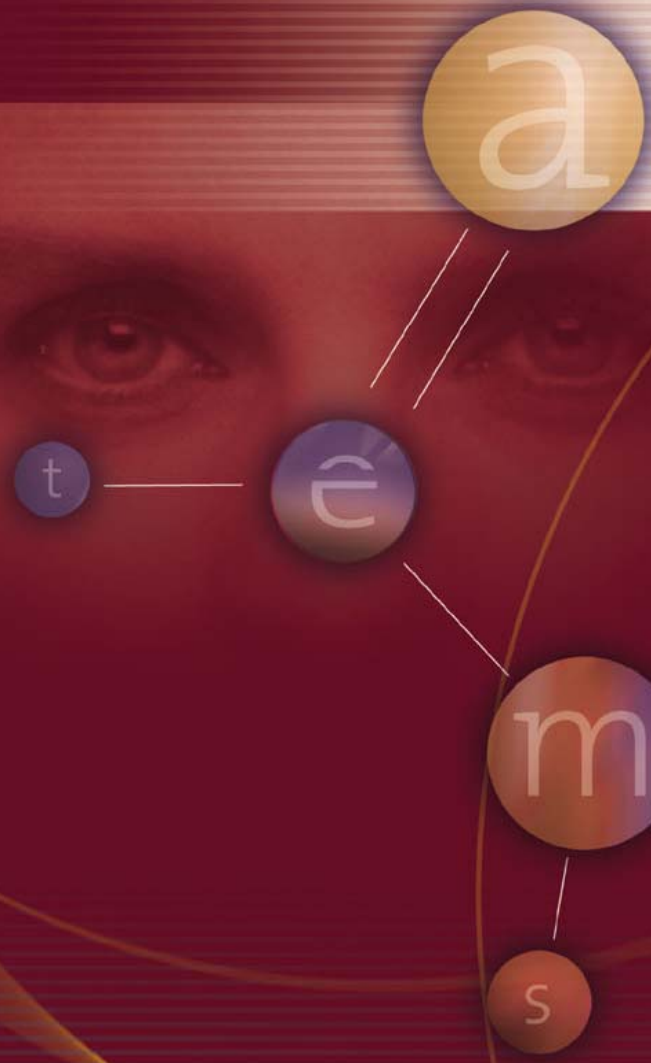
Photodynamic Therapy in the Treatment of Exudative Age-Related Macular Degeneration (ARMD) with Subfoveal Neovascularization

A Technology Assessment

SUMMARY



AGENCE D'ÉVALUATION DES TECHNOLOGIES
ET DES MODES D'INTERVENTION EN SANTÉ

Québec

Evaluation of photodynamic therapy for the treatment of exudative age-related macular degeneration (AMD) with subfoveal neovascularization

A Technology Assessment

Summary

Report prepared for AETMIS
by Kathy Larouche and Sophie Rochon

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Agence d'évaluation des technologies et des modes d'intervention en santé
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This report was translated from an official French publication of the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS). Both the original report, entitled *Évaluation de la thérapie photodynamique pour le traitement de la dégénérescence maculaire liée à l'äge (DMLA) de type exsudatif avec néovascularisation sous-fovéale* and the English summary are available in PDF format on the Agency's Web site.

Scientific review
Jean-Marie R. Lance, M. Sc. (Economics), Senior Scientific Adviser

Translation
Mark Wickens, Ph.D., Certified Translator

Page layout
Jocelyne Guillot
Frédérique Stephan

Proofreading
Suzie Toutant

Bibliographic research
Micheline Paquin
Mathieu D'Amours

Coordination
Lise-Ann Davignon

Communications and dissemination
Richard Lavoie, M.A. (Communication)

For further information on this publication or any other AETMIS activity, please contact:

Agence d'évaluation des technologies et des modes d'intervention en santé
2021, avenue Union, bureau 1050
Montréal (Québec) H3A 2S9

Tel.: (514) 873-2563
Fax: (514) 873-1369
e-mail: aetmis@aetmis.gouv.qc.ca
http://www.aetmis.gouv.qc.ca

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MISSION

The mission of the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) is to contribute to improving the Québec health-care system and to participate in the implementation of the Québec government's scientific policy. To accomplish this, the Agency advises and supports the Minister of Health and Social Services as well as the decision-makers in the health care system, in matters concerning the assessment of health services and technologies. The Agency makes recommendations based on scientific reports assessing the introduction, diffusion and use of health technologies, including technical aids for disabled persons, as well as the modes of providing and organizing services. The assessments take into account many factors, such as efficacy, safety and efficiency, as well as ethical, social, organizational and economic implications.

FOREWORD

PHOTODYNAMIC THERAPY IN THE TREATMENT OF EXUDATIVE AGE-RELATED MACULAR DEGENERATION (ARMD) WITH SUBFOVEAL NEOVASCULARIZATION: A TECHNOLOGY ASSESSMENT

In Western countries, age-related macular degeneration (ARMD) is the leading cause of blindness in people over the age of 55. This disease is characterized mainly by degenerative changes in the macular region of the retina that result in a gradual decrease in central vision. In Québec, it is estimated that about 37,200 people are affected, hence the need for effective therapeutic modalities to treat the disease.

It was in this context that ophthalmologists in the New Technologies Axis of the Vision Network, which is sponsored by the *Fonds de la recherche en santé du Québec* (FRSQ), asked the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) to assess the efficacy of photodynamic therapy for the treatment of ARMD. There was also the need to examine the costs associated with this therapeutic modality in Québec and to look at the organization of the care and services involved.

AETMIS's assessment is based on a rigorous examination of the existing scientific data. According to this assessment, the efficacy of photodynamic therapy using verteporfin as a photosensitizer is well established for two forms of ARMD: 1) exudative subfoveal ARMD with predominantly classic neovascularization, and 2) exudative subfoveal ARMD with pure occult neovascularization. AETMIS also concludes that, given the potentially rapid progression of neovascular ARMD, its early detection could help reduce severe, irreversible vision loss and consequently major expenses, by the public system, for managing this disease and its sequelae.

The report proposes several options for detecting the disease earlier. The optimal implementation of this technology will, however, require major changes to the organization of the care and services in the area of ocular health. Lastly, AETMIS presents various recommendations that urge ministerial and professional authorities to recognize ARMD as a major public health problem and to encourage initiatives for the population-based management of ARMD in the broader context of managing preventable blindness.

In submitting this report, AETMIS wishes to provide the best possible information to the policymakers in Québec's health-care system to assist them in taking action on this important problem.

Dr. Luc Deschênes
Chairman and Chief Executive Officer

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Dr. Jean-Daniel Arbour
Ophthalmologist, Clinique ophtalmologique de l'Ouest, Montréal

Dr. Marie-Carole Boucher
Ophthalmologist, Centre Michel-Mathieu, Hôpital Maisonneuve-Rosemont, Montréal

Jacques Gresset, OD, Ph.D.
Optometrist, Assistant Director and Full Professor, Department of Optometry, Université de Montréal

Dr. Daniel Reinharz
Public Health Specialist, Executive Director, Department of Social and Preventive Medicine, Faculty of Medicine, Université Laval, Québec City

Prof. Gisèle Soubrane, M.D.
Ophthalmologist, Department Head, Clinique ophtalmologique universitaire de Créteil, Centre hospitalier intercommunal de Créteil, France

CONFLICT OF INTEREST

None declared.

SUMMARY

PROBLEM AND OBJECTIVES

Over the past few decades, most industrialized countries have experienced an increase in their elderly populations. This inversion of the age pyramid is leading to an increased incidence of many diseases, including age-related macular degeneration (ARMD). ARMD is characterized by degenerative lesions in the macular region of the retina resulting in a gradual decrease in vision that can lead to a loss of central vision. In fact, this disease is the leading cause of blindness in Western countries. Its prevalence is approximately 0.2% in people aged 55 to 64 and climbs to more than 13% in the over-85 population. Based on epidemiological data, the number of affected individuals in Québec can be estimated at approximately 37,200.

ARMD has been divided into three histopathologic forms: an early form, also known as age-related maculopathy (ARM) or pre-ARMD (it should be noted that the early form is not included in the prevalence and incidence data provided in this report), and two advanced or progressive forms, called atrophic and neovascular (or exudative) forms. At the present time, only the neovascular form is treatable. It accounts for about 47% of the cases of advanced ARMD, which, in Québec, number close to 16,000. This disease therefore generates significant social costs, hence the need for effective therapeutic modalities to treat it.

It was in this context that ophthalmologists representing the New Technologies Axis of the Vision Network, which is sponsored by the *Fonds de la recherche en santé du Québec* (FRSQ), asked the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) to assess the efficacy of photodynamic therapy (PDT) using verteporfin as a photosensitizer for the treatment of ARMD. This report also looks at the costs associated with this therapeutic modality and examines, on an exploratory basis, the organization of the care and services involved.

RESEARCH METHODOLOGY

A literature search was conducted in the PubMed, Current Content Search and Cochrane Library databases by combining the terms *macular degeneration*, *photodynamic therapy* and *verteporfin* (Visudyne®); *Amsler grid; antioxidant*; *vitamin*; *risk factors*; *side effects* and *fluorescein angiography* for the period from 1975 to June 2004. We also used reports from several health technology assessment agencies that have examined PDT, abstracts of papers presented at international scientific conferences, a number of Web sites and interviews with experts in ophthalmology and visual rehabilitation.

The decision tree for the economic analysis was designed for the purpose of predicting the costs and effects of PDT in individuals with ARMD. The population selected for this Markov-type model includes all Quebecers who were over the age of 55 in 2001 (1,730,000). The incidence data for the disease are applied to this cohort. Two options are compared in the model: a *treatment* option and a *no-treatment* option. To include all the possible treatment scenarios, the time horizon in this model was set at eight years, and the outcomes used are the *loss* and *non-loss* of three lines of vision. It will be noted that visual rehabilitation costs are included in both options on the basis of the patient's visual acuity.

The exploratory study of the organization of the care and services provided to ARMD patients was conducted in the summer 2002 using a qualitative approach based on semistructured telephone interviews with eye specialists at all of the university and community hospitals and at certain private clinics in Québec that offer PDT and with

receptionists and nurses who work at these facilities.

PHOTODYNAMIC THERAPY

Photodynamic therapy involves irradiating, with low-intensity light, a tissue that has been subjected to a photosensitizer. At present, the only photosensitizer approved for the treatment of ARMD is verteporfin (Visudyne®). Generally, photosensitizers cause cytotoxic damage only when activated by an appropriate light source, and the damage is limited to a relatively precise area. Verteporfin also offers the advantage of rapid hepatic elimination, which limits the duration of visual or cutaneous photosensitization. Verteporfin is especially effective in ophthalmology, since it is light-activated by a monochromatically red diode laser that easily penetrates blood and fibrous tissues. It can therefore act on choroidal neovasculature and ultimately cause its destruction.

EFFICACY OF PHOTODYNAMIC THERAPY

The examination of the clinical efficacy of PDT using verteporfin as a photosensitizer is based on the results of two randomized, double-blind, multicentre clinical studies: the TAP study (Treatment of Age-related Macular Degeneration with Photodynamic Therapy) and the VIP study (Visudyne in Photodynamic Therapy). Overall, the clinical protocols in these two studies were very rigorous, and the results for the main endpoints were significant. The TAP and VIP studies showed that PDT can effectively slow the progression of two forms of ARMD:

1) Subfoveal neovascular ARMD with more than 50% classic neovascularization, and

2) Subfoveal neovascular ARMD with pure occult neovascularization.

The efficacy of PDT has been demonstrated for these two forms of ARMD when the patient's visual acuity is at least 6/60 in the eye to be treated.

Overall, PDT reduces moderate to severe loss of visual acuity in individuals with these two forms of ARMD. It also reduces the number of individuals who become legally blind (visual acuity less than 6/60) after two years.

For patients with minimally classic ARMD (< 50% classic neovascularization), we cannot, from the existing studies, draw any conclusions regarding the efficacy of PDT.

No study has compared photodynamic therapy with other therapeutic modalities for treating subfoveal neovascular ARMD, since the other modalities (with the exception of laser photocoagulation) are still in the clinical trial stage. Laser photocoagulation is, however, effective in treating patients with extrafoveal and juxtafoveal neovascular ARMD, but this technique cannot be used for subfoveal neovascular ARMD because the laser destroys the retina immediately adjacent to the target area, which would cause a loss of central visual acuity.

PREVENTION OF ARMD

The AREDS study (Age-Related Eye Disease Study Research Group) examined the effect of the daily use of dietary antioxidant (vitamins C and E and beta-carotene) and zinc supplements by individuals with ARMD. The results of this randomized, double-blind, multicentre study showed that the recommended supplements can be effective in preventing the onset or progression of the disease in patients at risk for a progressive form of ARMD (patients with age-related maculopathy [ARM] with large drusen or with unilateral neovascular ARMD). However, there is no evidence to support the use of these supplements when the disease has not been detected in at least one eye. Furthermore, under no circumstances should patients take them without first having consulted a physician, since considerable side effects can occur in certain types of individuals.

RESULTS OF THE ECONOMIC ANALYSIS

In the economic analysis, we basically compare the PDT treatment option with the no-treatment option by calculating the total cost of the services involved in diagnosing, treating, following and managing poor eyesight and blindness, and the utility associated with the loss or non-loss of visual acuity. The results of this analysis are favourable with regard to the use of photodynamic therapy in exudative ARMD with predominantly classic or pure occult neovascularization. An estimate of the cost-utility ratio incremental per QALY (quality-adjusted life-year), calculated on the basis of an 8-year time horizon, yields the following figures:

- For patients with classic neovascularization: $33,880;
- For patients with classic neovascularization and those with pure occult neovascularization: $43,253.

The net annual budget impact is approximately $17.3 million if all the prevalent and incident cases are taken into account, but only $0,3 million if only the incident cases are considered (1,261 patients eligible for treatment over a 2-year period).

Given the potentially rapid progression of neovascular ARMD, its early detection could considerably lower the risk of severe, irreversible vision loss and thus avoid considerable expenses to the public system by reducing the costs associated with the rehabilitation and treatment of the other problems associated with vision loss (depression, falls, etc.). This improvement has repercussions on the cost-utility ratios. Thus:

- For patients with neovascular ARMD with 50% classic neovascularization, the cost-utility ratio decreases from $33,880 to $20,701 per QALY;
- For patients with 50% classic neovascularization and those with pure occult neovascularization, the cost-utility ratio decreases from $43,253 to $22,813.

ACCESS TO OPHTHALMOLOGIC SERVICES

Different sources of information, including an exploratory study on the organization of the care and services relating to photodynamic therapy (PDT), yielded several observations on this important issue:

- ARMD patients cannot always access photodynamic therapy within a reasonable amount of time.
- Problems accessing eye specialists (ophthalmologists and retinologists) and fluorescein angiography lengthen the waiting time for obtaining a first treatment with PDT.
- The amount of time between the onset of macular degeneration and when the individual notices it can also be very long, which can contribute to a greater deterioration in vision.
- Also, in 2003, for budgetary reasons, some hospital patients who were receiving this treatment were transferred to the private sector. Since these patients have to assume a considerable portion of the cost of the drugs, access to photodynamic therapy is becoming even more limited.

CONCLUSION

From the evidence accumulated on photodynamic therapy using verteporfin as a photosensitizer we can conclude that this technology is effective in slowing the progression of subfoveal neovascular ARMD with predominantly classic neovascularization or with pure occult neovascularization. Furthermore, the estimated budget impact for a Québec cohort is acceptable if the improvement in quality of life is taken into

account. However, a major reorganization of services and ocular health care should be considered in the near future to permit the optimal implementation of this technology, to reduce waiting times for this treatment and to deal with the demand that will be increasing in the coming years. Furthermore, measures aimed at promoting the early detection of ARMD in the population, both at the individual and primary-care levels, could reduce the risk of severe, irreversible vision loss and thus reduce the social costs of this disease.

RECOMMENDATIONS

AETMIS recommends that:

1) Photodynamic therapy be considered a technology that can effectively slow the progression of certain forms of ARMD;
2) ARMD be recognized by the policymakers in Québec's health-care system as an important public health problem;
3) Québec-based initiatives for the population-based management of ARMD be part of a broader effort to manage preventable blindness;
4) The planning and implementation, in the wake of this report, of the next few steps in the broader context of managing preventable blindness be facilitated by the creation of a task force charged with proposing a concrete plan to the *Ministère de la Santé et des Services sociaux*;
5) The Vision Network/FRSQ consider the possibility of giving priority to the carrying out of studies evaluating the validity of Amsler's grid or other detection tools in the context of ARMD screening;
6) The Vision Network/FRSQ undertake more-thorough studies to determine, with the necessary rigour, the needs relating to the organization of the care and services pertaining to ARMD and preventable blindness in Québec:

LIST OF ABBREVIATIONS

AETMIS	*Agence d'évaluation des technologies et des modes d'intervention en santé*
AHQ	*Association des hôpitaux du Québec*
AI	Adequate intake
ARM	Age-related maculopathy
ARMD	Age-related macular degeneration
ANAES	*Agence nationale d'accréditation et d'évaluation en santé* (France)
AQDM	*Association québécoise de la dégénérescence maculaire*
AREDS	Age-Related Eye Disease Study Research Group
ARVO	Association for Research in Vision and Ophthalmology
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer
bFGF	Basic fibroblast growth factor
CARET	Beta-Carotene and Retinol Efficacy Trial
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CI	Confidence interval
CNV	Choroidal neovascularization/choroidal neovasculature
CS	Contrast sensitivity
DHA	Dehydroascorbic acid
DRI	Dietary reference intake
EAR	Estimated average requirement
ETDRS	Early Treatment Diabetic Retinopathy Study
FNB	Food and Nutrition Board
FRSQ	Fonds de la recherche en santé du Québec
HSP	Heat shock proteins
ICD-9	International Classification of Diseases (9th edition)
IHCMG	Illuminated high-contrast macular grid
INAHTA	International Network of Agencies for Health Technology Assessment
IPE	Iridial pigment epithelium
IU	International unit
JAT	Japanese AMD Trial
LC	Low contrast
MAR	Minimum angle resolution
MPS	Macular Photocoagulation Study

MSAC	Medical Services Advisory Committee
MSSS	*Ministère de la Santé et des Services sociauxdu Québec*
NEI	National Eye Institute (United States)
NICE	National Institute for Clinical Excellence (United Kingdom)
PDT	Photodynamic therapy
QALY	Quality-adjusted life-year
RAE	Retinol activity equivalent
RAMQ	*Régie de l'assurance maladie du Québec*
RDA	Recommended dietary allowance
RPE	Retinal pigment epithelium
SD_{REQ}	Standard deviation of requirements
SLO	Scanning laser ophthalmoscope
SMM	Norwegian Centre for Health Technology Assessment
SST	Submacular Surgery Trial
TAP	Treatment of Age-related Macular Degeneration with Photodynamic Therapy
TTT	Transpupillary thermotherapy
UL	Tolerable upper intake level
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VIO	Visudyne in Occult
VIP	Visudyne in Photodynamic Therapy
VIT	Verteporfin in Italy
WHO	World Health Organization

GLOSSARY

Atrophy
A decrease in the weight or size of an organ, tissue or cell. It may be physiological or pathological (hereditary, congenital or degenerative).

Contrast sensitivity
The ability to detect changes in lighting between two areas or to discriminate between an object and its background under varying degrees of lighting.

Drusen
Small, yellowish-white formations of acellular debris located either on the optic disc (in which they appear to be embedded and are accompanied by papilledema) or on Bruch's membrane (where they are clustered in the macular region).

Exudate
A serous or albuminous body fluid of inflammatory origin formed when serum passes through the vascular walls in the adjacent tissues.

Fibroblast
The stationary cell of connective tissue. It is very elongated or star-shaped and plays a role in the formation of collagen, reticulin and elastic fibers.

Fluorescein angiography
The photographing of vessels after the intra-arterial or intravenous injection of fluorescein.

Fovea
The part of the retina located at the centre of the macula. It consists solely of cones.

Macula
The posterior part of the retina, being a yellowish, horizontally oriented oval spot (2 mm wide and 1.5 mm high). At its centre is a funnel-shaped depression the very centre of which is the fovea.

Photosensitizer
A compound capable of storing light energy, of being activated by light energy and of thus lending itself to numerous biochemical combinations.

Scotoma
A gap or blind spot in the visual field due to the presence of insensitive points on the retina.

Verteporfin
A monoacid benzoporphyrin derivative that is activated at a wavelength of approximately 690 nm. This compound can act as a photosensitizer.

Visual acuity
The eye's discriminating power. Visual acuity can be defined as the minimum angle (or size) that a letter or form projected at a given distance from the eye must have for two separate black points, lines or spaces that make up the letter or form, to be discriminated by the retinal photoreceptors.

Agence d'évaluation des technologies et des modes d'intervention en santé

Québec