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Improvement in Glaucoma Patient Quality of Life by Therapy Switch to Preservative-Free Timolol/Dorzolamide Fixed Combination

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Key Words
Glaucoma medical treatment · Preservative-free glaucoma therapy · Glaucoma Symptom Scale · Visual-related quality of life

Abstract
Purpose: To assess a change in visual-related quality of life (QoL) in glaucoma patients after switching from preservative-containing medical therapy to preservative-free unit dose timolol/dorzolamide fixed combination (TDFC UD). ***Methods:*** Prospective, noninterventional, multicenter 8-week study. Primary outcome was a change in visual symptoms at week 8, as assessed by the Glaucoma Symptom Scale (GSS). ***Results:*** 80 patients completed the study. There was a clinically significant increase in the scores of all GSS-related categories at week 8 when compared to baseline (GSS symptom week 8: +21.15 ± 37.9%, GSS function week 8: +10.3 ± 31.6%, both $p < 0.001$ vs. baseline). Comparison between patients taking only TDFC UD and patients taking TDFC UD plus concomitant medications did not detect differences in any GSS category ($p > 0.50$ in all comparisons). ***Conclusions:*** Switching to TDFC UD significantly improved the self-reported QoL of glaucoma patients. This can be seen even in patients who are taking concomitant ocular treatments.

Introduction

Glaucoma is one of the major causes of irreversible blindness in the industrialized world [1]. Management of this disease has focused mainly on reducing the main modifiable risk factor which is intraocular pressure (IOP) [2]. As such, a large majority of glaucoma patients are under life-long topical IOP-lowering therapies in order to prevent or slow down disease progression. However, most drugs at the ophthalmologist's disposal have important drawbacks, one of them being the presence of preservatives such as benzalkonium chloride. These preservative agents have been consistently documented to potentiate dry-eye-related symptoms such as redness, foreign-body sensation and tearing [3–5]. The high prevalence of such complaints in glaucoma patients has been pointed out as a significant factor contributing to the decrease in visual-related quality of life (QoL) these patients are known to have [6–8]. This is particularly relevant as most of the symptoms the patients experience derive from the topical

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medication and not the underlying glaucomatous disease. As such, research has evolved to explore medical alternatives that can reduce this iatrogenically-induced discomfort. The introduction of preservative-free therapies, such as preservative-free unit dose timolol/dorzolamide fixed combination (TDFC UD), have demonstrated preservative-related ocular surface complaints to be at least partially reversible, while maintaining IOP-lowering efficacy [9, 10]. However, the question remains as to whether these ocular changes have a real impact on ocular comfort as perceived by a glaucoma patient taking preservative-containing topical medication, and whether switching to preservative-free therapies can actually increase the level of the patients' QoL.

We therefore conducted a prospective, observational tolerability study in order to assess the real-life impact on the visual-related QoL of switching from preservative-containing medical therapy to TDFC UD.

Methods

Design

This was an 8-week, prospective, multicenter, noninterventional, open-label single-arm study performed in Belgium between December 2011 and March 2012 in 16 participating centers. Medically treated glaucoma patients who were switched from preservative-containing IOP-lowering treatment to TDFC UD were asked to join the study. The decision to change therapy was entirely at the discretion of the treating ophthalmologist. A questionnaire concerning their ocular symptoms (Glaucoma Symptom Scale, GSS) was filled in prior to the therapy switch (baseline) and repeated at weeks 4 and 8 after initiation of the treatment with TDFC UD. Considering the noninterventional design, no specific study visits were planned. As such, patients with scheduled consultations for medical reasons within 1 week of the established time frame (weeks 4 and 8) would fill in the questionnaire at that consultation. If not, they were contacted within the same period of time to fill in and send back the questionnaire.

This study was approved by the Institutional Review Board of all the centers involved and adhered to the tenets of the Declaration of Helsinki. All eligible patients who agreed to participate in the study signed an informed consent before enrollment. The study has been registered in clinicaltrial.gov (NCT01923714).

Patients

Patients with glaucoma (as defined by characteristic optic disc damage and visual field defects [2]) who were switched from preservative-containing medical therapy to TDFC UD were eligible for this study. Disease stage was stratified using the modified classification of Hodapp et al. [11].

Inclusion criteria were defined as age ≥18 years, diagnosed as having open-angle glaucoma, currently treated with preserved IOP-lowering therapy and willing to sign a written informed consent. Ocular surgery within the past 6 months or a visual acuity higher than 1 in the logMAR scale on the study eye(s), mental or physical disability that could interfere with self-reported assessment, pregnancy, and known hypersensitivity to dorzolamide and/or timolol were considered exclusion criteria.

Glaucoma Symptom Scale

The GSS is a 10-item Likert-type questionnaire that evaluates the ocular complaints experienced by the patient by means of questions about symptomatic (GSS-SYMP: burning, smarting, stinging; tearing; dryness; itching; soreness, tiredness; feeling of something in the eye) as well as functional complaints (GSS-FUNC: blurry, dim vision; hard to see in daylight; hard to see in dark places; halos around lights). Each of these items is graded from 0 to 4 in a decreasing degree of severity of complaints (0 = very bothersome; 4 = symptom absent). The score in this questionnaire is then expressed on a scale ranging from 0 to 100, with lower scores indicating higher severity of symptoms. In this study, calculations were made for the overall GSS (GSS total), for GSS-SYMP and GSS-FUNC, and for each item individually. The questionnaire was performed for both eyes separately, and the results were averaged between the two eyes. All the items in the questionnaire had to be filled in at baseline; at weeks 4 and 8, questionnaires were accepted if missing information accounted for less than 50% of the main category (maximum 5 missing items in GSS total, 3 in SYMP or 2 in FUNC).

Outcomes

The primary outcome of this study was a change in ocular surface complaints (using the GSS-SYMP questionnaire) 8 weeks after switching preservative-containing therapy to preservative-free TDFC UD in glaucoma patients with symptomatic ocular surface disease. The secondary objectives included the same assessment (impact of the switch on GSS values) but at 4 weeks. Additionally, a change in self-reported ocular functional complaints (GSS-FUNC) 4 and 8 weeks after switching was also investigated. A mean increase larger than 7 in the GSS score was considered as clinically significant, as described in the literature [12].

Statistics

Data was assessed for normal distribution using the Kolgomorov-Smirnov test. Logarithmic transformation of the nonnormally distributed variables was made prior to the application of the statistical tests. Differences in GSS between baseline, week 4 and week 8 were assessed by the paired Student's t test. The χ^2 test and nonparametric matched-pairs signed rank test were used to determine differences in proportion of categorical variables and nonnormally distributed variables, respectively. Statistical analysis was performed using the SAS system version 9.1.3 (SAS Institute Inc., Cary, N.C., USA). Data are presented as means ± standard deviation unless otherwise indicated.

Results

Of the 102 patients who completed the initial GSS questionnaire (baseline population characteristics depicted in table 1), 99 (97.1%) filled in the questionnaire at week 4 and 80 patients (78.4%) completed the GSS form at the 8-week study. The remaining 22 patients (21.6%) did not complete the study for one of the following rea-

Table 1. Baseline characteristics of the study population (n = 102)

Mean age ± SD, years	66.2±12.8
Gender, n	
Male	41 (40.2)
Female	61 (59.8)
Mean visual acuity ± SD, logMAR	
Best eye	0.09±0.10
Worst eye	0.20±0.23
Mean IOP ± SD, mm Hg	
Right eye	18.1±5.1
Left eye	17.5±4.1
Mean disease duration ± SD, years	5.7±5.3
Disease stage, n	
Early (MD: 0–6 dB)	60 (58.9)
Moderate (MD: 6–12 dB)	26 (25.5)
Advanced (MD: >12 dB)	16 (15.7)
Previous ocular surgery, n	35 (34.3)
Ocular comorbidity, n	
Keratitis	8 (7.84)
Cataract	26 (25.5)
AMD	7 (6.9)
High myopia	3 (2.9)
Previous glaucoma therapy, n	
Monotherapy	57 (55.9)
Two drugs separate combination	19 (18.6)
Two drugs fixed combination	21 (20.6)
Three or more drugs	5 (4.9)
Mean duration of preserved treatment ± SD, years	3.0±3.1

MD = Visual field mean defect; n = patients numbers; IOP = intraocular pressure; dB = decibel; logMar = logarithm of the minimum angle of resolution; AMD = age-related macular degeneration; SD = standard deviation. Figures in parentheses indicate percentages. Disease stage indicates disease classification according to the Hodapp-Anderson-Parish score.

Table 2. GSS scores during the study

GSS score	Baseline (n = 102)	Week 4 (n = 99)	Week 8 (n = 80)	p value
Total score				<0.001
Mean ± SD	65.38±36.4	76.64±31.4	81.92±29.04	
95% CI	63.14–67.61	75.67–78.60	79.91–83.94	
GSS-SYMP				<0.001
Mean ± SD	59.57±36.01	74.24±31.55	80.25±28.91	
95% CI	56.71–62.42	71.70–76.79	77.65–82.64	
GSS-FUNC				<0.001
Mean ± SD	74.03±35.32	80.26±30.82	84.44±29.10	
95% CI	70.61–77.45	77.20–83.32	81.24–87.65	

Absolute values of the mean GSS ± SD, including symptomatic (SYMP) and functional (FUNC) categories during the study. All pairwise comparisons were statistically significant. CI = Confidence Interval; SD = standard deviation.

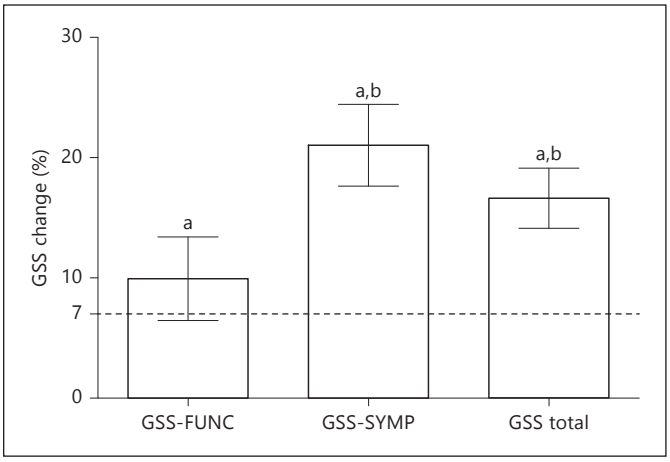

Fig. 1. Mean change from baseline (in percent) of GSS total scores and both symptomatic (GSS-SYMP) and functional (GSS-FUNC) subcategories at the end of the study (week 8). The superscript letter a indicates a statistically significant difference compared to baseline; the superscript letter b indicates a clinically significant difference compared to baseline (difference in GSS score greater than 7, which is the amount of change used as surrogate for clinically significant improvement) [23]. Data presented as means and 95% confidence interval.

sons: drug discontinuation due to the physician's/patient's decision (n = 16, 15.6%), lost to follow-up (n = 5, 4.9%) and mild allergic reaction (n = 1, 0.9%). No serious adverse events were reported during the study.

Glaucoma Symptom Scale

There was a significant increase in the GSS total score at weeks 4 and 8 after the switch to TDFC UD therapy when compared to baseline (GSS total baseline: 65.38 ± 36.4; week 4: 76.64 ± 31.4; week 8: 81.92 ± 29.04; $p < 0.001$; table 2). This improvement in self-perceived complaints was seen in symptomatic as well as functional questionnaire subcategories at both follow-up time points (SYMP baseline: 59.57 ± 36.01; week 4: 74.24 ± 31.55; week 8: 80.25 ± 28.91; FUNC baseline: 74.03 ± 35.32; week 4: 80.26 ± 30.82; week 8: 84.44 ± 29.10; vs. baseline: $p < 0.001$ in all comparisons).

A separate analysis of the change from baseline complaints was made for each of the GSS subcategories (SYMP/FUNC; fig. 1) and for each of those categories' items individually (table 3). At week 4, both GSS subcategories and the total GSS score were statistically higher than baseline (GSS total: 10.61 ± 32.8%; GSS-SYMP: 14.52 ± 34.9%; GSS-FUNC: 4.74 ± 28.5%; vs. baseline $p = 0.001$), with both GSS total and GSS-SYMP improvement crossing the clinically significant threshold (i.e. mean increase higher than 7; $p <$

Table 3. Change in GSS items during the study

GSS score	Type	Week 4 (n = 99)	Week 8 (n = 80)
(a) Burning, smarting	SYMP	13.38 (34.5)[a]	24.69 (38.4)[a, b]
(b) Tearing	SYMP	13.76 (34.7)[a]	16.09 (38.3)[a, b]
(c) Dryness	SYMP	17.17 (34.8)[a, b]	21.56 (35.6)[a, b]
(d) Itching	SYMP	15.03 (36.6)[a, b]	23.44 (37.3)[a, b]
(e) Soreness, tiredness	SYMP	9.85 (35.1)[a]	17.66 (42.4)[a, b]
(f) Blurry, dim vision	FUNC	8.97 (28.0)[a]	17.03 (31.1)[a, b]
(g) Feeling something in eye	SYMP	17.93 (34.0)[a, b]	23.44 (35.1)[a, b]
(h) Hard to see in daylight	FUNC	4.29 (28.5)	9.34 (34.9)[a]
(i) Hard to see in dark places	FUNC	4.80 (30.4)	8.91 (30.2)[a]
(j) Halos around lights	FUNC	0.88 (26.7)	4.84 (29.2)

Change from baseline for each of the 10 items and the overall change in GSS at weeks 4 and 8 of the study. Figures in parentheses indicate percentages. The superscript letter a indicates a statistically significant difference compared to baseline; the superscript b indicates a clinically significant difference compared to baseline (difference in GSS score greater than 7, which is the amount of change used as surrogate for clinically significant improvement) [23]. SYMP = symptomatic; FUNC = functional.

Table 4. Overall ocular therapies during the study

Characteristics	Week 0 (n = 102)	Week 4 (n = 99)	Week 8 (n = 80)
TDFC UD only	62 (61)	74 (75)	54 (68)
TDFC UD + other medication	40 (39)	25 (25)	26 (33)
IOP-lowering medication	7 (7)	12 (12)	12 (15)
Artificial tears	26 (25)	13 (13)	17 (21)
Antibiotics	3 (3)	2 (2)	2 (3)
NSAIDs	3 (3)	1 (1)	–
Steroids	2 (2)	4 (4)	2 (3)
Mast cell stabilizer	1 (1)	1 (1)	1 (1)

Results are expressed as patient numbers with percentages in parentheses. No differences were seen in either the proportion of patients under TDFC UD only or in the number of IOP-lowering medications during the study (p = 0.10, p = 0.20, respectively). NSAIDs = Nonsteroidal anti-inflammatory drugs; IOP = intraocular pressure; TDFC UD = preservative-free unit dose timolol/dorzolamide fixed combination

Table 5. Change in GSS according to overall ocular therapies

	TDFC UD only (n = 54)	TDFC UD + other drug (n = 26)	p value
GSS-SYMP			
Mean ± SD	22.45±39.3[a, b]	17.84±33.5[a, b]	0.56
95% CI	18.19–26.71	12.21–23.48	
GSS-FUNC			
Mean ± SD	10.53±29.7[a, b]	6.32±35.9	0.98
95% CI	6.55–14.52	–1.15–13.79	
GSS total			
Mean ± SD	17.73±36.2[a, b]	13.26±34.8[a, b]	0.80
95% CI	14.68–20.78	8.73–17.80	

Change from baseline at the end of the study between patients under TDFC UD treatment only and patients who were under additional medication. CI = Confidence interval; SD = standard deviation; TDFC UD = preservative-free unit dose timolol/dorzolamide fixed combination; GSS = Glaucoma Symptom Scale; SYMP = symptomatic; FUNC = functional. The superscript letter a indicates a statistically significant difference compared to baseline; the superscript b indicates a clinically significant difference compared to baseline (difference in GSS score greater than 7, which is the amount of change used as surrogate for clinically significant improvement) [23].

0.001). Moreover, at week 8, both GSS total and GSS-SYMP scores had reached a clinically significant improvement, meaning that the primary end point was achieved (GSS total: 16.7 ± 35.9%; GSS-SYMP: 21.15 ± 37.9%; p < 0.001). The GSS-FUNC subcategory had a statistically but no clinically relevant score increase (10.3 ± 31.57%; vs. baseline p < 0.001; vs. hypothetical score increase of 7%; p = 0.08).

All GSS-SYMP-related items changed positively from baseline assessment by week 4 but only 2 items (dryness, itching) fulfilled the criteria for clinically significant improvement at that time point. By the end of the study, all the GSS-SYMP items had a clinically relevant improvement in the self-report level of complaints (p < 0.001). On the other hand, none of the GSS-FUNC-related items had clinically significant score increases by week 4. After 8 weeks of therapy switch, 1 functional-related item (blurry, dim vision) was reported to have clinically improved.

TDFC UD Monotherapy

After the therapy switch, TDFC UD was the only ocular treatment in 62 (60.8%) of the 102 patients. The remaining 40 patients continued to administer other ocular therapies in addition to TDFC UD. The proportion of patients in which TDFC UD was the only ocular therapy did not change over time (p = 0.10). Concomitant medication is described in table 4.

The analysis of the GSS improvement after 8 weeks of TDFC UD switch in these two treatment subgroups is detailed in table 5. Clinically significant improvements in

GSS total and GSS-SYMP scores were seen in both treatment subgroups. However, only in the patients who were solely taking TDFC UD was there also a clinically relevant increase in the GSS-FUNC score. Pairwise comparison between the groups was not significant ($p > 0.50$ in all comparisons).

Discussion

There was a significant increase in the patients' perceptions of their ocular-related QoL improvement after the switch to TDFC UD treatment. This improvement in the self-reported complaints could be seen as early as 1 month after the change in therapy. In fact, our results show a positive trend up to the week 8 evaluation, thus suggesting a continued improvement throughout the study.

This significant improvement could relate to changes in the patients' ocular surface. Glaucoma patients are thought to have a significantly higher prevalence of ocular surface disorders when compared to otherwise healthy individuals [4, 6], with significant increases in the self-reported complaints related to dry-eye syndrome (such as dryness and itching) [13, 14]. Both the structural ocular surface changes and their clinically relevant associated symptoms are thought to be iatrogenic in nature and to relate to IOP-lowering topical medication and its preservative content [3, 13, 15]. Preservative-mediated toxicity to the ocular surface by increases in inflammatory cytokines, inducing corneal epithelial morphological changes and instability of the precorneal tear film have nevertheless been documented to be at least partially reversible [13, 16–18]. In fact, removing preservatives from treatment regimens has been suggested to significantly and rapidly decrease ocular symptoms and medication-related adverse reactions [13, 19]. The reports on the preservative-induced reversible changes support our results that show that a switch to preservative-free treatment regimens could lessen the burden of these ocular-related symptoms on the glaucoma patient's QoL.

Interestingly, our results have shown that significant improvements in symptomatic complaints were also seen in patients who were under concomitant medications besides TDFC UD. The fact that these patients also presented an improvement in the GSS score after switching to a TDFC-UD-containing regimen could imply that even a decrease in preservative exposure could be enough to produce clinically relevant results. The existing literature does suggest the extent of ocular surface damage (and associated complaints) to be related to the amount of preservative instilled by the patient [20]. Thus, significantly reducing this amount by switching to preservative-free TDFC UD may be enough to clinically improve the patient's QoL.

Other studies on switching therapies to preservative-free IOP-lowering treatment have documented similar improvements in the self-reported QoL [13, 21, 22]. These studies have however either looked at monotherapy drugs, such as tafluprost or timolol, or have used a wide variety of QoL/symptom-related enquiries, ranging from the 15-item Glaucoma Quality of Life questionnaire to simple, nonvalidated questionnaires which need to be completed by an external interviewer. Our real-life assessment of the patient's own perception led to the choice of the validated and simple-to-use GSS questionnaire. This questionnaire stems from an adaptation to the Ocular Hypertension Treatment Study protocol questions and has been widely used in glaucoma studies focusing on the QoL [3, 23, 24]. In addition, it has been shown to possess a good correlation with ocular surface disease-related symptoms and suggested as an ideal instrument to be used without the need for an external observer [12], thus circumventing the limitations of an observational study setting.

Considering that most existing preservative-free options currently available are monotherapies (such as prostaglandin analog or β-blockers), our results on the favorable tolerability profile of TDFC UD therapy support this preservative-free combination therapy to be a valid option when considering additional treatment options in patients whose target IOP has not been achieved under monotherapy. Not only has it been consistently reported to have a noninferiority IOP-lowering profile when compared to these agents [9, 25], but it provides a preservative-free alternative in a fixed combination treatment. This may be particularly important if surgery is to be eventually considered, as long-term preservative medication could interfere with conjunctival scarring and therefore affect surgical outcomes [26].

The noninterventional design imposes a number of limitations on the study setting. For instance, specific ocular surface testing was not possible. Our goal was however to identify whether, in a real-world setting, a change in therapy could have a significant impact from the patient's point of view. Given the freedom of action and decisions by both physicians and patients during the trial, we are confident our results represent a real-life scenario. Importantly, being an open-labeled study, patients were aware of changing to a preservative-free medication and could have felt encouraged to report some level of

improvement. Nevertheless, a biased patient would have reported an overall increase throughout the GSS questionnaire, while our patients significantly differentiated between the several items. Indeed, no changes were observed in the functional-related GSS items, whereas comfort-related items significantly improved, thus suggesting that these results are related to a true improvement in patient comfort rather than solely on a study-induced bias.

In summary, switching from preservative-containing IOP-lowering therapies to TDFC UD significantly increases the patient's QoL. This improvement is felt even in patients who continue concomitant medication, thus implying that even reducing the amount of preservatives can be important in improving the patient's ocular surface-related complaints.

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Disclosure Statement

None of the authors has a conflict of interest with the submission.

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