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Clinical and economic impacts of latanoprost 0.005% in first-line treatment of open-angle glaucoma and ocular hypertension in France

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PURPOSE. *To assess the cost-effectiveness of treatment strategies that utilize first-line latanoprost compared to those based on initial beta-blocker therapy in patients with open-angle glaucoma (OAG) or ocular hypertension (OH) in France.*
METHODS. *The study was based on a decision-analytic model that was populated with data from a retrospective chart review. A hypothetical cohort of patients newly diagnosed with OAG and/or OH was assessed over a period of 2 and 3 years. For each treatment strategy 10,000 patients were assumed.*
RESULTS. *First-line latanoprost therapy was significantly more effective than initial treatment with a beta-blocker, providing more days of intraocular pressure (IOP) control primarily due to its longer time until initial treatment failure. Latanoprost's higher acquisition cost was largely offset by reductions in costs associated with surgical procedures. The additional cost for latanoprost was estimated at approximately € 41 and € 27 over 2 and 3 years, respectively. The incremental cost per day of IOP control when latanoprost was used as first-line strategy compared to the first-line beta-blocker strategy was € 0.82 and € 0.36 over 2 and 3 years, respectively.*
CONCLUSIONS. *These results provide compelling evidence that first-line latanoprost therapy can provide superior clinical outcomes at a small additional cost in actual clinical practice.*
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KEY WORDS. *Cost-effectiveness analysis, Economic analysis, Glaucoma, Ocular hypertension*

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INTRODUCTION

Glaucoma is a large group of ocular diseases characterized by progressive optic nerve damage, elevated intraocular pressure (IOP), and visual field defects that if left untreated leads to impaired vision and eventual blindness (1). It has been estimated that 67 million people have glaucoma worldwide, 6.7 million of whom are bilaterally blind as a result (2, 3). The World Health Organization predicts that the number of cases of glaucoma will rise over the next 20 years as the number of people aged >60 years doubles from its present level to reach 1.2 billion by 2020 (4).

An elevated IOP level remains the primary treatable risk factor for open-angle glaucoma (OAG) and ocular hypertension (OH) (1). OAG is the most common

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form of glaucoma among Europeans (2) while OH, which is characterized in untreated individuals by an IOP >21 mmHg and no optic nerve damage, may affect as many as 10% of those over 40 years of age (1). The current mainstay of medical management of patients with OAG or OH is the use of eyedrops that act on aqueous humor dynamics to lower IOP levels (1, 5). Topical treatment options for patients with these conditions consist of selective and nonselective beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogues, adrenergic agonists, and cholinergic agonists. In France, as elsewhere, pharmacotherapy currently is dominated by topical beta-blockers as first-line therapy followed by either monotherapy or combination therapy with other drugs or surgery if adequate control is not achieved (6).

Over the past few years, an increasing number of patients have been treated with new therapeutic alternatives, such as latanoprost and brimonidine as first- or second-line therapy, and this shift has been associated with reductions in rates of trabecular surgery (7-9). Latanoprost is a once-daily-dose prostaglandin analogue that has been shown in controlled clinical trials to lower IOP levels more effectively than timolol (10-12), brimonidine (13, 14), or dorzolamide (15). It was approved in 2002 in France for use as a first-line agent for patients with OAG or OH.

As intervention options in all therapeutic areas grow, government and third-party payers, which are under increasing budgetary constraints, are seeking ways to allocate resources to achieve maximum health care benefits. One commonly used allocation tool is the cost-effectiveness analysis of available therapies. In the present study, efficacy data drawn primarily from a retrospective chart review were combined with information concerning the use of health care resources to assess the cost-effectiveness of treatment strategies that utilized first-line latanoprost 0.005% therapy compared to those based on initial beta-blocker therapy in patients with OAG or OH in France.

METHODS

The study was based on a decision-analytic model (16, 17) that was populated with data from retrospective chart reviews conducted in Germany, Italy, Spain, and the United Kingdom. A hypothetical cohort of patients newly diagnosed with OAG and/or OH was assessed over 2 and 3 years' duration. Ten thousand patients were assumed for each treatment strategy.

Model overview

A Monte Carlo simulation model (18) was used to estimate the cost-effectiveness of treatment strategies initially based on latanoprost or a beta-blocker. The model considers multistage treatment strategies where a patient can switch to specified therapies in a set order or can receive surgery (Fig. 1). Transitions from one model state to another are based on a survival function describing time to therapy discontinuation. Patients who fail therapy for any reason are assumed to switch to the next therapy in the strategy or to undergo surgery. Costs are assigned to each therapy in the model, to switching events, and to surgery.

Outputs of the model include months on each treatment, frequency of therapy switches, number of days

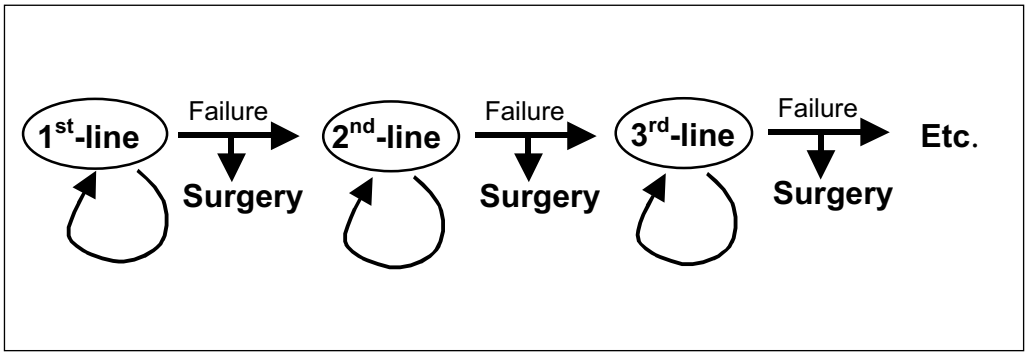

Fig. 1 - *Model structure and decision process. Patients start on first-line latanoprost therapy or beta-blocker therapy; each month they may remain on that therapy, fail and switch to a second-line therapy, or fail and undergo surgery. This pattern continues each month for 24 or 36 months. After failure of the sixth-line therapy, all patients are assumed to undergo surgery (not shown).*

of IOP control, frequency of ophthalmologist visits, proportion of patients undergoing surgery, and glaucoma-related costs. The following sections describe the input data and assumptions used in the model. Base-case values are provided in Table I.

Treatment strategies

Two strategies were considered: 1) first-line treatment with a beta-blocker followed by usual care for patients who switch therapy (Strategy A) and 2) first-line treatment with latanoprost followed by usual care for patients who switch therapy (Strategy B). The second-line, third-line, and subsequent treatment arms of Strategy A and Strategy B were based on weighted averages of single and combination therapies that reflected failure of first-line treatment with beta-blocker and latanoprost, respectively (Tabs. II and III). These data were derived from a 2-year European chart review study of patients with previously untreated primary OAG or OH and initially treated with latanoprost 0.005% or beta-blockers. The chart review was conducted in Germany, Italy, Spain, and the UK (Pharmacia Corporation, unpublished data, March 2002). When a patient in the model failed first-line treatment and moved to second-line treatment, the weighted average of the second-line therapies reported within the chart review study was used to determine the time on treatment and its cost for the second-line therapy. A French clinician reviewed the treatment strategies to validate that they reflected current practice patterns in France.

Time to therapy switch

Therapy switch was defined as any change in current therapy, including switch to an alternative therapy, addition of therapy, removal of therapy, and surgical intervention. Time to failure (survival) for first-line beta-blocker therapy, for first-line latanoprost therapy, and for patients using second-, third-, and fourth-line therapies was derived from pooled data for all countries in the European chart review study (Fig. 2). A random-number generator was used to select a point on the survival curve representing time to switch for each therapy in a strategy and for each patient. Outcomes and costs were calculated separately for each patient and pooled to provide average results for the population of patients. Second-, third-, and fourth-line survival estimates were based on the weighted average of survival for the mix of therapies after failure of beta-blocker or latanoprost as observed in the European chart review study. The effect of treatment was determined using a Cox model and was found to be statistically significant for first-line therapies. The product-limit method was used in conjunction with the Cox model to produce the survival curves, adjusting for therapy. Two-year curves were extrapolated for Year 3 assuming the same linear rate of decline as observed between Years 1 and 2.

Assessment visits

It was assumed in the model that ophthalmologists typically see patients at regularly scheduled intervals according to standard practice, with the time to the next visit dependent on whether or not a change in treatment occurred. Estimates of the frequency of ophthalmologist visits were obtained from the European chart review study, where patients returned for an assessment visit an average of 3 months following a change in current treatment (ie, initiation of a new treatment or addition of a new therapy) or an average of every 4 months if no therapy change was initiated (Pharmacia Corporation, unpublished data, March 2002).

Surgical interventions

Results of the European chart review study indicated that glaucoma-related surgeries are rarely performed within the first 2 years for a newly diagnosed patient; a total of 16 surgeries was performed for 348 patients (4.6%) within a 24-month period (Pharmacia Corporation, unpublished data, March 2002). Probability of surgery was incorporated into the model based on number of therapy switches: 2% of patients underwent surgery following failure of first-line therapy; 8% underwent surgery following failure of second-line therapy; 4% after third-line therapy; 11% after fourth-line therapy; and 50% after fifth-line therapy (Tab. I). It was assumed in the model that 100% of patients underwent surgery following failure of sixth-line therapy. After surgery, it was assumed that patients entered a maintenance phase, which included regular ophthalmologist visits and diagnostic testing.

TABLE I - MODEL ASSUMPTIONS AND INPUT DATA FOR ANALYSES*

Model parameter	Value
Discount rate	
	3% for costs 0% for outcomes
Treatment strategies	
	Beta-blocker 1st-line strategy (Strategy A): Beta-blocker 1st-line → post-beta-blocker 2nd-line → etc. Latanoprost 1st line strategy (Strategy B): Latanoprost 1st-line → post-latanoprost 2nd-line → etc.
Time until therapy failure Proportion of patients remaining on therapy at years 1 and 2	
	Beta-blocker 1st-line strategy: Beta-blocker 1st-line therapy – 46% and 29% Post-beta-blocker 2nd-line therapies – 53% and 35% Post-beta-blocker subsequent therapies – 60% and 42% **Latanoprost 1st-line strategy:** Latanoprost 1st-line therapy – 82% and 73% Post-latanoprost 2nd-line therapies – 54% and 36% Post-latanoprost subsequent therapies – 61% and 44%
Surgical rates Proportion of patients undergoing surgery following failure of:	
	1st-line therapy: 2% 2nd-line therapy: 8% 3rd-line therapy: 4% 4th-line therapy: 11% 5th-line therapy: 50% 6th-line therapy: 100% (model assumption)
Visit schedule Duration of time until the next assessment visit for:	
	Patients receiving a new therapy – 3 months Patients maintained on current therapy – 4 months
Cost of assessments Average cost of an ophthalmologist visit for:	
	Initial assessment visit in the model: € 40.88 Subsequent assessment visits in the model: € 36.05
Cost of therapy Average cost of prescription; average prescription duration:	
	Beta-blocker 1st-line strategy: Beta-blocker 1st-line therapy: € 5.57; 28 days Post-beta-blocker 2nd-line therapies: € 11.87; 28 days Post-beta-blocker subsequent therapies: € 15.02; 28 days **Latanoprost 1st-line strategy:** Latanoprost 1st-line therapy: € 11.49; 28 days Post-latanoprost 2nd-line therapies: € 11.77; 28 days Post-latanoprost subsequent therapies: € 13.22; 28 days
Cost of surgery Cost per patient undergoing surgery:	
	Acute cost: € 1120.00 (assumes both eyes) Monthly cost of postsurgical care: € 28.06 (assumes both eyes)

*See text for data sources; €=Euro

TABLE II - COST OF THERAPY FOR BETA-BLOCKER STRATEGY OF BASE-CASE ANALYSIS

Medication	Probability of therapy use (%)*	Cost per therapy prescription (€)†	Weighted total prescription cost (€)‡
First-line total:			5.57
BB	100.00	5.57	5.57
Second-line total:			11.87
BB/CAI	42.20	14.93	6.30
BB	9.17	5.57	0.51
CAI	14.68	9.36	1.37
AAA	1.83	10.14	0.19
Aceclidine	0.92	0.89	0.01
Brimonidine	11.93	9.02	1.08
Pilocarpine	0.92	1.72	0.02
BB/CAI	4.59	12.36	0.57
BB/pilocarpine	1.83	6.83	0.13
Latanoprost	1.83	11.49	0.21
BB/pilocarpine	1.83	7.29	0.13
BB/brimonidine	5.50	14.59	0.80
BB/latanoprost	1.83	17.06	0.31
BB/BB/CAI/CAI	0.92	27.28	0.25
Third/fourth/fifth/sixth-line total:			15.02
Brimonidine	7.14	9.02	0.64
BB/CAI	3.57	14.93	0.53
BB/CAI	8.93	12.36	1.10
Brimonidine/CAI	1.79	18.37	0.33
BB/brimonidine/CAI/pilocarpine	1.79	25.20	0.45
CAI/pilocarpine	1.79	11.08	0.20
BB	17.86	5.57	0.99
BB/brimonidine	1.79	14.59	0.26
AAA	1.79	10.14	0.18
Latanoprost/CAI	5.36	20.84	1.12
Latanoprost	8.93	11.49	1.03
BB/latanoprost/pilocarpine	1.79	18.31	0.33
Latanoprost/pilocarpine	1.79	13.20	0.24
BB/latanoprost	14.29	18.31	2.62
BB/latanoprost/CAI	16.07	26.41	4.24
BB/CAI/brimonidine	1.79	23.94	0.43
CAI	3.57	9.36	0.33

*Probability was obtained from European chart review data (Pharmacia Corporation, unpublished data, March 2002); describes probability of single or combination therapy being used as first-line, second-line, etc., therapy
†Describes cost for a prescription of that therapy; reflects IMS data on bottle sizes (IMS Health, unpublished data, March 2001)
‡Provides weighted cost for first-line, etc., therapy, total and individual components, weighted by probability of use
Therapies separated by "/" indicate combinations of therapies, AAA=Alpha-adrenergic agonist; BB=Beta-blocker; CAI=Carbonic anhydrase inhibitor; €=Euro

TABLE III - COST OF THERAPY FOR LATANOPROST STRATEGY OF BASE-CASE ANALYSIS

Medication	Probability of therapy use (%)*	Cost per prescription (€)†	Weighted total prescription cost (€)‡
First-line total:			11.49
Latanoprost	100.00	11.49	11.49
Second-line total:			11.77
Latanoprost/BB	21.74	17.06	3.71
Latanoprost/brimonidine	21.74	20.50	4.46
Brimonidine	8.70	9.02	0.78
Latanoprost/CAI	4.35	20.84	0.91
Pilocarpine	13.04	1.72	0.22
BB	30.43	5.57	1.70
Third/fourth/fifth/sixth-line total:			13.22
Latanoprost/BB/brimonidine	14.29	26.07	3.72
Latanoprost/CAI	14.29	20.84	2.98
Latanoprost	42.86	11.49	4.92
BB	28.57	5.57	1.59

*Probability was obtained from European chart review data (Pharmacia Corporation, unpublished data, March 2002); describes probability of single or combination therapy being used as first-line, second-line, etc., therapy; †Describes cost for a prescription of that therapy; reflects IMS data on bottle sizes (IMS Health, unpublished data, March 2001); ‡Provides weighted cost for first-line, etc., therapy, total and individual components, weighted by probability of use. Therapies separated by "/" indicate combinations of therapies; BB=Beta-blocker; CAI=Carbonic anhydrase inhibitor; €=Euro

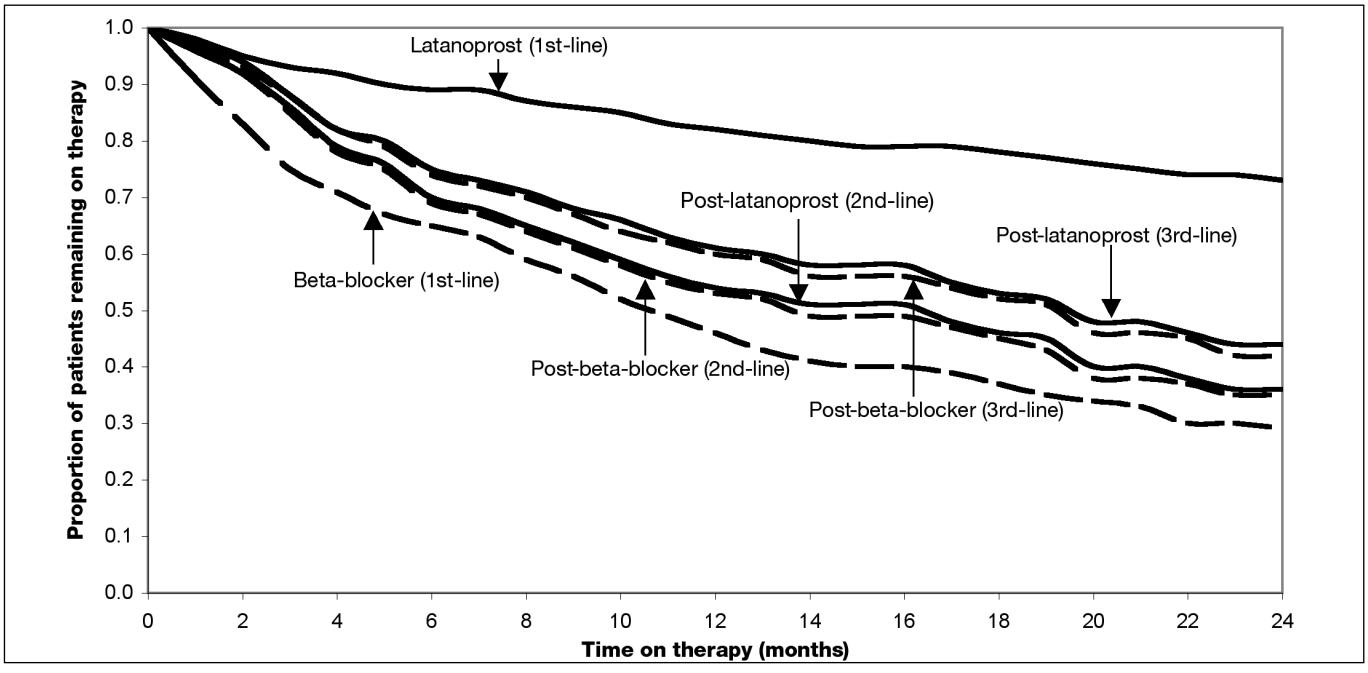

Fig. 2 - *Survival curves describing time to therapy switch for first-line latanoprost and beta-blocker therapies and for subsequent lines of therapy as derived from the European chart review study (Pharmacia Corporation, unpublished data, March 2002). Switch was defined as switch of therapy, addition of a therapy, or occurrence of surgery.*

Calculation of IOP-controlled days

In clinical practice, the reduction in IOP desired by a clinician varies among patients depending on the IOP level and degree of optic nerve damage at baseline and on clinician preference. Given this diversity, cost-effectiveness is measured herein in terms of the incremental cost per incremental IOP-controlled day gained, a variable that assumes that therapeutic failure leads to discontinuation and that persistency, defined as time on therapy, is a proxy for therapeutic success.

Therapy switches occurred at scheduled assessment visits and were assumed to be the result of therapy failure at some point since the previous visit. The analysis assumed that half the time since the last visit reflected "IOP-controlled days" and the other half reflected "days of no IOP control." For example, if a patient had scheduled assessment visits at months 6 and 12 and according to the survival curve failed therapy at a point within that time period, the patient's days with no IOP control were calculated as half of the time between visits 6 and 12 (ie, 3 months or 91 days). Monthly cycles were incorporated into the model in order to capture the potential for monthly reassessment visits.

Health care resource utilization and costs

Costs to the health care system were estimated for the management and treatment of OAG and OH. Events that triggered resource utilization and costs included assessment visits and associated tests, therapy prescription or modification, and surgical intervention. Included were all direct medical costs (such as hospitalization and medication) attributable to the treatment of glaucoma and covered by National Health Insurance. Unit costs for resources were priced from relevant sources in France, such as the Vidal 2002 (19), Union des Caisses Nationales de Sécurité Sociale (UCANSS) (20), and Programme de Médicalisation des Systèmes d'Information (21). Costs were reported in 2002 euros (€) using prices from France and included the value added tax.

Unit prices for ophthalmologist services were obtained from UCANSS (20) and included all costs associated with the visit, including clinician charges, fees associated with tests conducted or ordered, and technician charges for tests. Assessment visit costs attributed to the third-party payer perspective were calculated as 70% of the total cost to reflect local reimbursement rates; the remaining 30% would be covered by the patient or through private insurance (22). Frequency of use of diagnostic tests and procedures was obtained from the European chart review study, and costs were obtained from UCANSS. Costs applicable to the third-party payer perspective were calculated as 70% of the total cost to reflect local reimbursement rates (22).

The model required an average cost per prescription of medication(s). To calculate such costs, typical bottle sizes for each therapy used in the European chart review study were assessed using IMS (IMS Health, unpublished data, March 2001), and the cost per bottle size was obtained. A weighted average cost per therapy prescription then was calculated. Bottle duration for the base-case analysis relied on product labeling and local clinical expert recommendations to discard medication 28 days following the opening of a bottle. Costs applicable to the third-party payer perspective were calculated as 65% of the total cost of medication to reflect local reimbursement rates for medications (22).

The cost per patient related to the diagnosis and treatment of adverse events due to each therapy was assumed to be € 0 because adverse events related to topical glaucoma medications normally are minor and have few associated costs. Discontinuation due to adverse events was assumed to be expressed within the survival curves.

The costs of surgical procedures performed within hospital settings were calculated as the average cost per operated eye based on the 1-year interim analysis of a French prospective study (23). Medical costs included those for perioperative and postoperative medications, visits, and procedures. The total acute cost of surgery used in the base-case analysis was € 700 (95% confidence interval [CI]: € 485, € 915) per operated eye. This estimate was based on 65 patients in the French prospective study who had a surgical procedure. Costs applicable to the third-party payer perspective were calculated as 80% of the total cost to reflect local reimbursement rates for surgical procedures (22). All patients were assumed to have had bilateral glaucoma and bilateral surgery.

The cost of postsurgical care also was obtained from

the 1-year interim analysis of the French prospective study (23). The mean cost per month following surgery used in the base-case analysis was € 40 (95% CI: € 31, € 44).

Cost-effectiveness analysis

The cost-effectiveness of each treatment strategy was assessed in terms of the incremental cost of IOP-controlled days gained. The cost-effectiveness ratio was calculated by dividing the difference in total discounted costs between the two treatment strategies by the difference in discounted treatment effectiveness:

$$\text{Incremental cost per IOP-controlled day gained} = \left(\frac{\text{Costs}_{\text{Strategy A}} - \text{Costs}_{\text{Strategy B}}}{\text{Effects}_{\text{Strategy A}} - \text{Effects}_{\text{Strategy B}}} \right)$$

In the base-case analysis, costs were discounted at a rate of 3% while outcomes were not discounted.

Sensitivity analyses

The sensitivity of the base-case cost-effectiveness results to uncertainty regarding input parameters was explored by varying key parameters within ranges reflecting possible parameter values. Variables explored in these analyses included time on therapy, bottle duration, surgical rates, assessment visit intervals, discount rate, cost of surgery, and cost of monthly follow-up after surgery. See Table IV for details.

RESULTS

Clinical outcomes

A strategy of first-line latanoprost therapy resulted in better clinical outcomes than a strategy of first-line beta-blocker therapy over 2 and 3 years. Latanoprost-treated patients remained on initial therapy for an average of 20.5 months compared to 13.4 months for those treated first with a beta-blocker ($p<0.0001$). After 2 years, patients receiving first-line latanoprost therapy used fewer therapies than those treated initially with a beta-blocker (1.38 ± 0.74 versus 2.08 ± 0.94, respectively; $p<0.0001$), and a smaller proportion of patients in the latanoprost group underwent surgery compared to those in the beta-blocker arm (1.5% versus 4.4%, respectively; $p<0.0001$) (Tab. V). These trends continued through Year 3. Compared with patients receiving first-line beta-blocker therapy, those receiving first-line latanoprost therapy experienced an average of 50 more days of IOP control over 2 years and 74 more days of control over 3 years ($p<0.0001$ for both comparisons).

Costs

The higher acquisition cost of latanoprost was partially offset over 2 years by savings attributable to averted surgical procedures, and the cost was almost fully offset over 3 years (Tab. VI). Overall, the mean additional cost for patients using the latanoprost-first strategy was € 40.92 and € 26.59 over 2 and 3 years, respectively ($p<0.0001$ for both comparisons). This translates into an additional annual cost of approximately € 20.50 and € 9 or a cost of € 0.06 and € 0.02 per day over 2 and 3 years, respectively.

Cost-effectiveness analysis

Patients receiving first-line latanoprost therapy gained an average of 49.67 days of IOP control compared to patients on first-line beta-blocker therapy over 2 years at an additional cost of € 40.92 (Tab. VII); thus, the cost-effectiveness ratio or incremental cost of the first-line latanoprost strategy per additional IOP-controlled day gained was € 0.82. Over 3 years, those receiving first-line latanoprost therapy gained an average of 73.74 days of IOP control at an incremental cost of € 26.59; the incremental cost of the first-line latanoprost strategy per additional IOP-controlled day gained was € 0.36.

Sensitivity analyses

By varying key parametres within ranges that reflect possible values, the sensitivity of the base-case results to parameter uncertainty was assessed. The

TABLE IV - PARAMETER VALUES AND DATA SOURCES USED IN THE SENSITIVITY ANALYSES

Model parameter	Sensitivity analysis values		
Time to therapy failure	Upper 95% CI for beta-blockers Lower 95% CI for latanoprost Upper 99% CI for beta-blockers Lower 99% CI for latanoprost		
Bottle duration	**Durations from AdvancePCS data***		
	Timoptic	5 mL	49 days
		10 mL	60 days
		15 mL	68 days
	Timoptic XE	2.5 mL	31 days
		5 mL	49 days
	Timolol maleate	2.5 mL	31 days
		5 mL	49 days
	Latanoprost	2.5 mL	42 days
	All other medications	5 mL	37 days
		10 mL	49 days
		15 mL	60 days
Surgical rates following:	**French prospective study (23)**	**Aggressive (assumption)**	**Canadian rates†**
Failure of 1st-line therapy	2%	2%	2%
Failure of 2nd-line therapy	7%	8%	7%
Failure of 3rd-line therapy	15%	20%	16%
Failure of 4th-line therapy	10%	50%	15%
Failure of 5th-line therapy	12%	75%	14%
Failure of 6th-line therapy	100%‡	100%‡	100%‡
Discount rate	**Costs**	**Effects**	
	5%	0%	
	3%	3%	
	5%	5%	
Assessment interval for:			
Patients not modifying therapy	5 and 6 months for controlled patients		
Patients modifying therapy	1 and 2 months for controlled patients		
Acute surgical costs	Upper and lower 95% CIs		
Cost of surgical follow-up	Upper and lower 95% CIs		

*S. Hutchinson, unpublished data, February 2001; †Pharmacia Canada, unpublished data, October 2002; ‡Model assumption; CI=Confidence interval

analysis was sensitive to time to therapy failure, bottle duration, assessment visit schedule for patients who switched treatments, surgical rates, and cost of surgical procedures.

An increase in the cost-effectiveness ratio of latanoprost to € 2.32 was found when estimates of time to therapy failure were adjusted using the lower 95% CI on survival for treatments incorporated in the latanoprost strat-

TABLE V - BASE-CASE ANALYSIS: OUTCOMES OF TREATMENT STRATEGIES, WITH NO DISCOUNTING OVER 2- AND 3-YEAR PERIODS

Outcomes	2-year period		3-year period	
	Beta-blocker 1st-line strategy Mean (SD)	Latanoprost 1st-line strategy Mean (SD)	Beta-blocker 1st-line strategy Mean (SD)	Latanoprost 1st-line strategy Mean (SD)
Days of IOP control	653.35 (99.15)	702.98 (65.83)	973.27 (168.00)	1,046.97 (112.39)
	95% CI on the difference: 47.34 to 52.00 p-value <0.0001 (z=41.74)		95% CI on the difference: 69.78 to 77.71 p-value <0.0001 (z=36.50)	
Physician visits*	6.87 (0.77)	6.96 (0.43)	9.71 (1.38)	9.89 (0.81)
Number of therapies used	2.08 (0.94)	1.38 (0.74)	2.46 (1.10)	1.59 (0.94)
	95% CI on the difference: -0.72 to -0.67 p-value <0.0001 (z=69.00)		95% CI on the difference: -0.90 to -0.84 p-value <0.0001 (z=87.00)	
Patients undergoing surgery	4.4%	1.5%	7.0%	3.0%
	p-value <0.0001 (χ^2=148.42)		p-value <0.0001 (χ^2=189.24)	
Months of postsurgical follow-up	10.88 (6.62)	10.17 (6.51)	16.26 (10.08)	14.25 (9.67)

*Excludes physician visits associated with postsurgical management
CI=Confidence interval; IOP=Intraocular pressure; SD=Standard deviation

TABLE VI - BASE-CASE ANALYSIS: COSTS (in euros) OF TREATMENT STRATEGIES, WITH NO DISCOUNTING OF COSTS OVER 2- AND 3-YEAR PERIODS

Cost Component	2-year period		3-year period	
	Beta-blocker 1st-line strategy Mean (SD)	Latanoprost 1st-line strategy Mean (SD)	Beta-blocker 1st-line strategy Mean (SD)	Latanoprost 1st-line strategy Mean (SD)
Management cost*	252.33	255.59	355.00	361.44
Treatment cost	232.11	311.75	374.28	462.31
Surgical cost†	63.01	21.08	113.19	44.53
Total cost	547.45 (259.51)	588.43 (142.12)	842.46 (343.19)	868.28 (203.31)
	95% CI on the difference: € 35.18 to € 46.78 p-value <0.0001 (z=13.84)		95% CI on the difference: € 18.00 to € 33.63 p-value <0.0001 (z=6.47)	

*Excludes costs associated with postsurgical care
†Includes costs associated with surgery and postsurgical care, including postsurgical medications, physician visits, and diagnostic tests; CI=Confidence interval; €=Euro; SD=Standard deviation

egy and the upper 95% CI on survival for treatments incorporated in the beta-blocker strategy. When the 99% CIs were used in the same scenario, the cost-effectiveness ratio of latanoprost increased to € 3.23. Utilizing estimates based on AdvancePCS Information Warehouse (United States) prescription claims data (S. Hutchinson, unpublished data, February 2001) for bottle duration decreased the cost-effectiveness ratio of latanoprost to € 0.38. When the assessment visit schedule for patients who switched treatments was varied to 1 and 2 months from 3 months, the cost-effectiveness ratio changed to € 0.32 and € 0.70, respectively (Fig. 3).

TABLE VII - BASE-CASE ANALYSIS: COST-EFFECTIVENESS RESULTS FOR LATANOPROST COMPARED TO BETA-BLOCKERS, WITH 3% DISCOUNTING OF COSTS AND 0% DISCOUNTING OF OUTCOMES (cost in euros)

Treatment strategy	Mean costs	Incremental cost	Days of IOP control	Incremental days of IOP control	Cost per IOP-controlled day gained
2-year period					
Beta-blocker 1st-line	539.46	-	653.3	-	-
Latanoprost 1st-line	580.38	40.92	703.0	49.67	0.82
3-year period					
Beta-blocker 1st-line	817.43	-	973.2	-	-
Latanoprost 1st-line	844.02	26.59	1046.9	73.74	0.36

IOP=Intraocular pressure

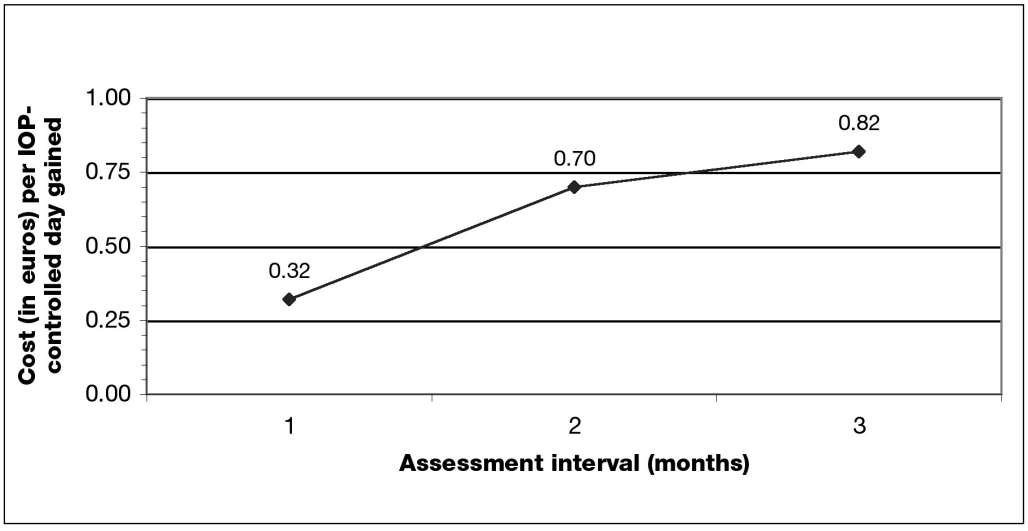

Fig. 3 - *Cost-effectiveness results for latanoprost compared to beta-blockers, with varying assessment intervals for patients initiating new treatment. IOP=Intraocular pressure.*

Including more aggressive surgical rates resulted in a decrease in the cost-effectiveness ratio of latanoprost to € 0.56. Utilizing alternate estimates from the French prospective study (24) for surgical rates decreased the cost-effectiveness ratio of latanoprost slightly to € 0.71, and utilizing estimates from a Canadian glaucoma chart review study (Pharmacia Canada, unpublished data, October 2002) further decreased the cost-effectiveness ratio of latanoprost to € 0.69. The effect of increasing and decreasing the cost of surgical procedures by the 95% CIs of the French prospective study (23) had a moderate effect on the cost-effectiveness of latanoprost. Using the upper 95% CI resulted in a decrease in the cost-effectiveness ratio of latanoprost to € 0.62, and utilizing the lower 95% CI increased the cost-effectiveness ratio of latanoprost to € 1.02.

The model was not sensitive to the discount rate, assessment visit schedule for patients who did not switch treatments, or estimates of the cost of monthly surgical follow-up (results not shown).

DISCUSSION

To evaluate the cost-effectiveness of first-line latanoprost therapy, an economic analysis comparing the costs and consequences of latanoprost versus a beta-blocker as first-line treatment in patients with OAG and/or OH was conducted over 2 and 3 years

in France. The study focused on short-term patient management because insufficient epidemiological data were available either to model the natural history of glaucoma over time or to evaluate the long-term benefits of topical therapy. Over the short term, poor IOP control does not result in the kind of immediate high-cost clinical events that may occur in other chronic diseases such as hypertension. However, previous research has indicated that failure of topical therapies results in increasingly intensive disease management, increased resource utilization, higher costs, and an elevated probability of surgery (24, 25). Continued failure to control IOP can lead to deterioration in patients' eyesight, which can impact their ability to perform daily activities and reduce overall quality of life. The short-term cost-effectiveness of an IOP-lowering therapy, therefore, is driven by the avoidance of the increased resource utilization associated with therapy failure. This analysis used patients' time on therapy without modification (persistence) to capture a therapy's ability to control IOP as well as its tolerability and convenience.

From the perspective of a third-party payer, this analysis provides strong economic evidence for the use of first-line latanoprost therapy in patients with OAG and/or OH when compared to initial treatment with a beta-blocker. Latanoprost provided significantly more days of IOP control primarily due to its longer time until initial treatment failure. The drug's higher acquisition costs were largely offset by reductions in costs associated with surgical procedures, resulting in an additional cost for latanoprost of approximately € 41 and € 27 over 2 and 3 years, respectively. The incremental cost per day of IOP control gained when using the first-line latanoprost strategy compared to the first-line beta-blocker strategy was € 0.82 and € 0.36 over 2 and 3 years, respectively.

It is notable that most model inputs were taken from a European chart review study rather than from clinical trials. Such data may be preferable to those from trials because they provide an estimate of persistence on therapy in normal clinical practice by a heterogeneous patient population having a range of baseline IOP levels and other risk factors. As such, these data capture real-world product use, including the effects of imperfect compliance and therapy discontinuation due to adverse events or patient dissatisfaction.

The current model is subject, however, to limitations common to all decision-analytic models in that it combines data from numerous sources, requires structural and data assumptions, and can be subject to biases (17). The first two limitations cannot be avoided because the primary motivation for creating any decision-analytic model is to compare strategies in the absence of comprehensive, comparative data. The present model also did not consider long-term outcomes or costs; additional data are needed to evaluate the long-term implications of early IOP control through the instillation of topical medications.

As evidenced by the European chart review study and IMS data, current practice patterns for the treatment of OAG and OH involve the use of a wide range of single and combination therapies after first-line therapy fails. Results of the European chart review, which included patients from Germany, Italy, Spain, and the United Kingdom, were used to approximate ophthalmologic practice patterns in France, leaving some uncertainty in terms of the absolute mix of therapies in second and subsequent lines of treatment in the latter country. A French clinician affirmed the face validity of the patterns used in the study, and overall the data were felt to adequately reflect the therapeutic strategies currently used in France and to be free of any clear bias for or against either treatment strategy.

The sensitivity of the model was tested extensively. The greatest change in cost-effectiveness results was produced when alternate survival curves were employed. Using the lower 95% and 99% CIs for survival on treatments in the latanoprost strategy in conjunction with the upper 95% and 99% CIs for survival on treatments in the beta-blocker strategy resulted in increased cost-effectiveness ratios compared to the base case. The ratio was € 3.23 in the most extreme case.

Given the lack of data concerning actual bottle duration, the base-case analysis reflected the general clinical recommendation to discard bottles of IOP-lowering drugs 28 days after opening. Varying bottle duration had a notable effect on results, and duration is expected to vary considerably in practice because bottles typically include more than 28 days of medication. Bottle duration also is affected by patient usage patterns, such as temporary stoppages in therapy, noncompliance, bottle loss, and simultaneous use of multiple bottles. Overall, as bottles are used beyond 28 days, the cost of treatment per day will decrease; nevertheless, this will not affect the incremental cost-ef-

fectiveness findings unless one therapy is used for more than 28 days while others are used for 28 days only.

Similarly, intervals between assessment visits for patients continuing on current therapy or switching therapy were based on the European chart review study. Such intervals vary considerably in actual practice due to physician preferences. The base-case analysis used the conservative estimate that patients prescribed a new therapy or who had a therapy added were not reassessed for 3 months. When shorter assessment intervals were modeled, cost-effectiveness ratios shifted in favor of first-line latanoprost therapy.

Lastly, surgical rates following therapeutic failure also vary considerably in actual practice due to patient- and physician-specific factors. The base-case model used rates from the European chart review study; however, current surgical rates in France are not known. When higher surgical rates were used, the cost-effectiveness of first-line latanoprost therapy improved, that is, the ratio decreased.

CONCLUSIONS

A treatment strategy utilizing latanoprost as a first-line agent compared to that using a beta-blocker first provides significantly more days of IOP control and fewer surgeries over 2 or 3 years at an additional annual cost of € 20.50 and € 9, respectively. The incremental cost per additional IOP-controlled day for first-line latanoprost therapy versus beta-blocker therapy was € 0.82 over 2 years and € 0.36 over 3 years. Overall, these results provide compelling evidence that first-line latanoprost therapy can provide superior clinical outcomes at a small additional cost in actual clinical practice.

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