Pharmacologic management of neovascular age-related macular degeneration: systematic review of economic evidence and primary economic evaluation

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ABSTRACT • RÉSUMÉ

Objective: To examine the economic implications for the Canadian health system of pharmacologic treatment of neovascular age-related macular degeneration (AMD).

Design: Systematic review of economic literature and a primary economic evaluation.

Participants: Economic literature search identified 392 potentially relevant articles, 12 of which were included for final review.

Methods: Studies were included if they met the following criteria: (*i*) provision of a summary measure of the trade-off between costs and consequences; (*ii*) participants of 40 years and older with neovascular AMD; (*iii*) interventions and comparators: comparison of photodynamic therapy using verteporfin (V-PDT), pegaptanib, bevacizumab, ranibizumab, anecortave acetate, intravitreal triamcinolone, placebo, or clinically relevant combinations; and (*iv*) outcome reported as an incremental measure of the implication of moving from the comparator to the intervention. The following databases were searched through the OVID interface: MEDLINE, EMBASE, BIOSIS Previews, CINAHL, PubMed, Health Economic Evaluations Database (HEED), and the Cochrane Library. For the economic evaluation, we took a decision analytic approach and modeled a cost-utility analysis, conducting it as a microsimulation of a Markov model.

Results: In general, V-PDT is more cost effective than conventional macular laser, and pegaptanib is likely more cost effective than V-PDT. The primary economic analysis revealed ranibizumab to be effective but at an unacceptably high cost per quality-adjusted life year (QALY) (>$50 000 per QALY).

Conclusion: Although ranibizumab is effective for wet AMD, its cost is unacceptably high based on cost-utility theory.

Objet : Examen des implications économiques du mode de traitement pharmacologique de la dégénérescence maculaire néovasculaire liée à l'âge (DMLA), dans le système de santé canadien.

Nature : Un examen systématique de la littérature économique et une évaluation économique primaire.

Participants : La recherche dans la littérature économique a permis d'identifier 392 articles potentiellement pertinents; 12 ont été inclus dans la revue définitive.

Méthodes : Ces études devaient respecter les critères que voici : (*i*) provision d'une mesure sommaire de compromis entre les coûts et les conséquences; (*ii*) participants de 40 ans et plus avec DMLA néovasculaire; (*iii*) interventions et comparables : comparaison de la thérapie photodynamique à l'aide de verteporfin (V-PDT), pégaptanib, bévacizumab, ranibizumab, acétate d'anecortave, triamcinolone intravitréen, placébo ou combinaisons cliniquement pertinentes; et (*iv*) résultats signalés comme mesures incrémentielles de l'implication du changement du comparable à l'intervention. Les bases de données qui suivent ont fait l'objet de la recherche par l'interface *OVID : MEDLINE, EMBASE, BIOSIS Previews, CINAHL, PubMed, Health Economic Evaluations Database (HEED)* et *Cochrane Library*. Aux fins de l'évaluation économique, nous avons pris une approche analytique décisionnelle et avons modélisé une analyse coût-utilité, sous forme de microsimulation d'un modèle de Markov.

Résultats : En règle générale, le V-PDT est plus rentable que le laser maculaire conventionnel, et le pégaptanib est vraisemblablement plus rentable que le V-PDT. L'analyse économique primaire a révélé que le ranibizumab est plus efficace mais à un coût élevé inacceptable par année de vie qualité ajustée (QALY) (>50 000 $ par QALY).

Conclusion : Bien que le ranibizumab soit efficace pour la DMLA humide, son coût élevé est théoriquement inacceptable sur une base de coût-efficacité.

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Age-related macular degeneration (AMD) is the leading cause of visual loss in people older than 50 years in North America. AMD is also the leading cause of registered visual impairment in Canada. Over the next 25 years, the increase in the number of legally blind individuals aged 40 years and older is expected to be greatest for AMD (111%) but will also be substantial for open-angle glaucoma (105%) and diabetes (85%).[1] Neovascular AMD may also be subdivided angiographically into classic, predominantly classic (PC), minimally classic, and pure occult lesions.

Photodynamic therapy (PDT) using verteporfin (V-PDT) (Visudyne, Novartis Ophthalmics, Menlo Park, Calif.) has been a mainstay of therapy for neovascular AMD throughout most of this decade, especially in eyes with classic subfoveal choroidal neovascularization. Verteporfin has been approved in Canada for the treatment of AMD since 2000.[2] However, occult subtypes of choroidal neovascularization often convert to classic if left untreated. Pegaptanib (Macugen, Pfizer, Franklin Lakes, N.J.) has been approved in Canada for AMD since 2005.[3] Pegaptanib is an anti-vascular endothelial growth factor (VEGF) aptamer that binds VEGF 165, the main pathologic isoform. Newer anti-VEGF therapies are emerging, specifically ranibizumab (Lucentis, Genentech, San Francisco, Calif. and Novartis Ophthalmics, Basel, Switzerland), which has now been approved in Canada, and bevacizumab (Avastin, Genentech, San Francisco, Calif. and Roche, Basel, Switzerland), as well as a new steroid analog, anecortave acetate (Retaane, Alcon, Fort Worth, Tex.), given as a juxtascleral depot injection.

The purpose of this study was to examine the economic implications for the Canadian health system of pharmacologic treatment of neovascular AMD. A systematic review of the economic literature was undertaken.

Methods

Search strategy

The following bibliographic databases were searched through the OVID interface: MEDLINE (1950 to present; In-Process & Other Non-Indexed Citations), EMBASE (1980 to present), BIOSIS Previews (1985–1989 and 1989 to present), CINAHL (1982 to present), PubMed, the Health Economic Evaluations Database (HEED), and the Cochrane Library. Controlled vocabulary and keywords used in the search included terms for AMD and the drugs of interest in this project (verteporfin, bevacizumab, pegaptanib, ranibizumab, and anecortave acetate) and their brand names. An economic filter was used to limit retrieval to relevant economic records. A detailed search strategy is available upon request.

OVID AutoAlerts were set up to send monthly updates with any new economic literature. Monthly updates were also performed in PubMed, HEED, and the Cochrane Library database. We obtained supplementary cost information for the economic model by contacting experts and researching administrative databases.

An economic evaluation was included for review if it satisfied all of the following criteria: (*i*) provision of a summary measure of the trade-off between costs and consequences; (*ii*) adults aged 40 years or older with neovascular AMD; (*iii*) interventions and comparators: comparison of V-PDT, pegaptanib, bevacizumab, ranibizumab, anecortave acetate, intravitreal triamcinolone, placebo, or clinically relevant combinations; and (*iv*) outcome reported as an incremental measure of the implication of moving from the comparator to the intervention (e.g., a summary measure such as the incremental cost-effectiveness ratio [ICER]).

Two reviewers applied the selection criteria to the title and abstract (if available) of studies obtained in the first phase of the literature search to identify its relevance to our objective and then in the second phase for full-text articles.

One reviewer used a data-extraction sheet to extract the principal content of each included study. Data extracted from included economic studies were checked by a second reviewer.

Two reviewers used a checklist developed for the *British Medical Journal* to assess the quality of the included economic evaluations.[4] The quality measures were not formally used to quantitate results but are presented to guide reader interpretation of the available evidence.

The economic literature search identified 392 potentially relevant articles. After applying the inclusion criteria, 12 articles were included for review. Most of the articles compared V-PDT with placebo or best supportive care;[5–12] one compared bevacizumab and ranibizumab in a threshold analysis;[13] one compared anecortave acetate and V-PDT, also in a threshold analysis;[14] two compared pegaptanib with best supportive care or usual care;[12,15] and one compared pegaptanib with V-PDT and standard care.[16]

Figure 1 summarizes the QUORUM diagram for this study. Table 1 summarizes the characteristics of the included economic studies and Table 2 summarizes their results.

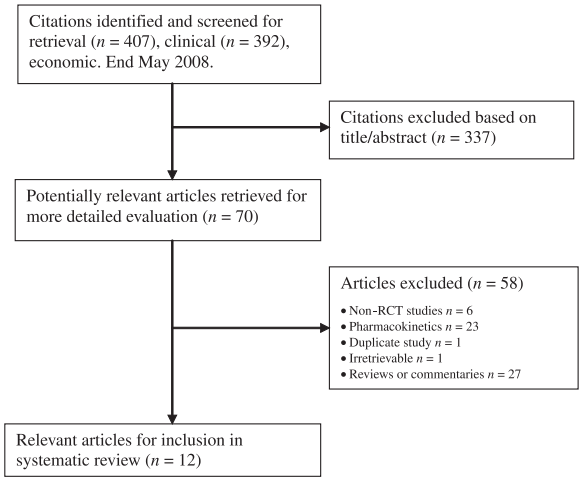

Fig. 1—QUORUM diagram. RCT, randomized control trials.

Economic evaluation

We took a decision analytic approach and modeled a cost-utility analysis, conducting it as a microsimulation of a Markov model.[17] Microsimulation models are computer models that operate at the level of the individual behavioural entity, in this case the patient. A hypothetic cohort of patients was followed throughout the study time horizon (in this case, the patient's expected life span), rather than an actual cohort of patients as would be the case in a clinical trial. A Markov model uses transition probabilities between health states for each cycle of the model. The microsimulation approach includes randomized individual patient characteristics and tracks the progress of individual patients through particular health states, in terms of health outcomes and costs.[18,19]

For people with PC lesions, the comparators to ranibizumab were pegaptanib and V-PDT. For people with lesions of any subtype (including PC), the comparator to ranibizumab was pegaptanib. In each case, it was assumed that treatment was provided according to the schedule outlined in the clinical trials. For ranibizumab, this was administered once per month, and for pegaptanib, it was every 6 weeks. People undergoing V-PDT were treated twice per year unless their visual acuity had progressed to ''severe visual impairment'' (i.e., worse than 6/33).

The perspective was that of a provincial payer. Only direct medical costs relevant to a provincial health provider were considered. Indirect costs accruing only to the patient were not included. The time horizon of the model was the lifetime of the patients.

Separate models were created for those with PC lesions and those with lesions of any subtype. The reason for this distinction was that V-PDT has been shown to be effective in slowing the progression of neovascular AMD in people with PC lesions, but has not been shown in clinical trials to have similar efficacy in the treatment of people with

Table 1—Characteristics of economic evaluations included in review

Author	Industry sponsorship	Study perspective	Interventions and comparators	Study design	Location	Outcome and sources
Brown[5]	Yes	Third party insurer	PDT with verteporfin Placebo	Cost-utility analysis	U.S.	Cost per QALY Costs from U.S. Medicare data Visual acuity from TAP study
Earnshaw[16]	Not clear*	Public payer	Pegaptanib PDT with verteporfin and standard care	Cost-utility analysis and cost-effectiveness analysis	Canada	Cost per QALY and cost per vision-year Costs from Quebec, federal government, and clinical experts Outcomes from VISION, VIP, and TAP studies
Greiner[6]	No	Societal	PDT with verteporfin Placebo	Cost-effectiveness analysis	Switzerland	Cost per vision-year Costs from Swiss prices, taxes, and wages Vision-years derived from TAP study
Hopley[7]	No	Third party payer	PDT with verteporfin Placebo	Cost-utility analysis	Australia	Cost per QALY Costs from Australian Medicare Benefits Schedule Visual acuity from TAP study
Javitt[15]	Yes	Third party payer	Pegaptanib Usual care	Cost-utility analysis and cost-effectiveness analysis	U.S.	Cost per QALY and cost per vision-year Costs from published sources in U.S. Outcomes from the VISION study
Larouche[8]	No	Societal	PDT with verteporfin No treatment	Cost-utility analysis	Canada	Cost per QALY Economic data from Institut Nazareth and Louis-Brailee in Que. Visual acuity from TAP and VIP studies
Meads[9]	No	Direct costs to NHS and local and central government	PDT with verteporfin plus BSC BSC	Cost-utility analysis	U.K.	Cost per QALY Costs from sources in U.K. Effectiveness measures from TAP study
Raftery[13]	No	I: Health care provider (NHS) II: Government†	Bevacizumab (Avastin) Ranibizumab (Lucentis)	Cost-utility analysis with threshold analysis	U.K.	Cost per QALY simulations Bevacizumab cost based on price per injection in U.S. Ranibizumab cost based on reducing price of colon cancer drug in U.S. based on reduced required dose Ranibizumab visual acuity and adverse effects data from licensing trial For bevacizumab, a range of visual acuity assumptions were used for simulation
Sharma[10]	No	For-profit third-party insurer	PDT with verteporfin Placebo	Cost-utility analysis	U.S.	Cost per QALY Costs from U.S. Medicare reimbursement data Visual acuity from TAP study
Smith[11]	Yes	I: PDT treatment costs II: Government‡	PDT with verteporfin Placebo	Cost-utility analysis	U.K.	Cost per QALY Cost estimates from NICE's technology assessment report Visual acuity from TAP study
Wolowacz[12]	Yes	Government	Pegaptanib BSC	Cost-utility analysis	U.K.	Cost per vision-year saved and cost per QALY Costs from various sources in U.K. Patient-level data from VISION trials

*One author is listed as an employee of Pfizer and another works for an organization that has received funding from Pfizer.
†Includes NHS costs as well as personal social service costs.
‡Includes other NHS costs besides treatment costs, plus personal social service costs.
Note: PDT, photodynamic therapy; QALY, quality-adjusted life year; NHS, National Health Service (UK); BSC, best supportive care.

minimally classic or occult lesions. Therefore, our model for the treatment of PC lesions compared treatment with V-PDT, pegaptanib, and ranibizumab. Our model that considered treatment of any lesion subtype (i.e., PC, minimally classic, or occult) considered only pegaptanib and ranibizumab. Because of the lack of clinical evidence on responsiveness to combination treatments, we did not model combinations of treatments such as pegaptanib plus V-PDT or ranibizumab.

The modeled cohort was a cross-sectional sample of patients with macular degeneration as presented in the ANCHOR[20] and MARINA trials.[21] Comparison was made with the characteristics of participants included in the TAP trial[22] and no significant differences were seen. Therefore, the distributions of age and baseline visual acuity of participants entered into the model reflected those seen in the former 2 trials. No adjustments were made in the model for race or gender because there is no evidence that these factors affect either costs or quality-adjusted life years (QALY). All analyses were based on the assumption that visual acuity was based on that found in the "better seeing eye," as is customary in ophthalmology studies considering quality of life.

The main clinical effectiveness outcome incorporated into the model was the change in visual acuity, defined as the number of letters correct at 2 meters. Pooling was done by means of a random-effects meta-analysis. In addition to visual acuity change, the model incorporated rates of adverse events.

Table 2—Results of economic evaluations included in review

Author	Currency/year	Estimate of cost effectiveness	Conclusions
Brown[5]	U.S. dollars/2004	Cost per QALY was $31 103 (range $20 736 to $62 207)	PDT with verteporfin is a very cost-effective treatment by conventional standards.
Earnshaw[16]	Canadian dollars/2004	Cost per QALY: $49 052 relative to V-PDT, $59 039 relative to standard care Cost per vision-year gained: $20 401 relative to V-PDT, $21 559 relative to standard care	Pegaptanib is cost effective for subfoveal wet AMD in elderly patients, regardless of lesion type, relative to PDT with verteporfin and to standard care.
Greiner[6]	Swiss francs/1998	Costs per vision-year for PDT with verteporfin: 14 907 CHF Costs per vision-year placebo group: 21 047 CHF Incremental cost per vision-year saved by verteporfin therapy: 9624 CHF	Verteporfin therapy is cost effective.
Hopley[7]	British pounds (some costs in Australian dollars)/2003	Reasonable initial VA, £31 607 per QALY (range £25 285 to £37 928) Poor initial VA, £63 214 per QALY (range £54 183 to £75 856)	For reasonable initial VA, PDT with verteporfin is moderately cost effective. For poor initial VA, it is relatively cost ineffective.
Javitt[15]	U.S. dollars/2006	Cost per QALY at respective stage of NV AMD: Early: $36 282 Moderate: $58 280 Late: $132 381 Cost per vision-year gained: Early: $15 279 Moderate: $20 350 Late: $57 230	For patients with subfoveal NV AMD, pegaptanib treatment should be started as early as possible to maximize the clinical and economic benefits.
Larouche[8]	Canadian dollars/NS	PC AMD: $33 880 per QALY PC AMD and pure occult AMD: $43 253 per QALY	Economic results are favorable for PDT treatment of PC AMD and pure occult AMD.
Meads[9]	British pounds/2000	Cost per QALY between £182 188 and £151 179	PDT with verteporfin is unlikely to be cost effective.
Raftery[13]	U.S. dollars/NS	For PC AMD, the efficacy of bevacizumab relative to ranibizumab would have to be around 40% for ranibizumab to meet the NICE threshold for cost effectiveness (£30 k per additional QALY) For MC/OC AMD, results are somewhat worse for ranibizumab	Ranibizumab is highly unlikely to be cost effective relative to bevacizumab at current prices.
Sharma[10]	U.S. dollars/Sept. 1, 2000	For 20/40 vision, $86 721 per QALY (2 y model) and $43 547 per QALY (11 y model) For 20/200 vision, $173 984 per QALY (2 y model) and $87 197 per QALY (11 y model)	PDT is of modest-to-poor cost effectiveness. It is of minimal cost effectiveness for AMD patients with good VA and is cost ineffective for those presenting with poor VA.
Smith[11]	British pounds/ Dec. 2000	Government perspective, 2 y time horizon: £286 000 for starting VA 20/100 £76 000 for starting VA 20/40 Government perspective, 5 y time horizon: £30 000 for starting VA 20/100 £9000 for starting VA 20/40 Cost of treatment perspective, 2 y time horizon: £412 000 for starting VA 20/100 £90 000 for starting VA 20/40 Cost of treatment perspective, 5 y time horizon: £69 000 for starting VA 20/100 £38 000 for starting VA 20/40	From a broad government perspective, and a 5 y time horizon, PDT with verteporfin may yield reasonable value for money.
Wolowacz[12]	British pounds/2005	Cost per vision-year saved £2696 Overall cost per QALY £8023 Cost per QALY for subgroups: £2033 for $<$75 y £11 657 for $\geq$75 y £8023 for starting VA 6/12–6/95 £6664 for starting VA 6/12–6/60 £1920 for starting VA 6/12–6/24	Pegaptanib likely to be cost effective relative to best supportive care in all groups studied. This result is not contingent on stopping rules.

Note: QALY, quality-adjusted life year; PDT, photodynamic therapy; V-PDT, photodynamic therapy using verteporfin; AMD, age-related macular degeneration; CHF, Swiss franc; VA, visual acuity; NV, neovascular; PC, predominantly classic; NS, not stated; NICE, National Institute for Health and Clinical Excellence; MC/OC, minimally classic or occult.

Valuing outcomes

Utilities were calculated based on the equation developed by Sharma et al.[23] for converting visual acuity to utility scores:

$$\text{Utility} = 0.374 \times (\text{visual acuity in better seeing eye}) + 0.514$$

This approach values health outcomes based on patients' opinions. Although Sharma included a multivariate version of the formula in his report, the only significant variable in the model was visual acuity. Therefore, we relied on the univariate version with visual acuity only, to estimate utilities.

All costs and health outcomes were discounted at a base rate of 5% per year, and a sensitivity analysis was carried out at a 3% and at a 0% rate, as suggested in the Canadian Agency for Drugs and Technologies in Health economic guidelines.[24]

The precision of the estimates was tested using 1-way sensitivity analyses of all variables to determine at what change in the value of a parameter the cost-effectiveness decision is changed. For this, we used a willingness to pay of $50 000 per QALY.

The precision of the overall model was tested using a second-order Monte Carlo simulation to produce cost-effectiveness acceptability curves.[25] In constructing the Monte Carlo simulation, all clinical variables were parameterized as distributions, and most cost variables. However, the cost of treatment was treated as a constant exogenous variable, as was utility gained, because of the difficulties of introducing uncertainty into the above formula.

RESULTS

Based on the literature available and summarized in Tables 1 and 2, V-PDT is more cost effective than standard macular photocoagulation laser treatments, and pegaptanib is likely more cost effective than V-PDT or ''best supportive care.'' However, economic reviews of other VEGF inhibitors that are now standard of care are sparse and thus a primary economic evaluation was performed in these cases.

The participants in the simulation lived for 9 years on average, and the maximum was 45 years. Our ICER results are presented in Tables 3 and 4. Table 3 provides a comparison of the 3 therapies considered for treatment of PC lesions. Table 4 provides a comparison of pegaptanib and ranibizumab in the treatment of all lesions.

In Table 3, we see that for treatment of PC lesions, pegaptanib is the least expensive option, and V-PDT is the least efficacious. Treatment with V-PDT is marginally more expensive and less efficacious than pegaptanib, meaning that treatment with pegaptanib dominates V-PDT (i.e., better efficacy and less cost).

Table 3 details the components of the ICER for ranibizumab when compared with V-PDT. Here, we find that the improved efficacy of ranibizumab results in an average gain of 0.78 QALY for people with PC lesions after discounting over their remaining lifetime. However, this gain comes at a cost of $43 731, resulting in an ICER of $56 382 per QALY when compared with pegaptanib.

In Table 4, we describe the results of the treatment of lesions of all subtypes using ranibizumab and pegaptanib. The superior efficacy of ranibizumab again results in a gain in lifetime QALY, here 0.73. This gain comes at a cost of $41 163, resulting in an ICER of $56 194.

Sensitivity analyses

The results of our sensitivity analyses are provided in Table 5. Although all variables in the model were tested across the entire clinically relevant range, only the cost of ranibizumab and the change in visual acuity were found to result in a change in the cost-effectiveness decision (i.e., the results in an ICER for ranibizumab versus the comparator of a willingness to pay less than $50 000 per QALY). Because V-PDT was dominated by pegaptanib, we report only the results of sensitivity analyses for ranibizumab versus pegaptanib.

For treatment of PC lesions, the cost of ranibizumab must be less than $20 500, or there must be a reduction in annual cost of treatment of $663 (5% base case discount rate), to meet a willingness to pay of $50 000 per QALY. This could also be achieved with a 5% reduction in injection

Table 3—Comparison of the cost effectiveness of strategies for the treatment of persons with predominantly classic lesions

Strategy	Total cost, $	Total effectiveness, QALY	Incremental cost, $	Incremental effectiveness, QALY	Incremental cost-effectiveness ratio, $/QALY
Treat with pegaptanib (Macugen)	96 975	5.98	—	—	—
Treat with V-PDT	102 472	5.60	5497	−0.37	Dominated
Treat with ranibizumab (Lucentis)	140 706	6.75	43 731	0.78	56 382

Note: For treatment of predominantly classic lesions, pegaptanib is the least expensive option, and photodynamic therapy using verteporfin is the least efficacious. QALY, quality-adjusted life year; V-PDT, photodynamic therapy with verteporfin.

Table 4—Comparison of the cost effectiveness of strategies for the treatment of persons with all neovascular lesions

Strategy	Total cost, $	Total effectiveness, QALY	Incremental cost, $	Incremental effectiveness, QALY	Incremental cost-effectiveness ratio, $/QALY
Treat with pegaptanib (Macugen)	96 975	5.98	—	—	—
Treat with ranibizumab (Lucentis)	138 733	6.72	41 163	0.73	56 194

Note: The superior efficacy of ranibizumab results in a gain in lifetime QALY, here 0.73. This gain comes at a cost of $41 163, resulting in an incremental cost-effectiveness ratio of $56 194. QALY, quality-adjusted life year.

rate. Alternatively, if it were shown that treatment with ranibizumab resulted in an additional improvement of 0.5 letters correct (to 10.73) over 10.23 letters, then treatment with ranibizumab would meet that standard. Finally, if the improvement in utility associated with a decimal unit improvement in vision were 0.41 instead of 0.37, then ranibizumab would also meet that standard.

Another issue that merits discussion is the role of bevacizumab, in the treatment of macular degeneration. Bevacizumab is a drug that many clinicians have argued has similar clinical performance to ranibizumab in the treatment of choroidal neovascular disease because they share similar molecular properties.[26–28] However, it is considerably less expensive than ranibizumab. Although our systematic review did not identify strong clinical evidence concerning the efficacy of bevacizumab, we conducted an analysis of its cost effectiveness as a treatment of macular degeneration, making the assumption that the clinical performance of bevacizumab would be similar to that of ranibizumab. The results are provided in Table 6 for treatment of PC lesions. With this approach, the annual cost of treatment with bevacizumab was $2461, or 12% of the cost of treatment with ranibizumab. Our results show that bevacizumab would dominate either pegaptanib or PDT for treatment of PC lesions. Similar results were found for treatment of all lesions, so bevacizumab would also dominate ranibizumab for this application.

Discussion

Of the 3 treatments for neovascular macular degeneration that were analyzed (PDT with verteporfin, pegaptanib, and ranibizumab), only ranibizumab demonstrated a reversal of the degenerative process. However, our analyses indicated that the premium required for this medication marginally exceeded cost effectiveness based on a willingness to pay of $50 000 per QALY. This threshold could be achieved if the price of ranibizumab was reduced by 3.5% from $1575 per dose.

A second possible approach to reducing the cost of treatment by ranibizumab would be to reduce the frequency of treatment. Because a 3.1% reduction in the total cost of treatment is required at a willingness to pay of $50 000 per QALY, this could be achieved by reducing the number of treatments per year to below the 12 used in the ANCHOR[20] and MARINA[21] trials. Although some anecdotal reports have supported less frequent treatment, good-quality clinical evidence that suggests the benefit can be maintained with such a strategy is lacking. Therefore, we were required to assume a monthly dosage schedule for the model. Should new clinical evidence be brought to light, this issue might be revisited. A summary of the number of retinal specialists in practice using pro re nata dosing schedules has been reported previously.[29]

As we noted in Table 5, the cost-effectiveness decision is sensitive to the utility estimates on which effectiveness (as measured by QALY) is based. Relatively small changes in the coefficient defining the relationship between visual acuity as measured in decimal units (see equation) influence the cost-effectiveness decision. Indeed, for someone with 20/100 vision at baseline, a change in utility of 0.01 units over that gained in the base case would result in treatment with ranibizumab being considered cost effective at $50 000 per QALY. This being the case, it should be recognized that this utility algorithm, although having undergone the rigors of peer review, has not been widely validated in other studies and has limitations.

Bevacizumab is a drug that many clinicians have argued has a clinical performance similar to that of ranibizumab in the treatment of choroidal neovascular disease. Our results show that bevacizumab would dominate both pegaptanib and PDT in the treatment of PC lesions. Similar results were found for treatment of all lesions, so bevacizumab would also dominate ranibizumab for this application. Because it might be argued that bevacizumab might have inferior clinical performance than ranibizumab, or more severe adverse events, we performed sensitivity analyses to evaluate how much weaker the performance of bevacizumab would have to be for ranibizumab to meet the standards of cost effectiveness. We found that use of bevacizumab must generate less than 4.21 QALY for ranibizumab to meet the $50 000 per QALY willingness-to-pay threshold if both treatments are included in the evaluation. This would imply

Table 5—Sensitivity analysis for comparison of ranibizumab and pegaptanib

		Threshold value that makes ranibizumab cost effective at $50 000/QALY at discount rate		
Variable	Base case	0%	3%	5%
Annual cost of ranibizumab treatment, $	21 163	19 800	20 300	20 500
Change in visual acuity due to ranibizumab treatment (letters correct)	10.23 (SD 0.44)	11.28	10.95	10.73
Utility associated with vision (coefficient for equation)	0.37	0.43	0.42	0.41

Note: QALY, quality-adjusted life year.

Table 6—Comparison of the cost effectiveness of strategies for the treatment of persons with predominantly classic lesions: bevacizumab vs alternatives

Strategy	Total cost, $	Total effectiveness, QALY	Incremental cost, $	Incremental effectiveness, QALY	Incremental cost-effectiveness ratio ($/QALYs)
Treat with bevacizumab (Avastin)	13 433	6.73	—	—	—
Treat with pegaptanib (Macugen)	97 356	5.99	83 922	−0.75	Dominated
Treat with V-PDT	103 743	5.61	90 309	−1.13	Dominated

Note: QALY, quality-adjusted life year; V-PDT, photodynamic therapy with verteporfin.

that bevacizumab would be less efficacious than either pegaptanib or V-PDT. Because this is highly unlikely, it would seem that if bevacizumab were found to be an appropriate agent for the treatment of choroidal neovascular disease, it would be unlikely that ranibizumab would be considered to be an effective medication for this purpose. In this finding, we support the work of Raftery et al.,[13] who found that the efficacy of bevacizumab would need to be less than half of that of ranibizumab to justify the cost premium for the latter medication. It should be recognized, however, that bevacizumab has not been approved for intravitreal injection in Canada and that there is currently no compelling clinical evidence concerning its efficacy or adverse events in the treatment of retinal disease.

Another strategy that has received some attention is the use of combinations of ranibizumab and other treatments. For instance, some have speculated that PDT might be used to induce a better, longer-lasting response to ranibizumab, and thus would require fewer treatments. Alternatively, treatment might be started with ranibizumab and, once response is gained, it would be maintained by pegaptanib. Either of these might present a cost-saving option (and thus meet the standards of cost effectiveness), but again, in the absence of clinical evidence to support evaluation, it would be premature to consider these options in a detailed cost-utility framework.

Overall, ranibizumab is an effective medication but at a very high cost to the public health payer. Alternative treatments need to be studied for both efficacy and cost-utility reasons in our public health system.

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References

1. Buhrmann R, Hodge W, Gold D. Forecasting the vision loss epidemic in Canada current and projected estimates of age-related eye disease: interim summary tables prepared for the National Coalition on Vision Health 2006.
2. Drugs & health products: notice of compliance. Ottawa, Ont.: Health Canada; 2000. Available at: http://205.193.93.51/NocWeb/viewnoce.jsp?noc=cngj. Accessed January 10, 2008.
3. Notice of decision for Macugen. Ottawa, Ont.: Therapeutic Products Directorate, Health Canada; June 2, 2005. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/nd_ad_2005_macugen_094022_e.pdf. Accessed September 15, 2005.
4. Drummond MF, Jefferson TO, BMJ Economic Evaluation Working Party. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 1996;13:275–83. Available at: http://www.bmj.com/cgi/content/full/313/7052/275. Accessed February 19, 2007.
5. Brown GC, Brown MM, Campanella J, Beauchamp GR. The cost-utility of photodynamic therapy in eyes with neovascular macular degeneration–a value-based reappraisal with 5-year data. *Am J Ophthalmol* 2005;140:679–87.
6. Greiner RA. Cost of care for patients with age-related macular degeneration in Switzerland and cost-effectiveness of treatment with verteporfin therapy. *Semin Ophthalmol* 2001;16:218–22.
7. Hopley C, Salkeld G, Mitchell P. Cost utility of photodynamic therapy for predominantly classic neovascular age related macular degeneration. *Br J Ophthalmol* 2004;88:982–7.
8. Larouche K. *Photodynamic therapy for the treatment of exudative age-related macular degeneration (ARMD) with subfoveal neovascularization*. Montréal: Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS); 2004. Available at: http://www.aetmis.gouv.qc.ca/site/275.447.0.0.1.0.phtml. Accessed February 28, 2007.
9. Meads C. Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess* 2003;7:v–vi, 1–98. Available at: http://www.ncchta.org/fullmono/mon709.pdf. Accessed February 28, 2007.
10. Sharma S, Brown GC, Brown MM, Hollands H, Shah GK. The cost-effectiveness of photodynamic therapy for fellow eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology* 2001;108:2051–9.
11. Smith DH, Fenn P, Drummond M. Cost effectiveness of photodynamic therapy with verteporfin for age related macular degeneration: the UK case. *Br J Ophthalmol* 2004;88:1107–12.
12. Wolowacz SE, Roskell N, Kelly S, Maciver FM, Brand CS. Cost effectiveness of pegaptanib for the treatment of age-related macular degeneration in the UK. *Pharmacoeconomics* 2007;25:863–79.
13. Raftery J, Jones J, Clegg A, Lotery A. Ranibizumab (Lucentis) versus bevacizumab (Avastin): modelling cost effectiveness. *Br J Ophthalmol* 2007;91:1244–6.
14. Sharma S, Bakal J, Sharma SM, Covert D, Shah GK. Drug pricing for a novel treatment for wet macular degeneration: using incremental cost-effectiveness ratios to ensure societal value. *Can J Ophthalmol* 2005;40:369–77.
15. Javitt JC, Zlateva GP, Earnshaw SR, et al. Cost-effectiveness model for neovascular age-related macular degeneration: comparing early and late treatment with pegaptanib sodium based on visual acuity. *Value Health* 2008;11:563–74.
16. Earnshaw SR, Moride Y, Rochon S. Cost-effectiveness of pegaptanib compared to photodynamic therapy with verteporfin and to standard care in the treatment of subfoveal wet age-related macular degeneration in Canada. *Clin Ther* 2007;29:2096–106.
17. Weinstein MC. Recent developments in decision-analytic modelling for economic evaluation. *Pharmacoeconomics* 2006;24:1043–53.
18. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 2nd ed. New York, N.Y.: Oxford University Press; 1997.
19. Markovitz JH, Roubin GS, Parks JM, Bittner V. Platelet activation and restenosis after coronary stenting: flow cytometric detection of wound-induced platelet activation. *Coron Artery Dis* 1996;7:657–65.
20. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1432–44.
21. Rosenfeld P, Brown D, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419–31.

22. Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP report. *Arch Ophthalmol* 1999;117:1329–45.
23. Sharma S, Brown GC, Brown MM, et al. Converting visual acuity to utilities. *Can J Ophthalmol* 2000;35:267–72.
24. Canadian Agency for Drugs and Technologies in Health. *Guidelines for the Economic Evaluation of Health Technologies: Canada*. 3rd ed. Ottawa, Ont.: The Agency; 2006. Available at: http://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf. Accessed March 12, 2007.
25. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;10:779–87.
26. Costa RA, Jorge R, Calucci D, Cardillo JA, Melo LA Jr, Scott IU. Intravitreal bevacizumab for choroidal neovascularization caused by AMD (IBeNA Study): results of a phase-1 dose-escalation study. *Invest Ophthalmol Vis Sci* 2006; 47:4569–78.
27. Michels S, Rosenfeld P, Puliafito CA, Marcus EN, Venkatraman AS. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology* 2005;112:1035–47.
28. Moshfeghi A, Rosenfeld P, Puliafito C, et al. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twenty-four-week results of an uncontrolled open-label clinical study. *Ophthalmology* 2006;113:2002.e1–12.
29. Brown DM, Regillo CD. Anti-VEGF agents in the treatment of neovascular age-related macular degeneration: applying clinical trial results to the treatment of everyday patients. *Am J Ophthalmol* 2007;144:627–37.

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