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RETINAL DISORDERS

Cost-effectiveness of ranibizumab compared with pegaptanib in neovascular age-related macular degeneration

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Abstract
Objective To assess the cost-effectiveness of ranibizumab compared with pegaptanib in the treatment of patients with minimally classic/occult neovascular age-related macular degeneration (AMD), from a societal perspective in Spain.
Methods We constructed a Markov model with five states defined by visual acuity (VA) in the better-seeing eye (Snellen scale): VA >20/40, ≤20/40 to >20/80, ≤20/80 to >20/200, ≤20/200 to >20/400, ≤20/400, and an additional death state. Two cohorts of patients were distributed along the VA states, and treated with either ranibizumab or pegaptanib. Transition probabilities assigned for movement between these states with both drugs were obtained from published randomized clinical trials. Medical costs related to AMD treatment and follow-up, medical costs related to AMD comorbidities, and non-medical-related costs were taken into account. Costs (2008 Euro), health outcomes (Quality-adjusted life years—QALYs), both discounted at a 3.5% annual rate, and incremental cost-effectiveness ratios (ICER: €/QALY), were determined for a lifetime horizon in the base case analysis. Sensitivity analyses were conducted to explore different scenarios and assumptions in the model.
Results Treating patients with varying degrees of visual impairment with monthly ranibizumab instead of pegaptanib was €71,206 more costly and provided 2.437 additional QALYs (€29,224/QALY). When administered on an as-needed basis, as in the Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intraocular Ranibizumab (PrONTO) trial, the cost per QALY gained with ranibizumab was reduced to €4,623.
Conclusions The cost per QALY gained with monthly ranibizumab compared with pegaptanib in the minimally classic/occult neovascular AMD population is just below the €30,000 threshold below which new drugs are sometimes regarded as cost-effective strategies in Spain. In this model, the key variables with greater impact on the cost-effectiveness results were the selected time horizon and the chosen extrapolation method, the source for data on pegaptanib efficacy and the number of ranibizumab injections. When administered on an as-needed basis, ranibizumab was a cost-effective strategy compared to pegaptanib in this population.

Keywords Age-related macular degeneration · Ranibizumab · Pegaptanib · Cost-effectiveness · Cost-utility

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Introduction

According to the World Health Organization, age-related macular degeneration (AMD) is the most common cause of legal blindness in developed countries and ranks third globally, with an increasing incidence due to population aging [1].

Late AMD has two forms: non-neovascular, in which central or pericentral gradual visual loss typically develops, and neovascular, in which profound visual loss develops as a result of hemorraghe, fluid collections beneath the retina

or fibrosis due to subretinal neovascularization. Although neovascular AMD represents only 10 to 15% of the overall prevalence of AMD, it is responsible for more than 80% of cases of severe visual loss or legal blindness [2]. Intravitreal anti-angiogenic drugs are currently the primary therapy for neovascular AMD [3].

Pegaptanib, an oligonucleotide aptamer which blocks the 165 isoform of the vascular endothelial growth factor (VEGF), was the first anti-angiogenic drug to become available. It demonstrated a statistically significant delay in vision loss in the VEGF Inhibition Study In Ocular Neovascularization (VISION) clinical trial [4, 5]. Ranibizumab is the humanized Fab fragment of the murine monoclonal antibody which blocks all the active isoforms of the VEGF. Ranibizumab demonstrated statistically significant improvements in visual acuity (VA) in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-related Macular Degeneration (MARINA) trial [6] and in the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-related Macular Degeneration (ANCHOR) trial [7].

With regard to bevacizumab, the full monoclonal antibody which is used off-label, initial studies were short-termed, and included a small number of patients [8–10]. To date, there is considerable ammount of evidence to support the use of intravitreal bevacizumab in neovascular AMD, [3, 11, 12] with prospective studies up to 1 year of follow-up [13]. Randomized controlled trials comparing ranibizumab and bevacizumab are ongoing [14], but results are not yet available.

The high cost of newer therapies against AMD has brought the attention of ophthalmologists to the field of pharmacoeconomics [15]. In a previous study, we examined the cost-effectiveness of ranibizumab compared to photodynamic therapy (PDT) in the predominantly classic AMD population [16]. In the present study we sought to examine the cost-effectiveness of ranibizumab compared to pegaptanib in the minimally classic/occult neovascular AMD population. Bevacizumab was not included in this study. However, if both ranibizumab and bevacizumab are found to be clinically equivalent in on-going clinical trials, the cheapest one, bevacizumab, would be the therapy of choice to maximize healthcare resources.

Material and methods

Modelling approach

We constructed a Markov model with five states defined by the VA in the better-seeing eye: better than 20/40 in the Snellen scale, ≤20/40 to >20/80, ≤20/80 to >20/200, ≤20/200 to >20/400, ≤20/400, and an additional "death" state. The model scheme with allowed transitions is illustrated in Fig. 1.

Briefly, Markov models are used in the field of decision analysis to model the progression of chronic diseases. The disease in question is divided into distinct states, and transition probabilities are assigned for movement between these states over a discrete time period called the 'Markov cycle'. By attaching estimates of resource use and health outcomes to the states in the model, it is possible to estimate the long-term costs and outcomes associated with different healthcare interventions [17]. In the context of economic evaluations, models provide the appropriate framework to synthesize all available evidence, to compare all relevant treatment options, and to systematically study the impact of different scenarios and assumptions through sensitivity analysis [18].

In this model, a cohort of patients was distributed along the five VA states at treatment start, according to data from a Spanish study [19]. The transition probabilities for ranibizumab were obtained from efficacy results of the MARINA trial [6]. In this trial, 94.6% of patients given ranibizumab 0.5 mg monthly lost fewer than 15 letters of VA in the first year, as compared with 62.2% of patients

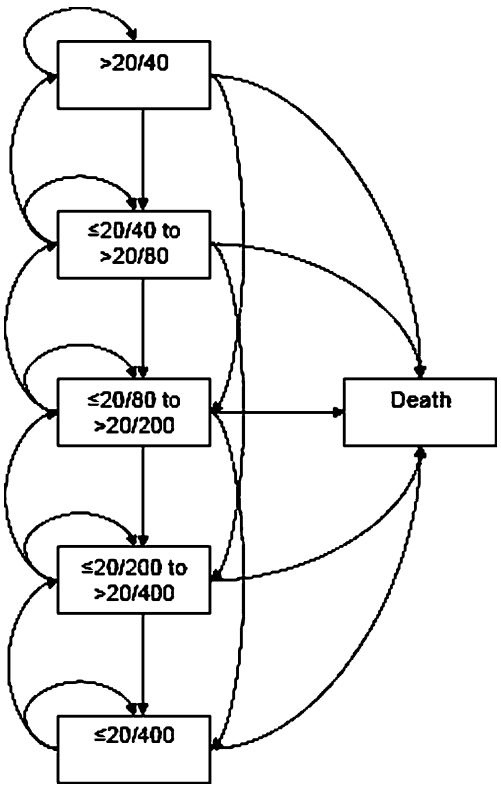

Fig. 1 Markov model with five sates defined by visual acuity in the better-seeing eye, and an additional death state. *Arrows* indicate allowed transitions

receiving sham injections. VA improved by 15 or more letters in 33.8% of parients, as compared with 5.0% in the sham-injection group [6]. Transition probabilities between VA states for patients treated with pegaptanib were obtained from the VISION trial [4]. In this trial, a loss of fewer than 15 letters of VA during the first year was observed in 70% of patients in the pegaptanib group, as compared with 55.4% of those in the sham injection group. Of the patients in the pegaptanib group, 9.5% had severe vision loss (i.e. 30 letters or more), as compared with 21.9% of those in the sham-injection group. The transition probability matrix between VA states is shown in Table 1. These transitions were allowed provided that the patients were still alive at the beginning of each cycle. The transition probabilities to the "death" state were taken from Spanish life tables [20]. We selected a 3-month cycle length for the model. One-year probabilities obtained from clinical trials [4, 6] were transformed into 3-month probabilities with the formula $p=1–e^{-rt}$ [21]. The model was constructed and solved with the TreeAge Pro Suite 2008 software package (TreeAge Software, Williamstown, MA, USA).

Perspective and costs

We conducted this study from the societal perspective in a Spanish setting. Costs are presented in 2008 Euro (€). We took into account the following costs: direct medical costs related to AMD treatment and follow-up (i.e. drugs, physicians' honoraries, diagnostic procedures, adverse reactions, vision rehabilitation related costs and vision-enhancing equipment related costs), direct medical costs related to AMD comorbidities (i.e. fall/accidents, depression/anxiety and other conditions requiring medical treatment) and non-medical-related costs (i.e. assistance from paid professionals for daily activities and social benefits received for visual disabilities).

Medical costs related to AMD comorbidities and non-medical-related costs were obtained from a multi-country, cross-sectional, observational study in which information was gathered directly from patients with bilateral AMD and compared to control subjects [22]. Patients from Canada, France, Germany, Spain and the United Kingdom participated in this study. Demographic and clinical characteristics of the surveyed population were similar among countries. Mean age varied between 76.2 years in Spain and 79.6 years in the United Kingdom. Caucasians represented 97.7% to 100% of the patients. Mean best corrected VA (logMAR) in the better-seeing eye varied from 0.59 in Germany to 0.66 in Spain. Mean number of co-morbid diseases varied from 1.8 in France to 3.7 in Germany [22].

With regard to medical costs related to AMD treatment, unit costs for physician consultations and diagnostic procedures were obtained from the previous study [22]. Resource use was determined by a retina specialist. To calculate drug costs, ranibizumab and pegaptanib vial prices were taken from the Spanish Council of Pharmacists database, and then multiplied according to the number of injections performed in the MARINA [6] and VISION [4] trials. Costs derived from adverse reactions were calculated by multiplying endophthalmitis, lens damage and retinal detachment trial rates [4, 6] by the cost of the diagnosis-related group in Spain [23]. We also included mean annual per-patient vision rehabilitation related costs and vision-enhancing related costs which accounted for €69 and €211 respectively [22]. Table 2 depicts direct medical costs as previously described.

Table 1 Three-month transition probabilities between visual acuity states for ranibizumab and pegaptanib

Ranibizumab					
Visual acuity	>20/40	≤20/40 to >20/80	≤20/80 to >20/200	≤20/200 to >20/400	≤20/400
To					
>20/40	0.9863	0.0979	0	0	0
≤20/40 to >20/80	0.0107	0.8884	0.0979	0	0
≤20/80 to >20/200	0.0030	0.0107	0.8884	0.0979	0
≤20/200 to >20/400	0	0.0030	0.0107	0.8884	0.0979
≤20/400	0	0	0.0030	0.0137	0.9021
Pegaptanib					
Visual acuity	>20/40	≤20/40 to >20/80	≤20/80 to >20/200	≤20/200 to >20/400	≤20/400
To					
>20/40	0.9199	0.0153	0	0	0
≤20/40 to >20/80	0.0542	0.9046	0.0153	0	0
≤20/80 to >20/200	0.0259	0.0542	0.9046	0.0153	0
≤20/200 to >20/400	0	0.0259	0.0542	0.9046	0.0153
≤20/400	0	0	0.0259	0.0801	0.9847

Table 2 Direct medical costs related to AMD treatment and follow-up (€ 2008) for ranibizumab and pegaptanib

	Unit cost[a] mean (SD)	Annual resource use[b]	
		Ranibizumab	Pegaptanib
Retina specialist consultation	112 (24)	12 (6–18)	8 (4–12)
Fundus photography	20(4)	12 (6–18)	8 (4–12)
Optical coherence tomography	149 (30)	6 (3–9)	4 (2–8)
Flurescein angiography	42 (8)	2 (1–3)	2 (1–3)
Ranibizumab vial	1,038 (208)	12[c]	-
Pegaptanib vial	697 (139)	-	8
Adverse reactions[d]			
-endophthalmitis	3,156 (631)	0.006	0.0128
-lens damage	1,600 (320)	0.004	0.006
-retinal detachtment	3,702 (740)	0.004	0.007

[a] Unit costs were obtained from an observational study [22] and inflated to €2008 with Spanish health care indices [24]. Unit costs for drug vials were obtained from the Spanish Council of Pharmacists Database. Ranibizumab and pegaptanib are 100% reimbursed by the Spanish National Health System. SDs were selected to produce variation coefficients of 20%.

[b] The number of follow-up consultations and diagnostic procedures per patient/year were determined by a retina ophthalmologist. In parenthesis, we provide the range of values tested in the probabilistic sensitivity analysis. The number of drug injections and adverse reactions per patient/year were obtained from the MARINA and VISION trials.

[c] The number of per-year ranibizumab injections was tested in the sensitivity analysis.

[d] Unit costs for the diagnosis-related group in Spain were obtained from the Spanish Health Ministry, http://www.msc.es/, accesed 23rd december 2008).

SD: standard deviation.

Table 3 Medical costs related to AMD comorbidities and non-medical costs [22]

Cost component	Unit cost (€ 2008)
Medical costs related to AMD comorbidities	
Fall-related treatment (average cost per visit)	
Hospital emergency room	122
Primary care physician office	21
Specialists	32
Hospitalization	4,302
Mean annual cost per patient	**170**
Treatment for depression/anxiety	
Prescription medications (average cost per month)	20
Primary care physician (average cost per visit)	21
Psychiatrist (average cost per visit)	70
Other specialist (average cost per visit)	94
Mean annual cost per patient	**115**
Other medical treatment(average cost per visit)	
Hospital emergency room	122
Primary care physician office	21
Specialists	32
Hospitalization	1,093
Mean annual cost per patient	**486**
Non-medical costs	
Profesional fee for homecare (mean annual cost per patient)	**970**
Societal benefits recieved for visual disability (mean annual cost per patient)	**607**

Medical costs were inflated to 2008 Euro with specific healthcare price indices. Non-medical costs were inflated with general consumer price indices [24]. AMD: age-related macular degeneration.

Components of direct medical costs related to AMD comorbidities and non-medical costs are depicted in Table 3. Total mean annual costs per patient were estimated to be €771 and €1,577 respectively. These costs were compared across VA levels in the better-seeing eye, and observed differences did not reach statistical significance, [22] thus we used the same figure for each VA state in the model.

Indirect costs (i.e. costs related to productivity loss) were not included in the base-case analysis. However, it is unlikely that many people of this age are employed. The impact of including indirect costs derived from productivity loss by family members is explored in the sensitivity analysis.

Health care costs (2005 Euro) were inflated to 2008 Euro with specific Spanish health care price indices. Non-medical costs were inflated with general consumer price indices [24].

Time horizon

The time horizon is the period over which costs and benefits for both alternatives are taken into account. The duration of ranibizumab therapy is not restricted to 2 years, which is the follow-up duration of both the MARINA [6] and the VISION [4] trials. Thus, we selected a life-expectancy time horizon in the base-case analysis. We explored several approaches for extrapolating clinical trial data over the entire lifetime horizon. In the reference case, patients started treatment at the age of 74 years old; the mean age at diagnosis was obtained from a Spanish study [19]. Survival probabilities according to patient's age were obtained from Spanish life tables [20]. This approach allowed for variability in life expectancy.

Utilities

Medical interventions improve either survival, quality of life, or both. Ophthalmologic treatments directed towards AMD improve quality of life by means of improving VA. Cost-utility analyses are economic evaluations in which quality of life is taken into account. The Quality Adjusted Life Year (QALY) is usually the health outcome measure used in cost-utility analyses. QALYs are calculated by multipliying years spent in a certain health state by a factor—utility—that quantifies preference for that health state. By convention, utilities vary from 1.0 (perfect health) to 0.0 (death). The better the quality of life, the closer the value is to 1.0. Several techniques for obtaining individuals' preferences for health outcomes are available. Individuals' preferences can be directly measured using rating techniques like the visual analogue scale, or choice-based instruments, such as the *standard gamble* and the *time trade-off*. The measurement task with these instruments is complex, and may be time- consuming. The measurement task can be bypassed using a pre-scored multiattribute health-status classification system. Among the general health systems most widely used are the Health Utilities Index (HUI) or the Short Form 6D (SF-6D). Detailed explanations of these methods are available elsewere [25]. However, it is important to remark that the choice of one method over another has an impact on the health utilities obtained. Thus, in economic evaluations it is important to mention the chosen instrument, and perform sensitivity analysis when different data are available. In this study, we used published utilities obtained from a cohort of AMD patients with the time trade-off methodology (Table 4). Utilities correlated with VA in the better-seeing eye [26].

Discount

Future costs and health gains are weighted in economic evaluations in relation to the time at which they occur. Future costs and effects are given less weight than present ones. In order to obtain the net present value of future costs and health outcomes accruing over the entire time horizon, a discounting rate of 3.5% was applied to both, as recommended by the National Institute for Clinical Excellence guidelines [27].

Table 4 Utilities for each visual acuity state

Visual acuity	Time trade-off	Standard gamble
>20/40	0.89 (0.82–0.96)	0.96 (0.92–1.0)
≤20/40 to >20/80	0.81 (0.73–0.89)	0.88 (0.83–0.93)
≤20/80 to >20/200	0.57 (0.47–0.67)	0.69 (0.52–0.86)
≤20/200 to >20/400	0.52 (0.38–0.66)	0.71 (0.57–0.85)
≤20/400	0.40 (0.29–0.50)	0.55 (0.36–0.74)

Utilities according to visual acuity in the better-seeing eye obtained in a cohort of 72 patients with age-related macular degeneration [26].

Sensitivity analysis

Uncertainty in decision analytical modelling is handled by sensitivity analysis. In this kind of analysis, alternative scenarios regarding structural assumptions or unknown parameters in the model are explored. Parameter uncertainty was addressed by probabilistic sensitivity analysis, in which parameters in the model are sampled from specified ranges and distributions. This approach allows parameter uncertainty to be simultaneously reflected in the results of the model [28]. The following parameters were included in the probabilistic sensitivity analysis: costs, transition probabilities, VA state utilities assigned by patients and resource use (i.e. number of fundus photography, optical coherence tomography, fluorescein angiography, and ophthalmologist consultations). Probability distributions were chosen for each parameter according to published recommendations [28]. For transition probabilities (Table 1) and patients' utilities (Table 4), which range from 0 to 1, we selected a beta distribution. The parameters α and β in the beta distributions were approximated using mean and standard deviation (SD) values obtained from the MARINA trial [6] and published utilities [26]. A gamma distribution, which is positively skewed, was selected for costs. In order to account for variability in costs, we selected SDs that produced variation coeficients of 20% for unit costs of diagnostic procedures and consultations (Table 2), as well as costs related to AMD comorbidities and non-medical costs (Table 3) [22]. A uniform distribution was selected for resource use (Table 2).

As mentioned earlier, we explored several approaches for extrapolation beyond the 2-year follow-up duration of clinical trials [4, 6]. Under the '*continuous treatment effect*' approach selected for the reference case, both treatments are performed, each with efficacy lasting over the whole time horizon [21]. This approach was selected on the basis of the disease-modifying effect observed for pegaptanib [29]. In addition to the '*continuous treatment effect*' approach, we tested both a '*one-time benefit*' approach and a '*rebound*' or ''*catch-up*' approach [21]. Under the '*one-time benefit*' approach, both treatments stop after 2 years. From then on, patients' quality of life declines at the same rate for both drugs. Additional QALYs are therefore gained by projecting the area under the curve over a longer period. Under the '*rebound*' approach, we assumed that benefit obtained with ranibizumab is lost 3 years after stopping treatment.

On the other hand, we also explored costs and health outcomes in the shorter 2-year time horizon. This short-time horizon represents a worst-case scenario for ranibizumab because clinical benefit is assumed to last for 2 years only.

We performed a sensitivity analysis using the number of administrations from the Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intraocular Ranibizumab (PrONTO) trial [30]. Contrary to the fixed monthly dosing schedule used in the MARINA trial [6], in the PrONTO trial [30] a variable dosing regimen was used. After three consecutive monthly intravitreal injections, further retreatment was performed on an "as needed" basis. In the MARINA [6] trial, 94.6% of patients did not lose more than 15 letters of VA at 12 months with monthly ranibizumab. In the PrONTO trial, 95.0% of patients achieved the same outcome at 12 months with a mean of 5.6 injections [30]. Ranibizumab efficacy was mantained throughout the second year of the PrONTO trial with 4.3 injections [31].

We also undertook sensitivity analyses on the cohort's starting age and VA, the chosen method for utility elicitation used for QALYs calculations (Table 4), the discounting rate and the cycle length.

We also explored the impact of including indirect costs derived from family members' time to assist patients [22].

Finally, we used efficacy data from a study of naïve AMD patients who underwent treatment with pegaptanib [32] and for whom greater efficacy was observed compared to the VISION trial [4].

Model validation

Thorough internal testing of the model was performed, and the expected outcomes were obtained when different input values were used. The model could not be calibrated against external data, due to the absence of data over the time frame being modelled. Indeed, we explored different assumptions in the sensitivity analyses to model long-term effectiveness data. The model is available upon request to the authors.

Outcomes

Costs (Euro 2008), health outcomes (QALYs) for both ranibizumab and pegaptanib, and incremental cost-effectiveness ratios (ICER; €/QALY) were obtained for the base-case analysis and for those alternative scenarios considered in the sensitivity analyses.

Results

In the base-case analysis (Table 5), treating patients with minimally classic/occult CNV secondary to AMD with monthly ranibizumab instead of pegaptanib is €71,206 more expensive, and provides 2.437 more QALYs in the lifetime horizon, thus providing an ICER of €29,224/QALY. According to the probabilistic sensitivity analysis, ranibizumab was the therapy of choice in 54% of cases below the threshold of €30,000/QALY in the lifetime horizon (Fig. 2). Alternative sensitivity analyses results are depicted in Table 6. We also provide a tornado plot (Fig. 3) to allow the reader to intuitively assess those factors with greater impact in the incremental cost-effectiveness ratio.

Table 5 Results for the reference case

	Cost (€)	Incremental cost (€)	Efficacy (QALYs)	Incremental efficacy (QALYs)	ICER (€/QALY)
Pegaptanib	93,664	-	4.474	-	-
Ranibizumab	164,870	71,206	6.911	2.437	29,224

ICER: incremental cost-effectiveness ratio. QALY: quality-adjusted life year.

Costs are presented in 2008 Euro.

Discussion

The dilemma of whether or not to adopt a new drug has a simple answer if it produces more health gain than the competing alternatives at a lower cost. On the contrary, if the new drug is more effective but more expensive than the competing alternatives, clinicians and decision makers have to study whether the new drug provides "good value for money". We constructed a Markov model with five states defined by VA in the better-seeing eye and an additional death state, and we compared two antiangiogenic drugs, ranibizumab and pegaptanib, in terms of costs and health outcomes (QALYs) over a lifetime horizon. In a context of limited healthcare resources, the cost per extra unit of effect

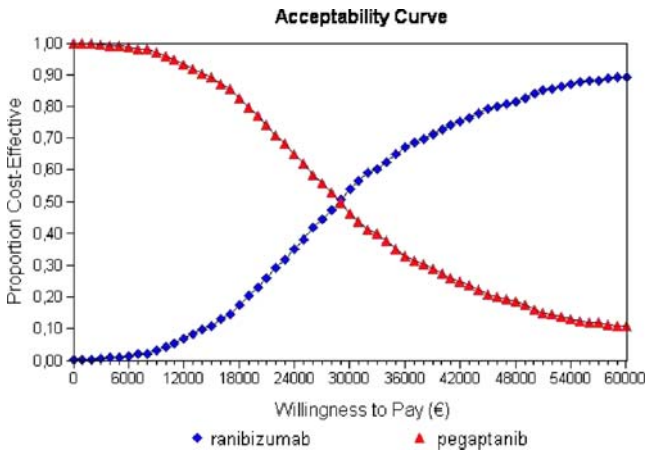

Fig. 2 Acceptability curve obtained with probabilistic sensitivity analysis in the lifetime horizon. Below the €30,000/QALY, monthly ranibizumab is the therapy of choice in 54% of cases

Table 6 Results of the sensitivity analysis

Parameter/variable	ICER
Reference case	29,224
No extrapolation (2-year time horizon)	119,953
Extrapolation beyond 2 years	
One-time benefit approach	32,795
Rebound approach	52,031
Injections taken from the PrONTO trial[a]	4,623
2-year time horizon	20,472
Efficacy for pegaptanib from naive patients[b]	14,302
Starting age	
58 years[c]	24,553
90 years	51,798
Starting VA stage	
>20/40	33,653
≤20/40 to >20/80	27,855
≤20/80 to >20/200	26,268
≤20/200 to >20/400	29,874
≤20/400	36,372
Method for utility elicitation[d]	36,186
Discounting rate	
0%	26,990
5%	30,247
One-year cycle length	30,642
Including indirect costs derived from family members' time to assist patients	26,900
Efficacy for pegaptanib from naive patients[b]	85,300

ICER (€/QALY): incremental cost-effectiveness ratio. SA: sensitivity analysis. VA: visual acuity.

[a] According to the prospective optical coherence tomography imaging of patients with neovascular AMD treated with intra-ocular ranibizumab (PrONTO) trial, we took 5.6 injections for the first year [30] and 4.3 for the second [31] and subsequent years.

[b] Efficacy rates taken from a case-series study of age related macular degeneration patients naïve to treatment [32].

[c] Productivity costs were not included in the sensitivity analysis, as they were not included in the base-case analysis either. A better outcome for ranibizumab would be expected if these costs were included in the younger population.

[d] Cost per QALY when utilities are obtained with the standard gamble method instead of the time trade-off [26].

(ICER) is obtained, and referred to a threshold below which the studied intervention is regarded as "cost-effective". Although these thresholds have been criticized [33], published economic evaluations generally use them to tag a new drug as "cost-effective" or "not cost-effective" [34]. These thresholds implicitly represent the health gain forgone when one drug is discarded in favour of the competing intervention, in other words, the opportunity cost of choosing a drug over another. Our analyses show that the cost per QALY gained with monthly ranibizumab in a lifetime horizon is €29,224, just below the €30,000/QALY threshold recommended [35] in Spain. This outcome, however, is sensitive to alternative scenarios explored in the sensitivity analyses. Sensitivity analyses are used to explore the impact of alternative scenarios and uncertainty in model parameters on the cost-effectiveness results. We handled parameter uncertainty by probabilistic sensitivity analysis [28]. According to this analysis, ranibizumab was the therapy of choice in 54% of cases below the threshold of €30,000/QALY in the lifetime horizon (Fig. 2). In addition to probabilistic sensitivity analysis, we performed several univariant and bivariant sensitivity analyses relevant to the clinician. According to these analyses, the factor with greatest impact on the cost-effectiveness results is the chosen time horizon (Fig. 3). We obtained an ICER of €119,953/QALY in a 2-year time horizon, which is the duration of available clinical trials [4, 6]. Duration of ranibizumab therapy is not restricted to 2 years. Thus we analyzed costs and outcomes over a lifetime horizon. We explored several approaches for extrapolating data from clinical trials over the lifetime horizon. In the reference case we tested the '*continuous treatment effect*' approach, under which both treatments are administered, with efficacy lasting for both, over the entire time horizon [21].

This scenario, however, may be too optimistic. Thus, in the sensitivity analysis we tested both a '*one-time benefit*' approach and a '*rebound*' or '*catch-up*' approach [21]. The '*one-time benefit*' scenario, provided an ICER of €32,796/QALY (Table 6). On the other hand we explored an alternative scenario—'*rebound approach*'—in which we assumed that clinical benefit obtained with ranibizumab is lost 3 years after stopping treatment. Under this scenario the cost per QALY rises to €52,031 (Table 6).

A dosing strategy similar to that used in the PrONTO trial [30] has been adopted by ophthalmologists in routine clinical practice [36]. In the PrONTO trial, [30] after a loading phase of three consecutive monthly injections, subsequent injections were performed on an "as needed" basis based on monthly OCT assessment. Similar efficacy to that observed in the MARINA trial [6] was achieved. The PrONTO trial [30] is a well-conducted prospective study, but lack of randomization and comparison with a control group make the results less reliable than those observed in the MARINA trial [6]. However, if we assume that VA gains observed in the MARINA trial [6] can be achieved following the PrONTO trial protocol [30], an ICER of €4,623/QALY is obtained. We undertook threshold sensitivity analysis on the number of ranibizumab injections needed to surpass the €30,000/QALY threshold in the shorter 2-year time horizon, and obtained the number of 6.4 injections per year. This means that even in a short

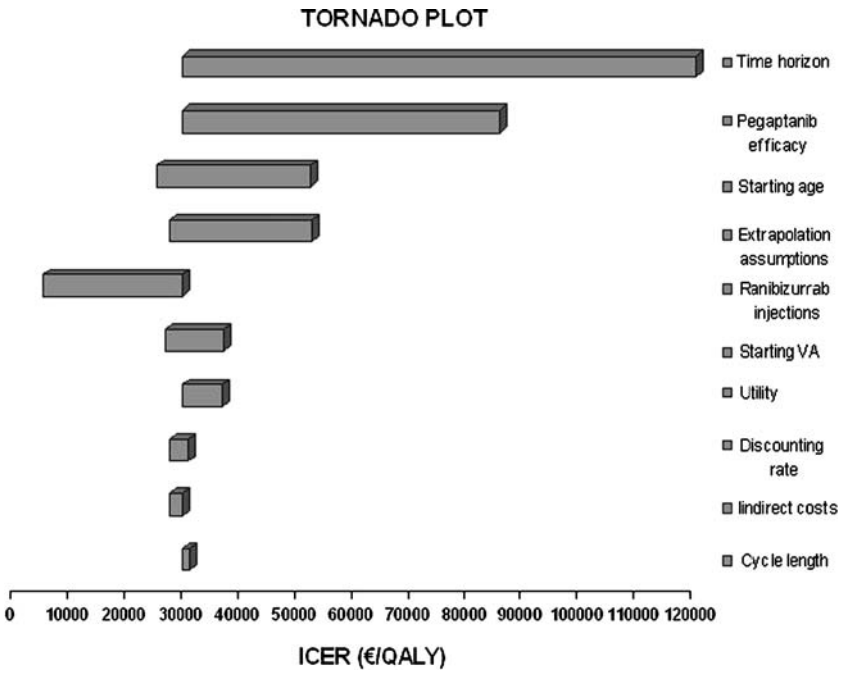

Fig. 3 Tornado plot. The time horizon and the chosen extrapolation method, the source for pegaptanib efficacy, and the number or ranibizumab injections are the key model drivers, with greater impact on the cost-effectiveness results

time horizon ranibizumab is a cost-effective strategy, provided the number of intravitreal injections is below 6.4 injections per year.

In the reference case, we selected the starting age of 74 years for patients who entered the model. This was the mean age at diagnosis in a Spanish study [19]. We performed sensitivity analysis taking the upper and lower limits of the 95% confidence interval for this variable [19]. When patients started at the age of 58 years, we obtained an ICER of €24,553/QALY in the lifetime horizon. When patients started at the age of 90 years, the ICER rose to €51,798/QALY, also in the longer lifetime horizon (Table 6). This difference can be attributed to the shorter life expectancy of older patients, for whom VA improvement with ranibizumab lasts over fewer years.

We also explored the impact of the degree of initial VA loss on the cost-effectiveness results. Compared to the reference case, the cost per QALY rose when the cohort started with a VA better than 20/40, probably because patients cannot improve their vision from this state. When the cohort started at the lower VA state (VA ≤20/400), ICERs rose as well, probably because fewer patients were able to reach those states with better VA and utility values. Initial VA states with corresponding ICERs are shown in Table 6.

The method for utility elicitation had an impact on the cost-effectiveness results. In the study by Brown et al. [26] from which we took utilities, patients' preferences for the same VA state were higher when obtained by the standard gamble method compared to the time tradeoff method (Table 4). We explored how the choice of one method over the other influenced the cost-effectiveness results, and we found greater ICERs with utilities obtained by the standard gamble method.

Study limitations

A limitation of this study is that the efficacy data for ranbizumab and pegaptanib involved different populations. In contrast to the MARINA trial [6], in which patients were presumed to have a recent progresion of the disease, in the VISION trial [4] all lesions including blood, scar or atrophy up to 12 optic-disk areas were included. Although differences in efficacy between the two drugs should be attributed to their distinct mecanism of action (i.e. ranibizumab is a pan VEGF-A blocker, whereas pegaptanib selectively inhibits the $VEGF_{165}$ isoform [37]), the poor prognosis of lesions included in the VISION trial [4] may also have been a contributing factor [32]. Indirect comparisons are potentially subject to methodological flaws, mainly due to populations differences among trials [38]. To account for these differences, we performed a sensitivity analysis in which we used improved pegaptanib efficacy rates obtained from a study of AMD patients naïve to treatment [32]. As expected, in this case the ICER rose to €85,300/QALY. In the absence of a head-to-head trial between ranibizumab and pegaptanib, there is the potential for some degree of bias when comparing both drugs.

We conducted this study from the second-eye, or better-seeing eye perspective. From this perspective, both treatments are applied to the eye which has the greatest impact on patients' quality of life [26]. If treatments are applied to the worst-seeing eye, overall VA may not

improve in many cases. This second-eye perspective, however, is common in clinical practice. CNV develops in the contralateral eye in ≥87% of patients with AMD over 5 years if ≥4 risk factors are present [2]. Moreover, vision loss in the first eye may be secondary to diseases other than AMD. We believe this approach does not bias results, because the better-case scenario is applied to both ranibizumab and pegaptanib.

We obtained costs related to AMD comorbidities and non-medical costs from a multicountry, cross-sectional, observational study in which information was gathered directly from patients with bilateral AMD [22]. Given the age of the study population, recall bias may have led to under-reporting of medical resource utilization. Additionally, this study did not include nursing-home patients. As a result, costs derived from VA loss may be underestimated. If all these costs were taken into account, the disease burden would increase, and a more favourable result for ranibizumab (i.e. a lower ICER), would be obtained.

As we mentioned, bevacizumab was not the chosen comparator in this study. Randomized controlled trials comparing ranibizumab and bevacizumab are ongoing [14], but results are not yet available. It is not difficult, however, to obtain conclusions in the absence of randomized controlled trial data. Raftery et al. found that the efficacy of ranibizumab in relation to bevacizumab would have to be around 2.5 times greater to be regarded as a cost-effective strategy [39].

In the present study, we examined the cost-effectiveness of ranibizumab compared to pegaptanib in the minimally classic/occult neovascular AMD population from the societal perspective. In a lifetime horizon, we obtained an ICER of €29,224/QALY, which is just below the €30,000/QALY threshold recommended [35] in Spain. This ICER was sensitive to alternative scenarios, mainly the selected time horizon and the chosen extrapolation method, the source for pegaptanib efficacy and the number of ranibizumab injections. When administered on an as-needed basis, as in the PrONTO trial, [30] ranibizumab was consistently cost-effective.

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