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The Cost-Effectiveness of Ranibizumab for the Treatment of Diabetic Macular Edema

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Purpose: To assess the incremental, comparative effectiveness (patient value gain) and cost effectiveness (financial value gain) associated with 0.3-mg intravitreal ranibizumab injection therapy versus sham therapy for diabetic macular edema (DME).

Design: Value-Based Medicine (Center for Value-Based Medicine, Flourtown, PA) 14-year, cost-utility analysis using patient preferences and 2012 United States real dollars.

Participants: Published data from the identical Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus (RISE and RIDE) clinical trials.

Methods: An incremental cost-utility analysis was performed using societal and third-party insurer cost perspectives. Costs and outcomes were discounted with net present value analysis at 3% per annum.

Main Outcome Measures: The incremental comparative effectiveness was measured in: (1) quality-adjusted life year (QALY) gain and (2) percent patient value (quality-of-life) gain. Cost effectiveness was quantified with the cost-utility ratio (CUR) measured as $/QALY.

Results: The 14-year, incremental patient value gain conferred by intravitreal ranibizumab therapy for diabetic maculopathy was 0.9981 QALY, equating to an 11.6% improvement in quality of life. The direct, ophthalmic medical cost for ranibizumab therapy in 1 eye was $30 116, whereas for 2 eyes it was $56 336. The direct, nonophthalmic, medical costs saved from decreased depression, injury, skilled nursing facility admissions, nursing home admissions, and other vision-associated costs totaled $51 758, resulting in an overall direct medical cost of $4578. The net mean societal cost for bilateral ranibizumab therapy was −$30 807. Of this total, decreased caregiver costs accrued a $31 406 savings against the direct medical costs, whereas decreased wage losses accrued a $3978 savings. The third-party insurer CUR for bilateral ranibizumab therapy was $4587/QALY. The societal cost perspective for bilateral therapy was −$30 807/QALY, indicating that ranibizumab therapy dominated sham therapy because it conferred both a positive QALY gain of 0.9981 and a financial value gain (positive financial return on investment) of $30 807 referent to the direct ophthalmic medical costs expended.

Conclusions: Intravitreal ranibizumab therapy for the treatment of DME confers considerable patient (human) value gain. It also accrues financial value to patients, public and private insurers, and society. *Ophthalmology 2015;■:1−10 © 2015 by the American Academy of Ophthalmology.*

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The Centers for Disease Control and Prevention[1] (CDC) estimated the 2010 prevalence of diabetes mellitus in the adult United States population to be 8.3%, or 25.8 million people. The CDC also estimated an incidence of 1.9 million new cases per year. However, based on fasting glucose, hemoglobin A1c levels, or both, approximately 79 million people 20 years of age or older have prediabetes.[1] Diabetic retinopathy is present in 4.2 million people 40 years of age or older and is the leading cause of new cases of blindness in the 20- to 74-year-old United States population.[1]

Ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA), a recombinant, humanized, monoclonal antibody fragment,[2,3] binds and inactivates all active isoforms of human vascular endothelial growth factor A, a molecule believed causative for the choroidal neovascularization seen with neovascular age-related macular degeneration. Ranibizumab also decreases leakage of plasma and blood from retinal blood vessels, a feature believed responsible for the visual benefit it exhibits in eyes with diabetic macular edema (DME).[4−8]

Recently, the Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus (RISE and RIDE) clinical trials[9,10] have shown a superior visual benefit for ranibizumab therapy for DME compared with sham injection.[11] Intravitreal ranibizumab therapy for neovascular age-related macular degeneration has been shown to be comparatively effective and cost effective using standardized Value-Based Medicine (Center for Value-Based Medicine, Flourtown, PA) cost-utility analysis principles.[12−17] The purpose of the analysis herein was to quantify the Value-Based Medicine (standardized) comparative effectiveness and cost effectiveness associated with

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intravitreal ranibizumab injections for the treatment of central DME.

Methods

This research adhered to the tenets of the Declaration of Helsinki and the principles of the Health Insurance Portability and Accountability Act. The Wills Eye Hospital Institutional Review Board approved the protocol for interviewer acquisition of patient utilities.[13–17]

Our analysis used published data from the RISE and RIDE clinical trials.[9,10] These were protocol-identical, double-masked studies comparing monthly, intravitreal sham injections with 0.3-mg and 0.5-mg ranibizumab injections in a 1:1:1 ratio for the treatment of DME.[9,10] The sham cohort (n = 257) data from RISE and RIDE were pooled, as were those from the 0.3-mg ranibizumab treatment cohorts (n = 250). Data for the 0.3-mg dose, which were approved by the Food and Drug Administration for the treatment of DME, were used in the current analysis. Macular laser was permitted for use in each of the 3 groups, at the discretion of the researcher, starting at month 3. The 0.3-mg ranibizumab cohort received a mean of 0.8 laser treatments over 24 months, whereas the sham cohort averaged 1.8 laser treatments over the same period ($P < 0.0001$).

Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus Trials

The RIDE and RISE[9,10] trials enrolled a single eye of patients with vision loss from 20/40 to 20/320 from central DME. Enrollment criteria, baseline features, study data, and cost-utility analysis assumptions are shown in Table 1 (available at www.aaojournal.org).[9,10,13,18–32] The trials were double masked and randomized for 24 months.[9,10] The protocol was amended to allow crossover of sham patients to receive 0.3-mg ranibizumab therapy from 25 to 36 months, thus terminating the double-masked study aspect.

Timeline

Visual data include the randomized 2-year results, with the 24-month visions carried forward using a last observation carried forward methodology for months 25 through 168 (Table 2). A 14-year model is used, because 14 years (168 months) is the average life expectancy for the mean, baseline, 63-year-old diabetic patient, versus 21 years in an age-matched general population.[18,19]

Utilities and Patient (Human) Value Gain

Reliable time-tradeoff utilities from patients with ocular diseases were used to assess vision-associated quality of life.[13] These vision utilities demonstrate excellent validity in a comprehensive analysis that showed highly significant correlations with the logical constructs of vision in the better-seeing eye and Visual Function Index (VF-14) scores.[15] Vision utilities correlate most highly with vision in the better-seeing eye, rather than the cause of vision loss.[13–17]

The utilities were obtained from people who experienced a health state firsthand, because utilities can differ dramatically when obtained from surrogate respondents.[12–17] Vision and adverse event data herein were converted to utility format using the Pharmaceutical Utility Database, a catalog of 51 000 validated, time-tradeoff patient utilities across medicine.[12–17] The database contains more than 1000 reliable,[13] validated[15] vision utilities.

Table 2. Mean Visual Acuity Levels in Years 1 and 2 in the Combined Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus (RIDE and RISE) Studies,[10] Followed by a Last Observation Carried Forward Methodology from Years 3 through 14 (Months 25 through 168)

Time (mos)	Sham Cohort*	0.3-mg Ranibizumab Treatment Cohort
Baseline	$20/80^{+2}$	$20/80^{+2}$
1	20/63	$20/63^{+1}$
3	$20/63^{-1}$	$20/50^{-2}$
6	$20/63^{-2}$	20/50
9	$20/63^{-1}$	$20/50^{+1}$
12	$20/63^{-1}$	$20/50^{+2}$
15	20/63	$20/40^{-2}$
18	20/63	20/40
21	$20/63^{+1}$	$20/40^{-1}$
24	$20/63^{+1}$	$20/40^{-1}$
25–168	$20/63^{+1}$	$20/40^{-1}$

*Sham intravitreal injection.

The vision utility upper anchor was 1.00 (permanent 20/20 or better vision bilaterally), whereas a 0.26 utility was associated with no light perception bilaterally. The lower utility anchor was 0.00 (death).[13,14] Utilities in our current analysis ranged from 0.72 (20/80+2 vision in the better-seeing eye) to 0.97 (20/20–20/25 vision bilaterally).

Quality-Adjusted Life Year Gain

The QALY gain was equal to the utility gain from ranibizumab therapy multiplied by the number of years of treatment benefit.[13] Ranibizumab therapy for DME has not been shown to alter length of life; thus, the patient value gain herein derives solely from improvement in quality of life.[12,13]

Ocular Bilaterality

The model herein assumed that vision in each eye was similar and DME caused the vision loss. Data from one author's (G.C.B.) practice revealed that, among consecutive patients undergoing unilateral DME therapy, 43 (93%) of 46 eventually required second-eye therapy over weeks to years. Our analysis, therefore, assumed bilateral ranibizumab therapy as the base case. Other authors also have noted a high incidence of bilateral diabetic maculopathy.[20]

Value-Based Medicine Analyses

Value-Based Medicine is a methodology of cost-utility analysis using standardized input parameters (time-tradeoff utilities from patient respondents, average national Medicare costs, etc.). The standardized output parameters include: patient value gain (improvement in quality of life, length of life, or both) and financial value gain (cost effectiveness, both societal and third-party insurer cost perspectives, as well as the resources expended for the intervention), including any financial return on investment [ROI] referent to direct medical costs). It was created to obviate the more than 27 million possible input variant Value-Based Medicine cost-utility standards,[13] which are listed in Table 3 (available at www.aaojournal.org).