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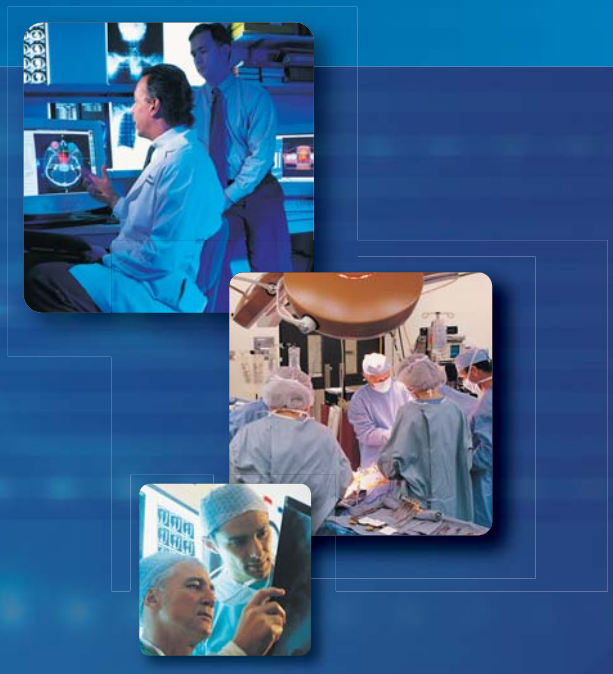

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Management of Neovascular Age-related Macular Degeneration: Systematic Drug Class Review and Economic Evaluation

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REPORT *IN BRIEF*

April 2008

Management of Neovascular Age-related Macular Degeneration: Systematic Drug Class Review and Economic Evaluation

Technologies

Single and combination therapy with photodynamic therapy using verteporfin (V-PDT); anti-vascular endothelial growth factor (anti-VEGF) therapies, including pegaptanib, ranibizumab, and bevacizumab; and steroids or analogues, anecortave acetate and triamcinolone.

Condition

Adults 40 years of age or older with neovascular age-related macular degeneration (AMD).

Issue

The recent emergence of several pharmacologic therapies for AMD has led to uncertainty regarding the impact of single and combination therapies as well as the optimal timing of therapy and the impact of re-treatment.

Methods and Results

Eighteen articles describing nine unique randomized trials, one controlled trial, and five case series were identified through a systematic literature review. Two cost-utility analyses in adults 40 years of age and older from the perspective of the Canadian public health care system and a patient lifetime time horizon were conducted. Pegaptanib, ranibizumab, and V-PDT were compared for predominantly classic lesions, and pegaptanib and ranibizumab were compared for all neovascular lesions. An analysis of budget impact and ethical and psychosocial issues was also conducted.

Implications for Decision Making

- **Uncertainty still remains.** No direct evidence demonstrating the effect of timing or re-treatment on health was found. There was insufficient evidence to suggest whether combination therapy (or which combinations) is better than monotherapy. Evidence for bevacizumab's effectiveness is less compelling than other anti-VEGF agents.
- **Pegaptanib or ranibizumab represent optimal treatment strategies.** Pegaptanib is the least costly strategy, and ranibizumab would be likely to be the most cost-effective strategy for those willing to pay more than an additional $59,000/quality-adjusted life year. These results are most sensitive to the cost of ranibizumab therapy and change in visual acuity. At its current price, bevacizumab is likely to be the most cost-effective strategy if it is more effective than V-PDT.
- **Access, equity, and legal issues remain.** Access is of issue in Canada and the UK as existing systems are over extended in meeting resource needs to achieve early referral, diagnosis, and treatment within an effective therapeutic window. Equity issues are encountered as patients incur the costs of treatment at private clinics. Continued off-label use of bevacizumab raises ethical, legal, equity, and policy implications.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca):
Brown A, Hodge W, Cruess A, Blackhouse G, Hopkins R, McGahan L, Sharma S, Pan I, Blair J, Vollman D, Morrison A. *Management of Neovascular Age-related Macular Degeneration: Systematic Drug Class Review and Economic Evaluation.*

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1 Introduction

Age-related macular degeneration (AMD) causes more visual impairment in people who are over 50 years old in Canada than any other condition. The number of people with AMD is expected to grow by 111% over the next 25 years as the population ages.[1] The two types of AMD are "dry" and "wet." This report focuses on wet AMD, which is known as "neovascular AMD." This form is less common — occurring in about 15% of cases — but causes greater visual impairment more quickly. More than 100,000 Canadians have neovascular AMD, which manifests itself in abnormal new blood vessels arising from the choroid, leading to the exudation of subretinal fluid, blood, and lipids and the destruction of macular vision due to scarring.[2]

Neovascular AMD can be classified as classic, predominantly classic, minimally classic, or pure occult. About 40% of neovascular AMD cases are classic, in which the lesion appears as an area of bright, well-demarcated hyperfluorescence. About 60% of cases are occult and characterized by a fibrovascular retinal pigment epithelial detachment or late leakage of an undetermined source (AC, unpublished observations, 2008.) The occult type has the slowest rate of progression.

Because choroidal neovascularization (CNV) commonly recurs, treatment can be a challenge. CNV recurred in more than 50% of cases in two studies that evaluated thermal laser therapy.[3,4] Persistent and recurrent CNV was observed in clinical trials of anti-vascular endothelial growth factor (VEGF) therapies designed to meet US Food and Drug Administration requirements, but with no stopping rules. Trials that are underway are designed to determine the stopping rules and guidelines for maintenance therapy.

In Canada, photodynamic therapy (PDT) using verteporfin (V-PDT) has been the mainstay of therapy for neovascular AMD since the drug was approved in 2000, particularly in patients with classic CNV.[5] Verteporfin is given intravenously and accumulates in the neovascular membrane of the choroid. It is then activated by laser, thrombosing the membrane. Anti-VEGF therapies have come on the market, starting with pegaptanib, the first to be approved in Canada for AMD in 2005. An injectable steroid, triamcinolone, is widely available. In the future, it may be replaced in some combination therapies by a new steroid analogue, anecortave acetate, which has been approved in Australia.[6,7] Table 1 summarizes the formulary status of AMD drugs in Canada.

Therapies may be used alone or in combination. Protocols for combination therapy are being investigated. Given the array of options, drug plan administrators need to know the impact of each treatment on health care budgets.

2 Objective

The objective of this report is to assess the impact of the pharmaceutical management of neovascular AMD by answering the following questions:

- What is the clinical evidence on the relative effectiveness of pegaptanib, bevacizumab, ranibizumab, triamcinolone, anecortave acetate, or placebo (alone or in combination) versus V-PDT in neovascular AMD?
- What is the relative cost-effectiveness of the various forms of pharmaceutical management of neovascular AMD?

- What is the evidence regarding the timing of the start of therapy for the comparisons listed?
- What is the evidence regarding treatment with a different regimen in persons who did not have a satisfactory clinical response to a particular regimen?

Table 1: Formulary status of AMD drugs in Canada

Publicly Funded Drug Plans	AMD Drugs Available in Canada					
	Verteporfin	**Pegaptanib**	**Ranibizumab**	**Bevacizumab**	**Triamcinolone Injection**	**Triamcinolone Acetonide (generic injectable)**
Alberta	Not listed	Not listed on any formulary	Not listed	Not listed on any formulary	B	B
British Columbia	Not listed		Not listed		B	B
NIHB	R		Not listed		B	B
Manitoba	Not listed		Not listed		B	B
New Brunswick	Not listed		Not listed		Not listed	Not listed
Newfoundland and Labrador	Not listed		Not listed		B	B
Nova Scotia	R		Not listed		B	B
Ontario	Not listed		L		B	B
Québec	Not listed		L		Not reported	Not reported
Saskatchewan	Not listed		Not listed		B	B

Source: National Prescription Drug Utilization Information System (NPDUIS) Database, October 2007 (available provinces) and Régie de l'assurance maladie du Québec.
In Nova Scotia, verteporfin use is restricted to the treatment of wet AMD as prescribed by an authorized ophthalmologist. The First Nations and Inuit Health Branch limit use of verteporfin to patients diagnosed with AMD and treated by a certified ophthalmologist.
B=benefit, no justification required for reimbursement; L=limited, requires that specific criteria be met for reimbursement (automated process); NIHB=Non-Insured Health Benefits; R=restricted, requires formal request to drug program for reimbursement (case-by-case review).

3 Systematic Review Methods

For this systematic review, we followed a protocol written a priori. We searched the following bibliographic databases using the OVID interface: MEDLINE (1950 to present; In-Process & Other Non-Indexed Citations), EMBASE (1980 to present), BIOSIS Previews (1985 to 1989 and 1989 to present), CINAHL (1982 to present), PubMed, and The Cochrane Library. For the economic review, we also searched the Health Economic Evaluations Database (HEED). Our search was limited to clinical controlled trials, comparative studies, observational studies, meta-analyses, and systematic reviews but imposed no language restrictions. We searched for all relevant articles until November 2, 2007. For economic studies, we used a filter to limit retrievals to economic records. A supplemental clinical search was performed to find literature on the timing of the start of therapy and its potential impact on disease progression.

We identified grey literature by searching the web sites of health technology assessment and related agencies, professional associations, and other databases; by searching the bibliographies and abstracts of key papers and conference proceedings; and by contacting experts.
Two reviewers independently screened studies. Clinical studies were included if they were randomized controlled trials (RCTs) (though we later included non-RCTs to search for information

on combination therapies). Patients were adults 40 years and older with neovascular AMD. The studies compared V-PDT with one of the following: pegaptanib, bevacizumab, ranibizumab, anecortave acetate, placebo, or clinically relevant combinations. (Intravitreal triamcinolone in combination with one or more of the others was acceptable.) Primary outcomes had to include a measure of visual acuity that was convertible to utility values. Secondary outcomes could include quality-of-life indicators, size of lesion before and after (measured by fluorescein angiography or ocular coherence topography), adverse events, and other harm information.

Studies were included if they were full economic evaluations and met the same criteria as those for the clinical studies in terms of population, interventions, and comparators. The primary outcome had to show an incremental measure of the implication of moving from the comparator to the intervention (for example, a summary measure such as the incremental cost-effectiveness ratio).

Two reviewers extracted relevant data from the selected studies using forms that were designed a priori. Differences were resolved by discussion or with the help of a third reviewer. To assess the quality of clinical studies, we used the Jadad scale, with the highest quality being 5,[8] and evaluated allocation concealment using the Schulz and Grimes method, where studies are rated as adequate, inadequate, or unclear.[9] For economic studies, we used a 35-question checklist developed for the *British Medical Journal* (BMJ).[10]

For clinical studies, we conducted a meta-analysis of RCTs. For economic studies, we reviewed the literature. We also conducted a primary economic evaluation.

Clinical Review Results

The nine RCTs that met the selection criteria had a mean Jadad score of 2.89.[11-19] Of the nine, six were unique RCTs with 1,915 subjects ranging in age from 72.7 to 77.7 years. Six studies did not report the methods for allocation concealment. Five studies, including two substudies, compared ranibizumab or anecortave acetate with V-PDT.[11-13,15,19] Another three RCTs that were included as a result of search updates all compared bevacizumab with V-PDT.[7,20,21] They were of lower quality than the others, however, with a mean Jadad score of 2.5. They were also smaller in sample size (mean n=86) and shorter in duration (mean of four months). They were excluded from our meta-analysis because of their outcome measures. None of the included RCTs involved pegaptanib, and only two compared V-PDT with combination therapy.[7,11] Six non-RCTs met all criteria, except for being an RCT, and were included because they analyzed combination therapies.[6,22-26]

Ranibizumab showed a statistically significant improvement in visual acuity based on the Early Treatment Diabetic Retinopathy Study (ETDRS) score, which is the preferred measure in trials where vision is the primary outcome. Monthly ranibizumab produced a gain of between 4.9 and 11.3 letters at 12 months, while the comparative V-PDT group had a loss of between 8.2 and 9.5 letters, for a net benefit for ranibizumab of 18.0 letters. Patients on ranibizumab were six times more likely to have a significant gain in vision than those on V-PDT. Ranibizumab was better than V-PDT at slowing the growth of lesions and shrinking them.[11,12] One study, which also measured quality of life using the National Eye Institute Visual Function Questionnaire, found that ranibizumab patients had higher overall improvement scores and better subscores in near and distant activities and vision-related dependencies. Those on 0.5 mg of ranibizumab monthly scored higher than those on 0.3 mg per month. Insufficient information was available for the pooling of results.

In the only study that compared anecortave acetate with V-PDT, both groups saw a large drop in visual acuity, and the former showed no statistical benefit over the latter. Results from two of the bevacizumab studies could not be pooled because their primary outcomes differed.[7,21] One reported a greater decrease in the thickness of the retina in the combination therapy group (bevacizumab plus V-PDT) compared with the control group.[7] The other study compared bevacizumab with V-PDT plus triamcinolone. After three months, those in the bevacizumab monotherapy group saw the biggest improvement in visual acuity.

No significant difference was found in the rate of systemic adverse events when the intervention groups were compared with V-PDT groups, but local adverse events reported with ranibizumab included post-injection increases in intraocular pressure and cataract formation, endophthalmitis, retinal detachment, retinal tears, and vitreous hemorrhages.[11,12] In the bevacizumab studies, the rates of retinal detachment were 7.7% and 14.8% for the combination of bevacizumab plus V-PDT group and bevacizumab group respectively, compared with 0% for the V-PDT groups.

A trial comparing V-PDT with PDT alone showed some benefit for the former within the first 18 months, but no difference afterwards.[14] Michels *et al.* investigated periodic V-PDT with one-time V-PDT and found no significant difference at six or 12 months.[18]

Combination therapies were typically a combination of anti-VEGF and V-PDT therapies in the six included non-RCTs. A study comparing intravitreal triamcinolone (IVTA) and V-PDT with V-PDT alone found that by one year the combination therapy group had more improvement in best-corrected visual acuity than the monotherapy group and fewer patients experienced moderate vision loss.[24] Similarly, Liggett *et al.* concluded that the triple combination therapy of IVTA, V-PDT, and pegaptanib sodium injection, was beneficial in improving and stabilizing visual acuity.[24]

A triple combination of V-PDT, bevacizumab, and dexamethasone over 40 weeks produced a significant increase in patients' visual acuity with no serious adverse events.[25] The dual therapy of V-PDT and bevacizumab stabilized visual acuity in 83% of patients and improved it in 67%.[23] Ladas *et al.* found that the same dual combination therapy improved visual acuity in four out of six patients with serious pigment epithelium detachment at nine months and decreased central retinal thickness.[26] Ahmadieh *et al.* reported that 15 out of 17 subjects improved their visual acuity after 24 weeks of combined V-PDT, intravitreal bevacizumab, and IVTA.[6]

None of these non-RCTs was of high quality. Therefore, their results need to be confirmed in larger RCTs.

Limitations

The scarcity of clinical studies limited subgroup analysis. Few studies reported the primary outcome of ETDRS visual acuity; and those that did, did not report the measures of dispersion around the primary endpoint. Thus, meta-analysis, forest plots, and statistical tests were not possible for the change in the number of letters that were readable on the ETDRS scale.

Economic Review

The economic search identified 12 articles that met the inclusion criteria. More than half compared V-PDT with placebo or best supportive care.[27-33] Of two threshold analyses, one compared bevacizumab with ranibizumab,[34] and the other compared anecortave acetate with V-PDT.[35] Two

studies compared pegaptanib with best supportive or usual care,[36,37] and one compared pegaptanib with V-PDT and standard care.[38]

All the studies were cost utility analyses, using cost per quality-adjusted life year (QALY) as the primary outcome, except for Grenier's study, which was a cost-effectiveness analysis.[28] Ten of the 12 studies were of high quality, scoring five or lower on the BMJ checklist.[27,29-33,35-38] Five studies were sponsored by industry.[27,33,35-37] Two studies were set in Canada,[30,38] four in the US,[27,32,35,36] four in the UK,[31,33,34,37] one in Switzerland,[28] and one in Australia.[29]

Of the seven studies comparing V-PDT with placebo or best supportive care, four had results favouring V-PDT,[27,28,30,33] two had mixed results,[29,32] and one concluded that V-PDT was unlikely to be cost-effective.[31] Of the two threshold analyses, Rafferty *et al.* found that ranibizumab is unlikely to be cost-effective compared with bevacizumab because of the price, and Sharma *et al.* determined that anecortave acetate is likely to be cost-effective compared with V-PDT.[35] Because of limited evidence, both made assumptions about efficacy. All three studies with pegaptanib as the intervention found results favouring pegaptanib.

In terms of timing for the start of therapy, Javitt *et al.* concluded that treatment with pegaptanib should begin as early as possible for maximum clinical and economic benefits.[36] One study looked at whether the cost-effectiveness of pegaptanib was sensitive to treatment discontinuation and found that it was not.[37]

4 Primary Economic Evaluation

Because none of the studies analyzed each intervention in a Canadian context, we performed an economic evaluation using decision analytic software (TreeAge Pro by TreeAge Software Inc.) and followed a hypothetical cohort of patients 40 years of age and older with neovascular AMD through their expected life spans. The patient cohort was a cross-sectional sample from two clinical trials.[12,39] We used a Markov model, which includes health states, transition probabilities between states, health outcomes, and costs for each cycle of the model.[40-42] For patients with predominantly classic (PC) lesions, we compared ranibizumab with pegaptanib and V-PDT. For patients with lesions of any type, including PC, we compared ranibizumab with pegaptanib. Our perspective was that of a provincial health provider, and we looked only at direct medical costs.

To determine the absolute change in visual acuity scores for each treatment (based on the ETDRS score), the difference between treatment and control was added to the pooled placebo efficacy of all trials, with the following results, including standard error in parentheses: PDT −9.97 (0.68); pegaptanib (Macugen®, Pfizer) −3.27 (0.45); and ranibizumab (Lucentis®, Genentech) 10.23 (0.44).

Results

Among pegaptanib, V-PDT, and ranibizumab, pegaptanib had the lowest total cost of treatment, and V-PDT was the least efficacious. Only ranibizumab reversed the degenerative process, on average. Ranibizumab is cost-effective for those willing to pay $56,000 for a QALY (Tables 2 and 3). To meet a target of $50,000, the price could be reduced by 3.5% from $1,575 per dose, or the frequency of treatment could be reduced, though evidence to support the latter option is lacking. Another option is substituting bevacizumab for ranibizumab. Assuming that the effectiveness of the two would be similar, bevacizumab would be the most cost-effective (Table 4). Evidence on the efficacy and safety

of bevacizumab, however, is more limited. Our results were sensitive to the cost of ranibizumab, visual acuity outcomes, and the utility loss associated with visual impairment.

Table 2: Comparison of cost-effectiveness of strategies for treatment of persons with predominantly classic lesions

Strategy	Total Cost	Total Effectiveness (QALYs)	Incremental Cost	Incremental Effectiveness (QALYs)	Incremental Cost-Effectiveness Ratio (Cost/QALYs)
Treat with pegaptanib (Macugen®)	$96,975	5.98			
Treat with PDT with verteporfin	$102,472	5.60	$5,497	−0.37	Dominated
Treat with ranibizumab (Lucentis®)	$140,706	6.75	$43,731	0.78	$56,382

V-PDT=verteporfin plus photodynamic therapy; QALYs=quality-adjusted life years.

Table 3: Comparison of the cost-effectiveness of strategies for treatment of persons with all neovascular lesions

Strategy	Total Cost	Total Effectiveness (QALYs)	Incremental Cost	Incremental Effectiveness (QALYs)	Incremental Cost-Effectiveness Ratio (Cost/QALYs)
Treat with pegaptanib (Macugen®)	$97,569	5.98			
Treat with ranibizumab (Lucentis®)	$138,733	6.72	$41,163	0.73	$56,194

QALYs=quality-adjusted life years.

5 Health System Implications

Approximately 183,000 Canadians or 1.16% of the population aged 40 or older had neovascular AMD in 2006.[1,2] New treatment options requiring regular monitoring and repeat injections are increasing the workload of ophthalmology clinics. One systematic review in Québec found that patients cannot always have access to timely treatment. This may result in further loss of vision or less effective treatment.[30] Drug fees vary, even in the same jurisdiction, and physicians sell some drugs directly to patients, creating issues of equity. The off-label use of bevacizumab raises ethical, legal, and policy implications.

Table 4: Comparison of the cost-effectiveness of strategies for treatment of persons with predominantly classic lesions assuming similar effectiveness for bevacizumab and ranibizumab					
Strategy	**Total Cost**	**Total Effectiveness (QALYs)**	**Incremental Cost**	**Incremental Effectiveness (QALYs)**	**Incremental Cost-Effectiveness Ratio (Cost/QALYs)**
Treat with bevacizumab (Avastin®)	$13,433	6.73			
Treat with pegaptanib (Macugen®)	$97,356	5.99	$83,922	−0.75	Dominated
Treat with PDT with verteporfin	$103,743	5.61	$90,309	−1.13	Dominated

V-PDT=verteporfin plus photodynamic therapy; QALYs=quality-adjusted life years.

6 Conclusions

The review of clinical evidence found that, with the exception of trials comparing ranibizumab with V-PDT, there was a significant lack of trials comparing the other anti-VEGF agents in general. There is only one RCT that looked at the efficacy and safety of anecortave acetate compared with V-PDT. However, although results have shown seemingly effective visual acuity improvement with bevacizumab, this was based only on three poor quality RCTs. Whether generalizations from ranibizumab to bevacizumab can be made is not clear from the evidence identified.

Six non-RCT studies suggest the combination therapies analyzed are effective. These combination therapies are typically a combination of V-PDT and anti-VEGF therapies. However, inferences regarding relative efficacy cannot be made from these study designs. Conclusions drawn by these studies need to be confirmed by results of future larger-scale randomized controlled trials.

Overall, the efficacy of anti-VEGF therapies over V-PDT is well supported by RCTs. What remains unclear is whether combination therapy (and which combinations) are superior or merely equal to monotherapy. Furthermore the efficacy of one anti-VEGF agent compared with another is also unclear and this has very important practical and economic implications. The scant nature of the evidence does not allow us to draw conclusions regarding optimal timing of initiation of therapy and re-treatment.

Between V-PDT, pegaptanib, and ranibizumab, only ranibizumab demonstrated a reversal of the degenerative process for neovascular CNV, on average. The primary economic evaluation found that the premium for using ranibizumab would not be considered cost-effective using a willingness-to-pay threshold of $50,000. A 3.5% reduction in the price of ranibizumab would be required to achieve that. Alternately, this might be achieved by reducing the frequency of treatment below that used in the clinical trials. However evidence for the impact this might have on effectiveness is lacking. Using bevacizumab as a substitute for ranibizumab could be more effective and less costly than either V-PDT or pegaptanib. However, currently there is limited clinical trial evidence on the efficacy and safety of bevacizumab in the treatment of AMD.

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