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Endothelial Growth
Factor Drugs for
Retinal Conditions:
A Therapeutic Review

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INTRODUCTION AND RATIONALE

With the aging Canadian population, retinal conditions are likely to be increasingly encountered in clinical practice. For example, age-related macular deterioration (AMD) is the main cause of irreversible blindness in persons aged 65 years or older in industrialized countries; an estimated 2 million Canadians aged 50 years or older have this condition.¹ These conditions therefore represent an important health issue from both a clinical and health policy perspective.

Angiogenesis is the process by which new blood vessels are created from pre-existing vasculature. Abnormal angiogenesis is a hallmark of diseases such as cancer and the wet form of AMD (wAMD).² In the eye, angiogenesis occurs due to the carefully balanced interplay of growth-promoting and growth-inhibiting factors. Evidence suggests that vascular endothelial growth factor (VEGF) is one of the primary factors promoting abnormal angiogenesis within the eye. Elevated intraocular VEGF levels appear to be associated with intraocular neovascularization, a vascular abnormality that is common to many retinal conditions such as AMD, diabetic retinopathy, and retinal vascular occlusion. This provides the rationale for pharmacological inhibition of abnormal angiogenesis to treat these retinal conditions.³

In February 2004, the FDA approved bevacizumab (Avastin) for the treatment of metastatic cancer of the colon and rectum. Bevacizumab is a recombinant, humanized monoclonal antibody that reduces angiogenesis that is associated with certain metastatic cancers by inhibiting VEGF. The first anti-VEGF agent to be approved by the FDA for intravitreal use was pegaptanib (Macugen), in December 2004.³ This approval was followed by the approval of ranibizumab (Lucentis) 18 months later, in June 2006. The latest anti-VEGF agent, approved in 2011 for intravitreal use, is aflibercept (Eylea) or VEGF Trap, which is a type of soluble decoy receptor generated with Trap technology.² Table 1 describes anti-VEGF drugs used in Canada to treat retinal conditions.

TABLE 1: ANTI-VEGF DRUGS USED FOR THE TREATMENT OF RETINAL CONDITIONS IN CANADA

Drug Products (Manufacturers)	Drugs	Health Canada–Approved Indication ^a
Avastin (Hoffmann-La Roche)	bevacizumab	NA
Lucentis (Novartis)	ranibizumab	Treatment of neovascular (wet) AMD
		Treatment of visual impairment due to DME
		Treatment of visual impairment due to macular edema secondary to RVO
		Treatment of visual impairment due to CNV secondary to PM
Eylea (Bayer Inc.)	aflibercept	Treatment of neovascular (wet) AMD
		Treatment of visual impairment due to macular edema secondary to CRVO
		Treatment of DME

AMD = age-related macular degeneration; CNV = choroidal neovascularization; CRVO = central retinal vein occlusion; DME = diabetic macular edema; NA = not applicable; PM = pathologic myopia; RVO = retinal vein occlusion; VEGF = vascular endothelial growth factor.

^a Source of information: Health Canada Drug Product Database.⁴

Ranibizumab is an affinity-matured antigen-binding fragment (Fab) derived from the same parent mouse antibody as bevacizumab. Although not approved for the treatment of retinal conditions, bevacizumab started to be used off-label to treat retinal conditions within a year of it becoming available for cancer

therapy.⁵ The process by which bevacizumab came to be used for intravitreal injection is interesting. After it had been approved by the FDA for an oncology indication, Dr. Phillip Rosenfeld from the University of Miami administered bevacizumab intravenously (IV) to 18 patients with neovascular AMD. Their preliminary findings suggested that the clinical benefits of IV bevacizumab were similar to those of intravitreal ranibizumab; however, Dr. Rosenfeld's group was concerned about the serious thromboembolic adverse events of bevacizumab, such as myocardial infarction (MI) and stroke, reported in patients with cancer. In the summer of 2005, Rosenfeld converted the molar amount of bevacizumab to be injected into the eye using the same low volume as ranibizumab; his group then published two successful case reports in July 2005. The first patient had AMD, whereas the second patient had central retinal vein occlusion (CRVO). The publication of these case reports led to the quick uptake of intraocular use of bevacizumab around the world.⁵

There is a substantial difference in the cost of intraocular injection of bevacizumab and ranibizumab. From a payer's perspective, the use of bevacizumab in clinical practice for the treatment of AMD may be associated with expenditures that are 30 times lower than for ranibizumab.¹ Therefore, interest has grown among drug regulators and payers in reconsidering current reimbursement policies favouring use of ranibizumab over bevacizumab. For example, in November 2014, the French National Security Agency of Medicines and Health Products (Agence Nationale de Sécurité du Médicament et des Produits de Santé [ANSM]) sent a letter to the manufacturer of Avastin asking for any data it had on file regarding the use of bevacizumab in the treatment of wAMD, as well as any information on ongoing trials on this topic. This initiative highlights possible plans at ANSM to issue a temporary authorization to use bevacizumab for treating wAMD.⁶ Other European countries have already developed reimbursement policies for bevacizumab; in Italy, bevacizumab is reimbursed by the national health service, whereas in Germany, the national association of ophthalmologists (BDOC) developed contractual agreements with several private insurance companies to reimburse bevacizumab.¹ In the US, Medicare as well as private insurers are reimbursing intravitreal use of bevacizumab.¹ In Canada, British Columbia now reimburses bevacizumab, in addition to ranibizumab, for three retinal disorders; i.e., wAMD, diabetic macular edema (DME), and CRVO.⁷ Two other provinces also reimburse ranibizumab and bevacizumab. In Nova Scotia, these two anti-VEGF drugs have exceptional drug formulary status for the treatment of AMD; however, patients must receive the treatment in one of the hospital-based designated eye centres.¹ In Manitoba, ranibizumab has been reimbursed since 2010; bevacizumab therapy is available at the Eye Care Centre of Excellence of Misericordia Health Centre in Winnipeg.^{1,8}

Now, with the availability of observational studies and randomized clinical trials evaluating intravitreal bevacizumab, and the recent approval of an additional anti-VEGF for retinal conditions (aflibercept), there is interest in assessing the clinical and cost-effectiveness of anti-VEGF drugs for the treatment of retinal conditions. This project will include a review of the clinical effectiveness of anti-VEGF drugs for the treatment of retinal conditions as well as an economic evaluation. This evidence will be used by the Canadian Drug Expert Committee (CDEC) to develop recommendations regarding the reimbursement of anti-VEGF drugs by public payers in Canada.

1. DELIVERABLES

The following deliverables are planned:

- A Science Report, including a systematic review of the comparative efficacy and safety of anti-VEGF drugs for the treatment of retinal conditions and an economic analysis of comparative costs of treatment for different conditions
- A CDEC Recommendation document, based on the Science Report and stakeholder feedback.

2. POLICY QUESTIONS

There are three policy questions for this project. These reflect the information needs of CADTH jurisdictional clients. Policy questions will also feed the deliberations of the CDEC members when they develop the therapeutic review recommendations.

1. Based on clinical evidence and cost, which anti-VEGF drug(s) should be reimbursed for the treatment of each of the following retinal conditions?
 - Neovascular (wet) AMD
 - Visual impairment due to DME
 - Macular oedema due to retinal vein occlusion (RVO)
 - Choroidal neovascularization (CNV) secondary to pathologic myopia (PM)
2. Are there subgroups within the aforementioned indications within which drug(s) identified in Question 1 should be reimbursed?
3. What is the preferred dosing regimen(s) for drug(s) identified in Question 1?

3. RESEARCH QUESTIONS

The research questions for this project are presented below. These will form the basis of the clinical and economic evaluations.

1. What is the comparative efficacy and safety of anti-VEGF drugs for treating patients with the conditions listed below?
2. What is the comparative cost-effectiveness of anti-VEGF drugs for treating patients with the conditions listed below?
 - Neovascular (wet) AMD
 - Visual impairment due to DME
 - Macular oedema due to RVO
 - CNV secondary to PM

4. METHODS

4.1 Literature Search Strategy

The literature search will be performed by an experienced information specialist using a peer-reviewed search strategy.

Published literature will be identified by searching the following bibliographic databases: MEDLINE (1946 to June 2015) with in-process records and daily updates via Ovid; Embase (1974 to June 2015) via Ovid; and PubMed. The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts are anti-VEGF agents, i.e., aflibercept (Eylea), bevacizumab (Avastin), pegaptanib (Macugen), or ranibizumab (Lucentis), and wet/neovascular age-related macular degeneration, diabetic retinopathy, macular edema, or myopic choroidal neovascularization.

Methodological filters will be applied to limit retrieval to randomized controlled trials. Where possible, retrieval will be limited to the human population. Retrieval will not be limited by publication year or by language.

Grey literature (literature that is not commercially published) will be identified by searching relevant websites from the following sections of the Grey Matters checklist (<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>): Drug Class Reviews, Clinical Trials (ongoing), and Free Databases. Google and other Internet search engines will be used to search for additional web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts.

4.2 Selection Criteria

4.2.1 Clinical

a) Study selection process

To ensure reliability, a training exercise will be conducted prior to commencing screening. Using the inclusion and exclusion criteria identified in Table 2, a random sample of 50 titles and abstracts from the literature search will be screened by all team members during the level 1 screening (screening of titles and abstracts). Full screening will commence after 90% agreement is achieved in the training exercise. This often occurs after two calibration exercises. This training exercise will be repeated for the level 2 screening (screening of full-text papers). Subsequently, all citations and full-text articles will be screened in duplicate for inclusion, independently, for level 1 and level 2 screening by pairs of reviewers. Conflicts will be resolved by discussion or the involvement of a third reviewer. All screening will take place using Synthesi.SR.⁹

TABLE 2: INCLUSION AND EXCLUSION CRITERIA FOR PRIMARY STUDIES¹

Inclusion Criteria	
Study Design	Parallel RCTs
Population	Adults ^a with any of the following: <ul style="list-style-type: none"> • Neovascular (wet) AMD • Visual impairment due to DME • Macular edema due to RVO^b • CNV secondary to PM
Interventions	Aflibercept, bevacizumab, and ranibizumab
Comparators	Aflibercept, bevacizumab, ranibizumab, placebo
Outcomes	<p>Efficacy outcomes:</p> <ol style="list-style-type: none"> 1. Change (gain or loss) in BCVA of ≥ 15 ETDRS letters 2. Change from baseline in BCVA 3. Blindness (legal) 4. Vision-related function^c <p>Harms outcomes:</p> <ol style="list-style-type: none"> 1. AEs 2. SAEs 3. WDAEs 4. Mortality 5. Harms of special interest: <ul style="list-style-type: none"> • Arterial/venous thromboembolic events • Bacterial endophthalmitis • Increased intraocular pressure • Retinal detachment
Time Periods	All periods of time for publication and duration of follow-up are included.
Exclusion Criteria	
<p>Study design: Quasi-RCTs, non-randomized studies, crossover trials. Population: Age < 18 years. Intervention: Administration of anti-VEGF agents by any means other than intravitreal injection. Comparators: Surgery (e.g., cataract removal). Outcomes: No outcomes of interest.</p>	

AE = adverse event; AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CNV = choroidal neovascularization; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; PM = pathologic myopia; RCT = randomized controlled trial; RVO = retinal vein occlusion; SAE = serious adverse event; VEGF = vascular endothelial growth factor; WDAE = withdrawal due to adverse event.

^a Age ≥ 18 years.

^b Macular edema due to central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) will be investigated separately in subgroup analyses.

^c Assessed by validated measures

4.2.2 Economic

One reviewer will screen titles and abstracts relevant to the economic research questions on the use of available therapies for the treatment of patients with the included retinal conditions that might inform data inputs in the health economic analyses. Full papers will be obtained for those that appear to be potentially relevant.

¹Note that this study is part of a larger research project addressing the comparative effectiveness of anti-VEGF drugs for retinal conditions. For more details, see http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015022041.

4.3 Data Extraction and Critical Appraisal of Clinical Studies

4.3.1 Data items and data abstraction process

Data will be abstracted on study characteristics (e.g., study design, year of conduct, sample size, setting [e.g., multi-centre, single centre], country of study conduct, duration of treatment, duration of follow-up), patient characteristics (e.g., number of patients, age mean and standard deviation, condition, comorbidities), and the definitions of outcomes (e.g., quality of life scale used). Data will be abstracted for all relevant outcomes for this report (see Protocol, above). Outcome results (e.g., number of patients with legal blindness) will be abstracted only for the longest duration of follow-up only, as this is the most conservative approach (Cochrane Handbook). A draft data item form will be established after consultation with clinical and patient stakeholders. Prior to data abstraction, a calibration exercise of the data abstraction form will be completed on a random sample of five articles. Subsequently, all of the included studies will be abstracted by two reviewers, independently. A third reviewer will compile the statistics files and ensure that the data are correct, including resolving conflicts.

4.3.2 Risk of bias appraisal

The risk of bias in each of the included studies will be appraised using the Cochrane risk of bias tool¹⁰ by two reviewers, independently. Conflicts will be resolved by discussion or the involvement of a third reviewer.

4.4 Data Analysis and Synthesis

4.4.1 Clinical

Where possible, a random-effects pairwise meta-analysis will be conducted using odds ratios (OR) for dichotomous outcomes and the mean difference for continuous outcomes. A random-effects model will be employed, as methodological and clinical heterogeneity is expected across the included studies that compared the same pairs of interventions. For studies with dichotomous outcomes where zero events are reported in one treatment arm, 0.5 will be added to all cells. Between-study heterogeneity (τ^2) will be examined using the restricted maximum likelihood (REML)¹¹ method, and quantified using the I^2 statistic.¹² The R 3.1.2¹³ and metafor package¹⁴ will be used to conduct all pairwise meta-analyses.

Where necessary (e.g., in the absence of head-to-head study data) and feasible (i.e., if there are sufficient data), a random-effects network meta-analysis (NMA) will be conducted to indirectly compare the efficacy of the anti-VEGF agents.¹⁵ Separate network meta-analyses will be conducted for each of the following patient populations:

- Neovascular (wet) AMD
- Visual impairment due to DME
- Macular edema due to RVO
- CNV secondary to PM.

NMA treatment nodes will be selected by the clinicians and statisticians on the research team. Prior to conducting an NMA, the transitivity assumption will be evaluated by examining the comparability of the distributions of potential treatment-effect modifiers across comparisons.¹⁶ These will be selected after discussions among the team, but will be examined prior to conducting the analyses. Statistical inconsistency will be examined using a global chi-square test and the design-by-treatment interaction model.¹⁵ In the presence of statistically significant inconsistency, the loop-specific approach^{17,18} will be applied to locally assess the network and identify the treatment comparisons responsible for inconsistency. After checking the data for errors, subgroup analyses or meta-regression analyses will be conducted until the statistical inconsistency is no longer present. In the NMA and design-by-treatment interaction models, a common within-network heterogeneity will be assumed, whereas in the loop-

specific method, a common within-loop heterogeneity will be assumed. A common heterogeneity across all treatment comparisons will be assumed, as the included treatments are of the same nature and it is clinically plausible to share a common heterogeneity parameter. In all approaches, the magnitude of between-study heterogeneity will be estimated using the REML method.¹¹ Important heterogeneity (e.g., an I^2 statistic > 75%)¹⁹ will be explored using meta-regression analysis and subgroup analysis. To evaluate the robustness of the NMA results, a sensitivity analysis will be conducted excluding studies with high risk of bias.

We will present the NMA summary treatment effects along with their 95% confidence intervals (CI). We will rank the effectiveness of the anti-VEGF agents using the surface under the cumulative ranking (SUCRA) curve.²⁰ NMAs will be conducted in Stata 13²¹ using the `mvmeta` command.²²

4.4.2 Economic

Whether cost-effectiveness analyses are performed as part of these reviews will be based upon the evidence from the clinical review for each patient population. The options for economic analysis can be summarized into three basic scenarios:

- Where the evidence from the clinical review for a particular population suggests clinically meaningful differences among the comparators, then a cost-effectiveness analysis will be undertaken, contingent upon available data to populate the analyses.
- Where the evidence from the clinical review for a particular population suggests similarity among key clinical outcomes for all comparators, then a cost minimization analysis will be undertaken and possibly a budget impact analysis, contingent upon available data.
- If there is insufficient evidence to assess comparative clinical effects of comparators, then a cost-effectiveness analysis will not be conducted, but some budget or other costing analyses may be undertaken, contingent upon available data to populate the analyses.

The results of the clinical review and the availability of clinical data will drive what type of economic analyses can be performed.

4.5 Data Availability

In accordance with the CADTH Therapeutic Framework: *“The primary source of data is in the public domain. All stakeholders will be given the option of identifying and providing unpublished data on the condition that, if used, it would be included in publicly available reports and documents related to the therapeutic review”*. If the necessary clinical data required to address the research questions are not made publicly available by the manufacturers at the time of project initiation, there may be limited information available to address all of the research or policy questions listed in the Protocol.

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