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Cost-Effectiveness Analysis of Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema:

Economic Analysis of Diabetic Macular Edema Treatments

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Abstract

Objective—Perform a cost-effectiveness analysis of the treatment of Diabetic macular edema (DME) with ranibizumab plus prompt or deferred laser versus triamcinolone plus prompt laser. Data for the analysis was drawn from reports of the Diabetic Retinopathy Clinical Research Network (DRCRnet) Protocol I.

Design—Computer simulation based on Protocol I data. Analyses were conducted from the payor perspective.

Participants—Simulated participants assigned characteristics reflecting those seen in Protocol I.

Methods—Markov models were constructed to replicate Protocol I's 104 week outcomes using a microsimulation approach to estimation. Baseline characteristics, visual acuity (VA), treatments, and complications were based on Protocol I data. Costs were identified by literature search. One-way sensitivity analysis was performed and the results were validated against Protocol I data.

Main Outcome Measures—Direct cost of care for two years, change in VA from baseline, and incremental cost-effectiveness ratio (ICER) measured as cost per additional letter gained from baseline (ETDRS).

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Results—For sham plus laser (S+L), ranibizumab plus prompt laser (R+pL), ranibizumab plus deferred laser (R+dL), and triamcinolone plus laser (T+L), effectiveness through 104 weeks was predicted to be 3.46, 7.07, 8.63, and 2.40 letters correct, respectively. ICER values in terms of dollars per VA letter were $393 (S+L vs. T+L), $5,943 (R+pL vs. S+L), and $20 (R+dL vs. R +pL). For pseudophakics, the ICER value for comparison triamcinolone with laser versus ranibizumab with deferred laser was $14,690 per letter gained. No clinically relevant changes in model variables altered outcomes. Internal validation demonstrated good similarity to Protocol I treatment patterns.

Conclusions—In treatment of phakic patients with DME, ranibizumab with deferred laser provided an additional 6 letters correct compared to triamcinolone with laser at an additional cost of $19,216 over two years. That would indicate that if the gain in visual acuity seen at two years is maintained in subsequent years, then the treatment of phakic patients with DME using ranibizumab may meet accepted standards of cost-effectiveness. For pseudophakic patients, first line treatment with triamcinolone appears to be the most cost-effective option.

Introduction

Diabetic macular edema (DME) is the most common cause of visual impairment among people with diabetes living in the United States.[1] While risk of DME has been shown to vary with a number of factors including type of diabetes, disease duration, and insulin-dependence, it is expected to grow along with the prevalence of diabetes. Until recently, focal laser photocoagulation has been the standard treatment for DME as established by the Early Treatment of Diabetic Retinopathy Study (ETDRS).[2] Other modalities such as corticosteroid and anti-vascular endothelial growth factor (VEGF) and intravitreal (IV) injections have been investigated for DME treatment. The use of ranibizumab and triamcinolone were evaluated in the recently-published Diabetic Retinopathy Clinical Research Network (DRCR.net) randomized controlled trial Protocol I.[3,4] IV Ranibizumab plus either prompt or deferred laser treatments yielded greater increases in VA from baseline compared to sham injections plus laser treatment (control) and IV triamcinolone plus laser treatment. Compared to the control group, only regimens involving ranibizumab significantly increased the chance of improving by two or more lines of vision and significantly decreased the chance of losing two or more lines of vision. In subgroup analysis the investigators found that visual outcomes in pseudophakic eyes treated with ranibizumab and triamcinolone were similar. This would indicate that the effectiveness of triamcinolone may be reduced by lens toxicity associated with ocular steroid use.

Current estimates place annual health care expenditures at 17.6% of the GDP, the monetary value of all the finished goods and services produced within a country's borders in a specific time period, and this percentage may increase to over 20% over the next twenty five years.[4, 5] The cost of diabetic care, particularly among that of people suffering diabetic eye disease, makes a substantial contribution to this total. Although economic evaluation studies have not been heavily relied upon in this country, the information provided by this type of research is increasingly being recognized as a potentially helpful guide for policy makers, insurance companies, and other institutions responsible for allocating medical resources.[7] Published economic evaluations within the field of ophthalmology include reports on age-related macular degeneration (ARMD) treatment and diabetic retinopathy screening.[6-8] The current standard of care DME treatment was evaluated in a cost-effectiveness analysis (CEA) model based on ETDRS data.[11] Here we present an economic evaluation based entirely on Protocol I to provide direction to policy makers considering how to best incorporate the study's results into clinical practice.

Methods

We constructed a Markov decision model employing microsimulation to estimate the costs and effectiveness of the four treatment arms in Protocol I: sham injection plus laser therapy, IV ranibizumab plus laser therapy, IV ranibizumab plus deferred laser therapy, and IV triamcinolone plus laser therapy. The 104 week duration of the model was based on the time to two-year follow-up in Protocol I.[4] Subjects were assigned baseline characteristics and received monthly updated values of VA and ocular coherence tomography (OCT) measurement of macular thickness; all of these values were based on Protocol I data. Subjects accrued costs and were placed at risk for treatment complications as they progressed through the model. Analysis was conducted from the payor's perspective using Medicare allowable charges.[12] Total costs, effectiveness, and incremental cost effectiveness ratio (ICER) values were calculated from the model's microsimulation output. Uncertainty was assessed using one-way sensitivity analysis, and the internal validity of our model's output was validated against corresponding parameters from Protocol I.

Economic Evaluation with the Markov Model

The purpose of economic evaluation is to compare competing management strategies. Decision trees provide the mathematical framework for the evaluation of a process of care. The Markov model is a type of decision tree in which an iterative process is represented as a series of cycles of fixed time length (i.e., the Markov cycle; one month in our model to correspond to the follow-up periods in Protocol I). The microsimulation method of model estimation affords "subjects" memory of the paths they traverse in the model; in this way, our subjects retained their individual characteristics, treatment data, and costs. The flow of subjects through the model is depicted in Figure 1. The probabilities guiding subjects through branching decision points, costs of treatment, and treatment benefits were derived from Protocol I data and costs were drawn from the published literature.

Data Sources

We used the 2010 Medicare allowable charge for our costs. Change in VA, the number of injections required, and frequency of laser treatment were based upon data published in Protocol I. The DRCR investigators conducted a subgroup analysis of pseudophakic participants to consider the impact of lens toxicity on the cost-effectiveness of DME treatment. A separate economic model was constructed to estimate cost and benefit of treatment of pseudophakic eyes based upon Protocol I results.

Additional details of data sources and methods used to construct these models are provided in Technical Appendix, Tables 1-6 (available at http://aaojournal.org).

Data analysis

The model was estimated using a two stage Monte Carlo simulation. A simulated cohort of 1,000 "subjects" was modeled 100 times, each time re-sampling each parameter estimate from a specified distribution (for a total of 100,000 simulated trials). Mean values for total cost (dollars) and effectiveness (number of VA letters gained from baseline) were estimated for each group. The four groups were ranked from the least to most expensive strategy and the ICER was calculated by comparing each strategy to its next least expensive alternative. While cost-utility analysis is widely accepted as a method of analysis in Europe and Canada, it is not typically used by payors in the United States.[13] Consequently, we conducted our analyses to estimate the cost per letter gained. The value of a letter correct to health policy makers in the United States is unknown; therefore, we cannot determine whether a more effective (yet more expensive) treatment might be "cost-effective". We addressed this by we estimating what the change in visual acuity would translate into for quality adjusted life

years (QALYs) using the methods described by Sharma et al. to convert our baseline and primary endpoint visual acuities into units of utility.[14] These utilities were subsequently used to calculate incremental cost-utility ratio (ICUR) values. To do this we extrapolated the efficacy and cost of care beyond 104 weeks by recognizing that most of the gain in efficacy (and cost incurred) for both treatments was seen in the first year. Therefore, for ranibizumab we assumed that the VA seen in second year was continued in subsequent years; and for triamcinolone that the VA decline that began in year 2 was continued in subsequent years. We assumed that the cost of treatment in year 2 continued for subsequent years as well.

Validation

The model's internal validity was established by comparing output parameters to Protocol I data. Parameters considered included baseline characteristics, complication rates, visual outcomes, and treatment data.

Sensitivity Analysis

Due to the inherent uncertainty in model parameters, we performed one-way sensitivity analysis to determine if the model is sensitive to clinically relevant fluctuations in certain variables. We varied parameters over a 33% to 300% range in order to detect variables to which our model is sensitive. We considered altered cost-effectiveness relationships among treatment strategies as evidence of sensitivity.

Results

The variables used in the model are listed in Table 7. The absolute and incremental cost and effectiveness values of the four primary groups are detailed in Table 8. The incremental cost per letter gained in visual acuity was $393 (S+L vs. T+L), $5,943 (R+pL vs. S+L), and $20 (R+dL vs. R+pL). These results are illustrated in Figure 2.

Pseudophakic subgroup outcomes

The absolute and incremental cost and effectiveness values of the four subgroups among pseudophakic patients are detailed in Table 9. As sham laser and ranibizumab with prompt laser were dominated, only the ICER value for triamcinolone vs. ranibizumab with deferred laser ($14,690/letter) is reported. These are also illustrated in Figure 2.

Estimating incremental cost-utility ratio (ICUR)

The cumulative costs, utilities, and ICUR values associated with our extrapolation of multi-year regimens for triamcinolone and ranibizumab are detailed in Table 10. (Additional detail in Technical Appendix, Table 11 available at http://aaojournal.org.) Assuming the retreatment costs and visual outcomes seen in weeks 52-104 of Protocol I can be extrapolated to future years, we estimate that treatment with ranibizumab would be considered to be cost-effective at a willingness to pay of $100,000 within 10 years of treatment initiation.

Sensitivity Analysis

A total of eighteen variables were evaluated by one-way sensitivity analysis. No clinically relevant changes resulted in altered cost-effectiveness relationships.

Validation

The baseline characteristics, treatments, complication rates, and visual outcomes of simulated model subjects were compared to their corresponding values in Protocol I. Model

output was generally very similar to Protocol I data. The validation findings are detailed in Technical Appendix, Table 12 (available at http://aaojournal.org).

Discussion

In our analyses, we found that treatment of DME with ranibizumab with deferred laser is not likely to meet most accepted standards of cost-effectiveness at an incremental cost of $3,084 per letter gained in comparison to triamcinolone with laser if we limit our analyses to the benefit (and cost) experienced at two years. However, the economic benefit of treatment of DME is not experienced for only two years; it is experienced for the patient's remaining lifetime. When we extrapolate the experience of Protocol I participants beyond the trial, we find that by year 10 the benefits that the patient has enjoyed (in terms of years of useful vision) when compared to the cost of treatment over those years would be likely to meet the standards of cost-effectiveness in the U.S.

Assertions of "cost-effectiveness" only have meaning in the context of comparison to a standard that is set by a decision maker that defines what is cost-effective.[9] Policy makers in the United States---be they in government or the private sector---have not established any standards for cost-effectiveness, although they most certainly exist (they are simply not published).[10] Outside the U.S. other nations have relied on standards based upon the use of the quality adjusted life year (QALY) as a measure of effectiveness, with a standard of a willingness to pay of $50,000/QALY generally accepted as the standard for cost-effectiveness.[11] However, in the U.S. recent legislation banned the use of the QALY for making coverage decisions in the U.S.[12, 13] This leaves practitioners of economic evaluation in the U.S. without either a measure of effectiveness or a standard by which to evaluate the cost-effectiveness of our interventions. This is why we chose to use the cost per letter correct as the incremental cost-effectiveness ratio for our primary analysis. However, the willingness to pay for a letter correct is unknown.

It was to give some context to the "cost per letter correct" calculations that we converted to utility units using a method defined by Sharma et al.[14] At two years, an ICUR of $171,285 would not meet any published standard of cost-effectiveness. However, if the modest divergence in efficacy favoring ranibizumab over triamcinolone that was seen in the first two years continues; and the differences in retreatment costs also follow the pattern seen in these two years, then the ICUR for ranibizumab would be $87,584/QALY after ten years. This assumption concerning comparative efficacy is not unreasonable as the age-related macular degeneration literature has provided evidence that that visual outcomes are maintained for ranibizumab[14] but are less promising for triamcinolone.[14] Even if we correct in this assumption, at an ICUR of $87,584/QALY, treatment with ranibizumab would not meet accepted European and Canadian standards of cost-effectiveness. However, investigators assessing the implied standards of cost-effectiveness employed in the U.S. have found that many drugs and technologies in common use in the U.S. cost considerably more per QALY gained than $87,584.[15] For instance, the ICUR for mammography in women under the age of 50 is over $200,000 per QALY gained[16], and the use of FDG-PET for diagnosis of lung cancer ranges from $16,000 to over $200,000/QALY depending upon the pretest characteristics of the subject population.[17]

Treatment of Pseudophakic Eyes

We evaluated the cost-effectiveness of Protocol I treatment strategies in pseudophakics because this group is not at risk of cataract formation related to steroid exposure. In this simulation, we found that gaining an additional letter correct cost over $14,690/letter. This makes it highly unlikely that first line treatment of pseudophakic patients with ranibizumab

would be considered to be cost-effective. Instead, intravitreal triamcinolone should be considered for treating DME in pseudophakic eyes in patients not at high risk for glaucoma.

Validation

The similarities between model parameters and their corresponding values in Protocol I data support the validity of our model's output. The largest discrepancies between the model and Protocol I concerned variance of VA outcomes and the frequency of laser treatments. In modeling changes in VA we replicated the results of Protocol I very well, but we did find less statistical variation than reported by the DRCR investigators. However, health policy is typically based upon the mean values (as the entire population is being treated), not the entire distribution of values, and our model would become unstable if we incorporated the outliers reflected by the larger variance reported by the Protocol I group. The consequence of this was while we fit the overall VA outcomes well, we report fewer extreme outcomes (positive and negative) than Protocol I. It should be noted, however, that our sensitivity analyses did not find this deviation from Protocol I results to influence the cost-effectiveness decision.

We have conducted the first economic evaluation of DME treatment involving anti-VEGF agents and corticosteroids. Our findings indicate that for phakic patients, it is likely that treatment with ranibizumab would be considered to be cost-effective versus triamcinolone assuming that efficacy of ranibizumab is maintained over time. In pseudophakic patients at low risk for glaucoma, triamcinolone merits consideration as a first line therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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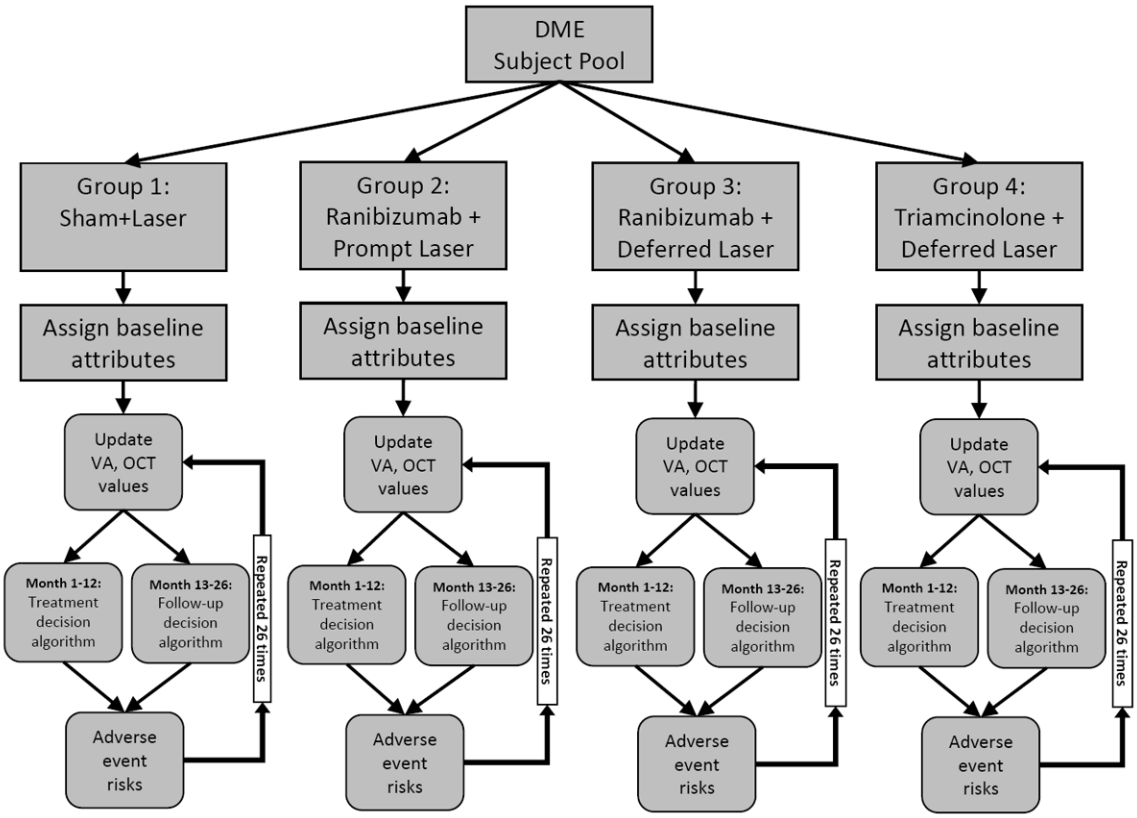

Figure 1. Bubble diagram of the treatment of diabetic macular edema (DME)

Schematic showing flow of Markov subjects through model.

DME-diabetic macular edema VA-visual acuity OCT-optical coherence tomography

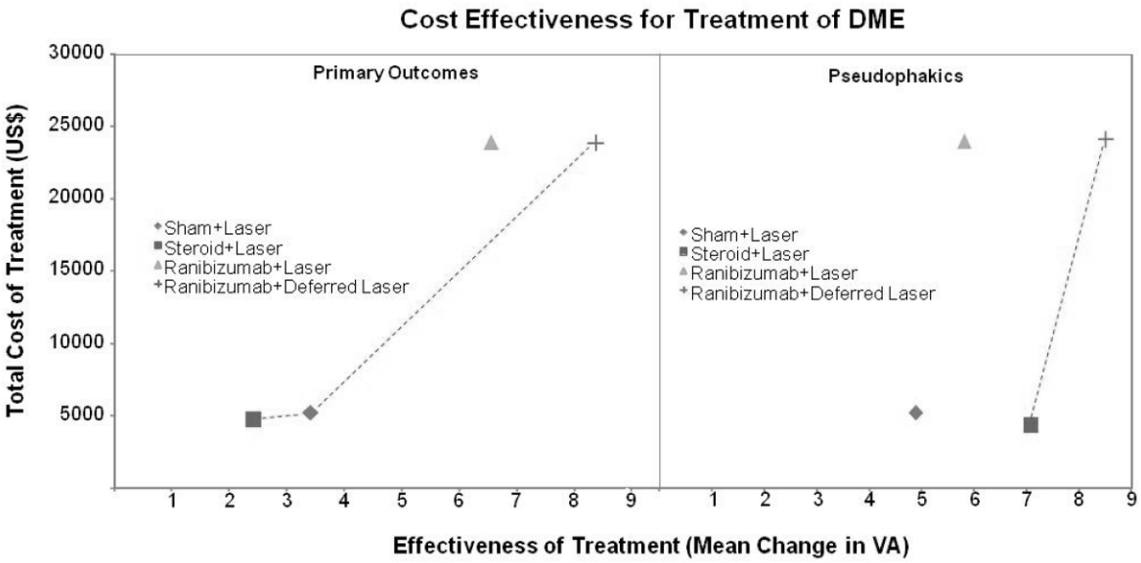

Figure 2. Primary and subgroup outcomes

Graph depicting incremental cost-effectiveness ratio values for primary outcome groups (left) and pseudophakic subgroups (right).

DME-diabetic macular edema VA-visual acuity US-United States

Table 7

Model Variables

Parameter	Category	Value	Source	Sensitivity Analysis Range
Cataract surgery	fixed cost	$2,300	[7]	$765-$6900
DME laser	fixed cost	$636.12	2010 Medicare	$200-$2000
Endophthalmitis treatment	fixed cost	$891.90	[7]	$300-$2700
IOP increase (18 months IOP-lowering monotherapy)	fixed cost	$226.21	[8]	$75-$1000
IV injection	fixed cost	$193.03	2010 Medicare	$60-$580
Office visit	fixed cost	$75.39	2010 Medicare	$25-$225
Single dose ranibizumab	fixed cost	$1,913	2010 Medicare	$23-$6000
Single dose triamcinolone	fixed cost	$3.23	2010 Medicare	$1-$50
Endophthalmitis risk, groups 1/2/3/4	monthly rate	0/.0006/.0006/0	Protocol I, Table 15	0 - .01
Cataract surgery risk groups 1/2/3/4	monthly rate	.005/.004/.005/.0125	Protocol I, Table 15	scalars: 1x - 60x
IOP increase rate, groups 1/2/3/4	monthly rate	.004/.004/.003/.03	Protocol I, Table 15	scalars: 1x - 25x
% subjects under OCT 250um, groups 1/2/3/4	dynamic monthly rate	varied monthly	Protocol I, Figure 6	scalars: 0.5x - 1.25x
Monthly VA change	probabilistic distribution	N/A	Protocol I, Table 5	see sensitivity analysis section
Baseline VA	probabilistic distribution	N/A	Protocol I, Table 2	not performed
Baseline age	probabilistic distribution	N/A	Protocol I, Table 2	not performed
Gender	probabilistic distribution	N/A	Protocol I, Table 2	not performed
Baseline phakic status	probabilistic distribution	N/A	Protocol I, Table 2	not performed

DME-diabetic macular edema IOP-intra ocular pressure IV-intra venous OCT-optical coherence tomography; um- microns VA-visual acuity

Table 8

Main Outcomes

Main Group Strategy	Total Cost	Effectiveness	Incremental Cost	Incremental Effectiveness	ICER ($/VA letter)
4: Triamcinolone, laser	$4,874	2.40 letters	N/A	N/A	N/A
1: Sham, laser	$5,250	3.36 letters	$376	0.96 letters	393 $/letter
2: Ranibizumab, prompt laser	$24,054	7.07 letters	$18,803	3.16 letters	5,943 $/letter
3: Ranibizumab, deferred laser	$24,090	8.63 letters	$36	1.81 letters	20 $/letter

ICER-incremental cost effectiveness ratio VA-visual acuity N/A-not applicable

Table 9

Pseudophakic Outcomes

Subgroup Strategy	Total Cost	Effectiveness	Incremental Cost	Incremental Effectiveness	ICER ($/VA letter)
4: Triamcinolone, laser	$4,508	7.18 letters	N/A	N/A	N/A
1: Sham, laser	$5,268	4.94 letters	$759	-2.23 letters	Dominated
2: Ranibizumab, prompt laser	$24,229	5.83 letters	$19,720	-1.35 letters	Dominated
3: Ranibizumab, deferred laser	$24,560	8.54 letters	$20,051	1.36 letters	14,690 $/letter

ICER-incremental cost effectiveness ratio VA-visual acuity N/A-not applicable

Table 10

Triamcinolone vs. Ranibizumab Utility

Years	triamcinolone cumulative cost	triamcinolone cumulative utility	ranibizumab cumulative cost	ranibizumab cumulative utility	ICUR ($/QALY)
2	$4,513	0.027	$24,443	0.144	171,285
5	$7,732	0.025	$46,577	0.359	116,445
10	$13,097	- 0.086	$83,467	0.718	87,584

ICUR-incremental cost utility ratio QALY-quality adjusted life year

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