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RETINAL DISORDERS

Cost-effectiveness sequential modeling of ranibizumab versus usual care in age-related macular degeneration

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Abstract
Aims To assess effectiveness, cost, and cost-effectiveness of ranibizumab versus the current medical practices of treating age-related macular degeneration in France.
Methods A simulation decision framework over 1 year compared ranibizumab versus the usual care using two effectiveness criteria: the "visual acuity improvement rate" (greater than 15 letters on the ETDRS scale) and the "rate of legal blindness avoided". Two decision trees included various sequences of current treatments, with or without ranibizumab.
Results Ranibizumab appeared significantly more effective than the usual care ($p<0.001$), providing greater treatment success rate of visual acuity improvement (48.8% versus 33.9%). The cost of the ranibizumab strategy was higher (9,123 euros (€) over 1 year for ranibizumab versus 7,604 € for the usual care) but the average cost-effectiveness was lower – 18,721 € /success for ranibizumab versus 22,543 €/ success for usual care ($p<0.001$). Considering the "legal blindness avoided" success criterion, the ranibizumab strategy appeared significantly more effective ($p<0.001$), providing greater treatment success rate for of legal blindness avoided than usual care (99.7% versus 93.1%) although it was more expensive (9,196 € over 1 year for ranibizumab versus 5,713 € for the usual care).
Conclusion Ranibizumab significantly improved the rate of visual acuity improvement and reduced the rate of legal blindness. Ranibizumab appeared significantly more cost-effective than the usual treatments in terms of visual acuity improvement.

Keywords Age-related macular degeneration · Cost-effectiveness · Ranibizumab · Modelling

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Introduction

Age-related macular degeneration (AMD) is the leading cause of legal blindness in industrial countries in patients over 65 years old [1]. The molecular events presaging AMD have grown in the last decade but its etiology and

pathogenesis remain poorly understood [2]. The exudative stage of AMD with choroidal neovascularization (CNV) usually has a severe outcome with sudden or progressive visual loss [3]. AMD leads to legal blindness, a significant public health problem, and its treatment aims to stabilize or improve visual loss. The treatment strategy for the exudative stages of the disease aims to destruct the CNV, and recently new therapeutic possibilities have emerged. These treatment options include laser photocoagulation, photodynamic therapy (PDT) with verteporfin, and intravitreal VEGF inhibitors (pegaptanib, ranibizumab, bevacimizumab) and their combination [4]. VEGF inhibitors aim to reverse the disease process, allowing patients to gain greater visual acuity. Two of these new drugs (pegaptanib, ranibizumab) are available and licensed for AMD, and the last one (bevacimizumab) is off-license for AMD. Since conventional laser coagulation destroys the treated retina, its use is reserved for extrafoveal classic CNV lesions. For subfoveal lesions with predominantly classic CNV, or occult forms with non-classic CNV, PDT with verteporfin has been shown to be a safe and effective treatment (TAP study) [5]. Its strategy consists in repetitive thrombosis of CNV with progressive occlusion of the exudative lesion adjusted to the angiographic appearance. However, improvements in visual acuity are infrequent with verteporfin PDT.

Given the various treatment options and their rising costs to insurance providers, it is difficult and costly to assess the effectiveness and cost of different therapy combinations in clinical trials. Although a number of studies are available for the two AMD licensed drugs [6–8], treatment switches have not been assessed in clinical trials. Furthermore, the alternative treatment courses in managing neovascular AMD are not well defined, and costs-effectiveness analyses need to be performed to recommend evidence-based guidance for non-surgical therapies. The steady flow of innovative drugs has provided clinicians with a plethora of effective treatments. With healthcare providers continuing to struggle with rising costs, clinical effectiveness alone will no longer be the only criteria for evaluating a new treatment [9]. Economic evaluations of health care technologies typically utilize models to make assumptions and synthesize evidence from multiple sources in order to estimate costs and outcomes of new therapies [10]. Within the therapeutic management of AMD, a variety of current medical practices using specific treatment courses can be identified and modeled. The originality of this model is that it takes into account the effectiveness and costs of sequential treatment alternatives. The objective of this model is to assess the cost-effectiveness of ranibizumab as a first-line strategy compared with sequential treatments are they currently offered to patients with AMD in France.

Materials and methods

Model framework

Creating a model involves the use of mathematical language to link selected parameters in the framework of a mathematical formula. “Simulation models” refer to advanced analytical methods that represent real-life variability with the use of a random number generator and various parameter distribution laws. This type of model becomes especially relevant in the absence of data or when real-life studies are too difficult to conduct. Furthermore this evaluation approach is safer since it does not jeopardize the health of patients with potentially inadequate treatment options.

The main treatment sequences have been defined by an expert panel composed of four experienced clinicians and one expert in modeling methodology with affiliations presented in the authorship. The panel members are independent from the pharmaceutical industry so that the clinicians can objectively represent private and public practices. The consensus process was based on the unanimity approach. The expert panel defined medical practice, validated model assumptions and data sources. The authorship contribution of the Novartis employee consisted of providing clinical trials results and costing data.

The defined population entering the model is a cohort of patients suffering from AMD. This model is called a “sequential model” because it takes into account potential treatment switches, similar to current medical practices. Patients achieving treatment success are maintained on their existing therapy for up to 1 year. Those with an inadequate response are switched to the subsequent treatment in the sequence, with future decisions at 3-month intervals in cases of a continued inadequate response. To assess and compare the cost-effectiveness of ranibizumab used as first-line specific strategy in this patient population, the comparative model was defined as the usual treatment based on the most common treatment option in France at the time of model development, namely: simple surveillance, laser therapy, verteporfin, pegaptanib, ranibizumab or combination therapies ranibizumab verteporfin or pegaptanib verteporfin.

Two clinically meaningful effectiveness endpoints have been used:

- Visual acuity improvement (at least 15 letters on the ETDRS scale)
- Legal blindness avoided

These two outcomes have been selected because they appear conservative for ranibizumab and in line with the final expected goal of any new active therapeutic strategies.

For each of the two effectiveness outcomes, two comprehensive decision trees have been developed to represent the different treatment patterns and their corresponding outcomes, transition probability distribution, and cost distributions: two "ranibizumab" decision trees and two "usual care" decision trees.

In this model, each strategy that is to be assessed and compared is composed of 3-month duration treatment plans used successively following an inadequate response to the previous one. The same treatment should continue as long as it is efficacious. The decision tree illustrated in Fig. 1 is composed of 59 health states (branches) and 42 transition probabilities.

The "ranibizumab first-line strategy" decision tree (Fig. 1) begins with a split between AMD with classic CNV and AMD with occult CNV, and then another split distinguishes extrafoveolar and retrofoveolar AMD. Various sequences of laser therapy, ranibizumab, combination ranibizumab verteporfin, or "surveillance only" are proposed according to the AMD type.

The "usual treatment" strategy also distinguishes AMD with classic and occult CNV, then extrafoveolar and non-extrafoveolar AMD. Various sequences of laser therapy, verteporfin, pegaptanib, combination pegaptanib verteporfin, or "surveillance only" are proposed according to the AMD type.

These decision trees were programmed to take into account the entire cost distribution and effectiveness distribution for each pre-defined parameter according to specific distribution laws [11]. Simulation models consuming large amounts of computer processing time, powerful workstations with parallel-processors, and adapted programming languages (Dscript language – DecisionPro 4.1) were used to develop this model.

Uncertainty management

Uncertainty occurs when the true value of a parameter is unknown, thus reflecting the fact that our knowledge or measurement is imperfect. In this model, uncertainty was managed by assessing acceptable ranges of values from descriptive retrospective patient databases validated by the expert panel. For each variable (effectiveness and cost parameters), probability distributions have been selected. The "Beta distribution" shape has been used to program effectiveness transition probabilities distribution [12]. Beta distribution law used two parameters, a and b, to produce a "normal" type curve specifically shaped between 0 and 100%. The "uniform distribution" curve, a flat curve between a minimum and a maximum limit, was selected to program costing variability because it allows for the screening of all possible costs between a minimum and a maximum value, taking into account both various patient medical consumption and medical practices variability.

An extensive sensitivity analysis using 5,000 Monte Carlo simulations was used to manage the uncertainty of the model. Monte Carlo simulations randomly select a value from the defined possibilities (range and shape of the distribution) of each parameter, and then recalculate the outcomes. By screening all uncertain parameter values to construct outcome confidence intervals, this approach is considered a robust sensitivity analysis ("probabilistic sensitivity analysis").

Effectiveness endpoints

Costing assessment

Charge tables are listed in Table 1 and Table 2 with the perspective of the society.

Direct medical costs have been considered plus relevant social allowance for patients suffering from legal blindness (disability and helper allowance). These allowance costs can be considered as "transfer costs" but not "indirect costs" as loss of production costs (wages/opportunity costs) have not been included.

The sources of the effectiveness data are clinical trials, literature, and clinical reports. Expert opinion was used to define confidence intervals to take into account medical practice variability (Table 3). The primary objective when treating AMD is to improve visual acuity and avoid the progression to blindness. In order to avoid classical

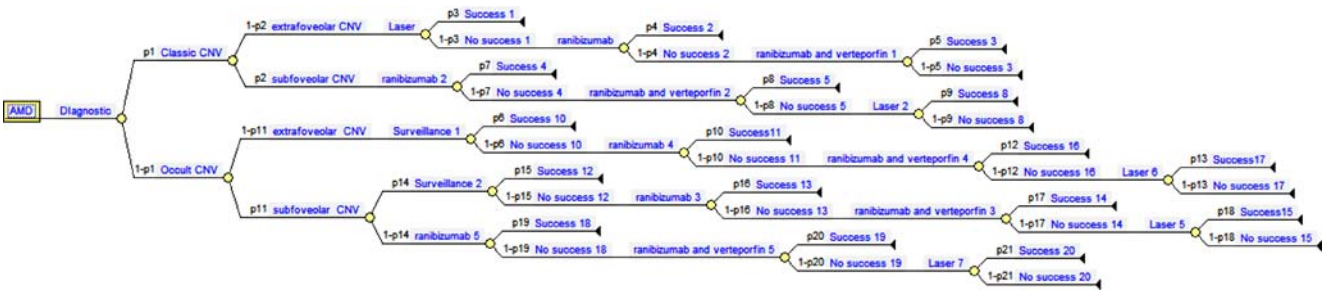

Fig. 1 Ranibizumab strategy sequential decision tree

Table 1 Legal blindness adaptive aids and social allowance charge table* (in €)

		Minimum	Maximum
Adaptive aids	*Adapted telephone*	*0*	*91.6*
	Special calculator	*0*	*450.3*
	Video enlarger	*0*	*7864.5*
	Total	**0**	**8,406**
Social allowance	*Disabled adult allowance*	*0*	*1341/month*
	Caregiver allowance	*0*	*999.83 /month*
	Disability special allowance	*0*	*771.82/month*
	Total	**0**	**37,351.80/year**

*Source: Actualités Sociales Hebdomadaires, 7 Sep 207, 2521, p19

methodological limitations of "utility" indicators often presented in modeling studies generating "quality adjusted life years" ("cost-utility analyses"), two clinically meaningful success indicators were proposed in order to provide a real and robust "cost-effectiveness analysis", which was not "utility" based.

The first effectiveness outcome is the rate of visual acuity improvement defined as an improvement of at least 15 letters on the ETDRS scale. The second effectiveness outcome is the rate of legal blindness avoided.

Each of the two models "ranibizumab" and "usual care" have been simulated twice using the two defined effectiveness criteria. Each effectiveness transition probability has been expressed as a range of values according to a Beta-type distribution law programmed with a lower limit, an upper limit, a mean, and standard deviations.

Total costs linked to AMD were measured in the monetary unit of € (2006) and include therapeutic regimen costs, physician visits, surveillance, and imaging such as angiography, potential visual adaptive devices for blindness (big keyboard telephone, special calculator, video enlarger) and potential social allowance for blindness (disabled adult allowance, caregiver allowances, autonomy personal allowance).

Direct medical costs were measured in the monetary unit of € (2006). The "uniform distribution" curve, a flat curve between a minimum and a maximum limit, was selected to program costing distribution because it allows to screen all possible costs between a minimum and a maximum value, taking into account both various patient medical consumption and medical practices variability.

Results

1. Rate of visual acuity improvement (Tables 4, and 5):

The model simulations established that using ranibizumab as a first-line agent was significantly more effective ($p<0.001$), providing greater treatment success rate of visual acuity improvement than usual treatment options (48.8 versus 33.9%).

Table 2 Therapeutic strategies charge table: frequency of medical resources per year

		Visudyne	MACUGEN	Laser	Lucentis	Surveillance
AMD with occult CNV	Med. Visit: 23 €	4	9	8	9	4
	Angio.: 64.07 €	3.4	4	4	4	4
	ICG: 71.9 €	4	4	4	4	4
	OCT: 42.72 €	4	4	4	4	4
	PDT: 181.3 €	4				
	Number of treatment cure/year	3.4	8.4	4	8	0
	Annual treatment costs (€)	5,175.07	7,639.21	585.2	11,050.96	0
	Total annual costs (€)	***5,943.39***	***8,560.97***	***1,483.96***	***11,972.72***	***806.76***
AMD with classic CNV	Med. Visit: 23 €	4	9	8	9	4
	Angio.: 64.07 €	3.4	4	4	4	4
	OCT: 42.72 €	4	4	4	4	4
	PDT: 181.3 €	4				
	Number of cure/year	3.4	8.4	4	8	0
	Annual treatment costs (€)	5,175.07	7,639.21	585.2	11,050.96	0
	Total annual costs (€)	***5,694.23***	***8,273.37***	***1,196.36***	***11,685.12***	***519.16***

ICG angiography Indocyanine Green angiography
OCT Optical Coherence Tomography
PDT Photodynamic Therapy

Table 3 Transition probabilities (lower and upper limit of 95% confidence intervals)

Transition probabilities	Lower limit 95%	Upper limit 95%
AMD with classic CNV	0.2	0.4
AMD with occult CNV	0.7	0.85
"No Legal Blindness "outcome		
Success rate Surveillance	0.95	0.98
Ranibizumab decision tree		
AMD with classic CNV		
Success rates laser	0.9	1
Success rate ranibizumab	0.9	0.95
Success rate ranibizumab - Visudyne	0.85	0.95
AMD with occult CNV		
Success rates laser	0	0.1
Success rate ranibizumab	0.95	0.98
Success rate ranibizumab - Visudyne	0.85	0.95
Usual care decision tree		
AMD with classic CNV		
Success rates laser	0.9	1
Success rate - Visudyne	0.8	0.9
Success rate - MACUGEN	0.75	0.95
Success rate - MACUGEN - Visudyne	0.95	0.98
AMD with occult CNV		
Success rates laser	0.85	0.95
Success rate - Visudyne	0.8	0.9
Success rate - MACUGEN	0.75	0.95
Success rate - MACUGEN - Visudyne	0.65	0.85
Visual acuity improvement		
Ranibizumab decision tree		
AMD with classic CNV		
Success rates laser	0.9	1
Success rate ranibizumab	0.3	0.5
Success rate ranibizumab - Visudyne	0.15	0.3
AMD with occult CNV		
Success rates laser	0	0.02
Success rate ranibizumab	0.15	0.3
Success rate ranibizumab - Visudyne	0.15	0.3
Usual care decision tree		
AMD with classic CNV		
Success rates laser	0.05	0.25
Success rate - Visudyne	0.05	0.1
Success rate - MACUGEN	0	0.1
Success rate - MACUGEN - Visudyne	0	0.05
AMD with occult CNV		
Success rate Surveillance	0.05	0.1
Success rates laser	0.05	0.15
Success rate - Visudyne	0.05	0.1
Success rate - MACUGEN	0	0.1
Success rate - MACUGEN - Visudyne	0	0.05

2. Direct medical costs were 9,123 € over 1 year for ranibizumab compared to 7,604 € for the usual care. Mean cost-effectiveness was 18,721 € /success for ranibizumab versus 22,543 €/success for the usual care ($p<0.001$).

Rate of legal blindness avoided (Tables 3 and 4): ranibizumab as first-line agent is significantly more effective ($p<0.001$), providing a greater treatment success rate of legal blindness avoided than usual care (99.7 versus 93.1%).

Direct medical costs were 9,196 € over 1 year for ranibizumab compared to 5,713 € for the usual care. Mean cost-effectiveness was 9,224 € /legal blindness avoided for ranibizumab versus 6,133 €/legal blindness avoided for usual care.

Discussion

The main model assumptions have been considered that are consistent with clinical management of AMD: the same treatment should continue as long as it is efficacious; an efficacious treatment was considered efficacious over the rest of the year; treatment may be switched only in case of treatment failure, but due to all causes (e.g., lack or loss of efficacy, adverse event, intolerance, etc); the model allowed for switches to occur every 3 months. Regarding costing aspects, legal blindness related costs include social allowance and have been included only for 1 year, even if these costs will occur during the rest of the patient's life. This is considered a conservative assumption that does not favor ranibizumab, which leads to a lower rate of legal blindness.

As a cost-effectiveness model is both an effectiveness model and a cost model, clinical evidence data are important parameters to consider. Randomized controlled trials (RCT) on patients with subfoveal choroidal neovascularization associated with wet AMD have been recently reviewed by Takeda [13]. Most of RCT concern ranibizumab [14–16] (or pegaptanib [17–19]. There is a lack of data on bevacizumab but this molecule does not have marketing authorization in France. These studies showed statistically significant benefit on different measures of visual acuity for patients receiving either pegaptanib, ranibizumab, or ranibizumab with PDT compared to control after 12 months. Pegaptanib and ranibizumab appear to slow down or stop the progression of neovascular AMD. Results from ranibizumab RCT tended to show a greater effect on visual acuity than results from pegaptanib trials. However, there is no generally accepted consensus to propose the "most appropriate" therapeutic strategy for patients. The current medical management of AMD involves not just one therapeutic agent on a long time duration, but rather a sequence of therapies, (observation, laser photocoagulation, verteporfin, ranibizumab, pegaptanib, etc.) [20, 21]. Unfortunately, no clinical trial is able to compare treatment sequences. Only a few retrospective descriptive studies on small patient populations, not evidence-based, present limited data of sequential treatments, such as the study from Ligget et al. [22].

Table 4 Costs, success rate (visual acuity improvement rate), and cost per success for ranibizumab and usual care strategies over 1 year

		Medical costs over 1 year (in €)	Success rate	Cost per success (in €)
Ranibizumab	**Mean**	9,123	0.488	18,721
	Standard deviation	3,849	0.024	7,919
Usual care	**Mean**	7,604	0.339	22,543
	Standard deviation	2,621	0.027	7,937

One practical way to compare sequential treatment regimens and combination therapies is to use the modeling approach. But one important difficulty of any model is to take into account the heterogeneity of real-life phenomena. The originality of this simulation model is that it captures variability of medical practices, patient profiles, and treatment effectiveness on the basis of available data and expert opinions. Monte-Carlo simulations allow for performing "full" sensitivity analyses of all parameters (costs and effectiveness parameters) at the same time, compared to a classical sensitivity analysis assessing only the impact of one parameter on the results, as opposed to one parameter value against every other parameters potential values.

The fact that this model uses two ambitious clinical endpoints such as "visual acuity improvement rate" (greater than 15 letters on the ETDRS scale) and "rate of avoided legal blindness" suggests that the majority of AMD patients has not been addressed. Then stable patients or patients losing fewer than 15 letters on the ETDRS scale have not been considered, even if they represent the target population of the clinical trials primary outcome. Of course the "stability" endpoint can be modelized in the same way but the interest would be limited because the expected results would just be the mirror of the clinical trial. The real advantage of the modeling approach is to be able to go beyond and to complete clinical trial data.

Considering the importance of the social impact of legal blindness, the perspective of this model is "societal", and takes into account the cost of adaptive aid and social allowance. Ranibizumab prevents legal blindness at a superior rate, however the overall direct cost is higher, with or without taking adaptive aids and social allowance into account. However, considering the fact that avoiding legal blindness is an absolute medical and social need, the cost-effectiveness ratio represents the cost per legal blindness avoided.

Modeling of therapeutic sequences is therefore of particular importance in evaluating the cost-effectiveness of an innovative anti-AMD agent. Such an approach helps to identify where the new specific agent may be best positioned within a therapeutic sequence.

In the present study, decision trees and sequence of treatments were built according to French medical practices and then validated by the expert panel at the time of the study, which was finalized on the 1st Quarter of 2007. Only labeled therapeutic regimens have been taken into account in this model (therefore, bevacizumab was excluded since this product has no marketing authorization in France).

Another economic evaluation that is often used consists of conducting a cost-utility assessment that uses "utility" scores (preference assessment) to generate *Quality Adjusted Life Years* (QALYs) as a potential synthetic assessment indicator [23, 24]. Raftery et al. [25] have carried out a cost-utility model assessing the cost per QALY over 10 years of bevacizumab versus ranibizumab. They conclude that ranibizumab would unlikely be a cost-effective alternative to bevacizumab. These authors used a "conversion" table proposing correspondences between "visual acuity value" and "utility value" expressed between 0 and 1. The QALY indicator is often used by health economists from the commonwealth countries (United Kingdom, Canada, and Australia) to address the need for a universal indicator and to allow for comparison between different diseases. However, the QALY indicator requires various methods of assessing utility values which introduce significant methodological challenges, which directly influence the results. For example, the uncertainty of the predictive calculated utility value proposed by Raftery et

Table 5 Costs, success rate (rate of legal blindness avoided), and cost per success for ranibizumab and usual care strategies over 1 year

		Total costs over 1 year (in €)	Success rate	Cost per success (in €)
Ranibizumab	**Mean**	9,196	0.997	9,224
	Standard deviation	7,238	0.00075	7,260
Usual care	**Mean**	5,713	0.931	6,133
	Standard deviation	5,948	0.018	6,384

al. has not been explored or even discussed in presenting confidence intervals of predictive calculated values. It is therefore important to examine the potential significance of estimated utility values using a conversion table and their potential to discriminate different alternatives. Any model carries uncertainty over transformed values from one scale to another, and this uncertainty must be taken into account before using predictive values to compare drugs. Since any scale conversion between a clinical scale and a preference scale (utility) is characterized by a high level of uncertainty, it may compromise the relevance of such cost-utility results. Thus, results generated by this approach cannot be considered as scientifically valid without addressing and presenting uncertainty inherent to any scale transpositions.

Furthermore, there is increasing evidence that the QALY indicator may lead to divergent results depending on the utility assessment method used [26, 27]. Real cost-effectiveness analyses that measure cost per clinical outcome raise fewer methodological issues than cost-utility analyses based on the cost per QALY indicator (which is rarely used in medical practice). Nevertheless, improvement in quality of life (QOL) is of paramount importance in the management of AMD, and using a real cost-effectiveness demonstration (expressed as cost per clinical outcome) should not prevent the separate consideration of the improvement in quality of life as an important and relevant additional outcome. Such measures can be assessed by appropriate and validated QOL instruments [28].

This original cost-effectiveness model seems to be the first robust sequential simulation model in AMD medical management comparing complex strategies because it takes into consideration the variability inherent to real-life phenomena, the 1st line, 2nd line, 3rd line, and 4th line potential therapeutic regimens. Potential future long-term observational and experimental data would allow for developing similar models simulating costs and effectiveness of medical practices beyond the first year of treatment.

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