Geographic atrophy remains an important cause of permanent vision loss despite historic progress made in managing vitreoretinal diseases over the past decade. Fortunately, our understanding of age-related macular degeneration pathophysiology has reached a level that has allowed us to embark on several clinical trials to discover treatments to manage this difficult disease. Availability of animal models and advances in imaging (OCT and autofluorescence) have aided in the possibility of upcoming breakthrough treatments for GA.

Drs. Patel and Eichenbaum discuss a wide variety of treatment approaches, including neuroprotection, LDL-lowering agents, antibodies binding amyloid, anti-inflammatorieis, visual cycle modulators, and stem cell transplantation. Although many of these approaches are in the early stage, the community is encouraged by the progress of the Genentech lampalizumab development program entering phase 3 this year.

I am certain that the insights and review of this complex topic provided by Drs. Patel and Eichenbaum will be valued by the community.

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Geographic atrophy: clinical impact and emerging treatments

by Hershel R. Patel, MS, MD, and David Eichenbaum, MD

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the developed world. Severe central visual impairment develops as a result of neovascular derangement (wet AMD) or non-neovascular abnormalities (dry AMD). Slight alterations in central visual acuity can have profound effects on activities of daily living such as reading or driving. Dry AMD, which constitutes 85% to 90% of cases, is clinically associated with large confluent drusen formation and hyperpigmentation, with subsequent resorption of drusen and eventual loss of retinal pigment epithelium (RPE), choriocapillaris, and photoreceptors, leading to geographic atrophy (GA).\textsuperscript{1,2} This advanced stage of dry AMD is responsible for 20% of all cases of legal blindness in North America.\textsuperscript{3}
Although there is no current treatment to specifically target the onset or progression of GA, improved understanding of the underlying pathophysiology has spawned potential new therapies that are currently undergoing evaluation in clinical trials (Table, pages 10 and 11). Although the probable initial insult has been characterized, halting progression to GA will likely require augmentation of multiple molecular pathways. Broad classes of therapeutics under study include pharmacologic approaches to preserving and restoring RPE cells and photoreceptors, maintaining blood flow to the choriocapillaris, reducing beta-amyloid accumulation, preventing or reducing oxidative damage, reducing accumulation of retinal toxins, and minimizing inflammatory damage (Figure, page 12).4

Prevention
It remains important to counsel patients about modifiable risk factors that may allow for a better final visual outcome. These factors include smoking, hypertension, and body mass index, and controlling these factors has been reported to reduce the risk of developing AMD by 50%.5

Oxidative stress
Antioxidants and neuroprotective drugs are two classes of drug that can reduce stress by free radical damage. Nutritional supplements have been employed for their antioxidant properties as preventative therapy for AMD. The AREDS formulation includes 500 mg vitamin C, 400 IU vitamin E, 15 mg beta-carotene, 80 mg zinc oxide, and 2 mg cupric oxide.6 While there are no reported adverse effects associated with consumption of the AREDS formulation, beneficial effects were seen only in relation to reduction of the risk of progression to wet AMD. Vitamin supplementation has not shown a reduction in the risk of progression to central GA.7

Neuroprotection
Brimonidine tartrate (Alphagan-P; Allergan, Irvine, CA) is an alpha-2 adrenergic receptor agonist that has been shown in animal studies to protect retinal function after acute ischemia. It confers protection on retinal ganglion cells, bipolar cells, and photoreceptors in models of ischemia, ocular hypertension, retinal phototoxicity, and partial optic nerve crush.8 Activation of alpha-2 adrenergic receptors potentially slows neuronal loss by reducing apoptosis.9 Brimonidine tartrate has been tested in a randomized, double-blind phase 2 trial as an intravitreal implant inserted at day 1 and month 6. A 200-µg and a 400-µg implant were tested using the fellow eye as a control in a sham arm. At the 2-year mark, the data appear to show efficacy, with less expansion of baseline GA area in a dose-dependent pattern.10 Allergan is now enrolling the prospective placebo-controlled phase 3 BEACON study of the 400-µg brimonidine implant injected quarterly for 24 months.11

LDL-lowering agents
Many risk factors for the development of cardiovascular disease parallel those of AMD, including genetics, smoking, hypertension, and hyperlipidemia. Aberrant accumulations of lipids play an important role in the pathogenesis of both diseases. There has been a logical conjecture that statins may be useful for prevention and treatment. Longitudinal studies to date have not consistently demonstrated a benefit of statin therapy on the advancement of GA. The dose and duration of therapy are factors not often considered by these studies. In addition, no randomized, controlled trials with long-term follow-up have been undertaken, leaving the beneficial effects of statins for AMD unclear.12

Amyloid
Drusen formation along the basal surface of the RPE is a long-known significant risk factor for AMD, and the resorption of these drusen are the clinical sign identified before the progression to GA. The mechanisms associated with drusen resorption are believed to be associated with the development of GA. Drusen contain immunomodulatory molecules and components that are common to glomerulonephritis, atherosclerosis, and Alzheimer’s disease. Beta-amyloid has been shown to be a common protein between the neuritic plaques in Alzheimer’s disease and drusen in AMD.13 GSK933776 (GlaxoSmithKline) is currently being investigated in a phase 2 multicenter, randomized, double-masked trial for GA secondary to dry AMD. This drug is a humanized monoclonal antibody administered via an intravenous infusion that binds with high affinity to the beta-amyloid N terminus. In addition, the Fc portion of GSK933776 is designed to reduce complement fixation and Fc receptor binding, which theoretically provides additional anti-inflammatory effects.14

Choroidal circulation, perfusion
The choriocapillaris provides all of the metabolic needs of the photoreceptors, including 90% of the oxygen consumed by the photoreceptors in the darkness. Clinical studies suggest that choroidal blood flow is compromised in age-matched control subjects with AMD. Lack of perfusion of the chorio-
### Agents Currently in Clinical Development for Dry Age-Related Macular Degeneration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Structure, Administration Route</th>
<th>Mechanism of Action</th>
<th>Patient Population</th>
<th>Clinical Study Phase, Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>AREDS2²</td>
<td>National Eye Institute</td>
<td>Dietary supplement: lutein/zeaxanthin, DHA/EPA</td>
<td></td>
<td>Patients with AMD</td>
<td>Phase 3 (n = 4,000) started Sep 2006, now complete (NCT00345176), addition of lutein and zeaxanthin did not significantly reduce progression to advanced AMD</td>
</tr>
<tr>
<td>OT-551¹</td>
<td>Othera Pharmaceuticals, Exton, PA</td>
<td>Disubstituted hydroxylamine; topical solution</td>
<td>Is converted to TEMPOH, a potent free radical scavenger and antioxidant</td>
<td>Patients with geographic atrophy</td>
<td>Phase 2 (n = 11) started Mar 2006, complete Mar 2011 (NCT00306488), limited treatment benefit for GA</td>
</tr>
<tr>
<td>Omega-3 fatty acid</td>
<td>Willis Eye Institute</td>
<td>AREDS2 Vitamin formula, 1 g; Eye Omega Advantage, 2g</td>
<td></td>
<td>Patients with AREDS category 3 or 4 disease; Category 3: Many medium sized drusen or 2 large drusen in one or both eyes; Category 4: Geographic atrophy or CNV in one eye.</td>
<td>Phase 3 (n = 100) currently recruiting, started Jul 2012, expected completion, Feb 2013 (NCT01653184)</td>
</tr>
<tr>
<td>Omega-6/omega-3 ratio and progression of AMD</td>
<td>University of Alberta, Canada</td>
<td>AREDS vitamins or equivalent</td>
<td></td>
<td>Patients with wet AMD in one eye and early/intermediate dry AMD in fellow eye</td>
<td>Phase 3 (n = 200) started Mar 2012, expected completion Mar 2014/2017 (NCT00987129)</td>
</tr>
<tr>
<td>Lutein and omega-3 fatty acids (LUTEGA)</td>
<td>University of Jena, Germany</td>
<td>Lutein, zeaxanthin, omega-3 fatty acids (MPOD)</td>
<td></td>
<td>Patients with nonexudative AMD</td>
<td>Phase 3 (n = 172) completed Sep 2011. After 1 year, increase in MPOD and VA was seen (NCT00763659); LUTEGA2 (n = 80), a continuation and crossover of LUTEGA, completed Dec 2012.</td>
</tr>
<tr>
<td>Lutein (Nutrof)</td>
<td>University Hospital, Bordeaux, France</td>
<td>Lutein and zeaxanthin (increase in MPOD)</td>
<td></td>
<td>Patients whose parents had a history of wet AMD</td>
<td>Phase 1 (n = 128) started Jan 2011; status: currently recruiting (NCT01269697)</td>
</tr>
<tr>
<td>Lutein and zeaxanthin</td>
<td>Peking University, China</td>
<td>Changes in MPOD during 96 weeks</td>
<td></td>
<td>Patients with AMD</td>
<td>Phase 2/3 (n = 162) started Jun 2010, expected completion June 2012; status: currently recruiting (NCT01528605)</td>
</tr>
<tr>
<td>Lutein and zeaxanthin</td>
<td>Peking University, China</td>
<td>Changes in MPOD and multifocal electroretinograms</td>
<td></td>
<td>Phase 1/2 (n = 120) started Sep 2009, status: currently recruiting (NCT01046476)</td>
<td></td>
</tr>
<tr>
<td>Visual cycle modulators</td>
<td></td>
<td></td>
<td></td>
<td>Development terminated</td>
<td></td>
</tr>
<tr>
<td>Fenretidine</td>
<td>Siion Therapeutics, Tampa, FL</td>
<td>Synthetic retinoid derivative, oral</td>
<td>Prevents the transport of retinal to the RPE</td>
<td>Geographic atrophy</td>
<td></td>
</tr>
<tr>
<td>ACU-442951</td>
<td>Alcon Laboratories, Bothell, WA</td>
<td>Small non-retinoid molecule; oral</td>
<td>Inhibits conversion of all-trans-retinyl ester to 11-cis-retinol via the isomerase RPE65. Prevents accumulation of A2E</td>
<td>Geographic atrophy; Primary endpoint is change from baseline in total area of GA lesions</td>
<td>Phase 2 safety study (n = 84) started in Oct 2009. Fast Track Status granted in March 2010, study completed (NCT01002950). Phase 2/3 (n = 440) currently recruiting, estimated completion by Jul 2016 (NCT01802866).</td>
</tr>
<tr>
<td>ALK-001</td>
<td>Allux</td>
<td>Deuterium-enriched Vitamin A</td>
<td>Slows the formation of A2E and lipofuscin</td>
<td>Dry AMD</td>
<td>Predichoral</td>
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<tr>
<td>Anti-inflammatory agents</td>
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<tr>
<td>Fluocinolone (Iluvien)</td>
<td>Allergan Sciences, Alhambra, CA</td>
<td>Corticosteroid, IVT</td>
<td>Non-bioerodable polyamide tube containing 180 µg corticosteroid</td>
<td>Geographic atrophy</td>
<td>Phase 2 (n = 40) started Dec 2008, estimated completion Dec 2014; status: currently recruiting (NCT00695318)</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>Teva Pharmaceuticals, Kfar Saba, Israel</td>
<td>Immuno-modulator</td>
<td>Dose regulates inflammatory cytokines</td>
<td>Geographic atrophy (halting progression, including progression to wet AMD)</td>
<td>Status of two clinical trials (NCT00466076 and NCT0054133) unknown</td>
</tr>
<tr>
<td>Sirolimus (Rapamycin)</td>
<td>Wyeth, Madison, WI</td>
<td>Subconjunctival</td>
<td>Inhibits mTOR and HIF-1a, anti-inflammatory and immunosuppressant</td>
<td>Patients with geographic atrophy. Enrolling patients with bilateral geographic atrophy. Enrolling patients with progressively worsening central geographic atrophy.</td>
<td>Phase 1/2 (n = 11) complete; subconjunctival sirolimus was not effective in delaying progression of geographic atrophy (NCT00766499); phase 1/2 study (n = 15) started Sep 2011, expected completion July 2014 (NCT01445548); phase 2 study (enrolling by invitation, so far n = 50) expected completion Dec 2014 (NCT: 1775947)</td>
</tr>
<tr>
<td>LFG316</td>
<td>Novartis Pharmaceuticals Corporation, New Hanover, NJ</td>
<td>NT</td>
<td>12 monthly doses</td>
<td>Growth of lesions in patients with geographic atrophy</td>
<td>Phase 2 (n = 120) started Jan 2012, expected completion Jun 2014 (NCT01527500)</td>
</tr>
<tr>
<td>POT-4</td>
<td>Patentia Pharmaceuticals, Louisville, KY; Akon Research, Fort Worth, TX</td>
<td>Cyclic 13-amino acid peptide; IVT</td>
<td>Inhibits conversion of comple ment C3 to C3a/b</td>
<td>Wet AMD (prolongation of anti-VEGF effects of ranibizumab)</td>
<td>Phase 1 complete (NCT00473928)</td>
</tr>
</tbody>
</table>
**Amyloid d**

RN60 (PF-4382923) | Pfizer Inc, New York, NY | Humanized monoclonal antibody, IV | Prevents accumulation of amyloid β 40/42 | Phase 2 efficacy study (n = 276) recruiting, started Jul 2012, expected completion Jul 2014 (NCT01577381); phase 2 safety and tolerability studies (NCT01003691, NCT00877032) completed.

Oxodextrin/Fx1, Research Triangle Park, NC | Humanized monoclonal antibody, IV | Modulation of amyloid levels β 40/42 | Phase 2 (n = 162) started Jun 2011, currently recruiting, estimated completion Mar 2014 (NCT01342926).

**Choroidal ciculation/perfusion**

Trimetazidine12 | Institute de Recherches Internationales Servier, France | Anti-ischemic agent | Patients with soft drusen and/or RPE abnormalities in study eye and CNV in the fellow eye | Phase 3 (n = 1,086) ISRCTN99532788.

MC-1101 | MacuCLEAR Inc, Plano, TX | Antihypertensive, vasodilator, antioxidant; 1% ophthalmic solution TID | Prevents rupture of Bruch's membrane | Phase 2 (n = 60) currently recruiting, started Jul 2012, expected completion Jul 2014 (NCT01601483).

UF-021 (Ocuause) | Sucampo Pharmaceuticals, Tokyo, Japan | Prostaglandin analog; 0.02% ophthalmic solution | Increases retinal and choroidal blood flow | Phase 2 (n = 112) started Jun 2011 in Japan for retinitis pigmentosa (NCT01379560); A U.S. trial in patients with dry AMD is planned.

**Neuroproteoctants**

CNTF/NT50134 | Neurotech, Lincoln, RI | Encapsulated cell technology | Encapsulated human cells genetically modified to secrete ciliary neurotrophic factor (CNTF) | Phase 2 (n = 48) completed Oct 2009 (NCT00447954).

AL-8309B (tandospirone) | Alcon Research, Fort Worth, TX | Selective serotonin 1A agonist | Protects retina from light damage; topical | Phase 2 (n = 119) started May 2008, estimated completion Apr 2011 (NCT00658619); phase 2 safety extension study (n = 215) started Feb 2010, estimated completion Feb 2014.

Brimonidine tartrate | Allergan, Irvine, CA | Alpha-adrenergic agonist; IVT implant | Stimulates production of neurotrophic factors | Phase 2 (n = 119) started May 2008, estimated completion Apr 2011 (NCT00658619); phase 2 safety extension study (n = 215) started Feb 2010, estimated completion Feb 2014.

RNA-144101 | University of Kentucky | Inhibitor of toll-like receptor 3 (TLR3) | Geographic atrophy (NCT01093170) | Study withdrawn prior to enrollment.

**Stem cell therapy**

CNTD2476 | Janssen Research/ Centocor Inc | Human umbilical tissue-derived cells (UTC), subretinal injection using the iTrack Model 275 micro catheter | Single dose | Patients with visual acuity impairment associated with geographic atrophy secondary to AMD | Phase 1/2a (n = 56) started Sep 2010, expected completion Aug 2017 (primary endpoint completion Sep 2013) (NCT01226628).

MA09-hRPE | Advanced Cell Technology | Subretinal transplantation of human embryonic stem cell-derived retinal pigmented epithelial (MA09-hRPE) cells | Patients with advanced dry AMD | Phase 1/2a (n = 12) started Apr 2011, expected completion Jul 2013 (NCT01344993).

MA09-hRPE | Advanced Cell Technology | Subretinal transplantation of human embryonic stem cell-derived retinal pigmented epithelial (MA09-hRPE) cells | Patients with Stargardt's macular dystrophy | Phase 1/2 studies (both n = 12) currently recruiting, NCT01345006 started Apr 2011, expected completion Sep 2013, NCT01469832 started Nov 2011, expected completion Apr 2014.

HuCNS-SC | StemCell Inc, Newark, CA | Subretinal transplantation of human neural stem cells | Patients with retinal degenerative diseases such as AMD | Phase 1/2 (n = 16) started June 2012, expected completion Aug 2014 (NCT01632527).

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*A2E = N-retinyl-N-retinylidene ethanolamine; AMD = age-related macular degeneration; AREDS = Age-Related Eye Disease Study; CNV = choroidal neovascularization; DHA = docosahexanenoic acid; EPA = eicosapentaenoic acid; IV = intravenous; IVT = intravitreal; MPOD = macular pigment optical density; RPE = retinal pigment epithelium; TID = three times daily.*
capillaris has been suggested as a potential cause of reticular drusen, which are a common phenotypic hallmark that portends a high risk for progression to GA.\(^4\)\(^,\)\(^15\) MC-1101 (MacuClear, Plano, TX) is a topically applied vasodilator that increases nitric oxide concentrations. MC-1101 was shown in preliminary studies to increase choroidal blood flow as measured with laser Doppler flow studies greater than five-fold in 1 hour after 1.0% administration. MacuClear is currently recruiting 60 patients for a phase 2/3 sham-controlled, double-masked, randomized, controlled trial for MC-1101 1.0% dosed twice daily.\(^16\)\(^,\)\(^17\)

**Visual cycle modulators**

Fenretinide (Sirion Therapeutics, Tampa, FL), also known as N-(4-hydroxyphenyl) retinamide, is designed to modulate the visual cycle and prevent toxic accumulation of lipofuscin in the RPE. It is an orally ingested vitamin A derivative that competitively binds retinol-binding protein (RBP) and subsequently decreases retinol bioavailability.\(^18\) Dose-dependent reductions in serum RBP-retinol with associated reduced lesion growth rates have been reported in a placebo-controlled, randomized, double-masked 2-year trial with 246 patients at a dose of 300 mg. The same study found a 45% decreased incidence of choroidal neovascularization compared to placebo.\(^19\) Despite encouraging results, changes in the manufacturing process during the trial have resulted in the U.S. Food and Drug Administration rejecting the data for review. Unless funding is acquired for a repeat trial, this drug will likely not come to market.\(^20\)

**Anti-inflammatory agents**

Anti-inflammatory agents target or inhibit a variety of proteins involved in the immunologic inflammatory process. These include matrix metalloproteinase (a protein vital for cellular migration), mTOR (a vital cellular proliferation protein), and the complement cascade (an innate pro-inflammatory/immunologic protein family). Lampalizumab (Genentech, South San Francisco, CA) is an intra vitreally injected monoclonal antibody that blocks factor D in the complement cascade. The multicenter, randomized, single-masked phase 2 MAHALO trial enrolled 129 patients, and those in the treatment arm of the study showed a 20.4% reduction rate in the area of GA at 18 months. Remarkably, 57% of the 93 patients in the treatment arm were positive for the complement factor I biomarker. In this subgroup, monthly lamalizumab was associated with a 44% decrease in rate of disease progression at 18 months (\(P < .005\)). In those treated every other month, the rate of disease progression decreased by 18% (\(P = .23\)). The enhanced treatment effects of lampalizumab associated with the complement factor I biomarker emphasize the potential importance of genotype identification in future targeted therapies.\(^21\)

**Prevention of RPE, photoreceptor loss**

A great deal of controversy has surrounded the transplant and harvesting of embryonic stem cells. In January 2012, a landmark study by Schwartz et al published in *Lancet* offered the first description of human embryonic stem cell transplant into human subjects with retinal disease. In that study, MAO9-hRPE cells (human embryonic stem-cell-derived retinal pigmented epithelial cells; Advanced Cell Technology, Marlborough, MA) were transplanted subretinally. Safety was demonstrated in the two patients, one with Stargardt’s disease and another with GA, with no evidence of hyperproliferation, tumorigenesis, ectopic tissue formation, or rejection after 4 months.\(^22\) A phase 1/2 clinical trial is currently recruiting participants with one or more areas with greater than 250 \(\mu\)m of GA. Four cohorts are planned, with each receiving between 50,000 to 200,000 cells.\(^23\)
Conclusion

GA remains an important cause of irreversible blindness in North America, and challenges remain in fully understanding the underlying pathophysiology, identification of an appropriate animal model, and a primary clinical endpoint correlated to visual acuity. Despite this, 15 years of work and clinical trials by many scientists and physicians have resulted in numerous potential treatments. Although stem cell therapy shows a great deal of promise based on preliminary reporting, it is still in its infancy. Pharmacologic therapy, however, is progressing, with anti-inflammatory lampalizumab therapy entering phase 3 trials this year. With improvements in the efficiency of molecular science and the clinical trial networks, the future has never been brighter for patients with GA.

REFERENCES


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