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Age-related macular degeneration

Hanna R Coleman, **Chi-Chao Chan**, **Frederick L Ferris III**, and **Emily Y Chew**
Division of Epidemiology and Clinical Research, (H R Coleman MD, F L Ferris III MD, E Y Chew MD), and Laboratory of Immunology (C-C Chan MD), National Eye Institute, National Institutes of Health, Bethesda, MD, USA

Abstract

Age-related macular degeneration is the leading cause of blindness in elderly populations of European descent. The most consistent risk factors associated with this ocular condition are increasing age and cigarette smoking. Genetic investigations have shown that complement factor H, a regulator of the alternative complement pathway, and LOC387715/HtrA1 are the most consistent genetic risk factors for age-related macular degeneration. Although the pathogenesis of this disease is unknown, oxidative stress might have an important role. Treatment with antioxidant vitamins and zinc can reduce the risk of developing advanced age-related macular degeneration by about a quarter in those at least at moderate risk. Intravitreal injections of ranibizumab, a monoclonal antibody that inhibits all forms of vascular endothelial growth factor, have been shown to stabilise loss of vision and, in some cases, improve vision in individuals with neovascular age-related macular degeneration. These findings, combined with assessments of possible environmental and genetic interactions and new approaches to modulate inflammatory pathways, will hopefully further expand our ability to understand and treat age-related macular degeneration.

Introduction

Age-related macular degeneration is the most common cause of visual impairment in individuals over the age of 55 years in developed countries.[1] The disease, in its early stages, develops slowly and asymptomatically over a number of years. Although the definition of age-related macular degeneration differs in various studies, the condition is generally characterised by extensive drusen, often associated with pigmentary abnormalities. Drusen are visualised as whitish yellow deposits under the retinal pigment epithelium and neurosensory retina. In elderly individuals, a restricted number of small drusen (<63 μm in diameter) are common; such patients are not deemed to have age-related macular degeneration because they are at low risk of developing vision loss.[2] Although drusen are the common denominator for age-related macular degeneration, the disease has been subdivided into three categories on the basis of the risk of developing vision loss (panel, figure 1, figure 2, and figure 3).

Two classification schemes have been developed to estimate the risk of progression from the early stages of age-related macular degeneration to the advanced stage. The first is a detailed scheme that generally needs careful photographic review for implementation.[7] The second is a simplified scale that is easy to use clinically.[8] In both schemes the risk of developing the advanced forms of age-related macular degeneration is directly associated with the extent of

Correspondence to: Dr Emily Y Chew, Division of Epidemiology and Clinical Research, National Eye Institute/National Institutes of Health, Building 10, CRC, Room 3-2531, 10 Center Drive, MSC-1204, Bethesda, MD 20892-1204, USA echew@nei.nih.gov.

Conflict of interest statement

FLF is one of the inventors on US patent 6660297 (Nutritional supplement to treat macular degeneration), owned by Bausch and Lomb. He has assigned his interest in the patent to the US Government and receives government compensation. All other authors declare that they have no conflict of interest.

the drusen and the amount of hypopigmentary or hyperpigmentary changes of the retinal pigment epithelial layer. For example, based on the simplified scale, individuals with both large drusen and the pigmentary changes in both eyes, or with these lesions in one eye and advanced age-related macular degeneration in the other, have about a 50% risk of developing advanced age-related macular degeneration in 5 years.[8] The pathogenesis of age-related macular degeneration is not well known, although a number of theories have been put forward, including oxidative stress, mitochondrial dysfunction, and inflammatory processes.[9–13]

Epidemiology

Age-related macular degeneration accounts for more than 54% of all vision loss in the white population in the USA.[1] An estimated 8 million Americans are affected with early age-related macular degeneration, of whom over 1 million will develop advanced age-related macular degeneration within the next 5 years.[14] In the UK, age-related macular degeneration is the cause of blindness in almost 42% of those who go blind aged 65–74 years, almost two-thirds of those aged 75–84 years, and almost three-quarters of those aged 85 years or older.[15]

Data pooled from three population-based studies—the Beaver Dam Eye Study, the Rotterdam Study, and the Blue Mountains Eye Study—have estimated the prevalence of advanced age-related macular degeneration to be 0·2% in those aged 55–64 years, increasing to 13% in those older than 85 years.[16] These three large population-based studies have found that the incidence of advanced age-related macular degeneration increases with age, as does the development of large drusen and pigmentary changes. The Blue Mountains Eye Study estimated the overall 5-year incidence of advanced age-related macular degeneration to be 1·1%; increasing from 0% in individuals under 60 years of age to 5·4% in those aged 80 years or older. The overall 5-year incidence of the development of large drusen or pigmentary changes was 8·7%, ranging from 3·2% in those aged less than 60 years to 18·3% in those aged 70–79 years and 14·8% in those older than 80 years.[17,18] The 15-year incidence of neovascular macular degeneration in the Beaver Dam Eye Study ranged from 0·4% in individuals under 55 years of age to 4·4% in those older than 75 years; the 15-year incidence of soft indistinct drusen ranged from 4·7% to 16·3% in the same age-groups.[19] The 5-year progression rate to advanced age-related macular degeneration in individuals who had intermediate age-related macular degeneration and who were 80 years or older was 42% in the Rotterdam Study.[20] The 5-year progression rate to advanced age-related macular degeneration in another population-based study—the Visual Impairment Project from Melbourne, Australia—ranged from 0% in people aged 60 years and younger to 6·3% in those 80 years and older.[21]

Search strategy and selection criteria

We searched PubMed and Web of Knowledge for the term “age-related macular degeneration”. Most publications were from the past 8 years, but we also included older references that were commonly referenced or highly regarded. We limited our search to English language publications only.

Panel: **Classification of age-related macular degeneration**

Early age-related macular degeneration

Multiple small drusen (<63 μm) or intermediate drusen (≥63 μm and <125 μm) with no evidence of advanced age-related macular degeneration.

Intermediate age-related macular degeneration

Extensive intermediate drusen or large drusen (≥125 μm)with no evidence of advanced age-related macular degeneration (figure 1).

Advanced age-related macular degeneration

Advanced age-related macular degeneration is characterised by the presence of one or other of geographic atrophy or neovascular age-related macular degeneration.

Geographic atrophy is the presence of a discrete area of retinal depigmentation at least 175 μm in diameter with a sharp border and visible choroidal vessels in the absence of neovascular age-related macular degeneration in the same eye (figure 2).[3] Geographic atrophy results from the continued loss of retinal pigment epithelium, with the eventual development of focal areas of total loss of the retina, retinal pigment epithelium, and the small blood vessels directly under the epithelium. The disease is generally slowly progressive. Central geographic atrophy involves the centre of the macula.

Neovascular age-related macular degeneration is characterised by the serous or haemorrhagic detachment of either the retinal pigment epithelium or sensory retina, the presence of subretinal fibrous tissue, or minimal subretinal fibrosis (figure 3).[3] Neovascularisation developing under the retina, which can leak fluid or bleed. Onset of vision loss is acute. Neovascular age-related macular degeneration is the most common cause of severe central visual loss.[4–6]

Risk factors

Age is the strongest risk factor for age-related macular degeneration; all population-based studies confirm that the prevalence of age-related macular degeneration increases with age in white individuals.[3,22–27] Female sex may be a risk factor in individuals aged over 75 years, [16] with the relative risk for neovascular age-related macular degeneration in women possibly as much as twice that observed in age-matched men. However, in regression models that adjust for age as a continuous variable, rather than by decade, the effect of sex on risk of age-related macular degeneration was not statistically significant.[17]

Results from a number of case-control studies,[28–33] population-based studies,[34–36] and prospective studies of both physicians[37] and nurses[38] strongly confirm cigarette smoking as a risk factor for age-related macular degeneration. There exists a direct association between the risk of developing advanced age-related macular degeneration with the number of cigarettes smoked.[29,39] Only one epidemiological study failed to find an association between smoking and age-related macular degeneration.[40] The mechanism by which smoking might affect the retina is unknown, although oxidative insults to the retina have been implicated.

Age-related macular degeneration is more common in white individuals than in people of other ethnic origin.[21,41,42] Data from the Barbados Eye Study,[42] the Baltimore Eye Study,[25] the Age-Related Eye Disease Study (AREDS),[28] and the National Health and Nutrition Examination Survey III (NHANES III)[41] have shown that drusen are seen at similar frequencies in white and non-white individuals. However, these studies also show a definite increased prevalence of advanced age-related macular degeneration in white people compared with others. It is postulated that increased levels of melanin could increase the free-radical scavenging potential of the retinal pigmented epithelium and Bruch's membrane, thereby protecting against the risk of advanced age-related macular degeneration. More recently, the Multi-ethnic Study of Atherosclerosis showed the prevalence of age-related macular degeneration in individuals aged 45–85 years to be 2·4% in African-American people, 4·2% in Hispanic individuals, 4·6% in Chinese, and 5·4% in white individuals.[43] The neovascular

form of age-related macular degeneration was highest in Chinese individuals, compared with white people.[31] These ethnic differences in prevalence need further validation.

Increasing evidence suggests that there are genetic factors involved in age-related macular degeneration.[44,45] Results from population-based studies implicate a familial component in the disease's pathogenesis,[46–49] as have studies of monozygotic[50,51] and dizygotic[52] twins.[53] Klaver and colleagues[47] have estimated that siblings of individuals with end-stage age-related macular degeneration have about a five-fold increased risk for intermediate age-related macular degeneration and a twenty-fold increased risk for advanced age-related macular degeneration. They suggest that about 23% of advanced age-related macular degeneration can be attributed to a genetic component.

More recently, several studies have found an association between advanced age-related macular degeneration and complement factor H, an integral component of the alternative pathway of complement activation.[54–65] The gene for this compound is located on chromosome 1q32. The complement system may indeed have an important role in the pathogenesis of age-related macular degeneration, since other factors such as factor B and complement components C2 and C3 are also associated with age-related macular degeneration.[66,67] These observations suggest that age-related macular degeneration, like other age-related diseases such as Alzheimer's disease and atherosclerosis, might involve a major inflammatory component.

A second important locus LOC387715(ARMS2)/HtrA1 (high temperature requirement factor A-1), located on chromosome 10q26, has also been found to be associated with advanced age-related macular degeneration.[60,68–71] Both neovascular age-related macular degeneration and geographic atrophy have similar risk allele distribution.[72] It is possible that variants of this protein and complement factor H contribute to the pathogenesis of age-related macular degeneration through their effect on precursors, such as drusen or changes in retinal pigment epithelial or Bruch's membranes. Both genetic variants seem to have independent effects on the progression of age-related macular degeneration.[70] A few studies have assessed gene/gene interaction as well as gene/environment interaction.[73–75] No definitive interaction has yet been found.

A number of other genes have been implicated in the pathogenesis of age-related macular degeneration, although their association has not been replicated in other studies or they account for only a small proportion of the disease. Understanding the dynamic interaction between genetic and environmental factors with cell biology and the pathology of the disease could be important in further understanding the pathophysiology of age-related macular degeneration.

The association of age-related macular degeneration with cardiovascular risk factors has also been investigated, with inconsistent results. Besides the consistent link between smoking and age-related macular degeneration, other factors such as hypertension, total serum cholesterol, HDL cholesterol, body-mass index, and the presence of cardiovascular disease do not seem to be associated with age-related macular degeneration in all studies. Using Medicare data—which could be confounded by smoking—patients with age-related macular degeneration were shown to have an increased risk of myocardial infarction.[76] These findings were not confirmed in other studies, although these studies included fewer individuals with advanced age-related macular degeneration.[77–79]

Increased concentrations of HDL cholesterol—considered to be cardioprotective—have been shown to be associated with a reduced risk of age-related macular degeneration.[80,81] Another study found no association between late age-related macular degeneration and hypertension, a history of cardiovascular disease, or with serum lipid concentrations.[82] Some studies have shown a direct association between age-related macular degeneration and raised concentration

of cholesterol, both in the serum[81] and in the diet.[83] Some evidence exists for a link between risk for age-related macular degeneration and increased levels of total dietary fat,[84] although other studies have refuted this link.[85] Specific types of fats might be differentially associated with the risk for age-related macular degeneration.[86] Hypertension was found to be associated with age-related macular degeneration in some studies.[87–89]

Results from observational studies that assessed the effect of dietary antioxidants on risk for age-related macular degeneration have been inconsistent.[90–95] In the Rotterdam Study, a high dietary intake of beta-carotene, vitamins C and E, and zinc was associated with a substantially reduced risk of age-related macular degeneration in elderly individuals.[96] A multicentre randomised trial has shown that oral supplements including high levels of antioxidants and minerals are effective in slowing the progression of advanced stages of age-related macular degeneration.[2] By contrast, a trial of vitamin E in an Australian population with lower risk of developing advanced age-related macular degeneration failed to find a beneficial effect.[97]

Some case-control studies have found evidence of decreasing risk of neovascular age-related macular degeneration among individuals who reported the highest intake of dietary lutein and zeaxanthin, the major macular carotenoids[98] that are found mostly in green leafy vegetables such as spinach, collard greens, and kale.[90,91,99,100] However, another study found no such association.[101] Population-based studies have shown in consistent associations of dietary levels of these compounds with age-related macular degeneration.[94,96,102,103] Lutein and zeaxanthin might affect processes modulating light and oxidant exposure:[104] both compounds reflect short-wavelength light, and reduced exposure to these wavelengths might reduce both photochemical and oxidant damage to cellular lipids, proteins, and nuclear material.

Docosahexanoic acid and eicosapentaenoic acid are part of the family of omega-3 long-chain polyunsaturated fatty acids that are found in high concentrations in the retinal tissue. Such fatty acids might affect factors and processes important in the angiogenesis cascade and in gene expression, and could be potent regulators of retinal cell survival, inflammation, and energy balance. The main sources of omega-3 fatty acids are fish products. Some case–control studies have found evidence of decreasing risk of neovascular age-related macular degeneration among individuals reporting the highest intake of omega-3 fatty acids and fish,[105,106] especially if in conjunction with lower levels of intake of linoleic acid.[107] The Blue Mountains Eye Study showed that a reduction in incident early changes of age-related macular degeneration and the eating of fish three times per week could reduce the risk of advanced age-related macular degeneration.[108]

A number of other risk factors have been found. Blue iris colour has been inconsistently implicated as a risk factor for age-related macular degeneration and has been considered a possible marker for pigment content in the retinal pigment epithelium.[109,110] There has also been considerable interest in whether sunlight exposure could be a risk factor for the development of age-related macular degeneration. The possibility that high levels of exposure to blue or visible light might cause ocular damage, especially in the development of age-related macular degeneration in the later years of life, has been suggested.[111] The Pathologies Oculaires Liees a l'Age study reported that individuals who wore sunglasses regularly were less likely to develop soft drusen.[112] Results from the Beaver Dam Study suggest that people who spent leisure time outdoors were at an increased risk of developing early age-related macular de generation.[113] However, other epidemiological studies have shown little or no association between sunlight exposure and the risk of age-related macular degeneration.[28,33,114]

Pathophysiology and pathology

The pathology of age-related macular degeneration is characterised by degenerative changes involving the outer portion of the retina, retinal pigment epithelium, Bruch's membrane, and less prominently, the choriocapillaris. Late stage age-related macular degeneration shows the presence of neovascularisation, exudative change, or disciform scar in neovascular age-related macular degeneration. In atrophic age-related macular degeneration, there is retinal pigment epithelium loss or choriocapillaris attenuation without neo vascularisation.[115] Early pathological changes in age-related macular degeneration involve basal deposits in Bruch's membrane. These deposits, which can only be shown on pathological specimens and not by clinical evaluation, are of two distinct types:[116] basal laminar, composed of basement membrane protein and long-spacing collagen located between the retinal pigment epithelium plasma and basement membrane, and basal linear, which is more specific for early age-related macular degeneration and composed mainly of membraneous material located external to the basement membrane of the retinal pigment epithelium in Bruch's membrane.[117] The combination of these deposits with secondary changes in the retinal pigment epithelium results in the formation of drusen (figure 4). Many different molecules have been identified in drusen, including glycoconjugates and a variety of components found in atherosclerotic plaques including vitronectin, apolipoprotein B and E, alpha-crystallin, complement components, HtrA1, and lipids.[11,118–121] Macrophages have been detected in regressing drusen,[122] suggesting that macrophages are recruited to eliminate the age-accumulated deposits within Bruch's membrane (figure 5). Activated microglia also accumulate in age-related macular degeneration lesions.[123] Discrete nodules or hard drusen deposits composed of a hyaline-like material are found between the retinal pigment epithelium and Bruch's membrane. Soft drusen are often large and are associated with the detachment of the retinal pigment epithelium and diffusely abnormal Bruch's membrane alterations.[122,124] Soft drusen might be associated with further damage to the retina, retinal pigment epithelium, and choroid, thereby leading to choroidal neovascularisation or cell death in the retinal pigment epithelium and geographic atrophy.

On microscopy, geographic atrophy is seen as abnormal retinal pigment epithelium cells with hypotrophy, hypertrophy, hypopigmentation, hyperpigmentation, atrophy, migration, loss of outer retinal cells (particularly the photoreceptors), attenuation of Bruch's membrane, and choriocapillaris degeneration.[115,125,126] Although the retinal pigment epithelium is the most affected cell type, the retinal outer nuclear layer is severely affected, with a 77% reduction compared with age-matched control eyes.[127] In the geographic atrophy associated with age-related macular degeneration, atrophy of the retinal pigment epithelium is usually more severe than the loss of choriocapillaris. However, the surviving choriocapillaris in areas of complete loss of the retinal pigment epithelium seem to be highly constricted.[126] Macrophages are often seen in areas of geographic atrophy and are apparently phagocytosing pigment and debris, as seen by electron microscopy or immunohistochemistry.

Emerging evidence indicates that the autofluorescent pigments that accumulate as lipofuscin in the cells of the retinal pigment epithelium might reach levels that contribute to a decline in cell function, retinal ageing, and degeneration, mainly in the form of geographic atrophy.[128] Lipofuscin in the retinal pigment epithelium is the source of fundus autofluorescence. The compound is found as micrometre-sized spherical particles and is characterised by its yellow autofluorescence when exposed to blue light.[129] The major component of lipofuscin is N-retinylidene-N-retinylethanol-amine (A2E), a quaternary amine and retinoid byproduct of the visual cycle.[130] The generation of lipofuscin is a pathogenic cascade; the A2E that is produced interferes with the function of cells in the retinal pigment epithelium, leading to apoptosis of the retinal pigment epithelium and subsequent geographic atrophy. Recently, fundus autofluorescence has been used to detect lipofuscin fluorophores in the retinal pigment

epithelium.[131] Specific patterns of fundus autofluorescence were associated with progression of geographic atrophy; this technique could be an important imaging method to monitor patients with geographic atrophy associated with age-related macular degeneration.[132]

Choroidal neovascularisation can occur in the macular, peripapillary, and peripheral regions. Early choroidal neovascularisation occurs under the retinal pigment epithelium,[133,134] eventually breaking through[135] to develop exudative, haemorrhagic, or disciform age-related macular degeneration (figure 6). In neovascular age-related macular degeneration, lipid-rich fluid accumulates under the retinal pigment epithelium or neuroretina. In haemorrhagic age-related macular degeneration, blood breaks through the retinal pigment epithelium into the subretinal space and sometimes through the retina and into the vitreous. In disciform age-related macular degeneration, fibrous tissue with neovascularisation and alteration of the retinal pigment epithelium proliferates and can partly or totally replace the neuroretina. The outer nuclear layer can be severely attenuated, with an almost 70% reduction of photoreceptor length shown in one study.[136] Additional pathological findings include retinal pigment epithelium tear, serous exudation, haemorrhage, gliosis, and calcification. Macrophages have been documented both morphologically and functionally in neovascular age-related macular degeneration.[137–142] Activated macrophages and microglia may secrete chemokines and cytokines, causing further cellular damage, Bruch's membrane degradation, and angiogenesis.[143]

Complement factor H, which downregulates the activity of the alternative complement pathway, is located in normal human retinal pigment epithelium, Bruch's membrane, and choroid.[54] HtrA1, a secretory protein and an inhibitor of transforming growth factor β,[144] is also associated with the development of age-related macular degeneration.[69,70,72,73] The rs11200638 allele of HtrA1 occurs at a higher frequency in patients with age-related macular degeneration than in those without the disease; the increased expression of HtrA1—at both the mRNA and protein levels by reverse transcriptase PCR and immunohistochemistry—in age-related macular degene ration lesions are consistent with a possible role of this protein in neovascular and atrophic age-related macular degeneration (figure 7).[145] Recently, ARMS2 has been reported to be involved in mitochondrial homoeostasis.[146]

Management

Prevention

Since there is no cure for age-related macular degeneration, prevention is the first approach to reduce vision loss. Control of modifiable risk factors such as smoking, hypertension, and body-mass index could reduce the risk of developing age-related macular degeneration by half.[147] Nutritional supplements can be used as a preventive therapy—the AREDS formulation of antioxidant multivitamins (vitamin C 500 mg, vitamin E 400 IU, beta-carotene 15 mg) and zinc (zinc oxide 80 mg and cupric oxide 2 mg) has been shown to reduce the risk of developing advanced age-related macular degeneration and its associated visual loss by as much as 25% over 5 years in individuals with at least moderate risk of age-related macular degeneration.[2] This was accompanied by a 19% reduction in the risk of moderate vision loss (three or more lines of vision loss on the visual acuity chart) at 5 years. However, this formulation is not recommended for smokers because beta-carotene has been shown to increase the risk of lung cancers.[148,149]

Recent analyses regarding potential harmful adverse effects of supplementation with high doses of vitamins have raised concerns.[150] One meta-analysis found no increased risk of mortality overall, although subgroup analyses that excluded those studies that had no deaths found an increased risk of mortality. However, the methodology of this meta-analysis has been refuted by other investigators.[151,152] Another concern was that large trials, especially those of

beta-carotene in which heavy smokers were included, contributed substantially to the weight of the analyses, potentially biasing the final analyses towards a negative outcome.[152,153] Another meta-analysis concluded that vitamin E in high doses (400 IU) was associated with an increased risk of mortality,[154] while further analyses of three large clinical trials that used a dose of about 400 IU showed no statistical differences.[155]

The Age-Related Eye Disease Study 2 (AREDS2) is currently assessing the use of dietary supplements of lutein (10 mg), zeaxanthin (2 mg), and omega-3 fatty acids (1 g) for the prevention of advanced age-related macular degeneration. The study will also investigate whether the current AREDS formulation could be modified by reducing the amount of zinc or eliminating the beta-carotene. The level of zinc in the current formulation is considered high and there is evidence that only 25 mg can be absorbed by the body per day. Beta-carotene, which is not present within the eye, is a problem for smokers.

Laser treatment

The Complications of Age-Related Macular Degeneration Prevention Trial, a controlled clinical trial that assessed the role of laser photocoagulation for the treatment of individuals with large drusen, showed that although drusen disappeared with treatment, there was no reduction in the risk for the development of advanced age-related macular degeneration.[156] At 5 years, about 20% of both the treated and untreated group experienced vision loss; 15% in each group developed neovascular age-related macular degeneration and about 7% developed geographic atrophy. Laser treatment did seem to delay the development of choroidal neovascularisation by 6 months in studies that included patients with unilateral advanced age-related macular degeneration.[157,158]

Laser photocoagulation

For patients who have already developed neovascular age-related macular degeneration, early detection—before significant visual loss develops—is associated with a better prognosis. In the 1980s, the Macular Photo-coagulation Study[159,160] showed a reduction in vision loss associated with thermal laser photocoagulation, provided the neovascular lesion had well-demarcated (classic) boundaries. However, such lesions are present in no more than 15–20% of patients with neovascular age-related macular degeneration. Furthermore, thermal laser photocoagulation can cause visual loss because of laser-induced retinal damage, and is associated with high recurrence rates, usually along the foveal side of the lesion, that often lead to eventual vision loss.

Photodynamic therapy

In 2000, photodynamic therapy with verteporfin was approved as an alternative treatment for patients with neovascular age-related macular degeneration. Two large randomised controlled trials[161,162] showed a significant reduction in moderate vision loss in patients with predominantly classic choroidal neovascularisation. Vision was stabilised in 61% of patients treated with verteporfin, compared with 46% of patients given placebo. One of the studies[163] showed a benefit for patients with minimally classic disease provided that their lesions were small (four disc areas or less) or their baseline visual acuity was reduced (Snellen equivalent of 20/50 or worse). The dose of verteporfin is determined by body surface area (6 mg/m^2) and the drug is given intravenously over 10 min. After a 5-minute accumulation phase, the drug is activated with low-energy laser light for 83 s using the peak absorbance wavelength for the drug (689 nm). This induces temporary closure of the choroidal neovascular complex while sparing the overlying retinal structures. Because the retina is largely spared, this treatment has, for the most part, replaced photocoagulation as the standard treatment for choroidal neovascularisation, even though the average patient requires a number of treatments over a 2-year period. Adverse effects are rare, but individuals are advised to avoid direct

sunlight or bright illumination for 5 days to prevent phototoxicity. Overdose of the drug or light can result in non-perfusion of the retinal vasculature, with subsequent severe visual loss due to macular infarction. About 3–4% of treated patients experience severe vision loss in the normal administration of this drug, although some of this loss is reversible.[162]

Vascular endothelial growth factor (VEGF) inhibitors

In December, 2004, the US Food and Drug Administration (FDA) approved pegaptanib, the first anti-angiogenic drug for the eye. This drug targets vascular endothelial growth factor (VEGF), a protein that acts as one of the signals that triggers angiogenesis and increased permeability. Findings from two phase III randomised trials of pegaptanib, involving about 1200 patients with all subtypes of neovascular age-related macular degeneration, showed a significant benefit over 2 years. Vision was stabilised in 70% of patients treated with pegaptanib compared with 55% of patients receiving placebo.[163] During the 48 weeks of the trials, pegaptanib was administered intravitreally every 6 weeks at a dose of 0·3 mg. Among the adverse events that occurred, the most serious were endophthalmitis (1·3%), traumatic injury to the lens (0·7%), and retinal detachment (0·6%), leading to severe visual loss in 0·1 % of patients.

In June, 2006, the FDA approved another VEGF inhibitor—ranibizumab—for the treatment of neo-vascular age-related macular degeneration. Ranibizumab is a fragment of a monoclonal antibody that binds to and inhibits all forms of VEGF-A.[164,165] This drug, when injected intravitreally on a monthly basis, prevented vision loss and, for the first time with any treatment for age-related macular degeneration, was associated with a remarkable proportion of patients with an improvement in vision. At 12 months, 95% of patients given ranibizumab 0·5 mg lost fewer than 15 letters (three lines of vision) compared with 62% of the placebo group ($p<0·001$). Additionally, 34% of this group improved by 15 or more letters of vision compared with the 5% in the placebo group ($p<0·001$). These benefits persisted through 24 months of follow-up. Mean differences in visual acuity score in the treated and control groups were also impressive, with a mean increase of seven letters in the treated group compared with a mean decrease of 10 letters in the placebo group ($p<0·001$). The adverse effects included endophthalmitis (1%) and serious uveitis (1%).

Before the FDA approval of this drug, some ophthalmologists had begun to use a closely related monoclonal antibody, bevacizumab, to treat neovascular age-related macular degeneration, with impressive results.[166] Because ranibizumab had not yet been approved by the FDA, and since bevacizumab was licensed for use in colon cancer, the off-label use of the latter drug spread worldwide. At present, there are no data to compare the two drugs directly, although a randomised comparison has begun. This study will also assess the potential effects of reduced treatment frequency to alleviate the treatment burden of monthly intravitreal injections. There is also a need to gather further information of a potential increase in risk of strokes with these anti-VEGF agents.

Other therapies

The quest for treatment for this blinding condition continues, since only a portion of treated patients experience an improvement in visual acuity. A number of other therapies have been tried, including surgery, radiation, and other pharmacological agents. It is possible that like cancer therapies, combination treatments could improve both visual gain and durability of therapies in individuals affected by age-related macular degeneration. With better understanding of the inflammatory pathways that may be implicated in the pathogenesis of this disease, and an increased knowledge of the interactions between genetics and the environment (environmental epigenomics and disease susceptibility), we may find improved therapies for age-related macular degeneration.

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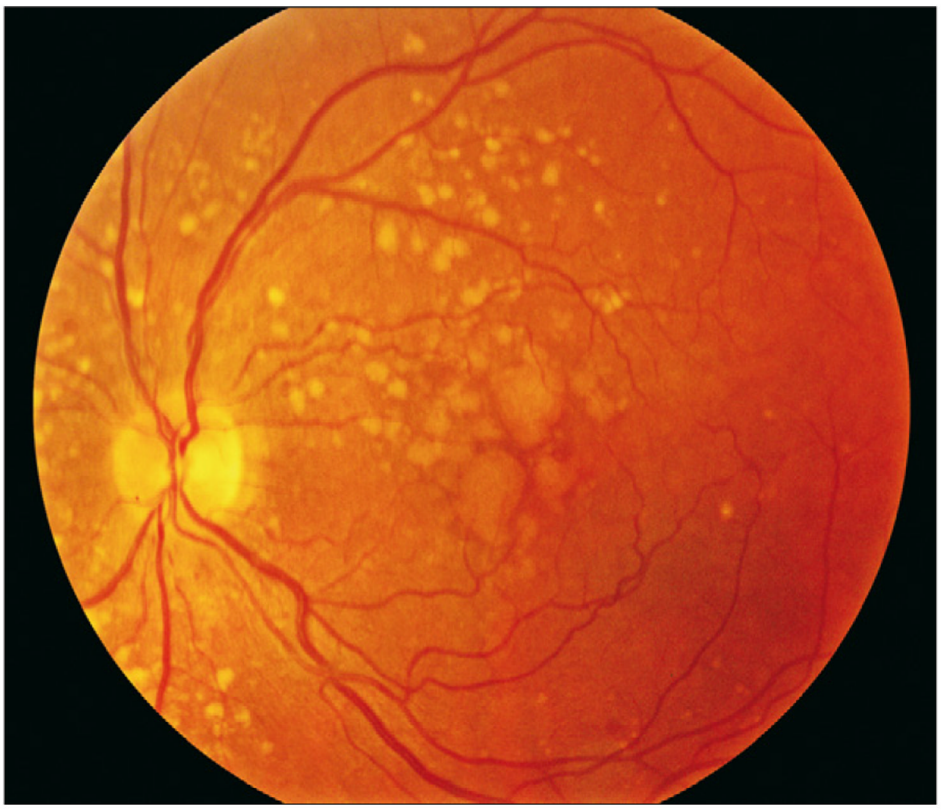

Figure 1.
Left eye of a patient with intermediate age-related macular degeneration with large drusen

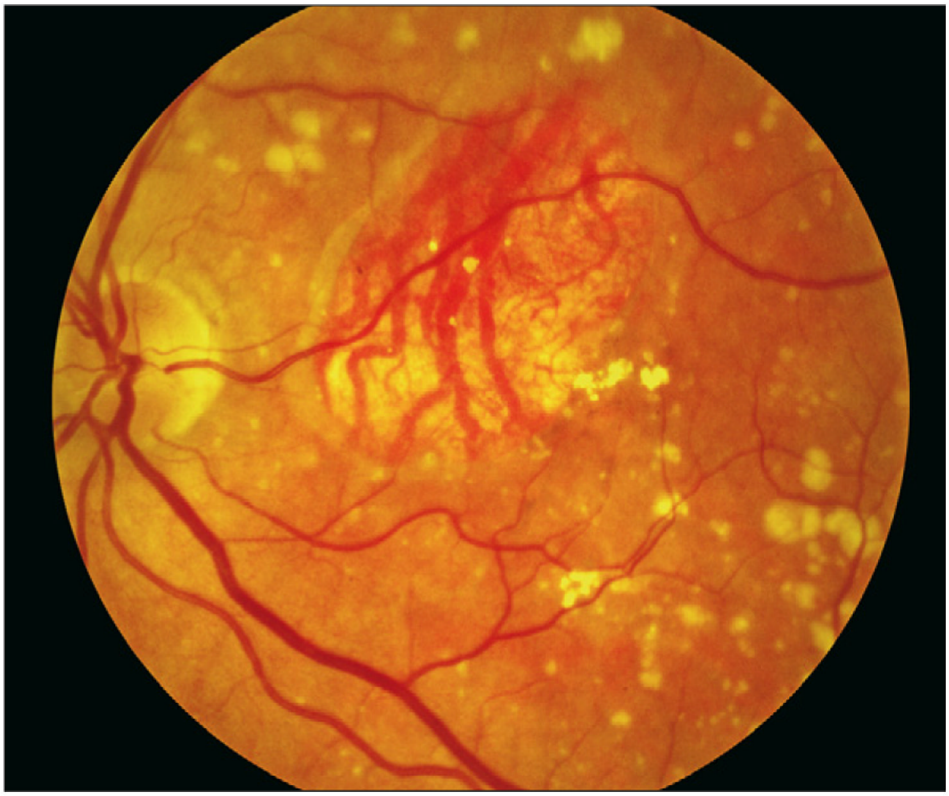

Figure 2.
Geographic atrophy involving the centre of the fovea, with sharply demarcated loss of normal retinal pigment epithelial cells and evidence of deeper larger choroidal vessels

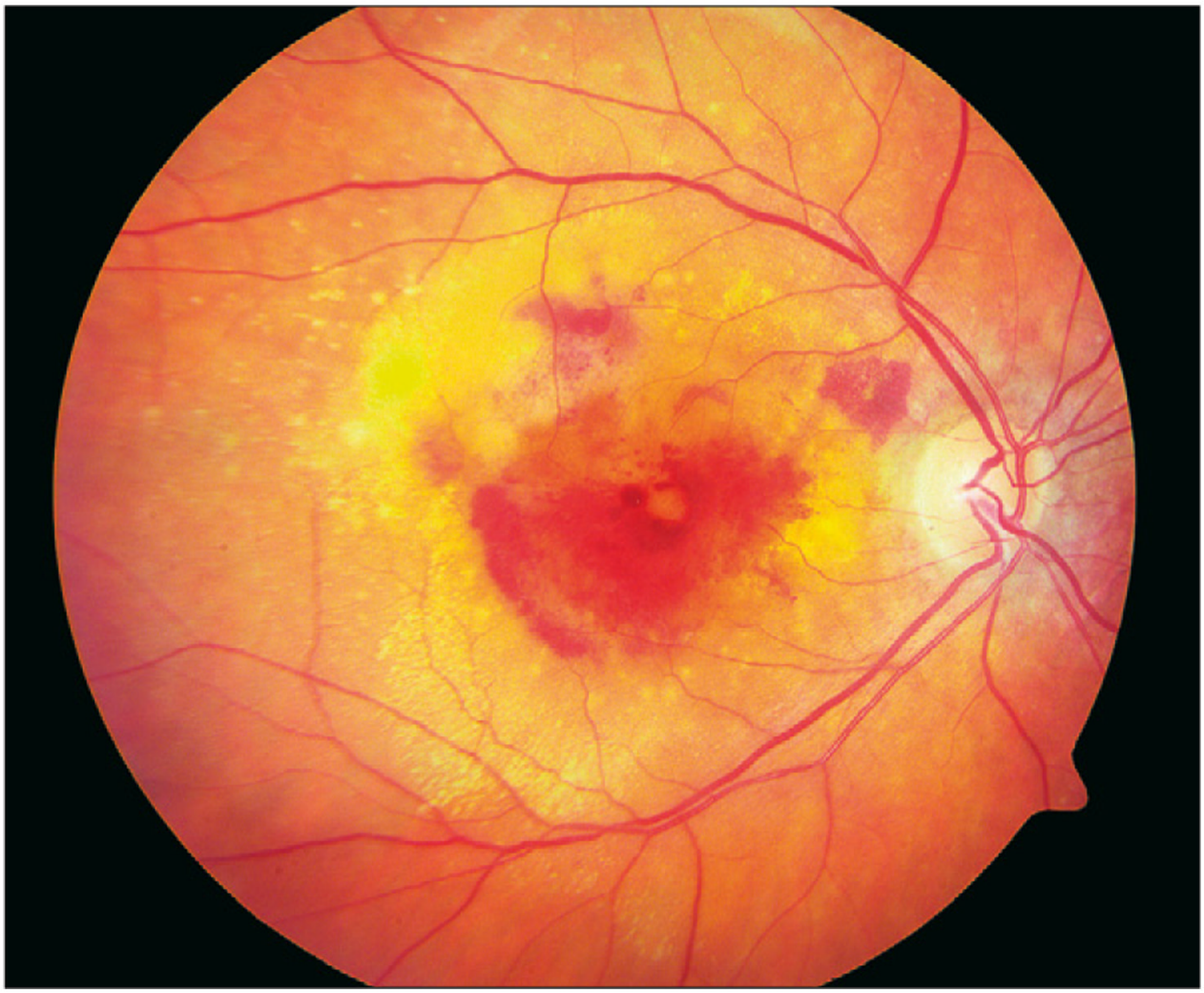

Figure 3.
Neovascular age-related macular degeneration, with retinal haemorrhage, lipids, or retinal hard exudate and subretinal fluid

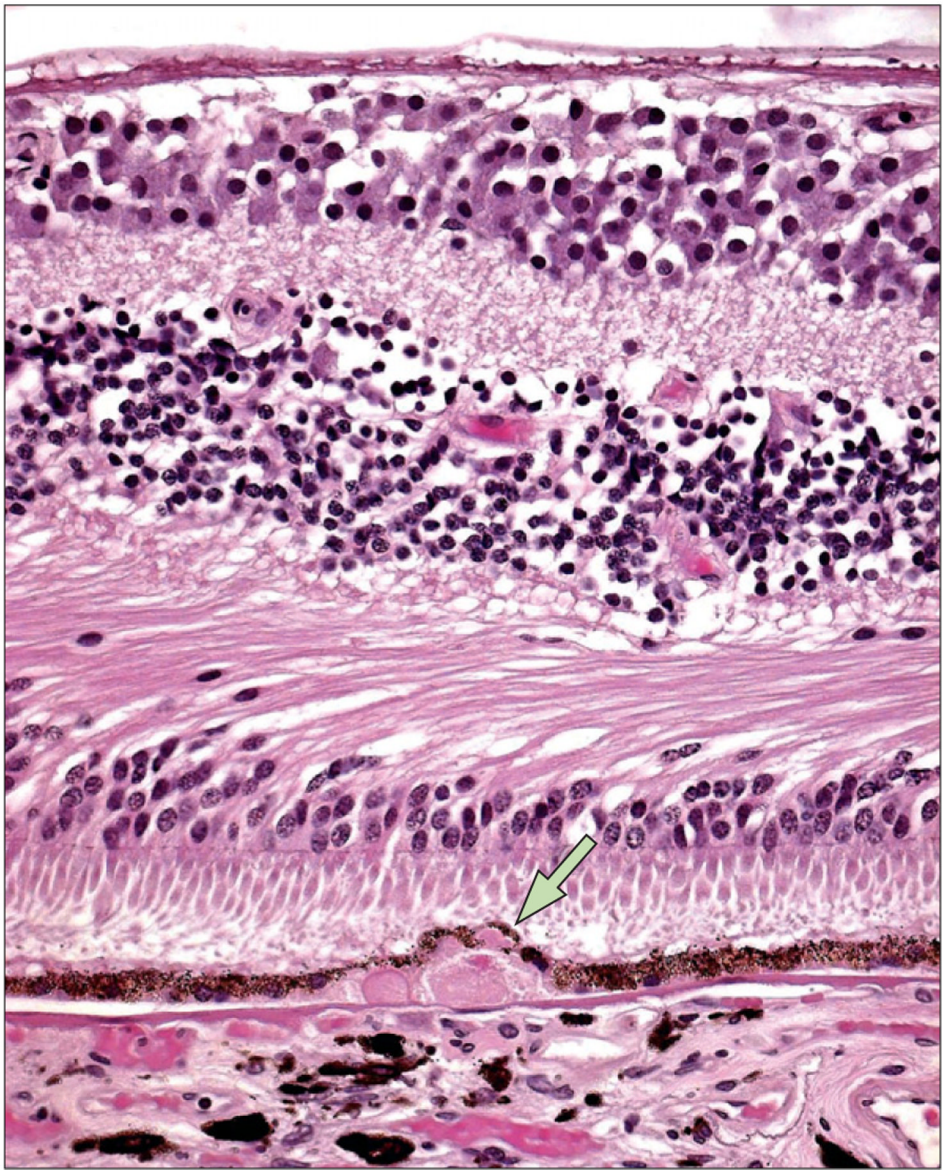

Figure 4. A typical large drusen (arrow) composed of hyaline deposits with granular ground substance from the inner aspect of Bruch's membrane

The underlying retinal pigment epithelium cells are thin and compressed. Photoreceptors appear to be mildly atrophied in an age-related macular degeneration eye.

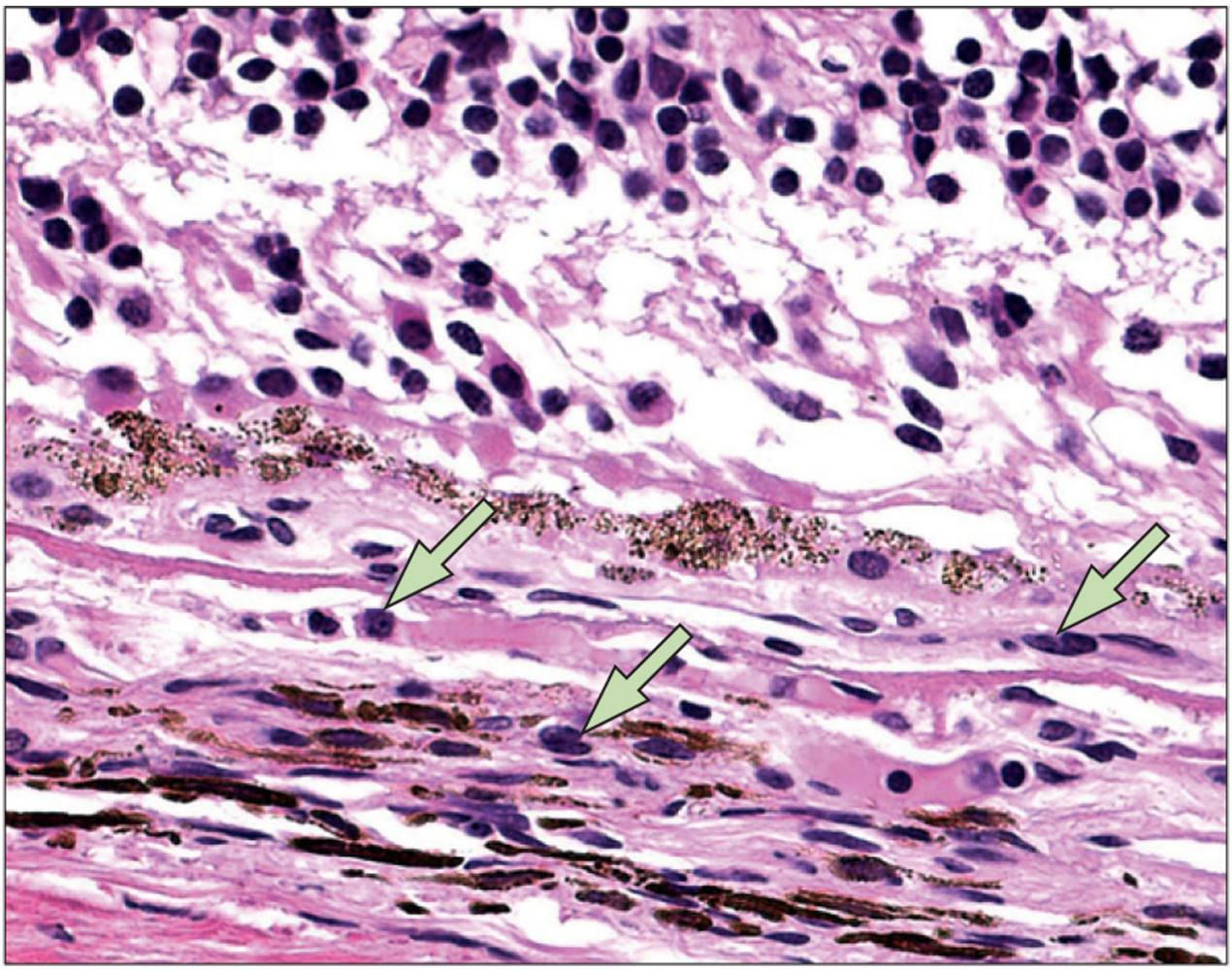

Figure 5.
Macrophages (arrows) in and surrounding a small choroidal neovascular lesion, with breaks at Bruch's membrane

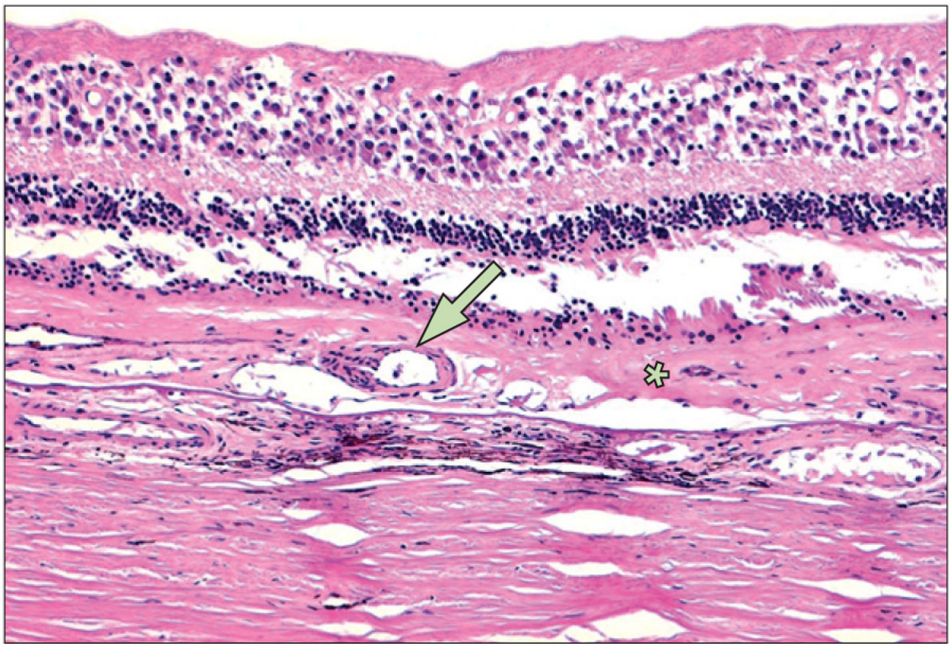

Figure 6.
Dense collagen fibrous tissue (asterisk) between the degenerative photoreceptor cells and Bruch's membrane and a large feeder vessel (arrow) penetrating through the macular scar

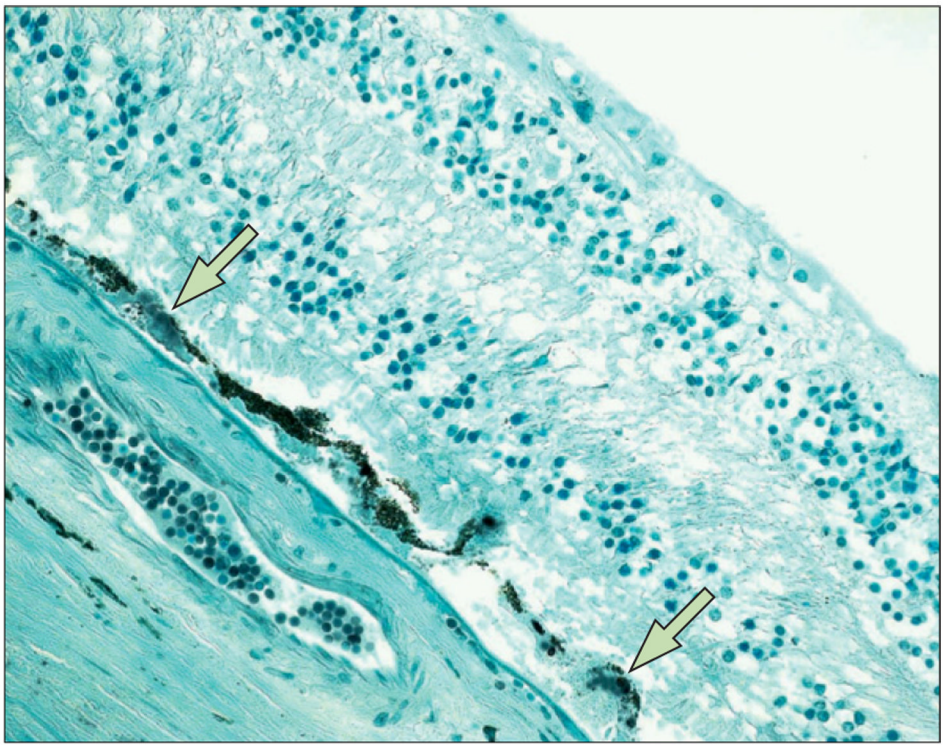

Figure 7.
Positive HtrA1 immunoreactivity (arrows) in soft drusen