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The costs of treating glaucoma with combinations of topical drugs in Spain

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PURPOSE. *This study describes the treatment in ordinary clinical practice in Spain of patients with glaucoma with a two-drug combination therapy. The authors present the treatment outcome as end-of-period intraocular pressure (IOP) and the calculated direct medical costs over a 2-year period.*
METHODS. *Data were extracted retrospectively from patient charts recording the use of all medical resources related to glaucoma. Costs were estimated using unit costs from public sources (2005). Descriptive cost analysis according to combination treatment at baseline was performed.*
RESULTS. *The study included 216 patients from 21 centers. Around half of the patients were started on a β-blocker/prostaglandin analogue combination, while the rest received various other combinations containing either an α2-agonist or a carbonic anhydrase inhibitor. Across the seven groups considered, there was a statistically significant difference in the costs of the least and the two most costly groups, while the confidence intervals were overlapping in all other pairwise comparisons. The least costly drug combination was brimonidine/timolol. Assessing IOP at the end of follow-up, all the groups were equally effective (overlapping confidence intervals). In a multivariate regression analysis, the drug combination did not have an independent, significant impact on total direct medical costs, drug costs, or end-of-period IOP. Significant determinants of these variables were surgical interventions and one or more changes of drug combination during the follow-up.*
CONCLUSIONS. *Costs are determined by the response to treatment. Inadequate response triggers treatment changes and sometimes eventually surgical interventions, thereby increasing costs significantly. (Eur J Ophthalmol 2008; 18: 52-9)*

KEY WORDS. *Combination therapy, Cost analysis, Glaucoma treatment, Spanish costs*

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INTRODUCTION

The predominant treatment pattern for glaucoma is administering eyedrops with various topical pharmaceutical agents, alone or in combination, possibly followed by surgical interventions for patients with insufficient response to drug therapy.

All glaucoma treatments focus on lowering intraocular pressure (IOP). Some recent studies have examined the effectiveness of controlling IOP with respect to preventing visual field changes. The Advanced Glaucoma Intervention Study (1) has demonstrated that IOP values kept below 18 mmHg over a 6-year time period practically prevent visual field deteriorations. The Early Manifest Glaucoma Trial (available at: www.soikos.es) has shown that each mmHg reduction of IOP is related to a reduction of the risk of progression of approximately 10%. Even though a final outcome measure such as avoidance of blindness or deterioration of patients' quality of life (QoL) would be more satisfactory for carrying out medical eco-

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nomic assessments, these results indicate that IOP is a useful surrogate outcome measure. It is also easily monitored at low costs and little risk of adverse effects. Furthermore, IOP is used in standard clinical practice as a trigger of initiating therapy, to monitor the effects of treatment, and to assess the need for therapeutic changes.

Since the mid-1990s, many new topical agents have been introduced for glaucoma treatment, such as α2-agonists, prostaglandin analogues, carbonic anhydrase inhibitors (CAI), and others. As monotherapy with topical agents frequently neither achieves satisfactory decreases in IOP nor ensures that an acceptable IOP level is maintained over time, extensive use of combination therapy with two or more topical agents has developed in clinical practice. As a consequence, a number of fixed drug combinations have been introduced to reduce the amount of excipients and make the administration of treatment easier for an elderly patient population.

The purpose of the observational study presented in this article was to examine and describe the clinical management of patients with glaucoma started on combination drug therapy in Spain in 2002. Due to the limited sample size, results are presented without attempting to perform an actual economic evaluation of the relative cost effectiveness of the various combination treatments compared to each other.

METHODS

Eligible patients

Data were collected retrospectively for a 2-year period from patient charts in 21 clinical centers, after ethical committee approval. The study included consecutive patients with a diagnosis of primary open angle glaucoma (POAG) or ocular hypertension (OH), starting first- or second-line combination therapy during the period February 2002 to April 2003.

Patients with major ocular comorbidity (other than cataract) or any ophthalmic comorbidity with an influence on visual field deterioration or optic nerve head damage were excluded. Also excluded were patients having undergone ophthalmic surgery within 3 months prior to the start of combination therapy and patients with a predictable indication of surgery within 6 months. Finally, patients starting combination therapy with more than two IOP-lowering agents and patients participating in clinical trials were also excluded.

Resource use data

In addition to patient demographics, diagnosis, and comorbidities, all glaucoma-related medical visits, procedures, surgical interventions, and topical drugs prescribed were abstracted to a specially designed data collection form. IOP and visual field measurements were noted as recorded in the charts.

Costs

The direct medical costs were estimated from a third-party payer perspective by applying publicly available resource unit prices. Drug costs were determined assuming the use of one bottle of topical agent per 28 days and that patients remained on the combination until next visit unless otherwise indicated. Drug prices were taken from a Web site provided by the Official Colleges of Pharmacists and the Spanish General Council of Official College of Pharmacists. Patient copayments were deducted where relevant (i.e., for patients below the age of 65 years), in accordance with the third party payer perspective chosen.

Unit prices of other medical resources were extracted from a public hospital (Hospital Miguel Servert, Zaragoza) and a publicly available resource costing data base (2). Procedures usually performed during a consultation, such as ophthalmoscopy, tonometry, and assessment of visual acuity, are not paid for separately in Spain and were thus considered part of the cost of a consultation. All unit costs are for 2005 and are listed in Table I. We present the nominal costs calculated over a 2-year period without any discounting.

Effectiveness of treatment

The worse eye at baseline, i.e., the eye with the highest IOP value, is designated as the study eye. Patients are grouped according to the drug combination prescribed at the start of the observation period. Any change of drug combination during the follow-up period is considered a treatment failure for the initial drug combination. Continuing therapy with the same combination throughout the period is therefore considered a treatment success, irrespective of the IOP value achieved. This reflects the individualized character of the target IOP value, which is adapted by the clinician's assessment of the particular patient's characteristics and risk profile.

Effectiveness of treatment is also assessed by the IOP

TABLE I - UNIT COSTS, IN €, 2005 PRICES

Medication or procedures	Cost, €
Medication	
Alphagan® 0.2%	12.56
Lumigan® 0.03%	21.16
Travatan® 0.004%	20.64
Trusopt® 2%	12.56
Xalatan® 0.0005%	22.39
Cosopt® 20 mg/5 mg	20.83
Xalacom® col 2.5 mL	24.64
Complementary procedures	
Tonometry*	—
Visual field exploration (perimetry)	50.00
Gonioscopy	13.30
Ophthalmoscopy*	—
Paquimetry (tonometry)	60.00
Visual acuity*	—
Photography	60.00
Surgical interventions	
Trabeculoplasty	400.00
Cataract surgery†	90.74
Glaucoma filtration surgery	1,000.00
Phacotrabeculectomy	1,200.00
Other‡	250.00
Visit to ophthalmologist	43.08
Hospital admission, ophthalmology, per night	389.29

*Included in visit cost.
†10% of the regular price, as cataract surgery was considered an indirect glaucoma treatment strategy.
‡Needling filtration

value observed at the last visit for which data have been recorded. There is no generally agreed optimal target IOP value. Rather, target levels are individualized according to patients' risk profile. In the clinical literature target values may range between 13 mmHg and 22 mmHg (3, 4). We therefore only present a binary analysis using 18 mmHg as the threshold.

Drug combinations

The data collection focused on drug combinations with α2-agonists, CAI, and prostaglandins or prostamides. The principal objective of the study was to determine the costs of ordinary clinical management with combination drug therapy of these patients and not to focus on any particular combination. Patients were therefore enrolled into the study consecutively as they had presented over a prespecified recruitment period, and all combinations that had been prescribed were included. Consequently, some of the combination groups in the study are quite small, in particular those containing the most recently introduced drugs. The drug combinations included are listed below. Patients are grouped according to their initial drug combination, regardless of any subsequent changes of therapy that may have occurred.

- α2-agonist + β-blocker (brimonidine + timolol)
- α2-agonist + any other (brimonidine + any other, mostly prostaglandins)
- CAI + β-blocker (dorzolamide + timolol)
- Prostaglandin/prostamide + β-blocker (bimatoprost + timolol or travoprost + timolol, or latanoprost + timolol)
- Other combinations (predominantly prostaglandin + CAI).

Statistical methods

We present the estimated means and 95% confidence intervals (95% CIs) for the variables of interest. All inferential statements and indications of statistical significance apply the conventional 5% level of significance. The principal determinants of the observed variations in total costs, drug costs, and end-of-period IOP have been analyzed by means of multivariate OLS regression analysis.

RESULTS

Baseline characteristics

Table I shows the baseline characteristics of the 216 patients included in the study and their distribution on the initial drug combinations singled out for analysis.

There were no differences in patient age and baseline IOP between the groups. Overall, 83% of the patients had POAG and 17% OH, and similar distributions were found in each of the groups. Twenty percent of the patients had received combination treatment as first-line therapy, while the rest of the patients started combination as second-line therapy or higher. Mean baseline IOP was significantly higher in de novo patients, 28.2 (95% CI: 26.2–30.2), compared to patients having failed a previous treatment, 23.9 (23.3–24.4).

The data in Table II indicate that the brimonidine containing combinations were used most often for patients starting second line treatment, while latanoprost + timolol was selected more often for de novo patients. This difference may have affected the IOP level at the end of the observation period, as the response in patients having already failed a therapy may be less strong. As expected,

β-blocker monotherapy was the most frequent prior drug therapy (39% of patients starting second line), followed by prostaglandin analogue monotherapy (35%) and an α2-agonist (12%).

Effectiveness of treatment

Mean IOP at the end of the observation period was not significantly different in the groups and more than two thirds of the patients reached a target IOP of ≤18 mmHg. Fifty-eight percent of the patients continued on the initial treatment over the entire follow-up period. This proportion was similar across the groups, varying between 52% in the brimonidine + Other group and 66% in the Other group, and differences observed were not statistically significant. Of the patients with a treatment switch, half changed only once, while the remainder changed treatment twice or more. Table III shows that the effectiveness of treatment was significantly lower in the group of patients who changed treatment once or more during the follow-up period. Only 56% of the patients with a treatment change achieved an IOP of ≤18 mmHg, compared to 78% of the patients who continued on the same therapy (p<0.001).

The motivations given for changing drug combination were predominantly failure to achieve sufficient control of IOP (47%), adverse effects (23%), and other reasons such as surgery, a wash-out period, or a reassessment of the patient (24%). Across the groups, these proportions vary somewhat from the general pattern, but because of the small sample sizes involved these differences should be interpreted cautiously.

Costs

Table IV describes the average number of control visits and procedures performed during the 2-year period, according to whether the patients continued the initial drug

TABLE II - BASELINE CHARACTERISTICS OF PATIENTS BY GROUP

Group	No.	Proportion of sample, %	Age, yr, mean (95% CI)	Baseline IOP, mean (95% CI)	Proportion on treatment prior to starting combination therapy, % (95% CI)
Brimonidine+ timolol	13	6.0	64.3 (55.4–73.2)	23.1 (21.0–25.1)	0.92 (0.76–1.09)
Brimonidine + other	29	13.4	64.1 (59.0–69.3)	24.5 (22.6–26.4)	0.93 (0.83–1.03)
Dorzolamide + timolol	21	9.7	64.2 (59.7–68.7)	24.2 (21.7–26.6)	0.81 (0.62–0.99)
Bimatoprost + timolol	7	3.2	64.5 (52.1–77.0)	30.1 (22.1–38.1)	0.71 (0.26–1.17)
Travoprost + timolol	7	3.2	51.0 (41.1–61.0)	26.0 (23.4–28.6)	1.0
Latanoprost + timolol	101	46.8	63.7 (61.3–66.1)	24.8 (23.9–25.8)	0.74 (0.66–0.83)
Other	38	17.6	65.7 (61.6–69.8)	24.4 (22.7–26.1)	0.79 (0.65–0.93)
Total	216	100	63.8 (62.1–65.5)	24.8 (24.1–25.4)	0.80 (0.74–0.85)

Mean age, mean baseline intraocular pressure (IOP), and the proportion that started combination drug therapy after having failed previous treatment (95% CIs)

TABLE III - PROPORTION OF PATIENTS ACHIEVING A TARGET LEVEL OF INTRAOCULAR PRESSURE (IOP) AT LAST VISIT (here 18 mmHg), ACCORDING TO WHETHER THEY CONTINUED ON THE SAME DRUG COMBINATION OR CHANGED AT LEAST ONCE

Achieved IOP ≤18 mmHg	Continued therapy on same drug combination, %	Changed drug combination at least once, %	Total, %
Yes	77.8	55.6	68.5
No	22.2	44.4	31.5
Total	126	90	216

χ^2=12.1, p=0.001

combination therapy or changed one or more times. Examined across the drug combinations, the average use of medical resources was uniform and corresponded to the pattern for all patients shown in Table IV. However, the anticipated differences were found between patients continuing or changing the initial drug combination. Patients with treatment changes had significantly more consultations and tonometries, although the differences were not very large in absolute terms. The remaining procedures were performed equally often in the two groups.

More patients in the group with therapy changes required surgical interventions, but the difference between the groups was only marginally significant (p=0.067). Five of the 34 patients (16% of all) with surgical interventions had two or more operations. Half of all surgical interventions were trabeculectomies, one third cataract operations, while the rest were miscellaneous operations.

Table V presents the estimated direct medical costs, by cost categories and in total, for the different drug combinations. The cost for surgical interventions includes hospitalizations for the three patients who were admitted into the hospital in connection with their operation.

Due to the small sample sizes of the groups the estimated confidence intervals are wide and in most cases overlapping across the groups. Costs differed significantly between the least costly group (brimonidine + timolol) and the high cost groups (brimonidine + other, and other), while pairwise comparisons between all the other groups result in an assessment of equivalence, partly because of the wide confidence intervals. Differences in costs result from drug costs and surgical interventions, while the costs of consultations and medical procedures are almost indistinguishable across groups. For the brimonidine + timolol group, both the costs of the drugs and surgical interventions are low, while the reverse is found for the two high cost groups. For the dorzolamide + timolol group, low drug costs are offset by very high costs for surgical interventions.

TABLE IV - NUMBER OF CONTROL VISITS PER PATIENT AND MEDICAL PROCEDURES PERFORMED, PATIENTS CONTINUING ON INITIAL DRUG COMBINATION OR CHANGING AT LEAST ONCE

Procedure	Patients continuing first drug combination	Patients changing drug combination at least once	All patients
Visit	4.3 (4.1–4.6)	5.3 (4.9–5.6)	4.7 (4.5–4.9)
Tonometry	5.3 (5.0–5.5)	6.2 (5.9–6.6)	5.7 (5.4–5.9)
Campimetry	2.1 (1.9–2.2)	2.3 (2.0–2.5)	2.1 (2.0–2.3)
Corneal thickness	0.4 (0.2–0.6)	0.3 (0.2–0.4)	0.3 (0.2–0.5)
Visual acuity	4.5 (4.1–4.8)	4.6 (4.2–5.0)	4.5 (4.3–4.8)
Photography	1.4 (1.0–1.8)	1.2 (0.7–1.7)	1.3 (1.0–1.6)
Gonioscopy	2.2 (1.9–2.6)	2.6 (2.1–3.1)	2.4 (2.1–2.7)
Nerve optic papilla	4.1 (3.7–4.4)	4.9 (4.4–5.4)	4.4 (4.1–4.7)
Proportion with surgery	0.12 (0.06–0.18)	0.21 (0.13–0.30)	0.16 (0.11–0.21)

The difference in the proportion undergoing surgery approaches statistical significance at the 5% level, with a p value of 0.067. Values are mean (95% CI)

TABLE V - ESTIMATED AVERAGE DIRECT HEALTH CARE COSTS PER GROUP, ACCORDING TO COST CATEGORIES, € (95% CI)

Group	Drug cost	Consultations	Procedures	Surgical intervention	Total costs
Brimonidine + timolol	453 (314–593)	232 (196–268)	229 (145–313)	0	915 (736–1092)
Brimonidine + other	640 (530–750)	279 (255–304)	280 (194–366)	147 (–38–332)	1345 (1106–1585)
Dorzolamide + timolol	472 (293–651)	227 (199–256)	221 (128–314)	260 (–79–600)	1181 (760–1602)
Bimatoprost + timolol	550 (328–771)	277 (246–308)	214 (14–415)	13 (–19–45)	1054 (784–1325)
Travoprost + timolol	426 (315–538)	252 (199–306)	532 (250–814)	0	1210 (870–1551)
Latanoprost + timolol	558 (515–601)	241 (228–254)	216 (181–252)	65 (24–107)	1080 (1019–1143)
Other	698 (630–766)	245 (221–269)	226 (175–277)	163 (9–317)	1331 (1160–1503)
All patients	575 (540–609)	246 (237–255)	238 (212–264)	105 (53–156)	1163 (1096–1231)

Patients remaining on their initial therapy for the 2 years had, as expected, significantly lower costs than patients with treatment changes, although the difference is small: 1078 € (95% CI: 1011–1145) compared to 1283 € (95% CI: 1154–1412) in the group with one or more treatment changes. Costs were not correlated with the number of treatment changes, however. For patients changing twice, mean costs increased to 1304 € (95% CI: 1130–1479), while for patients changing three to five times they remained in the range between 1400 and 1500 €.

There was also a small difference in the mean IOP achieved in the study eye at the end of the follow-up: 16.9 (95% CI: 16.3–17.4) in the group remaining on their first treatment versus 18.0 (95% CI: 17.3–18.7) in the group with changes.

Table VI shows estimates of several multivariate OLS regression equations aiming at identifying the most important determinants of the observed variations in 1) total direct medical costs, 2) drug costs only, and 3) end-of-period IOP. In each of these analyses, the equations first included dummy variables for each of the drug combinations analyzed. However, none of the coefficients for these variables even approached statistical significance, so they were excluded in the subsequent analyses.

Having undergone a surgical intervention or having changed drug combination at least once increased direct medical costs significantly. Increasing age had a small, marginally significant positive impact on costs, while baseline IOP and de novo treatment were nonsignificant. Drug costs as well as treatment changes were significantly higher with increasing age. Surgical intervention reduced drug costs significantly. Drug costs were not dependent on baseline IOP or the de novo treatment, essentially due to the inclusion criteria for the study (start of combination therapy only).

The mean IOP after 2 years was significantly lower in patients undergoing glaucoma surgery, while higher baseline IOP, de novo treatment, and therapy changes significantly increased the IOP at the end of the observation period.

DISCUSSION

The actual choice of drug combination does not have a significant impact on any of the outcomes examined, when other factors of potential importance are adequately controlled for in a multivariate regression analysis. Surgery was a significant factor in all equations, contributing significantly to increased total medical costs, while exerting an opposite impact on drug costs and end-of-period IOP. Changing drug treatment was an equally significant driver of both drug costs and total medical costs, but patients with changes did not reach the same low IOP as surgical patients, or patients with no changes. This is not surprising, as these patients are presumably those less responsive to treatment with topical agents, triggering more intensive management.

There are few data available in the literature on the effectiveness of combination therapy with topical antiglaucoma agents to which the results of the present study may be compared. Given this, it is only to be expected that there are no data whatsoever on the costs of these treatments. The volume by Jönsson and Krieglstein (5, 6) presents calculations for nine different countries, including

TABLE VI - RESULTS OF REGRESSION ANALYSES ESTIMATING THE DETERMINANTS OF VARIATIONS IN TOTAL HEALTH CARE COSTS, MEDICATION COSTS, AND INTRAOCULAR PRESSURE (IOP) AT THE END OF THE FOLLOW-UP PERIOD

Variables	y = log (total costs)			y = log (drug costs)			y = end of period IOP		
	coeff.	t ratio	p value	coeff.	t ratio	p value	coeff.	t ratio	p value
Constant	2.8	28.9	0.000	2.7	29.6	0.000	11.8	5.44	0.000
Age	0.002	1.93	0.056	0.004	5.38	0.000	–0.02	–1.24	0.22
Initial IOP	0.001	0.51	0.612	–0.002	–1.18	0.24	0.152	3.66	0.000
Surgical intervention	0.136	4.61	0.000	–0.118	–4.74	0.000	–3.7	–6.35	0.000
Drug change	0.057	2.92	0.004	0.054	3.30	0.001	1.29	3.29	0.001
First line Tx	0.011	0.41	0.684	–0.001	–0.07	0.95	1.74	3.29	0.001
N		216			216			216	
R^2 (adjusted)		0.21			0.29			0.28	

Each of the three models was initially estimated with dummy variables for the seven different drug combinations included. In no case were any of the estimated coefficients for these drug variables more than marginally significant

Spain. However, that study is 10 years old and included new patients starting on monotherapy, even though some combinations were included during the 2-year follow-up.

We found in this observational study that altogether 69% of the patients achieved a target level of 18 mmHg at their last visit, varying from 78% of the patients continuing on the same drug to 56% of the patients changing combination at least once (Table III). This may be compared with the findings of Holmström et al (7), who performed a systematic review of the published clinical studies of the effectiveness of treatment over 2 years with prostaglandins. They found that the proportion of patients reaching a target of 18 mmHg varied between 40% and 75% in these clinical studies, depending upon the particular mono- or combination therapy considered. Given that it is usually considered difficult to achieve the same effectiveness of treatments in ordinary practice as in clinical trials, it is noticeable that the effectiveness of drug therapy in our Spanish patients is generally higher than what was found in a number of clinical studies.

Recently published studies, such as those by Holmström et al (3) and Lindblom et al (8), only consider the costs of first-line monotherapy, making a comparison with our results less relevant. Another study, by Traverso et al (9), presents calculations of the costs of treating glaucoma patients based on 5-year follow-up data for patients from four different European countries. They show that the costs per year per patient increase as a function of disease severity, but they do not give sufficient details on the treatment patterns observed to allow an assessment of the appropriateness of comparing with the results of the present observational study.

It appears that the drug combinations examined here are largely equivalent in terms of both effectiveness and costs. A rigorous cost effectiveness analysis would be required to determine more precisely the incremental costs and effectiveness of changing from one drug combination to another. Such an assessment should also take into consideration that some patients may respond more or less favorably to the various drug combinations by using subgroup analyses. This would require substantially larger sample sizes than were available for the present study.

CONCLUSIONS

Between most of the drug combinations examined in this observational study, there is considerable overlap in terms of both costs and the surrogate outcome measure end-of-period IOP. This is partly due to the wide confidence intervals caused by the small sample sizes for some of the groups, and studies including more patients would certainly be warranted.

Between the least and the most expensive drug combination, there is a significant cost difference, while the difference in effectiveness is more difficult to assess. If measured by mean end-of-period IOP, all the drug combinations have overlapping confidence intervals, while there are certain differences in the distributions indicating the proportion of patients achieving a particular target IOP value. The precise value of IOP selected as target may therefore have a decisive impact on the assessment of the relative effectiveness of the drug combinations.

In multivariate analyses with appropriate control for possible confounding factors, it appears that the actual choice of drug combination does not have a significant, independent impact on total medical costs, on drug costs, or on end-of-period IOP. But each of these variables had two variables in common with a significant impact (albeit not always in the same direction): undergoing a surgical intervention after starting combination drug therapy and changing drug combination at least once, most likely an indication that these patients have a lowered responsiveness to drug therapy.

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