

### 2. Wet age-related macular degeneration

Age-related macular degeneration (ARMD) is the leading cause of severe vision loss in the Western world for those aged 50 years and older.<sup>1</sup> It is associated with degenerative, oxidative, and inflammatory changes in the macular region of the retina, which can cause central visual loss. Age-related macular degeneration is categorized into 2 forms: a dry or nonneovascular form and a wet or neovascular form. The dry form is more common and accounts for the vast majority of ARMD cases. The wet form, however, is more debilitating, and is responsible for more than 80% of the visual loss in such patients.<sup>1</sup> The prevalence of early ARMD increases from around 4% in those younger than 60 years to more than 30% in those aged 85 years and older.<sup>2</sup> Known risk factors of ARMD include family history, increasing age, smoking, and white race. With an aging population, the prevalence and incidence for ARMD will increase and are predicted to pose an enormous challenge to the provision of eye care in Canada.<sup>3</sup>

Age-related macular degeneration is believed to result primarily from dysfunction in the retinal pigment epithelium—a critical layer underneath the retina, which is multifunctional and responsible for retinal health. Dry ARMD, characterized by drusen on direct ophthalmoscopy, might convert to wet ARMD acutely or subacutely. Wet ARMD refers to the development of neovascularization within the neural retina from vessels originating from the choriocapillaris, a complex network of blood vessels underlying the retina and retinal pigment epithelium. The new choroidal vessels cause vascular leakage and hemorrhaging, resulting in devastating visual loss.<sup>4</sup>

On ophthalmoscopy, wet ARMD is characterized by the presence of subretinal fluid, intraretinal hemorrhage within the macular region, and sometimes exudates (**Figure 1**). The other diagnoses in question were incorrect based on typical funduscopy findings: Retinal detachment is diagnosed by an elevated translucent retina with no hemorrhage. Central retinal vein occlusion is characterized by the so-called blood-and-thunder picture, with cotton-wool spots, intraretinal hemorrhaging, and disc edema. A patient with diabetic retinopathy normally presents with microaneurysms, cotton-wool spots, and dot-blot hemorrhages throughout the retina.

Symptoms of wet ARMD include metamorphopsia, blurry vision, and central scotoma.<sup>4</sup> On examination, vision can have decreased to 20/400 or worse. An Amsler grid (**Figure 2**) tests for macular function and can detect early changes from wet ARMD.

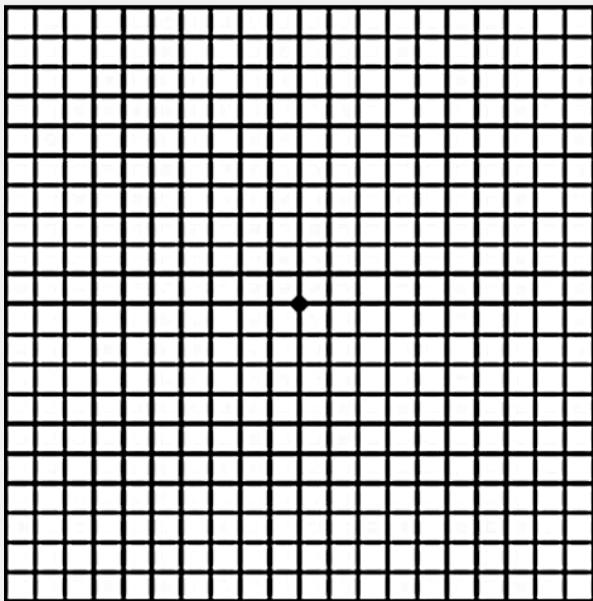
### Management

Patients with moderate to advanced dry ARMD can decrease their chance of progression to wet ARMD

**Figure 1.** Subretinal fluid, intraretinal hemorrhage within the macular region, drusen, and exudates consistent with wet age-related macular degeneration



**Figure 2.** Amsler grid: *the patient is asked to focus on the central dot and report whether any of the lines appear wavy, and whether any areas of the grid appear to be missing. This is useful in identifying ARMD and as a home test for monitoring changes*



with various methods. Dietary modification, with increased green leafy vegetable intake, and smoking cessation are important evidence-based lifestyle changes.<sup>5,6</sup> Furthermore, supplementation with a multivitamin that combines high-dose vitamins C and E,

$\beta$ -carotene, and zinc, in accordance with the formula used in the Age-Related Eye Disease Study, can decrease the progression to the wet form of ARMD by up to 25% for those with intermediate to severe dry ARMD.<sup>7</sup>

If exudative ARMD is suspected, an urgent referral (ie, within 1 week) to an ophthalmologist is necessary.<sup>4</sup> Diagnosis is determined by funduscopic examination combined with intravenous fluorescein angiography. Optical coherence tomography, a form of macular imaging, can also be obtained to assess for macular edema and to provide baseline data for assessment of response to therapy.

## Treatment

In recent years, the treatment for wet ARMD has undergone revolutionary changes. Previous treatments, such as thermal laser photocoagulation and photodynamic therapy with verteporfin, were only partially effective at stabilizing vision and only seldom resulted in visual improvement. These treatments have now given way to inhibitors of vascular endothelial growth factor (VEGF), namely ranibizumab and bevacizumab.

At present, ranibizumab is the treatment of choice for exudative ARMD and has been approved by the Common Drug Review. It is currently covered only by the provincial health care systems in Quebec and Ontario, but is being considered for coverage in the provincial formularies of other provinces. In several large randomized controlled trials, ranibizumab has been shown to stabilize vision in more than 95% of patients with wet ARMD. Further, it is the first treatment that is associated with a statistically significant mean improvement in visual acuity in such patients.<sup>8,9</sup>

Bevacizumab has not been studied in similar randomized controlled trials but is often employed for cost reasons; each intravitreal ranibizumab is more than 50 times the price of intravitreal bevacizumab (which is prepared by a compounding pharmacy from vials prepared for intravenous administration).<sup>10</sup>

The anti-VEGF treatments are administered by injection into the vitreous cavity, using a sterile technique in an office setting. Patients typically require a minimum of 3 injections, with each injection separated by approximately 1 month. Patients are then closely monitored for treatment response and potential need for further treatments.

Most patients tolerate intravitreal injection of ranibizumab and bevacizumab very well and do not experience serious problems; however, local and systemic complications can occur. Serious ocular complications include endophthalmitis (<0.2% per injection), retinal detachment (<0.1% per injection), and traumatic cataract (<0.1% per injection).<sup>8,9,11</sup>

The safety profile of ranibizumab has been documented during several randomized trials and includes risk

of hypertension (4.33% to 16.77%), myocardial infarction (1.44% to 1.89%), and stroke or cerebral infarction (0.72% to 1.89%).<sup>8,11</sup> Indeed, the manufacturer of ranibizumab has released statements warning of the potential increased risk of stroke with intravitreal injection.

The safety profile of intravitreal bevacizumab is not as well known. When given intravenously for colon cancer, bevacizumab has been shown to induce serious systemic problems, such as hypertension, bleeding, and thromboembolic events. Although it has been demonstrated that bevacizumab is detectable in serum after injection into the eye, the peak serum levels achieved are minuscule relative to the level attained during intravenous administration.<sup>9</sup> Nevertheless, patients are theoretically at risk of the aforementioned adverse events documented with intravenous bevacizumab.

## Recommendations

Patients with dry ARMD can benefit from a variety of lifestyle and nutritional measures to help prevent visual loss. Such patients should be encouraged to use an Amsler grid at home. Conversion to wet ARMD can manifest as acute visual loss with metamorphopsia or central scotoma. These patients should be referred to an ophthalmologist immediately for consideration of treatment with anti-VEGF agents. 

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### Competing interests

None declared

### References

1. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, et al. Global data on visual impairment in the year 2002. *Bull World Health Organ* 2004;82(11):844-51. Epub 2004 Dec 14.
2. Wang JJ, Rochtchina E, Lee AJ, Chia EM, Smith W, Cumming RG, et al. Ten-year incidence and progression of age-related maculopathy: the blue Mountains Eye Study. *Ophthalmology* 2007;114(11):92-8.
3. Cruess A, Zlateva G, Xu X, Rochon S. Burden of illness of neovascular age-related macular degeneration in Canada. *Can J Ophthalmol* 2007;42(6):836-43.
4. Riordan-Eva P, Whitcher JP. *Vaughan & Asbury's general ophthalmology*. 17th ed. New York, NY: McGraw-Hill; 2008.
5. Khan JC, Thurlby DA, Shahid H, Clayton DG, Yates JR, Bradley M, et al. Smoking and age related macular degeneration: the number of pack years of cigarette smoking is a major determinant of risk for both geographic atrophy and choroidal neovascularisation. *Br J Ophthalmol* 2006;90(1):75-80.
6. Chong EW, Kreis AJ, Wong TY, Simpson JA, Guymer RH. Dietary omega-3 fatty acid and fish intake in the primary prevention of age-related macular degeneration: a systematic review and meta-analysis. *Arch Ophthalmol* 2008;126(6):826-33.
7. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol* 2001;119(10):1417-36.
8. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *New Engl J Med* 2006;355(14):1432-44.
9. Andreoli CM, Miller JW. Anti-vascular endothelial growth factor therapy for ocular neovascular disease. *Curr Opin Ophthalmol* 2007;18(6):502-8.
10. Raftery JP, Lotery A. The cheaper drug, bevacizumab, should be referred to NICE. *BMJ* 2007;334(7590):381-2.
11. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. *New Engl J Med* 2006;355(14):1419-31.

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