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Cost-effectiveness of Intravitreous Ranibizumab Compared With Panretinal Photocoagulation for Proliferative Diabetic Retinopathy

Secondary Analysis From a Diabetic Retinopathy Clinical Research Network Randomized Clinical Trial

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IMPORTANCE The Diabetic Retinopathy Clinical Research Network Protocol S randomized clinical trial results suggest that ranibizumab is a reasonable treatment alternative to panretinal photocoagulation (PRP) when managing proliferative diabetic retinopathy (PDR), with or without concomitant baseline diabetic macular edema (DME). However, ranibizumab injections are costly. Thus, it would be useful to examine the relative cost-effectiveness of these 2 treatment modalities.

OBJECTIVE To evaluate incremental cost-effectiveness ratios of 0.5-mg ranibizumab therapy vs PRP for PDR.

DESIGN, SETTING, AND PARTICIPANTS Preplanned secondary analysis using efficacy, safety, and resource utilization data through 2 years of follow-up at 55 US sites for 213 adults with PDR. Data were collected from February 2012 to January 2015.

INTERVENTIONS Intravitreous 0.5-mg ranibizumab at baseline and as frequently as every 4 weeks based on a structured retreatment protocol or PRP at baseline for PDR. Eyes in both groups could receive ranibizumab for concomitant DME.

MAIN OUTCOMES AND MEASURES Incremental cost-effectiveness ratios of ranibizumab compared with PRP evaluated within 2 prespecified subgroups for the study eye: with baseline vision-impairing (Snellen equivalent 20/32 or worse) DME and without baseline vision-impairing DME.

RESULTS The study included 305 adults with PDR, the mean age was 52 years, 44% were women, and 52% were white. Of the 46 participants with PDR and vision-impairing DME at baseline, 21 were assigned to the ranibizumab group and 25 to the PRP group (plus ranibizumab for DME). Among the remaining participants without baseline vision-impairing DME, 80 and 87 were in the ranibizumab and PRP groups, respectively. For participants with and without baseline vision-impairing DME, the incremental cost-effectiveness ratios of ranibizumab therapy compared with PRP were $55 568/quality-adjusted life-year and $662 978/quality-adjusted life-year, respectively, over 2 years.

CONCLUSIONS AND RELEVANCE Over 2 years, compared with PRP, 0.5-mg ranibizumab as given in this trial is within the $50 000/quality-adjusted life-year to $150 000/quality-adjusted life-year range frequently cited as cost-effective in the United States for eyes presenting with PDR and vision-impairing DME, but not for those with PDR without vision-impairing DME.

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Supplemental content

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Diabetic retinopathy is the most common cause of blindness among working-age adults.[1,2] Many patients have nonproliferative diabetic retinopathy; however, some develop proliferative diabetic retinopathy (PDR), which can lead to blindness from traction retinal detachment, vitreous hemorrhage, or neovascular glaucoma. Panretinal photocoagulation (PRP) has been the standard care for treating most eyes with PDR for decades but destroys retinal tissue, which may cause iatrogenic peripheral vision loss or exacerbation of diabetic macular edema (DME), resulting in central vision loss. The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol S randomized clinical trial comparing intravitreous antivascular endothelial growth factor (anti-VEGF) therapy using 0.5-mg ranibizumab vs PRP for patients with PDR demonstrated that eyes in the ranibizumab group had a mean visual acuity change from baseline to 2 years that was noninferior to PRP.[3] In addition, the ranibizumab group had better outcomes across a variety of dimensions, including better visual acuity change from baseline over 2 years (area under the curve), less peripheral visual field sensitivity loss, fewer vitrectomies for complications of PDR, and fewer eyes developing DME with vision loss among eyes without DME at baseline. Eyes in both groups could receive ranibizumab for treatment of DME.

However, ranibizumab therapy is much more expensive than PRP treatment. Each single-use vial of 0.5-mg ranibizumab costs $1916 plus a $103 procedural or surgical fee for administering the injection.[4] By comparison, each PRP treatment costs $345.[4] Because patients often require multiple injections, the cost differential between the 2 treatment options can be substantial. Thus, while ranibizumab may be a viable alternative therapy to PRP for clinical outcomes, questions remain as to which is more cost-effective. This study reports a preplanned secondary analysis from the DRCR.net Protocol S assessing incremental cost-effectiveness of 0.5-mg ranibizumab vs PRP for the treatment of PDR.

Key Points

Question What are the incremental cost-effectiveness ratios of 0.5-mg ranibizumab therapy to panretinal photocoagulation for proliferative diabetic retinopathy?

Findings This preplanned secondary analysis of a randomized clinical trial found that for participants with and without baseline vision-impairing diabetic macular edema, the incremental cost-effectiveness ratios of ranibizumab therapy compared with panretinal photocoagulation were $55 568/quality-adjusted life-year and $662 978/quality-adjusted life-year, respectively, over 2 years.

Meaning Compared with panretinal photocoagulation, 0.5-mg ranibizumab was cost-effective for eyes presenting with proliferative diabetic retinopathy and vision-impairing diabetic macular edema but not for those with proliferative diabetic retinopathy without vision-impairing diabetic macular edema.

Methods

Overview

In a DRCR.net randomized clinical trial at 55 clinical sites throughout the United States from February 2012 to January 2015, trial participants were at least 18 years old, had type 1 or 2 diabetes, had PDR in at least 1 eye, no prior PRP, no intraocular anti-VEGF therapy in the prior 2 months, and a best-corrected visual acuity letter score of at least 24 (approximate Snellen equivalent of 20/320 or better). If both eyes were eligible, participants could have 2 eyes in the study, 1 eye treated with PRP and 1 with ranibizumab. However, because it is not possible to partition cost-effectiveness of each treatment when both eyes received different treatments, this analysis only evaluates the 213 participants (70% of study participants) with 1 study eye. The study adhered to the tenets of the Declaration of Helsinki and was approved by local institutional review boards or a central institutional review board if the site did not have a local board. Study participants provided written informed consent.

Eyes assigned to ranibizumab injections for PDR were treated as often as monthly based on specific retreatment criteria.[3] These eyes also could receive PRP if protocol-defined failure criteria were met. Eyes assigned to PRP for PDR received PRP at baseline and then again during follow-up if the size or extent of neovascularization increased. Eyes in both groups were required to receive 0.5-mg ranibizumab for vision-impairing central-involved DME (visual acuity letter score ≤78 [approximate Snellen equivalent 20/32 or worse]) at baseline and could receive ranibizumab injections to treat DME if needed during the course of the trial. Because eyes with vision-impairing DME at baseline were required to initiate ranibizumab therapy for DME at entry in both treatment groups, the cost-effectiveness analysis of the 2 interventions was performed within subgroups for persons with and without vision-impairing DME at baseline. Additional details on the study protocols and eligibility can be found in the publication on the primary outcome.[3]

Analysis Plan

All eyes had best-corrected visual acuity measurements obtained at baseline and every 16 weeks. The protocol planned an economic analysis and specified collection of data on cost and health-related quality of life, enabling a cost-utility analysis to be performed. During the trial, resource utilization data were collected, including number of clinic visits and number and types of diagnostic and therapeutic ocular procedures performed in each group. The study also collected functional outcome data related to vision at baseline and annually.[5-7] Other outcomes included patient-level health preferences using a time-tradeoff questionnaire.[8] A P value of < .05 was considered significant, and P values are 2-sided.

Costs

To capture patient resource utilization during the trial, cost data for all diagnostic/therapeutic ocular procedures performed were tabulated to obtain a total cost for eye care services during 2 years of follow-up. Costs were calculated based on the 2016 Medicare fee schedule of allowable charges and included physician and facility fees.[4] In addition, costs associated with treatment of ocular (eg, vitrectomy for complications of PDR or endophthalmitis) and systemic adverse events

Table 1. Mean per-Patient Costs of Ranibizumab and Panretinal Photocoagulation Groups Over 2 Years of Follow-up (in 2016 US Dollars)

Clinic Visits/ Diagnostic Procedures	Vision-Impairing DME At Baseline, $			
	With[a]		Without	
	PRP for PDR, Ranibizumab for DME (n = 25)	Ranibizumab for PDR and DME (n = 21)	PRP (n = 87)	Ranibizumab (n = 80)
Clinic visits/diagnostic procedures	908	1258	709	1287
PRP	667	131	517	26
Anti-VEGF injection procedure	724	1242	177	1017
0.5-mg Ranibizumab	13 413	22 994	3282	18 826
Vitrectomies	947	705	900	0
Other intraocular therapies[b]	763	684	562	9
Systemic adverse events[c]	7098	2560	1298	1411
Total[d]	24 520	29 574	7445	22 576

Abbreviations: Anti-VEGF, anti-vascular endothelial growth factor; DME, diabetic macular edema; PRP, panretinal photocoagulation.

[a] With visual acuity letter score less than 78 (approximate Snellen equivalent 20/32 or worse) at baseline.

[b] Includes treatment for ocular adverse events such as endophthalmitis.

[c] Systemic adverse events include myocardial infarction and cerebrovascular accident.

[d] Participants in all groups received 0.5-mg ranibizumab if they developed DME over the 2 years of the trial.

(eg, myocardial infarction and cerebrovascular accident) that potentially may be associated with treatment during the trial were computed. A detailed listing of costs can be found in eTables 1 and 2 in the Supplement.

Health Utility

To capture changes in health-related quality of life associated with receipt of the 2 interventions over the course of the trial, best-corrected visual acuities at the 16-week, 32-week, 52-week, 68-week, 84-week, and 104-week visit from the better-seeing eye were converted into quality-adjusted life-years (QALYs) using commonly used mappings by Brown et al.[9] Prior research has shown that quality of life is most closely related to vision in the better-seeing eye.[10] However, 3 other methods were used in the sensitivity analysis: 1 using the treated eye,[11] 1 using a utility scale with an upper anchor of perfect health instead of perfect vision, and 1 using patient time-tradeoff questions. More details can be found in the eAppendix in the Supplement.[12]

Cost-effectiveness

The incremental cost-effectiveness ratio (ICER) was calculated by taking the incremental cost of ranibizumab vs PRP and dividing by incremental QALYs gained of ranibizumab vs PRP. Incremental cost-effectiveness ratios were computed for subgroups with and without concomitant baseline DME. A higher ICER indicates a given intervention is less cost-effective than another.

Ten thousand bootstrap replications of the incremental effects and costs were created by sampling patients as well as sampling unit cost and visual acuity-to-utility data from distributions shown in eTable 1 in the Supplement. This nonparametric bootstrap creates incremental cost and QALY pairs used to create the cost-effectiveness acceptability curves that characterize overall uncertainty in the cost-effectiveness ratio.[13]

Results

Baseline characteristics of the study population for the cost-effectiveness analysis stratified by whether the eye was randomly assigned to receive PRP or ranibizumab and whether it had vision-impairing DME at baseline are shown in eTable 3 in the Supplement.

Costs

Participants in the PRP group receiving ranibizumab for vision-impairing DME at baseline received a mean of 7 ranibizumab injections during 2 years compared with 12 in the ranibizumab group with baseline DME. Over the 2-year study period, those with vision-impairing DME at baseline (**Table 1**) assigned to ranibizumab incurred costs of $29 574 compared with $24 520 for the PRP plus ranibizumab group (difference, $5053; 95% CI, −$7695 to $17 801). Those with PDR without vision-impairing DME at baseline assigned to ranibizumab incurred costs of $22 576 compared with $7445 for those given PRP, (difference, $15 131; 95% CI, $11 480 to −$18 782).

Health Utilities

When calculating health utilities based on best-corrected visual acuities in the better-seeing eye, ranibizumab showed a slight improvement vs PRP over 2 years. **Table 2** shows participants with baseline vision-impairing DME had improvement in QALYs with ranibizumab relative to PRP (0.031 vs −0.06); the difference between the therapies was 0.091 (95% CI, −0.079 to 0.261). For eyes without baseline vision-impairing DME, ranibizumab had a QALY of −0.007 compared with −0.03 QALY for eyes treated with PRP (difference, 0.023; 95% CI, −0.037 to 0.82). Differences in health utilities using other methods (eg, using visual acuities from the treated eye or using questionnaire data) are in eTables 4-6 in the Supplement.

Cost-effectiveness

For patients with PDR and vision-impairing DME at baseline, the ICER of ranibizumab compared with PRP during a 2-year horizon was $55 568/QALY. Among patients with PDR and no vision-impairing DME at baseline, the ICER was $662 978/QALY (Table 2). Results using alternative methods for evaluating utilities show that if best-corrected visual acuity in the study eye was used as a surrogate for health-related quality of life (rather than best-corrected vision in the better-seeing eye),

Table 2. Change in Quality-Adjusted Life-years and Cost-effectiveness Results During 2 Years (Utilities Converted From Visual Acuity in the Better-Seeing Eye)

Cost-effectiveness Results Over 2 y[a]	Vision-Impairing DME At Baseline					
	With[a]			Without		
	PRP for PDR and Ranibizumab for DME, $ (n = 25)	Ranibizumab for PDR and DME, $ (n = 21)	Difference, $ (95% CI)	PRP, $ (n = 87)	Ranibizumab, $ (n = 80)	Difference, $ (95% CI)
Costs	24 520	29 574	5053 (−7695 to 17 801)	7445	22 576	15 131 (11 480 to 18 782)
QALYs, y	−0.060	0.031	0.091 (−0.079 to 0.261)	−0.030	−0.007	0.023 (−0.037 to 0.082)
ICER	NA	NA	55 568/QALY	NA	NA	662 978/QALY

Abbreviations: DME, diabetic macular edema; ICER, incremental cost-effectiveness ratios; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; QALY, quality-adjusted life-year.

[a] Participants received ranibizumab or PRP for PDR with and without concomitant baseline DME (utilities converted from visual acuity in better-seeing eye). Individuals who died had a utility of 0 after the date of death. In converting from best-corrected visual acuity, letter scores were converted to Snellen visual acuities and then to utility levels using the mapping from Brown et al.[9]

the ICER of the ranibizumab group vs the PRP group was almost $200 000/QALY and more than $500 000/QALY for those with and without vision-impairing DME, respectively (eTable 7 in the Supplement). The directly elicited utilities were highly variable for patients in both treatment groups, partially owing to refusals to answer the time-tradeoff utility questions, further reducing statistical power on an already highly variable measure (details in the eAppendix in the Supplement). Therefore, calculating the ICER of ranibizumab vs PRP using this approach was not done. eTable 8 in the Supplement shows that varying the costs of the procedures performed based on their highest and lowest reimbursable values had minimal effect on the ICER.

Sensitivity Analyses

A 1-way sensitivity analysis (varying 1 parameter and keeping all other inputs the same) shows the largest driver of cost-effectiveness is the cost of the anti-VEGF agent (eTable 9 in the Supplement). If the cost of ranibizumab were to drop to $900 per dose, then use of the anti-VEGF therapy without PRP for patients with PDR and vision-impairing DME at baseline would be considered cost-saving (improve quality of life and cost less) compared with treatment using ranibizumab for DME along with PRP for PDR (**Figure 1**A and eTable 9 in the Supplement). In a 2-way sensitivity analysis (where all model inputs were kept the same except for 2 parameters varied), if the cost of ranibizumab dropped to $400 per dose and the cost of PRP rose to $600 per laser session, then the use of anti-VEGF therapy for patients with PDR and no vision-impairing DME at baseline would be about $100 000/QALY (Figure 1B and eTable 10 in the Supplement).

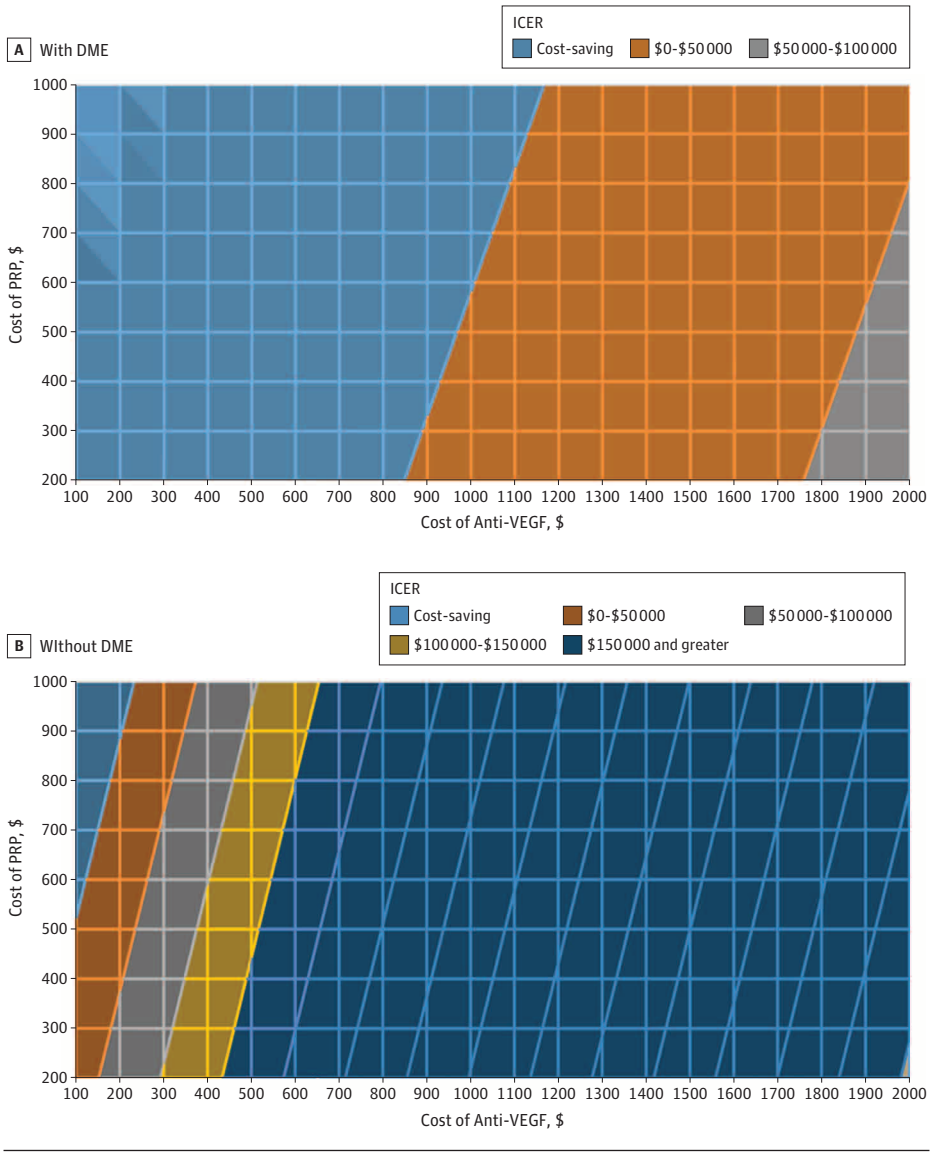
The cost-effectiveness acceptability curves show uncertainty in all parameters simultaneously. Among participants with vision-impairing DME at baseline, the ranibizumab group would be more likely to be considered cost-effective than PRP if a decision maker was willing to spend more than $60 000/QALY. However, for patients without baseline vision-impairing DME, PRP is more likely to be considered cost-effective unless the decision maker was willing to spend $700 000/QALY or more (**Figure 2**).

Discussion

This preplanned secondary analysis suggests that for patients with PDR without baseline vision-impairing DME, PRP is more cost-effective than ranibizumab treatment through the 2-year follow-up visit. However, ranibizumab alone may be a more cost-effective therapeutic option through at least 2 years for patients with PDR who also have concomitant vision-impairing DME at baseline compared with using PRP to treat PDR and ranibizumab to treat DME as given in this trial. These findings need to be considered in the context of the clinically relevant benefits of ranibizumab compared with PRP reported after 2 years of follow-up in this trial. These benefits included that the group assigned to ranibizumab without PRP for PDR had better visual acuity through 2 years, less peripheral visual field loss, required fewer vitrectomies, and, among eyes without vision-impairing DME at baseline, were less likely to develop DME with vision impairment. While ongoing follow-up of these study participants continues, outcomes beyond 2 years were not simulated in this cost-effectiveness analysis because to our knowledge, there are no data in the literature to provide a reasonable approximation of future visual acuity outcomes, frequency of adverse events including vitrectomies, number of treatments, and costs beyond 2 years for participants in each of the treatment arms. If the number of injections tapers off but vision gains persist, the longer-term cost-effectiveness may improve.

While the costs of 1 or 2 PRP treatments are less expensive than ranibizumab given 10 to 13 times over 2 years, it is important to compare the complexity of true costs with the complexity of gains in quality of life for the ranibizumab and PRP group as analyzed in this cost-effectiveness analysis. This DRCR.net cost-effectiveness analysis is substantially different from the methods used in a prior article[3,14] discussing costs of PRP vs ranibizumab using previously published data from the DRCR.net Protocol S but not from the DRCR.net investigators.[3,14] That article reported that intravitreous ranibizumab compared with no therapy would have an ICER of $19 150 over 2 years. Many differences exist between that analysis and the one presented here.

Figure 1. Two-Way Sensitivity Analysis Verifying Cost of Anti–Vascular Endothelial Growth Factor (VEGF) and Cost of Panretinal Photocoagulation (PRP) for Persons With and Without Vision-Impairing Diabetic Macular Edema (DME) at Baseline



Colors represent the incremental cost-effectiveness ratios. Although there are no official thresholds of cost-effectiveness in the United States, generally, interventions costing less than $50 000 to $150 000 would be considered cost-effective.[18]

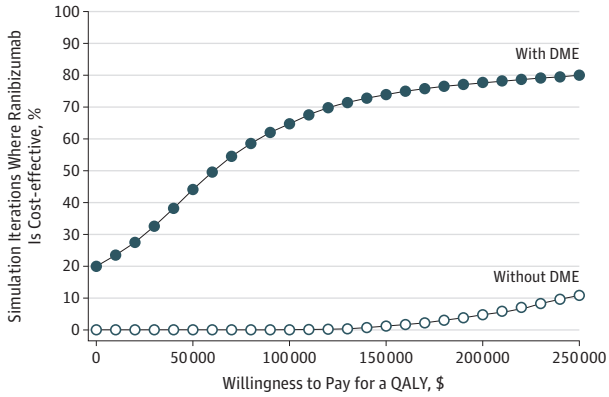
ICER indicates incremental cost-effectiveness ratios.

The other analysis used data from the Diabetic Retinopathy Study (from the 1970s) to model outcomes for eyes receiving PRP and assumed ranibizumab outcomes would be equivalent to PRP outcomes,[12,15] whereas our DRCR.net cost-effectiveness analysis used actual visual acuities along with other efficacy and safety outcomes from Protocol S. Our DRCR.net analysis also considered actual resource utilization from trial participants. Furthermore, our DRCR.net study directly compared cost-effectiveness of ranibizumab vs PRP as opposed to comparing each therapy vs a strategy of no treatment. Nowadays, observation of high-risk PDR would be considered unethical for most patients. In addition, our DRCR.net study examined the clinically relevant subpopulations of patients with vision-impairing DME at baseline vs those without baseline DME, demonstrating ranibizumab was cost-effective for patients with vision-impairing DME at baseline and not as cost-effective as PRP for patients without vision-impairing DME at baseline, justifying the need for a stratified analysis. Our DRCR.net analysis also performed a 2-way sensitivity analysis, simultaneously varying the costs of anti-VEGF and PRP, allowing readers to apply the study findings to other anti-VEGF agents (if one were to assume those agents have equivalent efficacy and safety profiles as 0.5-mg ranibizumab) and to different prices for these interventions in other countries.

Limitations

Nevertheless, there are several limitations to our DRCR.net analysis. First, the use of best-corrected visual acuity in the better-seeing eye or the study eye as a surrogate for overall health-related quality of life may not fully capture all aspects of quality of well-being associated with receipt of these inter-

Figure 2. Cost-effectiveness Acceptability Curve



Lines represent the probability ranibizumab was cost-effective (y-axis) at willingness-to-pay for quality-adjusted life-year (QALY) gains (x-axis).

ventions. A sensitivity analysis using patient-elicited utility scores rather than visual acuity levels to capture health-related quality of life was attempted; however, those measurements were highly variable and fraught with missing data, so they could not be incorporated into these analyses. Second, only direct medical costs of select events were captured. Other costs, such as costs associated with caregiver burden, transportation costs to visits, and costs associated with time away from work, were not considered. Third, this analysis only used a 2-year time horizon because, to our knowledge, there are no studies with longer follow-up periods to provide confident estimates on the resource use, adverse effects, and costs beyond 2 years. Fourth, the original Protocol S trial did not dictate the exact retreatment algorithm when using ranibizumab to treat DME for those participants who had DME requiring anti-VEGF therapy during the course of 2 years. Therefore, it is possible that differences in how participating physicians opted to treat the DME may have added additional variability to the results. It is not possible to know what the costs or QALYs would be if a strict regimen to treat vision-impairing DME, as was required by protocol in other DRCR.net studies for DME treatment,[16,17] was performed in this study. Fifth, this analysis did not attempt to quantify the health-related quality of life associated with peripheral visual field loss from PRP, which was substantially greater than the loss seen among eyes in the ranibizumab group and can have substantial effects on patients' quality of life. Sixth, diabetes often affects both eyes, but because of the design of this study, we caution the application of these results to patients with bilateral DME. Additional research is needed to assess this group. Finally, because this trial only examined 0.5-mg ranibizumab, these data do not provide cost-effectiveness estimates of other anti-VEGF agents that may be used in clinical practice such as aflibercept, bevacizumab, or 0.3-mg ranibizumab. While the costs of these agents are known, other costs and the QALYs cannot be computed because the visual acuity and other ocular outcomes, such as number of injections, rates of vitrectomy, or development of vision-impairing DME in the absence of such DME at baseline, when using the other agents, may differ compared with the findings in the DRCR.net trial that used 0.5-mg ranibizumab. The 2-way sensitivity analysis does provide information about the potential ICERs of these other anti-VEGF agents vs PRP if one assumes equivalent efficacy, safety, and resource use, as was noted when 0.5-mg ranibizumab was used in Protocol S.

Conclusions

Compared with PRP over 2 years, 0.5-mg ranibizumab as given in this trial is within the $50 000/QALY to $150 000/QALY range frequently cited as cost-effective in the United States for eyes presenting with PDR and vision-impairing DME but not for those without baseline vision-impairing DME. From a societal perspective, in developed countries such as the United States, ranibizumab through 2 years as an alternative therapy to PRP for PDR with vision-impairing DME at baseline provides clinically relevant benefits and also is cost-effective. However, for PDR without vision-impairing DME, which may be the more common clinical presentation, PRP is the more cost-effective treatment option through at least 2 years. These results should be tempered by the small numbers of eyes evaluated, especially for the subgroups with PDR and vision-impairing DME at baseline. The cost-effectiveness acceptability curves (Figure 2) highlight uncertainty related to the small numbers. Furthermore, the lack of cost-effectiveness among eyes without vision-impairing DME at baseline is at odds with the potential benefits of anti-VEGF therapy in this situation, including better visual acuity over 2 years, less peripheral visual field loss, fewer vitrectomies, and fewer eyes developing vision-impairing DME (among eyes without vision-impairing DME at baseline) for which anti-VEGF therapy subsequently would be considered. Additional data beyond 2 years would be valuable to determine whether the cost-effectiveness results obtained at 2 years persist with longer follow-up. Until then, considerations of visual acuity and other ocular outcomes (such as visual field loss, need for vitrectomy, and need for anti-VEGF therapy for DME among eyes without DME at the time of initiating treatment for PDR), ocular and systemic safety, adherence to and frequency of follow-up of each regimen, and patient preferences should be weighed by patients with physician guidance when deciding whether to consider initiating anti-VEGF or PRP for PDR.

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Invited Commentary

Incremental Cost-effectiveness of Proliferative Diabetic Retinopathy Treatments
The Certainty of Uncertainty

Steven M. Kymes, PhD

Kenneth J. Arrow, MA, PhD, is not a personality well known to most readers of *JAMA Ophthalmology*, but his groundbreaking work in economics and mathematics established a radically new paradigm for the social sciences. In 1963, with an article titled "Uncertainty and the Welfare Economics of Medical Care,"[1,2] he founded an entirely new field of economic research, health economics,[1,2] and in 1972 he received the Nobel Memorial Prize in Economics reflecting this body of work. More than 5 decades later, this remains the most cited article in the health economic literature, and the annual award for achievement given by the International Health Economic Association is the Kenneth Arrow Award.[1]

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Arrow's insight was that the lack of perfect knowledge concerning the risk of disease and the efficacy of treatment causes markets that are efficient in distributing products and services to be inefficient in allocating health services.[1] Arrow speculated that it was this asymmetry and inefficiency that led European governments to create strict regulatory regimens to seek to improve equity in distribution of health resources by controlling access to services.

Economic evaluation, or modeling of the cost and benefit of health care interventions, is a subdiscipline of health economics that benefited from Arrow's insights. Treatment processes are complex, and every value in the mathematical models of treatment developed by economic evaluators has a confidence interval representing uncertainty of the estimate. Thus, a proper economic evaluation includes 2 elements: (1) a point estimate referred to as the net benefit or incremental cost-effectiveness ratio (ICER); and (2) a sensitivity analysis that characterizes the uncertainty of the estimate and the confidence the decision maker can have in the model's result.

In this issue of *JAMA Ophthalmology*, Hutton et al[3] demonstrate the importance of exploring uncertainty when considering a treatment decision.[3] They present a comparison of ranibizumab with panretinal photocoagulation (PRP) for treatment of proliferative diabetic retinopathy. Hutton et al[3] examined the use of ranibizumab vs PRP in 2 settings: (1) the patient is experiencing visual impairment from diabetic macular edema, and (2) the patient is not experiencing visual impairment and treatment is used prophylactically. Their analyses yielded an ICER of $55 568 per quality-adjusted life-year (QALY) gained when the patient is experiencing visual impairment and $662 978/QALY when there is no edema-related impairment. The ICER is best interpreted as the value society must surrender to "purchase" a year of "perfect" health (ie, a QALY). Thus, a lower ICER is preferable to a high one, and whether a treatment is cost-effective is determined by comparing the ICER with the value society places on a QALY (willingness to pay [WTP]). In Canada and Europe, health authorities set the WTP for a QALY (typically a range between $50 000 and $100 000). In the United States, no payer authority has set a WTP, and indeed, by statute, the Centers for Medicare and Medicaid Services is banned from incorporating a QALY into their coverage decisions.[4] However, US investigators rely, as have Hutton et al, on a rule of thumb that tests a range of $50 000 to $150 000. By that standard, Hutton et al[3] found that use of ranibizumab for patients who already experience visual impairment would meet that standard. When clinicians are seeking to prevent progression to visual impairment, PRP would