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MODELING COST OF TREATMENT WITH NEW TOPICAL TREATMENTS FOR GLAUCOMA

Results from France and the United Kingdom

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Abstract

Several new topical agents have been introduced recently and it can be expected that the treatment of glaucoma will change, depending on how effectively these agents control intraocular pressure (IOP). IOP is considered the major risk factor in the development of glaucomatous damage. In order to estimate the impact of these new agents on the cost of treating glaucoma, a simulation model was created to estimate the cost of treating patients with a recent diagnosis of primary open-angle glaucoma or ocular hypertension in different countries. The Markov model is based on retrospective chart reviews in different countries and calculates only cost, not outcome. Results are presented for France and the United Kingdom, where current treatment appeared to be comparable. Average one-year costs per patient with current treatment were FF2,389 (US $389) and £380 (US $627), respectively. Costs with the new treatments were lower than with current therapy.

Keywords: Modeling, Cost, Glaucoma

Primary open-angle glaucoma (POAG) is defined as damage to the optic nerve head and/or visual field defect, which can lead to blindness. It affects an estimated 2% of the population over 45 and causes considerable cost to society (23). The underlying mechanism for the disease has not yet been fully elucidated (21). Elevated intraocular pressure (IOP) is considered the major risk factor for the development of glaucomatous damage (12), but it has not yet been shown conclusively to be directly related to the progression of the disease (16;17). Nevertheless, available treatments focus on lowering IOP as much as possible, although no definite desirable level for IOP has been established.

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Interventions for lowering IOP are either surgical or medical. Since the introduction of topical beta-blockers as an effective treatment to reduce IOP, primary intervention is generally medical rather than surgical, despite an ongoing debate on the justification of primary surgery (13). An early cost-effectiveness analysis for beta-blockers illustrated the potential savings of avoiding or delaying trabeculectomy (TRAB) with medical treatment (24). When argon laser trabeculoplasty (ALT) was introduced as an alternative to TRAB, there was a potential to further reduce surgical costs. However, cost reductions in glaucoma treatment during the past decade were mostly the result of increased surgical and hospital efficiency, with shorter length of stay per procedure or switching from inpatient to outpatient interventions (9).

Since the mid-1980s, innovation in glaucoma treatment has been limited, particularly as far as new topical agents are concerned. Monotherapy with topical treatments appears not to achieve entirely satisfactory decreases in IOP over time, leading to extensive combination therapy with two or more agents and ultimately to surgery. An observational study of the effectiveness of different topical treatments by the Canadian Collaborative Glaucoma Group (7) indicates a high frequency of treatment changes during the first year of therapy and an increased cost of treatment for patients with several changes. A recent study in nine countries of the resource utilization during the first 2 years of glaucoma therapy showed that a large proportion of patients required additional treatment already during the first year of monotherapy with beta-blockers, leading to frequent therapy changes, surgical interventions, and therefore increased cost (10;14;15;19). However, treatment patterns in the different countries were surprisingly similar, with the only major difference being the frequency of surgery and its use as either second- or third-line therapy.

During the past year, several new topical agents have been introduced for glaucoma treatment, and it can be expected that therapy approaches will be modified depending on their effectiveness. These agents have the potential to replace or supplement current topical treatments, many of which are inexpensive or generic. It is therefore important to estimate the impact of these potential changes in treatment approaches on costs.

We propose a simulation model that allows to calculate the direct cost of different new glaucoma treatments for the first year of therapy, compared with current therapy (prior to the introduction of these new agents), and to extrapolate to the second year. The model was created for a number of countries; the French and United Kingdom versions are described here.

MATERIALS AND METHODS

The Structure of the Model

The Markov model has been built in Decision Analysis by TreeAge (DATA) version 3.0 and allows for the comparison of second-line treatments after beta-blockers have failed to control IOP. The different versions of the model are based on the country-specific data of a large international observational study of patients newly diagnosed with POAG or OH between 1991 and 1994 (10;14;15;19) and treated with beta-blocker monotherapy. Detailed utilization of medical resources and services was collected retrospectively over 2 years after the start of treatment in a representative sample of sites in each country. The study included 225 patients in France and 208 in the United Kingdom who had no contraindications to beta-blockers and were initially treated with beta-blocker monotherapy.

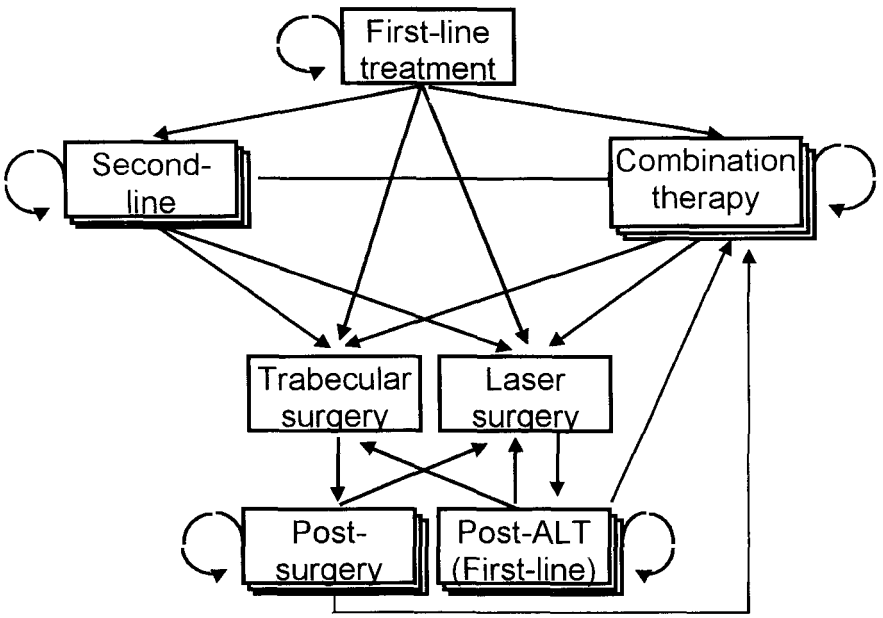

Figure 1. The structure of the Markov model.

The basic model calculates treatment costs for the first year of therapy, and an extension covering the full 2 years of the observational studies is presented as a sensitivity analysis. Clinical data on the new topical agents are still limited and most trials do not exceed 6 months. Thus, extrapolating these results beyond 1 or 2 years appears questionable. The utilization of health care services in the observational studies was higher in the first year than in the second year, representing between 60 to 70% of the 2-year costs. One year was therefore considered a relevant time frame for a first estimation of the costs of treatment with new drugs, since more effective drugs are likely to have an effect on treatment costs during the first year and maintain this effect over subsequent years.

Current therapy is reproduced in one branch of the model, with all patients starting on beta-blocker monotherapy and switching to alternative medical treatments or surgical interventions when IOP control is not satisfactory, as observed in the chart review. The majority of charts indicated unsatisfactory IOP control as the reason for switching therapy. Intervention with the new drugs is simulated in alternative branches of the model where patients receive the new topical treatments as second-line therapy when beta-blockers fail. Second-line drugs included are dorzolamide (a topical carbonic anhydrase inhibitor), latanoprost (a prostaglandin analogue), brimonidine (an alpha$_2$-adrenergic receptor agonist), and the fixed combination of timolol and pilocarpin hydrochloride. Assumptions in the alternative branches are identical, but the effectiveness rate of the individual products to control IOP and the proportion of patients given second-line treatments as monotherapy or in combination with beta-blockers vary.

Markov states are defined according to the treatment patients receive rather than according to clinical parameters. The possible treatment states are first-line monotherapy with a beta-blocker, second-line monotherapy with the new topical drugs, combination treatment of a beta-blocker with either of the new drugs or

pilocarpin, ALT, TRAB, and monotherapy with a first-line beta-blocker following surgery. The structure of the state transitions in each branch is shown in Figure 1.

Transitions from one state to another occur when a patient's IOP is no longer controlled. In the model, IOP is considered controlled when it is below 22 mm Hg or when the reduction from baseline is 15% or more. This criterion has been used recently in clinical trials for glaucoma medications (22). All patients start on first-line monotherapy with a beta-blocker and, as the transition arrows in Figure 1 show, they can then be switched to second-line monotherapy treatment, second-line combination treatment, ALT, or TRAB. Patients on second-line monotherapy can be switched to second-line combination therapy, ALT, or TRAB, while from second-line combination therapy, patients go to ALT or TRAB. After nonmedical therapy, if IOP is not controlled, patients go back to treatment with first-line monotherapy with a beta-blocker. If IOP is not controlled with beta-blocker monotherapy, postsurgical patients may return to second-line combination therapy or they may undergo further surgical interventions.

The model runs in 1-month cycles. This is considered relevant since Markov states are defined by treatment. Longer cycles would inaccurately reflect clinical management, particularly in the case of surgical interventions, while shorter cycles would not accurately reflect clinical observation in glaucoma. However, transitions between treatments can take place only during a contact between physician and patient. Based on the observational data, routine medical visits occur on average once every 3 months during the first year of treatment. In addition, control visits occur 1 month after any change in treatment. Thus, the Markov cycles and the treatment cycles have a different duration, making it necessary to keep track of the number of cycles patients spend in each state. This is modeled by using tunnel states. All states are defined as tunnel states, where a patient moves unidirectionally through a sequence of substates. Patients enter only at the beginning of the tunnel but can leave the tunnel at any point. As long as the patient stays in the tunnel, a transition is made each month to the next substate and transition probabilities to other treatments are accumulated. Patients will leave the tunnel if a treatment modification occurs at one of the medical visits after 1, 4, 7, or 10 months. This allows for the distinction among patients who have been on the therapy for different numbers of months and is necessary since both costs and transition probabilities depend on how long the patient has received treatment.

Effectiveness of Medical Treatments

The effectiveness of medical treatments is expressed as the proportion of patients whose IOP is controlled with a treatment during the 3-month periods between medical visits. For first-line monotherapy with beta-blockers, this proportion is calculated directly from the time to the first treatment switch in the observational cohorts and used in all branches of the model. Figure 2 shows the observed time to failure on first-line therapy for both countries.

When first-line therapy fails and surgery is not considered necessary, a second topical agent will be added to the beta-blocker or patients will be switched to monotherapy with a second-line drug. The effectiveness of the newer second-line agents was calculated from published clinical studies in populations similar to the observational cohorts and expressed as the probability to remain on the same treatment over each 3-month period.

Drug utilization surveys in countries where these new second-line products are being used indicate that dorzolamide and brimonidine are almost always used

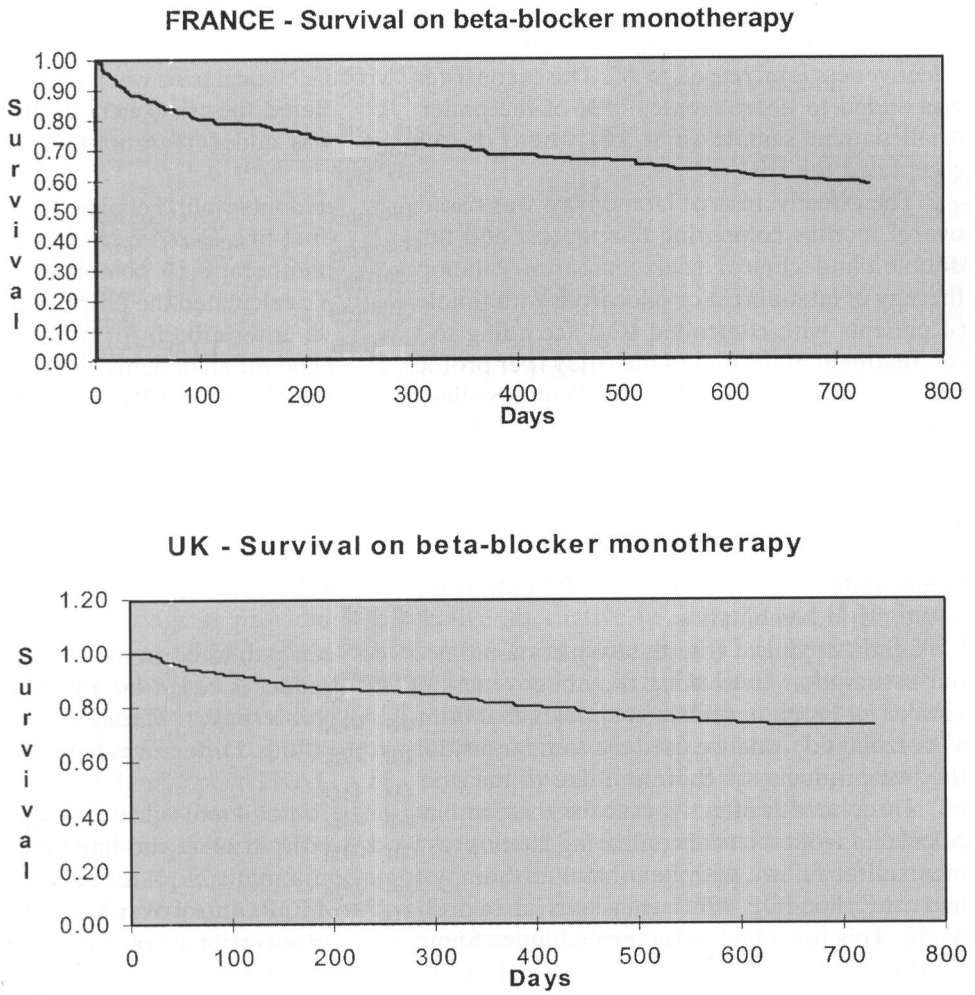

Figure 2. Time to first therapy change after treatment with first-line beta-blocker monotherapy in France and the United Kingdom over 2 years.

in combination, generally with beta-blockers, while latanoprost is used both as monotherapy and in combination (18). We therefore assumed in the basic models that all products except latanoprost would be used 100% in combination, while latanoprost would be used as monotherapy in half of the cases.

The effectiveness of dorzolamide was calculated from a published double-blind, randomized 1-year clinical trial (22). In this study, patients were initially treated with monotherapy with either timolol, dorzolamide, or betaxolol and were switched to combination therapy when IOP increased above 22 mm Hg or the difference from baseline was less than 15%. Thus, the proportion of patients with controlled IOP over 12 months on first-line monotherapy with dorzolamide could be calculated. Fifty-eight percent of all patients entered completed the study on dorzolamide monotherapy, representing a probability of IOP control during 3 months of .87. However, in the model dorzolamide is used when beta-blockers fail, and it is likely that these patients would be more difficult to treat than the patients in the clinical study. In addition, adherence to prescribed treatment outside a clinical trial is

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expected to be lower. Thus, we reduced the 3-month probability that IOP would remain controlled to .80. When dorzolamide is used in combination, the 3-month effectiveness is increased to .85. This is consistent with the clinical trial: when timolol was added to dorzolamide, 74% of the patients completed the trial, while in the small patient sample (n = 20) where dorzolamide was added to timolol, 87% completed the trial.

The effectiveness of latanoprost was based on three double-blind clinical trials over 6 months comparing latanoprost and timolol in first-line use (1;3;25), and a double-blind clinical trial comparing latanoprost monotherapy to combination therapy of latanoprost or pilocarpin with timolol (20). We calculated the proportion of patients with controlled IOP according to the above criteria both for patients on treatment at the end of the study (per protocol [PP]) and for all patients enrolled in the trial (intent to treat [ITT]). With first-line treatment, 98% of the PP population and 85% of the ITT population fulfilled the criteria at the end of 6 months. In the clinical study where latanoprost was used as second-line treatment, monotherapy controlled 98% of the PP population and 94% of the ITT population over 6 months. This yields a 3-month probability of .97. However, as for dorzolamide and to account for settings outside the clinical trial, we reduced the effectiveness rates used in the model and set the 3-month probabilities to remain controlled to .90 for monotherapy and to.95 in combination.

Limited clinical trial data on brimonidine have been published in detail, and our assumption concerning the effectiveness of this product is based on a review article (5). From these data, it appears that brimonidine has a similar efficacy profile as dorzolamide, and we used the same transition probabilities. Differences between the two products are therefore due to the price only.

Three-month effectiveness for the combination of timolol and pilocarpin was calculated from the trial comparing latanoprost and pilocarpin as second-line treatments after failure with beta-blocker therapy (20). At 6 months, 53% of patients had controlled IOP, which translates into a probability of IOP control over 3 months of .72. This is similar to the probabilities found in the observational study cohorts for this combination (.75). In the model, we used a probability of .75.

Probabilities of Nonmedical Treatment

The incidence of ALT and TRAB found in the observational cohorts is reproduced in the standard therapy branches. However, while some patients in the observational study in both countries had up to four ALTs and three TRABs in the first year, the model focuses mainly on the first intervention. Patients with frequent surgical interventions had typically more than 10 visits during the first year, while the average number of visits in the model is five, making it difficult to include multiple surgical interventions in more than a very small number of patients. Thus, the incidence of surgical interventions in the model is more conservative and reduced by about 30% compared to the observed values. The probability of undergoing ALT or TRAB when the newer second-line drugs are used will depend mostly on the effectiveness of these drugs to keep the patients' IOP controlled. Thus, due to this conservative incidence of ALT and TRAB in the standard treatment arm, the model may underestimate the potential of the new topical treatments to avoid surgical interventions.

In both France and the United Kingdom, a considerable number of patients underwent surgical interventions immediately after failure of first-line therapy (40% and 57%, respectively). In France, more patients went to ALT than to TRAB (70%

Table 1. Standard Costs of Treatments and Services (in 1997 French Francs and British Pounds)

Resource or service (per unit or month)	Cost/unit or month	
	France (FF)	UK (£)
Timolol	68.44	5.82
Standard treatment	65.89	3.99
Timolol + pilocarpin	74.82	—
Dorzolamide	97.33	9.31
Latanoprost	129.70	16.00
Brimonidine	—	10.80
Laser surgery (ALT)	1044.63	175.00
Trabeculectomy	9860.00	1262.84
Ophthalmologist visit	150.00	12.56
Diagnostic tests	179.64	28.82

US$1 = FF6.00; £0.61.

versus 30%), while in the United Kingdom half of the patients went to ALT and half to TRAB. We assumed that this pattern would change with the introduction of the new agents providing an effective alternative to surgery, and that most of these patients (90%) would first receive a second-line drug. Thus, effectively ALT and TRAB would become third-line interventions in the majority of patients.

If patients required drugs again after surgical intervention in the observational study, they received predominantly beta-blockers in monotherapy again (states post-ALT and post-TRAB). The probability of their IOP remaining controlled in these states was calculated from the survival curves on beta-blockers in the observational cohorts. However, as treatment failed for a considerable number of patients in these cohorts during the first 3 months of therapy, we used the more stable survival between months 3 and 15 for the states after surgery (Figure 2). The probability of undergoing a second procedure during the first year is very small.

Costs

Only direct medical costs are included in the model because indirect costs were not available from the chart reviews. Also, in glaucoma the patient population consists predominantly of elderly patients who are outside the labor force. The quantity of resources and services used was based on the observational study, and health inputs were valued from the perspective of society. We used the tariffs set nationwide by the Social Security in France, costs obtained from accounting departments in the National Health Service (NHS) in the United Kingdom, and public prices for drugs, including patient copayment or prescription charges in both countries. Table 1 summarizes the standard costs used in each country.

In France the standard costs used in the model are based on the actual chargeable utilization of each resource or service in the observational study, valued at the full tariff. Social Security will cover between 30–100%, and the remainder will be paid either by a complementary insurance (Mutuelle) or the patient. However, what is chargeable will depend on the number of services performed during the same visit. For instance, a test or a procedure such as ALT can be charged at the full tariff for the first eye and at 50% of the tariff for the second eye, while additional tests or procedures cannot be charged at all. In addition, charges for inpatient procedures differ between private and public hospitals. Therefore, we calculated

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weighted averages for all charges, based on the actual consumption in the observational study. Second-line drug costs for the current therapy was calculated as the weighted average public price (including copayment) of all drugs used in the observational study. Public list prices were used for the new drugs. Thus, standard costs used in the French model are really charges, and it may be problematic to use charges because they often are a poor reflection of the true opportunity cost (8). However, since in France all transactions in the health care market are based on Social Security tariffs and chargeable utilization, these charges represent the best available source for costing, and they are relevant for all payers, including the National Insurance, Mutuelles, and patients.

In the United Kingdom resources were valued based on total costs to the NHS and patients' out-of pocket expenses, such as prescription fees. Standard costs were obtained from the accounting departments in the three sites in the observational study, and a mean cost was calculated. However, some adjustments were required because the sites used different cost allocation procedures. Two sites allocated the cost of a nurse or a technician to the test because there would be no visit to a nurse without a test being performed, while the third site did the opposite. We therefore calculated the average time of a nurse required for each test and allocated this cost to the visit and the remaining cost to the test. The cost for the nurse was based on the midpoint of the salary scale (grade F) plus overhead. Visit costs included the mean time spent by the consultant at each site, weighted for an initial visit and follow-up visits. There were again major differences insofar as in two sites the consultants' time was essentially limited to determine the diagnosis from the tests, while in the third site the consultant was involved in the tests. For bed days and surgical procedures, the mean cost of the three sites was used. Variations in these costs were limited, with a bed day ranging from £460 to £565 and TRABs from £662 to £817. None of the centers provided costs for an ALT, so the average cost in the York Health Area was used. The price of propine was used as second-line drug costs for the standard therapy branch, since the vast majority of patients in the observational study who did not go to directly to surgical intervention received this drug. Public prices were used for dorzolamide, latanoprost, and brimonidine.

RESULTS

Base Case Simulations

The average cost per patient over 12 months for the standard therapy is FF2,389 (US $398) in France and £380 (US $627) in the United Kingdom (Table 2). Average total costs with all of the new treatments are lower in both countries than with current therapy. Latanoprost has the lowest cost at FF2,087 (US $348) and £307 (US $507). The savings are due to avoidance or delay of surgical procedures, both ALT and TRAB, with less need for diagnostic testing, and the higher drug cost is thus more than offset. When the models are extended to 2 years by integrating treatment modalities observed in the second year of the observational study, the results are maintained. Costs for the newer treatments are similar or slightly lower than with current treatment (Table 2).

In order to illustrate the difference in the proportion of patients that follow the different treatment paths and their respective costs, 10,000 Montecarlo simulations were produced. Figure 3 presents the simulations for both France and the United Kingdom when either dorzolamide or latanoprost are used after first-line therapy failure.

Table 2. Average Cost per Patient during the First Year after Diagnosis, for Intervention with Different Second-line Treatments after Beta-blockers Failed to Control IOP

	Timolol	Second-line drug	Visits	Tests	ALT	TRAB	Total 1 year	Total 2 years
France (FF)								
Standard treatment	739	68	750	211	129	492	2,389	3,943
Dorzolamide	814	179	751	198	74	289	2,305	4,159
Latanoprost	753	272	754	186	25	97	2,087	3,765
Timolol & Pilocarpin	811	11	751	206	107	419	2,305	4,057
UK (£)								
Standard treatment	69	1	63	148	12	87	380	617
Dorzolamide	70	8	63	146	5	33	324	548
Latanoprost	67	15	63	145	2	15	307	515
Brimonidine	70	9	63	146	5	33	325	551

Definitions: IOP = intraocular pressure; ALT = argon laser trabeculoplasty; TRAB = trabeculectomy.
£1 = FF10.00
US$1 = FF6.00; £0.61.

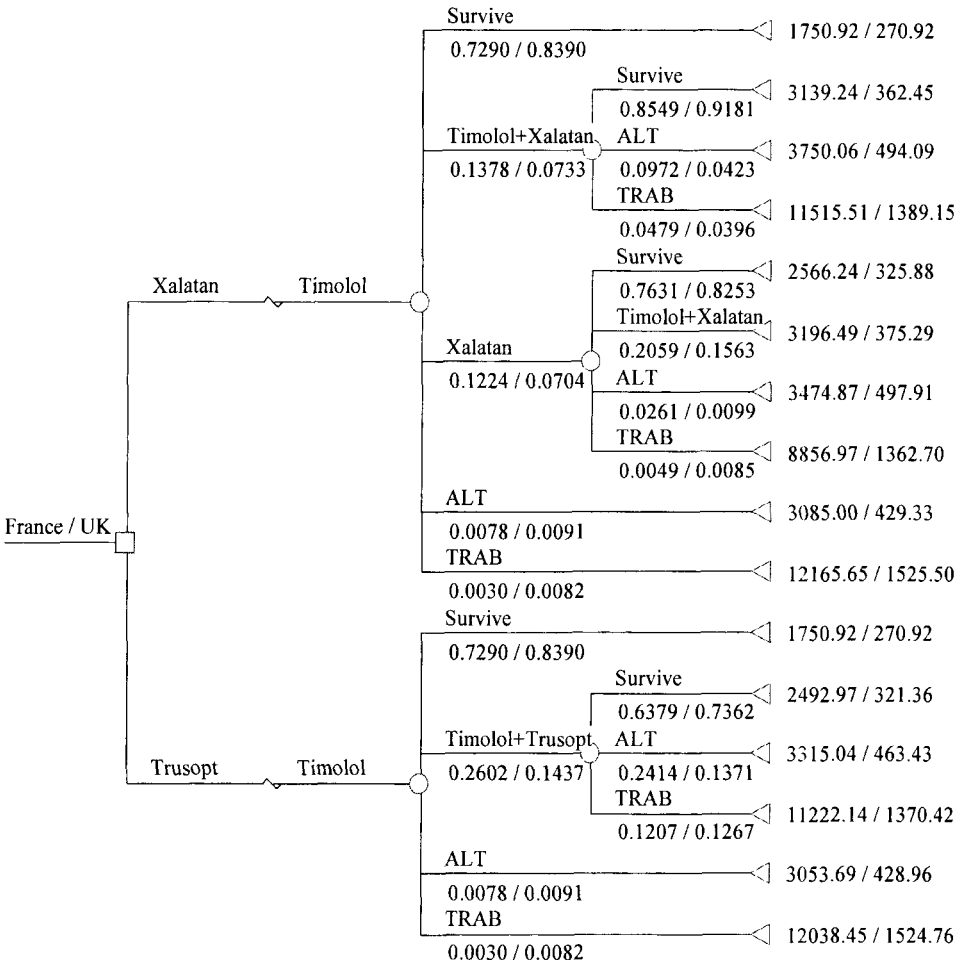

Figure 3. Montecarlo simulations for second-line therapy with either dorzolamide or latanoprost in France and the United Kingdom. Proportions of patients on different treatments (France/UK) and 1-year costs per patient and per branch (France, FF/UK, £).

Sensitivity Analyses

Sensitivity analyses were performed for dorzolamide and latanoprost only, because these two products are approved for identical indications and are in both models. We varied the effectiveness of both products between 75% and 95% of IOP control over 3 months, and the proportion of the usage as monotherapy over the full range between 0% and 100%. In the worst case, with lowest effectiveness and no monotherapy, the costs in France are FF2,383/FF2,440 and in the United Kingdom £332/£337 for dorzolamide and latanoprost, respectively. In the best case, costs are FF1945/FF1985 and £297/£301 for dorzolamide and latanoprost, respectively. When the drug cost is varied, costs for dorzolamide range from FF2,219 to FF2,292 and from £317 to £321, costs for latanoprost from FF2,033 to FF2,142 and from £304 to £311. Assuming the same price for both drugs, at the mid-point of the difference between the two prices, costs in France are FF2,334 for dorzolamide and FF2,053 for latanoprost. Respective figures for the United Kingdom are £327 and £304. Thus, it appears that a relatively small difference in effectiveness will lead to a

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difference in total costs. In all cases, savings compared to standard therapy are maintained for both products under all assumptions.

DISCUSSION

Innovative new treatments are likely to change the pattern of treatment, and it is therefore important to estimate their impact on outcome and cost. We present a model that allows for the calculation of the economic impact of new topical therapies for the treatment of glaucoma. The model, although based on the effectiveness of the interventions to control patients' IOP over time, focuses on cost calculations. Increased IOP control will reduce the need for treatment changes and therefore utilization of health care resources and services. The observational data have shown a strong positive correlation between the number of treatment changes and treatment costs, and therefore it appears relevant to focus on treatment costs only.

Markov states are thus defined according to the different treatments a patient may receive, rather than to disease parameters such as severity of visual impairment. As the epidemiological link between the progression of glaucoma to optic nerve damage and ultimately blindness and the level of IOP is not established, constructing a model based on levels of IOP is not relevant. It also is not possible to express outcome in terms of vision saved, because the effectiveness of treatments that lower IOP to delay progression to or to avoid blindness cannot be estimated. However, all glaucoma treatments today aim at reducing the IOP, and their effectiveness can therefore be calculated as their ability to maintain IOP at or below a certain level over time. In our model, this measure is therefore used to calculate state transitions from one treatment to another, generally more expensive, treatment. The advantage of using IOP control is that IOP is measured in all clinical trials, making the model more usable.

The basic model runs for 1 year, which may be considered a rather limited time frame in a chronic disease. However, in the international observational study we found that costs during the first year after initiation of treatments were substantially higher than during the subsequent year, representing around two-thirds of 2-year treatment costs. This seems to indicate that efforts to stabilize IOP at a lower level are more intensive early in the course of treatments. New treatments can therefore be expected to affect costs during the first year. Furthermore, available clinical data for the different new products are still limited to 6 or 12 months, and their long-term effect would thus necessarily have to be based on assumptions.

The calculations presented here focus on patients that have been newly diagnosed and treated initially with standard beta-blocker therapy. Thus, they are not representative for the entire glaucoma patient population. The majority of the new products are indicated for use as second-line medical intervention after beta-blocker failure. It is therefore relevant to calculate the impact of new treatments based on failure rates with first-line standard treatment. In France and the United Kingdom, ALT and TRAB are frequently used as second-line intervention, and a large number of patients will undergo surgical interventions when they first fail on beta-blocker therapy. We based our model partly on the assumption that with the advent of more effective second-line topical therapies, surgical interventions would become third- or fourth-line interventions. This seems a reasonable assumption according to data from a compassionate use study with latanoprost, where scheduled surgery was delayed for a majority of patients beyond the 3-month follow-up (2).

Guidelines for economic evaluation (4;6;11) state that economic evaluations should always be performed from the societal perspective in addition to any other chosen perspective such as third-party payers or patients. This is often interpreted as mandatory inclusion of indirect costs in the societal analysis. However, even if a study includes only direct costs, these can be calculated from a societal perspective by including all costs, regardless of the payer. Our model calculates the total direct costs of all health inputs used to treat early glaucoma or ocular hypertension. In France this includes costs incurred by the national health insurance, complementary insurance, and patients. We used Social Security tariffs to calculate the costs, to the extent that they are chargeable. This might underestimate the true opportunity cost, since some services cannot be charged at their full tariff, depending on when they occur. Alternatively, some costs may be overestimated because the tariff applies regardless of how many resources went into producing the service. However, as health care payments in France are centered on these tariffs, they represent the best basis to calculate direct costs and there is no evidence available that they are very different from the opportunity cost. In the United Kingdom, average costs were calculated based on indications from the accounting department in each study site. Their method of calculation, although different in the different sites, uses the time cost of health care personnel, use of facilities, supplies, and allocation of overheads. Therefore, these costs represent true opportunity costs for the NHS and include prescription charges for patients.

CONCLUSION

It is important to be able to calculate the impact of new therapies that have the potential to not only affect clinical outcome, but to change treatment patterns. In glaucoma, where the relation of intervention, addressing what is considered to be the major risk factor, and the final outcome (loss of vision) is not fully elucidated, cost appears to be a relevant measure to express treatment success in the short or medium term. We propose a Markov model that allows calculating average treatment costs for newly diagnosed patients when using recently introduced topical agents.

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