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Optical Coherence Tomography Monitoring Strategies for A-VEGF–Treated Age-Related Macular Degeneration: OHTAC Recommendation

Ontario Health Technology Advisory Committee

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Conflict of Interest Statement

All authors in the Evidence Development and Standards branch at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

About Health Quality Ontario

Health Quality Ontario (HQO) is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. The Evidence Development and Standards branch works with advisory panels, clinical experts, developers of health technologies, scientific collaborators, and field evaluation partners to provide evidence about the effectiveness and cost-effectiveness of health interventions in Ontario.

To conduct its systematic reviews of health interventions, the Evidence Development and Standards branch examines the available scientific literature, making every effort to consider all relevant national and international research. If there is insufficient evidence on the safety, effectiveness, and/or cost-effectiveness of a health intervention, HQO may request that its scientific collaborators conduct economic evaluations and field evaluations related to the reviews. Field evaluation partners are research institutes focused on multicentred clinical trials and economic evaluation, as well as institutes engaged in evaluating the safety and usability of health technologies.

About the Ontario Health Technology Advisory Committee

The Ontario Health Technology Advisory Committee (OHTAC) is a standing advisory subcommittee of the Board of Directors of Health Quality Ontario. Based on the evidence provided by Evidence Development and Standards and its partners, OTHAC makes recommendations about the uptake, diffusion, distribution, or removal of health interventions within the provincial health system. When making its recommendations, OHTAC applies a unique decision-determinants framework that takes into account overall clinical benefit, value for money, societal and ethical considerations, and the economic and organizational feasibility of the health care intervention in Ontario.

Publishing Health Quality Ontario Research

When the evidence development process is nearly completed, draft reviews, reports, and OHTAC recommendations are posted on HQO's website for 21 days for public and professional comment. For more information, please visit: http://www.hqontario.ca/evidence/evidence-process/evidence-review-process/professional-and-public-engagement-and-consultation.

Once finalized and approved by the Board of Directors of Health Quality Ontario, the research is published as part of the *Ontario Health Technology Assessment Series*, which is indexed in MEDLINE/PubMed, Excerpta Medica/Embase, and the Centre for Reviews and Dissemination database. Corresponding OHTAC recommendations and associated reports are also published on the HQO website. Visit http://www.hqontario.ca for more information.

When sufficient data are available, OHTAC tracks the ongoing use of select interventions it has previously reviewed, compiling data by time period and region. The results are published in the Ontario Health Technology Maps Project Report.

Disclaimer

This report was prepared by the *Evidence Development and Standards branch* at Health Quality Ontario or one of its research partners for the Ontario Health Technology Advisory Committee and was developed from analysis, interpretation, and comparison of scientific research. It also incorporates, when available, Ontario data and information provided by experts and applicants to HQO. The analysis may not have captured every relevant publication and relevant scientific findings may have been reported since the development of this recommendation. This report may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations.

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Background

Overuse, underuse, and misuse of interventions are important concerns in health care and lead to individuals receiving unnecessary or inappropriate care. In April 2012, under the guidance of the Ontario Health Technology Advisory Committee's Appropriateness Working Group, Health Quality Ontario (HQO) launched its Appropriateness Initiative. The objective of this initiative is to develop a systematic framework for the ongoing identification, prioritization, and assessment of health interventions in Ontario for which there is possible misuse, overuse, or underuse.

For more information on HQO's Appropriateness Initiative, visit our website at www.hqontario.ca.

Age-related macular degeneration (AMD)—a major retinal disease with genetic, aging, and environmental risk factors—is the leading cause of irreversible vision loss and blindness in older adults in the developed world. Visual acuity loss in AMD occurs through 2 distinct mechanisms: dry or wet AMD. Although the dry form accounts for most cases, the wet or neovascular form (n-AMD) accounts for more than 80% of severe vision loss. In n-AMD, vision loss occurs secondary to a neovascularization or abnormal angiogenesis. Vascular endothelial growth factor (VEGF) produced by the retinal pigment epithelial cells is a key factor in this ocular angiogenesis cascade and leads to a breakdown of the blood-retinal barrier.

The emergence of such new anti-angiogenesis pharmacotherapies as VEGF inhibitors has dramatically altered the treatment of n-AMD. Two important regulatory efficacy trials published in 2006 involved ranibizumab (Lucentis, Genentech), a second-generation biologic anti-VEGF (A-VEGF) pharmacotherapy for n-AMD patients. Protocols required a 3-month course of monthly loading doses of ranibizumab injections followed by a maintenance schedule of monthly injections for 24 months. In both trials, all visual outcome measures were significantly better in ranibizumab-treated groups. For the first time, not only was vision stabilized in most patients, but many regained vision. These trials also had other important results. Visual outcomes in the sham-treated control arm declined rapidly in monthly follow-up visits, and patients treated with photodynamic therapy (the current standard of care) lost vision at a rate similar to that of the sham-treated group.

These trials established monthly injections with ranibizumab as the gold standard treatment for n-AMD patients, and ranibizumab has become the standard comparator for regulatory approvals of new therapies. The monthly intra-ocular injection regimen, however, is extremely burdensome to ophthalmologists, patients, and their families. Repeated injections also increase risks of potential complications or adverse events, such as infection, injury, or immune reactions. Although the pharmacokinetics of A-VEGF drugs are fairly well known, individuals' AMD presentation and the pharmacodynamics or response to the drug have been shown to vary greatly. Therefore treating everyone with the same fixed regimen has potential for undertreating or overtreating. The drug costs are also not trivial—approximately $1,500 per intra-ocular injection of ranibizumab.

OHTAC Findings

Since approval and widespread use of A-VEGF therapies, various monitoring strategies have been developed involving various flexible dosing schedules and re-treatment criteria for detecting and treating recurrence in order to decrease injection burden and maintain initial visual acuity (VA) gains. Optical coherence tomography (OCT), a non-contact, high-resolution, cross-sectional imaging technique, has had a key role in treatment monitoring for AMD and other retinal disorders. The high speed and greater resolution of modern OCT devices allows better sampling of the macula and visualization of retinal anatomy less affected by eye movements. As well, the automated generation and real-time tracking of clinically significant quantitative measures, such as retinal thickness, increases the reliability of change measurements in monitoring follow-up exams. Optical coherence tomography also provides qualitative assessments of other anatomic features representing active disease, particularly those associated with choroidal neovascularization, to further guide re-treatment decisions.

The overall objective of this review was to evaluate these monitoring strategies and OCT guidance for patients with n-AMD actively treated with A-VEGF pharmacotherapy. An evidence-based analysis (1) was therefore conducted by the Evidence Development and Standards branch at Health Quality Ontario to answer the following research question:

- What is the appropriate OCT monitoring interval for patients with n-AMD undergoing treatment with VEGF anti-angiogenesis pharmacotherapy?

A systematic review of published trials between 2008 and February 2013 involving A-VEGF–treated n-AMD patients in longitudinal follow-up identified 18 randomized controlled trials and 20 observational studies involving various A-VEGF therapies, monitoring, and re-treatment protocols.

Several maintenance strategies were unsuccessful, resulting in lower VA gains and stabilization than monthly injections in A-VEGF–treated n-AMD. These strategies included fixed quarterly treatment; fixed quarterly monitoring and as-needed (PRN) re-treatment; and monthly monitoring with either mainly VA-guided re-treatment or quantitative-only VA- and OCT-guided re-treatment.

As-needed re-treatment strategies in A-VEGF randomized controlled trials based on monthly follow-up and guided by rigorous reviews of OCT qualitative and quantitative measures of disease activity have decreased injection burden while maintaining visual gains.

In the setting of usual retinal clinical practices, however, the VA gains reported for PRN-treated n-AMD patients have been significantly lower than those reported in PRN-guided clinical treatment trials. Reduced success in these practices could be related to the significantly reduced frequency of visits and imaging investigations attributable to logistics or the inability of patients or their physicians to maintain the frequent monitoring visits.

The use of new long-acting A-VEGF agents, such as aflibercept, could reduce the need for monthly visits in the first year, but successful PRN-guided re-treatment strategies in subsequent years will continue to depend on close monitoring with tightly defined OCT-guided PRN re-treatment strategies.

Conclusions

To reduce treatment burden and provide more efficient individualized treatment for n-AMD patients, OCT/VA–guided PRN treatment strategies have become the preferred and the dominant maintenance programs in retinal practices. The success of these strategies, however, depends on close monitoring and adherence to tightly defined re-treatment criteria. The VA outcomes in A-VEGF–treated n-AMD patients might be more affected by adequate follow-up and monitoring than by the initial A-VEGF pharmacotherapy.

Decision Determinants

OHTAC has developed a decision-making framework that consists of 7 guiding principles for decision making and a decision determinants tool. When making a decision, OHTAC considers 4 explicit main criteria: overall clinical benefit, consistency with expected societal and ethical values, value for money, and feasibility of adoption into the health system. For more information on the decision-making framework, please refer to the *Decision Determinants Guidance* document available at: http://www.hqontario.ca/evidence/evidence-process/evidence-review-process/decision-making-framework.

Appendix 1 provides a summary of the decision determinants for this recommendation.

On the basis of the DD criteria, OHTAC weighted in favour of increasing access to OCT-imaging investigations for monitoring patients undergoing A-VEGF treatment for such retinal diseases as n-AMD, given the life-altering consequences of vision loss with potential undertreatment in PRN re-treatment strategies.

OHTAC Recommendation

On the basis of currently available evidence, OHTAC recommends that:

- During active anti-angiogenic therapy for macular disease, access to optical coherence tomography be provided monthly as the basis for treatment.

Appendices

Appendix 1: Decision Determinants

Table A1: Decision Determinants for Optical Coherence Tomography Monitoring Strategies for A-VEGF–Treated Age-Related Macular Degeneration

Decision Criteria	Subcriteria	Decision Determinants Considerations
Overall clinical benefit How likely is the health technology to result in high, moderate, or low overall benefit?	**Effectiveness** How effective is the health technology likely to be (taking into account any variability)?	Use of OCT along with clinical examinations is essential to decision making for timely re-treatment of a rapidly progressing major eye disease. Follow-up monitoring of patients treated with A-VEGF therapies for n-AMD resulted in clinically significant vision loss without close OCT monitoring.
	Safety How safe is the health technology likely to be?	There are no safety concerns with the use of OCT.
	Burden of illness What is the likely size of the burden of illness pertaining to this health technology?	Age-related macular degeneration is an important retinal disease and is the leading cause of irreversible vision loss and blindness in older adults. The macula is the part of the retina that enables sharp central vision needed for close work, such as reading and writing, and for driving and recognizing faces. The estimated prevalence of any stage AMD is 6.5% and the prevalence of n-AMD increases from 0.04% in 50-year-olds to 2.79% in 80-year-olds to 10.49% (95% CI, 7.45%–14.37%) in 90-year-olds.
	Need How large is the need for this health technology?	All patients treated with A-VEGF pharmacotherapies for macular disease, including diabetic macular edema and n-AMD, require close monitoring with OCT—no other imaging modality provides reliable and accurate measures of early signs of disease progression.
Consistency with expected societal and ethical values[a] How likely is adoption of the health technology to be congruent with societal and ethical values?	**Societal values** How likely is the adoption of the health technology to be congruent with expected societal values?	Declining visual acuity and uncertain variable disease progression has profound effects for patients with macular degeneration. Vision quality-of-life assessments are severely affected by n-AMD, and utility values that measure vision loss in these patients have ratings similar to those with myocardial infarction or strokes.
	Ethical values How likely is the adoption of the health technology to be congruent with expected ethical values?	No incongruent ethical issues are expected with this technology
Value for money How efficient is the health technology likely to be?	**Economic evaluation** How efficient is the health technology/intervention likely to be?	No formal economic analysis was done. The fact that an imaging exam costing approximately $25 CAD was used to guide decisions on a monthly ocular drug injection costing approximately $1500 CAD was considered sufficient evidence.

Decision Criteria	Subcriteria	Decision Determinants Considerations
Feasibility of adoption into health system How feasible is it to adopt the health technology into the Ontario health care system?	**Organizational feasibility** How organizationally feasible is it to implement the health technology?	Use of OCT in ophthalmologic practice is already routine, and the decision consideration involves only increased access to the technology.

AMD, age-related macular degeneration; A-VEGF, A-vascular endothelial growth factor; n-AMD, neovascular age-related macular degeneration; OCT, optical coherence tomography.

[a] The anticipated or assumed common ethical and societal values held in regard to the target condition, target population, and/or treatment options. Unless there is evidence from scientific sources to corroborate the true nature of the ethical and societal values, the expected values are considered.

References

(1) Pron G. Optical coherence tomography monitoring strategies for A-VEGF–treated age-related macular degeneration: an evidence-based analysis. Ont Health Technol Assess Ser. [Internet]. 2014 August; 14(10):1–64. Available from: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ontario-health-technology-assessment-series/OCT-monitoring-strategies.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: EvidenceInfo@hqontario.ca
www.hqontario.ca