abstract

Age-related macular degeneration (ARMD) is a progressive disease affecting the central vision of patients older than 55 years. ARMD is classified as atrophic (dry) or exudative (wet) forms based on clinical characteristics. Management of atrophic ARMD includes vitamin supplementation with high-dose antioxidants in appropriate patients. Patients who develop exudative ARMD may be eligible for treatment depending on flourescein angiogram characteristics. Options available to close a choroidal neovascular membrane include thermal laser photocoagulation or photodynamic therapy. Other treatment modalities are currently under investigation that may lead to more therapeutic options in the future.

Key words: *macular degeneration, vitamins, laser, photodynamic therapy, angiogenesis*

Latest Treatment Options in Age-Related Macular Degeneration

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Age-related macular degeneration (ARMD) is the leading cause of central vision loss in North America in people older than 55 years.[1] While it is still considered an incurable disease, various treatment options are emerging to help control this otherwise progressive ailment. As Figure 1 illustrates, ARMD is classified as either atrophic (dry) or exudative (wet or neovascular). The purpose of this article is to provide an update of current treatment modalities and those still under investigation for these two forms of ARMD (Table 1).

Mechanism of Disease

Atrophic ARMD is characterized by atrophy of the retinal pigment epithelium and accumulation of drusen (Figure 1). As a result of the progressive dysfunction of overlying photoreceptors, the vision loss in atrophic ARMD tends to be gradual. Drusen that are larger, more extensive, and confluent tend to present a higher risk of progressing to exudative ARMD. In addition to drusen characteristics, two other major risk factors are age and cigarette smoking. Other associated risk factors include cardiovascular disease, obesity, white race, sunlight exposure, and positive family history.[2] Addressing modifiable risk factors (e.g., smoking cessation) remains an important step in current disease management.

Exudative ARMD is characterized by the growth of choroidal vessels through breaks in bruch's membrane into the subretinal and subretinal pigment epithelial space (Figure 1). Fluid, lipid, and/or hemorrhage from these choroidal neovascular membranes (CNVM) result in dysfunction of overlying photoreceptor cells and vision loss that tends to be more acute. Recently, another form of exudative ARMD has been described where the neovascularization begins in the retina and can proliferate into the deeper subretinal tissues forming a CNVM.[3] Understanding the mechanisms by which CNVM formation occurs and the important role ocular neovascular growth factors, such as vascular endothelial growth factor (VEGF), play are current areas of research.[4]

Management of Dry ARMD

The Age-Related Eye Disease Study (AREDS) found that vitamin supplementation was effective in slowing the progression of ARMD by up to 25% in certain patients.[5] They concluded that nonsmoking patients over 55 with extensive intermediate drusen, one large drusen, noncentral geographic atrophy, or advanced unilateral ARMD benefited from high-dose antioxidant vitamin and mineral supplementation. The specific formulation studied was: beta-carotene 15mg, vitamin C 500mg, vitamin E 400mg, and zinc 80mg. There are currently two commercially available preparations that match the AREDS formulations in Canada: Vitalux® AREDS and Ocuvite® PreserVision tablets.

Because the above products are contraindicated in smokers and recent ex-smokers, beta-carotene–free formulations are also available. Interestingly, a recent meta-analysis has suggested that high dosages of vitamin E supplementation may increase all-cause mortality.[6] Due to the confusion over how that may impact AREDS formulation users, the AREDS study group

Figure 1:

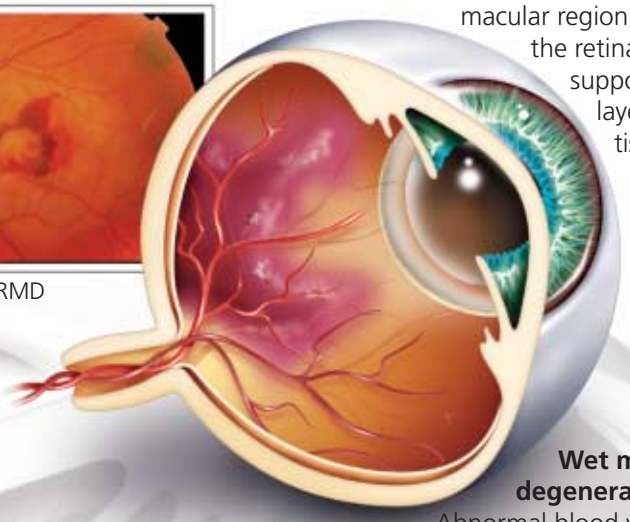
Age-Related Macular Degeneration

Atrophic ARMD

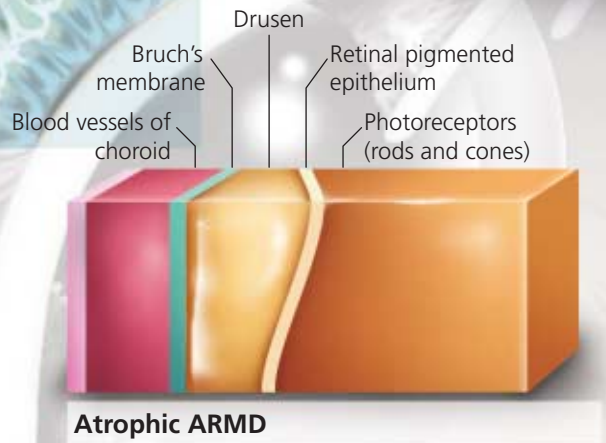
Exudative ARMD

Age-related macular degeneration (ARMD) is a progressive disease affecting the central vision of older patients. ARMD is classified into atrophic (dry) and exudative (wet) forms based on clinical characteristics.

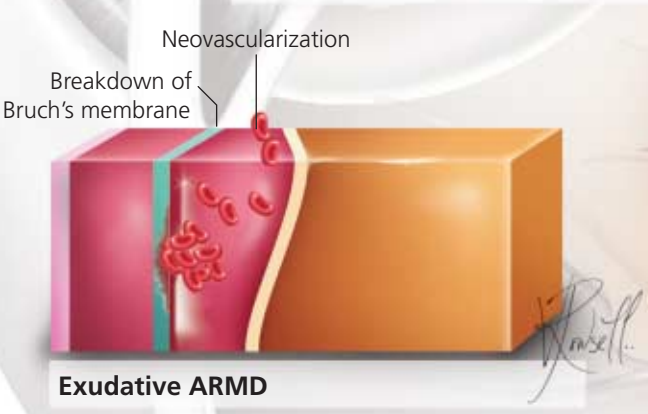
Dry macular degeneration Cells of the macula slowly begin to break down. Yellow deposits, referred to as 'drusen' form in the macular region between the retina and its supporting layer of tissue.



Wet macular degeneration Abnormal blood vessels grow behind the macula and may leak or rupture, resulting in scarring of the macula. There is a breakdown in Bruch's membrane, usually occurring in close proximity to drusen deposits and neovascularization.



Atrophic ARMD



Exudative ARMD

Original colour photographs courtesy of Cynthia VandenHoven, Ophthalmic Imaging Specialist, Hospital for Sick Children, Toronto, ON.

Table 1: Treatment Options for ARMD

Atrophic ARMD
High-dose antioxidant vitamin supplementation (as per AREDS guidelines)
Smoking cessation
Amsler grid home monitoring
Low vision assessment
Exudative ARMD
As listed above, plus the following:
Thermal laser photocoagulation (if CNVM extrafoveal or juxtafoveal)
Photodynamic therapy (in select subfoveal CNVMs)

published a letter stating that the dose of 400IU used in the AREDS study and other studies with similar doses was not associated with an increase in all-cause mortality in their study population. They suggest the conclusions of the meta-analysis may be more applicable to those patients taking higher doses of vitamin E (i.e., doses above 500IU).

Observational data from the AREDS group also suggests that increased intake of lutein and zeaxanthin (both are major human retinal carotenoids concentrated in the macula) and omega-3 long-chain polyunsaturated fatty acids were associated with a decreased risk of developing neovascular ARMD.[7] A randomized clinical trial (AREDS II) will address these observations in the near future. Furthermore, another report suggests that a higher total fat intake (particularly vegetable fat more than animal fat and processed baked goods) is associated with an increased risk towards ARMD progression, while nuts and fish were found to be somewhat protective.[8]

Atrophic ARMD Therapies under Investigation

A low intensity macular diode laser treatment is currently under investigation for eyes with high-risk drusen to help reduce the incidence of severe vision loss. The Complications of AMD Prevention Trial (CAPT) is comparing this laser treatment to observation and is expected to yield results in 2006. Rheophoresis is another therapy currently being investigated for atrophic ARMD. This technique filters out certain protein and fat macromolecules thought to have negative effects on the microvascular circulation, which lead to subsequent atrophic ARMD.

Management of Exudative ARMD

Although only about 10% of patients have the exudative form, it accounts for 90% of visual morbidity among the ARMD population. As such, much of the therapeutic research is geared towards controlling or eradicating CNVMs. CNVMs are characterized by their size, location with respect to the fovea (centre of vision), and composition. These characteristics are evaluated critically with flourescein angiography in order to determine the most appropriate treatment strategy (Figure 2). The following discussion reviews some of these modalities.

Conventional Thermal Photocoagulation

Conventional thermal photocoagulation is essentially a warm laser used to generate thermal damage to the retina and underlying tissue resulting in subsequent scar formation. The rationale is that thermal damage induced by the laser results in closure of the CNVM. Due to unavoidable damage to the overlying retinal photoreceptors, this treatment has been shown to clinically benefit those ARMD patients that have CNVMs that are extrafoveal or juxtafoveal in location.[9] Although successful closure of the CNVM may occur, recurrences can occur in up to 50% of treated eyes.

Photodynamic Therapy with Verteporfin

Photodynamic therapy (PDT) with verteporfin has been an increasingly popular modality in treating certain CNVMs. Essentially, an intravenous infusion of a photo-activating drug (verteporfin) having a unique affinity for neovascular complexes, such as those in CNVMs, is administered. The drug is activated by a nonthermal laser, resulting in closure of the neovascular complex. Because a nonthermal laser is used, the overlying retinal photoreceptors are not damaged. Usually, multiple sessions are required to ultimately close a CNVM. PDT has been shown to demonstrate a statistically significant treatment effect in those patients with certain types of subfoveal CNVMs.[10,11] Recent evidence suggests that lesion size is perhaps a better marker for treatment success than initial lesion characteristics as defined by angiography.[12] It is important to emphasize that the treatment goal with PDT is vision stabilization, although some patients may appreciate modest vision improvement after all treatment sessions are complete. Although PDT is an expensive treatment and may not be covered by all public or private health insurance plans, it is considered to be an especially cost-effective intervention.[13] Complications related to PDT are infrequent, and include photo-sensitivity reactions, injection-related adverse events, infusion-related low back pain, visual disturbances, and sudden vision loss in up to 4% of patients. The drug is contraindicated in patients with porphyria.

Exudative ARMD Therapies under Investigation

Antiangiogenic therapy is aimed at blocking one or more pathways integral to the growth and viability of the neovascular complexes in the CNVM. This

Figure 2: Clinical Photo of a Flourescein Angiogram. Intravenous flourescein angiogram of right fundus illustrating a subfoveal choroidal neovascular membrane.

Original photograph courtesy of Beth Selkirk, ophthalmic photographer, Sunnybrook and Women's College Hospital, Toronto, ON.

continues to be an emerging area of research in wet ARMD therapy and various drugs are currently under investigation, including intravitreal triamcinilone acetonide, anacorteve acetate, and anti-vascular endothelial growth factor compounds (Anti-VEGF).

Triamcinolone Acetonide

This is a synthetic glucocorticoid that is being used in other areas of medicine for its anti-inflammatory properties. Triamcinilone also has an effect on the blood-retinal barrier function and downregulation of VEGF. This property is being studied in ophthalmology with respect to decreasing vascular permeability in diseases such as diabetic macular edema and, more recently, wet ARMD.[14] The drug is delivered directly into the vitreous cavity through an intravitreal injection. Although its effect when used as monotherapy in wet ARMD is not entirely clinically significant, preliminary studies have suggested it may play a significant role when combined with PDT.[15] As such, randomized controlled trials are underway to determine the effectiveness and role of triamcinilone as a potential adjunct to PDT therapy. Adverse effects of intravitreal triamcinolone include injected related complications (infection, lens injury, retinal detachment) and glucocorticoid related complications (secondary glaucoma and cataract). Finally, because the duration of action is approximately four to six months, repeat injections are often necessary.

Anacortave Acetate

Anacortave acetate is a synthetic steroid devoid of glucocorticoid activity and its associated complications, such as secondary glaucoma and cataract. Its angiostatic effects are achieved by the inhibition of proteases necessary for endothelial cell migration. Promising initial results comparing anacortave acetate to placebo[16] have prompted further evaluation in comparing it to PDT therapy in the treatment of subfoveal CNVM. Anacortave is also being studied in another trial as a prophylactic agent in high-risk atrophic ARMD. In addition to anacortave's favourable safety profile compared to triamcinolone injections, other advantages include longer duration of action and a posterior juxtascleral target delivery site that is less invasive than an intravitreal injection.

Anti-VEGF

Ocular vascular endothelial growth factor (VEGF) appears to be important in the development of neovascularization in wet ARMD by promoting angiogenesis and vascular permeability. Research trials are currently underway that use anti-VEGF agents delivered by intravitreal injections in treating subfoveal CNVMs. Recently, one-year phase III data were published that demonstrated a beneficial effect of pegaptanib delivered via intravitreal injections every six weeks compared to sham injections.[17] Although the long-term effects are still unknown, short-term adverse effects include injection-related complications such as infection, retinal detachment, and lens injury. Ranibizumab is another anti-VEGF therapy that is currently under study, and results are expected in the near future.

Other Potential Therapies

Macular translocation is a surgical approach to treating wet ARMD. With this technique, the retina is detached and the macula rotated away from diseased tissue and placed over healthier subretinal tissue. After the macula is relocated, the diseased tissue and residual CNVM are now considered "extrafoveal" in location and amenable to conventional thermal photocoagulation. Other areas in the early stages of surgical experimentation include iris/retinal pigment epithelial transplantation, implantable miniaturized telescopes, and artificial vision microchips.

Conclusion

Further understanding of the disease's mechanism has lead to novel approaches in the treatment of ARMD. Although current treatment strategies are not curative, they are aimed at slowing or preventing an otherwise progressive disease. Current strategies include vitamin supplementation in atrophic ARMD and thermal laser or PDT in select patients with exudative ARMD. Future approaches may be multifaceted and include some form of anti-angiogenesis therapy. ◆

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