ORIGINAL RESEARCH ARTICLE

Clin Drug Invest 2008; 28 (3): 183-198
1173-2563/08/0003-0183/$48.00/0

Assessment of the Cost Effectiveness of Travoprost versus Latanoprost as Single Agents for Treatment of Glaucoma in France

Stéphanie Payet,[1] *Philippe Denis*,[2] *Gilles Berdeaux*[3,4] and *Robert Launois*[1]

1 Réseau d'Evaluation en Economie de la Santé, Paris, France
2 Hôpital Edouard Herriot, Lyon, France
3 Alcon France, Rueil-Malmaison, France
4 Conservatoire National des Arts et Métiers, Paris, France

Abstract

Background and objective: Control of intraocular pressure (IOP) is a major factor in avoiding visual impairment related to glaucoma. Both the cost and the effectiveness of therapy should be considered when initiating this lifelong treatment. The aim of this study was to assess the cost effectiveness of travoprost versus latanoprost as single agents for the treatment of glaucoma in France.

Methods: Two surveys, one documenting efficacy and the other costs, were used to provide data for a Markov model. The model reproduced the 5-year course of patients receiving a prostaglandin analogue, travoprost or latanoprost, as monotherapy. The effectiveness criterion was fitted with a Weibull distribution from a national study. Transition probabilities and costs per treatment line were extracted from two French observational databases. Bootstrap techniques were implemented to drive the probabilistic sensitivity analyses. The study compared both treatments given once daily as monotherapy to ambulatory patients with primary open-angle glaucoma or ocular hypertension. The main outcome measure was mean time to treatment change (MTTC). Possible treatment changes were the addition of adjunctive medication, treatment substitution, laser therapy or surgery. After laser therapy or surgery, patients could continue with no treatment or proceed to prostaglandin analogue as monotherapy or treatment substitution. IOP was stratified at treatment onset as ≤20, 21–23 and ≥24 mmHg, respectively. All costs were expressed in 2005 euros.

Results: MTTC was 44.3 months for travoprost and 37.8 for latanoprost. Additional 5-year costs for travoprost were €51, resulting in an incremental cost-effectiveness ratio without treatment change of €95 per year. Of patients treated with latanoprost, 1.9% underwent laser therapy or surgery, compared with 1.2%

of patients treated with travoprost. The results differed with baseline IOP values, such that 55.6%, 53.9% and 50.4% of patients with pretreatment IOP values of ≤20, 21–23 and ≥24 mmHg, respectively, continued to receive travoprost treatment at 5 years, compared with 32.3%, 26.1% and 26.1% of patients, respectively, receiving latanoprost. Thus, incremental cost-effectiveness ratios (ICERs) without treatment change were €140, €45 and €123 per year, respectively.

Conclusion: Travoprost demonstrated a longer effectiveness profile than latanoprost and minimized early treatment changes. The smaller proportion of patients needing a new treatment, laser therapy or surgery virtually compensated for the higher travoprost acquisition cost. Overall, travoprost is cost effective compared with latanoprost, and is most cost effective in patients with pretreatment IOPs between 21 and 23 mmHg.

Introduction

Glaucoma is an optic neuropathy characterized by progressive loss of retinal ganglion cells and their axons, resulting in progressive loss of the visual field. If untreated or inadequately treated, glaucoma can lead to blindness, and indeed is a major cause of blindness in developed Western countries. In 2000, it was estimated that 66.8 million people worldwide have glaucoma, of whom 6.7 million develop bilateral blindness.[1] Worldwide, there will be an estimated 60.5 million people with glaucoma by 2010 and 79.6 million by 2020.[2] In 2010, 4.5 million people worldwide will experience bilateral blindness from open-angle glaucoma, and this number will increase to 5.9 million by 2020. The prevalence of primary open-angle glaucoma (POAG) in Western populations is estimated at between 1% and 4% for persons older than 40 years, and increases with patient age.[3-9] Because high intraocular pressure (IOP) is correlated with progressive visual field loss, it is essential to decrease IOP to preserve visual function.[10] Thus, the conventional first step in POAG management is initiation of ocular hypotensive therapy. Apart from raised IOP, other risk factors for glaucoma include race, diabetes mellitus, arterial hypertension and a family history of glaucoma.[11-15] Of the risk factors listed above, IOP is the only one that is modifiable and its control was associated with less glaucoma progression.

Treatment to decrease IOP must continue for the rest of a patient's life. As preventative action also carries a cost, a health economic evaluation may help therapeutic decisions.[16] The economic burden of glaucoma in the UK in 1994 was £62m (approximately $US93 million) in direct medical costs.[17] The average annual cost of treatment of patients with glaucoma is more than twice that of patients with ocular hypertension.[18,19] Glaucoma patients with more than three drug treatment changes per annum cost five times more than patients with unchanged treatment. Calissendorf[20] found that medication costs increased steadily before surgical treatment and then subsequently declined. In addition to the cost impact of treatment switches, an association was found between the number of switches and the probability of developing a new visual field defect.[21] Therefore, maintained treatment (measured as the mean time to a treatment switch) is an important parameter of treatment effectiveness in glaucoma, since treatment switches are associated with both high costs and a poor clinical outcome.

Classes of pharmacological treatments aimed at lowering IOP include β-adrenoceptor antagonists (β-blockers), carbonic anhydrase inhibitors, α_2-adrenoceptor agonists and prostaglandin analogues.

Prostaglandin analogues provide better efficacy in terms of controlling IOP than other classes and are indicated as first-line treatment either as single agents or in combination with other treatments for POAG and ocular hypertension.[22] Prostaglandin analogues appear to be free of systemic adverse effects and their established ocular adverse effects are generally cosmetic in nature (iris and eyelid hyperpigmentation, eyelash changes), with few reports of iritis and macular oedema.[23] Given their good safety and efficacy profile, and once-daily administration (allowing better adherence), prostaglandin analogues are commonly used as first-line therapy for glaucoma.[24]

Latanoprost (Xalatan®, Pfizer, New York, NY, USA)[1] and travoprost (Travatan®, Alcon Inc., Fort Worth, TX, USA) were the first two prostaglandin analogues marketed in France (1997 and 2001, respectively), followed by bimatoprost (Lumigan®, Allergan, Irvine, CA, USA). There is extensive literature on latanoprost and travoprost. Randomized clinical trials[25-32] comparing the drugs head-to-head demonstrated greater efficacy with travoprost than with latanoprost in lowering IOP, although not consistently so.[33-35] Furthermore, the advantage of travoprost (better IOP control) was confirmed by a meta-analysis[36] of all published clinical trials that compared the drugs directly, although Vass et al.,[37] conducting a meta-analysis in 2007, were unable to identify clear evidence of a beneficial effect (on glaucoma onset or progression) for any drug individually. Nevertheless, based upon the results of many clinical trials, several health economics analyses have concluded that travoprost is a cost-effective alternative to latanoprost.[38,39]

According to most health economics guidelines,[40] the effectiveness of a therapy should be estimated by observational studies and not solely on the results of randomized clinical trials, so as to capture the clinical benefit at a population level. In France, one observational study[41] aimed to evaluate the IOP control of travoprost and latanoprost in daily practice when given as monotherapy. This study confirmed the results of the randomized studies of Netland et al.[25] and Dubiner et al.,[26] who showed that IOP control was better with travoprost throughout the day and over the 24-hour period after an instillation had been missed.

The relative efficiency of travoprost and latanoprost has never been documented by observational data. Therefore, the observational study conducted in France referred to above[41] was used to derive a model for estimating the cost effectiveness of travoprost versus latanoprost when given as single agents for glaucoma treatment.

Methods

Markov Model States and Time Horizon

The model was designed to accurately reproduce the 5-year drug regimen of patients who had initially received prostaglandin analogue monotherapy. A Markov model was primarily chosen based on the following clinical considerations: (i) glaucoma is a chronic irreversible pathology assessed over time by measuring the control of IOP resulting from treatment; (ii) patients need to be monitored regularly (i.e. full treatment efficacy is obtained after 6 weeks and patients must visit an ophthalmologist for an IOP control assessment three times per year).[19] The Markov cycle length was therefore set at 1 month.

The model was constructed using TreeAge Pro 2006, Healthcare (Williamstown, MA, USA) decision analysis software (figure 1). The modelled period began with all patients under treatment with either travoprost or latanoprost as a single agent. At the end of each Markov cycle, a patient could continue with the original monotherapy, receive an additional (pharmacologically different) glaucoma

1 The use of trade names is for product identification purposes only and does not imply endorsement.

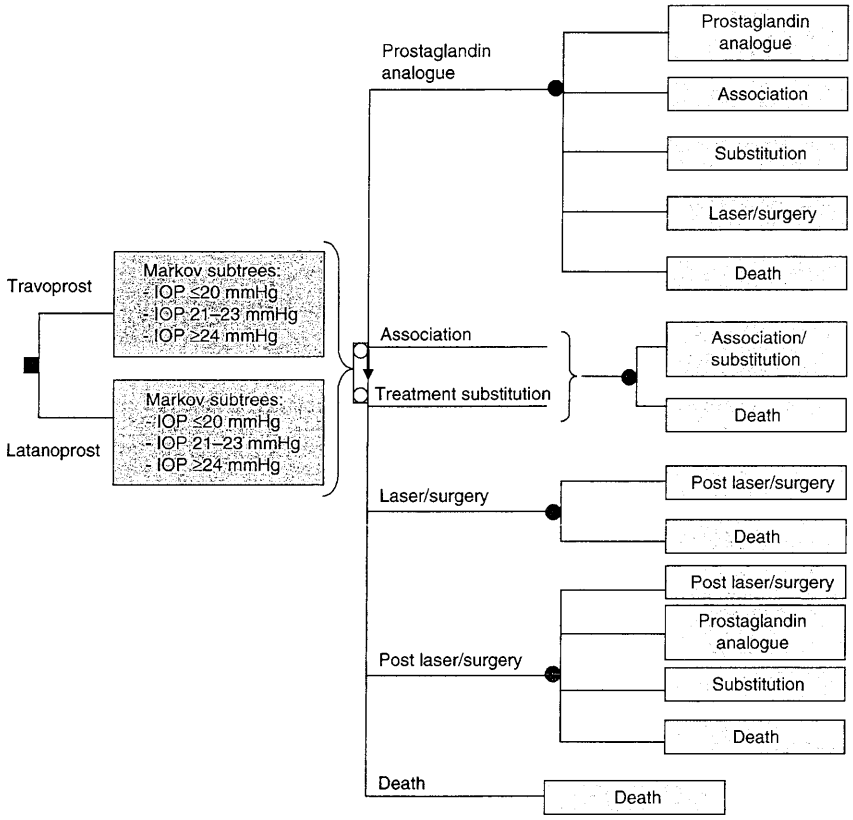

Fig. 1. Health states of the Markov model. **IOP** = intraocular pressure.

treatment, switch to a new treatment, undergo laser therapy or surgery, or die. According to the model, once a new medication had been added or substituted, a patient could not proceed to any further medication change. However, after laser therapy or surgery, patients could remain without medication, restart prostaglandin analogue monotherapy, or change to a different medication. The effectiveness criterion was the time spent taking prostaglandin analogue monotherapy before switching to a new state. Therapy change was defined as the prescription of a new treatment, either alone or together with the prostaglandin analogue.

Since the IOP-lowering effect depended on IOP at treatment onset, three Markov subtrees were constructed for each strategy: IOP ≤20 mmHg, IOP 21–23 mmHg and IOP ≥24 mmHg. The choice of three IOP thresholds was dictated by the dispersion of patients included in the observational survey.

Treatment cost is known to be associated with treatment switches.[21] Consequently, we used a Monte Carlo micro-simulation with a probabilistic sensitivity analysis using tracker variables to hold memory (treatment change order) from one cycle to another. A sample of 5000 hypothetical patients was generated. The seed (random number generator) was fixed always at '1' to allow comparisons between simulations.

Observational Studies

Databases from two French observational studies were used to document the model. The 'change database' (see below) originated from an observational study of daily practice designed to evaluate the IOP control achieved by travoprost or latanoprost used as single agents.[41] The 'cost database' (see below) was originally designed to estimate medical factors predictive of glaucoma treatment costs.[19,21]

Change Database

The cross-sectional, retrospective, observational study used was conducted in November 2003 and November 2004. Each of 280 French ophthalmologists enrolled ten patients within a 4-week time period. Patients of either sex with POAG or ocular hypertension (OHT) were enrolled if they conformed to the following criteria: (i) >18 years of age; (ii) use of prostaglandin analogue monotherapy for ≥6 weeks; (iii) no surgical intervention or laser therapy after commencement of prostaglandin analogue treatment; and (iv) no participation in another clinical study. It was also necessary that information in the patient's medical file be accessible. Patients who received additional therapy for POAG or OHT were excluded, as were patients with secondary glaucoma (e.g. congenital, inflammatory, neovascular, partial or complete angle closure, aphakic glaucoma).

Patients were characterized by socio-demographic criteria (age, sex, profession), type of glaucoma, concomitant risk factors for glaucoma (diabetes, dyslipidaemia, arterial hypertension or hypotension, vasomotor instability, cardiovascular disease, migraine, tobacco smoking, family history of glaucoma), presence of any associated ocular pathology (high myopia, cataract, age-related macular degeneration, dry-eye syndrome), glaucoma duration and diagnostic circumstances (routine examination, spontaneous visit for vision problems, eye symptoms).

The start date of the prostaglandin analogue prescription was also noted, as were the date and time of the last medication. In addition, the consultation date and time, IOP measurement and the ophthalmologist's therapeutic decision (no change, additional treatment, treatment substitution, complementary examinations, laser therapy or surgery) were recorded. Duration of treatment could thus be estimated.

Cost Database

The study used was a cross-sectional investigation with retrospective data collection. Ophthalmologists were selected at random from a list of physicians specializing in glaucoma treatment, stratified by region. 100 investigators agreed to participate in a prospective study whereby each would enrol four consecutive patients during routine consultations in a single week between December 2000 and February 2001. Patients were required to be ≥18 years of age with relevant information in their medical records and a diagnosis of POAG, normal pressure glaucoma or OHT. Patients were also required to have been treated for their condition at least once with a drug, laser therapy or surgery. Patients with secondary glaucoma (congenital, inflammatory, neovascular or narrow/closed angle following cataract surgery) or serious co-morbidity were excluded, as were patients involved in another clinical trial or epidemiological survey.

Medical item consumption included the number of laser treatments received and surgical operations undergone since diagnosis. Information on drug prescriptions for glaucoma (since 1995) was collected with start and end dates. The number, duration and reasons for hospitalizations linked to glaucoma and the number of visits to ophthalmologists, general practitioners and nurses and associated eye examinations (IOP measurement, visual field, gonioscopy, optic nerve and/or optic fibre photography, C/D

ratio, biomicroscopy) were documented for the year preceding the patient's inclusion in the study.

Statistical Analysis

Data analysis was performed with SAS software (SAS Institute Inc., Cary, NC, USA) release 9.1. The monthly probability of success with each prostaglandin analogue was calculated from the treatment duration of patients in the 'change database', which was to be ≥4 weeks. The duration of an unchanged treatment at the end of a visit was defined as 'right censored'. The Weibull (λ,γ) distribution, comprising a simple function of two parameters λ and γ: log [−log(survival(t))] = γlog(λ) + γlog(t), was used. First, Kaplan-Meier survival distribution functions, corresponding to the cumulative probability of success, $P_{success}(t)$, were estimated. The regression of log [−log($P_{success}(t)$)] on log(t) was then plotted for each prostaglandin analogue. When the determination coefficient (R^2) of a linear regression was sufficiently high (0.77 and 0.98 in these analyses), the Weibull model was accepted. Accordingly, the two parameters λ and γ were estimated (intercept and slope). The cumulative probability of success was thus defined as $P_{success}(t) = \exp((-\lambda t)^{\gamma})$ and the monthly probability of success was given by (Pt+1/Pt).

Use of the Weibull distribution had two major advantages. First, it allowed specification of a risk function that varies with time (because of the γ parameter). Second, the Weibull distribution was easy to estimate. We also validated the Weibull choice by regression.

The number of baseline IOP thresholds (predicting persistence) was fixed arbitrarily at 2, thus making it possible to identify three IOP groups with sample sizes sufficient for precise estimates. Cox models (one for each prostaglandin analogue) were performed to determine whether or not the probability of success was linked to IOP level.

Markov Transition Probabilities

Table I describes the Markov transitional probability matrix and gives the probability of switching from one state at time t to t + 1. The monthly probability of success with each prostaglandin analogue treatment was derived from a Weibull distribution. The probability of laser therapy or surgery was estimated directly from the 'change database'. Rates of monotherapy failure followed by a combination of the prostaglandin analogue with another drug, together with the associated frequencies, were estimated from the UK General Practice Research Database (UK GPRD).[42] The probability of no medication after laser treatment or surgery was estimated from survival curves reported by Nordmann et al.[43] Exponential functions were used to model the latter probability as a function of time. In the absence of specific data, the probability of receiving a prostaglandin analogue as monotherapy when a patient relapsed after laser therapy or surgery was set arbitrarily at 0.5. A sensitivity analysis was performed on this variable. Death transitional probabilities were estimated from a function combining age and gender published by Billotte and Berdeaux.[44] The model explained 98% of mortality variance.

Costs Definition

Monthly costs common to the two treatments studied were derived from the 'cost database'. These comprised costs linked to the number of visits made to ophthalmologists and general practitioners, complementary examinations carried out by ophthalmologists, and visits to other healthcare professionals for opinions. Data on item consumption before and after a treatment switch were estimated independently.

All costs were expressed in 2005 euros. An annual discount rate of 3.5% was adopted. Annual direct medical costs were calculated. Unit drug costs were

Table I. Transition probabilities of health states from time t to t + 1, distribution functions, and costs associated with each health state

t/t +1	TVP	LTP	Assoc. with TVP	Assoc. with LTP	Subst. after TVP	Subst. after LTP	Laser/surgery	Post laser/ surgery	Death
TVP	$P_{Success}$ ~ Weibull(λ,γ) λ,γ obtained from bootstrap[41]	0	$P_{Association}$ ~ Bin(1;0.8261)[42]	0	1–Σ(Pi)	0	P_{ls} ~ Bin(1;0.026)[41]	0	ref.[44]
LTP	0	$P_{Success}$ ~ Weibull(λ,γ) λ,γ obtained from bootstrap[41]	0	$P_{Association}$ ~ Bin(1;0.8711) [42]	0	1–Σ(Pi)	P_{ls} ~ Bin(1;0.026)[41]	0	ref.[44]
Assoc. with TVP	0	0	1–Σ(Pi)	0	0	0	0	0	ref.[44]
Assoc. with LTP	0	0	0	1–Σ(Pi)	0	0	0	0	ref.[44]
Subst. after TVP	0	0	0	0	1–Σ(Pi)	0	0	0	ref.[44]
Subst. after LTP	0	0	0	0	0	1–Σ(Pi)	0	0	ref.[44]
Laser/ surgery	0	0	0	0	0	0	0	1-Σ(Pi)	ref.[44]
Post laser/ surgery	$P_{Retreatment}$ ~ U(0.25;0.75)	$P_{Retreatment}$ ~ U(0.25;0.75)	0	0	1–Σ(Pi)	1–Σ(Pi)	0	$P_{Success}$ = ½ (Exp(−λ_l)+Exp(−λ_s)) λ_l ~ N(0.0323;0.0018) λ_s ~ N(0.0917;0.003)[43]	ref.[44]
Death	0	0	0	0	0	0	0	0	1
Cost	First- or second-line cost + cost of TVP nbo ~ Poisson(3.12) nbGP ~ Poisson(0.37) nbex ~ Poisson(7.37) nbopinion ~ Dirichlet (55;1;7;1;2;1)[19]	First- or second-line cost + cost of LTP nbo ~ Poisson(3.12) nbGP ~ Poisson(0.37) nbex ~ Poisson(7.37) nbopinion ~ Dirichlet (55;1;7;1;2;1)[19]	Second-line cost + cost of assoc. nbo ~ Poisson(3.08) nbGP ~ Poisson(0.55) nbex ~ Poisson(7.24) nbopinion ~ Dirichlet (17;3;1;4)[19] Cost of assoc. ~ U(34.2;41.8)[42]	Second-line cost + cost of assoc. nbo ~ Poisson(3.08) nbGP ~ Poisson(0.55) nbex ~ Poisson(7.24) nbopinion ~ Dirichlet (17;3;1;4)[19] Cost of assoc. ~ U(31.5; 38.5)[42]	Second-line cost + cost of switch nbo ~ Poisson(3.08) nbGP ~ Poisson(0.55) nbex ~ Poisson(7.24) nbopinion ~ Dirichlet (17;3;1;4)[19] Cost of switch ~ U(17.8;21.7)[42]	Second-line cost + cost of switch nbo ~ Poisson(3.08) nbGP ~ Poisson(0.55) nbex ~ Poisson(7.24) nbopinion ~ Dirichlet (17;3;1;4)[19] Cost of switch ~ U(15.0;18.4)[42]	Cost laser × pl + cost surgery × DRGs × (1–pl) pl ~ β(10195;5985) DRGs ~ Dirichlet (287;80;54;2;1;1;1)	0	0

λ_l = for laser; λ_s = for surgery; **assoc.** = association; **bin** = binomial; **DRGs** = surgery's diagnosis-related groups distribution; **exp** = exponential; **first-line cost** = cost of ophthalmologist × nbo + cost of GP × nbGP + cost of examination × nbex + cost of opinion before switch; **GP** = general practitioner; **LTP** = latanoprost; **N** = normal distribution; **nbex** = number of complementary examinations carried out by ophthalmologists; **nbGP** = number of visits to the GP; **nbo** = number of visits to ophthalmologist; **nbopinion** = number of visits for opinion before switch; $P_{Association}$ = probability of combining a drug with the correct treatment; **pl** = proportion of laser treatments among all operations; P_{ls} =probability of having laser or surgery; $P_{Retreatment}$ = probability of starting a glaucoma treatment immediatetly after laser or surgery; $P_{Success}$ = cumulative probability of success; **ref.** = reference; **second-line cost** = cost of ophthalmologist × nbo + cost of GP × nbGP + cost of examination × nbex + cost of opinion after switch; **subst.** = substitution; **TVP** = travoprost; **U** = uniform distribution.

taken from the Vidal compendium.[45] The Nomenclature Générale des Actes Professionnels[46] was used to estimate unit costs for outpatient procedures and visits, whereas the national DRG database[47] was used to determine costs for inpatient care. The Institut National de la Statistique et des Etudes Economiques inflation rate[48] was applied to obtain euro 2005 values. The economic perspective was that of society. Costs associated with each health state are described in table I.

The monthly costs of patients with unchanged treatment (prostaglandin analogue state) included the costs of drugs (latanoprost or travoprost), visits to ophthalmologists, general practitioners and other healthcare professionals, and complementary examinations. After a failure of prostaglandin analogue monotherapy, the average costs incurred by a patient increased, as described by Denis et al.[19] Costs of failed laser therapy or surgery were taken into account for patients who restarted prostaglandin analogue monotherapy.

Clinical Outcomes

The main clinical outcome determined by the model was the mean time to treatment change, defined as the time spent in the prostaglandin analogue monotherapy state before a treatment modification. Other outcomes were the proportion of patients undergoing laser therapy or surgery, and the proportion of patients still taking prostaglandin analogue monotherapy at 5 years.

Sensitivity Analysis

Acceptability curves were estimated in order to reflect the uncertainty of results, as recommended by most health economics guidelines.[40] Such curves describe the probability that a treatment will be cost effective in relation to degrees of a payer's willingness to pay.

A probabilistic sensitivity analysis was performed with 3000 simulations of 5000 patients per cohort. The distributions used are shown in table I.

As the two parameters (λ and γ) determining the probability of success for each prostaglandin were correlated, a nonparametric bootstrap was employed. In total, 10 000 replicates of the population in the 'change database' were generated by sampling with replacement, N to N. The empirical distribution of the 10 000 regression coefficients was used for the stochastic analysis. With respect to the probability of 'no treatment' after laser therapy or surgery, a normal distribution was applied to the exponential estimate using its standard error. Poisson distributions were used to fit count variables, for example, number of ophthalmologist consultations or complementary examinations conducted per month. Dirichlet distributions were employed to fit multinomial variables. Finally, the acquisition cost of supplementary drugs, or drugs other than prostaglandin analogues, were allocated as a uniform distribution with 10% variation around the mean.

Results

Observational Studies

Cost Database

The sociodemographic parameters of patients included in the 'cost database' are described in table II. In total, 64% of 337 patients underwent one or more treatment change. The mean cost of patients receiving a prostaglandin analogue was €238.51 a year ('first-line costs'). After treatments changed, the annual cost reached €246.87 ('second-line costs').

Change Database

The sociodemographic characteristics of patients included in the 'change database' and treated for ≥4 weeks[41] were quite similar to those of patients in the 'cost database', except for disease duration

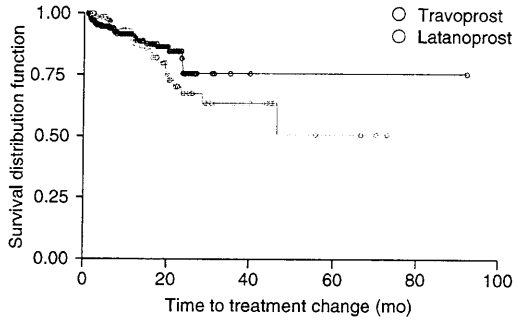

Fig. 2. Time to treatment change in subgroup of patients with intraocular pressure (IOP) ≤20 mmHg at onset of treatment. p = 0.3005 between treatment groups.

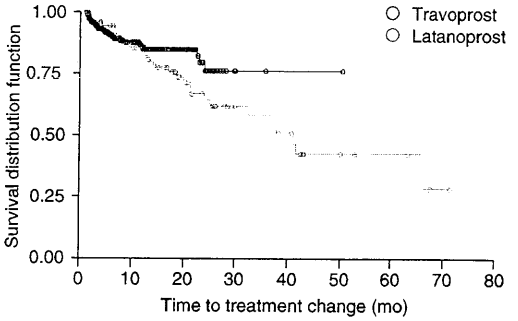

Fig. 3. Time to treatment change in subgroup of patients with intraocular pressure (IOP) 21–23 mmHg at onset of treatment. p = 0.1456 between treatment groups.

(which was half that of patients in the 'cost database'). Males represented nearly 46% of this population, which had a mean age of 65 years. Cataract was the most frequent eye co-morbidity and arterial hypertension affected 40% of patients.

The survival curves of patients in the three IOP strata at treatment onset, and for all patients, are shown in figure 2, figure 3, figure 4 and figure 5. Patients receiving travoprost at treatment initiation were more likely to change treatment than patients using latanoprost. In the long term, patients receiving travoprost were more likely to continue with their initial treatment. No statistically significant differences between the three IOP strata were found. However, the overall survival curve showed a longer duration of travoprost treatment before medication compared with latanoprost ($p < 0.05$).

Because the hypothesis of risk proportionality was not observed (treatment curves crossed), when comparing the two treatments, a single Cox model was applied to each treatment. For patients receiving travoprost, IOP values at treatment onset were significantly linked to time of treatment change ($p = 0.0439$). Patients with IOP values ≤20 mmHg at onset of travoprost treatment were less likely to change treatment than patients with values between 21 and 23, who in turn were less likely to change treatment than patients with values ≥24 mmHg. The IOP effect was not significant ($p = 0.3424$) for patients treated with latanoprost. However, a trend indicated that patients with IOP values ≤20 mmHg

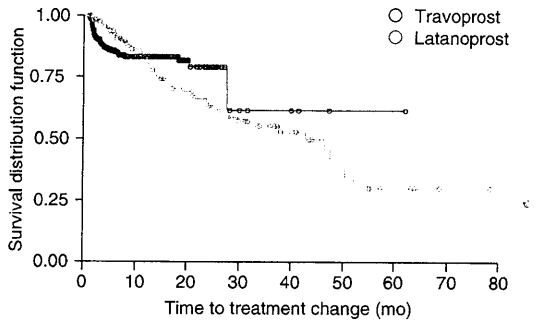

Fig. 4. Time to treatment change in subgroup of patients with intraocular pressure (IOP) ≥24 mmHg at onset of treatment. p = 0.3005 between treatment groups.

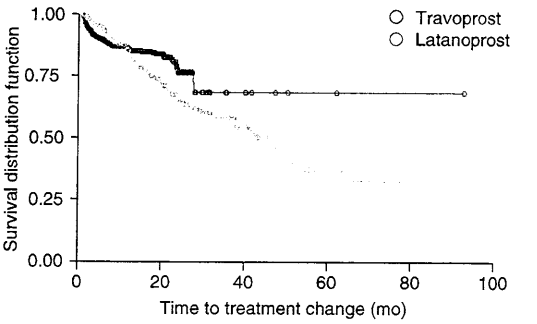

Fig. 5. Time to treatment change in all patients. p = 0.0509 between treatment groups.

Table II. Patient characteristics in the two observational studies[19,21,41]

Characteristic	Cost database	Change database
No. of patients	337	1681
Male (%)	44.5	45.9
Age (y) [mean]	64.6	64.9
Disease duration (mo) [mean]	90.7	47.4
Eye co-morbidities (%)		
myopia	7.7	6.3
cataract	29.4	34.2
ARMD	3.6	6.4
Risk factors for glaucoma (%)		
diabetes mellitus	11.0	14.8
dyslipidaemia	17.5	23.8
family history of glaucoma	33.5	24.5
arterial hypertension	35.9	39.7
arterial hypotension	3.3	1.4
smoker	12.2	13.9
vasospastic syndrome	7.1	4.4

ARMD = age-related macular degeneration.

were less likely to change treatment than patients with IOP values ≥24 mmHg (hazard ratio = 0.677; p = 0.1650). Consequently, all three IOP groups were retained in the analysis for patients receiving travoprost, but only two groups (IOP ≤20 mmHg and IOP ≥21 mmHg) in the analysis for patients using latanoprost.

Markov Model

Table III summarizes the Markov model results. The mean time to treatment change was 44.3 months for patients receiving travoprost and 37.8 months for patients taking latanoprost, which corresponded to a mean difference of 6.5 months at the end of the simulation. Treatment effects differed according to IOP values at treatment onset. The mean prostaglandin analogue treatment difference was 8.2 months for patients with IOP 21–23 mmHg, compared with 5.5 months for patients with IOP ≤20 mmHg. Accordingly, at the end of simulation, the proportion of patients remaining on prostaglandin analogue monotherapy was higher for travoprost (53%) than for latanoprost (28%). In addition, the proportion of patients undergoing laser treatment or surgery was less in the travoprost group than for those receiving latanoprost (1.2% vs 1.9%, respectively).

The greater effectiveness of travoprost was associated with moderately higher acquisition costs (the cost of one bottle of travoprost in France was ×1.14 that of one bottle of latanoprost). The 5-year treatment costs of a patient treated with travoprost amounted to €2411, compared with €2360 for latanoprost, a difference of only €51 that never exceeded €64 when pre-treatment IOP values were taken into account. Moreover, the model showed that use of travoprost as first-line treatment reduced the costs of subsequent treatment changes. Finally, the incremental cost-effectiveness ratio (ICER) of travoprost versus latanoprost was €7.93 per month with no treatment change, corresponding to an ICER of €95 per year. The ratio varied from €45 to €140, depending on IOP at treatment onset. Thus, travoprost was a cost-effective alternative to latanoprost, especially for patients with IOP values between 21 and 23 mmHg at treatment onset.

Table III. Results of the Markov model at 5 years

Variable	All		IOP ≤20 mmHg		IOP 21–23 mmHg		IOP ≥24 mmHg	
	travoprost	latanoprost	travoprost	latanoprost	travoprost	latanoprost	travoprost	latanoprost
Patients still taking prostaglandin analogue monotherapy after 60 mo (%)	53.04	27.85	55.64	32.30	53.94	26.08	50.40	26.08
Patients undergoing laser therapy or surgery (%)	1.24	1.91	1.24	1.78	1.26	1.96	1.22	1.96
First-line drug cost (€ 2005)	891.20	673.54	933.41	728.91	899.48	651.60	853.64	651.60
Second-line or greater drug cost (€ 2005)	434.76	591.72	365.21	498.15	421.81	628.80	496.08	628.80
Other medical costs (€ 2005)	1085.54	1094.33	1083.74	1091.53	1085.47	1095.44	1086.90	1095.44
Total mean cost (€ 2005)	2411.49	2359.60	2382.35	2318.59	2406.76	2375.85	2436.61	2375.85
Mean time to treatment change (mo)	44.28	37.74	46.40	40.93	44.70	36.47	42.39	36.47
Cost-effectiveness ratio								
Euros per year without treatment change	95.16		139.92		45.12		123.12	
Euros per avoided treatment changes	205.99		273.18		110.95		249.84	

IOP = intraocular pressure.

Sensitivity Analysis

A total of 3000 simulations were conducted. In terms of time to treatment change, each simulation showed travoprost to be more effective than latanoprost, irrespective of the IOP values at treatment onset. In some simulations travoprost was dominant, being both more effective and less costly than latanoprost. The latter simulations comprised all patients (36.7%), patients with IOP ≤20 mmHg (25.1%), patients with IOP between 21 and 23 mmHg (45.5%), and patients with IOP ≥24 mmHg (31.6%).

Acceptability curves are reported in figure 6. These show that whatever the level of willingness to pay and the IOP value at treatment onset, the probability that travoprost would be more cost effective than latanoprost was never <25%. With a payer willingness to pay set at €50, the probability that travoprost would be more cost effective was 94.8%, ranging from 90.6% in patients with a pre-treatment IOP ≥24 mmHg to 98.3% in patients with a pre-treatment IOP between 21 and 23 mmHg. In other words, if one were willing to pay €50 to avoid a treatment change during a given year, the probability of making the right decision when initiating a travoprost prescription would be 94.8%.

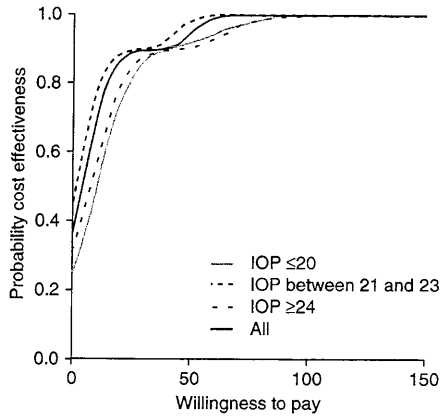

Fig. 6. Cost-effectiveness acceptability curves according to intraocular pressure (IOP) [mmHg] at treatment onset.

Discussion

Travoprost is an effective IOP-lowering medication, providing 6.5–9.0 mmHg of IOP reduction when used as monotherapy.[49] Furthermore, the efficacy of travoprost is at least as great as that of other drugs in the prostaglandin analogue class,[34,35] and in some studies[26,27] travoprost may have demonstrated greater efficacy than latanoprost. The duration of action of travoprost is longer than its 24-hour dosing interval, with significant IOP reductions from baseline being evident as long as 63 hours after the last dose.[26] These data suggest that travoprost provides greater IOP control at the end of each dose than does latanoprost.

The present Markov model was developed to extrapolate forward (over a 5-year period) the results of a cross-sectional observational study.[41] The study provided data on the probability of a prostaglandin analogue monotherapy change during the treatment of glaucoma. The model used this information to estimate the mean time to the first treatment change in patients taking two treatment strategies of interest: travoprost and latanoprost. The model allowed only one treatment switch, as information on subsequent treatment switches was unavailable. This might appear to be a weakness of our model, since is known that patients with glaucoma commonly experience several switches during a lifetime.[43] To circumvent this problem, we adapted the model's time horizon. A period of 5 years seemed appropriate because it conformed to the constraint of a single switch and was sufficiently long to reveal any differences between the two strategies. A longer time horizon, taking into account second-line, third-line and other treatment options, would allow full capture of the cumulated benefit[43] of starting a treatment with latanoprost or travoprost, especially if the first-line compound (travoprost or latanoprost) was associated with another drug as a second-line treatment. The consequences in terms of visual function could then be quantified as reported by Denis et al.[50] Indeed, when observational data on β-adrenoceptor antagonist/prostaglandin analogue fixed combinations become available, the time horizon of this model could encompass second-line treatment, meaning the incremental benefit in visual function might become measurable. Lastly, since both the costs and probability of developing new visual field defects are known to increase with treatment switches, our approach may be considered conservative because benefits of travoprost over latanoprost after third-line treatments were not taken into account.

The effectiveness data for our model were extrapolated from an observational study dedicated to comparing the IOP control of latanoprost and travoprost, the results of which have been published elsewhere.[41] Due attention was paid to control for selection bias and confounding factors, which is of considerable clinical relevance given that the two drugs have the same indications. Known potential confounders of treatment persistency (e.g. age, race, IOP before treatment, type of glaucoma) were identified. Baseline comparisons showed no major differences between the two treatment groups, and the small number of variables that differed between the groups were found not to be linked to clinical outcomes. In addition, two adjustment techniques (regression and propensity scores) revealed no major adjustment-related changes in treatment effect.

Many researchers claim that nonrandomized studies yield unreliable results and have advocated exclusive use of randomized clinical trials (RCTs).[51] The latter are considered the 'gold standard' since RCTs imply comparability of distribution of variables at the time of randomization.[52] Conversely, nonrandomized studies cannot guarantee that the populations being compared share the same distribution of prognostic factors, with the resultant possibility of biases. Despite the risk of producing biased treatment effect estimates, some investigators favour the use of nonrandomized stud-

ies on the basis that, when correctly conducted, they can produce results similar to those reported in RCTs.[53] Indeed, there are some arguments in favour of nonrandomized studies. Even if their results are prone to more scepticism than those arising from RCTs, there are some situations where randomization is unfeasible, unethical or simply too costly. In a recent review of this question, the UK National Health Service concluded that only nonrandomized studies should be conducted in these cases.[54] However, there are other possible advantages of nonrandomization. First, some sources of already available observational data can provide valuable information. Moreover, RCTs tend to be conducted under strict protocol-driven conditions, which differ from those operating in actual practice. Consequently, some authors assert that randomized studies do not provide much information that is relevant to decision makers.[55] Thus, while most clinical researchers view observational studies as exploratory tools that provide results that need to be confirmed by RCTs, nonrandomized studies can also be conducted after an RCT in order to assess the external validity of its findings. Our observational study is an example of such an application.

According to our findings, treatment persistency was greater with travoprost than with latanoprost. This result has not been consistently reported using patient claim analysis. Covert and Robin[56] found that use of adjunctive therapy was less common with travoprost than with latanoprost. Rait and Adena[57] reported a similar persistency between bimatoprost and latanoprost. Wilensky et al.[31] found small differences in treatment persistency between travoprost and latanoprost, while Reardon et al.[58] showed a longer treatment persistency with latanoprost than with other topical ocular hypotensive therapies. These discrepancies might be explained by misclassification of added versus switched medications.[59] Whatever it may be, and taking into account the previous limitation, large claims databases allow conclusions to be drawn regarding patient cooperation with glaucoma eye therapy.[60] Also, channelling bias might explain the results of Reardon et al.,[58] whose analysis was conducted close to the launch of travoprost and bimatoprost: the better IOP control with the two new prostaglandin analogues might have meant these agents were prescribed to patients with more severe symptoms. In our analysis, treatment persistency was estimated from a survey and therefore was less sensitive to the abovementioned biases and should be interpreted in the context of the results of the meta-analysis reported by Denis et al.[36]

The objective of the model was to determine whether or not use of travoprost instead of latanoprost as first-line prostaglandin analogue monotherapy would yield cost savings by delaying the need for an associated medication, laser therapy or surgery. Therefore, the main clinical outcome was the mean time to treatment change (treatment persistence). This outcome was selected for two principal reasons. First, the model assumed that switching was a reasonable proxy for ineffectiveness and that continued use of a treatment would depend on both an immediate reduction of IOP and sustained IOP control. Second, a previous study demonstrated that costs and disease progression increase with the number of treatment switches.[19,21] Thus, the longer the amount of time that a treatment remains efficacious the more likely it is that savings may be expected. The results of our model showed that a smaller proportion of patients required a change of medication, laser treatment or surgery after travoprost compared with latanoprost, and that this almost fully compensated for the higher travoprost acquisition cost.

Data concerning changes from prostaglandin analogue monotherapy to treatment combinations, or to other medications, could not be derived from our 'change database'. Hence, the UK GPRD database[42] was used for this purpose instead. The latter

comprises a large and representative patient sample with detailed medical information on primary-care patients in the UK. We used it as a source of data highlighting treatment patterns. While the database consisted of UK and not French patients, it nevertheless revealed real-life change behaviours between treatments available in both France and the UK.

The value accorded by society to an amount of additional health effect is a sociopolitical judgement that the analyst cannot judge. There is no theoretical justification for asserting that an efficient strategy with a higher cost per extra outcome unit is less desirable. The crucial value judgement must be left to the decision makers. The results of the current study must be analysed in the light of varying degrees of willingness to pay by the purchaser through construction of the acceptability curve for the treatment. The UK National Institute for Health and Clinical Excellence has eschewed the concept of an ICER 'threshold' above which a technology would invariably be deemed cost ineffective.[61]

IOP at baseline is known to be a predictive factor of reaching a prespecific IOP target. In one such study, for example, IOP reduction was higher for patients with IOP ≥21 mmHg prior to travoprost or latanoprost treatments.[62] Therefore, we also examined whether initial IOP values would influence the mean time to treatment change. We found from our 'change database' that, in fact, the probability of switching treatments did increase with IOP levels, especially with travoprost treatment, with patients with less severely raised IOP being more likely to continue with travoprost as their initial treatment. Moreover, the model revealed that travoprost is a cost-effective alternative to latanoprost, with a 98% probability of benefit to patients with IOP between 21 and 23 mmHg prior to treatment with an estimated payer willingness to pay of €50 per avoided treatment change. Lastly, the ICERs reported in this paper (€45 to €140) are within the same range as other glaucoma expenses: for example, Denis et al.[19] estimated the yearly cost of glaucoma treatment to be between €111.45 and €369.47, depending on the severity of disease.

Conclusion

The model used in this study provided an effective tool for depicting the effects of treatment on a chronic disease, in this case glaucoma. It showed that travoprost has a profile of more prolonged effectiveness and fewer early treatment changes than latanoprost. Consequently, fewer patients needed modification of their medication, laser treatment or surgery, which virtually compensated for the higher travoprost acquisition cost and amounted to an incremental cost of only €51 over 5 years. Travoprost can be considered a very cost-effective treatment for glaucoma, especially in patients with pretreatment IOPs between 21 and 23 mmHg. Given a payer's willingness to pay as little as €50 per year per patient to avoid a treatment change, the probability of travoprost being cost effective was 98%. This is both a very small sum to spend to delay treatment changes and a very important benefit in that medical costs have been shown to increase with the number of treatment switches.

Acknowledgements

This study was supported by an unrestricted grant from Alcon France SA, Rueil-Malmaison, France and was contracted to Réseau d'Evaluation en Economie de la Santé, Paris, France. Alcon France SA employed Dr Gilles Berdeaux who held Alcon stock options. Prof. Philippe Denis has participated in clinical trials sponsored by Alcon Research Ltd. The other authors have no conflicts of interest that are directly relevant to the content of this study. We would like to thank Robert Pigache MD, Fellow of the Faculty of Pharmaceutical Medicine (UK), for his review of the use of English language in this article.

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Correspondence: Dr *Gilles Berdeaux,* Alcon France, Rue Henri Sainte-Claire Deville 4, F-92563 Rueil-Malmaison cedex, France.
E-mail: gilles.berdeaux@alconlabs.com