COST-EFFECTIVENESS OF BEVACIZUMAB AND RANIBIZUMAB FOR NEWLY DIAGNOSED NEOVASCULAR MACULAR DEGENERATION (AN AMERICAN OPHTHALMOLOGICAL SOCIETY THESIS)

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ABSTRACT

Purpose: To determine the most cost-effective treatment for patients with newly diagnosed neovascular macular degeneration: monthly or as-needed bevacizumab injections, or monthly or as-needed ranibizumab injections.

Methods: Using a Markov model with a 20-year time horizon, we compared the incremental cost-effectiveness of treating a hypothetical cohort of 80-year-old patients with newly diagnosed neovascular macular degeneration using monthly bevacizumab, as-needed bevacizumab, monthly ranibizumab, or as-needed ranibizumab. Data came from the Comparison of Age-Related Macular Degeneration Treatment Trial (CATT), the Medicare Fee Schedules, and the medical literature.

Results: Compared with as-needed bevacizumab, the incremental cost-effectiveness ratio of monthly bevacizumab is $242,357 per quality-adjusted life year (QALY). Monthly ranibizumab gains an additional 0.02 QALYs vs monthly bevacizumab at an incremental cost-effectiveness ratio of more than $10 million per QALY. As-needed ranibizumab was dominated by monthly bevacizumab. In sensitivity analyses assuming a willingness to pay of $100,000 per QALY, the annual risk of serious vascular events would have to be at least 2.5 times higher with bevacizumab than that observed in the CATT trial for as-needed ranibizumab to have an incremental cost-effectiveness ratio of <$100,000 per QALY. In another sensitivity analysis, even if every patient receiving bevacizumab experienced declining vision by one category (eg, from 20/25-20/40 to 20/50-20/80) after 2 years but all patients receiving ranibizumab retained their vision level, as-needed ranibizumab would have an incremental cost-effectiveness ratio of $97,340 per QALY.

Conclusion: Even after considering the potential for differences in risks of serious adverse events and therapeutic effectiveness, bevacizumab confers considerably greater value than ranibizumab for the treatment of neovascular macular degeneration.

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INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness among adults older than 65 years. With the aging of the US population, it is estimated that by the year 2020, nearly 3 million persons will experience visual impairment from AMD.[1-3] Since AMD causes blurring of central vision and visual distortions, it can severely limit one's ability to perform daily activities such as operating a motor vehicle or reading. Thus, it is not surprising that vision loss from AMD can dramatically affect health-related quality of life (HRQL).[4-7]

For many years, the conventional first-line treatment for extrafoveal neovascular AMD was focal argon laser photocoagulation (FALP). The landmark Macular Photocoagulation Study (MPS) demonstrated that patients with extrafoveal choroidal neovascularization who underwent FALP were 35% less likely than untreated patients to experience severe vision loss at 18 months, and 18% less likely at 5 years.[8,9] Although FALP was effective at stabilizing best-corrected visual acuity (BCVA), few patients had improved vision with this treatment, and it was contraindicated in patients with subfoveal disease. Photodynamic therapy (PDT) with verteporfin became available as an alternative to FALP in 2000. An advantage of PDT over FALP was the ability to safely treat not only patients with extrafoveal choroidal neovascularization but also those with occult and subfoveal disease. However, similar to FALP, PDT with verteporfin stabilized the disease, but few patients experienced improved BCVA.[10]

In recent years, new treatment options revolutionized the treatment of patients with neovascular AMD. Anti–vascular endothelial growth factor (anti-VEGF) agents, including pepgaptanib, ranibizumab (Lucentis; Genentech/Roche, South San Francisco, California), and bevacizumab (Avastin; Genentech/Roche), are antibodies or antibody fragments that bind and block VEGF. The Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) trial proved that intravitreal injections of ranibizumab, 0.3 mg or 0.5 mg, were more efficacious than sham treatment at preserving and improving vision.[11] The Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) trial showed that either dose was better than PDT with verteporfin.[12]More recently, two large randomized controlled trials, the Comparison of Age-Related Macular Degeneration Treatment Trial (CATT)[13,14] and the Inhibit VEGF in Age-Related Choroidal Neovascularization (IVAN)[15] trial, directly compared the efficacy of ranibizumab and bevacizumab in patients with neovascular AMD. Through 2 years of follow-up, using similar dosing regimens, the CATT trial found bevacizumab to be non-inferior to ranibizumab in efficacy. The study also compared monthly dosing with an as-needed dosing regimen of these agents and found that participants who received monthly dosing of these agents experienced slightly more vision gain.[14] The 1-year findings from the IVAN study also demonstrated bevacizumab and ranibizumab to have relatively similar efficacy.[15]

While the CATT and IVAN trials are providing clinicians and researchers with high-quality evidence of the comparative efficacy and safety of ranibizumab and bevacizumab for neovascular AMD, and there are several studies in the literature which demonstrate that anti-VEGF agents are cost-effective relative to supportive care[16-25] or PDT with vertiporfin,[18,19,23,26-29] little is known about the

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cost-effectiveness of bevacizumab relative to ranibizumab.[30] To our knowledge, only one study, conducted by Raftery and colleagues,[31] has directly compared the cost-effectiveness of bevacizumab and ranibizumab for neovascular AMD. Because this study predated the CATT and IVAN trials, the researchers needed to make several assumptions about the safety and efficacy of bevacizumab and ranibizumab. Now that high-quality data on the safety, efficacy, and differences in outcomes using different dosing regimens of these anti-VEGF agents has been well-established, data from these trials can be used to determine which of these anti-VEGF treatments confers the greatest value.

Considering the high prevalence of neovascular AMD, the large cost differential between bevacizumab and ranibizumab, the risks for potentially serious side effects associated with use of these agents, the need for multiple injections in many patients, and differences in efficacy based on the dosing regimen, a well-designed cost-effectiveness analysis would help identify which treatment and dosing regimen confers the greatest societal value. Given that more than $1.6 billion is spent annually on ranibizumab therapy for retinal diseases[32] and that ranibizumab was the single largest expenditure for Medicare Part B in 2010, accounting for nearly 10% of the entire drug budget,[33] a rigorous cost-effectiveness analysis would be important to policymakers seeking cost savings to the US health care system.

In this study, we compared the cost-effectiveness of monthly and as-needed dosing regimens using bevacizumab and ranibizumab for patients with newly diagnosed neovascular AMD.

METHODS

STUDY DESIGN

Using a societal perspective, we developed a Markov model to capture the total costs and HRQL for patients with newly diagnosed neovascular AMD under four treatment options: monthly injections of bevacizumab (monthly bevacizumab), as-needed injections of bevacizumab (as-needed bevacizumab), monthly injections of ranibizumab (monthly ranibizumab), and as-needed injections of ranibizumab (as-needed ranibizumab). A societal perspective was taken to encompass all parties who may be affected by the treatment choice: patients, providers, and payers. The model followed a hypothetical cohort of patients aged 80 years (the mean age for neovascular AMD onset) with neovascular AMD (as defined in the CATT trial) over a 20-year time horizon. Markov modeling is a standard method used in general health technology assessments and also has been used in previous cost-effectiveness analyses for neovascular AMD.[34-36]

HEALTH STATES

We followed patients through health states based on BCVA levels (Figure 1). In the analysis, we assume that the level of BCVA used captures vision in the better-seeing eye.

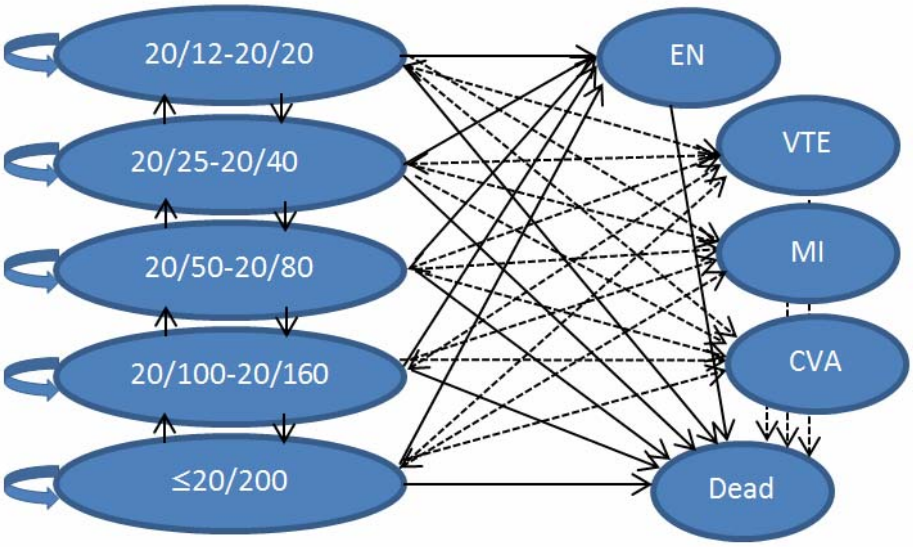

FIGURE 1

Markov model visual acuity and health states for neovascular age-related macular degeneration. Ovals represent levels of visual acuity and arrows represent possible annual changes in vision. Dotted lines represent secondary analysis including venous thrombotic event (VTE), myocardial infarction (MI), and cerebrovascular accident (CVA) outcomes. Individuals have costs for endophthalmitis (EN), VTE, MI, and CVA. Individuals with MI, CVA, and blindness from EN have long-term costs. Individuals with VTE have only the short-term costs of the event.

PROGRESSION RATES

Vision in each intervention group followed the observed BCVAs from the CATT trial at years 1 and 2 (Table 1).[13,14] Since, to our knowledge, no study to date has reported on the natural history of neovascular AMD treated with anti-VEGF agents beyond 2 to 3 years, we evaluated BCVA in the longer term using several different scenarios. In our baseline model, we assumed that the distribution of BCVA from the CATT trial did not change after year 2 for all treatment groups. In sensitivity analyses, we allowed the BCVA of patients in each treatment group to decline each year.

TABLE 1. VISION OUTCOMES AND ADVERSE EVENTS AFTER YEAR 1 AND 2 FROM THE COMPARISON OF AGE-RELATED MACULAR DEGENERATION TREATMENT TRIAL

	MONTHLY BEVACIZUMAB		AS NEEDED BEVACIZUMAB		MONTHLY RANIBIZUMAB		AS NEEDED RANIBIZUMAB	
	YEAR 1	YEAR 2	YEAR 1	YEAR 2	YEAR 1	YEAR 2	YEAR 1	YEAR 2
Proportion of patients in each vision state								
20/12-20/20	17.0%	13.2%	14.8%	13.9%	14.8%	17.9%	13.3%	16.7%
20/25-20/40	50.6%	47.3%	46.9%	48.2%	52.5%	50.0%	49.5%	46.6%
20/50-20/80	17.7%	24.0%	21.0%	18.3%	18.3%	17.2%	23.2%	22.3%
20/100-20/160	7.9%	10.9%	8.9%	11.2%	8.1%	8.2%	8.1%	8.7%
≤20/200	6.8%	4.7%	8.5%	8.4%	6.3%	6.7%	6.0%	5.7%
Adverse event rates*								
Endophthalmitis	1.4%	0.68%	0.00%	0.68%	1.00%	0.33%	0.00%	0.33%
VTE	1.40%	0.85%	0.33%	0.85%	0.00%	0.17%	0.67%	0.17%
MI	0.70%	0.68%	0.33%	0.68%	0.66%	0.67%	1.01%	0.67%
CVA	0.70%	0.68%	0.67%	0.68%	1.00%	0.67%	0.34%	0.67%
Vascular death	0.70%	1.19%	1.67%	1.19%	0.66%	1.34%	0.67%	1.34%

CVA, cerebrovascular accident; MI, myocardial infarction; VTE, venous thrombotic event.
*Year 2 event rates were reported only for each drug, and not for frequency of delivery, so the year 2 adverse event rates are the same for "monthly" and "as needed."

SERIOUS SYSTEMIC AND OCULAR ADVERSE EVENTS

Using data from the CATT trial, we also tracked rates of cerebrovascular accident (CVA), myocardial infarction (MI), and venous thrombotic events (VTEs).[13,14] Once a patient experienced a CVA, MI, or VTE, the costs increased, HRQL declined, and the risk for death increased for the remainder of the patient's lifetime (Figure 1). We also tracked patients with blindness due to endophthalmitis. In addition, we incorporated age-adjusted mortality data from US life tables to capture mortality rates for persons with neovascular AMD.[37]

COSTS

Direct medical costs of managing neovascular AMD were based on office-based Centers for Medicare and Medicaid Services (CMS) allowables for 2011 in the state of Michigan and included the costs of eye-care provider visits, ancillary testing (optical coherence tomography [OCT] and intravenous fluorescein angiography [IVFA] to evaluate for and quantify the amount of neovascular AMD present), each intervention, treatment of side effects caused by the interventions, and costs associated with blindness when BCVA remained ≤20/200 (Table 2[37-44]). For pharmaceutical products administered in the office, such as bevacizumab and ranibizumab, we included the drug cost, professional fee, and facility fee reimbursed by CMS in 2011. The cost of all drugs paid for outside of the office setting was calculated by using *Red Book* costs from 2005.[45]All costs were adjusted for inflation to 2012 dollars. The number of office visits and injections for each therapeutic regimen came directly from the CATT trial.[13,14]

UTILITIES

The main value of treating neovascular AMD comes from the quality of life gained by improving or maintaining BCVA. We measured this quality of life using a quality-adjust life year (QALY) so that these results could be compared with interventions for other diseases. A QALY incorporates both quality and length of life with one QALY representing one year in perfect health. HRQL, or "utility," is quantified as a value ranging from 1.00 (perfect health) to 0.00 (death). This "utility" is multiplied by the number of years in a particular health state to get the QALYs. We incorporated utility scores for each level of BCVA as captured by Brown and colleagues[42]; these scores range from 0.97 for 20/20 BCVA to 0.61 for <20/200 BCVA (Table 2). Because neovascular AMD affects the macula and often spares the peripheral retina, it is uncommon for patients to experience BCVA <20/200 from neovascular AMD

alone. Utility scores obtained from the literature for complications of the various interventions and utility scores for MI, CVA, VTE, and death are included in Table 2. These parameters were varied in sensitivity analyses.

TABLE 2. INPUT PARAMETERS FOR THE COSTS, UTILITIES, AND SIDE EFFECTS INCLUDED IN THE MARKOV MODEL OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

PARAMETER VALUE	VALUE IN USD (RANGE)	REFERENCE*
Costs (2012 USD)		
Visits and diagnostic testing		
Initial office visit	242	CPT 99204
Subsequent office visits	185	CPT 99214
Optical coherence tomography (at each visit)	74	CPT 92134
Fluorescein angiography (one-time)	260	CPT 99235
Interventions		
Intravitreal ranibizumab	2389	CPT 67028
Intravitreal bevacizumab	356	CPT 67028
Short-term		
Endophthalmitis†	4140	CPT 67015/67028
Blindness	2846	Frick[38]
VTE	32141	Mahan[39] and MacDougall[40]
MI	18326	Freeman[41]
CVA	13307	Freeman[41]
Long-term		
MI	3557	Freeman[41]
CVA	62796	Freeman[41]
Utilities		
Health states		Brown[42]
20/12-20/20	0.92	
20/25-20/40	0.84	
20/50-20/80	0.76	
20/100-20/160	0.66	
≤20/200	0.61	
Short-term side effects (QALYs lost)‡		
Endophthalmitis	-0.1	Aaberg[43]
VTE	-0.004	Bajaj[44]
Long-term side effects (annual utility)§		
Blindness from endophthalmitis	0.37	Brown[42]
CVA	0.39	Freeman[41]
MI	0.84	Freeman[41]
Relative risk of mortality after MI or after CVA	2	Assumption
After MI		
All other nonvascular mortality	Varies by age	CDC Wonder database[37]

CVA, cerebrovascular accident; MI, myocardial infarction; QALY, quality-adjusted life years; VTE, venous thrombotic event.
*2011 Medicare Payments for physician and facility fees, *Red Book*. All costs adjusted to 2012 prices.
†Includes cost of topical antibiotics, corticosteroids, and cycloplegics.
‡Short-term side effects affected patients only during the first year after receipt of the intervention.
§Long-term side effects affected patients for the remainder of time they cycled through the model.

All costs are in 2012 US dollars. Costs and health utilities were discounted at 3% per year. Interventions with higher costs and worse health outcomes than other interventions are considered dominated. Undominated interventions *a* and *b* were compared to each other by using an incremental cost-effectiveness ratio (ICER) or net monetary benefit (NMB) defined as:

$$ICER = (TC_a - TC_b) / (E_a - E_b)$$

$$NMB_a = WTP * (E_a - TC_a)$$

In these equations, *TC* is the total cost; *E* is effectiveness measured in QALY; *WTP* is willingness to pay for a QALY; and

intervention *a* is the intervention of interest and intervention *b*, a lower-cost undominated alternative intervention.[46] We used TreeAge Pro 2012 Healthcare (TreeAge Software, Williamstown, Massachusetts) to calculate and compare costs and health effects of each of the interventions.

SENSITIVITY ANALYSES

We performed sensitivity analyses on the estimates of costs, utilities, and health state transitions to cover a range of assumptions. One-way sensitivity analyses were performed on all parameters to determine which ones had the largest impact on results. We also conducted several two-way sensitivity analyses. Finally, we conducted a probabilistic sensitivity analysis using Monte Carlo simulation of all input assumptions simultaneously and created a cost-effectiveness acceptability curve to determine how robust the results were to changes in all parameters and how likely each therapy was to be the most cost-effective option.

Since all of the information used in this analysis came from the existing medical literature and from publicly available sources (eg, CMS fee schedules), we did not seek institutional review board approval to perform this study.

RESULTS

BASE MODEL

Over 20 years, the expected costs for a single patient with newly diagnosed neovascular AMD receiving monthly bevacizumab, as-needed bevacizumab, monthly ranibizumab, and as-needed ranibizumab were $79,771, $65,267, $257,496, and $163,694, respectively, and the QALYs for a patient receiving these treatments were 6.66, 6.60, 6.68, and 6.64, respectively. The ICER of monthly bevacizumab over as-needed bevacizumab was $242,357 per QALY. The ICER of monthly ranibizumab over as-needed bevacizumab was $10,708,377 per QALY. As-needed ranibizumab was dominated by monthly bevacizumab because monthly bevacizumab had lower costs and higher QALYs (Figure 2 and Table 3).

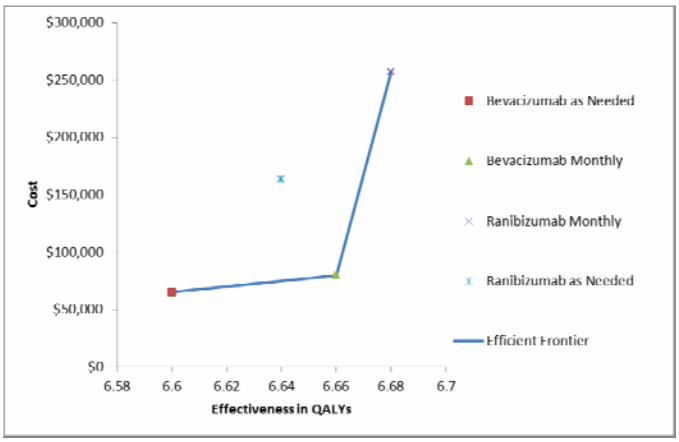

FIGURE 2

Cost-effectiveness of the different treatment alternatives for neovascular macular degeneration. Total costs and total effectiveness over 20 years are depicted with each of the four treatment alternatives. Monthly ranibizumab confers the most costs and the most improvement in quality-adjusted life years (QALY), whereas as-needed bevacizumab confers the least costs and least improvement in QALY. Therapies on the blue line (efficient frontier) are undominated. As-needed ranibizumab therapy is dominated by the others (specifically, monthly bevacizumab).

BASE MODEL, WITHOUT INCLUDING COSTS OF VISITS AND OPTICAL COHERENCE TOMOGRAPHY FOR THOSE RECEIVING MONTHLY TREATMENTS

Since some clinicians do not charge for a clinic visit or OCT when they know that they plan to perform an injection, as would be the case for those in the monthly ranibizumab and monthly bevacizumab groups, we reran our models excluding all costs of all subsequent visits and OCT tests after those incurred during the initial examination. With this adjustment, the expected costs for a single patient with newly diagnosed neovascular AMD receiving monthly bevacizumab, as-needed bevacizumab, monthly ranibizumab, and as-needed ranibizumab were $55,261, $65,267, $233,108, and $163,694, respectively, and the QALYs for a patient receiving these treatments were 6.66, 6.60, 6.68, and 6.64, respectively. The ICER of monthly ranibizumab over monthly bevacizumab was $10,715,692 per QALY. Because monthly bevacizumab had fewer office visits and OCTs, it was less expensive than as-needed bevacizumab (Table 3). If monthly bevacizumab had fewer than 5 office visits and OCTs per year, the total costs were lower than as-needed bevacizumab. If monthly bevacizumab had between 5 and 7.8 office visits and OCTs per year, it was more costly than as-needed bevacizumab, but had an ICER <$100,000 per QALY when compared to as-needed bevacizumab.

BASE MODEL, WITHOUT CONSIDERING SYSTEMIC SIDE EFFECTS OF ANTI-VEGF AGENTS

Since the difference in safety profile between intravitreal bevacizumab and intravitreal ranibizumab is not fully understood, we performed a sensitivity analysis, rerunning the model after excluding systemic side effects such as VTE, CVA, and MI. In this scenario, over 20 years the expected costs for a single patient with newly diagnosed neovascular AMD receiving monthly bevacizumab, as-needed bevacizumab, monthly ranibizumab, and as-needed ranibizumab were $68,705, $54,339, $276,510, and $169,008, respectively, and the QALYs for a treatment recipient was 7.32, 7.30, 7.40, and 7.35, respectively. The ICER of monthly bevacizumab over as-needed bevacizumab was $678,250 per QALY. The ICER of monthly ranibizumab over as-needed bevacizumab

was $2,569,040 per QALY. As-needed ranibizumab was dominated by monthly bevacizumab and monthly ranibizumab, meaning as-needed ranibizumab had fewer QALYs and a higher cost per QALY than monthly bevacizumab or monthly ranibizumab (Table 3).

TABLE 3. COST AND HEALTH RESULTS OF THE DIFFERENT THERAPIES FOR NEOVASCULAR MACULAR DEGENERATION

BASE MODEL

Therapy	Cost (USD)	QALYs	ICER
As-needed bevacizumab	65,267	6.60	Lowest cost*
Monthly bevacizumab	79,771	6.66	242,357
As-needed ranibizumab	163,694	6.64	Dominated†
Monthly ranibizumab	257,496	6.68	10,708,377

BASE MODEL (EXCLUDING SERIOUS SYSTEMIC ADVERSE EVENTS)

Therapy	Cost (USD)	QALYs	ICER
As-needed bevacizumab	54,339	7.30	Lowest cost*
Monthly bevacizumab	68,705	7.32	678,250
As-needed ranibizumab	169,008	7.35	Dominated‡
Monthly ranibizumab	276,510	7.40	2,569,040

BASE MODEL (EXCLUDING COSTS OF VISITS AND OCTS FOR THOSE GETTING MONTHLY INJECTIONS)

Therapy	Cost (USD)	QALYs	ICER
As-needed bevacizumab	65,267	6.60	Dominated†
Monthly bevacizumab	55,261	6.66	Lowest cost*
As-needed ranibizumab	163,694	6.64	Dominated†
Monthly ranibizumab	233,108	6.68	10,715,692

ICER, incremental cost-effectiveness ratio; OCT, optical coherence tomography; QALY, quality-adjusted life year.
*Intervention had the lowest costs, so other interventions are measured against it. The lowest cost intervention will not have an ICER.
†Dominated by monthly bevacizumab, which had higher QALYs at a lower cost.
‡Dominated by "extended dominance" by monthly bevacizumab and monthly ranibizumab. If an ICER of as-needed ranibizumab were created relative to monthly bevacizumab, it would be 3,760,854, which is higher than the ICER of monthly ranibizumab relative to monthly bevacizumab, implying that there is greater value gained per dollar spent with monthly ranibizumab than with as-needed ranibizumab.

SENSITIVITY ANALYSES

Sensitivity analyses examine the impact of changes to model assumptions.

Varying the Cost of Ranibizumab and the Risk of Systemic Side Effects

If the risks for serious systemic effects associated with a ranibizumab injection were 50% lower than those observed in the CATT trial, the injection cost would still need to be reduced to less than $1210 for as-needed ranibizumab to be the preferred treatment option at a WTP of $100,000 per QALY. Likewise, if the risk of serious systemic side effects with ranibizumab were 75% lower than those observed in the CATT trial, the cost per injection of ranibizumab would need to be reduced to $1556 per injection for as-needed ranibizumab to confer the greatest value (Figure 3).

Varying the Utility of Severe Vision Loss

Our initial assumption was that the vision category of <20/200 had a utility of 0.61, which assumes vision is in the range of 20/200 to 20/400. In sensitivity analysis, we change the utility of the <20/200 category to 0.47 to represent the possibility of even worse vision, including no light perception. Under this assumption, the bevacizumab monthly strategy looks better in relation to the others, since it had the fewest patients with vision in the <20/200 category after 2 years. The bevacizumab monthly strategy has an ICER of $156,360 per QALY relative to bevacizumab as needed. Under this assumption, the ranibizumab strategies have equivalent or worse health outcomes (and higher costs) when compared to bevacizumab monthly.

Varying the Long-Term Effectiveness of Bevacizumab and Ranibizumab

In another sensitivity analysis, we simultaneously varied the long-term effectiveness of ranibizumab and bevacizumab to assess the effect on which is the preferred treatment alternative. If every patient who received ranibizumab (as-needed ranibizumab and monthly

ranibizumab) had no decline in BCVA after year 2 and all patients who received bevacizumab (as-needed bevacizumab and monthly bevacizumab) had vision decline by one category (eg, from 20/12-20/20 to 20/25-20/40) each year, the patients receiving as-needed ranibizumab would gain 0.9 discounted QALYs at a cost of $87,940, leading to an ICER of $97,340 per QALY.

Varying the Costs of Bevacizumab and Ranibizumab

Because the BCVA and health outcomes associated with bevacizumab and ranibizumab are similar, the price premium for ranibizumab vs bevacizumab is only approximately $100 to $300, by assuming a WTP of $100,000 per QALY. For example, if the cost per injection of bevacizumab is less than $355, bevacizumab would be the preferred treatment option even if ranibizumab cost as little as $500 per injection (Figure 4).

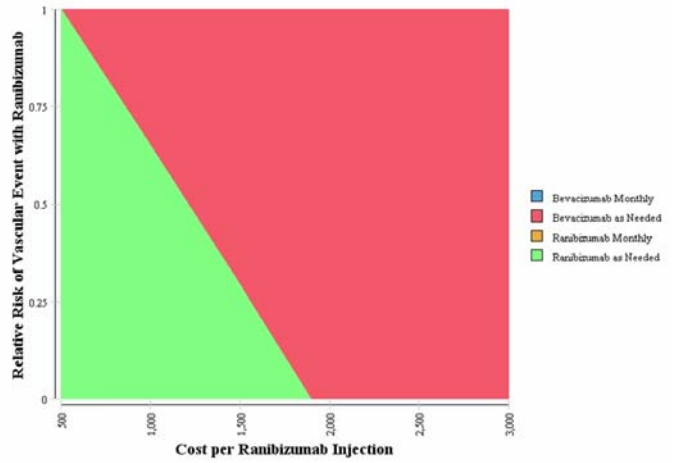

FIGURE 3

The impact of the cost per ranibizumab injection and the risk of serious vascular events associated with intravitreal ranibizumab use on the preference for therapy for neovascular age-related macular degeneration. Two-way sensitivity analysis varying the cost of each injection of ranibizumab and risk of serious vascular thrombotic events associated with ranibizumab on which is the preferred treatment option. The color reflects the treatment alternative that is most cost-effective given a willingness-to-pay of $100,000 per QALY. For example, if the cost of each ranibizumab injection was reduced to $1000 and the relative risk of serious vascular events with ranibizumab was 50% lower than those reported in the CATT trial, as-needed ranibizumab would be the preferred treatment alternative. Likewise, if the cost of each ranibizumab injection was reduced to $2000 and the risk of serious vascular thrombotic events was 0%, as-needed bevacizumab would be the preferred treatment alternative.

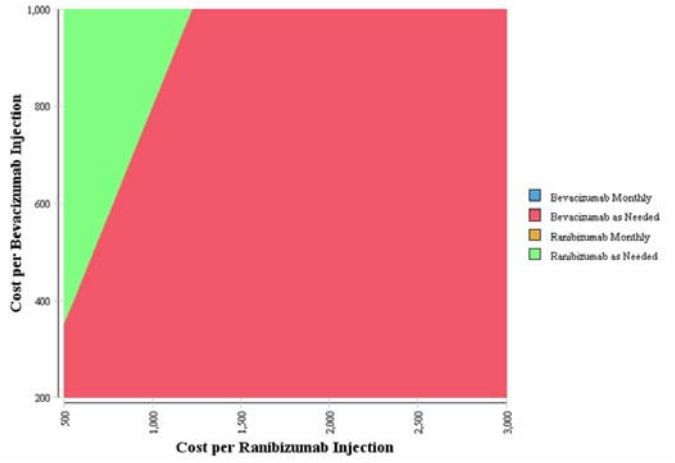

FIGURE 4

The impact of the cost per bevacizumab and ranibizumab injection on the preference for therapy for neovascular age-related macular degeneration. Two-way sensitivity analysis varying the cost of each injection of bevacizumab and ranibizumab on which is the preferred treatment option. The color reflects the treatment alternative that is most cost-effective given a willingness-to-pay of $100,000 per QALY. For example, if the cost of each ranibizumab injection was reduced to $1500 and the cost of each bevacizumab injection was increased to $600, as-needed bevacizumab would be the preferred treatment alternative. Likewise, if the cost of each ranibizumab injection was reduced to $750 and the cost of each bevacizumab injection was increased to $800, as-needed ranibizumab would be the preferred treatment alternative.

Varying the Risks of Serious Systemic and Ocular Adverse Events of Each Anti-VEGF Agent

At a WTP of $100,000 per QALY, the risk of all serious systemic adverse events (CVA, MI, and VTE) would need to be about 2.5 times greater with bevacizumab than with ranibizumab for as-needed ranibizumab to be the preferred treatment option (Figure 5). Figure 6 shows the impact of varying the risk of endophthalmitis by using the rates reported in the CATT trial. It shows that even if the risk of endophthalmitis is 10 times greater with bevacizumab as compared to the risk reported in CATT, as-needed bevacizumab would continue to confer the greatest value. If the annual risk of endophthalmitis with bevacizumab were 40% per person per year, then as-needed ranibizumab would have an ICER of less than $100,000 per QALY. This is because of two main factors: ranibizumab is very expensive, and this patient population has a relatively limited life expectancy to benefit from averted endophthalmitis. Thus,

for a patient receiving as-needed bevacizumab who gets, on average, 7 injections annually, the risk of endophthalmitis per bevacizumab injection would be approximately 7% to give a 40% risk over the course of the year.

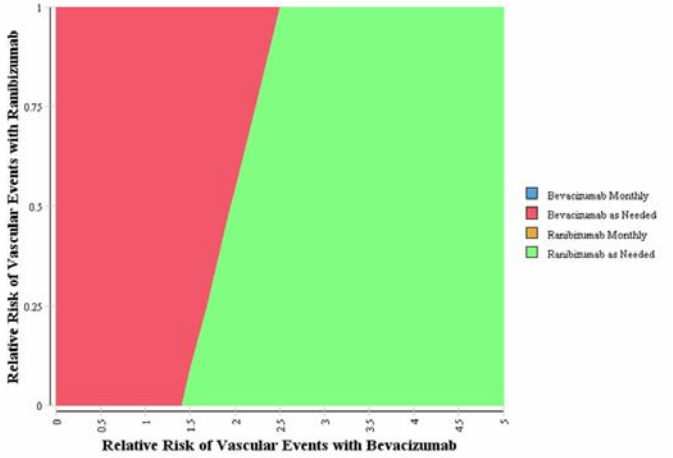

FIGURE 5

The impact of the rate of serious vascular thrombotic events with bevacizumab and ranibizumab on the preference for therapy for age-related macular degeneration. Two-way sensitivity analysis demonstrating the impact of varying the rates of serious vascular thrombotic events associated with injections of bevacizumab and ranibizumab on which is the most cost-effective alternative. The color reflects the treatment alternative that is most cost-effective given a willingness-to-pay of $100,000 per QALY. For example, if the rate of serious vascular thrombotic events from ranibizumab injections is 50% lower than rates observed in the CATT trial and vascular thrombotic event rates with bevacizumab are three times higher than those in the CATT trial, as-needed ranibizumab would be the preferred treatment alternative. Likewise, if the rate of serious vascular thrombotic events from ranibizumab injections is 25% lower than rates observed in the CATT trial and vascular thrombotic event rates with bevacizumab are two times higher than those in the CATT trial, as-needed injections of bevacizumab would still be the preferred treatment alternative. Rates reflected in the Figure are multiples of the rates of all vascular events (venous thrombotic event, cerebrovascular accident, myocardial infaction) as observed in the CATT trial. Note different scales on the x- and y-axes.

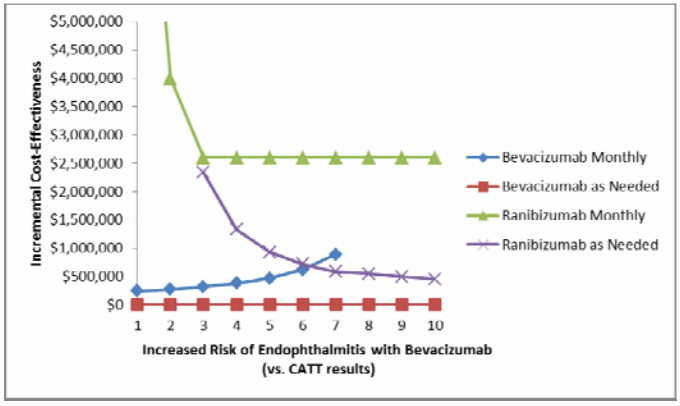

FIGURE 6

The impact of the risk of endophthalmitis with bevacizumab on the cost-effectiveness of ranibizumab therapy for neovascular age-related macular degeneration. This figure shows the impact of varying the risk of endophthalmitis associated with bevacizumab use from the rates that were reported in the CATT Trial. As the risk of endophthalmitis increases with bevacizumab, the monthly strategy becomes less favorable because it has higher baseline risks of endophthalmitis relative to the as-needed dosing. The ranibizumab strategies become more favorable, but even if the risk of endophthalmitis is 10 times higher with bevacizumab than the risk reported in the CATT Trial, the ranibizumab therapies would have very high cost-effectiveness ratios: as-needed ranibizumab would cost $450,000 per QALY and monthly ranibizumab cost over $2.5 million per QALY.

Varying the Cost of Bevacizumab and Risk of Endophthalmitis from Bevacizumab

Single-use vials of bevacizumab are more costly than multi-use containers; however, the risk of endophthalmitis is reduced by using single-use vials. Thus, we explored the impact of simultaneously varying the cost per bevacizumab injection and the risk for endophthalmitis, assuming similar costs and endophthalmitis risk levels for ranibizumab as used in the base model and a WTP of $100,000 per QALY. If the single-use vial completely eliminated the risk of endophthalmitis, a single-use vial could command a premium of up to $35 per bevacizumab injection above the cost of multi-use containers (Figure 7) for single-use vials to be considered cost-effective at a WTP of $100,000 per QALY. At today's prices, the risk of endophthalmitis would need to be three times greater with multi-use containers than with single-use vials for single-use vials of bevacizumab to be the preferred treatment option.

Varying the Number of Ranibizumab Injections

If the number of intravitreal injections for the as-needed bevacizumab group were the same as those performed in the CATT trial (7.05 injections per year), the number of injections for the as-needed ranibizumab group would need to be reduced to 1.3 injections or fewer per year for it to have an ICER of <$100,000 per QALY.

Other Parameters

Additional sensitivity analyses explored the effects of varying other model parameters: life expectancy (Figure 8) and the age at onset of neovascular AMD (Figure 9). These did not substantially affect conclusions.

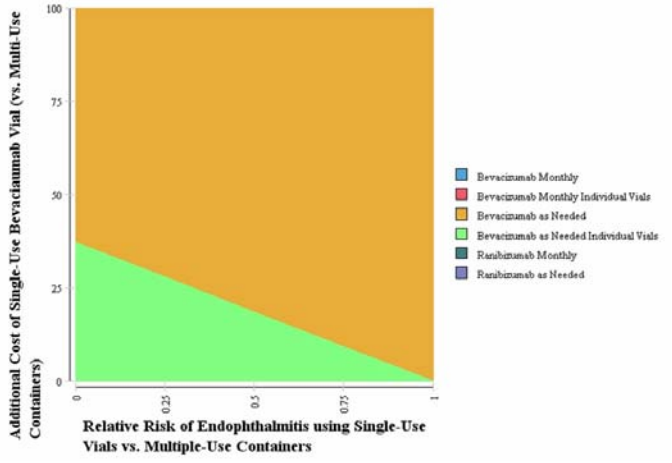

FIGURE 7

The impact of the cost of a single-use vial of bevacizumab and risk of endophthalmitis on the preference for therapy for neovascular age-related macular degeneration. Two-way sensitivity analysis demonstrating the impact of varying the cost of a single-use vial of bevacizumab and the relative risk of endophthalmitis when using a single-use vial vs a multi-use vial. The color reflects the treatment alternative that is most cost-effective for any given level of cost of a single-use vial of bevacizumab and relative risk of endophthalmitis given a willingness-to-pay of $100,000 per QALY.. For example, if the cost of a single-use vial of bevacizumab was $25 more than multiple-use containers and a single-use vial had a relative risk of endophthalmitis of 25% of multiple-use containers, then as-needed injections of bevacizumab using single-use vials would be the preferred treatment. Alternatively, if the cost of a single-use vial was $50 more than multiple-use containers and a single-use vial had a relative risk of endophthalmitis of 0% of multiple-use containers (zero risk of endophthalmitis), as-needed bevacizumab in the standard multi-use vials would be the preferred treatment option

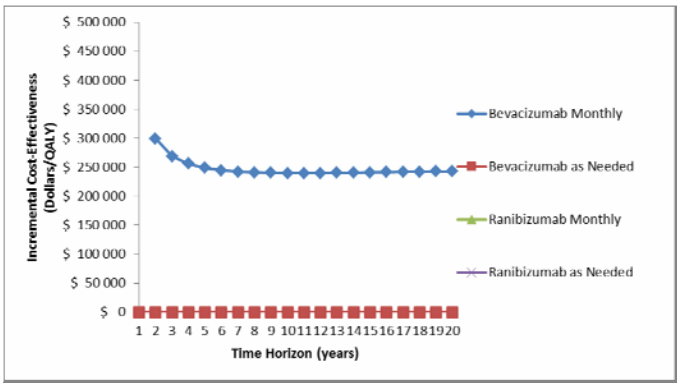

FIGURE 8

The impact of varying life expectancy on the cost-effectiveness of bevacizumab and ranibizumab therapy for age-related macular degeneration. The Figure shows that a shorter time horizon leads to less time to reap the benefits of anti–vascular endothelial growth factor therapy. The incremental cost-effectiveness ratio of ranibizumab monthly varies between $3 million and $11 million per quality-adjusted life year (QALY), and so is off the top of the chart. Ranibizumab as needed is dominated by bevacizumab as needed and/or ranibizumab monthly (more costs and fewer QALYs) and therefore does not have an incremental cost-effectiveness ratio.

Probabilistic Sensitivity Analysis

A cost-effectiveness acceptability curve was created by varying all model parameters simultaneously in 10,000 simulation iterations (Figure 10). Bevacizumab strategies are most likely to be cost-effective at WTP values of less than $600,000 per QALY. As-needed bevacizumab was the preferred therapy choice in 68% of simulations at a WTP threshold of $0 per QALY and in 62% of simulations at a WTP threshold of $100,000 per QALY. Monthly bevacizumab therapy was preferred in 18% to 20% of simulations when the WTP was less than $100,000 per QALY. Due to uncertainty in all parameters, ranibizumab therapies were occasionally (14% to 17%

of the time) cost-effective at a WTP less than $100,000 per QALY. Even at a WTP of $1 million per QALY, ranibizumab therapies were cost-effective in about 50% of the simulations.

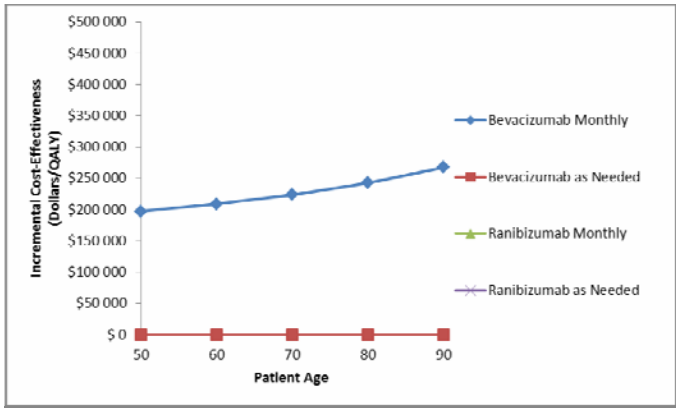

FIGURE 9

The impact of varying age of initial diagnosis of neovascular macular degeneration on the cost-effectiveness of bevacizumab and ranibizumab therapy for age-related macular degeneration. Figure shows the impact of varying the age at first diagnosis and treatment of exudative macular degeneration on the output of the model. As one might expect, those who are first diagnosed with exudative macular degeneration at a younger age achieve greater value from undergoing treatment with anti-VEGF agents relative to those who are older in age at first diagnosis of the condition. The Figure shows that as-needed bevacizumab is highly cost-effective, irrespective of the age at initial macular degeneration diagnosis. Bevacizumab as needed is always the lowest cost and therefore has an incremental cost-effectiveness ratio of zero. Even among patients who are diagnosed with exudative macular degeneration as young as age 50, the incremental cost-effectiveness of monthly bevacizumab is about $197,000 per quality-adjusted life year (QALY), and this number goes up with increasing age. Treatment with ranibizumab does not incur much value relative to the other interventions irrespective of age. Ranibizumab monthly either is dominated by bevacizumab monthly (more costs and fewer QALYs) at the lower ages or has an incremental cost-effectiveness ratio above $7 million per QALY and is thus off the top of the chart. Ranibizumab as needed is dominated by bevacizumab as needed and therefore does not have an incremental cost-effectiveness ratio.

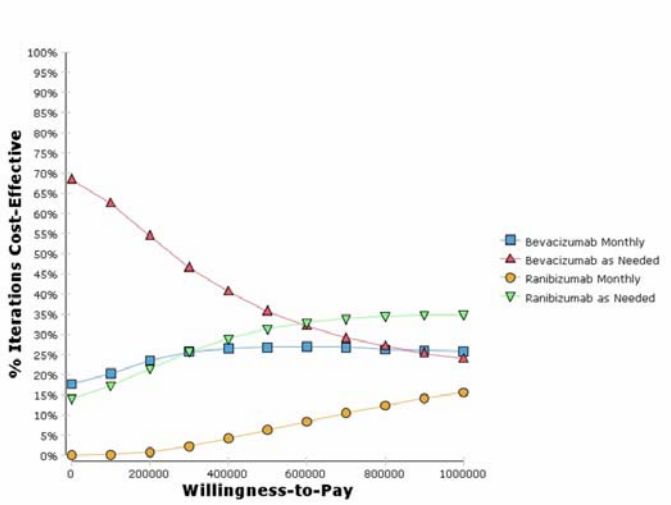

FIGURE 10

Probability that bevacizumab and ranibizumab therapy for neovascular age-related macular degeneration will be cost-effective given uncertainty in all parameters. Cost-effectiveness acceptability curves derived from 10,000 iterations of Monte Carlo simulations simultaneously varying all model parameters. Note that the x-axis goes up to $1 million per quality-adjusted life year (QALY). Bevacizumab strategies are most likely to be cost-effective at willingness-to-pay values of less than $600,000 per QALY. As-needed ranibizumab, however, is about 14% likely to be cost-effective at a willingness-to-pay of $0 per QALY, about 17% likely to be cost-effective at a willingness-to-pay of $100,000 per QALY, and about 50% likely to be cost-effective at a willingness-to-pay of $1 million per QALY. Bevacizumab as needed is highly likely to be cost-effective, although there still is a reasonable chance (15%-30%) that monthly bevacizumab therapy would be considered cost-effective at all willingness-to-pay levels.

DISCUSSION

As health policy makers look to curtail rising health care costs, treatments that confer the greatest relative value need to be identified. Using data from the CATT trial, we find that compared with as-needed dosing of bevacizumab, the ICER of monthly bevacizumab

and monthly ranibizumab for neovascular AMD are $242,357 per QALY and $10,708,377 per QALY, respectively. Furthermore, as-needed ranibizumab was dominated by as-needed bevacizumab, meaning that the as-needed ranibizumab is more costly and less effective. Sensitivity analyses highlight the impact of varying the model parameters, including the proportion of patients who experience serious systemic side effects from these agents, the number of injections administered, the cost per injection of each agent, and patient's life expectancy on the ICER of the treatment options. Finally, when each parameter was simultaneously varied in a probabilistic sensitivity analysis, as-needed bevacizumab was the preferred treatment option in nearly two-thirds of the simulations using a WTP of $100,000 per QALY, and monthly bevacizumab was the preferred alternative in another 18% to 20% of the simulations.

Several previous cost-effectiveness analyses have compared some of the older treatments for neovascular AMD, such as FALP vs supportive care,[16,47,48] PDT with verteporfin vs supportive care,[16,17,49-55] pegaptanib vs supportive care,[16,18-21] ranibizumab vs supportive care,[17,22-25] and PDT with verteporfin vs pegaptanib or ranibizumab.[18,19,23,26-29] Little, however, has been known of the cost-effectiveness of the two most commonly used interventions presently for neovascular AMD, bevacizumab and ranibizumab, relative to one another. We are aware of only one study that directly compared the cost-effectiveness of bevacizumab and ranibizumab; that analysis, reported in 2007, was conducted by Raftery and colleagues[31] before the results of the CATT and IVAN trials were available. The researchers found that monthly injections of bevacizumab for predominantly classic and occult choroidal neovascularization conferred considerably more value relative to monthly injections of ranibizumab at a cost per QALY of more than £100 000 ($161,840 USD). They also reported that ranibizumab would need to be at least 2.5 times as efficacious as bevacizumab to be the preferred treatment option, and that doubling the rates of serious ocular side effects associated with bevacizumab use had little effect on their findings. Potential differences in the risk of serious systemic side effects were not considered in their analyses. Although Raftery and colleagues could not incorporate CATT trial data in their models, their finding that bevacizumab was considerably more cost-effective than ranibizumab is similar to our results, based on models that use the CATT trial data.

Although the CATT and IVAN trials provide strong evidence of non-inferior efficacy between ranibizumab and bevacizumab, some contend that providers should use ranibizumab instead of bevacizumab because intravitreal bevacizumab carries an increased risk for serious systemic side effects. The evidence for an elevated risk of side effects often comes from comparisons of systemic use, not intravitreal injection, of these agents to treat patients with colon and gastric cancers.[56,57] The CATT and IVAN trials monitored participants for serious systemic side effects, such as CVA, MI, and VTE, and found no major differences in the rates of these adverse events between the two agents; however, neither trial was adequately powered to determine with certainty whether any potential, statistically significant differences in safety exist between ranibizumab and bevacizumab. In addition, because participants in the monthly arms were randomly assigned to as-needed treatment after 1 year, there is a particular lack of power for monthly outcomes in the second year. Recent studies have found that serum levels of VEGF in patients with neovascular AMD may differ between ranibizumab users and bevacizumab users. Carneiro and colleagues[58] found that after three monthly injections of anti-VEGF agents, serum concentrations of VEGF were significantly lower in the bevacizumab-treated patients than in the ranibizumab users, yet the VEGF levels had been similar among patients at baseline. This research suggests that bevacizumab may have more effects on the cardiovascular system than ranibizumab does. In our sensitivity analysis exploring the impact of potential differences in the risk of serious systemic side effects between the two agents, we found that recipients of intravitreal bevacizumab would need to experience three times as many serious vascular events (CVAs, MIs, and VTEs) per year as ranibizumab recipients for ranibizumab to be the preferred treatment option.

Another debatable issue is how often anti-VEGF agents must be administered to maintain their effectiveness. In the CATT trial, the group randomized to monthly anti-VEGF injections had slightly greater improvements in vision than the group assigned to treatment on an as-needed basis.[13,14] Given how expensive each actual anti-VEGF injection is (especially each ranibizumab injection), if patients who receive fewer injections experience similar vision gains as those who receive monthly injections, this could have a big impact on the value of these different treatment options relative to one another. In our analyses we find that monthly bevacizumab is considerably less cost-effective than as-needed bevacizumab ($242,357 per QALY), whereby it does not meet the $100,000 per QALY cutoff which some researchers use to designate whether a given intervention is acceptable.[59] However, monthly bevacizumab would be preferred over as-needed bevacizumab if only the costs of the injection, without accompanying costs of a visit and OCT, are considered.

With a recent outbreak of fungal meningitis in the United States associated with the use of medications coming from compounding pharmacies, the very small, albeit real, increased risk for serious ocular side effects such as endophthalmitis with the use of bevacizumab from compounding pharmacies is a pertinent consideration for physicians in deciding whether to recommend ranibizumab or bevacizumab in patients with neovascular AMD; ranibizumab, in contrast, comes directly from the drug manufacturer. In one of our two-way sensitivity analyses, we simultaneously varied the cost per bevacizumab injection and endophthalmitis risk to capture the increased cost associated with the presumably safer, single-use vials of bevacizumab rather than the cheaper bevacizumab packaged in multiuse containers. We find that the risk of endophthalmitis would need to be three times greater with multi-use containers than with single-use vials for the latter to become the preferred treatment option at today's prices.

In our analyses we sought to identify which treatment option confers the greatest value from a societal perspective. Because the resources that can be devoted to health care are not unlimited, there is an opportunity cost associated with choosing therapies that are relatively costly or less effective. For example, in their analyses, Raftery and coworkers[31] point out that a year of treatment with monthly ranibizumab at £1000 (roughly $1615 USD) per injection costs £300 million ($485 million USD), whereas monthly bevacizumab would cost £8 million ($13 million USD) per year, resulting in a savings of £292 million ($472 million USD). These savings could instead be used to expand treatment to patients from disadvantaged communities who might otherwise lack access to

affordable anti-VEGF therapies, to help pay for low vision aids or provide supportive care to patients with scarring from neovascular AMD in whom anti-VEGF agents have been unresponsive, or simply to help curtail rapidly rising health care costs in the United States. These sorts of analyses can be performed from other perspectives, such as that of patients with Medicare coverage, many of whom lack the supplemental insurance necessary to cover a copay of 20% of the cost of injections; the perspective of eye-care providers who need to spend resources to safely store these medications; or the perspective of the manufacturer, Genentech, who sells both of these anti-VEGF drugs. The inputs to the model would vary considerably depending on whose perspective is considered.

Our study has several limitations. The CATT trial compared the level of efficacy, the need for additional injections, and the side effects from the injections over only 2 years duration. Extrapolating the findings of the trial beyond year 2 can be challenging because little is known about the longer-term natural history of neovascular AMD among persons taking ranibizumab or bevacizumab. Although we performed sensitivity analyses to address the uncertainty of the various model parameters beyond year 2, varying model inputs beyond the ranges used in our analyses could affect our findings. In addition, participants who enroll in a clinical trial such as the CATT trial may differ systematically from other patients in their health behavior, affecting the generalizability of the findings. Another limitation is an assumption we made that BCVA is an acceptable surrogate for the impact of neovascular AMD on overall HRQL. Visual needs vary from patient to patient, and different levels of BCVA could affect the overall HRQL of patients differently. Unfortunately, the CATT trial collected no additional information on HRQL that we could incorporate in our models. Finally, it is known that increased anti-VEGF use can worsen geographic atrophy, but since it is unclear the frequency and extent by which this occurs or whether it is more common with one intervention vs another, we could not incorporate this into our models.

As treatment paradigms for patients with neovascular AMD continue to rapidly evolve, there will be a need to revisit some of these analyses in the future. Such research should explore the incremental cost-effectiveness of newer medications such as aflibercept (Regeneron Pharmaceuticals, Inc, Tarrytown, New York) relative to ranibizumab and bevacizumab. Other newer treatments aimed at reducing the need for frequent intravitreal injections are currently under development or testing, such as one in a Phase III clinical trial involving injection of viral vectors coding for a molecule that has anti-VEGF properties that is secreted into the eye (Genzyme Corporation, Cambridge, Massachusetts) or an implant, currently in a Phase II clinical trial, that slowly secretes anti-VEGF medications (Neurotech Pharmaceuticals, Cumberland, Rhode Island). If these or other newer treatment options are proven more effective, resulting in greater improvements in BCVA or longer stabilization of disease, or less costly than existing options, they may confer greater value. In addition to exploring new medications on the horizon, further work should be done to assess whether some of the newer treatment algorithms that clinicians are using, such as "treat and extend," are more cost-effective than existing protocols. Finally, since our probabilistic sensitivity analysis found that ranibizumab was the preferred treatment in 14% to 17% of the Monte Carlo simulations, additional research should be conducted to further explore the impact of varying some of the model parameters on our study's findings.

CONCLUSION

In conclusion, among the four treatment options for neovascular AMD tested in the CATT trial, bevacizumab administered on an as-needed dosing schedule confers the greatest value. Ranibizumab dosed monthly or as needed confers considerably less value than bevacizumab, mainly because of its considerably higher per-injection cost. Monthly treatments of bevacizumab are preferred over as-needed treatments of bevacizumab if providers charge simply for the injection alone without an accompanying visit or OCT. Insurers and health policy makers should consider endorsing the use of intravitreal bevacizumab over other treatment alternatives as first-line therapy for neovascular AMD, as this may curtail some of the rapidly rising costs of managing patients with this condition.

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