PROGRESS IN AGE-RELATED MACULAR DEGENERATION:
A REVIEW

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ABSTRACT

This article discusses the manifestations of age-related macular degeneration (AMD), its prevalence and impact on quality of life, its pathophysiology, and some of the currently available therapies. AMD is a progressive condition characterized by worsening visual acuity. In the developed world, AMD is the primary cause of severe, irreversible loss of vision in those individuals 55 years and older. Evidence suggests that AMD may be an inflammatory disorder with a prominent genetic component. Increased understanding of the molecular regulators of inflammation and angiogenesis in AMD has led to the development of pharmacologic approaches that complement and improve upon older treatments. Vascular endothelial growth factor (VEGF), in particular, contributes integrally to angiogenesis, and anti-VEGF pharmacotherapy constitutes an important advance in the treatment of AMD. (Adv Stud Ophthalmol. 2006;3(3):60-66)

MANIFESTATIONS OF AMD

Age-related macular degeneration (AMD) is a progressive disease involving damage and death of cells of the macula, the area of the retina that is necessary for central vision. Thought to arise as a result of genetic and environmental factors, AMD is the primary cause of severe, irreversible loss of vision in those individuals 55 years and older in the developed world. AMD is a complex disease, the primary defect(s) of which have not yet been definitively identified. Although AMD is currently incurable, advances in the understanding of its pathophysiology have led to significant therapeutic innovation over the past decade. This review discusses the manifestations of AMD, its prevalence and impact on quality of life, its pathophysiology, and some of the currently available therapies.
or a central scotoma may occur. In advanced dry AMD, geographic atrophy causes more severe blurring of central vision. Scotomas may become larger and distortion may worsen over time.

Drusen may progress to neovascular AMD with the appearance of CNV. CNV is characterized by new blood vessels that grow from the choroid through Bruch's membrane into spaces beneath the retina and RPE (Figure). These new blood vessels are fragile and often bleed and leak fluid. Untreated, CNV causes photoreceptor damage with corresponding loss of central vision. Neovascular AMD accounts for approximately 10% of cases of AMD, but advanced AMD (geographic atrophy involving the macular center and neovascular AMD) causes 90% of vision loss.

Choroidal neovascularization is characterized on the basis of the location of the lesion relative to the fovea as extrafoveal, juxtafoveal, or subfoveal. Subfoveal lesions are the most common type. CNV is also characterized by its appearance on fluorescein angiography as classic and occult. Classic lesions are characterized by an area of well-demarcated hyperfluorescence seen in the early phase of the angiogram with progressive dye leakage pooling into the subretinal space and subsequent blurring of the borders of the lesion identified in the early phase of the angiogram. Occult lesions include fibrovascular pigment epithelial detachments and late leakage of undetermined source. Late leakage of undetermined source is characterized by areas of speckled hyperfluorescence corresponding to late choroidal fluorescein leakage. In these lesions, there is no discrete well-demarcated area of hyperfluorescence that is considered the source of leakage. CNV lesions may have only classic CNV or occult CNV or have some elements of both classic and occult CNV.

PREVALENCE AND IMPACT OF AMD

Worldwide, an estimated 25 to 30 million people suffer from AMD. In the United States, AMD affects approximately 1.75 million people, and the majority of cases occur in individuals older than 75 years. The prevalence of AMD in the United States is expected to increase dramatically with the aging of the population. Besides age, other risk factors consistently associated with AMD include Caucasian race, smoking, and family history. Female gender, cardiovascular disease, and excess chronic exposure to ultraviolet light have also been implicated as risk factors, but data are inconsistent across studies.

Age-related macular degeneration is a progressive condition characterized by steadily worsening vision and clinical manifestations. Loss of central vision in AMD can severely restrict or prevent performance of normal daily activities, including driving, reading, and walking. AMD can also impair or prevent recognition of faces and people. Activities, such as using appliances with dials, reading product labels, reading watches, and using the telephone directory, can be rendered difficult or impossible depending on the degree of vision loss. The effect of AMD on daily functioning is manifest in both self-reported and directly measured performance on vision-related tasks. The Activities of Daily Vision Scale, a vision-related quality-of-life measure, has demonstrated that these difficulties are associated with decrements in health-related quality of life. In a study of 201 patients with AMD and visual acuity of at least 20/200 in at least one eye, severity of AMD as determined by an ophthalmologist was inversely related to quality-of-life scores on the Activities of Daily Vision Scale.

The personal impact of AMD is also demonstrated in assessments of patients' psychological function. AMD can cause significant emotional distress. In a sample of 86 patients having AMD with at least one eye legally blind, emotional distress as measured on the Profile of Mood States was significantly worse than that...
for a group of community-based adults of similar ages and having similar concomitant illnesses as the study sample.\textsuperscript{22} Somewhat unexpectedly in this study, the duration of perceived vision loss was inversely related to the level of emotional distress. Moreover, emotional distress was less marked in patients blind in both eyes than patients blind in 1 eye. The latter 2 findings are consistent with the possibility that greater uncertainty regarding vision loss (because of shorter duration of illness and/or not being able to predict occurrence or rate of vision loss in the better eye) is associated with heightened emotional distress. Emotional distress associated with AMD can manifest as clinical depression.\textsuperscript{23}

In a sample of 151 patients with AMD and visual acuity of 20/60 or worse in the better eye, the prevalence of depression meeting \textit{Diagnostic and Statistical Manual}, fourth edition criteria was 32.5\%—twice that in age-matched community controls.\textsuperscript{24}

**PATHOPHYSIOLOGY OF AMD**

The mechanisms underlying AMD have not been fully elucidated, but significant progress in the understanding of its pathophysiology has been made in the past decade. Inflammation appears to play an important role in the development of AMD. Drusen might constitute markers of inflammation in AMD, as they contain many inflammatory constituents, such as amyloid, a main inflammatory component of Alzheimer’s disease plaques, in addition to components of the complement cascade and lipids typically found in atherosclerotic plaques.\textsuperscript{6} It is hypothesized that drusen might result from a localized inflammatory response following injury to the RPE.\textsuperscript{24,25} The recent association of a single nucleotide polymorphism within the complement Factor H gene with development of AMD supports an important role of inflammation in the disease.\textsuperscript{6,26-28}

The inflammatory response in AMD contributes to the upregulation of cytokines and growth factors, such as vascular endothelial growth factor (VEGF), leading to pathological angiogenesis and CNV.\textsuperscript{29-32} VEGF is a growth factor with angiogenic, vasoactive, and pro-inflammatory properties (Table 1) and exists in several isoforms, including the 121-, 165-, 189-, and 205-amino acid isoforms.\textsuperscript{31-32} VEGF\textsubscript{165} accounts for most of the VEGF in the human eye.\textsuperscript{33} VEGF binds to the tyrosine kinase receptors VEGFR-1 and VEGFR-2 on the surface of vascular endothelial cells, such as those in the retina.\textsuperscript{31} Binding of VEGF to these cell-surface receptors (primarily the VEGFR-2 receptor) activates an intracellular signal-transduction cascade that causes proliferation and migration of vascular endothelial cells. Other mechanisms of VEGF-associated angiogenesis have also been described.\textsuperscript{32} The identification of VEGF and elucidation of its role in pathological angiogenesis have stimulated the development of novel anti-VEGF therapies for AMD.

**TREATMENT OF AMD: CURRENTLY AVAILABLE THERAPIES**

Evidence suggests that progression of intermediate to advanced AMD can be slowed with high doses of antioxidant vitamin and mineral supplements, particularly those containing zinc. Patients in the Age-Related Eye Disease Study (AREDS), a placebo-controlled trial of high-dose supplementation with antioxidants (vitamins C and E, beta carotene) and zinc for AMD, were randomized to receive antioxidants alone, zinc and copper alone, antioxidants plus zinc, or placebo.\textsuperscript{4} Both antioxidants plus zinc (adjusted odds ratio [OR], 0.66; 99\% confidence interval [CI], 0.47–0.91) and zinc alone (adjusted OR, 0.71; 99\% CI, 0.52–0.99) significantly reduced the odds of developing advanced AMD in participants with extensive intermediate-size drusen, at least 1 large drusen (>125 µ), noncentral geographic atrophy in 1 or both eyes, or advanced AMD in 1 eye. In addition, participants taking antioxidants plus zinc were less likely to lose 15 or more letters of visual acuity (adjusted OR, 0.73; 99\% CI, 0.54–0.99). Furthermore, the mortality rate was lower in patients receiving zinc than in patients not taking zinc.\textsuperscript{33} Adverse effects of the components of these supplements include kidney stones with vitamin C; fatigue, muscle weakness, decreased thyroid gland function, heart fail-

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<th>Table 1. Properties of VEGF</th>
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<tr>
<td>Stimulates angiogenesis</td>
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<td>Induces vascular permeability and fenestration</td>
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<td>Stimulates inflammation</td>
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<td>Has neuroprotective properties</td>
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\textsuperscript{VEGF} = vascular endothelial growth factor.

Data from Ng and Adamis.\textsuperscript{31}
ure, and increased hemorrhagic stroke risk with vitamin E; increased risk of lung cancer in smokers and yellow skin with beta carotene; and anemia, decreased high-density lipoprotein cholesterol, and gastrointestinal upset with zinc.\textsuperscript{34,37} The AREDS investigators concluded that patients with intermediate-to-advanced AMD, as defined earlier in this article, with no contraindications to antioxidant and mineral therapy should consider taking a supplement of antioxidants plus zinc similar to the ones used in the AREDS study.

A 2006 Cochrane review of 8 trials (\(n = 5369\), range 20–3640) of antioxidant vitamin and mineral supplements for AMD found that the AREDS trial was the largest (\(n = 3640\)) performed and the only one that found a beneficial effect of antioxidant and zinc supplementation on progression to advanced AMD as described earlier in this article.\textsuperscript{37} The other 7 trials were small and the results were inconsistent.\textsuperscript{37}

Both laser-based and pharmacologic treatments are available for neovascular AMD. Currently available treatments for CNV in neovascular AMD include laser photocoagulation, photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Pharma AG, Basel, Switzerland), and US Food and Drug Administration (FDA)-approved anti-VEGF therapies with pegaptanib (Macugen, Eyetech Pharmaceuticals, Inc and Pfizer Inc, New York, New York) and ranibizumab (Lucentis, Genentech, Inc, San Francisco, California). Bevacizumab (Avastin, Genentech, Inc, San Francisco, California) is also used for neovascular AMD, but it is not US FDA approved for use in the eye and will not be described in this monograph. Data on ranibizumab are described elsewhere in this monograph.

**Laser Photocoagulation**

Laser photocoagulation cauterizes blood vessels to stop vessel leakage and bleeding and can reduce the risk of severe vision loss compared to no treatment; however, it does not restore lost vision and can leave a permanent scotoma. It is considered as a treatment in only some cases of extrfoveal CNV and is not recommended for the majority of lesions associated with AMD.\textsuperscript{38}

**Photodynamic Therapy**

Photodynamic therapy involves intravenous administration of the photoexcitable dye verteporfin, which is preferentially accumulated in neovascular tissues. The abnormal blood vessels in the CNV are then coagulated with a low-intensity, photoactivating laser. Verteporfin is indicated for the treatment of predominantly classic subfoveal CNV.\textsuperscript{37} The efficacy of verteporfin was established in several studies, including the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) investigation and the Verteporfin in Photodynamic Therapy (VIP) trial.\textsuperscript{37-40}

In the TAP investigation (2 multicenter, placebo-controlled clinical studies in patients with some classic subfoveal CNV), verteporfin or placebo was administered and PDT was performed.\textsuperscript{37} At 1 year, 246 (61%) of 402 eyes that received verteporfin compared to 96 (46%) of 207 eyes that received placebo had lost fewer than 15 letters of visual acuity from baseline (\(P < .001\); the primary endpoint of the trials).\textsuperscript{37} At the month 24 examination, 213 of 402 patients (53%) in the verteporfin group compared to 78 of 207 patients (38%) in the placebo group lost fewer than 15 letters of visual acuity (\(P < .001\)).\textsuperscript{37} Verteporfin was superior to placebo in the subgroup of patients with predominantly classic lesions (defined as classic CNV that occupied \(\geq 50\%\) of the lesion area), but no significant benefit of verteporfin therapy over placebo was observed for patients with minimally classic lesions (defined as classic CNV in \(>0\%\) but \(<50\%\) of the lesion area). The authors concluded that the benefits of verteporfin were sustained for at least 2 years in patients with predominantly classic CNV, but there was no evidence for use of verteporfin therapy in patients with minimally classic (\(<50\%\) classic) CNV.

The VIP trial was a double-blind, placebo-controlled study in patients with either subfoveal occult CNV with no classic component with a visual acuity score of at least 50 (Snellen equivalent approximately 20/100) or evidence of classic CNV with a best-corrected visual acuity score of at least 70 (Snellen equivalent approximately 20/40).

Verteporfin therapy or placebo was administered at follow-up if angiography showed fluorescein leakage. Patients were followed for up to 2 years. For the primary endpoint of loss of at least 15 letters of visual acuity, verteporfin did not differ from placebo at the month 12 examination. However, verteporfin was significantly beneficial compared to placebo at the month 24 examination, when 54% of verteporfin-treated patients (121 of 225) compared to 67% of placebo-treated patients (76 of 114) lost at least 15 letters of visual acuity (\(P = .023\)).
Linear regression analyses of data from the TAP and VIP trials found that predominantly classic lesions were on average smaller than occult lesions treated in these studies (3.4 vs 4.7 disc areas, respectively). Furthermore, smaller (≤4.0 disc areas) verteporfin-treated lesions (regardless of lesion composition) lost less vision than large verteporfin-treated lesions. The authors concluded that lesion size was a more significant predictive factor for treatment benefit with verteporfin than either lesion composition or visual acuity and that treating smaller rather than larger CNV lesions would likely result in better visual acuity.

The most common systemic adverse events associated with verteporfin therapy include back pain, transient visual disturbance, injection-site reactions, and photosensitivity reactions. Acute severe decrease in visual acuity, defined in the TAP and VIP trials as a decrease in visual acuity of at least 20 letters within 7 days of verteporfin therapy, was reported in 0.7% of patients (3 of 402) in the TAP trials and 4.4% of patients (10 of 225) in the VIP trial.

PEGAPTANIB

Pegaptanib was licensed in December 2004 for the treatment of wet AMD. Pegaptanib is an anti-VEGF aptamer that specifically binds to 1 form of VEGF—the VEGF165 isoform. Binding of pegaptanib to the extracellular VEGF165 isoform prevents VEGF from binding to its receptor on the surface of vascular endothelial cells and thereby prevents initiation of the intracellular cascade of events causing proliferation and migration of vascular endothelial cells. Pegaptanib reduces vascular permeability and retinal neovascularization in vitro and in vivo.

Clinical data on the efficacy and tolerability of pegaptanib come primarily from the VEGF Inhibition Study in Ocular Neovascularization (VISION), which comprised 2 randomized, double-blind, placebo-controlled clinical trials. Eligible patients were at least 50 years old, had subfoveal CNV secondary to AMD, and best corrected visual acuity of 20/40 to 20/320 in the study eye and at least 20/800 in the other eye. Patients were randomized to receive intravitreous injection of pegaptanib (0.3 mg, 1 mg, or 3 mg) or sham injection into 1 eye once every 6 weeks for 48 weeks. All treatment groups could receive PDT with verteporfin at the physician’s discretion for predominantly classic lesions.

The number of patients who received at least 1 treatment was 1190 (295 pegaptanib 0.3 mg, 301 pegaptanib 1 mg, 296 pegaptanib 3 mg, and 298 sham injections). For the primary endpoint, which was loss of fewer than 15 letters of visual acuity, all doses of pegaptanib were significantly more effective than sham injection. The percentages of patients with loss of fewer than 15 letters of visual acuity at the end of the study were 70%, 71%, and 65% in the groups receiving pegaptanib 0.3 mg, 1 mg, and 3 mg, respectively, compared to 55% in the control group. A similar pattern of results was observed for the secondary endpoints of maintenance or gain of visual acuity (gain of letters or no loss of letters). No dose response for pegaptanib efficacy was apparent. Response to pegaptanib did not appear to differ as a function of angiographic lesion subtype, baseline visual acuity, or lesion size at baseline.

The VISION trial has been extended beyond 1 year, and time to 10 or more letter loss after cessation of treatment given in first year and safety data for patients receiving study treatment for up to 2 years are now available. At week 54, approximately 1024 of the originally enrolling patients were re-randomized to continue the study through week 102. Patients who had received pegaptanib during the first year of the studies were re-randomized either to continue the same treatment or to discontinue pegaptanib. Patients who had received sham injections during the first year of the studies were re-randomized to continue sham

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<th>Table 2. Most Common Adverse Events*</th>
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<td><strong>Pegaptanib 0.3 mg</strong></td>
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<td>(n = 128), %</td>
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<tr>
<td>Punctate keratitis</td>
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<td>Vitreous floaters</td>
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<td>Eye pain</td>
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<td>Reduced visual acuity</td>
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<td>Cataract (nontraumatic)</td>
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<td>Increased intraocular pressure</td>
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<td>Vitreous opacities</td>
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<tr>
<td>Visual disturbance</td>
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<tr>
<td>Anterior chamber inflammation</td>
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<td>Corneal edema</td>
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*Adverse events reported in ≥15% of patients treated for up to 102 weeks with pegaptanib 0.3 mg or placebo are listed. Data from Eyetech Pharmaceuticals, Inc and Pfizer Inc.
injections, discontinue sham injections, or switch from the control group to 1 of the 3 doses of pegaptanib. Study medication was administered once every 6 weeks. During the second year of treatment, the numbers of patients who continued to receive the treatment they received during year 1 were 128 in the 0.3-mg group, 126 in the 1-mg group, 120 in the 3-mg group, and 51 in the control group. These patients were administered 2663 intravitreous injections of pegaptanib.

More than half (59%) of patients who had received the recommended dose of pegaptanib 0.3 mg from week 0 to week 102 lost fewer than 15 letters of visual acuity at week 102 compared to 45% of patients receiving placebo (*P* < .05)—a 45% difference relative to placebo. Time to first 15-letter loss from week 52 to week 102 was significantly longer with pegaptanib 0.3 mg than placebo. The rate of premature withdrawals from the studies because of adverse events was low at 1% through week 54 and 4% from week 54 to week 102 in patients who received pegaptanib at the recommended dose of 0.3 mg. The most common adverse events in patients treated for up to 2 years with pegaptanib were punctate keratitis (41% of patients receiving pegaptanib 0.3 mg, 45% receiving sham injections), vitreous floaters (38% pegaptanib 0.3 mg, 18% placebo), and eye pain (36% pegaptanib 0.3 mg, 33% placebo; Table 2). Serious adverse events were related to the injection procedure and were reported in less than 1% of intravitreal injections (Table 3).

**CONCLUSIONS**

Age-related macular degeneration is an increasingly prevalent disease that significantly impacts quality of life and functional ability. Evidence suggests that AMD may be an inflammatory disorder with a prominent genetic component. Increased understanding of the molecular regulators of inflammation and angiogenesis in AMD has led to the development of pharmacologic approaches that complement and improve upon older laser-based approaches. Systematic study of combination approaches involving concurrent use of PDT and pharmacotherapy is in progress.

**REFERENCES**


43. Data on file, Eyetech Pharmaceuticals, Inc and Pfizer Inc.