European Journal of Ophthalmology / Vol. 18 no. 5, 2008 / pp. 778-786

A European perspective on costs and cost effectiveness of ophthalmic combinations in the treatment of open-angle glaucoma

A. HOMMER[1], J. THYGESEN[2], A. FERRERAS[3], J. WICKSTRØM[4], M.M. FRIIS[4], P. BUCHHOLZ[5], J.G. WALT[6]

[1]Krankenanstalt Sanatorium, Vienna - Austria
[2]Department of Ophthalmology, Rigshospitalet, University of Copenhagen - Denmark
[3]Department of Ophthalmology, Miguel Servet University Hospital, Zaragoza - Spain
[4]MUUSMANN Research & Consulting AS, Kolding - Denmark
[5]Allergan R&D Europe, Ettlingen - Germany
[6]Allergan, Inc., Irvine, CA - USA

PURPOSE. *Efficacy, safety, and cost implications are important considerations when choosing an ophthalmic treatment. Fixed-combination glaucoma medications containing brimonidine 0.2% and timolol 0.5%, or dorzolamide 2% and timolol 0.5%, were compared with brimonidine 0.2% and dorzolamide 2% that were used as adjunctive therapy to timolol 0.5%.*
METHODS. *A literature review was conducted to determine the outcome parameters of intraocular pressure reduction and tolerability after 3 months of use of brimonidine or dorzolamide, each together with timolol as a fixed-combination or in concomitant therapy. Modelled cost-minimization and cost-effectiveness analyses were performed to investigate the economic consequences of ophthalmic therapy with brimonidine, dorzolamide, and timolol from a societal perspective.*
RESULTS. *The literature review found that brimonidine and dorzolamide used as fixed combinations with timolol as well as in adjunctive therapy to timolol were equally effective and safe. Furthermore, in the European countries studied, the fixed combination of brimonidine/timolol represented a less costly option when compared to the fixed combination of dorzolamide/timolol evaluated over both a 3-month and a 12-month horizon.*
CONCLUSIONS. *Brimonidine used as a fixed-combination therapy with timolol provided better cost value than dorzolamide/timolol in all the countries studied. For most countries, the fixed combination of brimonidine and timolol also provided better cost value than adjunctive therapy with brimonidine, which was more cost effective than adjunctive therapy with dorzolamide. (Eur J Ophthalmol 2008; 18: 778-86)*

KEY WORDS. *Brimonidine, Cost effectiveness, Glaucoma, Primary open-angle glaucoma, Drug combinations*

Accepted: February 20, 2008

INTRODUCTION

Glaucoma is a major cause of blindness and visual impairment. Primary open-angle glaucoma (POAG), the most common form of adult glaucoma, is a progressive multifactorial optic neuropathy in which there is a characteristic atrophy of the optic nerve and loss of retinal ganglion cells (American Academy of Ophthalmology. Primary open-angle glaucoma, preferred practice pattern. San Francisco, CA: American Academy of Ophthalmology,

1120-6721/778-09$25.00/0

2005). The prevalence of POAG increases substantially with age and is estimated to be 1.44% for persons 40 years and older in white populations (1-3). In Segovia, Spain, the prevalence among individuals 40 to 79 years old has been estimated to be 2.1% (4), whereas in the United Kingdom, the prevalence is approximately 1.2% for persons aged 40 to 89 years (5). The National Institute of Public Health in Sweden estimates that POAG affects about 1% of the population over 50 years in Sweden (6). In Finland, about 60,000 patients (1.2%) were entitled to special refunds for glaucoma medications in 2000 (7). Further, glaucoma accounts for 8% to 15% of new registries for blindness in Western industrialized countries. Due to the aging population, the number of people with POAG is expected to increase substantially in the coming years (8). Hence, the management of glaucoma has significant resource and cost implications for current and future health services across Europe.

The severity of visual field loss in glaucoma disease varies considerably among patients. Studies in advanced glaucoma show a high degree of correlation between increased intraocular pressure (IOP) and the risk of visual field deterioration, and achieving a low target IOP has been shown to prevent further glaucomatous progression (8, 9). Hence, the main goal of treating POAG is to reduce IOP. The European Glaucoma Society emphasizes the importance and difficulty of predicting the IOP level at which no further damage may occur (10). Although there is no single target IOP level that is safe for every patient, it is generally assumed that a reduction of at least 20% from the initial damaging pressure is a useful initial goal. The results of the Advanced Glaucoma Intervention Study (11, 12), the Early Manifest Glaucoma Trial (13), and the Ocular Hypertension Treatment Study (14) have confirmed the importance of IOP reduction in preventing glaucomatous progression.

In many cases, topical medical monotherapy (eyedrops) with beta-blockers to control IOP is the first line of treatment in the management of POAG. Adjunctive therapies are often used as second-line treatment because many patients are not adequately controlled on single-agent therapy (10). It has been shown that more than half of all patients treated with topical beta-blockers will require adjunctive medication to control IOP (15). For patients on monotherapy, the need for adjunctive therapy results in extra follow-up visits to the ophthalmologist. Therefore, sufficient reduction of IOP by an initial treatment strategy can closely relate with lower treatment costs.

Several types of medications that can be used adjunctively are currently marketed, including brimonidine tartrate 0.2%, dorzolamide 2%, bimatoprost 0.003%, latanoprost 0.005%, travoprost 0.004%, and pilocarpine (2% and 4%). It has been estimated that the use of brimonidine tartrate as an adjunctive agent comprises between 60% and 80% of its utilization in the major European markets (Allergan, Inc. A + A Glaucoma Monitor Extracts. Data Extracts from A + A Panel Set. June 2006).

In recent years, new fixed-combination products containing the beta-blocker timolol 0.5% have become available in Europe. These new products contain two IOP-lowering agents in the same bottle. Two of these fixed-combination products licensed for patients whose IOP is insufficiently controlled by beta-blockers alone are the combinations of timolol 0.5%/brimonidine tartrate 0.2%, and timolol 0.5%/dorzolamide 2%. Each of these combinations is supplied in a single bottle, which can result in improved patient compliance because of the convenience of fewer required drops and greater ease of administration. Moreover, there is less overall exposure of chronically treated eyes to preservatives.

The objective of this review was to compare the costs and cost effectiveness of the fixed combination of timolol 0.5% and brimonidine 0.2% (Combigan®; Allergan, Inc.; Irvine, CA, USA) and three alternative therapies for POAG: the nonfixed combination of brimonidine 0.2% (Alphagan®; Allergan, Inc.) and timolol 0.5%, the fixed combination of timolol 0.5% and dorzolamide 2% (Cosopt®; Merck and Co., Inc.; Whitehouse Station, NJ, USA), and the nonfixed combination of dorzolamide 2% (Trusopt®; Merck and Co., Inc.) and timolol 0.5%. The present analyses were conducted for six European countries: the United Kingdom, Spain, France, Switzerland, Finland, and Sweden.

METHODS

An initial systematic literature search was performed to investigate the efficacy and safety of the four different treatment options. The literature search revealed that no single head-to-head clinical trial compared the efficacy and safety of the four chosen treatment options. The comparison of efficacy and safety was, therefore, based on four randomized controlled trials with pairwise comparison of the treatment options. In selecting these randomized controlled trials, the primary focus was on the

consistency of the study design and characteristics of the patient cohorts.

Efficacy and safety

The efficacy of IOP-lowering treatment, or its ability to control IOP in patients with POAG, can be measured in a number of different ways, but since most studies only reported the mean decrease in IOP, this measure served as the basis for this analysis. It was also a metric from which the mean percentage decrease in IOP was calculated. Safety data were derived from the number of serious adverse events, which were defined as drug-related adverse events that led to the discontinuation of treatment.

The four randomized controlled trials chosen are presented in Table I. Two studies (16, 17) compared the efficacy and safety of the fixed combination of timolol/dorzolamide and the nonfixed combination of timolol and brimonidine. Another explored the efficacy and safety of brimonidine and timolol given concomitantly and in fixed combination (18), and the fourth investigated the efficacy and safety of nonfixed combinations of timolol with brimonidine or dorzolamide (19). These clinical studies appeared to be similar with respect to time horizon, diagnosis, patient age, and baseline IOP. The study comparing brimonidine and timolol given concomitantly and in fixed combination (18) was characterized by a slightly lower mean age compared to the other studies, but this was not considered to have an impact on the comparability with the other studies. The study by Simmons and associates (19) was characterized by a lower baseline IOP level compared to the other studies, and was designed so that only patients who achieved a minimum 15% reduction in IOP after 1 month were continued on the current medication, whereas the remaining patients who experienced adverse events were switched to another medication. The studies by Sall and associates, Solish and associates, and Goni and associates were comparable (16-18), whereas the study by Simmons and associates (19) was slightly divergent.

The efficacy comparison was based on 3-month data since all the included studies reported efficacy at this timepoint. Three-month efficacy data showed no significant differences in mean IOP decrease among concomitant administration of brimonidine and timolol, fixed-combination dorzolamide/timolol, fixed-combination and concomitant administration of brimonidine and timolol (16-18), indicating that these three treatment options were equally effective (Tab. I).

On the contrary, Simmons and associates (19) found that concomitant brimonidine and timolol was significantly more effective in reaching the target IOP compared with concomitant dorzolamide and timolol after 1 and 3 months (Tab. I). Similar results have been achieved in other studies (Nixon DR, poster presented at the annual meeting of the Association for Research in Vision and Ophthalmology, 2006, Fort Lauderdale, FL; and Chan et al and Paczka et al, posters presented at the 6th International Glaucoma Symposium, 2007, Athens, Greece).

In terms of safety, there were only minor, nonsignificant differences in the occurrence of serious adverse events among the studies by Solish and associates, Sall and associates, and Goni and associates (16-18). The study by Simmons and associates (19), however, differed from the other studies due to its higher, albeit statistically nonsignificant, rate of serious adverse events in both groups. This may partly be explained by the design of the study, which permitted patients to be switched to the different treatment arm in the case of adverse events. Also, the adverse events in this study may not have been as severe as those reported in the other studies.

Cost and cost-effectiveness

Based on the data presented in Table I, equal effectiveness and safety may be assumed for three of the four treatment alternatives (fixed-combination brimonidine/timolol, fixed-combination dorzolamide/ timolol, and nonfixed timolol and brimonidine). A cost-minimization analysis of these three treatment strategies was performed to determine the least costly strategy. The concomitant (nonfixed) administration of brimonidine and timolol with the concomitant (nonfixed) administration of dorzolamide and timolol showed a difference in terms of effectiveness, which, as shown by Simmons and associates, should be taken into account (19). In this case, a cost-effectiveness analysis was conducted to compare differences in effectiveness and costs of the two treatment alternatives.

The cost-minimization analysis and the cost-effectiveness analysis were conducted for six countries: France, Spain, Switzerland, the United Kingdom, Finland, and Sweden. The analyses were performed from a healthcare sector perspective focusing on medical and treatment (i.e., ophthalmologist visits) costs. Other costs, such as transportation costs and the costs of adverse events, were identical across all four alternatives and were therefore

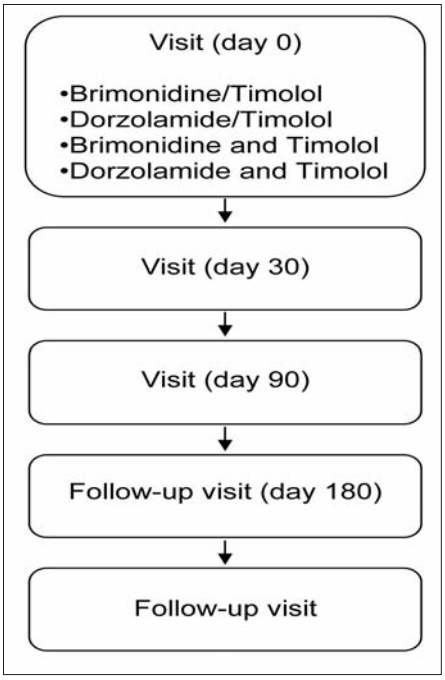

Fig. 1 - *Treatment pathway in the model.*

not included. Societal loss of productivity was also excluded due to the advanced age of the patients with POAG. Unit costs for ophthalmologist visits and drug costs were obtained from national sources. The cost of timolol was based on the lowest available price in each of the six countries. In Sweden and Finland, timolol was manufactured by Alcon (Timolol Alcon), in the United Kingdom and Switzerland by MSD (Timoptol and Timoptic), in Spain by Novartis (Nyolol), and in France by Teva Classic (Timolol Teva). The time horizon for the analysis was 12 months. Three-month results are also reported.

The decision analytic treatment pathway for each patient in the cost-minimization analysis and the cost-effectiveness analysis are presented in Figure 1. Assuming 100% patient compliance and that patients used one bottle of medication per month in accordance with the European Pharmacopoeia (Council of Europe. European Pharmacopoeia. 5th ed. Strasbourg, France: European Directorate for the Quality of Medicines & Healthcare; 2004),

TABLE I - COMPARISON OF THE FOUR RANDOMIZED CONTROLLED TRIALS AIMED TO EVALUATE THE EFFICACY AND SAFETY OF THE FOUR CHOSEN TREATMENT OPTIONS

Study	**Sall et al (16) (2003)**		**Solish et al (17) (2004)**		**Goni et al (18) (2005)**		**Simmons et al (19) (2001)**	
Design	**RCT, 6 months, n = 293**		**RCT, 3 months, n = 492**		**RCT, 3 months, n = 371**		**RCT, 3 months, n = 106**	
Diagnosis	**Open-angle glaucoma, ocular hypertension**		**Open-angle glaucoma, ocular hypertension**		**Glaucoma, ocular hypertension**		**POAG, ocular hypertension**	
Treatment	**Dorzolamide/ timolol**	**Brimonidine and timolol**	**Dorzolamide/ timolol**	**Brimonidine and timolol**	**Brimonidine/ timolol**	**Brimonidine and timolol**	**Brimonidine and timolol**	**Dorzolamide and timolol**
Mean age (yr)	64.9	63.7	64.2	64.1	58.5	59.6	61.5	62.8
Baseline IOP (mmHg)								
Trough	25.16	25.03	24.82	25.50	25.0	25.0	Mean 21.56	Mean 20.89
Peak	24.42	24.33	24.05	24.03	22.6	22.4		
Mean IOP decrease at 3 mo								
Trough	3.12	3.82	3.31	3.52	4.9	4.9	1 mo: 4.4	1 mo: 3.3
Peak	5.04	5.41	4.30	5.27	NA	NA	3 mo: 4.98	3 mo: 3.15
Mean % IOP decrease at 3 mo								
Trough	12.4	15.3	13.3	13.8	19.6	19.6	20.4	14.4
Peak	20.6	22.2	17.9	21.9	NA	NA	23.1	15.1
Discontinuation due to serious adverse events, %	5	5	3.7	5.7	2.1	1.1	9.3	9.8

RCT = Randomized controlled trial

each patient commenced treatment with a complete examination by the ophthalmologist. Thereafter, the patient had a follow-up visit within the first 3 months, resulting in a total of four follow-up visits within the first year.

In the cost-minimization analysis, it was assumed that lowering IOP was sufficiently effective for all patients and that no patient needed to switch treatment within the first year. In the cost-effectiveness analysis, differences in patients' efficacy and safety data were based on the outcomes reported by Simmons and associates (19) and expressed as the relative reduction of IOP. This study showed that after 3 months, 75% of patients with POAG using the nonfixed combination of brimonidine and timolol obtained a 20% reduction of IOP and reached an IOP level of 17 mmHg, whereas 33% of patients treated with the nonfixed combination of dorzolamide and timolol achieved the same results. Therefore, a target value of about 17 mmHg was set based on a 20% IOP reduction from the baseline mean IOP for both therapies. The cost-effectiveness ratio was defined as the cost per 1% of pa-

TABLE II - MONTHLY MEDICATION COSTS (€ 2006*)

Country	Timolol 0.5% (€)	Brimonidine 0.2% (€)	Dorzolamide 2% (€)	Fixed-combination timolol/brimonidine (€)	Fixed-combination timolol/dorzolamide (€)
United Kingdom	4.62	10.14	9.37	14.80	14.87
Switzerland	6.10	14.01	14.29	18.60	20.19
Spain	2.70	12.18	13.99	16.68	20.20
France	5.03	13.83	13.99	18.64	18.95
Finland	7.12	18.21	16.50	24.43	25.38
Sweden	9.85	15.00	14.51	19.20	19.58

Source: National Pharmacy Selling Prices (2006).

*Currency conversions are used according to national exchange rate as of December 12, 2006. For estimation of medication, the lowest market price per bottle is used, which primarily is based on a triple pack, if such packets were available

TABLE III - UNIT COST PER VISIT TO OPHTHALMOLOGIST (2006/2007 cost in €*)

Country	Ophthalmologist (first visit) (€)	Ophthalmologist (follow-up) (€)	Source
United Kingdom	73.00	73.00	Unit Costs of Health and Social Care 2006; summary of main resources and unit costs (a)
Switzerland†	127.88	127.88	Institut für Refraktive & Ophtalmo Chirurgie, Zürich. www.iroc.ch (b); adjusted to 2007 prices
Spain	71.40	71.40	Visit costs of Spain obtained from a private clinic Universidad Politécnica de Cartagena (c); adjusted to 2006 prices
France	28.00	28.00	L'Assurance Maladie, Assurés, Soins et Remboursements; http://www.ameli.fr/ (d)
Finland	98.00	98.00	Hujanen et al; Terveydenhullon yksikkökustannukset Suomessa vuonna 2001; STAKES (e); adjusted to 2006 prices
Sweden	157.85	89.21	Norlandstingent regionförbund (f) and personal mail correspondance with Sveriges kommuner och landsting (g)

*Currency conversions are used according to national exchange rate as of December 12, 2006.

†Information given by direct communications with Institut für Refraktive & Ophtalmol Chirurgie (IROC). The price includes 15 minutes' consultation and examination by an ophthalmologist in Switzerland.

[a]Curtis L, Netten A. Unit Costs of Health and Social Care 2006. Personal Social Service Research Unit, University of Kent, Canterbury, 2006.

[b]Institut für Refraktive & Ophthalmo-chirurgie, Zurich. Available at: www.iroc.ch. Accessed May 16, 2007.

[c]Universidad Politécnica de Cartagena. Available at: www.upct.es/servicios/rrhh/conte-convenios.htm. Accessed May 12, 2007.

[d]L'Assurance Maladie, Assurés, Soins et remboursements. Available at: www.ameli.fr/. Accessed May 10, 2007.

[e]Hujanen et al. Terveydenhullon yksikkökustannukset Suomessa vuonna 2001. STAKES.

[f]Norrlandstingens regionförbund. Prislista 2006. Available at: www.norrlandstingen.se. Accessed March 20, 2007.

[g]Sveriges Kommuner och Landsting. Available at: www.skl.se. Accessed March 20, 2007

tients to reach the target IOP, which may also be expressed as cost per successfully treated patient. Effects after 3 months (the study period in Simmons and associates) (19) were conservatively assumed to be equal to the effect after 12 months. In Tables II and III, the unit costs used in the analyses are presented. Due to the time horizon of the analysis, costs were not discounted.

RESULTS

The results from the cost-minimization analysis comparing the fixed combination of brimonidine/timolol versus the fixed combination of dorzolamide/timolol and the nonfixed combination of timolol with the adjunctive therapy of brimonidine in the six countries are presented in Table IV.

TABLE IV - COST-MINIMIZATION ANALYSIS (3 and 12 months, in €)

	Nonfixed combination brimonidine and timolol	Fixed-combination brimonidine/timolol	Nonfixed combination dorzolamide and timolol	Fixed-combination dorzolamide/timolol
UK				
3 mo	1.83	261.96	259.52	262.18
12 mo	539.67	540.20	530.43	541.09
Switzerland				
3 mo	443.96	439.45	444.79	444.19
12 mo	880.71	862.64	884.03	881.61
Spain				
3 mo	258.84	264.24	264.27	274.80
12 mo	535.55 5	57.15	557.27	599.39
France				
3 mo	140.58	139.92	141.06	140.85
12 mo	366.32	363.68	368.24	367.40
Finland				
3 mo	369.99	367.27	364.86	370.14
12 mo	793.98	783.10	773.44	794.56
Sweden				
3 mo	410.82	393.88	409.37	395.01
12 mo	812.90	745.14	807.07	749.65

TABLE V - COST-EFFECTIVENESS OF NONFIXED COMBINATION OF TIMOLOL AND BRIMONIDINE VERSUS TIMOLOL AND DORZOLAMIDE (12 months, in €)

Country	Nonfixed combination (adjunct) medication	Average cost-effectiveness ratio (C/E)* (€)	ICER (€)
UK	Brimonidine	7.20 per 1% on target	Brimonidine dominates
	Dorzolamide	15.91 per 1% on target	
Switzerland	Brimonidine	11.74 per 1% on target	Brimonidine dominates
	Dorzolamide	26.52 per 1% on target	
Spain	Brimonidine	7.14 per 1% on target	Brimonidine dominates
	Dorzolamide	16.72 per 1% on target	
France	Brimonidine	4.88 per 1% on target	Brimonidine dominates
	Dorzolamide	11.05 per 1% on target	
Finland	Brimonidine	10.59 per 1% on target	Brimonidine dominates
	Dorzolamide	23.20 per 1% on target	
Sweden	Brimonidine	10.84 per 1% on target	Brimonidine dominates
	Dorzolamide	24.21 per 1% on target	

*Cost per 1% of patients reaching target intraocular pressure (cost per successfully treated patient).
ICER = incremental cost-effectiveness ratio

In all countries, the fixed combination of brimonidine/timolol was slightly less costly than the fixed combination of dorzolamide/ timolol over both the 3-month and 12-month horizon. In four of the six countries, the fixed combination of brimonidine/timolol was less costly than the nonfixed combination of brimonidine and timolol. In the United Kingdom and in Spain, however, the concomitant administration of timolol and brimonidine was slightly cheaper than the fixed combination of brimonidine/timolol. Concomitant dorzolamide and timolol was slightly more expensive than the fixed combination of brimonidine/timolol in most countries with the exception of the United Kingdom and Finland.

The results of the cost-effectiveness analysis comparing the two concomitant administration regimens of brimonidine and dorzolamide are presented in Table V. Depending on the country, the 12-month average cost-effectiveness ratios for the nonfixed combination of timolol and brimonidine ranged from €4.88 to €11.74 per 1% of patients reaching target IOP (ie, 17 mmHg) compared with €11.05 to €26.52 for the nonfixed combination of timolol and dorzolamide (Tab. V). Hence, the use of brimonidine as adjunctive therapy reduced the cost per patient achieving target IOP compared with adjunctive therapy using dorzolamide.

DISCUSSION

Given the assumption of equal effectiveness and safety, a cost-minimization analysis was conducted to compare the costs of two fixed-combination therapies, dorzolamide/timolol and brimonidine/timolol, as well as therapy with concomitant timolol and brimonidine. A cost-effectiveness analysis was also performed to compare the incremental value of therapy with brimonidine or dorzolamide used concomitantly with timolol. Other concomitant therapies exist on the market, but fixed combinations were chosen for the present analysis based on the fact that fixed-combination therapies enhance patient compliance and thus optimize product use and efficacy. The fixed combinations of brimonidine/timolol and dorzolamide/ timolol were chosen due to their similar efficacy and safety characteristics, suggesting that the patient populations treated would also be similar. Other fixed combinations also exist, but they incorporate prostaglandin analogs and timolol and are not necessarily comparable with brimonidine or dorzolamide fixed combinations in terms of treated patient populations or outcome characteristics.

Preferably, a comparison of efficacy and safety of the four treatment options would be based on a single head-to-head randomized controlled trial to ensure consistent study design. However, no single study has compared the four fixed and concomitant combinations of brimonidine, dorzolamide, and timolol. In a recently published study by Arcieri et al (20), the efficacy of fixed-combination brimonidine/timolol versus dorzolamide/timolol was evaluated based on a randomized controlled trial with 30 patients. It was concluded that the two fixed-combination therapies were equally efficacious. However, this was a short-term crossover study with a therapy transition after 4 weeks, and a 4-week washout period before switching therapy, which is not comparable with the study designs in Table I; hence the study was left out of the present analysis. It is worth noting that the conclusion about the two treatment options as being equally efficacious supports the conclusion in the present analysis. Furthermore, in a recently presented study it was found that mean IOP lowering with 0.2% brimonidine/0.5% timolol was greater than or equal to mean IOP lowering with 2% dorzolamide/0.5% timolol after 3 months of therapy, regardless of whether the study regimen was used as fixed-combination monotherapy or as an adjunct to a prostaglandin analog (Nixon et al, poster presented at the annual meeting of the American Glaucoma Society, 2007, San Francisco, CA, USA). In addition, the fixed combination of 0.2% brimonidine/0.5% timolol was significantly more comfortable than 2% dorzolamide/0.5% timolol. These findings strengthen and support the conclusions from the present study.

Comparison of efficacy and safety was based on clinical data from four different clinical trials. Comparing data from several clinical trials can pose a problem since study design and patient population (e.g., severity of disease, demography) can never be completely identical. Addressing these differences and potential confounders and biases is of major importance whenever such comparisons are attempted. The patient samples included in the current analyses had identical characteristics in terms of age, baseline IOP, and diagnosis. Moreover, all of the studies were performed in developed, industrialized countries, and included patients primarily of white origin.

Fixed-combination therapies with brimonidine/timolol or dorzolamide/timolol have the same effect as adjunctive therapy with brimonidine. In most of the European coun-

tries presented, these combination therapies represented the less costly treatment option. Moreover, from the patients' perspective, fixed-combination products are more convenient to use and, therefore, improve compliance.

Clinical examination and confirmation of the presence of glaucoma as a result of elevated IOP is the primary reason to start medical treatment. However, due to different influencing factors, some patients discontinued their medical program. The most common explanations were treatment failure (i.e., lack of reduction in IOP) and adverse events (conjunctival hyperemia or a burning sensation in the eye). In an evaluation of the tolerability and efficacy of brimonidine/timolol and dorzolamide/timolol in patients with POAG or ocular hypertension, it was found that patients treated with brimonidine/timolol reported significantly fewer symptoms (i.e., decreased burning/stinging sensation and unusual taste) compared with those treated with dorzolamide/timolol (Nixon DR, poster presented at the annual meeting of the Association for Research in Vision and Ophthalmology, 2006, Fort Lauderdale, FL, USA). Furthermore, compared with patients treated with dorzolamide/timolol, patients treated with brimonidine/timolol were significantly more comfortable, as measured by a quality-of-life questionnaire.

In a single-center randomized, double-blinded clinical trial comparing the ocular comfort of fixed-combination brimonidine/timolol and dorzolamide/timolol, 24 of 30 patients (80%) found the former combination to be more comfortable than the latter 30 to 40 seconds following instillation (Chan et al, poster presented at the 6th International Glaucoma Symposium, 2007, Athens, Greece). According to a preliminary report of a prospective, open-label, phase 4 study, 300 patients with ocular hypertension or POAG who were treated with brimonidine/timolol had minimal side effects and 94% of patients expressed satisfaction with the treatment (Paczka et al, poster presented at the 6th International Glaucoma Symposium, 2007, Athens, Greece).

In summary, the fixed combination of brimonidine/timolol was more cost effective than the fixed combination of dorzolamide/timolol and nonfixed concomitant therapies using either brimonidine or dorzolamide plus timolol in four European countries (France, Switzerland, Sweden, and Finland). In two countries, the United Kingdom and Spain, the nonfixed combination of brimonidine was, however, slightly less costly than the fixed combination, and therefore, represented the more cost-effective choice. Given its superior effectiveness and lower cost, adjunctive brimonidine was more cost effective than adjunctive dorzolamide therapy in all the European countries. However, the fixed-combination therapy is expected to provide better compliance and convenience for the patient since the administration is easier. Given that this was not considered in the present analysis, the study may be considered conservative.

ACKNOWLEDGEMENTS

The study was supported by a grant from Allergan R&D Europe.

P. Buchholz and J.G. Walt are employees of Allergan, Inc. The other authors have no proprietary interest in the medications discussed. Drs. Hommer, Thygesen, and Ferreras are consultants to Allergan, Inc. and have received travel grants and honoraria from Allergan, Inc. in the past. J. Wickstrom prepared the health economic analyses for Allergan as a paid consultant.

Reprint requests to:
Jannie Wickstrøm, MD
Senior Consultant
MUUSMANN Research & Consulting A/S
Haderslevvej 36
DK-6000 Kolding
Denmark
jwic@muusmann.com

REFERENCES

1. Quigley HA. Number of people with glaucoma worldwide. Br J Ophthalmol 1996; 80: 389-93.
2. Infeld DA, O'Shea JG. Glaucoma: diagnosis and management. Postgrad Med J 1998; 74: 709-15.
3. Tuck MW, Crick RP. The projected increase in glaucoma due to an ageing population. Ophthalmic Physiol Opt 2003; 23: 175-9.
4. Anton A, Andrada MT, Mujica V, Calle MA, Portela J, Mayo A. Prevalence of primary open angle glaucoma in a Spanish population: the Segovia study. J Glaucoma 2004; 13: 371-6.
5. Tuck MW, Crick RP. The age distribution of primary open angle glaucoma. Ophthalmic Epidemiol 1998; 5: 173-83.
6. Berleen G. A healthier elderly population in Sweden. National Institute of Public Health, 2004.
7. Tuulonen A, Airaksinen PJ, Erola E, et al. The Finnish evidencebased guideline for openangle glaucoma. Acta Oph-

thalmol Scand 2003; 81: 3-18.
8. Kass MA, Gordon MO. Intraocular pressure and visual field progression in open-angle glaucoma. Am J Ophthalmol 2000; 130: 490-1.
9. Suzuki Y, Shirato S, Adachi M, Hamada C. Risk factor for the progression of treated primary open-angle glaucoma: a multivariate life-table analysis. Graefes Arch Clin Exp Ophthalmol 1999; 237: 463-7.
10. European Glaucoma Society. Terminology and Guidelines for Glaucoma, 2nd ed. Savona, Italy: Editrice DOGMA s.r.l., 2003; 3-3–3-45.
11. The AGIS Investigators. The advanced glaucoma intervention study, 6: effect of cataract on visual field and visual acuity. Arch Ophthalmol 2000; 118: 1639-52.
12. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000; 130: 429-40.
13. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M. Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol 2002; 120: 1268-79.
14. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 2002; 120: 701-13.
15. Kobelt G. Comparative data for all countries. In: Jönsson B, Krieglstein G, eds. Primary open-angle glaucoma. Differences in international treatment patterns and costs. Oxford, England: ISIS Medical Media, 1998; 116-26.
16. Sall KN, Greff LJ, Johnson-Pratt LR, et al. Dorzolamide/timolol combination versus concomitant administration of brimonidine and timolol: six month comparison of efficacy and tolerability. Ophthalmology 2003; 110: 615-24.
17. Solish AM, DeLucca PT, Cassel DA, Kolodny AH, Hustad CM, Skobieranda F. Dorzolamide/timolol fixed combination versus concomitant administration of brimonidine and timolol in patients with elevated intraocular pressure: a 3-month comparison of efficacy, tolerability, and patient-reported measures. J Glaucoma 2004; 13: 149-57.
18. Goni F; Brimonidine/Timolol Fixed Combination Study Group. 12-week study comparing the fixed combination of brimonidine and timolol with concomitant use of the individual components in patients with glaucoma an ocular hypertension. Eur J Ophthalmol 2005; 15: 581-90.
19. Simmons S; Alphagan®/Trusopt® Study Group. Efficacy of brimonidine 0.2% and dorzolamide 2% as adjunctive therapy to beta-blockers in adult patients with glaucoma or ocular hypertension. Clin Ther 2001; 23: 604-19.
20. Arcieri ES, Arcieri RS, Pereira AC, Andreo EG, Finotti IG, Sá Filho WF. Comparing the fixed combination brimonidine-timolol versus fixed combination dorzolamide-timolol in patients with elevated intraocular pressure. Curr Med Res Opin 2007; 23: 683-9.

on line

This paper has been selected to appear on the EJOWEB page free of charge

www.eur-j-ophthalmol.com/freearticle/index.htm