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Physician attitudes regarding prostaglandin treatment for glaucoma in the United States and Europe

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PURPOSE. *To evaluate physician use of prostaglandins (latanoprost, travoprost, and bimatoprost) in the United States (US) and Europe (EU).*
METHODS. *One thousand multiple-choice surveys were distributed via e-mail in the US and EU.*
RESULTS. *The authors received 71 responses (US 40 [8%] and EU 31 [6%]). Physicians preferred prostaglandin monotherapy (US 39 [98%] and EU 22 [71%], p=0.003), usually latanoprost (US 32 [80%] and EU 22 [71%], p=0.45). When more efficacy was required, US physicians would typically switch (23 [58%]) and EU physicians would add therapy (22 [71%], p=0.007). In both continents 45% of respondents stated bimatoprost was more efficacious.*
CONCLUSIONS. *US and EU physicians prefer prostaglandin monotherapy, most commonly latanoprost. Bimatoprost is often perceived as more effective, but having a higher incidence of conjunctival hyperemia. (Eur J Ophthalmol 2008; 18: 199-204)*

KEY WORDS. *Survey, Latanoprost, Travoprost, Bimatoprost, United States, Europe*

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INTRODUCTION

Over the past decade the pharmacologic therapy of glaucoma has changed markedly with the introduction of prostaglandin analogs. Three prostaglandin analogs are currently available in the United States (US) and Europe (EU): latanoprost (Xalatan™, Pfizer, Inc., New York, NY), travoprost (Travatan™, Alcon, Inc., Fort Worth, TX), and bimatoprost (Lumigan™, Allergan, Inc., Irvine, CA).

In most cases prostaglandins have replaced topical beta-adrenergic blockers as monotherapy, which were previously the most common therapy available to reduce intraocular pressure (1-3). However, the transformation to the use of prostaglandins as monotherapy has not been uniform. Many physicians, especially in the EU, have maintained their preference for beta-blockers as monotherapy (3). Apart from the guidelines of the European Glaucoma Society, few definitive guidelines exist from private glaucoma academic societies or government agencies to assist the ophthalmologist in knowing which class of medicine should be prescribed as monotherapy. Consequently, the choice of when to initiate prostaglandin therapy and which product to prescribe is usually left to the physician. However, very little public information exists regarding physician beliefs in the current role of prostaglandins in glaucoma therapy.

The purpose of this article was to evaluate by survey physician use of, and attitudes towards, prostaglandins in the US and EU. Since uniform agreement does not yet exist for prostaglandin use, this article was intended to allow practicing physicians to compare their own treatment patterns to those of their peers.

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METHODS

Physician selection

The survey was conducted from the administrative office of PRN Pharmaceutical Research Network, LLC, in Charleston, SC. Institutional Review Board/Ethics Committee approval was not required for this study. Physicians included in this survey were randomly chosen by the following techniques. In both the US and EU physician lists were compiled from www.yellowpages.com. In EU we searched in decreasing order by the most populated countries (as listed on www.en.wikepedia.org) until 500 names and corresponding e-mail addresses were obtained. In the US we selected names in decreasing order by the most populated cities (as listed on www.en.wikepedia.org) until 500 names and corresponding e-mail addresses were obtained. Within the US and EU we chose every fifth ophthalmologist in alphabetical order on www.yellowpages.com. If we could not locate an e-mail address for the randomly chosen physician the next name in order was chosen.

The survey was then sent to the physicians via e-mail. If we did not receive a response within 2 weeks the e-mail was sent again and then a third attempt was made, if needed, after another 2 weeks. Because we had an initial low response rate to the three e-mail attempts in the US we faxed surveys to the first 200 (of the 500 original) names on our physician list. After faxing the response rate improved to above the EU rate and we therefore discontinued faxing to maintain a relative balance in the response rates between continents.

The survey was developed internally at PRN Pharmaceutical Research Network, LLC, and included questions on the use of prostaglandins as monotherapy and how physicians would add to this therapy if required. In addition, the survey explored the perceived efficacy and safety of the available prostaglandins. Also, the use of prostaglandins before and after cataract surgery was queried. Questions were based on controversies noted in the literature or questions from US or EU ophthalmology congresses. The survey was multiple choice in design and most questions allowed the selection of "other" with space for a description if the respondent wished to supply an alternative answer.

An introductory letter accompanied the survey in English in the US and in the corresponding local language in the EU. However, the survey text itself was only provided in English to preserve the continuity of the questions. The same survey was provided in both continents despite the fact that the number of available fixed combinations is limited in the US. One question was excluded from the analysis because of an internal error in the provided choices.

Statistical analysis

All data were considered non-ranked and non-contiguous in type. Statistical analyses were performed between responses provided in the US and EU using a chi-square test (4). All statistical tests were two-way with a p level of 0.05.

RESULTS

The survey questions and responses can be found online as supplemental material (http://www.eur-j-ophthalmol.com/ejo/). In total we received 71 completed surveys (US 40 [8%] and EU 31 [6%]). The number of respondents from each country is listed in Table I.

Although not statistically evaluated, there were no marked differences between EU countries in regards to the number of returned surveys. Selected physician responses to the survey are found in Table II.

Monotherapy choice

Physicians in both the US and EU generally preferred the use of prostaglandins as monotherapy (US 39

TABLE I - NUMBER OF RESPONDENTS FROM EACH COUNTRY* IN THE EUROPEAN UNION (EU)

EU	Responses
Germany	3
France	6
Italy	6
Spain	4
Greece	6
Sweden	3
Austria	1
Switzerland	2
Total	31

*The following countries had no responses: United Kingdom, Poland, Netherlands, Portugal, Belgium, Czech Republic, Hungary, Slovakia, Denmark, Finland, Ireland, Lithuania, Latvia, Slovenia, Estonia, Cyprus, Luxembourg, Malta

[98%] and EU 22 [71%], p=0.003), being almost unanimous in the US. The most common reason cited for the preferred use of prostaglandins in both the US and EU was a combination of their greater efficacy, safety, and compliance (US 18 [45%] and EU 10 [32%], p=0.08).
Among individual prostaglandin brands, latanoprost was preferred most often (US 32 [80%] and EU 22 [71%], p=0.45). If a patient's intraocular pressure remained uncontrolled despite prostaglandin monotherapy physicians from the US would usually switch medications (US 23 [58%] and EU 6 [19%]) while in EU they would typically add therapy to better control the pressure (US 15 [38%] and EU 22 [71%], p=0.007). In the US the most commonly added therapy was a beta-blocker (US 18 [45%] and EU 13 [42%]) while in EU physicians were split between adding a beta-blocker or changing to a fixed combination (US 3 [8%] and EU 14 [45%], p=0.001). If physicians were to change to a fixed combination, the most popular cited was the dorzolamide/timolol preparation in the US (US 7 [18%, the only one available at the time the survey was performed] and EU 4 [13%]), and a prostaglandin/timolol preparation in EU (US 0 [0%] and EU 9 [29%], p=0.001).

Efficacy

In the US and EU approximately 45% of physicians believed that bimatoprost is superior in efficacy than the other prostaglandins while approximately the same percentage thought that all the brands are equally effective (p=0.21). Physicians in both continents, who indicated that bimatoprost was more effective, believed so because of an overall greater mean efficacy than the other brands (US 11 [28%] and EU 7 [23%]). However, the continents differed statistically because physicians in the US more often believed that bimatoprost was more effective for non-responders to another brand (US 8 [20%] and EU 1 [3%], p=0.002).

Adverse effects

Physicians in both the US and EU noted that bimatoprost more commonly caused conjunctival hyperemia than the other brands (US 25 [63%] and EU 14 [45%], p=0.01). Further, in the US, physicians believed that itching (US 12 [30%] and EU 4 [13%]), ocular pain (US 12 [30%] and EU 3 [10%]), and periocular pigmentation (US 18 [45%] and EU 8 [26%]) resulted more often from bimatoprost

TABLE II - SELECTED PHYSICIAN RESPONSES TO THE SURVEY

Question	Answer	US	EU	p value
Which prostaglandin do you most commonly prescribe?	Travoprost	1	3	0.45
	Latanoprost	32	22	
	Bimatoprost	5	3	
	Other	2	3	
If uncontrolled on prostaglandin monotherapy, do you typically:	Switch therapy	23	6	0.007
	Add therapy	15	22	
	Other	2	3	
Which prostaglandin do you believe is more effective?	Travoprost	0	4	0.21
	Latanoprost	2	1	
	Bimatoprost	18	14	
	Other	20	12	
Which prostaglandin is worse with conjunctival hyperemia?	Travoprost	5	5	0.01
	Latanoprost	0	2	
	Bimatoprost	25	14	
	Other	10	10	
Is conjunctival hyperemia a clinical problem?	Yes	29	18	0.17
	No	9	13	
	Other	2	0	
Do you currently stop a prostaglandin before cataract surgery?	Yes	7	15	0.01
	No	32	16	
	Other	1	0	

US = United States; EU = European Union

(p<0.55). In contrast, EU physicians thought that these symptoms were generally more equal among the three products. However, physicians in both the US and EU indicated that the incidence of cystoid macular edema, uveitis, and herpes keratitis were equal between prostaglandins (p<0.45).

Regarding conjunctival hyperemia, specifically, most physicians believed it represents a clinical problem (US 29 [73%] and EU 18 [58%], p=0.17). However, generally only physicians in the US indicated hyperemia was associated with an adverse effect on cosmetic appearance (28 [70%]), number of office visits (17 [43%]), compliance (18 [45%]), or ocular symptoms (12 [30%]). Most commonly, they associated these symptoms with bimatoprost (29 to 41%) primarily, travoprost (8 to 16%) secondarily, or both (0 to 5%).

In contrast, in the EU an adverse effect on cosmetic appearance (12 [39%]), number of office visits (7 [23%]), compliance (5 [16%]), and ocular symptoms (5 [16%]) by a specific prostaglandin was noted by only a minority of physicians (13 to 42%) and was not linked generally with any specific prostaglandin.

Cataract surgery

Most US physicians (32 [80%]) and approximately half of EU physicians (16 [52%]) noted they continued a prostaglandin with cataract surgery (p=0.01). EU physicians who stopped prostaglandin therapy perioperatively did so between 1 and 7 days prior to surgery, and most commonly between 5 and 7 days. Following surgery, they indicated that they resume a prostaglandin between 1 and >4 weeks, most commonly >4 weeks.

DISCUSSION

The results of the survey showed that physicians in both continents preferred prostaglandin monotherapy over other medicine classes. In the US prostaglandins were preferred almost unanimously. In both continents the reason given for the choice of a prostaglandin was the greater efficacy, safety, and compliance.

Nonetheless, a minority of physicians in the EU maintained beta blockers as their preferred monotherapy choice. The reason for this difference is not clear by our data. Prostaglandins were available in the US in 1996, before most countries in the EU, but only by about a year. It is unlikely that this short time interval difference in availability would influence this survey 10 years later. However, a number of countries in the EU urge, to varying degrees, physicians to prescribe beta-blockers before prostaglandins because of cost. This might influence some physicians to maintain beta-blockers as their preferred monotherapy.

In the US and EU approximately 45% of physicians believed that bimatoprost was more efficacious while approximately the same percentage thought that all prostaglandins are equally effective. The reason bimatoprost was indicated as more effective was due to overall greater mean efficacy compared to the other brands. In the literature the relative efficacy of the three prostaglandin brands remains controversial. Noecker and coworkers noted a greater efficacy with bimatoprost compared to latanoprost (5). Further, several articles have noted a slightly reduced efficacy with latanoprost in the afternoon compared to travoprost and bimatoprost (6-12). In contrast, Parrish and associates indicated no diurnal differences in absolute pressure levels among the three products (8).

If intraocular pressure remained uncontrolled despite prostaglandin therapy, the survey indicated that physicians in the US would most commonly switch therapy, versus adding therapy as favored in the EU. The reason for this difference is not clear by our results. Any real difference between switching and adding would be dependent upon a common understanding between both continents of the word controlled, which was not specifically defined in the question and might be understood differently between both regions.

Nonetheless, in both continents the most commonly added therapy would be a beta-blocker. In the US the most popular fixed combination was the dorzolamide/timolol preparation. However, this was the only fixed combination product available at the time the survey was conducted. In the EU, where multiple fixed combination preparations are available, a prostaglandin/timolol preparation was preferred. The prostaglandin based fixed combinations have an advantage of once daily dosing over other fixed combination preparations. However, any efficacy advantage of a prostaglandin based fixed combination compared to dorzolamide/timolol fixed combination, the most commonly prescribed, remains controversial (13, 14).

In regards to side effects, physicians in the US believed itching, ocular pain, and periocular pigmentation resulted more often from bimatoprost. In contrast, EU physicians

thought that these symptoms were generally equal among the three prostaglandins. Physicians in both continents indicated that the incidence of cystoid macular edema, uveitis, and herpes keratitis were equal between prostaglandins.

In contrast, in both continents physicians noted a greater incidence of conjunctival hyperemia with bimatoprost and that it represents a real clinical problem. However, differences between the US and EU were observed on the impact of the hyperemia in the clinical practice. Physicians in the US noted hyperemia was associated with an adverse effect on cosmetic appearance, number of clinic visits, compliance, and ocular symptoms. The most common medicines associated with these symptoms were bimatoprost primarily and travoprost secondarily. In contrast, in the EU these symptoms were noted in only a minority of cases and were not linked generally with any specific prostaglandin.

Conjunctival hyperemia is important because it is the most common side effect noted with the prostaglandins and it might adversely influence treatment (10, 15-18). Accordingly, one retrospective study including 1,200 cases by Day et al showed that bimatoprost treated patients, compared to those prescribed latanoprost, were less persistent, demonstrated worse pressure control, and had higher treatment costs (19). More data are needed regarding the clinical impact of hyperemia on cosmesis, patient adherence to the medicine, treatment costs, and associated clinical problems.

It is interesting to note that physicians maintained latanoprost as the favored prostaglandin in both continents despite the greater efficacy associated with bimatoprost by many ophthalmologists. The reason for this is not clear by our data. Several reasons could be the commercial availability of latanoprost 5 years prior to the other two brands and less perceived side effects as well as the reduced adverse impact upon clinical practice associated with latanoprost.

The fact that approximately 80% of physicians in the US continued prostaglandin treatment prior to cataract surgery, compared to about half of EU doctors, was a surprise to the authors. Prostaglandin use perioperatively with cataract surgery is a concern because of potential surface bleeding and cystoid macular edema from the conjunctival hyperemia and proinflammatory effects, respectively, associated with this class of medicine. The reason for this difference between continents was not apparent from our results. For EU physicians who discontinued prostaglandins with cataract surgery, there was no uniformity regarding how may days prior to and after surgery the medicine was withheld. However, most commonly the physicians stopped the prostaglandin 5 to 7 days prior to surgery and resumed the medicine >4 weeks after surgery. There are currently little published data that address whether prostaglandins should be discontinued with cataract surgery and for what period of time before and after the operation.

This survey suggests that physicians in the US and EU prefer prostaglandins as monotherapy, most commonly latanoprost. However, bimatoprost is perceived often as more effective, but having a higher incidence of conjunctival hyperemia. Further, physicians in the US more often believe bimatoprost contributes to hyperemia related problems and demonstrates additional side effects of itching, ocular pain, or periocular pigmentation.

The results of this survey are limited by the methods performed. Although physicians were randomly chosen, physicians in the US were less responsive to e-mail, which led ultimately to a difference in data collection methods between continents. Additionally, this survey may show bias towards practices that were technologically more advanced. It could be that the physicians who did not provide e-mail have different clinical methods. Further, the response rate and answers might have differed in the EU if the survey had been provided in the local language. This may have caused some physicians not to participate who may have had difficulty with English. Future research is needed to allow for a greater sampling of physicians in the US and EU to better evaluate practice attitudes.

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