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Cost-effectiveness of Aflibercept, Bevacizumab, and Ranibizumab for Diabetic Macular Edema Treatment
Analysis From the Diabetic Retinopathy Clinical Research Network Comparative Effectiveness Trial

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IMPORTANCE Anti–vascular endothelial growth factor (VEGF) medicines have revolutionized diabetic macular edema (DME) treatment. A recent randomized clinical trial comparing anti-VEGF agents for patients with decreased vision from DME found that at 1 year aflibercept (2.0 mg) achieved better visual outcomes than repackaged (compounded) bevacizumab (1.25 mg) or ranibizumab (0.3 mg); the worse the starting vision, the greater the treatment benefit with aflibercept. However, aflibercept and ranibizumab, respectively, are approximately 31 and 20 times more expensive than bevacizumab.

OBJECTIVE To examine the incremental cost-effectiveness ratios (ICERs) of aflibercept, bevacizumab, and ranibizumab for the treatment of DME.

DESIGN, SETTING, AND PARTICIPANTS Post hoc analysis of efficacy, safety, and resource utilization data at 1-year follow-up from the Diabetic Retinopathy Clinical Research Network Comparative Effectiveness Trial. Patients were enrolled from August 22, 2012, through August 28, 2013, and analysis was performed from August 21, 2014, through November 7, 2015.

MAIN OUTCOMES AND MEASURES The ICERs for all trial participants and subgroups with baseline vision of approximate Snellen equivalent 20/32 to 20/40 (better vision) and baseline vision of approximate Snellen equivalent 20/50 or worse (worse vision). One-year trial data were used to calculate cost-effectiveness for 1 year for the 3 anti-VEGF agents; mathematical modeling was then used to project 10-year cost-effectiveness results.

RESULTS The study included 624 participants (mean [SD] age, 60.6 [10.5] years; 45.7% female; 65.5% white), 209 in the aflibercept group, 207 in the bevacizumab group, and 208 in the ranibizumab group. For all participants, during 1 year, the ICERs of aflibercept and ranibizumab compared with bevacizumab were $1 110 000 per quality-adjusted life-year (QALY) and $1 730 000 per QALY, respectively. During 10 years, they were $349 000 per QALY and $603 000 per QALY, respectively. Compared with ranibizumab, aflibercept's ICER was $648 000 per QALY at 1 year and $203 000 per QALY at 10 years. For the subgroup with worse baseline vision, the 10-year ICERs of aflibercept and ranibizumab compared with bevacizumab were $287 000 per QALY and $817 000 per QALY, respectively. In eyes with decreased vision from DME, treatment costs of aflibercept and ranibizumab would need to decrease by 69% and 80%, respectively, to reach a cost-effectiveness threshold of $100 000 per QALY compared with bevacizumab during a 10-year horizon; for the subgroup with worse baseline vision, the costs would need to decrease by 62% and 84%, respectively.

CONCLUSIONS AND RELEVANCE Aflibercept (2.0 mg) and ranibizumab (0.3 mg) are not cost-effective relative to bevacizumab for treatment of DME unless their prices decrease substantially. These results highlight the challenges that physicians, patients, and policymakers face when safety and efficacy results are at odds with cost-effectiveness results.

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A recent Diabetic Retinopathy Clinical Research Network (DRCR.net) comparative effectiveness trial found that for patients with diabetic macular edema (DME) and approximate Snellen equivalent baseline visual acuity (VA) of 20/50 or worse aflibercept produced greater mean VA gains at 1 year than bevacizumab or ranibizumab. In contrast, no difference in mean VA improvement was identified for patients with baseline VAs of 20/32 to 20/40.[1]

These agents also vary substantially in cost. On the basis of 2015 wholesale acquisition costs, aflibercept (2.0 mg) costs $1850,[2] ranibizumab (0.3 mg) costs $1170,[2] and bevacizumab repackaged at compounding pharmacies into syringes for ophthalmologic use containing 1.25 mg of bevacizumab costs approximately $60 per dose.[3] Considering that these medicines may be given 9 to 11 times in the first year of treatment[1] and, on average, 17 times during 5 years,[4] total costs can be substantial. In 2010, when these intravitreous agents were being used predominantly for age-related macular degeneration, ophthalmologic use of anti-vascular endothelial growth factor (VEGF) therapy cost approximately $2 billion or one-sixth of the entire Medicare Part B drug budget.[3] In 2013, Medicare Part B expenditures for aflibercept and ranibizumab alone totaled $2.5 billion.[5] Given these costs, the DRCR.net investigators believed it was important to analyze the relative cost-effectiveness of treating DME using each agent.

Key Points

Question What is the incremental cost-effectiveness of different anti–vascular endothelial growth factor therapies over bevacizumab for the treatment of diabetic macular edema?

Findings Visual acuity benefits of aflibercept and ranibizumab translate into modest quality-of-life improvements but at a high cost relative to bevacizumab, with incremental cost-effectiveness ratios substantially higher than frequently cited thresholds (eg, $100 000 per quality-adjusted life-year).

Meaning Physicians and policymakers should keep in mind these results when considering the incremental cost-effectiveness of these agents compared with bevacizumab.

Methods

Overview

In a post hoc analysis, data from a randomized clinical trial were used to calculate clinical benefit, costs, and cost-effectiveness of aflibercept, bevacizumab, and ranibizumab for DME.[1] With the use of published cost and quality-of-life data, resource utilization and VA results from the trial were converted into estimates of overall medical costs and quality-adjusted life-years (QALYs) accrued during the first year of the trial.[6] A mathematical model projected longer-term costs and health outcomes with each therapy (eMaterial in Supplement). Each therapy's incremental cost-effectiveness ratio (ICER) was calculated, defined as the ratio of its incremental cost (in 2015 US $) to its incremental benefit (in QALYs) compared with the next-best therapy. Future outcomes were discounted at an annual rate of 3% to reflect their present value.

Because treatment efficacy in the DRCR.net trial differed significantly by baseline VA, the cost-effectiveness of these therapies also was assessed for better (approximate Snellen equivalent of 20/32-20/40 [Early Treatment Diabetic Retinopathy Study letter score of 78-69]) and worse (approximately 20/50 or worse [letter score <69]) VA subgroups.

Participants

The DRCR.net Protocol T trial included 660 patients randomized to aflibercept, bevacizumab, or ranibizumab for treatment of DME. Patients were enrolled from August 22, 2012, through August 28, 2013; this analysis was performed from August 21, 2014, through November 7, 2015. The study adhered to the Declaration of Helsinki and was approved by local and centralized institutional review boards. Detailed procedures, protocol, and statistical methods have been reported previously.[1] All study participants provide written informed consent.

Participants were 18 years or older and had 1 study eye with VA (Snellen equivalent) of 20/32 to 20/320 attributable to DME. Among the 660 participants, 329 eyes (49.8%) were in the worse VA subgroup, and 331 (50.1%) in the better VA subgroup. Patients were followed up every 4 weeks (termed *monthly* hereafter) for 1 year, with anti-VEGF injections provided on a monthly basis for the first 6 months in most cases. Thereafter, treatment was deferred if the eye was stable; laser treatment was added, if indicated, based on study-defined criteria. After deferring injections, if VA or macular thickness worsened because of DME, injections resumed until stability again occurred. If a participant's nonstudy eye also required anti-VEGF treatment during the trial, it was given the same agent as the study eye. Participants were excluded for unavailable for follow-up (not including deaths) before the 1-year visit (n = 29) or receiving an anti-VEGF agent other than randomized to receive (n = 7), leaving a total of 624 participants.

Quality of Life

Participant VA levels at each visit were converted to QALYs using data from Brown et al,[6] who linked VA in a patient's better-seeing eye with health-related quality of life. The VAs were obtained from the trial, converted to Snellen acuities, and assigned a utility based on conversion tables. Quality-of-life levels at monthly visits during the first year were summed, providing an aggregate QALY value for the entire year for each participant.

Calculated quality of life was reduced for participants experiencing adverse events possibly caused by the study agent, including myocardial infarction, cerebrovascular accident, endophthalmitis, retinal detachment, and vitreous hemorrhage. Both myocardial infarction and cerebrovascular accident were assumed to reduce quality of life for the remainder of one's life; other adverse events resulted in one-time quality-of-life decrements (eTable 1 in the Supplement). During the 1-year trial horizon, adverse events were identified and incorporated into the analysis based on patient-level trial data, differing nominally among the treatment arms. Because a difference in adverse event rates and mortality among the treatment arms was not identified at 1 year in the trial or previous meta-analyses,[1,7] the same pooled rates were used for all anti-VEGF agents in modeling projections beyond 1 year.

To assess cost-effectiveness beyond 1 year, a mathematical model based on prior cost-effectiveness analyses for DME was developed (eFigure 1 in the Supplement).[8,9] A prior trial using ranibizumab for DME found relatively stable mean VAs 1 to 5 years after treatment initiation[4]; accordingly, the model assumes a patient's VA at 1 year remains constant throughout the remainder of the patient's life, with ongoing monitoring and anti-VEGF therapy as needed. This assumption was varied widely in sensitivity analyses.

Costs

Overall costs were calculated by applying standardized unit costs to treatment and adverse event data from the trial, specifically including adverse events and treatments with the potential to vary among the treatment arms (eTable 2 and eTable 3 in the Supplement). Injection costs were based on the average wholesale prices of each anti-VEGF agent and Medicare physician fees for administration in an office-based setting. Because trial protocol dictated that participants requiring treatment in the nonstudy eye receive the same agent as the study eye, which could potentially affect quality-of-life outcomes, we included costs for both study eye and nonstudy eye treatments. Adverse event costs were based on studies[10,11] of long-term costs of myocardial infarction, cerebrovascular accident, and legal blindness. Costs not expected to vary among the treatment arms were not captured, including office visit costs, unrelated medical costs, and indirect costs, such as caregiver burden. Thus, this analysis provides an accurate estimate of incremental costs among the treatment arms but not of overall medical costs associated with DME. Five-year data from a prior trial[4] using ranibizumab were used to estimate the decreasing rates of injection and laser treatment during the longer term (eTable 1 in the Supplement).

Statistical Analysis

Unpaired, 2-tailed *t* tests assessed the significance of cost and quality-of-life differences in 1-year data from the trial. Calculated *P* values reflect subject-level variance from trial data but do not account for uncertainty in unit cost or quality-of-life data from outside sources.

Sensitivity Analyses

To assess robustness of these results and explore how different assumptions might affect cost-effectiveness of the therapies, several sensitivity analyses were performed. In univariate and bivariate sensitivity analyses, effects of varying 1 or 2 key parameters at a time were assessed. In the base case analysis, quality of life was mapped to visual acuity in the patient's better-seeing eye; a sensitivity analysis used data from the UK-based Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) trial of anti-VEGF therapy for DME to map quality of life to VA in the patient's treated eye (whether it was the better- or worse-seeing eye).[12] The effects of varying the time horizon of the modeling projections (1-30 years), changes in VA achieved from using the 3 agents for 10 years (±20 letters), adverse event rates (0%-100% of base case), and others were explored. Costs of aflibercept and ranibizumab were varied to determine at what prices they would have an ICER below $100 000 per QALY, a threshold commonly considered meaningful for determining cost-effectiveness in the United States.[13-17]

To assess uncertainty in model inputs, a probabilistic sensitivity analysis was performed. Synthetic trial treatment groups were created by randomly drawing 200 participants from each trial arm, with replacement; values for model parameters, including costs, quality of life, and adverse event rates, then were drawn at random from distributions, reflecting their uncertainty. This process was repeated 10 000 times with cost-effectiveness results calculated for each iteration to obtain a distribution of probabilities for each treatment strategy to be cost-effective at different societal willingness-to-pay values per QALY.

Results

Quality of Life

The study included 624 participants (mean [SD] age, 60.6 [10.5] years; 45.7% female; 65.5% white), 209 in the aflibercept group, 207 in the bevacizumab group, and 208 in the ranibizumab group. For the aflibercept, bevacizumab, and ranibizumab arms, respectively, the mean QALYs (**Table 1**) were 0.869 (95% CI, 0.857-0.880), 0.849 (95% CI, 0.835-0.862), and 0.857 (95% CI, 0.843-0.872) during the first year of the trial; 0.835 (95% CI, 0.817-0.854), 0.823 (95% CI, 0.807-0.840), and 0.829 (95% CI, 0.813-0.846) for participants with worse baseline vision; and 0.901 (95% CI, 0.891-0.911), 0.875 (95% CI, 0.855-0.895), and 0.884 (95% CI, 0.861-0.907) for those with better baseline vision (Table 1). Differences in mean QALYs among the treatment arms were largest for aflibercept vs bevacizumab among all participants ($P = .03$) (eTable 4 in the Supplement) and aflibercept vs bevacizumab among those with better baseline vision ($P = .02$) (eTable 4 in the Supplement). All other comparisons had $P > .15$ (eTable 4 in the Supplement).

Of note, these outcomes may appear at odds with original trial results indicating the greatest VA benefit of aflibercept vs bevacizumab among the worse baseline vision group. This difference reflects the nonlinear association between VA and quality of life, as well as the fact that QALYs were summed for each month in this analysis, whereas VA was compared only at 1 year in the original trial (eMaterial in the Supplement).

Resources and Costs

Total mean costs per participant during 1 year (including study eye and nonstudy eye anti-VEGF injections, laser photocoagulation, and adverse events) in the aflibercept, bevacizumab, and ranibizumab groups, respectively, were $26 100 (95% CI, $24 400-27 700), $4100 (95% CI, $3000-5200), and $18 600 (95% CI, $17 100-20 200) (all differences $P < .001$) (**Figure 1**). Anti-VEGF injections include the agent costs and a $102.97 fee per injection. Overall mean costs were higher for those with worse baseline vision ($28 100, $5000, and $20 400, respectively) and lower for those with better baseline vision ($24 100, $3200, and $16 900, respectively).

The largest component of total cost was study eye anti-VEGF injections, comprising 68%, 37%, and 63% of total cost in the aflibercept, bevacizumab, and ranibizumab groups, respectively (Figure 1). Regardless of baseline vision, study eye

Table 1. Cost-effectiveness Outcomes

	1-Year Horizon				10-Year Horizon (Projections)			
	Cost, 2015 US$	Utility, QALYs	ICER vs Bevacizumab, US$ per QALY[a]	ICER vs Ranibizumab, US$ per QALY	Cost, 2015 US$	Utility, QALYs	ICER vs Bevacizumab, US$ per QALY	ICER vs Ranibizumab, US$ per QALY[a]
All Patients								
Bevacizumab	4100	0.849	NA	NA	39 800	6.80	NA	NA
Ranibizumab	18 600	0.857	1 730 000	NA	79 400	6.87	603 000	NA
Aflibercept	26 100	0.869	1 110 000	648 000	102 500	6.98	349 000	203 000
Baseline Visual Acuity of ≤20/50[b]								
Bevacizumab	5000	0.823	NA	NA	40 700	6.60	NA	NA
Ranibizumab	20 400	0.829	2 450 000	NA	81 200	6.65	817 000	NA
Aflibercept	28 100	0.835	1 870 000	1 270 000	104 500	6.82	287 000	135 000
Baseline Visual Acuity of 20/32-20/40[c]								
Bevacizumab	3200	0.875	NA	NA	38 900	7.01	NA	NA
Ranibizumab	16 900	0.884	1 500 000	NA	77 700	7.09	506 000	NA
Aflibercept	24 100	0.901	798 000	422 000	100 600	7.14	474 000	428 000

Abbreviations: ellipses, data not applicable; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life-year.

[a] The ICERs for ranibizumab and aflibercept are presented in comparison to bevacizumab. When comparing all 3 agents, ranibizumab would be dominated by aflibercept (lower utility but higher ICER than aflibercept). The ICERs are calculated from unrounded cost and utility values and thus may differ from values calculated based on the rounded costs and utilities in the table.

[b] Electronic-Early Treatment Diabetic Retinopathy Study letter score of 69 (approximately 20/50 or worse).

[c] Electronic-Early Treatment Diabetic Retinopathy Study letter score of 78 to 69 (approximately 20/32-20/40).

anti-VEGF injection costs were higher with aflibercept compared with bevacizumab or ranibizumab and with ranibizumab compared with bevacizumab (all differences $P < .001$). A difference in cost for adverse events or laser photocoagulation was not identified among the treatment arms for any of the baseline vision subgroups.

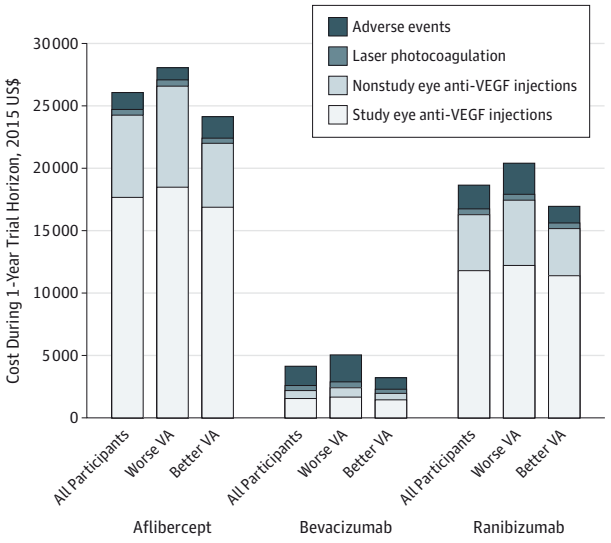
One-Year Cost-effectiveness

For all participants, the ICERs of aflibercept and ranibizumab compared with bevacizumab were $1 110 000 per QALY and $1 730 000 per QALY, respectively (Table 1). For the subgroup with worse baseline vision, the ICERs were $1 870 000 per QALY and $2 450 000 per QALY; with better baseline vision, they were $798 000 per QALY and $1 500 000 per QALY. The ICER of aflibercept compared with ranibizumab was $648 000 per QALY for all participants, $1 270 000 per QALY for the worse baseline vision subgroup, and $422 000 per QALY for the better baseline vision subgroup.

Longer-term Projections

The mathematical model of longer-term results produced similar 3-year adverse event rates, 5-year survival, and life expectancy to other published studies of similar populations, supporting the validity of these projections (eTable 5 in the Supplement).[10-12] Projected during a 10-year horizon, among all participants, the worse baseline vision subgroup, and the better baseline vision subgroup, respectively, the difference in QALYs with aflibercept vs bevacizumab was 0.18, 0.22, and 0.13 (Table 1). Among all participants, the worse baseline vision subgroup, and the better baseline vision subgroup, respectively, the ICERs of aflibercept and ranibizumab vs bevacizumab were $349 000 per QALY and $603 000 per QALY, $287 000 per QALY and $817 000 per QALY, and $474 000 per QALY and $506 000 per QALY (Table 1). Among all participants, the worse baseline vision subgroup, and the better baseline vision subgroup, respectively, the ICER of aflibercept vs ranibizumab was $203 000 per QALY, $135 000 per QALY, and $428 000 per QALY.

Figure 1. Costs During 1 Year Divided Into Study and Nonstudy Eye Anti-Vascular Endothelial Growth Factor (VEGF) Injections Separately, Laser Photocoagulation, and Adverse Events



Costs are presented for all participants and the worse and better visual acuity (VA) subgroups. Anti-VEGF injections include the agent costs and a $102.97 fee per injection.

Drug Cost Thresholds

Table 2 indicates how much the drug costs of aflibercept and ranibizumab would need to be reduced for them to become cost-effective ($100 000 per QALY) relative to bevacizumab. Across

Table 2. Cost Thresholds for Ranibizumab and Aflibercept

	Current Drug Cost per Dose, 2015 US$[a]	1-Year Horizon: Maximum Cost per Dose to Achieve ICER of $100 000 per QALY Relative to Bevacizumab, 2015 US$[a]	1-Year Horizon: Relative Reduction From Current Cost, %	10-Year Horizon (Projections): Maximum Cost per Dose to Achieve ICER of $100 000 per QALY Relative to Bevacizumab, 2015 US$[a]	10-Year Horizon (Projections): Relative Reduction From Current Cost, %
All Patients					
Ranibizumab	1170	100	91	230	80
Aflibercept	1850	240	87	570	69
Baseline Visual Acuity of ≤20/50[b]					
Ranibizumab	1170	94	92	190	84
Aflibercept	1850	250	87	700	62
Baseline Visual Acuity of 20/32-20/40[c]					
Ranibizumab	1170	94	92	260	77
Aflibercept	1850	230	88	410	78

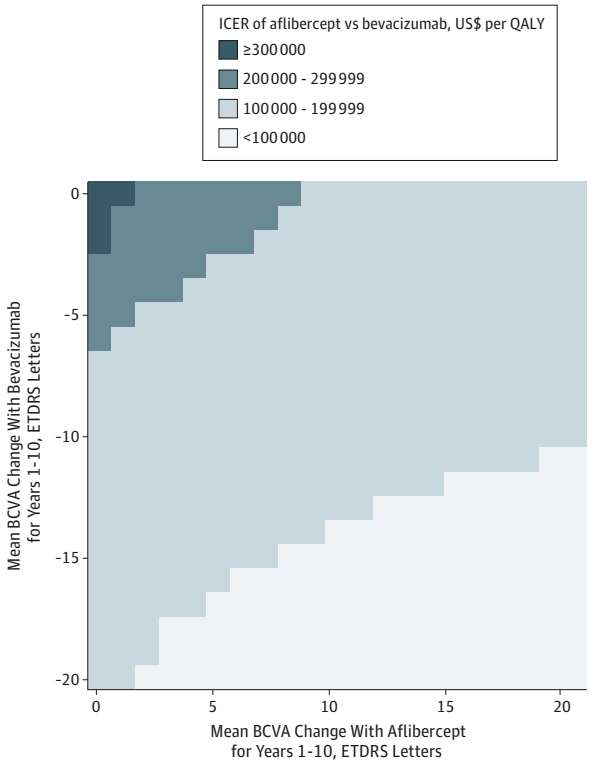
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

[a] Cost per dose includes drug cost and compounding cost for bevacizumab.

[b] Electronic-Early Treatment Diabetic Retinopathy Study letter score less than 69 (approximately 20/50 or worse).

[c] Electronic-Early Treatment Diabetic Retinopathy Study letter score of 78 to 69 (approximately 20/32-20/40).

Figure 2. The Aflibercept-Bevacizumab Incremental Cost-effectiveness Ratio (ICER) for Varying Assumptions for Visual Acuity (VA) Changes in 10 Years



The changing color indicates the 10-year ICER based on VA change with each drug. BCVA indicates best-corrected VA; ETDRS, Early Treatment Diabetic Retinopathy Study letter score.

varying time horizons and baseline vision subgroups, the per-dose cost of aflibercept would need to decrease by 60% to 90%. Considering all patients, those with worse baseline vision, and those with better baseline vision, respectively, the cost per dose of aflibercept would need to decrease below $240, $250, or $230 (vs a current cost of $1850) to become cost-effective relative to bevacizumab during 1 year and below $570, $700, or $410 for the same 3 groups during a 10-year horizon. Ranibizumab would require even larger cost decreases to become cost-effective relative to bevacizumab (75%-95%, depending on the subgroup and the time horizon). eTable 6 and eTable 7 in the Supplement give the costs required to reach alternative cost-effectiveness thresholds of $50 000 per QALY and $150 000 per QALY. When compared with ranibizumab, aflibercept's cost would need to be reduced by 18% considering all patients, 9% for those with worse baseline vision, and 28% for those with better baseline vision to reach a cost-effectiveness threshold of $100 000 per QALY at 10 years (eTable 8 in the Supplement). eTable 9 in the Supplement gives the 10-year ICERs for a wide range of costs for aflibercept or ranibizumab.

Sensitivity Analyses

In univariate sensitivity analyses, varying the time horizon (eFigure 2 in the Supplement), adverse event rates with the 3 drugs (eFigure 3 in the Supplement), longer-term anti-VEGF injection frequency (eFigure 4 in the Supplement), and the methods used to convert vision into quality of life (eTable 10 in the Supplement), aflibercept and ranibizumab never reached an ICER below $100 000 per QALY compared with bevacizumab.

Because quality-of-life benefits of treatment were linked to vision in the better-seeing eye in the base case analysis, a subgroup of only those with better vision in the study eye vs the nonstudy eye was examined. In this subgroup, the ICERs of aflibercept and ranibizumab, respectively, compared with bevacizumab were $467 000 per QALY and $603 000 per QALY at 1 year and $210 000 per QALY and $231 000 per QALY at 10 years.

When simulating variable long-term VA outcomes, aflibercept reached an ICER below $100 000 per QALY relative to bevacizumab only if aflibercept had unrealistic long-term gains in VA and bevacizumab had losses (**Figure 2**). For instance, if aflibercept produced a 12-letter mean gain in VA during years 2 to 10 of treatment and bevacizumab produced a 13-letter mean loss, then aflibercept would have an ICER below $100 000 per QALY relative to bevacizumab. For aflibercept to reach an ICER below $100 000 per QALY compared with ranibizumab at 10 years, it would require additional mean VA gains of at least 5 letters relative to ranibizumab for years 2 to 10 (eFigure 5 in the Supplement).

A probabilistic sensitivity analysis assessed overall uncertainty in patient outcomes and parameter assumptions. eFigure 6

in the Supplement shows the resulting estimates of the likelihood that each treatment will be optimal (ie, cost-effective), defined as producing the greatest QALYs while maintaining an ICER below a set willingness to pay per QALY. During a 1-year horizon, there was a greater than 95% likelihood that bevacizumab would be the optimal therapy, irrespective of baseline vision, as long as willingness to pay is less than $530 000 per QALY. During a 10-year horizon, bevacizumab would have a greater than 90% likelihood of being optimal at a willingness to pay $100 000 per QALY, irrespective of baseline VA. For the subgroup of patients with worse baseline vision, during a 10-year horizon aflibercept is more likely to be optimal than bevacizumab or ranibizumab at willingness-to-pay values of $230 000 per QALY or greater.

Discussion

In the first year results of a DRCR.net trial in eyes with VAs of 20/50 or worse because of DME, aflibercept produced greater mean VA gains compared with bevacizumab or ranibizumab. The current analysis suggests that the VA benefits of aflibercept translate into modest quality-of-life improvements but at a high cost relative to bevacizumab, with the ICERs substantially higher than thresholds of $50 000 to $150 000 per QALY frequently cited in cost-effectiveness literature and US guidelines. They remain above these threshold values even under broad alternative assumptions. It is unlikely that any realistic differences in VA achieved with the 3 agents during years 2 to 10 (in the range of changes seen in prior studies[1,4,18-20]) would alter their relative cost-effectiveness.

With rapidly increasing US health care costs and given the widely varying costs of intravitreous anti-VEGF agents, it seems important that payers, policymakers, and physicians consider both the costs and benefits of these agents. This analysis demonstrates that, from the payer or policymaker perspective, using bevacizumab rather than the more expensive agents would be cost-effective. Similarly, in contexts where bevacizumab is not available, 0.3 mg of ranibizumab would be more cost-effective than aflibercept.

From the perspective of patients or physicians, however, the decision seems less clear-cut. For some patients with DME, the expected additional visual benefits conferred by aflibercept compared with bevacizumab at 1 year or the perceived concerns over repackaging risks or lack of a US Food and Drug Administration indication with bevacizumab may outweigh the added health system cost ($22 000 at 1 year) and may outweigh any added personal expenses, such as copayments. This tension highlights the challenge of balancing varying perspectives of patients, physicians, payers, and policymakers when efficacy results and cost-effectiveness are at odds or when inconsistent comparative safety results across these agents are reported in the literature.

Study limitations include using trial data only through 1 year of follow-up; longer-term results relied on outside data sources and mathematical modeling. However, sensitivity analyses indicate that results beyond 1 year would have to be strikingly different from prior data on long-term anti-VEGF outcomes[1,4,18-20] to alter the study findings. Next, the bevacizumab in this trial was repackaged or compounded into sterile vials, which might cost more than typical costs of repackaging. However, even if the price per bevacizumab dose was raised to $710, such that a whole 4-mL container is used for every injection with the excess discarded,[2] thus forgoing the need for repackaging, bevacizumab remains the most cost-effective option (eTable 9 in the Supplement). In addition, quality-of-life outcomes were based on VA outcomes and prior data relating VA to quality of life; although VA is a reliable predictor of quality of life, direct measurement of quality of life still would be preferable.[6] Patient-specific factors, such as VA in the untreated eye, also could alter cost-effectiveness results for an individual patient. It is important to exercise caution in applying these results to other countries; although the data indicate that aflibercept and ranibizumab are not cost-effective in the United States, differing cost structures or lower negotiated prices may alter their cost-effectiveness in other health care systems.

Conclusions

Aflibercept (2.0 mg) and ranibizumab (0.3 mg) are not cost-effective relative to bevacizumab for treatment of DME unless their prices decrease substantially. Likewise, in contexts where bevacizumab is unavailable for DME treatment, aflibercept is not cost-effective relative to ranibizumab. From a societal perspective, bevacizumab as first-line therapy for DME would confer the greatest value, along with substantial cost savings vs the other agents. These results highlight the challenges that physicians, patients, and policymakers face when safety and efficacy results are at odds with cost-effectiveness results.

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Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: Ross, Hutton, Stein, Bressler, Jampol.
Drafting of the manuscript: Ross, Hutton, Stein, Jampol.
Critical revision of the manuscript for important intellectual content: All authors.
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