THE INTERMEDIATE STAGE OF AMD: WHY SHOULD WE IDENTIFY IT AND WHAT CAN WE DO ABOUT IT?*

Jennifer I. Lim, MD†

ABSTRACT

Early identification of the intermediate stage of age-related macular degeneration (AMD) is a key component toward preventing progression to advanced AMD and saving visual acuity. Preventive strategies include education of patients about self-monitoring for symptoms of metamorphopsia and scotomas and the importance of reporting these signs promptly; initiation of high-dose antioxidant vitamins combined with zinc, as used in the Age-Related Eye Disease Study (AREDS); and routine monitoring of patients at risk for early signs of choroidal neovascularization. This article reviews the AREDS definition and risk stratification of intermediate AMD, the role of antioxidants and zinc in reducing structural and functional risk, and the impact of smoking on AMD. It also addresses the roles of patient self-monitoring and periodic follow-up by the comprehensive ophthalmologist, with special emphasis on the Amsler grid and preferential hyperacuity perimeter testing. Lastly, the article discusses the findings of several laser studies that were undertaken to determine whether laser eradication of drusen could prevent progression of the intermediate stage of AMD to advanced AMD. (Adv Stud Ophthalmol. 2007;4(2):32-36)

The importance of identifying the intermediate stage of age-related macular degeneration (AMD) in a comprehensive ophthalmology practice cannot be overemphasized. Because patients with the intermediate stage of AMD are at increased risk of progressing to advanced AMD, early detection of the intermediate stage is, quite simply, a major key to saving vision.

In the United States alone, 8 million people older than 55 years of age have intermediate AMD, and 200,000 of them will develop advanced AMD (ie, the presence of choroidal neovascularization [CNV] or geographic atrophy of the foveal center) each year. Clearly, detecting the intermediate stage of AMD before it progresses is crucial.

DEFINITION AND RISK ASSESSMENT

As defined in the Age-Related Eye Disease Study (AREDS), the intermediate stage of AMD is characterized by the presence of numerous medium-sized drusen or at least 1 large druse or noncentral geographic atrophy on funduscopy examination. Large is defined as 125 μm or greater, or approximately the diameter of a vein as it emerges from the optic nerve; medium as between 63 mm and 124 μm; and numerous as more than 20 indistinct or more than 50 distinct drusen. Eyes with any of these features are at increased risk of progression to advanced AMD. Affected patients may be asymptomatic, may have mildly blurred central vision, or may complain of the need for more light.

The risk of progression from the intermediate stage of AMD to advanced AMD can be assessed clinically using a simplified 5-point scale (0-4). This scale was developed by AREDS investigators and based on grading of fundus photographs of patients who participated in AREDS and progressed to advanced AMD.

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Large drusen size and abnormalities of the retinal pigment epithelium, both of which are easily identifiable on funduscopy, were particularly predictive of progression and are thus included in the risk scoring scale.

**Preventive Strategies**

Once the intermediate stage of AMD is identified, several strategies may be employed to reduce the risk of progression to advanced AMD. These strategies include educating patients about self-monitoring their vision and reporting any changes promptly, initiating therapy with the vitamin and mineral supplements evaluated in AREDS, modifying some of the risk factors that are associated with AMD, and routinely monitoring patients at risk for signs of asymptomatic progression.

**Vitamin/Mineral Supplements**

In 2001, AREDS investigators evaluated the effect of high-dose antioxidants (vitamins C and E and beta carotene) and zinc on AMD progression and visual acuity in patients with the intermediate stage of AMD in 1 or both eyes or advanced AMD in 1 eye only. They found that the supplements, which were given as 2 oral tablets twice a day with meals (Table 2), provided both structural and functional protection in these patients. Structural protection was evidenced by an absolute reduction in the 5-year risk of progression (clinical fundus findings) of 11% (from 43%–32%), which represents a relative risk reduction of 25%. Protection of visual function was evidenced by a relative reduction of 27% for vision loss (ie, loss of 15 letters or 3 lines).

Based on these findings, the AREDS investigators recommended that antioxidants and zinc be given, in the doses listed in Table 2, to patients with extensive intermediate drusen, 1 or more large drusen, noncentral geographic atrophy in 1 or both eyes, or advanced AMD or visual acuity loss due to AMD in 1 eye. It should be noted that the recommendations are slightly different for patients who smoke. Studies have found that smokers are at considerably higher risk for AMD than nonsmokers. However, high doses of beta carotene increase the already significant risk of lung cancer in smokers, thus the use of high-dose beta carotene in patients with the intermediate stage of AMD who smoke is not recommended.

**Other Nutritional Approaches**

Other nutritional approaches aimed at preventing the progression to advanced AMD include supplementation with lutein and/or zeaxanthin and long-chain polyunsaturated fatty acids. Patients who ask about these supplements—and many do—should be told that it is unknown at this time if prospective supplementation lowers their risk for visual acuity loss or for developing neovascular AMD. Although there are reports in the literature that these supplements are associated with lower risk of AMD and neovascular AMD, the reports merely describe associations, not the findings of cause and effect studies. However, the associations have generated hypotheses for a future clinical trial known as AREDS-2.

<p>| Table 1. Simplified AREDS Scale for Assessing 5-Year Risk of Advanced AMD |</p>
<table>
<thead>
<tr>
<th>Summed Number of Points</th>
<th>5-Year Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5%</td>
</tr>
<tr>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>2</td>
<td>12%</td>
</tr>
<tr>
<td>3</td>
<td>25%</td>
</tr>
<tr>
<td>4</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Point scale:**
- Large drusen = 1 point for each eye
- Pigment abnormality = 1 point for each eye
- Advanced AMD in 1 eye = 2 points

Sum up values 0–4

AMD = age-related macular degeneration; AREDS = Age-Related Eye Disease Study.

Data from Ferris et al.

<table>
<thead>
<tr>
<th>Table 2. Recommended Doses of AREDS Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Vitamin C: 500 mg</td>
</tr>
<tr>
<td>• Vitamin E: 400 IU</td>
</tr>
<tr>
<td>• Beta carotene: 15 mg</td>
</tr>
<tr>
<td>• Zinc oxide: 80 mg</td>
</tr>
<tr>
<td>• Cupric oxide: 2 mg</td>
</tr>
<tr>
<td>• Zinc was evaluated alone and also with antioxidants</td>
</tr>
<tr>
<td>• Copper supplementation was used to prevent the possibility of induced anemia from zinc</td>
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</tbody>
</table>

AREDS = Age-Related Eye Disease Study.
Data from Age-Related Eye Disease Study Research Group.
**Modification of Other Risk Factors**

Except for smoking, which clearly increases the risk of AMD, the associations of obesity and lack of regular exercise with AMD, and of increased intake of fruits and vegetables, fish, and certain fats with lower rates of AMD, do not demonstrate cause and effect. Therefore, patients should not be advised to modify their diets and get more exercise solely to lower their risk of AMD. Rather, they should be encouraged to implement these changes (and also quit smoking) for better cardiovascular and overall health and fitness.

With regard to environmental risk factors, such as sun exposure, there is no evidence that sunglasses protect against AMD. However, because they do protect against cataract formation, they can be recommended if the lenses provide protection against ultraviolet rays.

**Monitoring for Signs of Neovascular AMD**

Periodic monitoring of patients with the intermediate stage of AMD is essential in order to detect progression to advanced AMD, and specifically the development of neovascular lesions. Early detection is the key to minimizing the risk of visual acuity loss.

Patient self-monitoring, in addition to regular ophthalmology visits, is integral to the timely identification of AMD progression. Patients should be taught to self-monitor 1 eye at a time for metamorphopsia and for scotoma formations, both of which would suggest the development of CNV. In the office, ophthalmologists can monitor patients for these symptoms with the Amsler grid or with preferential hyperacuity perimeter (PHP) testing. During the office visit, fundus biomicroscopy of the macular area is key to the detection of subretinal hemorrhage, hard exudates, and subretinal fluid, which are signs of CNV.

Although frequently used to test visual acuity, the Amsler grid has several inherent flaws that contribute to the underestimation of neovascular abnormalities. One of these flaws is that the grid does not force the patient to fixate (on the central black dot), a circumstance that may yield a “normal” finding in a patient with CNV. In addition, the Amsler grid does not overcome the crowding or cortical completion phenomena. In a study in which visual acuity was regularly monitored with the Amsler grid, only 20% of patients who developed CNV still had visual acuity of 20/40 or better. The remaining 80% of patients had already developed significant visual loss with subfoveal CNV.

Unlike the Amsler grid, PHP testing overcomes the crowding phenomenon and the cortical completion effects seen with Amsler grid testing. Studies show that PHP testing can detect early CNV and may also be useful in AMD monitoring. Testing is done by a machine that shows the patient a single dotted line with an area of artificial distortion that gets progressively smaller (Figure). When the elevation caused by CNV is larger than the area of artificial distortion, the patient will preferentially pick this spot of true distortion. The patient merely touches the screen of the PHP machine. When the test is completed, the machine will print a map of the central 14 degrees of the patient’s visual field, reporting on more than 500 data points across the entire visual field of the macula. The process takes approximately 5 minutes per eye.

Preferential hyperacuity perimeter testing is based on the concept of hyperacuity or Vernier acuity, which is the ability of humans to perceive minute differences in the relative spatial localization of 2 objects. The ability to discern 2 seconds of arc, which is equivalent to 0.03 minutes of arc or 0.00051 degrees or the width of a pencil viewed at 300 meters, is due to the exceptional sensitivity of the brain to detect minute shifts in the colinear arrangement of photoreceptors. By comparison, Snellen acuity of 20/15 is based on the ability to resolve 1 minute of arc, or 0.017 degrees.

When PHP findings were compared with retina specialists’ readings of stereoscopic color fundus photographs from 120 subjects with either the intermedi-
ate stage of AMD or recent-onset CNV, the sensitivity of the specialists in correctly detecting CNV was 70% versus 83% for the PHP machine. Specificity (ie, saying there was no CNV present when there truly was none) was 95% for retina specialists versus 88% for the PHP machine alone. Fluorescein angiography was used as the gold standard for detecting CNV in these patients and determining sensitivity and specificity.

However, fluorescein angiography is not useful for monitoring patients with suspected CNV. Monitoring should focus on the symptoms and signs of CNV, including metamorphopsia, blurred vision, and scotoma formation, in addition to the presence of blood, lipid, or fluid on examination before ordering a fluorescein angiogram. Optical coherence tomography, which is useful in detecting subretinal fluid and retinal edema, can also be used to follow patients with suspected CNV.

**LASER STUDIES**

Several studies have examined laser therapy of drusen as a means of lowering the risk of developing CNV. Prompted by reports of drusen resorption in patients who had received laser therapy for other reasons, these studies postulated that drusen are the earliest form of AMD and that obliterating them by laser would reduce the risk of CNV. However, the results of these laser studies have been disappointing.

In the unilateral arm of the Choroidal Neovascularization Prevention Trial (CNVPT), 41% of 120 eyes treated with focal argon green laser had a 50% reduction in the number of drusen at 6 months. However, there was a significantly higher rate of CNV in the treated eyes (risk ratio, 4.86) than in the observed eyes, and this arm of the study was halted. The majority of the CNV was occult.

In the bilateral arm of the CNVPT, 78% of 312 laser-treated eyes of 156 patients had a 50% reduction in the number of drusen at 6 months. Again, more treated eyes developed CNV (risk estimate, 2.0) than observed eyes.

The Prophylactic Treatment of Age-Related Macular Degeneration trial, which used subthreshold diode laser, also found an excess of CNV in the unilateral arm, and study recruitment was stopped. Although there was a reduction in drusen number, improvement of vision in some eyes, and the disappearance of drusen from the fovea, the investigators concluded that the increased risk of CNV did not warrant diode laser treatment.

The 3-year Drusen Laser Study (DLS) found no statistically significant difference in the rates of CNV development or in the percentage of eyes that lost 3 or more lines of visual acuity. However, the DLS also found that CNV onset was approximately 6 months earlier in laser-treated eyes than in eyes not treated with laser.

Similarly, the Complications of Age-Related Macular Degeneration Trial, which enrolled patients with bilateral intermediate drusen, found no statistically significant differences in the percentage of laser-treated eyes or observed eyes that developed CNV or lost visual acuity at 5 years. Rates of geographic atrophy were also similar in both groups—7.4% in laser-treated eyes and 7.8% in observed eyes.

As these studies demonstrate, there is no proven benefit of laser treatment, and it is therefore not recommended for preventive therapy in patients with the intermediate stage of AMD.

**CONCLUSIONS**

Patients with the intermediate stage of AMD are at high risk of progressing to advanced AMD. Although modification of potential risk factors for AMD, such as obesity and lack of exercise, is integral to better cardiovascular and overall health, it should not be recommended solely to reduce the risk of progression to advanced AMD. However, all patients should be advised to quit smoking, regardless of their risk for AMD.

Patients with extensive intermediate drusen, 1 or more large drusen, noncentral geographic atrophy in 1 or both eyes, or advanced AMD or visual acuity loss due to AMD in 1 eye should take high-dose antioxidants and zinc, as recommended by AREDS, to prevent disease progression. Because high doses of beta carotene increase the risk of lung cancer in those who smoke cigarettes, smokers should be advised to avoid beta carotene or take only low doses.

Comprehensive ophthalmologists should consider enrolling patients with the intermediate stage of AMD in the AREDS-2 clinical trial at the nearest study site. They should also encourage patients to self-monitor their vision, 1 eye at a time, for early signs of CNV. Comprehensive ophthalmologists should monitor patients at risk with periodic eye examinations to detect CNV early and prevent loss of visual acuity.
REFERENCES


