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Update on the Management of Age-related Macular Degeneration (AMD) Part II – Atrophic "Dry" AMD

By Luis G. Riveros, MD, and Michael H. Brent, MD, FRCSC

This issue of *Ophthalmology Rounds* presents Part II of an update on the management of AMD. This article discusses the epidemiology and genetic aspects of the disease and presents the relevant outcomes of clinical trials involving the atrophic or dry form of AMD.

Epidemiology

AMD is the leading cause of irreversible blindness in individuals aged >50 years.[1-6] It is estimated that AMD affects more than 8 million individuals in the United States (US),[2] while in Canada, 17,000 new cases of wet AMD and 180,000 new cases of dry AMD occur annually.[4] The prevalence of the disease is rising as the population ages and it is expected that, by the year 2020, the population aged >85 years will increase by 107%.[3-4] The only proven treatment for the dry or nonexudative form of this disease, which comprises 85% of cases, is an antioxidant/mineral supplement that has been demonstrated to slow the progression of the disease by 25% over 5 years.[7-9] Treatment options and the latest advances for the remaining 15% of cases (the exudative form) were discussed and reviewed in the previous issue of *Ophthalmology Rounds.*

Risk factors associated with the dry form of AMD have been identified and can be divided into 2 groups: modifiable and nonmodifiable. Among the modifiable risk factors, smoking is the most consistently identified, while others such as obesity, sunlight exposure, low levels of antioxidants, and high dietary fat intake, may also affect AMD incidence and progression. The nonmodifiable risk factors include increasing age, gender, iris colour, genetics, and a family history of the disease.

Classification

In dry AMD, visual loss is usually slow, but progressive. Clinically, it is characterized by yellow subretinal deposits called drusen and/or retinal pigment epithelial (RPE) irregularities, including hyperpigmentation and/or hypopigmentation. The soft, larger drusen may become confluent and progress to RPE detachments. This can lead to either geographic atrophy or neovascular AMD. Geographic atrophy involving the centre of the macula leads to visual loss. The international classification and grading system[3,78] divides dry AMD into 2 groups:

- early AMD, defined as the presence of drusen and RPE irregularities, and
- late AMD, defined as the occurrence of central geographic atrophy and/or neovascular disease. Late AMD is associated with greater visual loss.

Prevalence

Early forms of dry AMD are much more common than the late stages, and both types increase in frequency with increasing age. The Eye Disease Prevalence Group[3] calculated the overall prevalence of the neovascular AMD and/or central geographic atrophy to be 1.47% of the US population aged ≥40 years. For the Beaver Dam Eye Study (BDES), the prevalence of late AMD rises to 7.1% in persons who are ≥75 years.[6]

Incidence

The Framingham Eye Study (FES) estimated the 5-year incidence rates of AMD to be 2.5%, 6.7%, and 10.8% for individuals aged 65, 70, and 75 years, respectively.[3] The BDES determined the 5-year cumulative incidence of early AMD to increase from 3.9% in individuals aged 43 to 54 years to 22.8% in persons aged ≥75 years. The overall 5-year incidence of late AMD was 0.9%.[6]

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Table 1: AMD Eligibility Categories according to the AREDS study[8]

AMD Category	First Eye*			Second Eye
	Drusen Size†	Drusen Area†	Pigment Abnormalities‡	
1	None or small (<63 µm)	<125 µm diameter circle (~ 5-15 small drusen)	None	Same as first eye
2	Small (<63 µm) Or intermediate (≥63, <125 µm) Or none required if pigment abnormalities present	≥125 µm diameter circle (about $1/150$ disc area) At least 1 druse	Absent or present, but GA absent	Same as first eye or Category 1
3a	Intermediate (≥63, <125 µm) Or large (≥125 µm) Or none required if non-central GA† is present	≥360 µm diameter circle (about $1/16$ disc area) if soft indistinct drusen are present (~20 intermediate drusen) ≥656 µm diameter circle (about $1/5$ disc area), if soft indistince drusen are absent (~65 intermediate drusen) At least 1 druse	Absent or present, but central GA† absent	Same as first eye or Category 1 or 2
3b	First eye same as Category 3a			VA <20/32 not due to AMD§, or uniocular disqualifying disorder is present‖
4a	First eye same as Category 1, 2, or 3a			Advanced AMD‖¶
4b	First eye same as Category 1, 2, or 3a			VA <20/32 due to AMD, but advanced AMD¶ not present§

* Must have visual acuity (VA) ≥20/32, no advanced age-related macular degeneration (AMD), and no disqualifying lesions.
† Drusen and geographic atrophy (GA) are assessed within 2 disc diameters (3000 µm)[33] of the macula.
‡ Pigment abnormalities (increased pigmentation or depigmentation) within 1 disc diameter of the centre of the macula.
§ Eye not eligible for VA event.
‖ Eye not eligible for AMD event.
¶ The GA involving centre of macula or signs of choroidal neovascularization (presence beneath the retinal pigment epithelium or sensory retina of fluid, blood, or fibrovascular or fibrous tissue).

Nonmodifiable risk factors

Age: The disease is strongly age-dependent as demonstrated in all of the studies of prevalence, incidence, and progression of both forms of AMD. The FES reported a 17-fold increased risk of AMD between the youngest and the oldest age group. The Watermen Study revealed that the prevalence of moderate to advanced AMD doubled with each decade after age 60[3]. The BDES demonstrated that by the age of 75 and older, 7.1% of individuals had late AMD compared with 0.1% in the age group 43 to 54 years and 0.6% among persons aged 55 to 64 years.[5,6,10-12]

Gender: Although several studies have demonstrated that there are no overall differences in the frequency of AMD between men and women, the BDES suggested that women aged ≥75 years had twice the incidence of early AMD compared with men,[6] and the Age-Related Eye Disease Study (AREDS) also found that women had higher risk for intermediate drusen.[7,8]

Race: Different studies have shown that the prevalence of AMD is higher among Caucasians than any other ethnic group. The Baltimore Eye Survey reported AMD accounted for 30% of bilateral blindness among Caucasians compared to none among African Americans.[5] The Los Angeles Latino Eye Study also indicated that Hispanic-Latinos have a high rate of early AMD, but not late AMD.[11]

Ocular factors

Different ocular characteristics have been associated with AMD. Some studies have shown an association between AMD and hyperopia, while others suggest a link between light-coloured irises and AMD.[3,5,11] Apparently higher levels of melanin may be protective against light toxicity.[3] The relationship between the presence of cataracts and AMD is not consistent; however, investigators have postulated an association between cataract surgery and an increased risk for advanced AMD. The hypothesis is that yellowing and opacification of the lens blocks high energy blue and ultraviolet light.[7,8] Also, inflammatory changes after cataract surgery may cause progression from early to late AMD.[2,3,8]

Modifiable risk factors

Smoking: There is strong evidence indicating a positive association between smoking and the presence of both dry and wet AMD.[1-3,6,8,10,11] Smoking decreases levels of high-density lipoprotein (HDL) cholesterol and increases

Figures 1-4: Fundus photographs

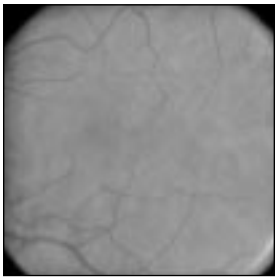


Figure 1: Left eye in Category 2 with multiple small and intermediate drusen

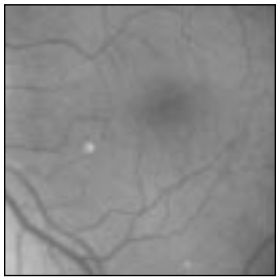


Figure 2: Left eye in Category 3 with a drusen >125 μm

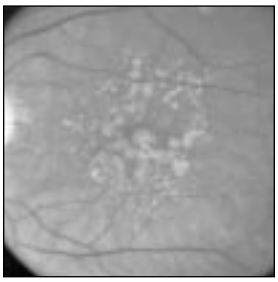


Figure 3: Left eye with many large drusen and pigment abnormalities (totaling at least 1 disc area)

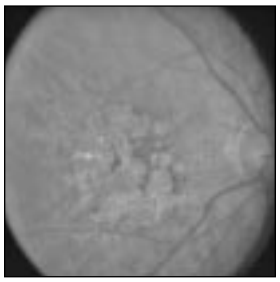


Figure 4: Right eye in Category 4 with central advanced geographic atrophy

platelet aggregability and fibrinogen. Smoking also increases oxidative stress and lipid peroxidation, and reduces plasma levels of antioxidants. Animal models also suggest that nonneuronal nicotinic receptors may play a role in advanced AMD.[3]

Obesity: Epidemiologic studies have shown a positive association between obesity and AMD. The level of obesity is directly proportional to the risk of progression of AMD. Studies have shown that the greater the body mass index (BMI), the greater the risk for progression of AMD. Vigorous physical activity 3 times a week reduces the risk of AMD progression by 25% compared to no physical activity.[2-3]

Alcohol intake and sunlight exposure: There is no clinical evidence supporting either the positive or negative effects of alcohol intake on the development or progression of AMD. There has been controversy regarding the association between ultraviolet radiation exposure and the risk of development and progression of AMD. The real challenge has remained in standardizing and measuring the life-cumulative sunlight exposure.

Antioxidants, vitamins, and minerals: The Age-Related Eye Disease Study (AREDS) has been the largest (4,757 participants) and longest (10 years) trial investigating dry AMD. It evaluated the role of micronutrient supplementation in altering the natural history of atrophic AMD. It classified the disease into different categories (Table 1 and Figures 1- 4) and found that high-dose antioxidants and minerals were effective in reducing the risk of progression of advanced AMD by 25% for those individuals in Categories 3 and 4 (intermediate and unilateral advanced AMD). The AREDS formulation was also found to reduce the risk of moderate vision loss (>3 lines) by 19% at 5 years.[1-2,7,8]

The dose of Vitamin C (500 mg) used in the AREDS formulation is approximately 5 times the daily dietary intake in the general population; the dose of Vitamin E (400 IU) is approximately 13 times the recommended dietary allowances (RDA), while the dose of zinc oxide (4 mg) is about 5 times the RDA. These amounts of vitamins C and E, and zinc in the AREDS formulation are higher than can be realistically achieved by dietary intake alone, and can only be obtained by supplementation. The dose of beta-carotene used in this study was 15 mg/day, similar to doses used in other studies. Studies have demonstrated that smokers who take high doses of beta-carotene are at higher risk of developing lung cancer. Therefore, smokers are advised to avoid vitamin preparations containing beta-carotene.[3]

Recruitment for AREDS2 recently started. This trial has been designed to evaluate the effect of dietary xanthophylls (lutein/zeaxanthin) and/or omega-3 long chain polyunsaturated fatty acids (LCPUFAs) on progression to advanced AMD. It is expected that this study will collect and assess data on approximately 4,000 participants aged 50 to 85 years, who have either bilateral large drusen or large drusen in one eye and advanced AMD (neovascular AMD or central geographic atrophy) in the fellow eye. In the first randomization, all participants will be given the original AREDS formulation (now considered standard of care). Of the 4,000 participants, 1,000 will act as control, 1,000 will receive lutein (10 mg)/zeaxanthin (2 mg), 1,000 will receive omega-3 LCPUFAs, docosohexanoic acid/eicosapentanoic acid (DHA/EPA), and 1,000 participants will receive both lutein/zeaxanthin and DHA/EPA. In a second randomization, 1,000 participants will serve as the control group and will receive the original AREDS formulation. The other 3 groups of 1,000 participants will receive a variation of the AREDS formulation, with either no beta-carotene, lower amounts of zinc (25 mg), or no beta-carotene and lower amounts of zinc.

The main objectives of AREDS2 are to study the effects of:

- high supplemental doses of dietary xanthophylls (lutein and zeaxanthin) and omega-3 LCPUFAs on the development of advanced AMD
- these supplements on moderate vision loss (doubling of the visual angle or loss of ≥15 letters on the Early Treatment Diabetic Retinopathy Study [ETDRS] chart)
- these supplements on cataract development
- eliminating beta-carotene in the original AREDS formulation on the development and progression of AMD
- reducing zinc in the original AREDS formulation on the development and progression of AMD

This study started on September of 2006 and its participants are expected to be followed for a minimum of 5 years.

Genetic and familial factors

Genetic or familial factors play a role in the etiologic basis of AMD. First-degree relatives of individuals with AMD are at an increased risk for developing disease (odds ratio 2.4), are affected at a younger age, and have an increased lifetime risk of late AMD (risk ratio 4.2), as

compared with first-degree relatives in families without the disorder.[13]

Several studies have implicated different genes in AMD, demonstrating that this is a complex oligogenic disease.[13-14] Drusen found in patients with AMD contain apolipoprotein E (APOE), and the various alleles of the APOE gene have been found to either protect against (APOE ε 4 allele) or contribute to the risk (APOE ε 2 allele) for AMD.[12] The complement factor H (CFH), factor B (CFB), and C2 genes are associated with 50% to 70% of all cases of AMD. The estimated relative risk among carriers of this polymorphism ranges from 2.7 to 7.4 as compared with noncarriers.[14]

The CFH protein inhibits the alternative complement cascade, in part by binding to C-reactive protein, which is induced by damaged tissue. Several other genes are being studied, but the results are pending or inconclusive. The difficulties in identifying these genes and their role in AMD arise from the multifactorial origin of the disease.[12-14]

Dry or atrophic AMD

Atrophic AMD comprises approximately 85% of all patients suffering from AMD and is responsible for 10% to 20% of cases of blindness caused by this disorder.[1-3] This form of AMD tends to affect vision in a gradual, slow, and progressive manner. The amount of vision compromised is determined by the number, size, morphology, and location of drusen in the macula, as well as the amount and location of associated retinal pigment epithelium (RPE) atrophy.

The AREDS has suggested the following descriptions of non-neovascular AMD with respect to features within 3000 µm of the centre of the macula.[7]

1. No AMD if there are no or only a few small drusen (<63 µm) in the absence of any other stage of AMD.
2. Early AMD if there are few (<20) medium-sized drusen (63 to 124 µm) or pigment abnormalities (hyperpigmentation and/or depigmentation) and no other stage of AMD.
3. Intermediate AMD if there is at least one large drusen (>125 µm) or numerous medium-sized drusen >20 µm when the drusen boundaries are indistinct or amorphous or soft; or > 65 µm if their boundaries are distinct or sharp or hard, or the presence of geographic atrophy that does not extend under the centre of the macula.
4. Advanced AMD if there is geographic atrophy extending under the centre of the macula or signs of choroidal neovascularization. In patients with advanced atrophic AMD, up to 43% of eyes progress to exudative AMD within 5 years.[78]

A simplified severity scale was proposed by the AREDS group. It assigned 1 point for each risk factor in each eye. It defined risk factors as the presence of large drusen (>125 µm, width of a large vein at disc margin), and retinal pigment epithelial abnormalities (Table 2). For clinical purposes, as the number of risk factors increases from 0 to 4, the 5-year risk of advanced AMD in at least one eye increases directly proportional in a sequence of 0.5%, 3.0%, 12%, 25%, and 50% (Table 3).[12]

Table 2: Risk factor scoring for patients with large drusen and pigment abnormalities in both eyes

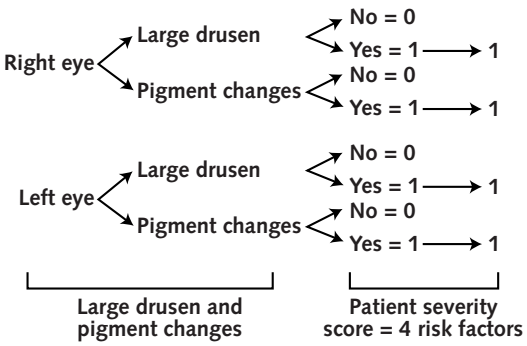
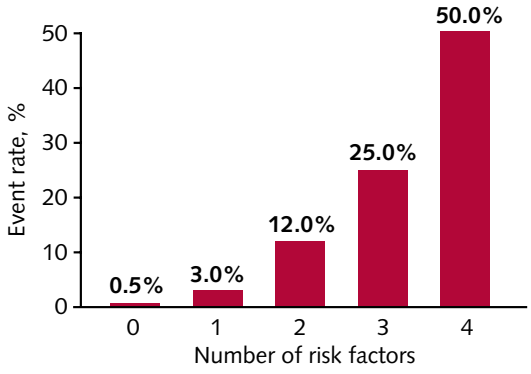


Table 3: Approximate 5-year rates of progression to advanced AMD according to number of risk factors[12]



Published clinical trials and studies for AMD

Multicentre Investigation of Rheopheresis for AMD (MIRA-1): Rheopheresis is a specific method of apheresis, in which a patient's blood is drawn outside the body and specific compounds are removed before the blood is returned to the body.[15,16] This method uses filters to remove excess levels of macro-proteins and fatty components in the blood that have been associated with AMD. It is hypothesized that these substances decrease blood flow, cause damage to capillaries, and lead to the atrophic degenerative process. Factors removed by rheopheresis include LDL-cholesterol, fibrinogen, and alpha-2-macroglobulin. Theoretically, after several sessions of rheopheresis, the blood is able to flow more easily through even the smallest capillaries in the body and it is believed that the improved microcirculation more effectively supplies the macular cells with the oxygen and nutrients needed to function properly.

The preliminary results of the MIRA-1 trial revealed that 28% of treated eyes vs. 18% of the placebo group increased at least 2 lines of best corrected visual acuity (BCVA) at 12 months, and that 12% vs. 0% respectively, increased 3 lines. Of all of the eyes, 8% vs. 18% in the 2 subgroups had

decreased BCVA of at least 2 lines at 12 months.[15,16] At 12 months post-baseline, analysis of MIRA-1 did not demonstrate a statistically-significant difference in the mean change in the ETDRS BCVA between the treated and placebo groups. However, subgroup analyses suggest a potential benefit in some cases. Rheopheresis treatment should be considered only in the context of a randomized study. Based on subgroup analyses from the MIRA-1 trial, a second phase 3 trial is in the planning stages.

Laser treatment in dry AMD: The Complications of Age-Related Macular Degeneration Prevention Trial evaluated whether laser treatment could prevent or slow the development of neovascular AMD in patients with bilateral large drusen.[17] This multicentre study (22 clinical centres) enrolled 1,052 participants who had ≥10 large (>125 µm) drusen and visual acuity of 20/40 or better in each eye. The initial laser treatment specified 60 barely-visible burns applied in a grid pattern within an annulus between 1500 and 2500 µm from the centre of the fovea. At 12 months, eyes assigned to treatment that had sufficient drusen remaining were re-treated with 30 burns, by targeting drusen within an annulus between 1000 and 2000 µm from the foveal centre. At 24 months, the study found that the results were comparable for both treated and untreated eyes. At 5 years, 33% of both groups had lost ≥2 lines of visual acuity. The results revealed that there was no evidence of either a clinically significant beneficial or harmful effect with preventive argon green laser treatment in eyes with bilateral large drusen.[16]

Transpupillary thermotherapy (TTT) for the treatment of exudative AMD: TTT has been proposed as a potential treatment for wet AMD. The procedure uses an 810 nm diode infrared laser to treat the subfoveal choroidal neovascular membrane (CNVM). This involves low irradiance, long exposure duration, and a large spot size to gradually raise the temperature of the blood vessels in the choroid. The goal is to close the CNVM without causing thermal damage to the overlying retina. The TTT4CNV trial examined the effectiveness of TTT vs sham for small occult subfoveal CNVM. The results were reported in 2004 and revealed that TTT was not only ineffective, but that 5% of eyes incurred ocular damage as a result of treatment. Although there have been some reports of success, others demonstrate no benefits or statistically significant differences when compared to regular standard of care.[18]

Anecortave acetate and AMD: Anecortave acetate is a modified molecule of cortisol acetate with angiostatic properties that have been shown to inhibit blood vessel growth in several models of ocular neovascularization. It has been suggested that anecortave acetate reduces the synthesis of the proteolytic enzymes necessary for vascular endothelial cell migration. In addition, it downregulates the induction of vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 in target ocular tissues. Anecortave acetate retains its anti-inflammatory activity.[9] To achieve therapeutic levels within the eye, it must be placed in direct contact with the sclera over the macula. Anecortave acetate is delivered as a periocular posterior juxtascleral depot by a specially-designed cannula. Clinical trials have demonstrated the safety and efficacy of anecortave acetate monotherapy for the treatment of subfoveal CNVM;[19] however, it was found to be inferior to photodynamic therapy (PDT) with verteporfin in a head-to-head trial evaluating the effectiveness in treating predominantly classic CNVM in wet AMD.

Anecortave acetate is currently under evaluation in a randomized, double-blind, placebo-controlled study – the Anecortave Acetate Risk-Reduction Trial (AART) – involving 2,596 patients with high-risk dry AMD in 1 eye and wet AMD in the fellow eye. The primary endpoint is to determine if the drug is safe and effective in arresting the progression of dry AMD to wet AMD in at-risk patients.[18] Enrollment in this trial was completed on January 31, 2006, and preliminary results are expected in the near future.

Current clinical trials and investigations

- Antioxidant Eye Drops to Treat Geographic Atrophy in Age-Related Macular Degeneration: This pilot study of up to 10 eye drop-tolerant participants with bilateral geographic atrophy is designed to characterize the effect of antioxidant eye drops given 3 times a day on the progression of geographic atrophy area over a 2-year period. Participants will have 1 eye randomized to receive the eye drop and the fellow eye will be observed only.[20]
- Retinal Transplantation for Dry Age-related Macular Degeneration: The aim of this clinical trial is to test the safety of transplanting human fetal neural retinal tissue and retinal pigment epithelium into the eyes of human patients with AMD. Fetal retinal transplantation is highly experimental.[21]
- A Phase II Study of Implants of Encapsulated Human NTC-201 Cells Releasing Ciliary Neurotrophic Factor (CNTF) in Participants with Visual Acuity Impairment Associated with Atrophic Macular Degeneration: The class of macro-biomolecules called "neurotrophic factors" has been demonstrated to retard loss of photoreceptor cells during retinal degeneration. One of these, CNTF, was found to be effective in retarding vision loss from photoreceptor cell death in 13 animal models of outer retinal degeneration. Further, CNTF has passed appropriate milestones in a human Phase I safety study and is now under consideration for efficacy in atrophic macular degeneration.[22]

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Upcoming events

Note: This year's (September 2006 to May 2007) VPP rounds will be held at Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, 'E" Wing, Ground Floor, Room EG61 at 5:30PM – 7:30PM.

May 3, 2007	VPP – Dr. Arif Samad, Halifax, NS "The Evolution of Retinal Anti-Angiogenic Therapy"
May 10, 2007	VPP – Dr. Mina Chung, Rochester, New York "Adaptive Optics Imaging of the Retina"
May 17, 2007	VPP – Dr. Phil Ferrone, Royal Oak "Safety and Efficacy of Higher Dose Avastin"
May 24, 2007	VPP – Dr. William Macrae "Quality Assurance Rounds"
May 31, 2007	VPP – Dr. Thomas Freddo, University of Waterloo "Conjunctiva-the Often Forgotten Tissue"
June 15, 2007	Annual Departmental Research Day JJR McLeod Auditorium, Medical Sciences Building, University of Toronto Guest Speaker: Dr. Paul Kaufman, Madison, WI. Contact: Stella Pang 416-813-7654 ext 2642
October 13, 2007	International Ocular Blood Flow Symposium Sutton Place Hotel Director: Dr. Neeru Gupta. Contact: University of Toronto CME office – 416-978-2719

Upcoming Meeting

10 to 13 November 2007
American Academy of Ophthalmology
111th Annual Meeting
New Orleans, Louisianna
Contact: www.aao.org

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