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Treatment carryover impacts on effectiveness of intraocular pressure lowering agents, estimated by a discrete event simulation model

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PURPOSE. *To compare the effectiveness of two treatment sequences, latanoprost–latanoprost timolol fixed combination (L-LT) versus travoprost–travoprost timolol fixed combination (T-TT), in the treatment of open-angle glaucoma (OAG) or ocular hypertension (OHT).*
METHODS. *A discrete event simulation (DES) model was constructed. Patients with either OAG or OHT were treated first-line with a prostaglandin, either latanoprost or travoprost. In case of treatment failure, patients were switched to the specific prostaglandin-timolol sequence LT or TT. Failure was defined as intraocular pressure higher than or equal to 18 mmHg at two visits. Time to failure was estimated from two randomized clinical trials. Log-rank tests were computed. Linear functions after log-log transformation were used to model time to failure. The time horizon of the model was 60 months. Outcomes included treatment failure and disease progression. Sensitivity analyses were performed.*
RESULTS. *Latanoprost treatment resulted in more treatment failures than travoprost ($p<0.01$), and LT more than TT ($p<0.01$). At 60 months, the probability of starting a third treatment line was 39.2% with L-LT versus 29.9% with T-TT. On average, L-LT patients developed 0.55 new visual field defects versus 0.48 for T-TT patients. The probability of no disease progression at 60 months was 61.4% with L-LT and 65.5% with T-TT.*
CONCLUSIONS. *Based on randomized clinical trial results and using a DES model, the T-TT sequence was more effective at avoiding starting a third line treatment than the L-LT sequence. T-TT treated patients developed less glaucoma progression. (Eur J Ophthalmol 2008; 18: 44-51)*

KEY WORDS. *Glaucoma, Ocular hypertension, Travoprost, Latanoprost, Timolol*

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INTRODUCTION

Intraocular pressure (IOP) reduction control is the critical strategy to prevent vision damage in patients with open angle glaucoma (OAG) or ocular hypertension (OHT) (1-3). Treatment aimed at decreasing IOP continues throughout a patient's life (4, 5). Widely diverse treatments, e.g., prostaglandin analogues, adrenergic agonists, muscarinics, beta blockers, carbonic anhydrase inhibitors (CAI), are now available for glaucoma and ocular hypertension. Prostaglandin F2α analogues are usually preferred as first-line therapy since they offer good efficacy with few side effects and a good systemic safety profile. However, for most patients, a single agent is no longer sufficient after 2 years of treatment to control IOP and a second agent is often added (6-8).
Moreover, as a key element in IOP control is treatment compliance (9-11), treatments such as dorzolamide–timo-

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lol, brimonidine–timolol, travoprost–timolol, or latanoprost–timolol are combined in single bottles to reduce the number of instillations and theoretically improve compliance.

The clinical efficacy of these agents, both as single agents and in fixed combinations, was demonstrated by IOP reductions obtained in randomized clinical trials designed to support market access authorizations. In Europe, results are reported in European Public Assessment Reports issued by the European Medicines Agency (EMEA) (EMEA European Medicines Agency. Available at: http://www.emea.eu.int/index/indexh1.htm). However, a national public health decision based solely on mean population IOP values is not a straightforward process. Moreover, the use of surrogate endpoints is questioned by most health economics guidelines (12). An acknowledged public health indicator uses responder rates to estimate the number needed to treat (13).

In addition, comparisons of second-line combination treatments should consider possible differences of efficacy between the first-line treatments with respect to cumulative effects across successive treatments, especially as the choice of a second-line combination is often influenced by the first-line prescription. As it would be difficult to conduct a well-controlled randomized clinical trial, comparing two treatment sequences in a large population, within a timeframe suited to a public health decision, it is possible that models would help decision makers.

Health economics evaluations may contribute to therapy decisions as preventative activities carry a cost (14). In the case of glaucoma, a common chronic disease, the UK economic burden in 1994 was ≤62 million sterling as direct medical costs (15). Knox et al (16) found that the volume and cost of glaucoma drugs in Ireland increased dramatically from 1996 to 2003 as a result of changing demographics and new approaches to patient management, with more use of prostaglandin analogues and drug combinations.

Several surveys have documented the costs of glaucoma in different countries (17-26). A consistent finding was the higher annual average cost of a patient with OHT compared to a glaucoma patient. Also, associations were found between disease severity, expressed clinically or defined by treatment line, and increased medical costs.

Pivotal clinical trials filed at the EMEA and a meta-analysis conducted by Denis et al (27) show that travoprost provided better evening IOP control than latanoprost (28) and that fixed travoprost–timolol combinations produced better morning IOP control than fixed latanoprost–timolol combinations (29). The aims of the study, presented below, were two-fold: 1) to establish the probability of switching treatments on account of IOP measurements in clinical trials; and 2) to compare the effectiveness of two treatment sequences, i.e., travoprost followed by travoprost–timolol (T-TT) versus latanoprost followed by latanoprost–timolol (L-LT).

MATERIALS AND METHODS

Discrete event simulation model

Decision trees and Markov models are the most common methods used in health economics evaluations of chronic diseases. In this article, we use an alternative and more natural way to model clinical reality, i.e., discrete event simulation (DES) (30). With this type of model, system operations (in the present case glaucoma treatment, clinical outcome) are represented as a chronological sequence of events. Each event occurs at a specified time and denotes a change in the system (e.g., a switch from first-line to second-line treatment at time t). The advantage of such models is a more natural representation of clinical progression with very few restrictions, e.g., no need for mutually exclusive branches or states, and no fixed cycles as in Markov models.

The 5-year time horizon of the present model was based on failure rates reported for clinical trials. Time was sequenced as a regular cycle of 1 month.

Two types of clinical events were included in the model, namely 1) treatment failure (first-line and second-line) and 2) disease progression (up to four new visual field defects [VFDs] or changes of the optic nerve head) due to poor IOP control. The model is described in Figure 1 where patients with OHT received either travoprost or latanoprost as first-line treatments. Following first-line treatment failure patients received a second-line treatment. After first-line travoprost they received a fixed dose combination of travoprost–timolol, i.e. sequence T-TT. After first-line latanoprost they received latanoprost–timolol, i.e., sequence L-LT.

Two types of clinical events were excluded from the model because of low probabilities within 5 years, i.e., third-line treatment failure and >4 VFDs. Concomitantly, failure of IOP control led to VFDs that accumulated over time.

The DES model was developed with Excel software (Microsoft Corporation). The sample size was fixed at 5,000

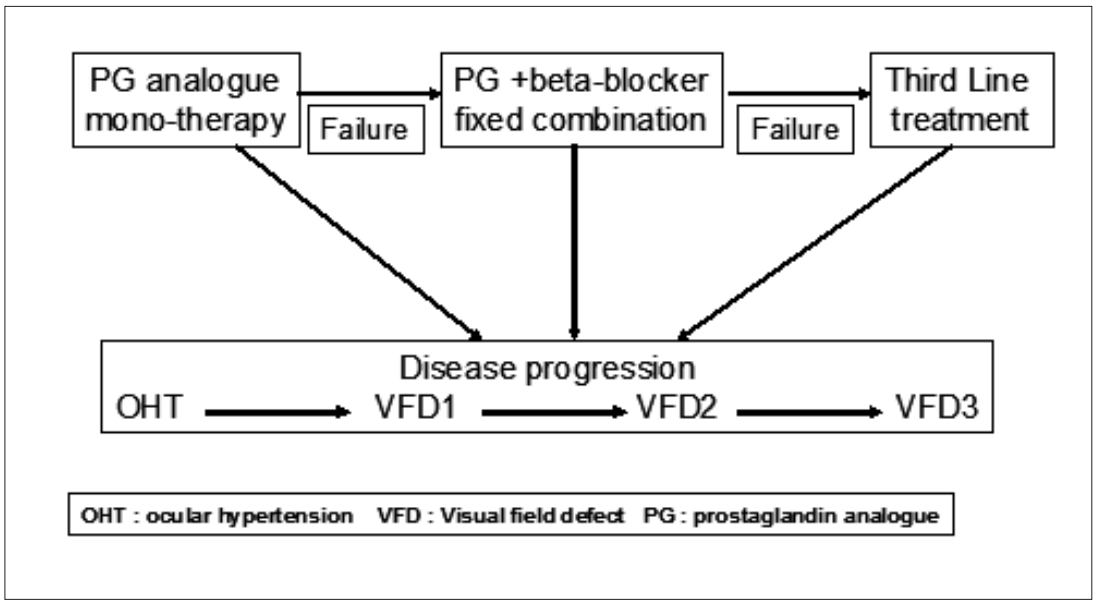

Fig. 1 - *Structure of the discrete event simulation model.*

units after several replications to guarantee, empirically, that the most sensitive parameter did not exceed 1.5/1,000.

Each unit represents a virtual patient which is randomly assigned to one of the two treatment sequences, T-TT or L-LT, using a random number generator (RNG) provided in any computer. This virtual patient experiences different type of events (treatment failure and disease progression), using the RNG, and according to risk functions that were estimated either from randomized clinical trials or from surveys. Some of the risk functions estimates are specific to the prescribed treatment. In this model, patients could experience events every month for 5 years. When the model ends, the final patient status is recorded. Once replicated for 5,000 patients, statistics are performed.

Clinical outcomes

Time to failure was extrapolated from the clinical trial data of Netland et al (28) and Topouzis et al (29), the two trials that were filed to EMEA.

Netland et al evaluated the safety and IOP efficacy of travoprost 0.004% versus latanoprost 0.005%, among other treatments, in patients with open-angle glaucoma or ocular hypertension. The 12-month phase III trial was randomized, double-masked, and included a parallel active-control group. Eligible patients underwent a washout of previous treatment over a period that depended on the treatment half-life, and were then required to provide IOP measurements between 24 and 36 mmHg, in the same eyes, at 08:00, on two visits at least 7 days apart. Subsequently, patients administered one drop of travoprost or latanoprost to each eye at 20:00 daily. Measurements of IOP were performed at baseline and on weeks 2, 6, 12, 18, 24, 36, and 48. At each study visit IOP was recorded at 08:00 and 10:00. Also, on weeks 2, 12, 24, and 48, IOP was measured at 16:00. A total of 396 patients received either travoprost (n=200) or latanoprost (n=196). Their demography constituted patients older than 65 years (55.5%), sex ratio close to 1, Afro-American origin (22.5%), isolated ocular hypertension (31.4%), with patient groups comparable on the confounding factors of OAG/OHT.

Topouzis et al reported a 12-month phase III multicenter, randomized, double-masked trial of travoprost–timolol versus latanoprost–timolol, both as fixed combinations. Eligible patients were defined as cases of OAG or OHT with IOP values ≥24 mmHg at 09:00 and ≥21 mmHg at 11:00 and 16:00. Treatment combinations were instilled in the morning. IOP was recorded at study entry, at 2 and 6 weeks, and at 3, 6, 9, and 12 months. Measurements of IOP at baseline, and on visits at month 6 and month 12, were performed at 09:00, 11:00, and 16:00. On other occasions data were collected at 09:00 only. A total of 399 patients received either travoprost–timolol (n=201) or latanoprost–timolol (n=198). Demographics data were the following: mean age 64.8 years, male 41%, OAG 70.2%, OHT 19.3%, pseudo-exfoliation glaucoma 8.1%, and pigmentary glaucoma 2.4%. Patient groups were comparable on the confounding factors of OAG/OHT.

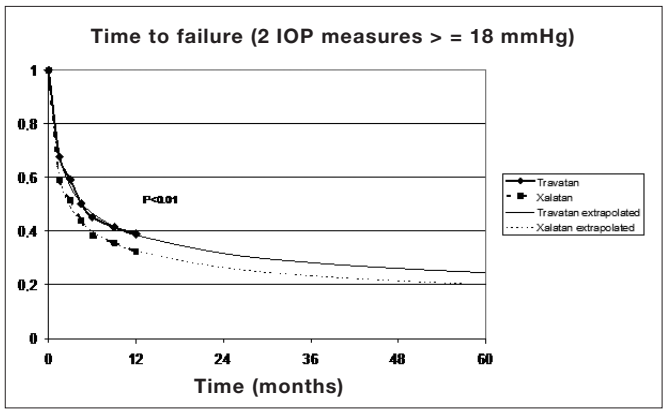

Fig. 2 - *Survival curves comparing time to failure following Travatan® and Xalatan® treatments. Likelihood ratio chi-square. Extrapolation to 5 years using a log-log transformation. Estimated from Netland et al (28).*

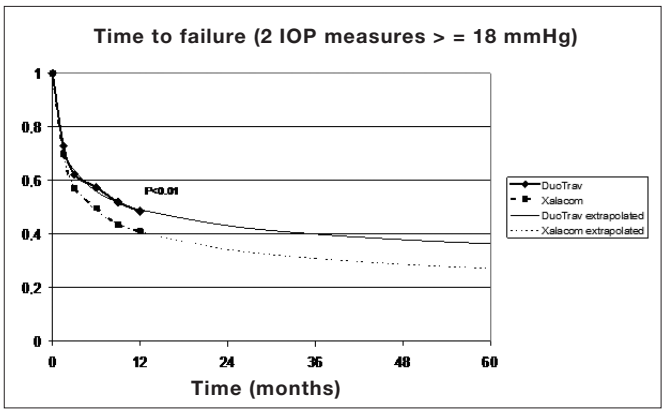

Fig. 3 - *Survival curves comparing time to failure following DuoTrav® and Xalacom® treatments. Likelihood ratio chi-square. Extrapolation to 5 years using a log-log transformation. Estimated from Topouzis et al (29).*

In both clinical trials, we hypothesized that two IOP measurements ≥18 mmHg (2), at two visits during the 1-year follow-up periods, would result in a treatment change, an acceptable proxy of treatment failure. The probability of a new VFD is known to increase with treatment changes. The risk function was published by Denis et al (31). Thus, stochastically, the transition probabilities of a new VFD depended on the treatment line. The Denis et al observational survey defined a new VFD as any optic nerve head change, or a worsening of perimetry.

Finally, the DES model permitted estimations and comparisons of two treatment sequences with respect to the following clinical outcomes: 1) the probability of starting a third-line treatment and 2) the distribution and mean frequencies of new VFDs.

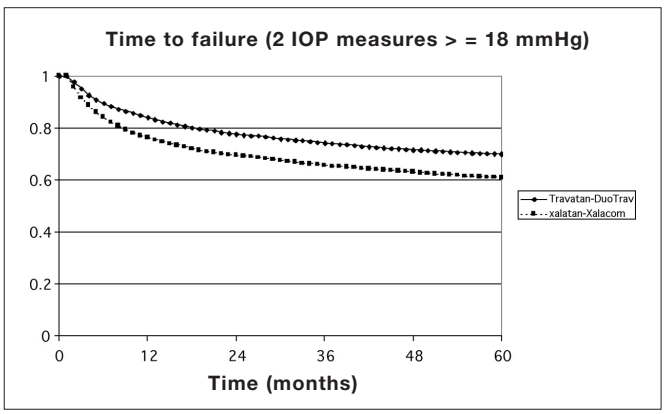

Fig. 4 - *Survival curves comparing time to failure following Travatan® – DuoTrav® and Xalatan® – Xalacom® treatment sequences, estimated from the discrete event simulation model.*

Statistical analysis

The statistical analysis was performed with SAS Software (SAS Institute, NC), release 9.1 for Windows XP.

Times to treatment failure after travoprost and latanoprost were taken from Netland et al (28), and after TT and LT were taken from Topouzis et al (29). Survival curves were estimated and compared by the likelihood ratio chi-square. All statistical tests were interpreted two-sided with alpha fixed at 5%. No alpha adjustment was performed for non-confirmatory analyses.

Both clinical trials collected IOP values during 1 year. Extrapolations to 5 years were performed using general forms of the following function: $f(t)=a.e^{b.t}$, where f = probability of failure and t = time, with the a and b parameters estimated from the clinical data, after log-log transformation, using a least square method. Graphics of the 5-year projections are provided to help readers judge the pertinence of the data extrapolation.

Relative risk (RR) was estimated as well as the number needed to treat (NNT).

Finally, sensitivity analyses were performed by varying efficacy by ±20% to allow for uncertainty.

RESULTS

Time to failure after first-line and second-line treatments are described by the survival curves in Figures 2 and 3, respectively. The probability of experiencing first-line

treatment failure was lower with travoprost than latanoprost (p<0.01). Extrapolations to 5 years suggested an almost constant difference between the two curves throughout the entire period. Similar results were observed between LT and TT (Fig. 3). Patients treated with travoprost–timolol reported fewer failures and longer times to failure than patients treated with latanoprost–timolol (p<0.01).

Figure 4 shows time to failure for the two treatment sequences T-TT and L-LT as estimated by the DES model. Again, more switches occurred with the L-LT sequence. At 5 years, 39.2% of L-LT patients began third-line treatment compared to 29.9% of T-TT patients (Tab. I). The relative risk of experiencing failure with L-LT, as compared to T-TT, was almost constant over time, varying from 1.299 to 1.481. Thus, at 60 months, travoprost used as the first-line prostaglandin, followed by TT as the second-line treatment, would avoid one third-line prescription in every 11 incident cases. At 5 years, 65.5% of T-TT patients showed no disease progression compared to 61.4% of L-LT patients. Thus, initiation of treatment in an OHT patient with travoprost, followed by timolol–travoprost, would avoid one incidence of glaucoma in every 24 incident cases.

Table I also shows that, on average, patients treated with the T-TT sequence developed fewer new VFDs (–0.07) than patients treated with the L-LT sequence. The probability of four VFDs (rare according to our model) was 1.6 times more frequent during the L-LT sequence.

Table II shows the results of various sensitivity analyses performed on discount rates and efficacy.

When efficacy was varied by 20% the results of the model changed slightly (mean number of new VFDs, percentages of patients switching treatment lines at 60 months) with both treatment sequences, but the trends continued to favor the T-TT sequence. With the T-TT sequence, a 20% increase of efficacy was associated with an average of 0.44 new VFDs, as compared to 0.48 new VFDs at baseline. With the L-LT sequence, a 20% increase of efficacy was accompanied by an average of 0.50 new VFDs, as compared to 0.55 at baseline.

TABLE I - CLINICAL OUTCOMES OF THE DISCRETE EVENT SIMULATION MODEL

		Travatan®-DuoTrav®	Xalatan®-Xalacom®	Difference	RR	NNT
Switch (%)	12 month	16.0	23.7	7.7	1.481	13
	24 month	22.3	30.5	8.2	1.368	12
	36 month	25.8	34.8	9.0	1.349	11
	48 month	28.4	36.9	8.5	1.299	12
	60 month	29.9	39.2	9.3	1.311	11
New VFD (%)	0	65.5	61.4	-4.1	1.067	24
	1	24.5	26.3	1.8	0.932	56
	2	7.1	8.8	1.7	0.807	59
	3	2.4	2.6	0.2	0.923	500
	4	0.5	0.8	0.3	0.625	333
	Mean	0.48	0.55	0.07	—	—

RR = Relative risk; NNT = Number needed to treat; VFD = Visual field defect

TABLE II - SENSITIVITY ANALYSIS : EFFICACY INCREASING WITH DISEASE SEVERITY

		Travatan®-DuoTrav®	Xalatan®-Xalacom®	Difference
Baseline	Mean new VFD	0.48	0.55	–0.07
	Switch at 60 months	29.9	39.2	–9.3
Efficacy +20%	Mean new VFD	0.44	0.50	–0.06
	Switch at 60 months	26.2	35.6	–9.4
Efficacy –20%	Mean new VFD	0.52	0.58	–0.06
	Switch at 60 months	35.7	41.3	–5.6

VFD = Visual field defect

DISCUSSION

The Markov model used by Nordmann et al (32) to estimate the lifelong outcome of glaucoma medical management had already suggested that the clinical consequences of glaucoma/OHT prescriptions extend far beyond the current treatment line. Hence, the prescription of a more effective drug as first-line treatment would be expected to delay both the switch to a second-line treatment and the associated risk of disease progression. Thus the choice of a first-line treatment can impact on the choice of a second-line treatment. But, after treatment failure with a first-line prostaglandin, should a patient be switched to a beta-blocker, when the latter is known to be less efficacious than the former (33), or should the original prostaglandin analogue be supplemented by a beta-blocker? The present DES model was constructed to compare the clinical consequences of two alternative treatment sequences: T-TT and L-LT. We found that the sequence T-TT was more efficacious than L-LT. Sensitivity analyses were performed and confirmed the robustness of our findings.

The use of a model to compare the effectiveness of treatment sequences within a time horizon of 5 years is meaningful. The alternative choice of a randomized clinical trial is not economically viable as its duration would be about 8 years, imposing an unacceptable delay before a decision, and incurring both high costs and the risk of eclipse by a new treatment that would invalidate the procedure. The DES model was appropriate because we were obliged to link treatment switches and disease progression together.

We extrapolated treatment failure from two pivotal, phase III, well-controlled, double-masked, randomized clinical trials in order to ensure high internal validity and research quality and thereby permit unbiased comparisons. We chose an IOP threshold of 18 mmHg because it was used by the AGIS study in which the level of risk for disease progression referred to advanced glaucoma patients. In addition our model assumed that two IOP measurements >18 mmHg within 1 year would incur a treatment switch. The decision was partly based on the number of visits imposed by the clinical trials, but we also believe that such patients are more prone to switching.

Patients participating in the Netland et al trial (28) were not newly diagnosed OHT/glaucoma patients and patients participating in the Topouzis et al trial (29) did not experience a first-line prostaglandin analogue failure. We therefore postulated the two following strong hypotheses: 1) the difference in efficacy observed by Netland et al could be extrapolated for what should be observed with first-line treatments and 2) the difference in efficacy estimated by Topouzis et al was an acceptable proxy for what should be observed following the failure of a first-line prostaglandin analogue. Most patients in the two trials were not incident cases, but underwent treatment washouts before enrollment. Hence in both trials disease progress was more difficult to control than in newly diagnosed patients.

National observational data that would allow an estimation of long-term latanoprost effects is not currently available in most of the Western developed countries; hence we could not adjust for differences between daily practice and clinical trials. However, the relative risks used here to compare treatments pairwise are available for country adaptation and further models.

Finally, the present DES model clearly reflects the Markov findings of Nordmann et al (32). Thus, effectiveness comparisons should not be limited to a specific treatment line, but should encompass the next treatment line. As treatment switches are associated with increasing costs, long-term effectiveness should be taken into account by drug budget holders when estimating the potential value of new glaucoma drugs.

This model has several limitations. Among them, first, the use of data from randomized clinical trials while the population being treated with a PG as a first-line treatment in daily practice might be very different: population-based switch rates should be collected from prescription databases to confirm our findings. Second, the risk function we used to predict disease progression copes with cup disk ratio and perimetry, but does not include baseline IOP and central corneal thickness. Third, a model is only an idealized simplified view of reality and it cannot reproduce the diversity of a glaucoma patient population: therefore our findings should be interpreted in the context of population decision making; i.e., not at patient level. Finally, a rational decision should encompass the economics dimension, which is not reported in this article.

To conclude, on the basis of our discrete event simulation model applied to two clinical trials, treatment failure was higher with L-LT sequence and time to failure was longer with the T-TT sequence. Consequently, disease progression was better controlled by the latter sequence and might result in cost savings.

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