

Age Related Macular Degeneration: Pearls for Primary Care

Why? Age related macular degeneration (AMD) is a disease of major public health importance. The incidence and severity of the disease increases with age. The Beaver Dam Eye Study has shown that 31.1% of the population will have either early or late AMD by the age of 75 years and 7.6% will have late AMD develop over the years from 75 to 86.¹

Since it is estimated that the US population greater than 75 years is expected to increase by 54% between 2005 and 2025,¹ the public health consequences are staggering. Recent advances in the treatment of AMD have dramatically reduced the morbidity but carry potential medical implications that need to be understood by physicians working in the primary care realm.

What is AMD?

The macula is a tiny area within the central retina. It is the area of retina where best vision occurs. AMD affects this area and in so doing may cause loss of the ability to read, recognize faces and colors, and drive. The first stage, dry AMD, is recognized when yellow spots called drusen form under the macular area. Usually dry AMD progresses slowly and may not cause severe visual problems unless pigment atrophy occurs under the central macula. The advanced form of AMD, the wet form, is associated with more rapid progression. It is associated with the development of abnormal blood vessels under the macular area that cause serum leakage, bleeding and eventually scarring of the macula. The patient often notices distortion, blank spots or blurred vision that can lead quickly to legal blindness.

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What can be done for dry AMD? Are there risks?

Current treatment modalities are aimed at decreasing the development of blood vessels in wet AMD. Patients with intermediate dry AMD are at significant risk for progression to wet AMD.² The results of the Age-Related Eye Disease Study (AREDS) demonstrated about a 25% reduction in risk of progression to wet AMD when vitamin supplementation was utilized.³ The current recommendation for non-smokers is a Centrum[®] Silver[®] daily plus 500 mg vitamin C, 400 IU vitamin E, 15 mg beta-carotene (vitamin A), 80 mg zinc (zinc oxide) and 2 mg copper (cupric oxide).³ A study done by NCI showed an increased risk of death from lung cancer in smoking men taking high dose beta-carotene.⁴ Thus, high dose beta-carotene is not recommended for smokers. Supplements without it are recommended.

In a population-based, cohort study with 30 years of follow-up, Swedish men with the highest serum levels of retinol had a risk of fracture 7 times that of men with lower levels (P<.001).⁵ Another article examined the Medicare data base and looked at the 4 year incidence of hip fracture using multiple logistic regression analysis. It found that patients with atrophic (dry AMD) had an 11% (P<.001) higher risk of hip fracture than reference patients.⁶ The association was not significant

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in exudative AMD. This study did not evaluate serum retinol or beta-carotene levels to see if that was a factor in the differences seen. These three studies demonstrate why it is important to use vitamin supplements according to the AREDS's guidelines.

In counseling patients with AMD it is also important to stress ways in which the patient can reduce his risk of progression. As in other vascular diseases the avoidance of smoking,⁷ control of hypertension,⁸ attention to diet to reduce dietary fat,⁹ and avoidance of obesity¹⁰ all pay long term dividends to the patient at risk.

What about wet AMD?

Once a patient develops exudative, wet AMD, aggressive treatment of the blood vessels and associated changes is instituted quickly to reduce morbidity and long term damage. Many treatments have been used over the years including standard laser, surgical removal, photodynamic therapy (intravenous verteporfin with laser), and anti-vascular endothelial growth factor (VEGF-A) therapies (administered as a series of intravitreal injections). VEGF-A is a "diffusible cytokine that promotes angiogenesis and vascular permeability."¹¹ Pegaptanib Sodium (Macugen) and Ranibizumab (Lucentis), have received FDA approval as anti-VEGF-A therapies. With the recent publication showing the effectiveness of Ranibizumab at stabilizing and improving visual function,^{11,12,13} the use of anti-VEGF-A agents has become the dominant treatment for

wet AMD. Ranibizumab has 94.6% rate of stability (less than 15 letter loss) compared to 62.2% of sham treatment¹¹ and 64.3% of photodynamic therapy.¹² Improvement in vision of 15 or more letters occurs in 24.8% - 40.3%^{11,12} depending on the dose of Ranibizumab used and the study referenced.

Bevacizumab (Avastin) approved by the FDA as an anti-VEGF-A treatment for metastatic colon cancer, is a full sized antibody while Ranibizumab is a Fab molecule. Both are genetically engineered from the same mouse monoclonal antibody.¹⁴ Prior to Ranibizumab's approval, investigators started using Bevacizumab, off label, in select patients with success.^{15,16,17} Large, controlled clinical trials with intravitreal injections of Bevacizumab have yet to be done. Bevacizumab, when used **intravenously**, has been associated with elevated blood pressure, proteinuria, heart attack and stroke.¹⁴ While studies with intravitreal Ranibizumab have shown no difference in these events in sham versus treated patients,¹¹ another study (SAILOR) comparing two doses of Ranibizumab has shown an increased risk of stroke in the higher dose group.¹⁸ Similar controlled data for Bevacizumab do not yet exist. Both Ranibizumab and Bevacizumab are now being widely used to treat wet AMD. The NEI is currently investigating the possibility of a controlled clinical trial of Ranibizumab versus Bevacizumab to find which is more effective and whether there are safety issues with either drug that should alter current practice.

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