate active principles	9 (5.8)	
Fixed combination + one active principle	25 (16.1)	30 (19.4)
3 separate active principles	5 (3.3)	
Fixed combination + 2 separate active principles	6 (3.9)	7 (4.5)
4 separate active principles	1 (0.6)	
Total	155	155

folds and  $P < 0.001$  for conjunctival hyperemia), the number of molecules used ( $P < 0.001$  for conjunctival folds,  $P < 0.001$  for conjunctival hyperemia), and the use of BAK ( $P = 0.024$  for conjunctival folds,  $P = 0.028$  for conjunctival hyperemia).

### Corneal damages

Corneal new vessels and corneal hypoesthesia were noted, in 13 patients (8.4%) and in 12 patients (7.7%), respectively. On multivariate analysis, the main predictors of these corneal alterations were the glaucoma treatment duration ( $P = 0.001$  for corneal new vessels,  $P < 0.001$  for hypoesthesia), and the number of molecules used ( $P < 0.001$  for corneal new vessels,  $P = 0.042$  for hypoesthesia).

### Lissamine green test

The Lissamine green test showed an abnormal staining in 77 cases (49.7%). On multivariate analysis, the main predictors of abnormal staining in Lissamine green test were the glaucoma treatment duration ( $P = 0.008$ ), the number of molecules used ( $P < 0.001$ ), and the presence of BAK ( $P < 0.001$ ). We found that the use of separate molecules was correlated with a significantly higher risk of a pathological test ( $P < 0.001$ ), as well as the use of beta-blockers as a monotherapy compared to other types of molecules ( $P < 0.001$ ).

### Fluorescein test

We observed superficial punctate keratitis (SPK) in 108 patients (69.7%), filamentary keratitis in four

**Table 4: Correlation between the clinical ocular surface damages and risk factors**

Signs	Age	Glaucoma treatment duration	Medications number	Fixed versus separate combination	Active principle	BAK
Pathological OSDI score	$P < 0.001$ $r = 0.299$	$P < 0.001$ $r = 0.285$	$P = 0.011$ $r = 0.204$	$P = 0.188$	$P = 0.188$	$P = 0.004$
Anterior blepharitis	$P < 0.001$ $r = 0.309$	$P < 0.001$ $r = 0.387$	$P < 0.001$ $r = 0.304$	$P = 0.291$	$P = 0.607$	$P = 0.605$
Meibomian glands dysfunction	$P < 0.001$ $r = 0.532$	$P < 0.001$ $r = 0.478$	$P < 0.001$ $r = 0.466$	$P = 0.285$	$P = 0.155$	$P = 0.004$
Palpebral telangiectasia	$P < 0.001$ $r = 0.479$	$P < 0.001$ $r = 0.279$	$P < 0.001$ $r = 0.332$	$P = 0.83$	$P = 0.605$	$P = 0.591$
Palpebral eczema	$P = 0.001$ $r = 0.265$	$P < 0.001$ $r = 0.291$	$P < 0.001$ $r = 0.318$			$P = 0.341$
Keratinisation	$P = 0.179$	$P < 0.001$ $r = 0.297$	$P < 0.001$ $r = 0.34$			$P = 0.194$
Symblepharon	$P = 0.273$	$P < 0.001$ $r = 0.325$	$P < 0.001$ $r = 0.278$			$P = 0.147$
Conjunctival hyperemia	$P < 0.001$ $r = 0.446$	$P < 0.001$ $r = 0.535$	$P < 0.001$ $r = 0.538$	$P = 0.15$	$P = 0.936$	$P < 0.001$
LIPCOF	$P < 0.001$ $r = 0.572$	$P < 0.001$ $r = 0.523$	$P < 0.001$ $r = 0.549$	$P = 0.475$	$P = 0.964$	$P < 0.001$
Corneal new vessels	$P = 0.002$ $r = 0.252$	$P < 0.001$ $r = 0.431$	$P < 0.001$ $r = 0.503$	$P = 0.3$		$P = 0.249$
Impaired corneal sensitivity	$P < 0.001$ $r = 0.344$	$P < 0.001$ $r = 0.555$	$P < 0.001$ $r = 0.394$	$P = 0.3$		$P = 0.072$
SPK	$P < 0.001$ $r = 0.465$	$P < 0.001$ $r = 0.465$	$P < 0.001$ $r = 0.465$	$P < 0.001$ $r = 0.465$ (sep) <sup>§</sup>	$P < 0.001$ $r = 0.465$ (Bb) <sup>  </sup>	$P = 0.001$
Filamentous keratitis	$P = 0.107$ $r = 0.13$	$P < 0.001$ $r = 0.36$	$P < 0.001$ $r = 0.36$			$P = 0.081$
Corneal ulcers	$P = 0.182$ $r = 0.108$	$P < 0.001$ $r = 0.32$	$P < 0.001$ $r = 0.32$			$P = 0.48$
Decreased TBUT	$P < 0.001$ $r = 0.49$	$P < 0.001$ $r = 0.445$	$P < 0.001$ $r = 0.485$	$P = 0.375$	$P = 0.819$	$P < 0.001$
Decreased Schirmer I value	$P < 0.001$ $r = 0.393$	$P < 0.001$ $r = 0.383$	$P = 0.002$ $r = 0.298$	$P = 0.837$	$P = 0.54$	$P = 0.03$
Decreased tear film	$P < 0.001$ $r = 0.505$	$P < 0.001$ $r = 0.381$	$P < 0.001$ $r = 0.384$	$P = 0.448$	$P = 0.679$	$P = 0.022$
Staining in lissamine green test	$P < 0.001$ $r = 0.422$	$P < 0.001$ $r = 0.397$	$P < 0.001$ $r = 0.385$	$P < 0.001$ (sep)	$P < 0.001$ (Bb)	$P < 0.001$

<sup>§</sup>Separated molecules, <sup>||</sup>Beta-blockers, Empty boxes: Not evaluated. BAK: Benzalkonium chloride, OSDI: Ocular surface disease index, SPK: Superficial punctate keratitis, TBUT: Tear break-up time, LIPCOF: Lid-parallel conjunctival fold

patients (2.6%), and corneal ulcers in two patients (1.3%). The SPK was more than Oxford III in 16.7% of cases. On multivariate analysis, the main predictors of SPK were the glaucoma treatment duration ( $P = 0.007$ ), the number of molecules used ( $P < 0.001$ ), and the presence of BAK ( $P < 0.001$ ). For filamentary keratitis and corneal ulcers, only the glaucoma treatment duration was retained ( $P = 0.007$  and  $P = 0.001$ ). We noted that the use of a separate combination can lead to a much higher risk of developing SPK than with a fixed combination.

### Classification of the clinical ocular surface damages

Ocular surface damages were mild in 51.2% of patients, moderate in 25.9% in patients, or severe in 22.9% of cases. On multivariate analysis, the main predictors of biomicroscopic

damage to the ocular surface were the glaucoma treatment duration ( $P < 0.001$ ), the number of molecules ( $P < 0.001$ ), and the use of BAK ( $P = 0.012$ ). A discrepancy between the severity of the OSDI score and that of ocular surface alteration signs was observed (Kendall's tau  $< 0.4$ ).

## DISCUSSION

Our study highlights the severity of the ocular surface diseases occurring in glaucomatous patients under preserved eye drops. The prevalence of the ocular surface pathologies in glaucomatous patients varied from one series to another and may reach 79%.<sup>12</sup> A higher prevalence in our country could be explained by environmental factors such as air pollution and high exposure to ultraviolet rays. Most studies have

categorized the severity of dry eye syndrome in glaucomatous patients based on OSDI scores only or combining OSDI scores and biomicroscopic signs. The lack of correlation between these two parameters in certain cases explains the absence of a global classification and makes the interpretation of the results more complicated.<sup>4,6,12</sup> Our study showed a higher prevalence of biomicroscopic signs with 87.1%, compared with the subjective symptoms 61.3%. In addition, some patients had a normal or a mild OSDI score contrasting with their severe clinical damages. On the contrary, some patients had an OSDI score categorized as severe with mild clinical damages. This discrepancy can have several causes. It may be due to a neuropathic pain caused by the somatosensory system disease.<sup>6,13,14</sup> It can also be compatible with a preclinical stage of the disease, especially when the symptoms are intermittent.<sup>15</sup> In other cases, it could be related to an impairment of corneal sensitivity, either by the antiglaucomatous eye drops,<sup>14</sup> which may explain the good tolerance of local treatment in these patients.<sup>14</sup> This was the case of 12 patients who were suffering from an impaired corneal sensitivity that led to severe clinical lesions. This contrasted with a normal or mild OSDI score. For these reasons, we chose to separate the functional signs using the OSDI score and the clinical signs following the DEWS classification.<sup>9</sup>

The management of ocular surface diseases requires, thus, both functional and clinical assessment. The OSDI questionnaire is the most used questionnaire to assess the severity of symptoms, especially in glaucomatous patients.<sup>16-18</sup> It has high sensitivity and specificity (80% and 79%, respectively) to identify dry eye syndrome patients from normal subjects, especially in severe cases (sensitivity of 87%; specificity of 96%).<sup>19</sup> In glaucoma patients, using the OSDI questionnaire, Leung *et al.* found symptoms of the dry syndrome in 59% of patients with a score categorized as severe in 27% of cases.<sup>12,16</sup> Our study categorized 22.6% of the cases as having a severe OSDI score. We are, however, aware of its limitations because it combines all responses into a single total score, which may hide differences among the various aspects of the disease. These differences become clear when the subscores are evaluated separately (two components: visual function versus ocular discomfort-related symptoms).<sup>20</sup>

Regarding the clinical signs, we found that the TBUT alteration occurred in 84.5% of cases. Our results concurred with the studies finding that altered TBUT was the most observed biomicroscopic sign in up to 60% of patients under BAK preserved eye drops. This was explained by the detergent effect of the BAK on the lipid component of tears and the mucous goblet cells destruction which cause tear film instability and may explain the TBUT alteration.<sup>6,13</sup> The active principle can also destabilize the precorneal tear film,<sup>6,13</sup> by decreasing the goblet cells number, altering the mucin layer, and decreasing the tears lysozymes.<sup>13,21</sup> Moreover, certain active principles (such as beta-blockers) decrease the production of tears<sup>21</sup> and lead to the tear meniscus impairment and Schirmer's test value decrease.<sup>14,22</sup>

The prevalence of meibomian dysfunction in glaucomatous patients reached 80%, and it was significantly correlated with the number of molecules used, the presence of BAK, and the use of prostaglandins.<sup>14-25</sup> The prevalence of blepharitis in glaucomatous patients varied in different studies between 16% and 22.2% of cases.<sup>25</sup> Palpebral eczema found in 6%–9% of patients, witnessed the allergic mechanism.<sup>25</sup>

The toxic effect of preserved eye drops leads to a conjunctival and limbic hyperemia, proving the inflammatory mechanism. That is why conjunctival hyperemia was very common, ranging between 41% and 60.3% of cases. Patients with high LIPCOF grades are more likely to suffer from severe dry eye syndrome.<sup>26</sup> In our series, 64.2% of glaucomatous patients had at least a LIPCOF 1 grade. Lesions might be more serious and might develop into ocular pseudopemphigoid and subconjunctival fibrosis.<sup>21,27,28</sup> Toxicity and inflammation induce tears hyperosmolarity and lead to corneal epithelial cells alterations and to SPK occurrence.<sup>12,13,21,29,30</sup> They also damage the deep corneal nerves, causing an impaired corneal sensitivity.<sup>31,32</sup>

Factors influencing the OSDI score and ocular surface damages were also studied.<sup>4,11</sup> Certain factors may influence the OSDI score in glaucomatous patients such as ethnicity, glaucoma treatment duration, molecules number,<sup>33</sup> or BAK preserved eye drops,<sup>20</sup> confirming our results. Some studies found a positive correlation between the OSDI score and biomicroscopic signs, especially ocular surface staining, and stipulated that OSDI score may be a predictor of corneal epithelial cells damage.<sup>12</sup>

The risk of ocular surface damage increases with age,<sup>15,34</sup> which we found in our study. We found no correlation between sex and OSDI score ( $P = 0.366$ ), nor between sex and biomicroscopic signs ( $P = 0.445$ ). Two recent meta-analyses have shown a correlation between the duration of eye drop treatment and the prevalence and severity of dry eye syndrome.<sup>4,35</sup> This goes in line with the results of our study which showed that a glaucoma treatment duration of more than 5 years constituted a threshold value for an OSDI score value to increase and for a biomicroscopic damage to appear. Several studies have found a positive correlation between the number of molecules and the OSDI score and between the number of molecules and the ocular surface alterations.<sup>35-37</sup> In our study, although we used a small subgroup to compare the fixed combination with the separate one (respectively, 35 and nine patients), we found that the fixed combination was correlated with a significantly lower risk of having PSK or a staining in the Lissamine green test.

Some active principles should be used with caution with these patients. In fact, topical beta-blockers have the most significant adverse effects on the ocular surface.<sup>38</sup> Prostaglandin analogs are associated with a higher risk of meibomian glands dysfunction.<sup>39</sup> To choose an additional treatment in a poorly balanced glaucoma patient, we must consider that the alpha-agonist seems to present a lower risk of dry eye syndrome compared to carbonic anhydrase inhibitors<sup>40</sup> but with a higher risk of ocular allergy.<sup>41</sup> The factor that plays a major role in ocular surface alterations in patients under

antiglaucomatous eye drops is the BAK.<sup>4,42</sup> Large series concluded that conjunctiva, cornea, and eyelids damages significantly decreased when patients were switched from preserved to preservative-free eye drops, or when the number of BAK preserved medication was decreased.<sup>25,27</sup>

Our study has several limitations such as a small sample size which is not nationally representative, a single grader, and the absence of photo documentation. We also used an Arabic version of the OSDI questionnaire not yet validated. Furthermore, although the high OSDI scores are generally associated with a significant alteration of the ocular surface, it can also be attributed to a deficit of the visual field.

In conclusion, preserved antiglaucomatous eye drops alter the patients' ocular surface and influence the outcomes of glaucoma management. The main risk factors found in our study were advanced age, duration of glaucoma treatment, multiple therapies, and the use of BAK. Clinicians should properly assess the ocular surface because topical glaucoma treatment may lead to the failure of future surgical interventions and ultimately vision loss.

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### Conflicts of interest

There are no conflicts of interest.

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