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Age Related Macular Degeneration

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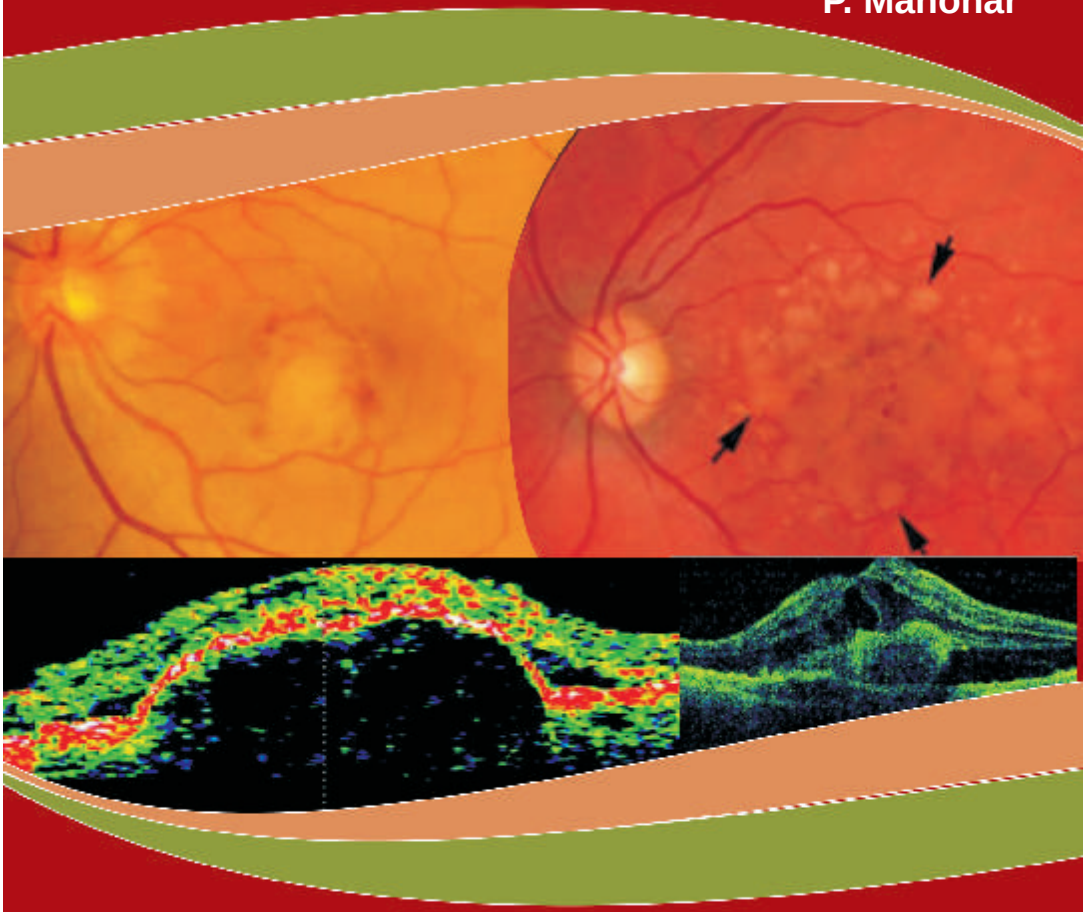

ALL INDIA OPHTHALMOLOGICAL SOCIETY

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About CME .....

Age Related Macular Degeneration is an important cause of Blindness / Visual handicap among the elderly. The Prevalence has apparently increased possibly due to increased awareness and availability of newer therapeutic options. Although not completely understood, newer investigative modalities including Fluorescein Angiography, ICG, & OCT have helped in easily diagnosis of this disease.

Gone are the days of laser photocoagulation (for Subfoveal / Juxtafoveal CNVM's). TTT has also met with virtually similar fate. PDT alone has limited or supplemental role. The arrival of Anti-VEGF's has created a ray of hope in the management of ARMD – Avastin, Lucentis, Macugen are being increasingly used in the effective management – their limitations being frequency of injections and predictability of response. VEGF-Trap & Si-RNA may see light of the day soon.

Hope with continued research, this debilitating disease of elderly will soon find a long lasting treatment & possibly a cure !!

Thanks to efforts of Dr. Sujata Rathod & her colleagues for compiling the present CME series for AIOS.

Rajvardhan Azad	**Ashok Grover**	**Lalit Verma**
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Foreword

Dear Colleagues,

Age related macular degeneration (ARMD) is a medical condition which usually affects older adults resulting in loss of vision in the center of the visual field (the macula). It occurs in "dry" and "wet" forms. It is a major cause of visual impairment in older adults (>50 years). Macular degeneration can make it difficult or impossible to read or recognize faces, although enough peripheral vision remains to allow other activities of daily life.

It is a topic widely discussed and debated in vitreo-retina conferences and CMEs. Most of the debates focus on the treatment aspect, especially the role of anti VEGF injections and photodynamic therapy. However a thorough knowledge of the pathophysiology and diagnosis of this condition is imperative before graduating to management.

In this issue of AIOS CME series titled "Age Related Macular Degeneration", the authors have presented the basics of this disease including pathophysiology, diagnosis and management in a simplified and illustrated manner. I am sure this will benefit all ophthalmologists.

I would like to appreciate the efforts of Dr. B L Sujatha Rathod, Dr. Arindam Chakravarti and Dr. P. Manohar in compiling an excellent practical guide on Age Related Macular Degeneration.

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Introduction

ANATOMY OF THE MACULA

The macular region is a specialized area of the central retina with a diameter of 5.5 mm. This area can be divided into several regions: the foveola, fovea, parafoveal area, and perifoveal region. The central portion of the macula contains the fovea and the foveola in a small depression in the internal surface of the retina. The foveola is located about 4 mm temporal and 0.8 mm inferior to the center of the optic disc. Centrally, the foveola is 0.35 mm in diameter and 0.25 mm deep. The sides of the depression containing the foveola are called the clivus. In the foveola, the retina is only 0.13 mm thick. The fovea measures 1.9 mm in diameter. The thickness of the retina in the fovea is one half of what it is elsewhere, about 0.37 mm. The only photoreceptors in the central fovea are cones. The central rod-free area within the fovea measures 0.57 mm in diameter and contains 35,000 cones. There are 100,000 cones within the 1.75-mm2. The cones in the fovea measure 80 µm in length. Their outer segments are 45 µm in length and 2 µm thick, and their inner segments measure 20 to 30 µm in length and 2 to 3 µm in thickness. This more closely approximates the shape and size of rods, which can measure up to 120 µm in length. In contrast, cones in the area of the equator measure 37 to 40 µm in length, and at the ora serrata they measure 6 µm in length. The inner nuclear layer is only two cell layers thick at the edge of the fovea and is absent within the fovea. The internal plexiform layer, ganglion cell layer, and nerve fiber layer are also absent in the fovea. Most of the inner aspect of the fovea contains the processes of Müller cells. The internal limiting membrane is 0.4 µm thick at the periphery of the fovea and 10 to 20 nm thick within the fovea. The capillary free zone of the macula measures about 0.4 mm in diameter. The entire vascular supply to the fovea is via the choriocapillaris.

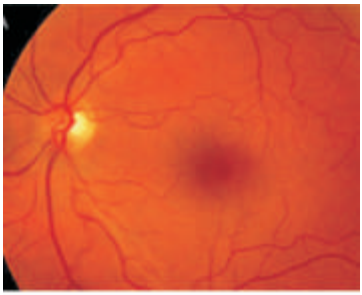


Fig 1

The parafoveal central retina is an annular zone 0.5 mm in width and along with the fovea measures 2.5 mm in diameter. It contains the largest number of nerve cells in the entire retina. The thickness of the photoreceptor layer in this portion of the retina is 40 to 45 µm. There are 100 cones per 100 µm in this area. The perifoveal central retina measures 1.5 mm in width beyond the parafoveal retina. The outer boundary of this area is 2.75 mm from the foveal center. There are 12 cones per each 100 µm in the perifoveal central retina. The macula measures 5.5 mm in horizontal width. This area corresponds to a central visual field subtending an angle of 18°.

RPE layer:

- The retinal pigment epithelium (RPE) is a single layer of hexagonally shaped cells They reach out to the photoreceptor layer of the inner retina. Bruch's membrane separates the RPE from the vascular choroid.
- Ultrastructurally it is composed of five elements and througout life can accumulate metabolic debris related to the build up of lipofuscin from the RPE. The functions of the RPE include the maintenance of the photoreceptors, absorbtion of stray light, formation of the outer blood retinal barrier, phagocytosis and regeneration of visual pigment.
- The macula has the highest concentration of photoreceptors and is the the area where the RPE is most metabolically active and as a consequence most likely to suffer the consequence of enzymatic failure over time with the accumulation of metabolic debris and lipofuscin .

Epidemiology

In the Beaver Dam Eye Study

In which the study population consists mostly of white men and women, prevalence of any AMD (referred to as age-related maculopathy) was less than 10% in persons aged 43 to 54 years but more than tripled for persons aged 75 to 85 years.4 The Beaver Dam Eye Study demonstrated that progression to any AMD in a 10-year period was 4.2% for persons aged 43 to 54 years and 46.2% for those aged 75 years and older.11 The Beaver Dam Eye Study has identified soft, indistinct drusen and pigmentary abnormalities, which also increase in frequency with increasing age, as strongly predictive of advanced AMD 2.

Risk Factors

1. Age: The Framingham study (5), it will be recalled, had investigated a study population in the town of Framingham Massachusetts for the risk factors of coronary artery disease since 1948.This study showed that a prevalence of AMD of 11% for those aged 65-74 years and 28% for those aged 75-85 years . A total prevalence in the population aged between 52-85 of 8.8% was recorded. By contrast, the prevalence of age related cataract was 15.5 % and that of open angle glaucoma 3.3%. Other studies also show the disease to be extremely comon in the elderly.

Blue Mountains Eye Study (1995)

Provides an accurate estimate for the age specific prevalence of ARM.

End stage macular degeneration was present in 1.9% of the elderly population studied and was bilateral in 56% of this group.

It was more frequently of the neovascular type (ratio neovascular: atrophic 2:1)

ARM rose in prevalence from 0% among people younger than 55 years to 18.5% among those 85 years or older.

Soft drusen were found in 13.3% of the surveyed population and retinal pigment abnormalities in 12.6%.

2. Gender: Pooled data from the Beaver Dam Eye Study, Blue Mountains Eye Study, and the Rotterdam Study revealed no sex differences in AMD risk. However, recent analyses from the Blue Mountains Eye Study suggest that the 5-year incidence of neovascular AMD among women is double that of men (1.2% vs. 0.6%)2.

3. Race: In the Baltimore Eye Survey, AMD accounted for 30% of bilateral blindness among whites and for 0% among blacks. The presence of melanin also seems to protect against oxidative damage.

4. High Blood Pressure (Hypertension): Investigative Ophthalmology and Vision Science reported a study in Rotterdam, The Netherlands demonstrating that high blood pressure may be associated with development of macular degeneration (September 2003).

5. Family history: The lifetime risk of developing late-stage macular degeneration is 50% for people that have a relative with macular degeneration, versus 12% for people that do not have relatives with macular degeneration, a fourfold higher risk.[6]

6. Oxidative Stress: It has been proposed that age-related accumulation of low-molecular-weight, phototoxic, pro-oxidant melanin oligomers within lysosomes in the retinal pigment epithelium may be partly responsible for decreasing the digestive rate of photoreceptor outer rod segments (POS) by the RPE. A decrease in the digestive rate of POS has been shown to be associated with lipofuscin formation - a classic sign associated with macular degeneration.[14][15]

7. Ocular Risk Factors: Weak association between hyperopia and early AMD have been suggested, but not with late AMD. Higher

levels of ocular melanin may be protective against light induced oxidative damage to the retina; however till date literature is inconclusive about this. Similarly data regarding the relationship between cataract and AMD is inconsistent.

8. Light Exposure: Photooxidative damage, mediated by reactive oxygen intermediates (ROI), has been implicated as a culprit in the development of AMD. Overall, the data do not support a strong relation between ultraviolet exposure and AMD.

9. Smoking: The Beaver Dam Study disclosed a relationship between the development of exudative lesions and a history of current cigarette smoking.The relative odds for exudative macular degeneration , in females was 2.5 times increased risk (95% confidence interval 1.01-6.20) compared with those who are ex smokers or never smokers. For males it was 3.2 (95% confidence interval 1.03- 10.50). The Eye Case Control Group also found smoking increases the risk of the exudative type of AMD 2.8 times in those who are current smokers. Smoking cessation lowers the relative risk of AMD

10. Drug Side Effects: Some cases of macular degeneration can be induced from side effects of toxic drugs such as Aralen (chloroquine, an anti-malarial drug) or phenothiazine. Phenothiazine is a class of anti-psychotic drugs, including brand names of Thorazine (chlorpromazine, which is also used to treat nausea, vomiting and persistent hiccups), Mellaril (thioridazine), Prolixin (fluphenazine), Trilafon (perphenazine) and Stelazine (trifluoperazine).

11. Dietary and Medication Factors: Data from the Age- Related Eye Disease Study (AREDS) suggests that supplementation with very high doses of zinc; vitamin C, vitamin E, and ß-carotene provide a modest protective effect on progression to advanced neovascular AMD, in patients with extensive drusen or fellow eyes with neovascular AMD. This benefit did not extend to patients without AMD or with few drusen. For instance, among male smokers, ß-carotene supplementation increases the risk of lung cancer and mortality, whereas

multivitamin supplementation increases overall cancer mortality. High serum levels of zinc are associated with Alzheimer's disease.

The AREDS results show a beneficial effect of high doses of antioxidant vitamins (vitamins C, E, beta-carotene) and zinc supplementation in reducing progression of intermediate AMD or advanced AMD in the fellow eye to advanced AMD by 25%.39

Increased risk of AMD was found in individuals with a higher intake of saturated fats and cholesterol, and in those with a higher body mass index.29 Markers of inflammation, such as C-reactive protein, may be associated with a higher risk of AMD progression.47

Pathophysiology of ARMD

Age-related macular degeneration (AMD) is a disorder of the macula and is characterized by one or more of the following:

- Drusen formation
- Retinal pigment epithelium (RPE) abnormalities such as hypopigmentation or hyperpigmentation
- Geographic atrophy of the RPE and choriocapillaris
- Neovascular (exudative) maculopathy

Age-related macular degeneration begins with characteristic yellow deposits in the macula (central area of the retina, which provides detailed central vision, called the fovea) called drusen between the retinal pigment epithelium and the underlying choroid. Most people with these early changes (referred to as age-related maculopathy) have good vision. People with drusen can go on to develop advanced AMD. The risk is considerably higher when the drusen are large and numerous and associated with disturbance in the pigmented cell layer under the macula. Recent research suggests that large and soft drusen are related to elevated cholesterol deposits and may respond to cholesterol-lowering agents.

NATURAL HISTORY

PATHOPHYSIOLOGY:

Normal retinal metabolism

Outer segment discs of rods and cones are transported to RPE for metabolism

Discs are engulfed into RPE and fuse with lysosomes where they are digested

TRADITIONAL THEORY:

1a. Senescence of the RPE leads to ARMD

RPE metabolically supports and maintains the photoreceptors.

It is thought that the senescent RPE accumulates metabolic debris as remnants of incomplete degradation from phagocytosed rod and cone membranes; progressive engorgement of these RPE cells leads to drusen formation with further progressive dysfunction of the remaining RPE.

Change in hydraulic conductivity of Bruch's membrane with age leads to a reduction of water movement and metabolic exchange between the RPE and choriocapillaris.

The Bruch membrane, thickened with drusen, could be predisposed to crack formation.

Calcification and fragmentation of the Bruch membrane is more prominent in eyes with exudative ARMD, and it is thought that these defects in the Bruch membrane could facilitate development of CNVM.

This theory is supported by findings in myopic degeneration and angioid streaks in which CNVMs develop through breaks in the Bruch membrane.

1b. Steen proposed another potential mechanism by which CNVM could develop in response to fragmentation of the Bruch membrane, relating to matrix metalloproteinases (MMP), which are extracellular matrix-degrading enzymes, which may play a key role in angiogenesis and CNVM formation. Also implicated are the VEGF,TGF -BETA, PDGF, b-FGF.

2. VASCULAR THEORY - Primary vascular changes in the choroid, secondarily affecting the RPE and lead to ARMD.

Friedman theorized that lipid deposition in the sclera and the Bruch membrane leads to scleral stiffening and impaired choroidal perfusion, which would adversely affect metabolic transport function of the RPE.

According to the vascular model, a generalized stiffening and increase in resistance occurs, not only in the choroidal vasculature, but also in the cerebral vasculature.

If the choroidal resistance increases more than the cerebral vascular resistance, a decrease in choroidal perfusion and an increase in the osmotic gradient occurs. The RPE must pump against this gradient, leading to an accumulation of metabolic debris in the form of drusen.

If the choroidal resistance increases less than the cerebral vascular resistance, there is higher choroidal perfusion pressure, which facilitates CNVM development. This mechanism partially accounts for the development of CNVM in the presence of the Bruch membrane senescence or cracks.

3. OXIDATIVE INSULTS

These insults may be a contributing factor that involve the macular pigments lutein (L) and zeaxanthin (Z). These pigments are found in dark green, leafy vegetables and account for the yellow pigmentation of the macula lutea. Macular pigment is thought to limit oxidative insults by filtering out harmful wavelengths of light or by protecting the eye via antioxidant properties of its components. The central fovea, which contains the highest concentrations of macular pigment, often is spared from atrophy until late in the course. Based on this finding, some investigators postulate that macular pigments account for the relative resistance of the central fovea against degenerative change.

Drusen, retinal pigment epithelial (RPE) detachment and subretinal neovascularization are important clinical findings in macular degeneration.

4. PIGMENT EPITHELIAL DETACHMENT- PATHOPHYSIOLOGY

As the Bruch's membrane becomes thicker with age there is an increase in the resistance to water flow resulting in fluid accumulation in the subpigment epithelial space along with the deposition of non-polar neutral lipid on the inner surface of Bruch's membrane.

RPE must pump against this gradient, leading to an accumulation of metabolic debris in the form of drusen.It is believed that RPE detachments that are destined to tear tend to become

progressively larger and more highly detached, generating sufficient tangential stress to cause a rupture. Change in hydraulic conductivity of Bruch's membrane with age leading to a reduction of water movement and metabolic exchange between the RPE and choriocapillaris ULTIMATELY RESULTS IN DRUSEN 8.

PATHOGENESIS OF SUBRETINAL NEOVASCULARISATION

Retinal pigment epithelial cells release factors that inhibit growth of vascular endothelial cells.

Substances derived from the retina stimulate the growth of RPE cells, Fibroblasts and vascular cells.

The vitreous of patients with PVR contains factors that stimulate RPE cell migration. Normal vitreous causes RPE cells to transform into fibrocyte-like cells. Normal vitreous inhibits stimulation of vascular cells by retinal extracts.

RPE cells produce many of the components of Bruch's membrane, which could act as a barrier to the spread of new vessels from the choroid into the subretinal space.

These findings suggest that choroidal vascular cells, in the absence of a barrier and inhibitory factors released by the normal RPE, may be exposed to mitogenic and chemotaxic retinal factors that stimulate development of SRNVM.

It is not required for Bruch's membrane to be broken for subretinal neovascularisation to develop.

Penetration through Bruch's membrane may result from RPE changes that lead to CNV proliferation11.

RPE

RPE is a cuboidal hexagonal monolayer comprising the outermost layer of the retina. Its apical portion faces the outer segments of the PRs and its basolateral surface interacts with the choriocapillaris. The RPE is a post-mitotic cell that does not proliferate under normal conditions, and its tight junctions represent the outer blood retinal barrier. Among them, RPE expresses several

fibroblast growth factors (bFGF, acidic FGF, and FGF5), as well as ciliary neurotrophic factor (CNTF)12. In addition, vascular endothelial growth factor (VEGF-A)-a very potent angiogenic growth factor-is secreted to act as a paracrine trophic factor for the epithelium of the choriocapillaris, and to maintain its fenestrations.13,14 In hypoxia, hyperglycemia, advanced glycation end products (AGE), and other pathologic stimuli, VEGF expression is up-regulated, thus playing a central role in ocular neovascularisation.15,16 Insulin-like growth factor (IGF-1) and its binding protein (IGF-BP) are synthesized also by the RPE and were found to be up-regulated in various ischemic retinal conditions.17 Most important, however, is the secretion of pigment epithelial derived factor (PEDF), which acts as the key coordinator of retinal neuronal and vascular function, and is a potent inhibitor of angiogenesis.

Classification

There are a number of classifications of AMD in the literature. This classification of the Age-Related Eye Disease Study (AREDS) defines the early and intermediate stages of AMD, because the current treatment recommendations are based on this classification. The AREDS was a prospective multicenter randomized clinical trial conducted between 1992 and 2006 designed to assess the natural course and risk factors of age-related cataract and AMD and the effects of antioxidant vitamins and minerals on these two ocular conditions.

The classification of AMD from the AREDS is as follows:

- No AMD (AREDS category 1) was the control group for the AREDS and had no or few small drusen (<63 microns in diameter).
- Early AMD (AREDS category 2) consists of a combination of multiple small drusen, few intermediate drusen (63 to 124 microns in diameter), or RPE abnormalities.
- Intermediate AMD (AREDS category 3) consists of extensive intermediate drusen, at least one large drusen (125 microns in diameter), or geographic atrophy not involving the center of the fovea.
- Advanced AMD (AREDS category 4) is characterized by one or more of the following (in the absence of other causes) in one eye:
- Geographic atrophy of the RPE and choriocapillaris involving the center of the fovea
- Neovascular maculopathy such as the following:
- Choroidal neovascularization (CNV)
- Serous and/or hemorrhagic detachment of the sensory retina or RPE

- Retinal hard exudates (a secondary phenomenon resulting from chronic leakage from any source)
- Subretinal and sub-RPE fibrovascular proliferation
- Disciform scar

Early AMD

As defined by the AREDS, early AMD is characterized by small and intermediate drusen and minimal or no pigment epithelial abnormalities in the macula (Fig 2).

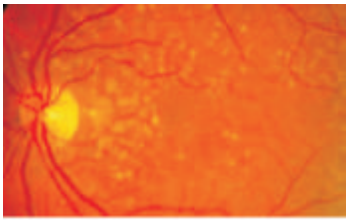


Fig 2

The International Epidemiological Age- related Maculopathy study Group has defined early ARM as a degenerative disorder in persons >50 years characterized by the presence of any of the following:

- Soft Drusen (>63µm). Soft indistinct are more pathognomonic than soft distinct & >125µm are still more significant.
- Areas of hyperpigmentation and/or hypopigmentation associated with drusen but excluding pigment surrounding small, hard drusen
- Visual acuity (VA) is not a criterion for diagnosis of ARM as advanced changes are sometimes seen with good VA due to sparing of the fixation.

Drusen

- The key lesion of ARM (Age Related Maculopathy) is the drusen. Most people over the age of 40 years have at least one drusen
- The drusen is an aggregation of hyaline material located between Bruch's membrane and the RPE.

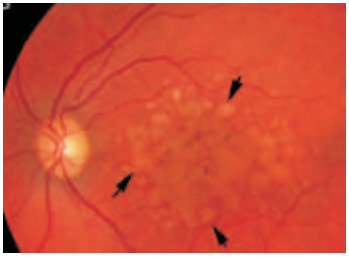


Fig 3.

Small, hard drusen are referred to simply as drusen, soft drusen over 63 microns in diameter are statistically associated with visual pathology and are termed early ARM.Hyper or hypopigmentation of the RPE also constitutes part of the description of ARM.

Large, Soft Drusen: These are >63µm, have ill defined borders & vary in size & shape. They have a tendency towards confluence. On the basis of pathogenesis these can be divided into three types

- Granular soft drusen: Clinically about 250µm (2x vein width) with a yellow solid appearance, there confluence resulting in sinuous shapes.
- Soft serous drusen and drusenoid pigment epithelial detachments (PEDs): Clinically larger than 500µm, may have pooled serous fluid, appearing blister like (Fig 4). Their further confluence leads to larger soft drusen that resemble serous PED. Both of the above show late fluorescence on FFA due to staining. Drusenoid PEDs are consistent with good vision although very large ones may cause distortion. However as they collapse, atrophy, rather than choroidal neo-vascularization (CNV) sets in & visual acuity then rapidly deteriorates.
- Soft membranous drusen: Clinically between 63- 175µm (0.5-1.5 vein widths), appear paler & shallower than the granular drusens. They herald a high risk of development of CNV. On angiography they fluoresce later & less brightly than small hard drusens.

Regressing Drusens: All drusens may disappear in time, but this does not mean a return to normal state. Drusens begin to regress when the overlying RPE fails. Now they become whiter & harder due to inspissation of contents. Hypo & hyper pigmentation develops over the surface, margins become irregular & foci of calcification appear.

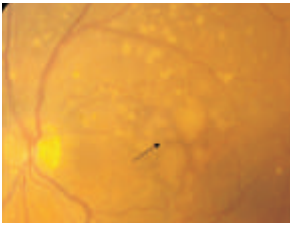


Fig 4

Ultimately drusens fade leaving multifocal patches of RPE atrophy.

2. Intermediate AMD

Intermediate AMD has been defined by the AREDS as having extensive medium-sized drusen or one or more large drusen (125 microns in diameter) in one or both eyes (Fig 5). The progression to advanced AMD at 5 years in this group is approximately 18% in the AREDS. However, for patients with large drusen in one eye, the rate of development of advanced AMD at 5 years is 6.3%, while the rate for patients with bilateral large drusen is 26% at 5 years.

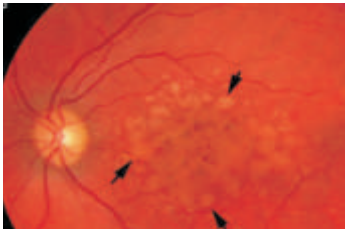


Fig 5

3. Advanced AMD

Advanced AMD as defined in the AREDS refers to either neovascular AMD or geographic atrophy involving the center of the macula.

3 a. Geographic atrophy

The advanced form of non-neovascular AMD, may consist of one or more zones of well-demarcated RPE and/or choriocapillaris atrophy. Drusen and other pigmentary abnormalities may surround the atrophic areas. Severe visual loss occurs less commonly in patients with geographic atrophy than in patients with neovascular AMD, nevertheless, geographic atrophy involving the center of the fovea causes approximately 10% of all AMD-related visual loss of 20/200 or worse. Patients with geographic atrophy often have relatively good distance visual acuity but a substantially decreased capacity for near visual tasks such as reading.

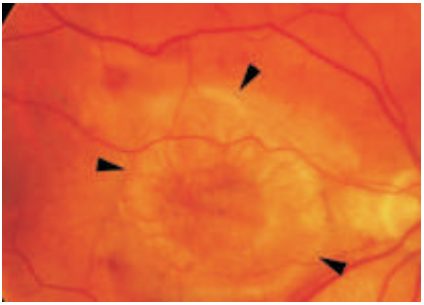


Fig 6

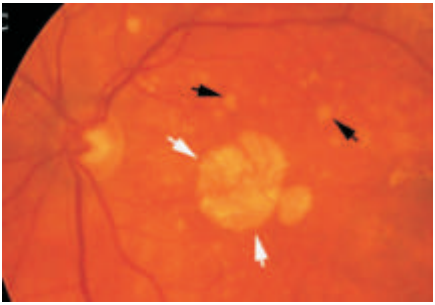


Fig 7

Central geographic atrophy, the "dry" form of advanced AMD, results from atrophy to the retinal pigment epithelial layer below the retina, which causes vision loss through loss of photoreceptors (rods and cones) in the central part of the eye

3.b . Wet AMD

Neovascular or exudative AMD, the "wet" form of advanced AMD, causes vision loss due to abnormal blood vessel growth (choroidal neovascularization) in the choriocapillaris, through Bruch's membrane, ultimately leading to blood and protein leakage below the macula (Fig 8).

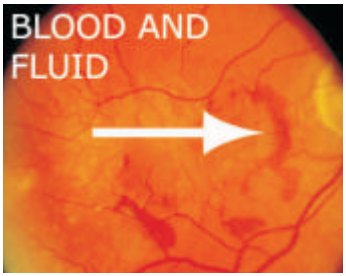


Fig 8

Neovascular AMD is characterized clinically and angiographically by occult, classic, or mixed occult-classic CNV; serous and/or hemorrhagic detachment of the sensory retina or RPE; and/or various stages of an elevated, fibrovascular disciform scar.

The CNV capillary network becomes more apparent after the atrophy of overlying RPE. CNV has been classified into classic and occult depending upon the angiographic appearance (described later). Depending upon its location CNV may be subfoveal, juxtafoveal (between 1&199µm from the centre of FAZ), or extrafoveal (>200µm from FAZ centre). Histologically CNV is growth of abnormal, fragile new vessels between the Bruchs membrane & RPE or between the latter & neurosensory retina. These vessels sprout from the chorio capillaries & proceed inwards through the defects in the Bruchs membrane

RPEDs: appear as sharply demarcated, dome shaped elevations of RPE. If filled with serous fluid they transilluminate (Fig 9). Three types of PEDs are seen & can be differentiated on the basis of their Angiographic pattern (described later)

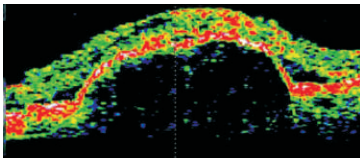


Fig 9

- Drusenoid PED -does not have CNV
- Fibrovascular PED-is a form of occult CNV
- Serous PED-may or may not overlie CNV

Overlying serous RD, lipid & blood within or surrounding a PED implies the presence of CNV. Sub RPE blood is seen as green or dark red mound.

RPE Tear: or rip occurs as a complication in serous or fibrovacular PED. It occurs at the border of attached & detached RPE due to stretching forces of the underlying fluid or from the contractile forces of the fibrovacular tissue (Fig 10). Clinically it is seen as area of hypopigmentation with hyperpigmented wavy border on one side due to rolling in of the free edge of torn RPE. Massive sub retinal hemorrhage and breakthrough vitreous hemorrhage though unusual complications of AMD, are seen sometimes and result in sudden profound visual loss both central as well as peripheral.

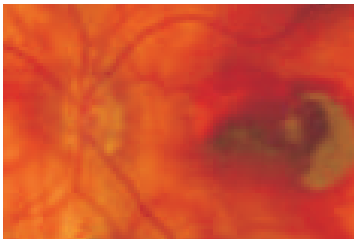


Fig 10

Disciform Scar: is the last stage in the evolution of neovascular AMD just as geographic atrophy is in dry AMD. CNV is a fibrovascular tissue; however, the fibrous component is not readily appreciated in the early stages of CNV due to immaturity of the fibrous tissue & also due to the overwhelming signs like serous RD, subretinal lipids and/or blood, of the vascular component. When the fibrous tissue becomes apparent clinically then the fibrovascular complex is called disciform scar. Clinically it appears as white to yellow subretinal scar with intervening areas of hyperpigmentation. If the vascular component has died its own death then the scar does not grow, however, it can expand with neovascularization occurring along the edges.

DRY OR NONEXUDATIVE ARMD	WET OR EXUDATIVE ARMD
* Atrophic and hypertrophic changes in the RPE underlying the central retina (macula) as well as deposits (drusen) on the RPE. * Can progress to the exudative, form of ARMD * More common. * Severe visual loss can occur, particularly when geographic atrophy of the RPE develops in the fovea and causes a central scotoma.	* Less common * Abnormal blood vessels called choroidal neovascular membranes (CNVMs) develop under the retina * Leak fluid and blood, and ultimately cause a blinding disciform scar in and under the retina. * Causes severe visual loss as a result of leaky CNVMs.

ARMD Clinical Features

History

An initial history should consider the following elements:

- Symptoms
- Metamorphopsia
- Decreased vision
- Medications and nutritional supplements
  - ➢ Ocular history
  - ➢ Medical history (including any hypersensitivity reactions)
  - ➢ Family history, especially family history of AMD
  - ➢ Social history, especially smoking

Signs

- Drusen
- Pigmentary alterations
- Exudative changes: hemorrhages in the eye, hard exudates, subretinal/sub-RPE/intraretinal fluid
- Atrophy: incipient and geographic
- Visual acuity drastically decreasing (two levels or more) ex: 20/20 to 20/80.

Symptoms

- Blurred vision: Those with nonexudative macular degeneration may be asymptomatic or notice a gradual loss of central vision, whereas those with exudative macular degeneration often notice a rapid onset of vision loss.
- Central scotomas (shadows or missing areas of vision)

- Distorted vision (i.e. metamorphopsia) - A grid of straight lines appears wavy and parts of the grid may appear blank. Patients often first notice this when looking at mini-blinds in their home.
- Trouble discerning colors; specifically dark ones from dark ones and light ones from light ones.
- Slow recovery of visual function after exposure to bright light
- A loss in contrast sensitivity.

Examination

Stereoscopic biomicroscopic examination of the macula Binocular slit-lamp biomicroscopy of the ocular fundus is often necessary to detect subtle clinical clues of CNV. These include small areas of hemorrhage, hard exudates, subretinal fluid, or pigment epithelial elevation (Fig 11).

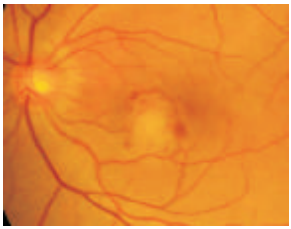


Fig 11

The Amsler Grid Test is one of the simplest and most effective methods for patients to monitor the health of the macula. The Amsler Grid is, in essence, a pattern of intersecting lines (identical to graph paper) with a black dot in the middle. The central black dot is used for fixation (a place for the eye to stare at). With normal vision, all lines surrounding the black dot will look straight and evenly spaced with no missing or odd looking areas when fixating on the grid's central black dot. When there is disease affecting the macula, as in macular degeneration, the lines can look bent, distorted and/or missing.

13 Preferential Hyperacuity Perimeter

Fig 12.

Its principle is hyperacuity ,verniers's acuity and is helpful in earlier detection than amslers grid.

Its useful in detection of conversion of dry form to wet form of ARMD.

Diagnostic Tests

Investigations that help in evaluation are:

- Fundus fluorescein angiography (FFA)
- Indocyanine green (ICG) angiography
- Optical coherence tomogram (OCT)
- Multifocal electroretinography (MERG)

Fluorescein Angiography

CNVs can be detected and categorized either as classic or occult, or a combination of the two, depending on the leakage patterns they present at various time points on the angiogram. This differentiation was imperative for laser treatments where well defined margins for treatment decision were necessary. Today the differentiation is still important to evaluate disease activity and to decide on drug selection in the area of intravitreal applications of antiinflammatory and anti-VEGF medication

Intravenous fundus fluorescein angiography is indicated when the patient complains of new metamorphopsia or has unexplained blurred vision, and/or when clinical examination reveals elevation of the RPE or retina, subretinal blood, hard exudates, or subretinal fibrosis and in the following situations (Fig 13 and Fig 14):

- To detect the presence of and determine the extent, type, size, and location of CNV. If verteporfin PDT or laser photocoagulation surgery is being considered, the angiogram is also used as a guide to direct treatment.
- To detect persistent or recurrent CNV following treatment.
- To assist in determining the cause of visual loss that is not explained by the clinical examination.

Fundus Fluorescein Angiography:

Two basic angiographic patterns for choroidal neovascular membranes (CNVM) were defined by the macular photocoagulation study (MPS).

- Classic CNVM present as discrete, early hyperfluorescence with late leakage of dye into the overlying neurosensory retinal detachment. A lacy pattern within the CNVM is most often not observed in exudative AMD.
- Occult CNVM are categorized into 2 basic forms, late leakage of undetermined source and fibrovascular PEDs.
- Late leakage of undetermined source manifests as regions of stippled or ill-defined leakage into an overlying neurosensory retinal detachment without a distinct source focus that can be identified on the early frames of the angiogram.
- Fibrovascular PEDs present as irregular elevation of RPE, which is associated with stippled leakage into an overlying neurosensory retinal detachment in the early and late frames of the angiograms.
- Fibrovascular PEDs can be differentiated from serous PEDs, which show more rapid homogenous filling of the lesion in the early frames without leakage in the late frames of the angiogram. Serous PEDs typically show smooth and sharp hyperfluorescent contours. Other causes of RPE elevation to differentiate from the entities listed above include hemorrhagic PEDs, RPE hyperplasia, and confluent soft drusen.
- Hemorrhagic PEDs present clinically with dark sub-RPE blood, which blocks choroidal fluorescence on angiography.
- RPE hyperplasia also will block choroidal fluorescence.
- RPE tears will present as regions of intense hyperfluorescence in the area bereft of RPE due to transmission of choroidal fluorescence and in the late stages as scleral staining. This is adjacent to sharply demarcated blockage of the choroidal

fluorescence by the redundant scrolled RPE. CNVM may be associated with the RPE tear, causing leakage in addition to the above findings.

- Confluent soft drusen, which often present in the fovea, typically show cruciate pigment clumping. Confluent soft drusen will show angiographic findings that are similar to serous PEDs with homogenous pooling of dye and no leakage, but they typically exhibit only faint fluorescence.
- Disciform scarring shows diverse angiographic characteristics. Angiographically, the fibrotic component will block the choroidal fluorescence in the early frames of the angiogram, followed by late staining. Hyperpigmented regions as well as subretinal hemorrhage will block the choroidal fluorescence throughout the angiogram. Regions of active CNVM will show leakage.

Indocyanine Green Angiography

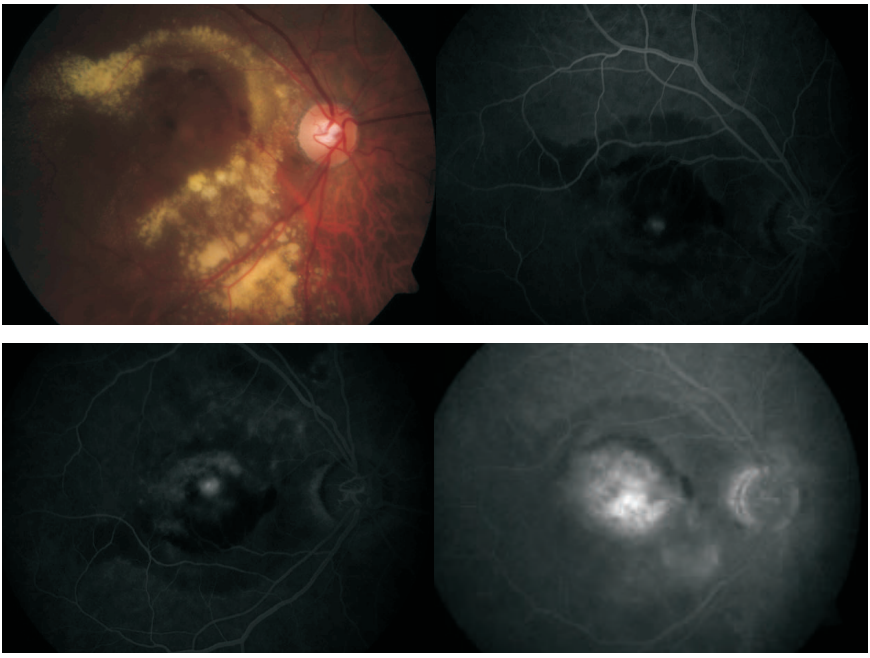


Fig 13 Occult CNVM

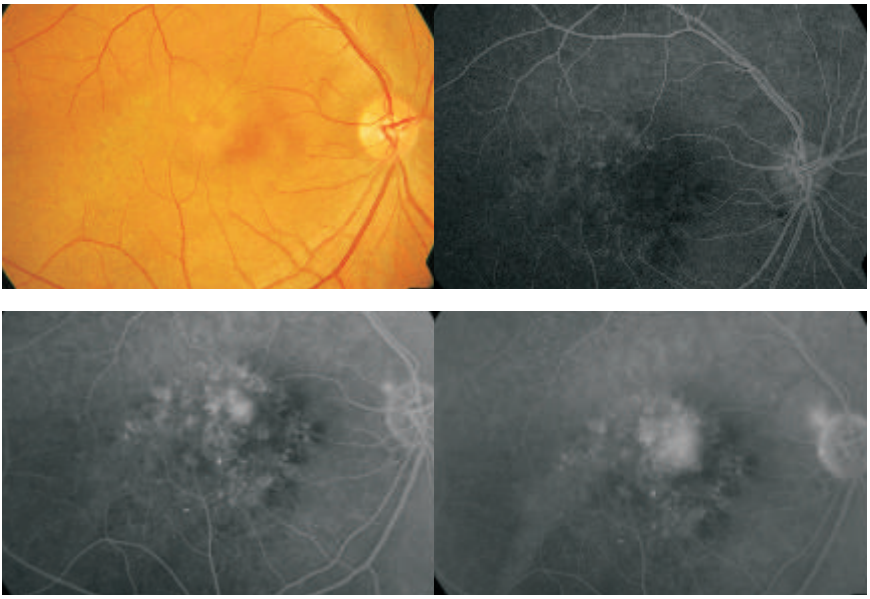
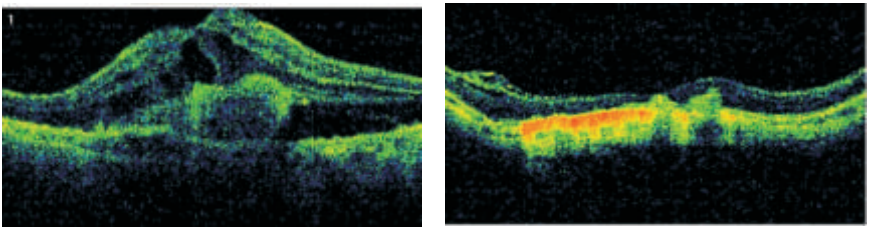


Fig 14 Mixed CNVM

Optical Coherence Tomography

Optical coherence tomography is helpful in determining the presence of subretinal fluid and in documenting the degree of retinal thickening (Fig 15). Optical coherence tomography offers a unique ability to define cross sectional architecture of the retina that is not possible with any other imaging technology and may assist in evaluating the response of the retina and RPE to therapy by allowing structural changes to be followed accurately. Advances in optical coherence tomography (e.g., spectral domain) may allow increased resolution.



Active CNVM **Scarred CNVM**

Fig 15

OCT Interpretation in a Case of ARMD

Interpretation of an OCT image in patients with ARMD should include the following points to be borne in mind:

Identification of the highly reflective RPE on the image and comment on its contour.

Identification of the intermediate reflectivity layers and look at their relative positioning with reference to the underlying highly reflective RPE.

Identification of the foveal region on the OCT image.

Identification of the areas of backscattering from the RPE and its quantification .

OCT Findings in Non Neovascular ARMD

a) Soft Drusen

1. Soft drusen present as small nodulations with shallow borders in the contour of the highly reflective RPE, appearing red on OCT, in vertical image causing both irregularities and undulations.
2. As the disease progresses the drusen increase in size, height, and become confluent and indistinct.
3. Drusen typically have moderate reflectivity ,appearing green on OCT and produce a corrugated elevation of RPE .
4. Drusen do not produce any shadowing towards the choroids which differentiates them from PED.

b) Geographic atrophy

1. Geographic atrophy on OCT presents as decrease in thickness of neurosensory retina.
2. Disappearance of hyporeflective band of rods and cones.
3. Increased hyperreflectivity of RPE choriocapillaris complex extending towards the choroid due to increased penetration of the light (both incident and reflected) through the atrophic retina.

4. Alteration in the contour of the fovea.

5. There is a clear delineation between the atrophic and normal retina.

OCT Changes in Neovascular AMD

a) Serous, Hemorrhagic and Fibrovascular PED of the retina:

Serous pigment epithelial detachment present as elevation of the neurosensory retinal with optically clear space (black on OCT) underneath them with underlying choroid showing shadowing of reflection. The elevation of the neurosensory retina alone does not show elevation of the central red line, which is elevated with pigment epithelium detachment. The angle of the edge of detachment is typically acute, probably because of the tight adherence of RPE cells to Bruch's membrane at the edge of the detachment.

Hemorrhagic PED presents with back scattering from the RPE which attenuates towards the entire retina. There is moderate reflectivity, appearing green beneath the detachment and not a optically clear space. Penetration through the hemorrhage is usually less than 100 microns. The RPE detachment produces a very steep angle with the choriocapillaris and the OCT beam penetration below the detachment is minimal because it is blocked by blood. A shadow area is formed which obsures the underlying choriocapillaris and all other posterior layers. Fibrovascular PED presents with separation of the neurosensory retina from the RPE and is associated with moderated back scattering below the RPE. The reflected band may be fragmented and thickened 'lumps and bumps' and represents subretinal neovascularisation.

b) Neovascular ARMD

Exudative or neovascular ARMD can be picked up on the OCT using a number of direct and indirect evidences.

However, OCT does not yet have the resolution to identify the exact location of CNV. We really can't determine if the CNV is under the retina, under the retinal pigment epithelium within Bruch membrane, or in the choroid, but OCT does show us a highly

reflective thickened Bruch/RPE complex that is characteristic of CNV in AMD.

1. The indirect evidence that point towards the presence of a neovascular ARMD are leaking vessels which produce an elevation or retinal thickening due to fluid (subretinal or intra retinal), decrease in the foveal depression and detachment of the RPE, thickening and fragmentation of the RPE, beginning at the inferior border.
2. Direct signs that point towards the presence of CNV are the visualization of vascular topography, extent of the vascularisation and spatial orientation of the RPE with regards to neurosensory retina and also the disease activity.

Classic choroidal neovascular membrane presents with

1. Increased thickness of the sensory retina which presents as highly reflective, nodular or fusiform, continuous band with thickened edges which is located either in front of, or in contact with or slightly separated from a slightly disrupted retinal pigment epithelium.
2. Flattening of the foveal depression and
3. RPE detachment.

Occult choroidal neovascular membrane produces

1. Hyper-reflective band in the RPE which is irregular and fusiform shape
2. Associated subretinal fluid / retinal edema.
3. Shadowing towards the choroid.

Optical coherence tomography can be used to distinguish a Type II choroidal neovascular membrane with most of the neovascular complex anterior to the RPE, from a Type I choroidal neovascular membrane having neovascular complex below the RPE band. In a Type II choroidal neovascular membrane, the OCT images demonstrate an area of increased reflection suggestive of choroidal neovascular membrane penetratrating through the RPE/

choriocapillaris band and lying in the subretinal space. On the contrary, a Type I choroidal neovascular membrane is located predominantly in the sub-RPE space and is a representation of a fibrovascular retinal pigment epithelial detachment. These lesions have a thickened, cystic retina associated with subretinal fluid, a pigment epithelial detachment, and a Bruch/RPE complex devoid of the thickening seen with CNV in AMD.

Monitoring of the treatment using OCT

OCT also helps monitoring the ARMD treatment, especially persistence of active CNVM and need for re-treatment.An open-label nonrandomized clinical study is currently under way and the decision when to stop and start therapy is determined by OCT imaging.

Chorio-Retinal Anastomosis (CRA) in Age-Related Macular Degeneration

Focal elevation of the retinal pigment epithelium is observed in eyes with stage 1 (pre-clinical) CRA. Small hyperreflections at the level of the elevated retinal pigment epithelium are observed in stage 2 CRA. In stage 3 CRA, a hyperreflective "bump" at the level of the elevated retinal pigment epithelium and associated thickened retina is observed. In stage 4 CRA fluid accumulates in sub-retinal pigment epithelium region, and complete macular disorganization occurs in stage 5 CRA.

Advantages of using OCT in ARMD

1. Non invasive
2. Accurate identification and differentiation of the various forms ranging from drusens to fibrovascular PED and neovascularisation.
3. Early identification of neovascular membrane in choriodal neovascualisation

Disadvantages of OCT in ARMD

1. Costly
2. Severe hemorrhagic or exudative RPE detachments reduce light

penetration to the choroid and may cause CNV lesions to go undetected.

3. Artifactual errors.

Newer advances in OCT

Scanning Laser Ophthalmoscopy (SLO) OCT provides fundus images along with high resolution OCT pictures, and helps to interpret the lesion more accurately. In vivo imaging of blood flow in human retinal vessels using color Doppler OCT. Color Doppler optical coherence tomography (CDOCT) is a novel technique using coherent heterodyne detection for simultaneous cross-sectional imaging of tissue microstructure and blood flow. This technique is capable of high spatial (20 mu m) and velocity (<500 mu m/sec) resolution imaging in highly scattering media. Quantification of retinal blood flow may lead to a better understanding of the progression and treatment of ARMD.

Three-Dimensional ULTRA High-Resolution Fourier- Domain Optical Coherence Tomography Imaging: 3D Fourier-Domain OCT is a non-invasive, modality that measures and localizes CNVM in patients with obscured media due to vitreous hemorrhage. High contrast B-scan and 3-D images of ARMD by high-speed FD-OCT provide a complete picture of the chorioretinal pathology. This high resolution and high contrast technique gives us an understanding of not only the epi, sub and intraretinal structures but also and understanding of the structures lying beneath the RPE which has help us enhance our current understanding of the complex disease like ARMD . It is not commercially available due to its high cost and stays presently as a research tool. Spectral OCT is another addition, which provides better image quality, segmentation of the macula & fundus reconstruction. [a virtual image of the fundus is generated]. S-OCT also provides a clear resolution of ERM's over the retina. How far its scores over the conventional stratus OCT (version 3 or 4) remains to be seen as it is pretty expensive, and the stratus images suffice quite well in neovascular AMD lesions.

Indocyanine Green

ICG facilitates the study of the choroidal circulation by better delineation of the choroidal circulation than fluorescein. Unlike fluorescein, ICG is strongly bound to plasma proteins, which prevents diffusion of the compound through the fenestrated choroidal capillaries and permits better delineation of choroidal details. ICG can facilitate visualization of choroidal vasculature and CNVM through hemorrhage.

ICG angiography can show CNVM as localized hot spots or as diffuse hyperfluorescent plaques. ICG could better reveal the occult CNVM with ICG angiography. ICG is particularly useful in delineating the other variant of AMD, the Polypoidal choroidal Vasculopathy (PCV). This disease thought to affect women in pigmented population, It is now found in Asians with an almost equal predisposition among men and women. The patterns of ICG fluorescence seen in PCV are: early phase filling of larger choroidal blood vessel and the network of polyps arising from the large choroidal blood vessels can also be identified; in late phase, reversal of the pattern is noted causing hypofluorescence in the center of the polyps. Late staining seen in CNVM is not noted in PCV. PCV in Indian population differ from those in other populations in being more common in males and in its macular location as compared to females and peripapillary location in western population.

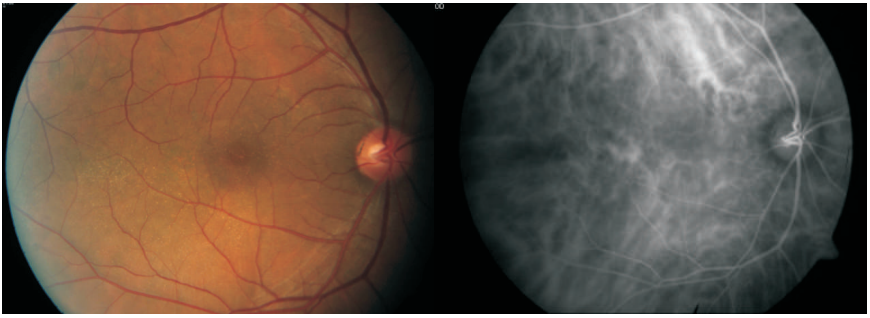


Fig 16 Polypoidal choroidal vasculopathy

It may prove useful in evaluating certain types of AMD, such as pigment epithelial detachment, poorly defined CNV, and lesions such as retinal angiomatous proliferation or polypoidal choroidal vasculopathy. Without indocyanine green, polypoidal choroidal vasculopathy may be identified as neovascular AMD, particularly in patients of African or Asian descent (Fig 16).

Besides visual acuity testing and biomicroscopic examination, the two most important additional examination methods are the angiography and optical coherence tomography of the retina.

Scanning Laser Ophthalmoscopy (SLO)

Confocal scanning angiography is a useful alternative to video-ICG angiography. Advantages compared to routine digital ICG videoangiography are, high image contrast, visualization of retinal vessels in the late phase, lower amount of light exposure and direct digital image acquisition. One group described the use of a 2-wavelength SLO to facilitate simultaneous recording of ICG and FA in 340 cases, two thirds of which had well-defined or occult choroidal neovascularization in ARMD. The angiograms are displayed as one combined red-green picture. They noted that this method allowed a precise comparison of the transit of both dyes through the circulation with perfect alignment of the critical retinal vascular landmarks provided by the fluorescein images onto the ICG angiogram.

Some studies have shown fundus auto fluorescence with SLO imaging provides a reliable means to delineate areas of geographic atrophy (GA). The automated image analysis allows more accurate detection and quantitative documentation of atrophic areas than manual outlining.

This method will be useful in longitudinal natural history studies and for monitoring effects of future therapeutic interventions to slow down GA progression in patients with advanced atrophic AMD and other retinal diseases associated with outer retinal atrophy.

Rationale and Modalities of Treatment

The cause of AMD is believed to be multifactorial. Prospective randomized controlled clinical trials support the use of antioxidant vitamins and mineral supplements, intravitreal injection of antivascular endothelial growth factor (VEGF) agents, PDT, and laser photocoagulation surgery to treat AMD.

Early AMD

The AREDS used a factorial design in which 4,757 participants were randomized to antioxidant vitamins, zinc, a combination of antioxidant vitamins and zinc, or a placebo, and they were followed for a mean of 6 years.1 Of these, 3,640 participants were enrolled in the study for AMD. In the AREDS, daily doses of vitamin C (500 mg), vitamin E (400 IU), beta-carotene (15 mg), zinc (80 mg as zinc oxide), and copper (2 mg as cupric oxide, to reduce the risk of zinc-induced 7 copper deficiency anemia) were evaluated (see Table 1). In early AMD (AREDS category 2), only 1.3% of participants progressed to advanced AMD in 5 years. The use of the combination of antioxidant vitamins and minerals did not reduce the progression of early AMD to the intermediate stage of AMD, and there was insufficient power to determine the effects of the combination treatment on the progression to more advanced AMD. Therefore, there is no evidence to support the use of these supplements for patients who have less than intermediate AMD. Approximately two-thirds of the study participants took an additional multivitamin (Centrum, Wyeth Consumer Healthcare, Madison, NJ) that had no effect on the clinical outcome.

TABLE 1 ANTIOXIDANT VITAMIN AND MINERAL SUPPLEMENTS USED IN THE AGE-RELATED EYE DISEASE STUDY

Supplement	Daily Dose*
Vitamin C	500 mg
Vitamin E	400 IU
Beta-carotene	15 mg (25,000 IU)
Zinc oxide	80 mg
Cupric oxide	2 mg

These doses are not those listed on the commercially available vitamin/mineral supplements because of a change in labeling rules by the U.S. Food and Drug Administration that specifies that the doses must reflect the amounts available at the end of the shelf life.

Data from The Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report number 9. Arch Ophthalmol 2001;119:1439-52.

Intermediate AMD

In the AREDS, the participants who benefited from antioxidant vitamin and mineral supplementation were those with either intermediate AMD or advanced AMD in one eye. For participants with extensive medium-sized drusen in one or both eyes, one or more large drusen in at least one eye, nonsubfoveal geographic atrophy in one eye, or advanced AMD (i.e., subfoveal geographic atrophy or CNV) in one eye, the rate of development of advanced AMD at 5 years was reduced by 25% by the combination treatment of all the antioxidant vitamins with zinc and copper. The risk of losing vision of three or more lines (doubling of the visual angle) also was reduced by 19% by this combination treatment. Although zinc alone or antioxidants alone reduced progression, the therapy that resulted in a statistically significant reduction in both the development of advanced AMD and vision loss was the combination treatment of antioxidant vitamins and minerals (see Table 2).

TABLE 2 SUMMARY OF RESULTS OF AREDS FOR DEVELOPING ADVANCED AMD AND VISION LOSS

Antioxidants	Plus Zinc	Zinc Alone	Antioxidants Alone
Reduction of the relative risk of developing advanced AMD	25%	21%	17%
Reduction of the relative risk of vision loss (three or more lines)	19%	11%	10%

AMD = Age-Related Macular Degeneration; AREDS = Age-Related Eye Disease Study

Data from The 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 number 8. Arch Ophthalmol 2001;119:1417-36. 8 A meta-analysis of the adverse effects of nutritional supplementation reported that there is an increased risk of death from vitamin A, beta-carotene, and vitamin E supplements (16%, 7%, 4%, respectively), but not from vitamin C supplements.The decision to take the AREDS supplement formulation must balance possible risks with possible benefit.90 Current smokers and patients with a smoking history should be advised to avoid taking beta-carotene and consider taking the other components of the AREDS formulation.

Neovascular AMD

With the introduction of the VEGF inhibitors pegaptanib sodium (Macugen, Eyetech, Inc., Cedar Knolls, NJ) in December 2004 and ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) in June 2006, effective treatments for neovascular AMD now exist. The VEGF inhibitors demonstrated improved visual outcomes compared with other therapies and have become the first-line therapy for treating neovascular AMD.91

Ranibizumab intravitreal injection has Food and Drug Administration (FDA) approval for the treatment of all subtypes of

neovascular AMD based on results from three double-masked randomized controlled trials (see Table 3 and Appendix 3). Ranibizumab is a recombinant, humanized immunoglobulin G1 kappa isotype therapeutic antibody fragment developed for intraocular use that binds to and inhibits the biologic activity of all isoforms of human VEGF-A.

Bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA) is a full-length monoclonal antibody that binds all isoforms of VEGF. It has FDA approval for intravenous use in the treatment of metastatic colorectal, metastatic breast, and non-small cell lung cancer. Bevacizumab was investigated first as a systemic intravenous treatment for AMD and then as an intravitreal injection before FDA approval of ranibizumab.93,94 Because preliminary reports appeared favorable, ophthalmologists began to use intravitreal bevacizumab off label to treat choroidal neovascularization. There are no long-term results on the safety and effectiveness of the use of intravitreal bevacizumab for neovascular AMD. There are short-term uncontrolled case series that report improvements in visual acuity and decreased retinal thickness by optical coherence tomography.94-100 Informed consent information is available on the benefits and risks of intravitreal bevacizumab and its off-label status.101

Because ranibizumab and bevacizumab have not been evaluated directly in a randomized controlled trial, the Comparison of AMD Treatment Trials (CATT), a multicenter clinical trial to compare the relative safety and effectiveness of ranibizumab and bevacizumab, is under way.102 The CATT will also investigate whether a reduced dosing schedule (monthly as needed) is as effective as a fixed schedule of monthly injections because the optimal dosing strategy for the anti-VEGF agents has not yet been determined. Further investigation beyond this study may be needed to evaluate other types of schedules for delivering anti-VEGF therapy.

Pegaptanib sodium is a selective VEGF antagonist that binds only to the 165 isoform of VEGF-A. Pegaptanib sodium injection has FDA approval for the treatment of all subtypes of neovascular AMD, with a recommended dosage of 0.3 mg injected every 6 weeks into the

vitreous based on results from two double-masked randomized controlled trials (see Table 3 and Appendix 3).105

Randomized trials are under way to study the adjunct use of intravitreal corticosteroids and/or anti-VEGF agents in various combinations with verteporfin PDT, following the publication of results from uncontrolled case series.106-108 Current published reports of this off-label use of 9 intravitreal injection of corticosteroids do not provide conclusive evidence of benefit, and there are limited data on risk.

Ongoing trials of combination treatment for AMD include the DENALI and MONT BLANC studies (ranibizumab and verteporfin PDT compared with ranibizumab alone), the Verteporfin Intravitreal Triamcinolone Acetonide Study (VERITAS), the Visudyne with Intravitreal Triamcinolone Acetonide (VisTA) study, and the Evaluation of Efficacy and Safety in Maintaining Visual Acuity with Sequential Treatment of Neovascular AMD (LEVEL), which compares anti-VEGF therapy plus pegaptanib sodium.

Subfoveal CNV

In addition to intravitreal injections of VEGF inhibitors, verteporfin PDT and thermal laser photocoagulation surgery are FDA-approved options for the treatment of subfoveal lesions. Photodynamic therapy with verteporfin has FDA approval for the treatment of predominantly classic neovascular AMD; treatment trial results are described in Appendix 3. The efficacy of thermal laser photocoagulation surgery for CNV was studied in the MPS, a randomized controlled multicenter study.109-112 In the MPS, 22% of eyes treated for subfoveal lesions progressed to visual loss of 30 or more letters (quadrupling of the visual angle) compared with 47% of untreated eyes after 4 years of follow-up.111 Because of the loss of vision associated with laser photocoagulation surgery (82% of treated patients have a resultant in visual acuity worse than 20/200), photocoagulation is no longer in general clinical use for subfoveal neovascularization.

Table 3 summarizes the findings from randomized controlled trials of verteporfin PDT and VEGF inhibitors for the treatment of subfoveal CNV. The entry criteria varied among these studies and may have contributed to the differences among treatment cohorts.

Juxtafoveal CNV

Although randomized controlled clinical trials did not include patients with juxtafoveal CNV, many clinicians extrapolated the data from current trials to consider intravitreal injections of anti-VEGF agent as the primary therapy for juxtafoveal lesions. Most of these lesions will recur regardless of treatment, and it is assumed that many will be eligible for retreatment as recurrent subfoveal CNV lesions with intravitreal injection of an anti-VEGF agent (off-label use) or PDT with verteporfin.

Photocoagulation of well-demarcated juxtafoveal CNV lesions resulted in a small overall treatment benefit.112 The rates of "persistence" (CNV leakage within 6 weeks of laser photocoagulation surgery) and "recurrence" (CNV leakage more than 6 weeks after laser photocoagulation surgery) were high (80%) at 5 years. Persistent or recurrent leakage after treatment was associated with a greater incidence of severe visual loss. After 5 years of follow-up, 52% of eyes treated for juxtafoveal lesions progressed to visual loss of 30 or more letters (quadrupling of the visual angle) compared with 61% of untreated eyes.112

Extrafoveal CNV

There is still a role for thermal laser treatment in eyes with extrafoveal CNV lesions as defined by the MPS.109 Photocoagulation of well-demarcated extrafoveal CNV lesions resulted in a substantial reduction in the risk of severe visual loss for the first 2 years. A recurrence rate of approximately 50% reduced this benefit over the subsequent 3 years of follow-up.109 After 5 years of follow-up, 48% of eyes treated for extrafoveal lesions progressed to visual loss of 30 or more letters (quadrupling of the visual angle) compared with 62% of untreated eyes.109 10

TABLE 3 EFFECTS OF TREATMENT ON VISION IN RANDOMIZED CONTROLLED TRIALS OF SUBFOVEAL CNV

Study	No. of Patients	Patient Characteristics	Duration and Frequency of Treatment	Treated Eyes	Untreated Eyes		Years after Enrollment
	Visual Loss of 15 Letters or More*		Visual Gain of 15 Letters or More*	Visual Loss of 15 Letters or More*	Visual Gain of 15 Letters or More*		
ANCHOR (ranibizumab injection)	423	Mean age 77 years; BCVA 20/40 to 20/320; total lesion size ?5400 ?m; no previous treatment (including verteporfin therapy) that might compromise an assessment of the study treatment	Monthly injections for 1 year Verteporfin or sham on day 0 and then as needed following FA at months 3, 6, 9, or 12	4% (treated only with ranibizumab 0.5 mg) 6% (treated only with ranibizumab 0.3 mg) 36% (treated only with verteporfin PDT)	40% (treated only with ranibizumab 0.5 mg) 36% (treated only with ranibizumab 0.3 mg) 6% (treated only with verteporfin PDT)	n/a (all patients received treatment)	1
MARINA (ranibizumab injection)	716	Mean age 77 years; BCVA 20/40 to 20/320; primary or recurrent CNV; minimally classic or occult with no classic CNV lesions; presumed recent progression of disease	Monthly injections for 2 years	8% (0.3 mg) 10% (0.5 mg)	26% (0.3 mg) 33% (0.5 mg)	47% 4%	2

Cont.....TABLE 3

PIER (ranibizumab injection)	184	Mean age 78 years; BCVA 20/40 to 20/320; primary or recurrent subfoveal CNV, with the total CNV area (classic plus occult CNV) ?50% of total lesion size; minimally classic or occult with no classic CNV only if criteria met for presumed disease progression. Any prior treatment with verteporfin PDT or antiangiogenic agent excluded	Injections every month for 3 doses, then doses every 3 months	17% (0.3 mg) 10% (0.5 mg)	12% (0.3 mg) 13% (0.5 mg)	51%	10%	1
TAP (verteporfin PDT)	609	Mean age 75 years; BCVA 20/40 to 20/200; classic CNV or occult CNV if >50% of total lesion size	Following first treatment, retreatment was considered every 3 months per FA findings through 21 months of follow-up	47% 41%†	8%	62% 69%†	4%	2

Cont.....TABLE 3

VIP (verteporfin PDT)	339	Mean age 75 years; subfoveal CNV lesions ?5400 ?m with either occult with no classic CNV, BCVA at least 20/100, evidence of hemorrhage or progression; or classic CNV with BCVA at least 20/40	Following first treatment, retreatment was considered every 3 months per FA findings through 24 months of follow-up	54%	5%	67%	1%	2
VISION (pegaptanib sodium injection)‡	590	Age ?50 years; BCVA 20/40 to 20/320; subfoveal CNV with total lesion size ?12 disc areas; IOP ?23 mmHg	Injection every 6 weeks for 54 weeks (9 total treatments); then re-randomized and injection every 6 weeks through week 96 (8 total treatments)	45%	10%	59%	4%	2

ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic CNV in AMD; BCVA = best corrected visual acuity; CNV = choroidal neovascularization; FA = fluorescein angiography; MARINA = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD; PDT = photodynamic therapy; PIER = A Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Neovascularization with or without Classic CNV; TAP = Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; VIP = Verteporfin in Photodynamic Therapy; VISION = VEGF Inhibition Study in Ocular Neovascularization

TABLE 4A TREATMENT RECOMMENDATIONS AND FOLLOW-UP FOR NON-NEOVASCULAR AMD

Recommended Treatment	Diagnoses Eligible for Treatment	Follow-up Recommendations	
Intervals		**Testing**	
Observation with no medical or surgical therapies1,77,136 [A:I]	Early AMD (AREDS category 2)	Return exam at 6 to 24 months if asymptomatic or prompt exam for new symptoms suggestive of CNV[A:III]	No fundus photos or fluorescein angiography unless symptomatic1 [A:I]
Advanced AMD with bilateral subfoveal geographic atrophy or disciform scars		Return exam at 6 to 24 months if asymptomatic or prompt exam for new symptoms suggestive of CNV[A:III]	No fundus photos or fluorescein angiography unless symptomatic1 [A:I]
Antioxidant vitamin and mineral supplements as recommended in the AREDS reports1 [A:I]	Intermediate AMD (AREDS category 3) Advanced AMD in one eye (AREDS category 4)	Return exam at 6 to 24 months if asymptomatic or prompt exam for new symptoms suggestive of CNV[A:III]	Monitoring of monocular near vision (reading/ Amsler grid) [A:III] Fundus photography as appropriate Fluorescein angiography if there is evidence of edema or other signs and symptoms of CNV

AMD = Age-Related Macular Degeneration; AREDS = Age-Related Eye Disease Study; CNV = choroidal neovascularization

TABLE 4B TREATMENT RECOMMENDATIONS AND FOLLOW-UP FOR NEOVASCULAR AMD

Recommended Treatment	Diagnoses Eligible for Treatment	Follow-up Recommendations
Ranibizumab intravitreal injection 0.5 mg as recommende in ranibizumab literature92 [A:I] Bevacizumab intravitreal injection as described in published reports94-98 [A:III] The ophthalmologis t should provide appropriate informed consent with respect to the off-label status.101 [A:III]	Subfoveal CNV Subfoveal CNV	Patients should be instructed to report promptly symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or increased number of floaters92 [A:III] Return exam approximately 4 weeks after treatment; subsequent follow-up depends on the clinical findings and judgment of the treating ophthalmologist[A:III] Monitoring of monocular near vision (reading/Amsler grid)[A:III] Patients should be instructed to report promptly symptoms suggestive of endophthalmitis, including eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, increased sensitivity to light, or increased number of floaters[A:III] Return exam approximately 4 to 8 weeks after treatment; subsequent follow-up depends on the clinical findings and judgment of the treating ophthalmologist [A:III] Monitoring of monocular near vision (reading/Amsler grid)[A:III]

AMD = Age-Related Macular Degeneration; AREDS = Age-Related Eye Disease Study; CNV = choroidal neovascularization; MPS = Macular Photocoagulation Study; PDT = photodynamic therapy; TAP = Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; VIP = Verteporfin in Photodynamic Therapy

Intravitreal Pharmacotherapy

Anti-angiogenic Therapies

Anti-angiogenic therapies for trans-scleral, intravitreal application have been introduced in AMD treatment and are currently used for all subgroups of CNV.

The first drug approved was Pegaptanib (Macugen*)-a 28-base ribonucleotid aptamer designed to bind and block specifically the activity of the extracellular VEGF 165 amino acid isoform-thus the main responsible VEGF for ocular neovascularization.

Ranibizumab (Lucentis*) was designed for ophthalmic use for better retinal penetration with a molecular size of 48 kD. It is a humanized monoclonal VEGF antibody fragment (rhu-fab V2) that binds all isoforms of VEGF. In several different multicenter clinical trials, it has been demonstratedthat 20-25 percent of patients treated monthly did gain vision, and 90 percent remained stable. Its effectiveness was demonstrated as a sole therapy, and in combination with PDT. When compared with PDT, Ranibizumab was superior (Marina-, Anchor-, Focus-, Pier- and Excite-Study).63

The basic substance, however, is Bevacicumab (Avastin*), a recombinant, humanized, full-lengh anti-VEGF monoclonal antibody with a molecular size of 150 kD. It binds all forms of VEGF-A, and has been approved for cholorectal cancer in addition to cytostatic therapy. For ophthalmic use, the molecule was considered too large to sufficiently penetrate the retina. Therefore, it was primarily used intravenously for a small series of AMD patients, showing positive results.64 To avoid side effects like thromboembolic events and increased blood pressure, Rosenfeld and his group decided to apply Bevacicumab intraviteally and soon presented efficacy and tolerability of the drug.65 Because of the much lower costs, Bevacicumab is injected today worldwide in patients with AMD in a dosage between 1.25 to 2-5 mg. Early studies have shown no side effects, and visual improvements, retinal penetration, and a lack of toxicity were also confirmed in an experimental study.66 Besides the three anti-VEGF substances used

today, it should be mentioned that many other stimulators of angiogenesis do exist and will need further exploration.

Ranibizumab Injection

Endophthalmitis (cumulative ≤1.0% over 2 years in MARINA study; <1.0% over 1 year in ANCHOR study)

Retinal detachment (<0.1% of treated cases during the first year of treatment)142,143

Traumatic injury to the lens (0.1% of treated cases during the first year of treatment)142,143

In addition to those listed above, other adverse events reported more frequently in the group treated with ranibizumab injection compared with the control group were conjunctival hemorrhage, eye pain, vitreous floaters, increased intraocular pressure within 60 minutes of injection, and intraocular inflammation. During the first year of the ANCHOR and MARINA trials, myocardial infarction and stroke rates were higher in the 0.5 mg group than in the control group (2.9% and 1.3%, respectively); these differences were not statistically significant and were not evident at 2-year follow-up. 142,143

A clinical trial using rhuFab V2 (ranibizumab, LucentisTM, Genentech) fragment of a recombinant humanized monoclonal antibody directed toward VEGF has also started. In experimental models of CNV, ranibizumab injections prevented formation of clinically significant CNV and decreased leakage of already formed CNV with no significant side effects other than acute anterior chamber inflammation. For the first time in trials of AMD a drug has shown improvement in visual acuity. The off-label use of intravitreal Becacizunab (Avastin) is new becoming popular to treat all types of CNV and has shawn excellent results.

Cortisone and Cortisene

Triamcinolone in dosages of 4, 8 and 25 mg was used intravitreally, mainly as an adjunct to PDT to minimize inflammation, exudation, and VEGF production. It was reported to

reduce the needed number of PDT retreatments, and allows PDT treatment in eyes with a primarily unfavorable prognosis.67,68 Because of its side effects-namely, high eye pressure up to 40 percent and more rapid cataract development- it is considered outdated today. However, the anti-inflammatory effect of Cortison in AMD should not be underestimated. To avoid an increase in pressure and cataracts and the risk connected with intravitreal application like endophthalmitis, bleeding, and cataracts, Anecortave (Retaane*)-a cortisene-was developed for iuxtascleral application. While one study had demonstrated that its effect is similar to PDT for classic CNV,69 its effect is rather slow and most likely not sufficient for active disease. However, it is being tested in a current study for patients with CNV and second eye Drusen as a preventative drug rather than a curative one.

In addition to the adverse events listed above, other events reported more frequently in the group treated with pegaptanib sodium injection compared with the control group were eye pain, vitreous floaters, punctate keratitis, vitreous opacities, cataract, anterior chamber inflammation, visual disturbance, eye discharge, and corneal edema.137

Laser Photocoagulation

The Macular Photocoagulation Study Group showed that laser photocoagulation was effective in the treatment of well-defined extrafoveal or juxtafoveal choroidal neovascularization secondary to AMD. In patients with subfoveal choroidal neovascularization, however, laser photocoagulation was not beneficial in eyes that had largelesions and moderate-to-good initial visual acuity.

Macular Photocoagulation Study (MPS)

In Patients with well-defined extrafoveal CNVM after a follow-up of 5 years, 64% of eyes assigned to no treatment compared with 46% of eyes randomized to argon laser experienced severe visual loss (six or more lines of visual acuity loss using Bailey-Lovie visual acuity charts). The difference was statistically significant. Although the risk of severe visual loss was reduced in treated patients, a high

rate of persistent and recurrent CNVM was observed.

The recurrence rate observed in treated eyes at 12, 24, and 60 months were of 41%, 51%, and 54%, respectively. Patients with well-defined juxtafoveal CNV were treated with krypton red laser. At 3 years after randomization, 49% of laser-treated eyes experienced severe visual loss compared with 58% of untreated eyes.

Laser to drusen

There have been attempts for drusen reduction by laser to decrease the risk of geographic atrophy and CNVM. No significant difference in the development of CNVM was noted in the treated and untreated groups. To date, however, prophylactic laser photocoagulation in patients with high-risk ARMD remains an experimental treatment and should not be performed outside randomized clinical trials.

Feeder-Vessel Laser Photocoagulation

Feeder vessels are defined as vessels that are seen in the earliest phases of the indocyanine angiogram, and appear to originate from a definite spot in the choroid and branch into a CNV with distinct blood vessels. Feeder vessels are identified in only a small percentage of patients examined with subfoveal CNV, so the treatment can be used in only a small number of cases. The first series published on the use of indocyanine green-guided feedervessel photocoagulation to treat subfoveal CNV in patients with ARMD was published by Shiraga and colleagues. To date, there are not enough data to support the use of feedervessel photocoagulation as a routine treatment for patients with CNV and ARMD.

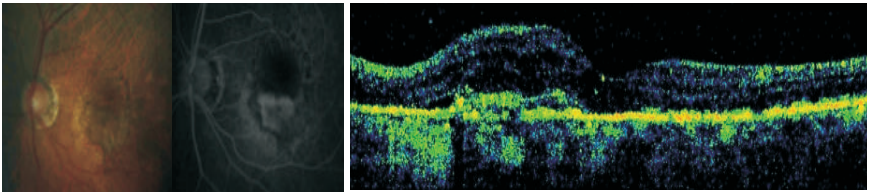
Photodynamic therapy

Photodynamic therapy (PDT) involves the intravenous infusion of a drug (photosensitizer) and the application of a continuous nonthermal laser light directed at the CNVM.

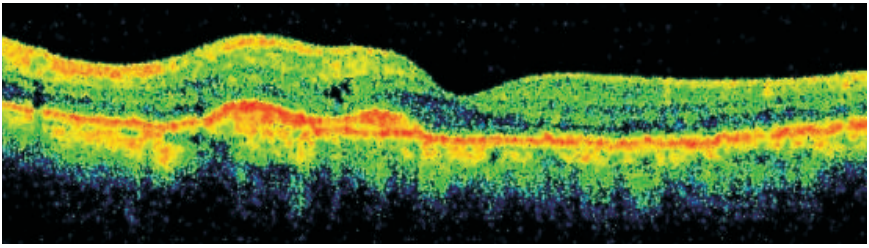
The wavelength of the laser light used corresponds to the absorption peak of the drug, but it is not strong enough to produce any thermal (photocoagulation) damage.

Mechanism of action: The drug gets concentrated in the immature endothelium of CNVM, and light-activation induces a photochemical reaction in the target area that causes immunologic and cellular damage, including endothelial damage of new vessels. Endothelial damage and the resulting platelet adhesion, degranulation, and subsequent thrombosis and occlusion of the vasculature might be the predominant mechanism by which lightactivated drugs work. Since the photosensitizer accumulates predominantly in the CNV, a fairly selective damage to the CNV is expected.

To date, only PDT with the photosensitizer Verteporfin has been proven to decrease the risk of visual loss in patients with neovascular ARMD. Verteporfin (a benzoporphyrin derivative monoacid, BPD-MA; Visudyne, Novartis AG) is a light-activated drug. The application of photodynamic therapy with verteporfin involves two main steps: intravenous infusion of the drug and activation of the drug by light at a specific wavelength (689 nm) with a low-power, nonthermal laser. The therapy includes retreatment as often as every 3 months if leakage from choroidal neovascularization is detected on follow-up fluorescein angiograms. (Fig 17)



Pre PDT and Injection Lucentis.



Post PDT and Injection Lucentis.
Fig 17

Procedure

The intravenous infusion of verteporfin is given throughout a 10- minute period. Then, 15 minutes after the start of the infusion the laser light is applied for 83 seconds. Guidelines for the treatment of patients with ARMD and subfoveal CNV with PDT have been recently published. In these guidelines, treatment with PDT is recommended for patients with predominantly classic CNV and for those with occult and no classic CNV with recent disease progression (e.g., presence of blood associated with the CNV, growth of the CNV, or deterioration of the visual acuity within the past 12 weeks) and a lesion size of four or fewer disk areas or a lesion size greater than four disk areas associated with low levels of vision (i.e., approximately in the level of 20/50 Snellen vision). In these guidelines, it is also recommended to treat juxtafoveal lesions that are so close to the fovea that conventional laser photocoagulation almost certainly would extend under the center of the FAZ, and extrafoveal lesions that are contiguous to the optic nerve provided that treatment spots do not overlie the optic nerve. The recommendations included a 3-month interval follow-up for at least 2 years from the time of initial treatment in all patients, except in those in whom no treatment was recommended for two consecutive visits (6-month period). Patients should receive retreatments as often as every 3 months if there is any fluorescein leakage from CNV noted. Although no data are currently available on the treatment of pregnant or nursing women and patients with moderate or severe liver disease, the guidelines suggest to carefully consider PDT in these patients. Photodynamic therapy is contraindicated in patients with porphyria. Patients must be warned, however, that they will be sensitive to direct sunlight or bright indoor lights for 24 to 48 hours after drug infusion and that they should avoid direct sunlight for about 2 to 5 days after treatment.

New PDT drug: SnET2 a new PDT drug is undergoing phase 3 trial of neovascularization of AMD. Initial results have not proven the efficacy convincingly. New study will likely be necessary to prove efficacy in a convincing manner.

TAP (Treatment of AMD with Photodynamic therapy)

- Two 24-month randomized, double-masked, placebo-controlled Phase III trials known as the TAP (Treatment of AMD with Photodynamic therapy) Investigation were published in the October 1999 issue of Archives of Ophthalmology.
- Photodynamic therapy with verteporfin achieved short-term cessation of fluorescein leakage from CNV without loss of vision or growth of classic CNV in some patients with age-related macular degeneration. Except for nonperfusion of neurosensory retinal vessels at a light dose of 150 J/cm, no other adverse events were of concern.
- The primary finding of these trials showed that in 243 patients with predominantly classic CNV, vision remained stable or improved in 67% of patients treated with Visudyne therapy compared to 39% of patients on placebo (p is less than 0.001).

TAP Study Group. Photodynamic Therapy of subfoveal choroidal neovascularisation in age-related macular degeneration with verteporfin. One year results of 2 randomized clinical trials. TAP report 1. Arch. Ophathmol., 1999;117:1329-45.

Transpupillary Thermotherapy

Transpupillary thermotherapy (TTT) was first described by Oosterhuis and colleagues and used in the management of choroidal melanoma. For this treatment a modified infrared diode laser (810 nm) attached to the slitlamp is used. Reichel and associates published the first report on the use of this form of therapy to treat patients with subfoveal occult CNV.

In a retrospective, non-randomized study of 28 eyes of 28 patients with subfoveal CNVM (classic, occult or mixed). Fifteen patients (53.57%) maintained their pre-treatment vision, 2 (7.14%) patients showed improvement of more than 2 lines and 11 (39.28%) patients showed deterioration of vision by >2 lines. Angiographic and clinical regression of CNVM was noted in 19 patients (67.8%). Recent interim results presented from Transpupillary.

Thermotherapy Trial for neovascularization in AMD did not meet the primary end points and resulted in a 5% vision loss at 1 month.

Steroids: Many corticosteroids, including triamcinolone acetonide (TAAC) and anecortave acetate, are potent antiangiogenic agents. The mechanism of action of steroids may be due to their effect on vascular endothelial cell turnover, inhibition of the inflammatory response, or another means.

In a study by Danis et al using TAAC, visual acuity was statistically significantly better in the treated group than in the control group at 6 months' follow-up. No patients in the control group had increased intraocular pressure, whereas 25% in the treatment group developed this complication. In the control group 22% of all phakic patients developed increased lens opacities compared with 57% in the treated group. Intravitreal injections of TAAC have been used also in the management of subfoveal recurrences following laser photocoagulation of extrafoveal CNV.

Use of combined intravitreal injection of TAAC and PDT with verteporfin. Although there seemed to be a possible benefit of this combined therapy, the number of patients treated was small and there was no control group. Masked, placebo-controlled randomized clinical trials have been designed and are currently underway to evaluate the effect of anecortave acetate, administered as subtenon juxtascleral injection once every 6 months. Preliminary reports at the end of 12 months failed to meet the primary end point. We may have to wait till the final results for deciding about the efficacy of this drug.

Brachytherapy

Brachytherapy techniques can deliver a relatively high dose to the involved macula with less irradiation of most normal ocular structures outside the targeted zone.23,25-31 In part because of dose gradient effects, ophthalmic plaque radiotherapy also allows for more focused irradiation to the affected choroid. The use of brachytherapy also avoids an anterior segment entry dose, a mobile target volume, and irradiation of the fellow eye, sinuses, and/or brain.26 Published reports on brachytherapy for exudative macular degeneration include our use of palladium-103 (103Pd), Jaakola and Freire's strontium-90 (90Sr) applicators, and Berta's ruthenium-106 (106Ru).23,26,29-31 Immonen et al suggested that 90Sr treated eyes

lost less vision than controls at the 2001 meeting of the Association for Research in Vision and Ophthalmology.32 In all the aforementioned studies, no complications that might preclude this approach to treatment of exudative macular irradiation have been noted.

Radiation typically induces acute vasculitis and oedema followed by slowly progressive vascular closure (which may take years to develop).33-37 These effects of radiation are both dose and dose rate dependent.38

Irradiation of a macula containing classic or occult subretinal neovascularisation can directly affect angiogenesis by destroying neovascular endothelial cells and cytokine producing macrophages, or alter the regulatory genes which produce endothelial growth regulating cytokines.

Widely employed to prevent scar formation, radiation has been used to inhibit the cutaneous keloid and more recently proved to prevent coronary artery stenosis.40 Similarly, Hart et al have suggested that radiotherapy inhibited disciform scar formation associated with end stage exudative macular degeneration.41

Chakravarthy and Bergink's studies have suggested that a higher dose may be required to control exudative macular degeneration. Clearly, brachytherapy offers a method to increase the dose to the affected macula with relative sparing of normal ocular, sinus, and intracranial structures.26,30,52-58 Implant radiation therapy is an investigational treatment that should be subjected to a prospective randomised efficacy trial.

- The value of routine screening, given the lack of effective treatment, is unproven. There may be a case for self assessment, using an Amsler Grid, in those patients with high risk of neovascular disease which includes those with large soft drusen and pigment hyperplasia and those with established exudative AMD in one eye.
- Prophylactic Laser studies (Bird, Guymer)

- Mild low risk disease (ARM) requires no special management and, coming on slowly, can be managed in the community. Optometrists would seem to be well placed to carry out routine examinations and offer advice about the value of magnification and lighting. Optometrists can reassure patients with minimal symptoms or signs of ARM and should not refer further. Referral from the primary sector usually occurs when visual impairment begins to interfere with normal lifestyle. Referral is indicated when:
- General practitioners and optometrists need to be aware of the urgent nature of referrals for patients with recent onset of distortion and visual loss (less than a month) and who still have reasonably good vision (6/12 or better).
- Such patients may still have treatable disease and should be referred urgently to either the ophthalmic casualty department or to the outpatient clinic following discussion with the local ophthalmologist. This is particularly true for the second eye when the other eye is already involved.
- In the elderly population with AMD concurrent ophthalmic disease, such as cataract and glaucoma, may also frequently occur and needs to be identified and treated appropriately.
- Good control of hypertension may favourably influence the surgical treatment of neovascular membranes.
- Diagnosis and assessment of macular disease including angiography and exclusion of other treatable causes of visual failure.
- Treatment by laser photocoagulation or otherwise as appropriate.
- Rehabilitation including:

    1) provision of suitable optical aids in the primary or secondary sector and training in their use.

    2) Completion when appropriate of the form BD8 (BP1 in

Scotland, A 655 in Northern Ireland) and referral to Social Services (Appendix 2).

3) Counselling and rehabilitation within the hospital and statutory or voluntary services in the community.

Surgical Treatments

Macular Translocation:

In 1983, Lindsey and colleagues introduced the concept of retinal relocation. However, it gained popularity in the management of patients with subfoveal CNV only after 1993, when the first results were presented. The aim of the surgery is to relocate the central neurosensory retina (fovea) away from the CNV, to an area of healthier RPE, Bruch's membrane, and choroid. This is still an experimental method of treatment as it lacks randomized prospective clinical trials to support this form of treatment.

Submacular Surgery:

In 1992, Thomas and colleagues, Berger and Kaplan, and Lambert and associates presented their results after surgical excision of CNV. The technique for CNV removal was as follows: After complete pars plana vitrectomy CNVM is removed from subretinal space by making retinotomy temporal to fovea (usually) and inducing localized retinal detachment. Fluid-air exchange is performed at the end of surgery and gas tamponade is given.

Recently, the first results of the Submacular Surgery Trial, a randomized clinical trial comparing laser photocoagulation to surgical removal of subfoveal CNV have been published. All patients enrolled in this trial had a subfoveal recurrent CNV following prior laser photocoagulation for extrafoveal or juxtafoveal CNV. No statistically significant differences in visual acuity were observed between patients randomized to laser photocoagulation and surgical excision of CNV in this pilot trial. Similarly, health-related quality of life was not statistically significant different between the two treated groups.

A new trial to evaluate the benefit of CNV removal in cases of

newly developed subfoveal CNV is currently underway (Submacular Surgery Trial, Group N). Patients are being randomized to either surgical excision of the CNV or observation. In this study, patients with lesions larger than those eligible for laser photocoagulation following MPS guidelines or with minimally classic lesions in which laser photocoagulation or PDT have not shown any treatment benefit are eligible for the trial. Patients with predominantly classic subfoveal lesions are being enrolled also if after detailed explanation of the benefits of PDT they still prefer to participate in the trial.

Iris/Retinal Pigment Epithelium Transplantation

Several reports on RPE transplantation in patients with neovascular ARMD have been published. Isolated cells and RPE-cell sheets have been used. Fetal or mature RPE have been transplanted. Only rarely have good levels of vision been achieved following RPE transplantation.

Due to possible difficulties in obtaining RPE cells for transplantation and complications related to this procedure, researchers have investigated the possibility of substituting RPE cells for iris pigment epithelial (IPE) cells. Iris pigment epithelial and RPE cells have a common embryonic origin, and some of the RPE functions have been demonstrated in IPE. Few series on IPE transplantation have been reported in the literature. In these series, visual acuity after transplantation remained low, in the level of 20/100.

Surgical Removal

Surgical removal of CNV was successfully performed in young patients and eyes with CNV related to histoplasmosis, but failed to show a beneficial effect on vision in elderly patients with AMD.70,71 The surgery includes pars plana vitrectomy, a small retinotomy close to the neovascular membrane, careful mobilization of the membrane, and gentle removal with subretinal forceps. The retina is reattached byfluid-gas exchange, and the retinotomy is sealed with laser application. In a meta-analysis evaluating 26 studies and a total of 647 cases of subretinal membrane excision in AMD patients, it was

shown that visual improvement was achieved in 33 percent and deterioration observed in 27 percent of the cases.72 Furthermore, progression of atrophy was demonstrated after surgery because of the simultaneous removal of the RPE on and around the CNV during surgery, leading to subsequent PR and choriocapillaris dysfunction.73,74 In two prospective studies comparing subretinal surgery with laser treatment and the natural course, there was only an advantage for surgery found in AMD patients with large pathologies including hemorrhages.75,76

Retinal Rotation

Retinal rotation techniques have given us proof of principle that extrafoveal RPE can maintain foveal function. A 360° full rotation was performed for the first time by Machemer and Steinhorst in 1993.77 Although very good successes have been demonstrated by few groups,78,79 the surgery has not been widely adopted for several major reasons: the length and complexity of the surgery, an initial association with a high rate of retinal detachment and PVR, lack of evidence from clinical comparative trials, and finally uncertain management of postoperative diplopia.80

Transplantation

Transplantation of the autologous RPE seems to be a logical approach to restore normal retinal function81 after homologous transplants have shown an immune reaction82 It is performed in two different ways-the transplantation of a freshly harvested RPE suspension immediately after membrane removal83,84 and transplantation of a full thickness RPE-choroidal patch excised from the midperiphery of the retina and translocated subfoveally.85,86 While the suspension technique is a relatively easy technique with complications similar to membrane removal alone, and a one-step procedure, best results were observed in AMD patients with small lesions. The flap technique makes silicone tamponade and removal necessary, and PVR rates of up to 40 percent were reported.87 However, the transplantation of a homogenous layer of polarized cells on their basal lamina is intriguing and seems to be more suitable for eyes with very large lesions that are the only candidates for

surgery today. Still, this surgery is considered experimental, and although it was demonstrated that better reading vision results can be obtained with RPE suspensions than with membrane removal alone,85 visual improvements are limited so far-although visual improvement in some cases can be remarkable. With further improvement of technique, and the combination of recent knowledge in molecular biology and genetic modifications of cells, cell-derived therapies might soon become a reasonable treatment option for eyes with AMD where other therapies have failed. NN-AMD

Prophylactic Treatments

Vitamin and Mineral Supplements

A randomized clinical trial, part of the Age-Related Eye Disease Study (AREDS), was conducted in order to try to evaluate the effect of antioxidants and zinc in patients with ARMD. At 5 years, a statistically significant reduction in the risk of progression to advanced ARMD and a 15- letter decrease in visual acuity score was found in those patients randomized to antioxidants plus zinc in categories three and four. No statistically significant adverse events were found with any of the formulations. However, possible complications of the study medications have been identified. Those with extensive intermediate size drusen (63 µ -124 µ), at least 1 large druse (>125 µ), noncentral geographic atrophy in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye, and without contraindications such as smoking, should considered for supplementation of antioxidants plus zinc.

Results from AREDS continue to be gathered and studied. Moreover, a new AREDS is being proposed. A few of the findings from the current AREDS include the following:

- Patients who ate fish more than once per week had a 40% reduction in neovascularization compared with patients who ate fish less than once per month;
- Zeaxanthin and lutein reduced the risk of neovascularization in AMD; and

- Patients taking the zinc regimen appeared to have a lower mortality rate than those patients not taking zinc.

Carotenoids: Lutein and Zeaxanthin:

Lutein and Zeaxanthin are the main constituents of the luteal pigment. This yellow pigment, present at the macula, absorbs blue light. Whereas zeaxanthin is the main pigment present at the fovea, lutein is more abundant in the rest of the macula. Lutein and zeaxanthin are localized mainly in Henle's fiber layer. It is possible that lutein and zeaxanthin may protect the retina from the damage caused by blue light exposure and subsequently decrease the risk for ARMD. In this respect, a case-control study in which plasma levels of lutein and zeaxanthin in patients with ARMD were compared to those in an age-matched control group showed an inverse relationship between plasma levels of these two carotenoids and the risk for ARMD.

However, to date, no well controlled intervention trials with lutein and zeaxanthin have been performed. Thus, it is not clear to what degree these pigments may decrease the risk of neovascular complications in ARMD.

Rehabilitation ***

- Provision of low vision aids.
- Visual handicap registration.
- Training and coping strategies.
- Explaining the management of AMD requires patience and sympathy. Patients with AMD greatly benefit from continuing support and information about their condition and all patients losing vision need hope and encouragement.
- Statutory and voluntary support services in the community.

The BD8 Form (1948 National Assistance Act) **

- Definitions
- Blindness- 'cannot do any work for which eyesight is essential.'

- Partial Sight- 'substantially and permanently handicapped by defective vision.'
- (The WHO definition of blindness is vision less than 3/60 in the better eye with best available spectacle correction)

Future Directions

Future directions for AMD treatment will concentrate on early detection and prevention. As more drugs are invented, available combination therapies will become more tailored to the stage and severity of the disease. To provide long-term effects, long-acting delivery systems for drug combinations need to be developed. In addition, combinations with surgical therapies, laser, or PDT might be reasonable to decrease dosage and treatment intervals. For non-responders or advanced cases of AMD, cell-derived therapies will be necessary-like retinal transplantation or gene therapies for better restoration of a more normal foveal condition in an aging patient to restore vision.

Fetal Cell Transplants

- Fetal RPE cells are transplanted into diseased RPE
- New cells can divide and proliferate

Tissue is harvested from spontaneous and elective second trimester abortions.

Prevention & Early Detection

Patients with early AMD and/or a family history of AMD should be encouraged to have regular dilated eye exams for the early detection of the intermediate stage of AMD.[A:III] Treatment with antioxidants and minerals as described in the AREDS is recommended for patients who have progressed to intermediate or advanced AMD in one eye.

Patients with intermediate AMD who are at increased risk of visual loss or of progression to advanced AMD should be educated about methods of detecting new symptoms of CNV. They should also be educated about the need for prompt notification to an ophthalmologist who can confirm if the new symptoms are from CNV and who can begin treatment if indicated. [A:III]

Follow-up examinations of patients at increased risk of visual loss or of progression to advanced AMD may facilitate the following: (1) they may permit early detection of asymptomatic but treatable neovascular lesions, which might improve the visual outcome; (2) they provide an opportunity to update the patient's education on preventive regimens; and (3) they can reinforce the need for self-monitoring and the need for prompt evaluation for new symptoms. For patients with no risk factors for AMD, a comprehensive medical eye evaluation performed every 2 to 4 years for patients between ages 40 and 54 years, every 1 to 3 years for patients between ages 55 and 64 years, and every 1 to 2 years for patients 65 and older seems to offer a reasonable approach for detection.113 Patients who check monocular near vision (reading/Amsler grid) may be more likely to become aware of subtle visual symptoms due to CNV, increasing the likelihood of detecting CNV at a treatable stage. Patients with neovascular AMD report a substantial decline in quality of life and increased need for assistance with activities of daily living, which progressed as visual acuity worsened.114 Early detection and treatment of AMD to arrest the deterioration in vision would preserve patients' quality of life and independence.

A clinical trial is under way to evaluate the efficacy of lutein and fish oil in the prevention of progression of advanced AMD. The Age-Related Eye Disease Study 2 has enrolled 4000 patients with non-neovascular AMD consisting of large drusen in both eyes or advanced AMD in one eye and large drusen in the fellow eye. The goal of this trial is to evaluate the effect of dietary xanthophylls (lutein and zeaxanthin) and/or omega-3 long chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) on progression to advanced AMD. FOLLOW-UP

A history and examination are the recommended elements of the follow-up visits. Recommended follow-up intervals are listed in Tables 4A and 4B.

History

The follow-up history should take into account the following:

- Symptoms, including decreased vision and metamorphopsia115 [A:II]
- Changes in medications and nutritional supplements[B:III]
- Changes in medical and ocular history7,116,117 [B:III]
- Changes in social history (smoking)24-28 [B:II]

Examination

The examination on the follow-up visit should include the following:

- Visual acuity[A:III]
- Stereoscopic biomicroscopic examination of the fundus[A:III]

Diagnostic tests used in the follow-up examination are identical to those listed under Diagnosis, and the treatment plan is identical to the one described under Treatment.

Follow-up after Treatment for Neovascular AMD

In addition to the above recommendations, patients who have been treated with ranibizumab, bevacizumab, or pegaptanib sodium injection; verteporfin PDT; or thermal laser photocoagulation

surgery should be examined at regular intervals by means of biomicroscopy of the fundus.[A:III] Optical coherence tomography,123 [A:III] fluorescein angiography,109,111,112 [A:I] and fundus photography[A:III] may be helpful to detect signs of exudation and should be used when clinically indicated.

Patients treated with ranibizumab injection should have follow-up examinations approximately 4 weeks following the treatment.145 [A:III] Subsequent follow-up is dependent on the clinical findings and judgment of the treating ophthalmologist. Patients treated with bevacizumab injection should have follow-up examinations approximately 4 to 8 weeks following the treatment.[A:III] Patients treated with pegaptanib sodium injection should have follow-up examinations approximately 6 weeks following the treatment.[A:III]

Subsequent examinations, optical coherence tomography, and fluorescein angiography should be performed as indicated depending on the clinical findings and the judgment of the treating ophthalmologist.[A:III] Treated patients should be instructed to report symptoms of endophthalmitis and should be re-examined promptly.[A:III]

Follow-up examinations and fluorescein angiograms have been recommended at least every 3 months for up to 2 years following verteporfin PDT treatment for subfoveal CNV.138,139

Fellow Eye

For patients with unilateral disease, the fellow eye without CNV remains at high risk of developing advanced AMD.146 The risk can be substantially lowered over a 5-year period by taking the AREDS supplements.1 Patients should be instructed to monitor their vision and to return to the ophthalmologist periodically, even in the absence of symptoms, but promptly after the onset of any new or significant visual symptoms.[A:III] Patients at exceptionally high risk (e.g., the presence of advanced AMD in one eye and large drusen with RPE changes in the fellow eye) may be examined more frequently in an effort to detect asymptomatic CNV at a treatable stage.19

Provider

Ancillary clinical personnel should be aware that patients with the onset of new symptoms suggestive of AMD (e.g., new visual loss, metamorphopsia, or scotoma) should be examined promptly.[A:III] The ophthalmologist will perform most of the examination and all treatment, and certain aspects of data collection may be conducted by other trained individuals under the ophthalmologist's supervision.

Physician Quality Reporting Initiative Program

The Physician Quality Reporting Initiative (PQRI) program, initially launched by the Centers for Medicare and Medicaid Services in July 2007, encourages quality improvement through the use of clinical performance measures on a variety of clinical conditions. A measure in the 2008 PQRI program for AMD is dilated macular examination, including documentation of the presence or absence of macular thickening or hemorrhage and the level of AMD severity. A measure proposed for the 2009 PQRI program is counseling of patients with AMD about the risks and benefits of the AREDS supplements.147

Counseling/referral

All patients with AMD should be educated about the prognosis of the disease and the potential value of treatment as appropriate for their ocular and functional status.[A:III] Patients can be told that although central visual loss is common, total visual loss is rare. Patients with AMD can be reassured that there is no harm in using their eyes, and they may be told that the effect of light and other factors on vision remains uncertain.

The informed consent process should include discussion of the risks and benefits of treatment and treatment alternatives. The off-label status of bevacizumab for neovascular AMD should be included in the discussion; information and a consent form are available from the Ophthalmic Mutual Insurance Company.101

Vision rehabilitation restores functional ability148 [A:I] and patients with reduced visual function should be referred for vision rehabilitation and social services.149 [A:III] Patients with severe

visual loss related to AMD who are referred for vision rehabilitation services often have unrealistic expectations. Special optical or electronic magnifying lenses, bright lights, and other reading aids may help patients to read more effectively, but not as well as they did before the onset of AMD. More information on vision rehabilitation, including materials for patients, is available at http://www.aao.org/smartsight.

Loss of visual acuity increases the risk of frequent falls.114,150 Depression and visual hallucinations (Charles Bonnet syndrome) are frequent accompaniments of severe central vision loss. Patients with Charles Bonnet syndrome and their family members should be informed that visual symptoms are not unusual and not a sign of psychosis or mental deterioration. The ophthalmologist may inquire about symptoms of clinical depression and, when appropriate, suggest that the patient seek professional advice, as depression may exacerbate the effects of AMD.151

Tips for AMD patients

If you've been diagnosed with AMD, making a few simple lifestyle changes could have a positive impact on the health of your retina.

- Monitor your vision daily with an Amsler grid. By checking your vision regularly, changes that may require treatment can be detected early.
- Take a multi-vitamin with zinc. (check with your eye physician for a recommendation). Antioxidants, along with zinc and lutein are essential nutrients, all found in the retina. It is believed that people with AMD may be deficient in these nutrients.
- Incorporate dark leafy green vegetables into your diet. These include spinach, collard greens, kale and turnip greens.
- Always protect your eyes with sunglasses that have UV protection. Ultraviolet rays are believed to cause damage to the pigment cells in the retina.

- Quit smoking. Smoking impairs the body's circulation, decreasing the efficiency of the retinal blood vessels.
- Exercise regularly. Cardiovascular exercise improves the body's overall health and increases the efficiency of the circulatory system.
- These are a few tips to make reading easier:
- Use a halogen light. These have less glare and disperse the light better than standard light bulbs.
- Shine the light directly on your reading material. This improves the contrast and makes the print easier to see.
- Use a hand-held magnifier. A drugstore magnifier can increase the print size dramatically.
- Try large-print or audio books. Most libraries and bookstores have special sections reserved for these books.

Consult a low vision specialist. These professionals are specially trained to help visually impaired patients improve their quality of life. After a personalized consultation, they can recommend appropriate magnifiers, reading aids, practical tips, and many resources.

o Use a bright reading light

o Wear your reading glasses if appropriate

o Hold the chart approximately 14-16 inches from your eye

o Cover one eye

o Look at center dot

o Note irregularities (wavy, size, gray, fuzzy)

o Repeat the test with your other eye

o Contact ophthalmologist if you see any irregularities or notice any changes

Nutrition and Macular Degeneration

Many researchers and eye care practitioners believe that certain nutrients - zinc, lutein, zeaxanthin and vitamins A, C and E - help lower the risk for AMD or slow down the progression of dry macular degeneration. Benefits of high levels of antioxidants and zinc for halting or slowing development of macular degeneration have been widely reported based on results released in 2001 from the Age-Related Eye Disease Study (AREDS) conducted by the National Eye Institute.

Phase two of the AREDS study began in late 2005 to evaluate whether similar protective effects against AMD might be associated with other nutrients such as omega-3 fatty acids or "good fats," and lutein and zeaxanthin found in green, leafy vegetables.

Archives of Ophthalmology reported findings in August 2001 that consumption of omega-3 fatty acids, which are particularly prevalent in cold-water fish, also had a protective effect against advanced macular degeneration. Meanwhile, consumption of omega-6 fatty acids, prevalent in vegetable oils, was associated with an increased risk of developing AMD.

Follow up

Dry AMD

- 3-6 months
- Home Amsler's chart
- Fundus photograph repeated at each visit
- FFA / OCT - if CNVM suspected

Wet AMD

- Initial 1-2 monthly follow up
- OCT at each visit
- FFA if required
- Repeat injection if fresh activity seen

o Gradual increase in duration of follow up

Conclusion

Increasing knowledge about the pathogenesis of this disease has led to new therapeutic strategies. As on today the treatment modalities have developed to arrest the disease process to some extent. Future treatments should likely concentrate in preventing the development of CNV in patients at risk, rather than in treating it once established.

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