A Cost Effectiveness Analysis of Intravitreal Injections of Bevacizumab, Ranibizumab, and Aflibercept for the Treatment of Diabetic Macular Edema

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ABSTRACT

Objective: This study determined which of the anti-vascular endothelial growth factors (anti-VEGF) agents is the most cost-effective in treating patients with diabetic macular edema (DME).

Methods: This study was a cost-effectiveness analysis. A decision-analytic Markov cohort model of the natural history and treatment of DME was developed. Data was obtained from a meta-analysis by Virgili *et al.* on anti-VEGFs for DME in which intravitreal injections of bevacizumab given monthly, 6-weekly, and 12-weekly; ranibizumab given monthly, bimonthly, and as necessary; aflibercept given monthly, bimonthly, and as necessary; and macular laser therapy were evaluated for efficacy and safety in 4,413 eyes. Costs were obtained from local standard retail price at a tertiary government institution and assumed an out-of-pocket expenditure. The study measured and compared gains in quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) for each treatment regimen.

Results: Quarterly bevacizumab, monthly ranibizumab (3.82 QALY), and bimonthly ranibizumab injections were the three most beneficial dosing schedules in terms of clinical effectiveness at 3.81, 3.82, and 3.89 QALY, respectively. However, in terms of cost, bevacizumab was substantially most affordable. Quarterly dosing of bevacizumab provided the best value for money, with an ICER of PhP 9,661.70 per QALY gained.

Conclusions: Quarterly intravitreal injections of bevacizumab were identified as the most cost-effective treatment regimen for DME. To be considered cost-effective alternatives, ranibizumab requires an 85% price reduction, while aflibercept needs a price reduction exceeding 95%. We recommend quarterly bevacizumab injections be included in the national insurance coverage package, given their cost-effectiveness and clinical efficacy in the treatment of DME.

Keywords: Anti-VEGF, economic study, cost-effectiveness analysis, diabetic macular edema, intravitreal injection

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According to the 2020 world data, diabetes mellitus (DM) affects 537 million worldwide.[1] Of these, 90 million belong in the Southeast Asian region and 4 million are in the Philippines.[2] Individuals with DM are at risk for developing systemic long-term sequelae of the disease, including ocular complications. Diabetic macular edema (DME) is a frequent ocular complication and is one of the leading causes of blindness globally. It results from abnormally increased permeability of retinal capillaries, leading to fluid leakage into the retinal tissues including the macula. It occurs in as many as 30% of diabetic patients and 8-13% would require treatment.[3] The burden of DME is likely to rise with the expected increase in DM cases to 643 million worldwide by 2030. Currently, the standard treatment for DME is intravitreal injections of anti-VEGF agents. Several studies have demonstrated the efficacy of the various anti-VEGF agents (i.e. bevacizumab, ranibizumab, and aflibercept) in DME. However, the cost of the medication and the frequency of injection pose significant barriers in developing countries, where healthcare is primarily financed through out-of-pocket expenditures by patients.

This study determined which anti-VEGF agent and its corresponding dosing regimen is the most cost-effective option in treating DME. Results of this study may guide local ophthalmologists in the cost-effective management of DME among Filipino patients.

METHODS

This was a cost-effectiveness analysis conducted at the Department of Health Eye Center, East Avenue Medical Center (EAMC), Quezon City, Philippines. The study protocol was approved by the EAMC Institutional Ethics Review Board.

A decision-analytic Markov cohort model was developed in this study to simulate the natural history and treatment outcomes of DME (**Figure 1**). This integrated visual acuity, complications, and treatment costs, representing the progression of a cohort of patients with DME through various health states over their lifetime. This was achieved by calculating transition probabilities, specifically the probability of gaining or losing 15 letters while undergoing treatment. In this study, health states were defined based on vision status, categorized as either improved or declined visual acuity. This economic model simulated the natural progression of DME and predicted long-term effects, enabling comparison of the health and cost implications of different treatment strategies: bevacizumab, ranibizumab, and aflibercept injections, along with their respective dosing regimens.

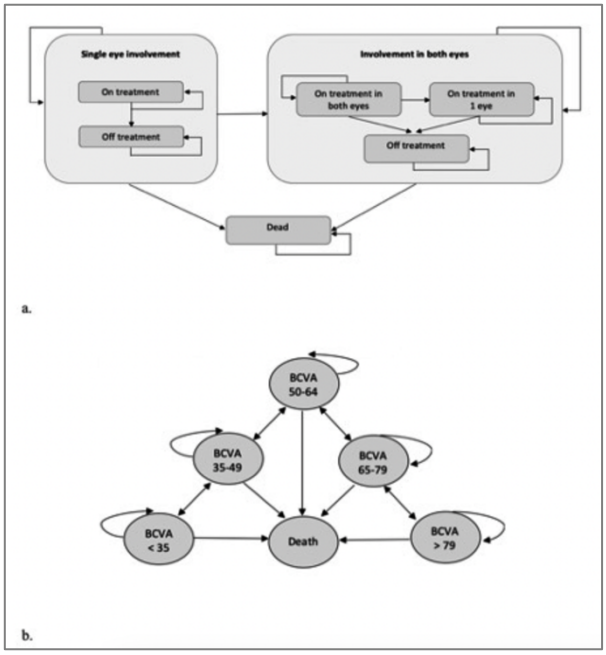

Figure 1. Markov Model Diagram of Health States and Substrates. (a) The Markov model represents how a cohort of patients with DME moved through different health states during their lifetime by calculating transition probabilities. (b) The substrates are depicted as 15-letter loss or gain in BCVA.

To operate the Markov cohort model, this study obtained data from the meta-analysis by Virgili *et al.* on anti-VEGF for DME.[4] This meta-analysis was selected due to its recent publication and its focus on the same medical interventions analyzed in the economic model. It synthesized information from 24 studies conducted globally, including in Asia, involving 3,919 participants (4,413 eyes) with DME. The participants had baseline visual acuity ranging from 20/40 to 20/200 and followed up for at least 12 months. Only anti-VEGF-naïve eyes were included, although eyes that had previous photocoagulation treatment were also considered, provided the procedure was performed at least 3 to 6 months before study inclusion. Data from these studies were incorporated into the Markov model to calculate for quality-adjusted life years (QALY). [5-25]

The primary outcome measures of this study were gains in QALYs and the incremental cost-effectiveness ratio (ICER). QALY is a measure used to assess the effectiveness of a medical intervention, wherein a higher QALY represented good health and a lower QALY represented poor health. ICER is a measure of the economic value of an intervention, representing the cost per additional unit of health benefit achieved.

Secondary outcome measures were the population size, baseline best-corrected visual acuity (BCVA), mean change in BCVA from baseline, average number of injections, study duration, and mortality.

The primary health outcome was QALY gained, which facilitated comparison with other treatment modalities. Several studies have demonstrated a correlation between quality of life and BCVA using utility values. This study adopted a utility value framework consistent with those cited in other ophthalmology cost-effectiveness literature.[26] The utility scores were assigned based on the BCVA of the better seeing eye of the cohort. Brown and colleagues used the time tradeoff and standard gamble methods to create algorithms for translating VA data into utility values.[27] The utility scores were used to approximate QALYs. QALY was calculated by multiplying the duration spent in a specific health state by a utility score that represents the value of that state, ranging from 0 (death) to 1 (perfect health).

The overall treatment cost in this study accounted for the following components: the cost of the anti-VEGF agent, operating room fees, ancillary fees, and professional fees, all adjusted according to the dosing frequency of each respective anti-VEGF agent. The prices of ranibizumab and aflibercept were obtained from standard retail prices provided by the local distributors, excluding any wholesale acquisition prices offered to certain institutions or physicians. The price of bevacizumab was based on aliquot pricing at the DOH Eye Center, EAMC. Operating room expenses and other related fees were also derived from this government hospital. These prices were derived from the DOH Eye Center Diagnostic Center and Procedure list and fees for the year 2022.

All expenses were considered out-of-pocket expenditures, as these fees were not reimbursable by the state insurance company and private insurance was not accepted at the institution. The professional fees for injections and consultations were obtained from specialists performing these procedures at the tertiary hospital. The fees were subsequently averaged for analysis. All costs were reported in Philippine Pesos (Php).

DME is a chronic condition, and thus the Markov model was designed to track the cohort over a 5-year period. Both costs and QALYs were discounted at a rate of 5%, as recommended by the DOH economic evaluation guidelines. The relative benefits of various intravitreal anti-VEGF injection regimens were assessed using ICER, which quantifies the additional cost incurred for every additional gain in QALY. ICER is calculated as the ratio of the difference in cost to the difference in effectiveness between two treatment strategies. In this study, the ICERs compared the different anti-VEGF regimens to laser photocoagulation therapy.

To calculate ICER, the incremental cost was first determined by subtracting the total cost of the comparator (laser) from the total cost of the anti-VEGF treatment regimen (bevacizumab monthly, 6-weekly, etc). The incremental QALY was then computed by subtracting the total QALY associated with the comparator (laser) from the total QALY of the anti-VEGF treatment. The ICER was subsequently computed by dividing the incremental cost by the incremental QALY for each treatment regimen. The ICERs for each anti-VEGF regimen were compared to identify the most cost-effective strategy.

Deterministic sensitivity analyses were conducted to assess the robustness of the model, examining whether the main findings were sensitive in key inputs such as treatment dosage, frequency, and price.

RESULTS

Table 1 summarizes the total cost, total QALY, incremental cost, incremental QALY, and ICER of the different anti-VEGF agents dosing regimens. Bevazicumab injected quarterly had the highest total QALY of 3.81 among the bevacizumab group. Ranibizumab injected bimonthly had the highest

total QALY of 3.89 compared to the other ranibizumab dosing schedules. Monthly injection of aflibercept yielded the highest total QALY 3.76 among the different dosing schedules of aflibercept. The slightly lower QALYs of bevacizumab ranging from 3.39 to 3.81 are attributed to the relatively higher number of adverse events, as documented in landmark clinical trials.[5-25] Quarterly injections of bevacizumab had the lowest total cost at PhP 127,587.71 among the anti-VEGF agents. Bimonthly dosing of ranibizumab had the lowest total cost at PhP 817,867.94 among the different ranibizumab dosing schedules. Consequently, the ICERs were PhP 9,661.70 and PhP 1,924,367.53 per QALY for 12-weekly bevacizumab and bimonthly ranibizumab, respectively.

Table 1. Deterministic results over 5 years.

Intravitreal Anti-VEGF Dosing Regimen	Total Cost (in Php)	Total QALYs	Incremental Cost (vs Laser)	Incremental QALYs (vs Laser)	ICER (in Php per QALY)
Bevacizumab					
Monthly	198,084.90	3.39	73,241.87	-0.14	-509,288.76
6-weekly	158,101.69	3.79	33,258.66	0.26	125,969.56
12-weekly	127,587.71	3.81	2,744.67	0.28	9,661.70
Ranibizumab					
Monthly	1,511,955.98	3.82	1,387,112.94	0.28	4,874,911.42
Bimonthly	817,867.94	3.89	693,024.91	0.36	1,924,367.53
As necessary	941,762.22	3.15	816,919.19	-0.38	-2,124,462.21
Aflibercept					
Monthly	1,602,670.58	3.76	1,477,827.54	0.23	6,391,101.99
Bimonthly	1,238,951.81	3.66	1,114,108.78	0.13	8,658,271.66
As necessary	768,437.59	3.26	643,594.56	-0.27	-2,379,500.91
Laser photocoagulation	124,843.03	3.53	--	--	--

VEGF – vascular growth endothelial factor; QALY – quality-adjusted life years; ICER – incremental cost-effectiveness ratio

In terms of incremental costs alone, the three regimens (monthly, 6-weekly, and 12-weekly) of bevacizumab were the least expensive. Among these dosing schedules, quarterly injections yielded the highest QALY. These results are illustrated in **Figure 2**.

Table 2 demonstrates that, according to price reduction computations, the cost of bimonthly ranibizumab dosing regimen must be reduced by at least 85% to be considered a cost-effective treatment. Given the Health Technology Assessment (HTA) Council recommendation that cost-effectiveness threshold be set at Php 150,000 per QALY, a more substantial price reduction exceeding 95% is needed for aflibercept to be considered acceptable.[28]

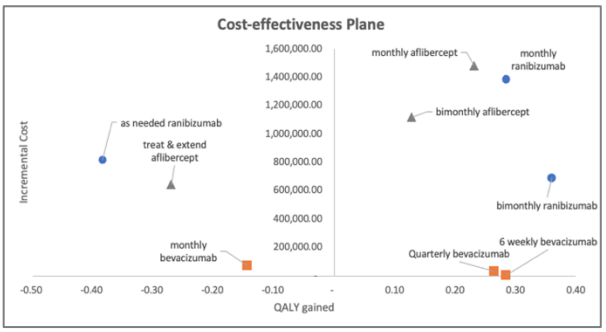

Figure 2. This cost-effectiveness plane shows the three treatment regimens, namely 6-weekly bevacizumab, quarterly bevacizumab, and bimonthly ranibizumab injections, plotted on the lower right quadrant or what is known as the low-cost, high-effectiveness quadrant signifying their cost-effectiveness.
QALY – quality-adjusted life years

Table 2. Price reduction for ranibizumab and aflibercept

Treatment Regimen	Baseline ICER	50% off (in PhP)	75% off (in PhP)	80% off (in PhP)
Ranibizumab				
Monthly	4,874,911.42	2,388,237.26	1,144,900.19	896,232.77
Bimonthly	1,924,367.53	865,001.46	335,318.43	229,381.82
As necessary	-2,124,462.21	-1,015,657.92	-461,255.77	-350,375.34
Aflibercept				
Monthly	6,391,101.99	3,158,517.28	1,542,224.93	1,218,966.45
Bimonthly	8,658,271.66	4,239,930.37	2,030,759.73	1,588,925.60
As necessary	-2,379,500.91	-1,093,263.88	-450,145.36	-321,521.66
Treatment Regimen	**Baseline ICER**	**85% off** (in PhP)	**90% off** (in PhP)	**91% off** (in PhP)
Ranibizumab				
Monthly	4,874,911.42	647,565.35	398,897.94	349,164.45
Bimonthly	1,924,367.53	123,445.21	17,508.60	-3,678.72
As necessary	-2,124,462.21	-239,494.91	-128,614.48	-106,438.40
Aflibercept				
Monthly	6,391,101.99	895,707.98	572,449.51	507,797.82
Bimonthly	8,658,271.66	1,147,091.47	705,257.34	616,890.52
As necessary	-2,379,500.91	-192,897.96	-64,274.25	-38,549.51

ICER – incremental cost-effectiveness ratio

A sensitivity analysis was conducted, revealing that the model is robust. The conclusions remained consistent, even with slight variations in ICERs when a 5% discount rate was applied and the time horizon was adjusted. **Table 3** shows deterministic results when the 5% discounting was implemented and time horizon was shortened to two years.

The probabilistic sensitivity analysis evaluated uncertainties in patient outcomes and parameter assumptions. This analysis estimated the probability that each treatment would be cost-effective, based on its ability to generate the greatest QALY while maintaining an ICER below a pre-determined willingness-to-pay threshold per QALY. Over a projected 5-year horizon, the results indicate that there is more than an 85% likelihood that

bevacizumab would be the optimal therapy at a willingness-to-pay threshold of Php 150,000 per QALY.

Table 3. Discounted Deterministic Results over a Period of Two Years

Treatment Regimen	Total Cost (in Php)	Total QALYs	Incremental Cost (vs Laser)	Incremental QALYs (vs Laser)	ICER (in Php per QALY)
Bevacizumab					
Monthly	87,075.49	1.40	35,216.72	-0.03	1,257,063.5
6-weekly	71,045.89	1.48	19,187.12	0.06	324,474.57
12-weekly	58,015.98	1.49	6,157.22	0.06	97,968.13
Ranibizumab					
Monthly	729,959.44	1.49	678,100.67	0.06	0,495,433.5
Bimonthly	392,598.15	1.50	340,739.39	0.08	4,306,352.69
As necessary	456,212.44	1.35	404,353.68	-0.08	5,189,231.7
Aflibercept					
Monthly	746,446.91	1.48	694,588.15	0.05	3,150,115.9
Bimonthly	581,677.18	1.46	529,818.41	0.03	6,201,044.6
As necessary	446,568.59	1.38	394,709.83	-0.04	9,324,869.5
Laser photocoagulation	51,858.76	1.42	--	--	--

VEGF – vascular endothelial growth factor; QALY – quality-adjusted life years; ICER – incremental cost-effectiveness ratio

DISCUSSION

The meta-analysis by Virgili *et al.* provides robust evidence supporting the efficacy of anti-VEGF intravitreal injections in the treatment of DME.[4] In addition, the meta-analysis demonstrated a slight superiority of aflibercept in terms of BCVA, specifically in gaining 3 or more ETDRS lines, while ranibizumab showed marginally better outcomes in reducing central retinal thickness. However, the difference in BCVA improvement among the three anti-angiogenic agents – aflibercept, ranibizumab, and bevacizumab – was not significantly substantial.

This is the first study to evaluate and compare the cost-effectiveness of different anti-VEGF medications and their respective dosing schedules in the Philippines. It integrated the aforementioned clinical factors with population-based data, ultimately demonstrating that ranibizumab and bevacizumab were favored in terms of QALYs and ICERs, likely due to their lower costs compared to aflibercept. Despite clinical preferences and established treatment regimens, the lack of previous cost-effectiveness models comparing different dosing schedules may be due to varying personal treatment practices.

Among the three anti-VEGF agents, quarterly bevacizumab emerged as the most cost-effective treatment for DME based on the pairwise ICER approach. Although bimonthly Ranibizumab had the highest QALY (3.89 vs 3.81 for bevacizumab), the difference was not clinically significant. However, the ICER values differed significantly between bevacizumab and ranibizumab, with bevacizumab at PhP 72,765 and ranibizumab at PhP 1,924,367. These findings align with a previous study by Ross *et al.*, which also compared the three anti-VEGF agents and concluded that aflibercept and ranibizumab are not cost-effective alternatives to bevacizumab for DME management.[13]

Due to theoretical systemic adverse events associated with bevacizumab, it may be contraindicated in some patients with preexisting comorbidities. The reduced risk of systemic adverse events is a key advantage of ranibizumab and aflibercept over bevacizumab.[17-23] Large randomized controlled trials have documented comparable safety profiles between ranibizumab and aflibercept, making them viable alternatives when safety is a primary concern. However, in such cases, aflibercept remains less cost-effective than ranibizumab.

Despite their safety advantages, the substantial financial burden associated with ranibizumab and aflibercept poses a significant barrier to widespread use, particularly for the average Filipino patient who may struggle to afford sustained treatment. In fact, the findings of this study indicate that ranibizumab and aflibercept would need to be discounted by at least 85% to be considered cost-effective treatment options.

The analysis in this study indicates that the BCVA gains associated with aflibercept result in only modest improvements in quality of life, comparable to those achieved with macular grid laser therapy. However, its ICER values are significantly higher than the cost-effectiveness threshold of PhP 150,000 per QALY, remaining above this threshold even under alternative assumptions.

This economic model was specifically adapted to account for the bilateral nature of DME. The investigators considered it more appropriate to use utility scores that reflect the impact of bilateral eye involvement, as activities of daily living (ADL) are

more significantly affected when both eyes are afflicted with DME.

Given the variability in healthcare expenditure in the Philippines and the differing costs of intravitreal anti-VEGF agents, it is crucial for patients, ophthalmologists and national policymakers to consider the cost-benefit analysis of these treatments. From the payer's perspective, quarterly administration of 1.25 mg bevacizumab is the most cost-effective option for treating DME. In cases where bevacizumab is unavailable or unsuitable, bimonthly injections of 0.3 mg ranibizumab remain a more cost-effective alternative compared to aflibercept.

This analysis indicates that quarterly intravitreal injections of bevacizumab represent the most cost-effective regimen for DME in a tertiary government hospital in the Philippines, as demonstrated through both the pairwise ICER and dominance approaches. In contrast, aflibercept and ranibizumab were not found to be cost-effective unless their prices are substantially reduced. These findings highlight the challenge faced by ophthalmologists, patients and policymakers when clinical effectiveness and safety outcomes do not align with cost-effectiveness considerations. We recommend that ranibizumab undergo an 85% price reduction to be considered a cost-effective alternative, while significant price reduction is necessary for aflibercept to be deemed an accepted treatment option.

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