Cost-Effectiveness of Ranibizumab Compared with Photodynamic Treatment of Neovascular Age-Related Macular Degeneration

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ABSTRACT

Objective: This study compared the cost-effectiveness of ranibizumab with that of photodynamic therapy (PDT) in the treatment of predominantly classic choroidal neovascularization secondary to age-related macular degeneration (AMD) from the perspective of a third-party payer in a Spanish setting.

Methods: We constructed a Markov model with 5 states defined by visual acuity (VA) in the better-seeing eye (Snellen scale), as follows: VA >20/40, ≤20/40 to >20/80, ≤20/80 to >20/200, ≤20/200 to >20/400, and ≤20/400. A death state was also included. We took transition probabilities, number of ranibizumab injections, and number of PDT treatments from the ANCHOR (Anti–Vascular Endothelial Growth Factor Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration) trial. Utilities were taken from a published study of patients' preferences. We used unit costs from our hospital and drug costs from a national database. Resource utilization was determined by an ophthalmologist according to current clinical practice. We performed univariate, threshold, and probabilistic sensitivity analyses. Incremental costs (2007 €) and quality-adjusted life-years (QALYs), both discounted at a 3% annual rate, and incremental cost-effectiveness ratios (ICERs; €/QALY) were determined for the 2-year and life-expectancy time horizons.

Results: Treating patients with varying degrees of visual impairment with ranibizumab instead of PDT, with a 2-year time horizon, was found to be €18,328 more costly and to confer 0.140 additional QALY (€131,275/QALY). This ICER was reduced to €39,398/QALY for the longer life-expectancy time horizon. According to the probabilistic sensitivity analysis, PDT is the therapy of choice in all cases below the threshold of €30,000/QALY for the 2-year time horizon. Ranibizumab was the optimal intervention in 26% of cases in the longer lifetime horizon. When the initial VA was ≤20/400, the ICER increased to €255,477 over 2 years. When ranibizumab was administered on an as-needed basis, as in the PrONTO (Prospective Optical coherence tomography imaging of patients with Neovascular AMD Treated with intra-Ocular ranibizumab) trial, the ICERs were reduced to €29,566/QALY and €11,469/QALY in the 2-year and life-expectancy horizons, respectively.

Conclusions: Based on these results, ranibizumab was not cost-effective when administered on a monthly basis. When administered as needed, ranibizumab was cost-effective compared with PDT for the treatment of AMD. (*Clin Ther.* 2008;30:2436–2451) © 2008 Excerpta Medica Inc.

Key words: age-related macular degeneration, ranibizumab, photodynamic therapy, cost-effectiveness, cost utility.

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, and its incidence is increasing because of the aging population.[1]

There are 2 forms of AMD: dry/atrophic and wet/exudative/neovascular. The former is more prevalent, but the latter has a poorer prognosis and has been associated with the majority of patients with legal blind-

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ness as a result of AMD.[2] In the dry form of the disease, photoreceptors are lost in certain areas of the retinal pigment epithelium, causing gaps in vision. The wet form is characterized by choroidal neovascularization (CNV) and vascular leakage, causing serous or hemorrhagic fluid collections beneath the retina. Fibrogenesis eventually leads to the loss of visual acuity (VA).[3]

CNV can be classified by findings on angiographic fluorescein examination. CNV is considered *predominantly classic* when ≥50% of the lesions have the classic pattern (neovascular membranes clearly delineated on angiography), *minimally classic* when <50% have the classic pattern, or *occult* when there is no classic neovascularization. The location of CNV with respect to the macula is classified as *subfoveal, juxtafoveal,* or *extrafoveal.*

Approved treatments for neovascular AMD include verteporfin photodynamic therapy (PDT), intravitreal ranibizumab, and intravitreal pegaptanib sodium. Intravitreal bevacizumab and triamcinolone acetonide are currently prescribed, but not approved, for this indication. Before the development of the antiangiogenic drugs ranibizumab and pegaptanib, PDT was considered the "gold standard" for treating classic CNV secondary to AMD.[4,5] Ranibizumab is the Fab fragment of a humanized murine monoclonal antibody that blocks the angiogenic properties of vascular endothelial growth factor (VEGF). Intravitreal administration of ranibizumab has been associated with improvements in VA in Phase III randomized controlled trials (RCTs) in patients with AMD, regardless of the CNV subtype.[6–9] However, ranibizumab is more expensive than other therapies.

This cost-utility analysis compared ranibizumab with PDT in patients with predominantly classic CNV secondary to AMD. A cost-utility analysis was chosen to include the quality-of-life losses caused by AMD.

MATERIALS AND METHODS

Model Structure

A Markov model was constructed with 5 states, defined as a VA in the better-seeing eye (Snellen scale), as follows: >20/40, ≤20/40 to >20/80, ≤20/80 to >20/200, ≤20/200 to >20/400, and ≤20/400.[10] The Snellen scale is the most widely adopted tool for VA assessment and is the primary method of VA measurement in clinical settings.[10] A "death" state was also included. The model scheme with allowed transitions is illustrated in **Figure 1.**

Cohort simulation was used to run the model. The starting cohort was distributed along the 5 VA states according to data from Spanish patients.[11] One-year cycles were defined to allow easy input of transition probabilities from the clinical trials. Half-cycle correction was applied to obtain precise results. The model was constructed and solved using Pro Suite 2008 (TreeAge Software, Inc., Williamstown, Massachusetts).

Perspective

This study was conducted from the perspective of a third-party payer in a Spanish setting. Costs are presented in 2007 euros. Detailed information about unit costs and resource utilization is provided later in this article.

Number of Treatments and Transition Probabilities

Several systematic reviews of ranibizumab[12,13] and PDT[14,15] have been published. With respect to ranibizumab, 4 RCTs have been published: MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration),[6] ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration),[7] FOCUS (RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety),[8] and PIER (Study of the Efficacy and Safety of Ranibizumab in Subjects With Subfoveal Choroidal Neovascularization [CNV] With or Without Classic CNV Secondary to Age-Related Macular Degeneration).[9] ANCHOR was the only trial that compared the efficacy of ranibizumab monotherapy with that of PDT in patients with AMD.[7] In that trial, intravitreal ranibizumab was administered once per month, and PDT was administered on the basis of the investigators' evaluation of angiography every 3 months. A total of 96% of patients who received ranibizumab 0.5 mg lost <15 letters of VA compared with 64% of those in the verteporfin PDT group. VA improved by ≥15 letters in 40% of patients in the ranibizumab 0.5-mg group, compared with 5% of those in the PDT group.[7] The transition probabilities between VA states used in the Markov model were taken from 1-year efficacy results from the ANCHOR trial.[7] The transition probability matrix between VA states is shown in **Table I.** These transitions were allowed provided that the patients were still alive at the beginning of each cycle. The transition probabilities

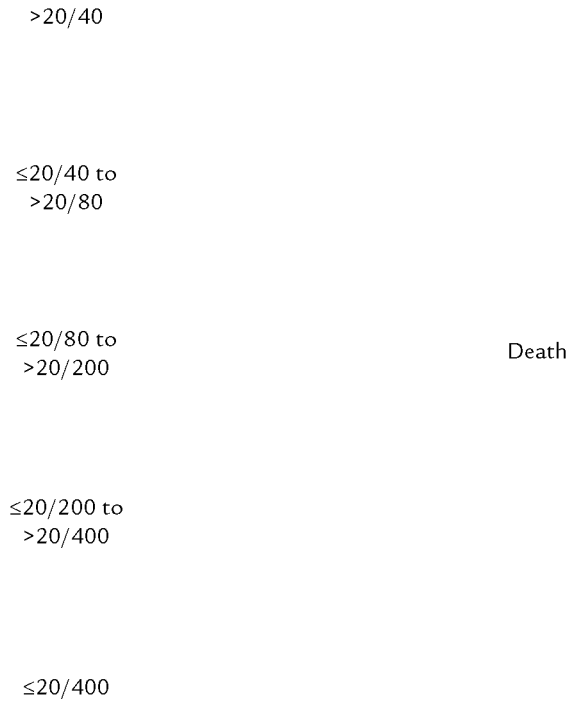

Figure 1. Markov model with 5 states defined by visual acuity in the better-seeing eye and a death state. Arrows indicate allowed transitions. Death is the absorbing state.

to the death state were taken from Spanish life tables.[16]

Time Horizons

In the base-case analysis, we selected a time horizon of 2 years—the duration of the ANCHOR trial.[7,17] This time horizon was associated with a low degree of uncertainty because no extrapolation of efficacy data was made. However, the duration of ranibizumab treatment is not restricted to 2 years in clinical practice, and this time horizon was probably not sufficient for including all of the relevant differences between the 2 treatments. Therefore, we also studied the cost-effectiveness of ranibizumab over a life-expectancy time horizon. In the reference case, treatment was started at age 74 years—the mean age at diagnosis obtained from a Spanish study[11] and it is similar to the mean age of 76 to 77 years reported in the ANCHOR trial. Survival probabilities according to patient's age were obtained from Spanish life tables.[16] This approach allowed for variability in life expectancy.

Several approaches have been proposed for efficacy extrapolation beyond the duration of a clinical trial. These approaches include the *one-time benefit approach*, in which clinical efficacy stops at the maximum clinical trial follow-up, and the *continuous treatment effect approach*, in which the efficacy of treatments lasts over the entire time horizon.[18]

In the ANCHOR trial, 96% of patients in the first year[7] and 90% of those in the second year[17] lost <15 letters of VA, the primary outcome. Of those assigned to PDT, 64% and 66% achieved the primary outcome in the first[7] and second[17] years, respectively.

With respect to PDT, we have further data from the TAP (Treatment of Age-Related Macular Degeneration with Photodynamic Therapy) trial,[19,20] which compared the efficacy of PDT and placebo over 2 years,

Table I. Transition probabilities for ranibizumab and photodynamic therapy.*

Visual Acuity	>20/40	≤20/40 to >20/80	≤20/80 to >20/200	≤20/200 to >20/400	≤20/400
To: (Ranibizumab)					
>20/40	0.964	0.403	0	0	0
≤20/40 to >20/80	0.036	0.561	0.403	0	0
≤20/80 to >20/200	0	0.036	0.561	0.403	0
≤20/200 to >20/400	0	0	0.036	0.561	0.403
≤20/400	0	0	0	0.036	0.597
To: (Photodynamic therapy)					
>20/40	0.643	0.056	0	0	0
≤20/40 to >20/80	0.224	0.587	0.056	0	0
≤20/80 to >20/200	0.133	0.224	0.587	0.056	0
≤20/200 to >20/400	0	0.133	0.224	0.587	0.056
≤20/400	0	0	0.133	0.357	0.944

*These transitions were allowed provided that patients were alive at the beginning of each cycle.

with an unmasked extension over 3 additional years. In the cohort with predominantly classic CNV initially assigned to receive PDT, 66% of patients at 24 months and 65% at 60 months lost <15 letters of VA. Although the differences might have been underestimated, PDT efficacy lasted over the entire trial, with a very low repeat treatment rate.[20]

On the basis of these data, we selected a continuous treatment-effect approach for extrapolating data over the lifetime horizon in the reference case.

Costs

We conducted this study from the perspective of a third-party payer; therefore, only direct costs related to treatment and patient follow-up were included.

Unit costs were obtained from the hospital in which the authors are employed and reflect third-party payer fees. Drug costs were obtained from a national database. Follow-up consultations and diagnostic procedures, which are intended to reflect clinical practice, were determined by a retinal ophthalmologist.

Costs in the ranibizumab group included fluorescein angiography at the initial consultation for diagnosis and monthly consultation with optical coherence tomography (OCT). Ranibizumab was administered according to the ANCHOR trial protocol[7]—once per month.

Costs in the PDT group included ophthalmologic consultation, fluorescein angiography, and OCT every 3 months. Verteporfin vials and laser activation were prescribed when necessary, depending on the results of fluorescein angiography. In our case, the number of PDT treatments was taken from the ANCHOR trial: 2.8 treatments during the first year[7] and 1 additional treatment during the second and each subsequent year.[17] **Table II** shows the data on unit costs and resource utilization.

Utilities

Several studies have published utility values assigned by patients to several degrees of VA impairment. These studies[21–24] have demonstrated that utility values correlate with VA in the better-seeing eye regardless of the underlying cause of vision loss and that these values do not differ among patients by educational level, sex, age, or race. **Table III** illustrates the published utilities[22] used for the Markov model.

Discounting

We applied an annual discounting rate of 3% for both costs and utilities, as recommended by Drummond et al.[25]

Table II. Unit cost and resource use for the base-case analysis.*

Parameter	Unit Cost (SD), €	Ranibizumab First Year Resource Use	Ranibizumab First Year Cost, €	Ranibizumab Subsequent Years Resource Use	Ranibizumab Subsequent Years Cost, €	PDT First Year Resource Use	PDT First Year Cost, €	PDT Subsequent Years Resource Use	PDT Subsequent Years Cost, €
1st Consultation	210 (42)	1	210	0	0	1	210	0	0
Subsequent consultations	107 (21.4)	11	1177	12	1284	3	321	4	428
Verteporfin PDT									
Verteporfin vial	1218 (243.6)	0	0	0	0	2.8	3410	1	1218
Laser	1135 (227)	0	0	0	0	2.8	3178	1	1135
FA	230 (46)	1	230	0	0	4	920	4	920
OCT	180 (36)	12	2160	12	2160	4	720	4	720
Ranibizumab vial	1038 (207.7)	12	12,456	12	12,456	0	0	0	0
Yearly costs	–	–	16,233	–	15,900	–	8759	–	4421

PDT = photodynamic therapy; FA = fluorescein angiography; OCT = optical coherence tomography.
*Costs are not discounted (2007 values). Drug costs were taken from the Spanish Pharmacy College drug database. Procedures and consultation fees for third-party payers were obtained from the hospital in which the authors are employed. SDs were selected to produce variation coefficients of 20%. Mean numbers of drug administrations per year were taken from the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) trial.[7,17] Resource use was determined by an ophthalmologist according to current practice at the ophthalmology department in our hospital.

Table III. Utility values assigned to Markov states.*

Visual Acuity in the Better-Seeing Eye	Utility Value, Mean (95% CI)
>20/40	0.89 (0.82–0.96)
≤20/40 to >20/80	0.81 (0.73–0.89)
≤20/80 to >20/200	0.57 (0.47–0.67)
≤20/200 to >20/400	0.52 (0.38–0.66)
≤20/400	0.40 (0.29–0.50)

*Utility values according to visual acuity in the better-seeing eye as reported by patients with age-related macular degeneration using the time tradeoff method.[22]

Sensitivity Analyses

We conducted extensive sensitivity analyses to test the model's robustness. Parameter uncertainty was addressed by probabilistic sensitivity analysis.[26] The following parameters were included: unit costs, transition probabilities, and VA state values assigned by patients. Probability distributions were chosen for each parameter according to published recommendations.[26,27] For transition probabilities and patients' values, which ranged from 0 to 1, we selected a β distribution. The parameters α and β in the β distributions were approximated using TreeAge Pro Suite from mean and SE values obtained from the ANCHOR trial[7] and published utilities,[22] as follows: $\alpha = \text{mean}^2 \cdot (1 - \text{mean})/(\text{SE}^2)$; and $\beta = \text{mean} \cdot (1 - \text{mean})/(\text{SE}^2) - \alpha$. Gamma distributions were selected for unit costs. Parameters α and γ were approximated from mean costs and SDs provided in **Table II**, as follows: $\alpha = (\text{mean}^2)/$

(SE^2); and γ = mean/(SE^2). We obtained acceptability curves of the probabilistic sensitivity analysis for both time horizons.

We performed a univariate sensitivity analysis taking the number of ranibizumab administrations from the Prospective Optical coherence tomography imaging of patients with Neovascular AMD Treated with intra-Ocular ranibizumab (PrONTO) trial.[28] In the ANCHOR trial,[7] intravitreal ranibizumab was administered once per month, and PDT was administered on the basis of the investigators' evaluation of angiography, every 3 months. The PrONTO trial[28] was designed to evaluate the efficacy of ranibizumab with a regimen of 3 consecutive monthly intravitreal injections. Thereafter, repeat treatment was performed when 1 of the following changes was observed between visits: a loss of 5 letters of VA in conjunction with fluid in the macula as detected by OCT, an increase in OCT central retinal thickness, new-onset classic CNV, new macular hemorrhage, or persistent macular fluid detected by OCT ≥1 month after an injection of ranibizumab.

Although the number of injections differed between the ANCHOR[7] and PrONTO[28] studies, the VA outcomes were similar. In the ANCHOR trial, 96% of patients did not lose >15 letters of VA at 12 months with 12 injections[7]; this value was 95% in the PrONTO trial with 5.6 injections.[28] The 2-year outcomes for both studies had not been published at the time of writing but were presented at the American Academy of Ophthalmology meeting in November 2007.[17,29] In the PrONTO trial,[28,29] 9.9 intravitreal ranibizumab injections were administered over 24 months, and the efficacy was maintained during that period.

Interim results of the ongoing SUSTAIN (Study of Ranibizumab in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration) trial,[30] in which the ranibizumab dose is individualized after a loading phase of 3 consecutive monthly injections, were presented at the 2008 Annual Meeting of the Association for Research in Vision and Ophthalmology. In the 69 patients who were ranibizumab naive, the mean VA at month 12 was increased by ~7 letters, with a mean of 5.3 injections. These results provide further evidence that a VA gain may be achieved with fewer injections when ranibizumab dosing is individualized.

Conversely, reports of retinal specialists using as-needed dosing schedules have also been published.[31,32] Based on previously published data, we performed a univariate sensitivity analysis, taking the number of ranibizumab injections from the PrONTO trial.[28,29] A threshold sensitivity analysis on the number of ranibizumab injections needed to change the decision was also performed.

Regarding resource use, we believe that the reference case, in which OCTs are performed monthly, reflects a conservative scenario for ranibizumab. Less frequent consultations for reevaluation would yield lower treatment costs. However, we performed a univariate sensitivity analysis, taking into account 1 fluorescein angiography every 3 months, as in the PrONTO trial.[28]

We performed a univariate sensitivity analysis on the annual discounting rate with both 0% and 5% rates, and a sensitivity analysis on the cohort's starting age and VA. Finally, we tested the 1-time benefit approach for efficacy extrapolation beyond 2 years.

Outcomes

Incremental costs (2007 €) and quality-adjusted life-years (QALYs), both discounted at a 3% annual rate, and incremental cost-effectiveness ratios (ICERs; €/QALY) were determined for the 2-year and life-expectancy time horizons. Life-years gained are not depicted because no differences were noted with regard to mortality in ranibizumab clinical trials.[6–9]

RESULTS

Reference Case

Table IV depicts outcomes for the reference case.

Sensitivity Analyses

Acceptability curves resulting from our probabilistic sensitivity analysis for both time horizons are depicted in Figures 2 and 3. Results from the remaining sensitivity analysis are presented in Table V.

DISCUSSION

Cost-Effectiveness of PDT

Before conducting an economic evaluation, an analyst should determine whether the competing therapy is cost-effective. We conducted a systematic review of economic evaluations of PDT to examine its cost-effectiveness.

A total of 62 MEDLINE entries were retrieved using the terms *photodynamic therapy* and *cost-effectiveness*, without limits, in December 2007. After discarding those articles not related to AMD or PDT, economic

Table IV. Results for the reference case.*

Time Horizon	Cost, €	Incremental Cost, €	Efficacy, QALYs	Incremental Efficacy, QALYs	ICER, €/QALY
2 Years					
PDT	12,937	–	1.003	–	–
Ranibizumab	31,265	18,328	1.143	0.140	131,275
Lifetime					
PDT	49,721	–	4.522	–	–
Ranibizumab	163,588	113,867	7.412	2.890	39,398

QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; PDT = photodynamic therapy.
*Costs are given in 2007 €. Discounting rate of 3% was applied to both costs and QALYs.

evaluations not fulfilling the definition of Drummond et al[33] (ie, they did not compare at least 2 alternatives and analyze both costs and outcomes), and articles not written in English or Spanish, 6 cost-utility analyses[15,34–38] and 2 cost-effectiveness analyses[39,40] were selected. These studies are summarized in **Table VI.**

The time horizon had a major impact on the selected economic evaluations: ICERs were greater in those studies with shorter time horizons. For example, Sharma et al[34] used 2 time horizons, 2 years and 11 years, and the shorter time horizon led to a larger ICER because expenses were greater during the first years,

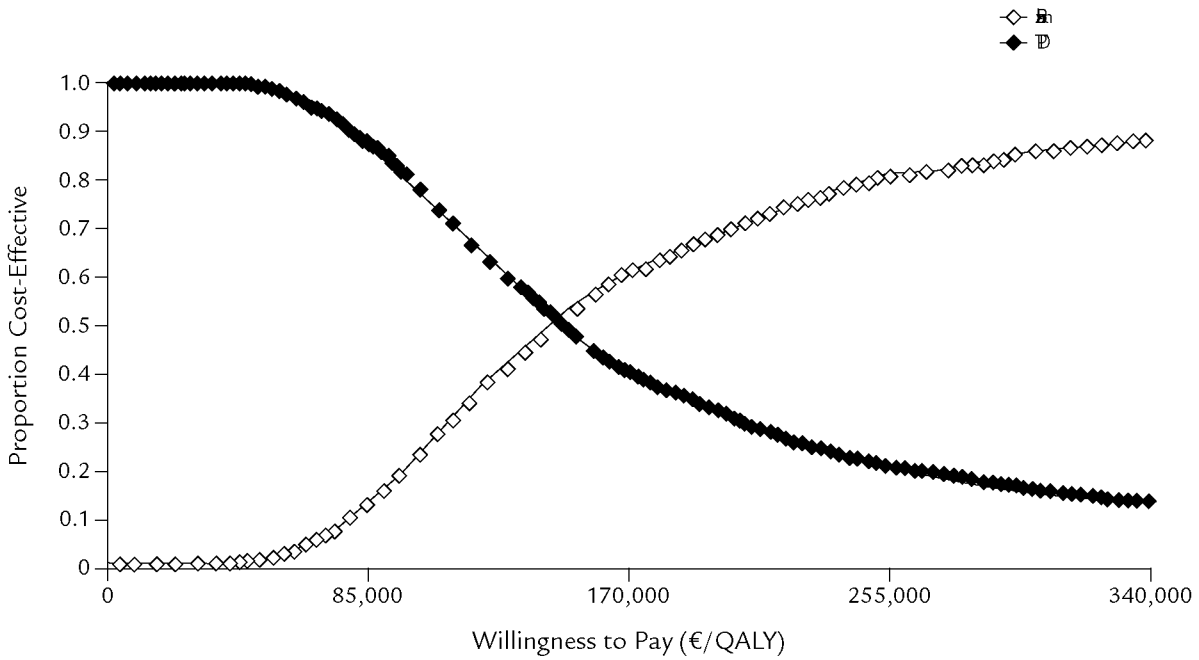

Figure 2. Acceptability curve obtained with probabilistic sensitivity analysis in the 2-year time horizon for ranibizumab and photodynamic therapy (PDT). Below the €30,000/quality-adjusted life-years threshold, PDT is the therapy of choice in all cases.

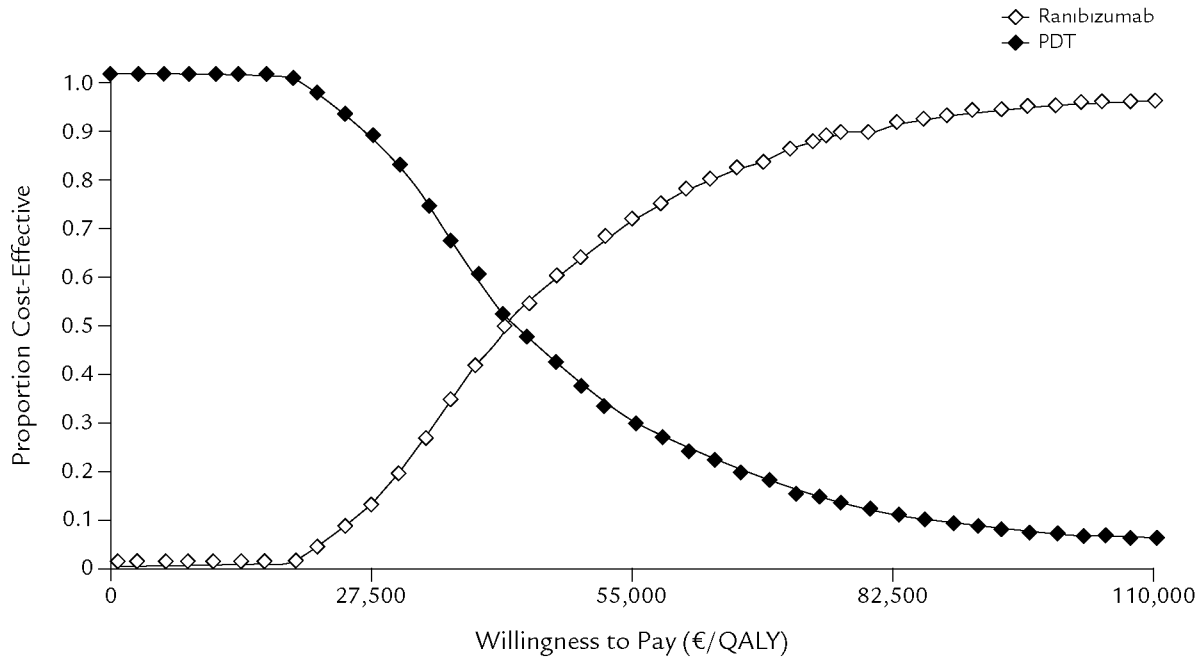

Figure 3. Acceptability curve obtained with probabilistic sensitivity analysis in the life-expectancy time horizon for ranibizumab and photodynamic therapy (PDT). Below the €30,000/quality-adjusted life years threshold, ranibizumab is the optimal intervention in 26% of cases.

whereas QALYs accrued over the whole time horizon. Among the studies presented in **Table VI**, the chosen perspective clearly influenced the final ICER. Some studies considered only direct costs.[34,35,37,39] Other studies adopted a broader perspective,[15,36,38,40] including the perspectives of society and government; took into account additional costs, such as those related to comorbid states, hip replacement, and depression; or accounted for tax exemption, government subsidies, and nursing home allocations. A broader perspective was associated with a higher disease burden and thus produced a lower ICER. This is illustrated in the study by Smith et al,[36] which was conducted from 2 perspectives.

The selected studies reported a broad range of results, which could be attributed to differences among data sources, assumptions, time horizons, and perspectives. Meads et al,[15] who did not use subgroup analysis for efficacy data and who selected a short time horizon, found ICERs ranging from £151,179/QALY to £182,188/QALY. On the other hand, Bansback et al[38] and Brown et al,[37] who selected outcomes from the predominantly classic CNV subgroup analysis of the TAP trial[19] and chose a longer time horizon, generated ICERs of £20,996/QALY for a 10-year horizon and $31,103/QALY for a 12-year horizon, respectively.

Cost-Effectiveness of Ranibizumab

We also searched MEDLINE in December 2007 for cost-effectiveness studies on ranibizumab, using the terms *ranibizumab and cost-effectiveness* and *ranibizumab and cost utility*, with no limits. Only 1 economic evaluation[43] was selected after discarding those not related to AMD, those not fulfilling the definition of Drummond et al,[33] and those not written in English or Spanish.

Brown et al[43] performed a cost-utility analysis comparing ranibizumab versus no active therapy in AMD patients with minimally classic or occult CNV. A third-party payer perspective with health insurance covering direct costs, including those of adverse reactions, was chosen for the analysis. Efficacy results

Table V. Results of the sensitivity analysis. Values are 2007 €/quality-adjusted life-year (QALY).

Variable/Parameter	ICER 2-Year Horizon	ICER Lifetime Horizon
Reference case	131,275	39,398
No. of injections from PrONTO[28,29] trial*	29,566	11,469
Fluorescein angiography every 3 mo	142,444	42,587
0% Discounting rate	127,890	36,914
5% Discounting rate	133,525	41,155
Age at the beginning of treatment		
58 y	128,683	32,616
90 y	149,740	69,787
Varying age†	132,972	48,912
VA state at the beginning of treatment		
>20/40	172,136	43,062
≤20/40 to >20/80	96,127	36,912
≤20/80 to >20/200	91,853	35,534
≤20/200 to >20/400	167,675	40,419
≤20/400	255,477	49,443
One-time benefit approach for extrapolation	–	28,727
Threshold SA on no. of ranibizumab injections‡	5	9.5

ICER = incremental cost-effectiveness ratio; PrONTO = the Prospective Optical coherence tomography imaging of patients with Neovascular age-related macular degeneration Treated with intra-Ocular ranibizumab[28]; VA = visual acuity; SA = sensitivity analysis.

*According to the PrONTO trial,[28] we took the number of 5.6 injections for the first year[28] and 4.3 injections for the second[29] and subsequent years.

†Results were obtained using a microsimulation and a normal distribution for the starting age.[11] Data are the median ICER.

‡Per-year number of ranibizumab injections to increase the ICER to >€30,000/QALY for both time horizons.

were taken from the MARINA trial.[6] Utility values were obtained from patients using the time tradeoff methodology. An ICER of $50,691/QALY was obtained at the selected 12-year time horizon, using the second-eye perspective with an annual discounting rate of 3% for both costs and QALYs. Brown et al did not include any costs, either for follow-up consultations or ranibizumab injections, after the initial 2 years, although QALYs accrued over the whole period. This assumption led to a total of 22 ranibizumab injections during the 12-year period.

While we were writing the manuscript, the National Institute for Health and Clinical Excellence (NICE) of the United Kingdom and the Canadian Agency for Drugs and Technologies in Health (CADTH) published their technology assessment reports on new antiangiogenic therapies for AMD.[42,44] In both cases, the chosen perspective was that of a national or provincial health service that includes the direct costs of therapy and follow-up, as well as other costs derived from visual impairment.

Colquitt et al[44] (NICE) developed a Markov model with 5 health states defined by VA and 1 death state from all causes to assess the cost-effectiveness of pegaptanib and ranibizumab independently. Best supportive care and PDT, for the subgroup of patients

Table VI. Summary of studies on cost-effectiveness of photodynamic therapy.*

Study	Perspective	Efficacy	Utility Values	Analysis	Discounting	Horizon, y	Reported ICER	ICER, 2007 €
Sharma et al[34]	3rd-party payer	TAP trial[19]	Brown et al[22]	Markov model	3%	2	20/40: $86,721 20/200: $173,984	20/40: 117,426 20/200: 235,585
						11	20/40: $64,259 20/200: $128,669	20/40: 87,011 20/200: 174,226
Meads et al[15]	Government NHS	TAP trial[19]	Brown et al[22]	Decision tree	None	2	£151,179–£182,188†	248,040–298,920
Hopley et al[35]	3rd-party payer	TAP trial[19]	Brown et al[22]	Decision tree	6%	7	£6/12: 31,607 £6/60: 63,214	6/12: 51,336 6/60: 102,673
Smith et al[36]	3rd-party payer	TAP trial[19]	Brown et al[22]	Markov model	6%/2%‡	2	20/40: £89,464 20/100: £411,533	20/40: 145,309 20/100: 668,422
						5	20/40: £38,088 20/100: £68,882	20/40: 61,863 20/100: 111,879
	Government					2	20/40: £75,580 20/100: £285,867	20/40: 122,759 20/100: 464,312
						5	20/40: £8823 20/100: £29,797	20/40: 14,331 20/100: 48,397

(continued)

Table VI (continued).

Study	Perspective	Efficacy	Utility Values	Analysis	Discounting	Horizon, y	Reported ICER	ICER, 2007 €
Brown et al[37]	3-party payer	TAP[19] and extension[20]	TTO§	Decision tree	3%	12	$31,103	26,754
Bansback et al[38]	Societal	TAP[19] and extension[20]	HUI3‖	Markov model	3.5%	2 10	£82,329 £20,996	120,304 30,680
Muslera and Natal[39]	3-party payer	TAP trial[19]	NA	Retrospective analysis	2.5%	2	Per-patient cost¶: €71,525 Per-year cost#: €36,530–34,804	74,028 37,808–36,022
Greiner[40]	Societal	TAP trial[19]	NA	Markov model	NS	3	Per-year cost#: 9624 CHF	7726

ICER = incremental cost-effectiveness ratio; TAP = Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; NHS = National Health Service; TTO = time tradeoff; HUI3 = Health Utilities Index 3; NA = not applicable; NS = not specified; CHF = Swiss francs.

* ICERs are given as costs per quality-adjusted life-year (QALY) if not specified. The "reported ICER" column gathers data from the original publication. Original currency was converted into € and corrected for inflation to obtain data presented in the second ICER column. Exchange rates for currency conversion were taken from the European Central Bank (http://sdw.ecb.europa.eu/; accessed December 2007). Inflation was corrected with Consumer Price Indexes published by the Organization for Economic Co-operation and Development (www.oecd.org; accessed December 2007).

† The cost per QALY depends on the moment when blindness occurs. A lower ICER is obtained if blindness occurs in the first year, thus incurring 2 years of costs associated with blindness.

‡ 6% for costs and 2% for benefits.

§ Utility values were obtained from 233 patients with the time tradeoff method.

‖ Utilities for each disease state were estimated from a study of 209 patients with AMD in which contrast sensitivity remained a statistically significant predictor of HUI3 utilities.[41]

¶ Cost per patient who maintains visual acuity.

Cost per year of maintained vision.

with classic AMD, were the chosen comparators. The 3-month transition probabilities were derived from RCTs. Ranibizumab was administered according to the approved labeling on a monthly basis. Two time horizons were selected for the analysis: a trial-based time horizon and a longer 10-year time horizon. To extrapolate effects over the longer time horizon, therapy and treatment effect were stopped at the end of the trial period. The ICERs obtained for ranibizumab compared with PDT in patients with predominantly classic lesions were £202,450/QALY at 1 year and £15,638/QALY at 10 years.

In the study by Brown et al[42] (CADTH), the chosen comparators were pegaptanib and PDT in the population with predominantly classic CNV, or pegaptanib in the population with CNV lesions of any type. Two separate Markov models were developed for these populations. Patients aged ≥40 years were included, and a lifetime horizon was selected for the analysis. Head-to-head trials comparing pegaptanib and ranibizumab or PDT were lacking; therefore, the mean VA change for each treatment was taken from single-arm efficacy results from RCTs. A random-effects meta-analysis was used to pool data when several trials were available. Ranibizumab was administered once per month; pegaptanib, every 6 weeks; and PDT, twice per year. In the predominantly classic CNV population, PDT was more expensive and provided fewer QALYs than pegaptanib, the least expensive alternative. Ranibizumab was more effective and more expensive than pegaptanib, with a calculated ICER of Can $56,382/QALY.

In the reference case, we obtained an ICER of €131,275/QALY for a 2-year time horizon (**Table IV**). For the longer lifetime horizon, the ICER fell to €39,398/QALY. As in other studies on PDT[34] or ranibizumab,[44] time horizon had a major impact on the final ICER. The difference relates to the higher upfront costs of therapy versus the subsequent cost reductions in the later years, during which health benefits continue to accrue.

Willingness-to-pay (WTP) thresholds are widely used to determine whether a new technology is cost-effective. In the United States, a threshold of US $50,000/QALY is commonly cited.[45] In the United Kingdom, a threshold of £20,000 to £30,000/QALY has generally been accepted.[46] A threshold of €30,000 has been proposed in Spain.[47] These thresholds are not exempt from criticism.[48, 49] Acceptability curves, however, have the advantage of assigning probabilities to different WTP thresholds. Acceptability curves resulting from our probabilistic sensitivity analysis for both time horizons are depicted in **Figures 2** and **3.** According to the probabilistic sensitivity analysis, PDT is the therapy of choice in all cases below the threshold of €30,000/QALY for the 2-year time horizon. For the life-expectancy horizon, ranibizumab is the optimal intervention in 26% of cases.

According to results from the univariate sensitivity analysis, ranibizumab is cost-effective when administered as needed, as in the PrONTO trial[28,29] (**Table V**). This finding shows that treatment efficiency is highly dependent on the frequency of repeat treatment. Drug costs accounted for 77% and 78% of total costs in the ranibizumab arm in the first and subsequent years, respectively. For PDT, drug costs plus the laser procedure accounted for 75% and 53% of the total in the first and subsequent years, respectively. Threshold sensitivity analysis identified 5 and 9.5 intravitreal injections per year in the 2-year horizon and the lifetime horizon, respectively, as the cutoff points above which ICER surpassed the WTP threshold of €30,000/QALY.

In the reference case, an annual discounting rate of 3% was applied to both costs and QALYs.[25] Discounting had only a slight influence on the final results (**Table V**).

According to data from the Spanish population,[11] we selected the starting age of 74 years for the reference case. We performed a sensitivity analysis taking the upper and lower limits of the 95% CI for this variable.[11] When patients started at the age of 58 years, we obtained an ICER of €32,616/QALY in the life-expectancy horizon. If patients started at the age of 90 years, the ICER rose to €69,787/QALY, also in the longer lifetime horizon (**Table V**). The difference is related to the shorter life expectancy of older patients, who accrue QALYs over fewer years.

Results from the univariate sensitivity analysis showed that higher ICERs compared with the reference case were obtained when the cohort started at the state defined by VA >20/40. This is probably the result of a ceiling effect; patients cannot improve their vision and quality of life 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 V**.

In the reference case, we selected a continuous-effect approach for extrapolation over the longer lifetime horizon, which assumes that efficacy for both treatments lasts during the entire time horizon.[18] In the sensitivity analysis, we tested the 1-time benefit approach for extrapolation. Under this approach, both treatments stop at the maximum duration of clinical trial follow-up. From then on, patients' quality of life declines at the same rate for both treatments.[18] Under this assumption, the ICER fell to €28,727/QALY.

The results of the univariate sensitivity analysis show that variables such as the patient's age, the number of treatments, and the initial VA have a major impact on the efficiency of ranibizumab. The PrONTO trial did not find a significant correlation between the number of injections needed at 12 months and the initial VA or lesion size, but a significant difference was noted between lesions of retinal angiomatous proliferation (RAP) and non-RAP lesions with respect to the number of injections in the first year (7.1 and 5.0 injections, respectively).[28] The observed difference highlights the need for further research to identify those populations for whom ranibizumab is more cost-effective.

Study Limitations

Results from the sensitivity analysis suggest that ranibizumab is cost-effective when administered as needed, as in clinical practice.[31,32] Based on efficacy outcomes from the PrONTO trial,[28,29] this sensitivity analysis assumed that the VA gain obtained with monthly ranibizumab could be achieved with fewer injections. Interim results from the SUSTAIN trial, which are similar to those observed in the PrONTO trial, provide further evidence that VA gain can be achieved with fewer injections.[30] However, although the outcomes were similar when ranibizumab was dosed in an individualized fashion, several methodologic differences limit trial comparisons. A head-to-head trial is the only reliable way of determining the equivalence of the dosing regimens. Based on the literature searches, a clinical trial comparing ranibizumab as needed with PDT has not been conducted. However, the Comparison of AMD Treatments Trials[50] might provide stronger evidence on the efficacy and tolerability of ranibizumab when administered in an individualized fashion compared with a fixed-dosing regimen.

The Markov states in our model were defined by the VA in the better-seeing eye. From this perspective, both treatments had a direct impact on patients' VA, which is linked to quality of life.[22] If treatments were applied to the worse-seeing eye, the efficiency of ranibizumab would be lower. The better-case scenario, however, was applied to both treatments; thus, the incremental benefit was not overestimated. On the other hand, the second-eye perspective is not unimportant; CNV develops in the contralateral eye in ≥87% of patients with AMD over 5 years if ≥4 risk factors are present.[51] Moreover, vision loss in the first eye can be caused by diseases other than AMD.

We chose the perspective of a third-party payer for this economic evaluation; thus, indirect costs were excluded. We did not take into account direct costs related to adverse reactions. These costs accounted for a small percentage (0.4%) in previous studies of ranibizumab.[43] Adverse reactions with ranibizumab have a low incidence, are mainly ocular (eg, endophthalmitis, intravitreal hemorrhage), and modify a patient's VA; thus, their impact on quality of life was taken into account in the efficacy results. In addition, we did not take into account direct costs related to comorbid states, hip replacement, or anxiety or depression.[52] If we took all of these costs into account, the disease burden would increase and a lower ICER would be obtained, as was the case in previous studies of PDT.[15,34–40] We do not know whether these costs had enough weight to reduce the ICER to less than the accepted threshold of €30,000/QALY. However, even if we did not take these costs into account, and if we admit that VA gains can be achieved with fewer injections, as in the PrONTO trial, ranibizumab was cost-effective.[28,29]

Although this study was conducted in Spain, we believe our results are useful in other settings. Efficacy data were taken from large Phase III clinical trials, which are generalizable to other populations. Resource utilization is probably similar among countries. Although some differences can be observed among clinicians from different hospitals, we believe that the data on resource utilization, as previously specified, reflects clinical practice. We are aware that our unit costs reflect those of a private hospital and thus are subject to great variation among settings. Accordingly, we varied them by 20% in the probabilistic sensitivity analysis to account for these differences. We refer to the accepted WTP threshold or ceiling ratio of €30,000/QALY in a Spanish setting. Acceptability curves, however, allow the estimation of cost-effectiveness probabilities for a variety of different thresholds.

Although ranibizumab has been reported to be effective regardless of CNV subtype,[6–9] the scope of this study was limited to those settings in which patients were eligible for PDT, mainly those with the predominantly classic subtype.[5] In other settings in which patients are not eligible for PDT, best supportive care or pegaptanib should be chosen as the preferred comparator.

CONCLUSIONS

The present study of the cost-effectiveness of ranibizumab versus PDT from the perspective of a third-party payer in Spain found that ranibizumab was not cost-effective when administered monthly. In a 2-year time horizon, the ICER rose to €131,275/QALY, whereas in the longer lifetime horizon, the ICER fell to €39,398/QALY. According to the probabilistic sensitivity analysis, PDT was the therapy of choice in all cases below the threshold of €30,000/QALY for the 2-year time horizon and 74% of cases in the life-expectancy time horizon. When administered as needed, ranibizumab was cost-effective compared with PDT for the treatment of AMD. The efficiency of ranibizumab was highly dependent on several variables, mainly, number of intravitreal injections, age, and starting VA. Further research is needed to identify those subgroups of patients for whom ranibizumab is more cost-effective.

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