

Drug Delivery Implants for Geographic Atrophy

A number of sustained-delivery technologies are under study.

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Geographic atrophy (GA), the late, atrophic form of dry age-related macular degeneration (AMD), is a major cause of moderate and severe vision loss.^{1,2} It typically follows a progressive course, leading to degeneration of retinal pigment epithelium (RPE) and photoreceptor cells. GA is thought to be the natural course of AMD if neovascularization does not develop first.³ There is currently no established treatment for GA.

Apoptosis, the process of programmed cell death that helps to clear injured or unneeded cells from the body, is normally an important homeostatic function. However, excessive, uncontrolled apoptosis has been implicated as a contributing factor in the pathogenesis of multiple ophthalmic diseases, including GA.³

Stopping the death of retinal neuronal cells associated with GA is a balancing act. In normal eyes, numerous factors promote either the death or the survival of retinal neurons and photoreceptors. The viability of these cells is the result of a balance between these signals of cell death and survival. If the balance shifts toward cell death signals, excessive apoptosis can result. The aim of neuroprotective therapy is to enhance cell survival signals, block cell death signals, and shift the balance in the other direction, in favor of survival.

A number of neuroprotective strategies for glaucoma have been investigated, including neurotrophins, vasoprotectants, calcium channel blockers, nitric oxide synthase inhibitors and other antioxidants, brimonidine, memantine, and betaxolol. Currently 3 potential neuroprotective strategies are being investigated for treatment of GA: ciliary neurotrophic factor (CNTF), brimonidine tartrate, and fluocinolone acetonide (FA).

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Because of the chronic nature of GA, which progresses over a period of years, long-term delivery of these agents is thought to be vital. Each of these 3 drugs is being investigated in patients with GA using a different extended-delivery technology: CNTF in an encapsulated cell technology (Neurotech); brimonidine in a biodegradable drug-delivery system (Allergan); and FA in the Iluvien drug-delivery

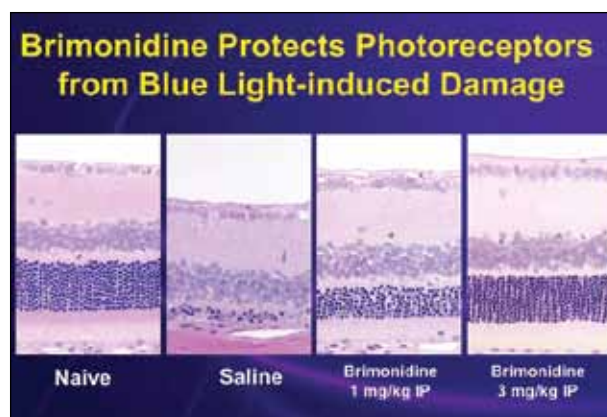


Figure 1. Brimonidine has been shown to protect photoreceptors from blue-light-induced damage.

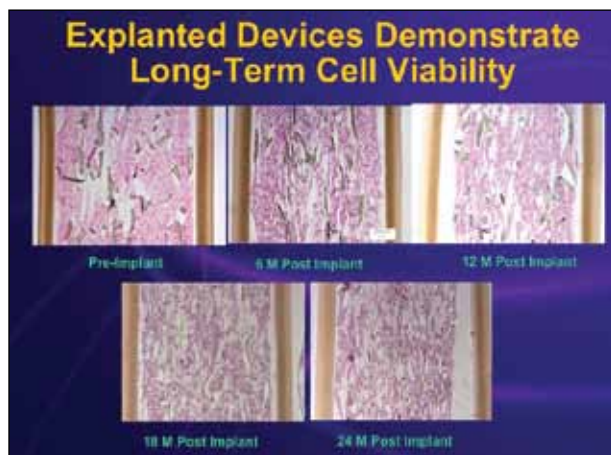


Figure 2. The ECT capsule is capable of secreting the CNTF protein continuously for more than 2 years, as demonstrated by explanted devices.

implant (Alimera). This article updates the status of clinical investigation of each of these drugs and their respective delivery technologies for treatment of GA.

BRIMONIDINE

In experimental studies, the alpha-2 adrenergic agonist brimonidine has demonstrated protection of retinal ganglion cells, bipolar cells, and photoreceptors from degeneration after a number of types of insults, including retinal ischemia, partial nerve crush, ocular hypertension, and retinal phototoxicity.⁴⁻⁷ Brimonidine has recently been shown to protect photoreceptors from blue-light–induced damage (Figure 1).⁸

The proposed mechanisms of action of brimonidine's neuroprotective properties include upregulation of endogenous production of trophic factors such as brain-derived neurotrophic factor in retinal ganglion cells; activation of intracellular cell-survival signaling pathways; stabilization of mitochondrial trans-membrane potential under conditions of oxidative stress; and attenuation of the activation of glial cells and the immunoreactivity of retinal glial fibrillary acidic protein.^{6,9-11}

A sustained-release formulation of brimonidine is currently being evaluated in 2 clinical trials—a phase 2 safety and efficacy study in patients with GA and an exploratory safety study in patients with retinitis pigmentosa (RP). The delivery device in the trials is a biodegradable polymer matrix containing the active ingredient brimonidine tartrate. Injected into the vitreous with a 22-gauge inserter similar to the injector used with the dexamethasone implant (Ozurdex, Allergan), the device slowly degrades with the goal of delivering sustained, nontoxic, therapeutic levels of brimonidine to the RPE.

In the phase 2 study, 125 patients with bilateral GA and

visual acuity of between 20/40 and 20/200 were randomized in a 2:2:1 ratio to receive the brimonidine delivery system containing either 200 µg or 400 µg of drug or sham treatment. Patients received the drug or sham treatment in 1 eye and sham treatment in the fellow eye on day 1 and a repeat of the assigned treatment and sham treatment at month 6. The GA trial is fully enrolled and in the second year of follow-up. The exploratory study in patients with RP is still enrolling patients.

CNTF

The Neurotech encapsulated cell technology (ECT) has been called an implantable cellular factory. The intraocular implant, designated Renexus (formerly NT-501), contains modified human cells that secrete CNTF for sustained, controlled delivery to the retina.¹² The capsule, implanted into the vitreoretinal space in an outpatient procedure, is capable of secreting the protein continuously for more than 2 years, as demonstrated by explanted devices (Figure 2).

Unlike other drug implants, this device does not primarily store the drug, but rather produces it in situ. The immunoisulatory membrane surrounding the encapsulated cells allows ingress of oxygen and nutrients and egress of therapeutic factors, but blocks the entry of immune system components (Figure 3). This results in levels of CNTF in the vitreous that are consistent over time and effectively achieve photoreceptor preservation.¹³

The use of growth factors to protect photoreceptors from degeneration was first demonstrated in 1990,¹⁴ and multiple growth factors, cytokines, and neurotrophic factors, including CNTF, have been explored since then in a variety of experimental conditions.^{15,16} In a rat model of retinal degeneration, Li et al¹⁷ showed that CNTF induced

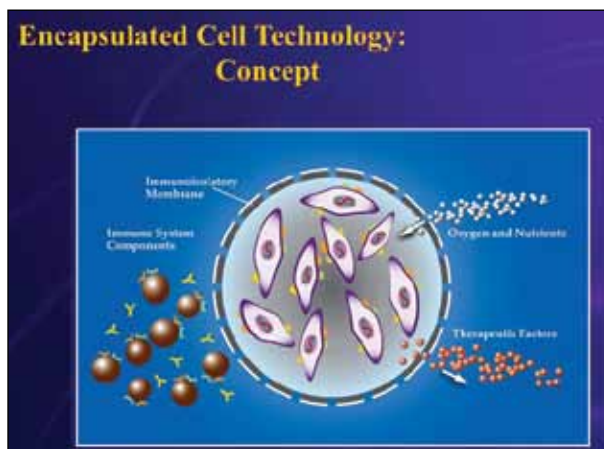


Figure 3. The immunoisulatory membrane surrounding the encapsulated cells allows ingress of oxygen and nutrients and egress of therapeutic factors, but blocks the entry of immune system components.

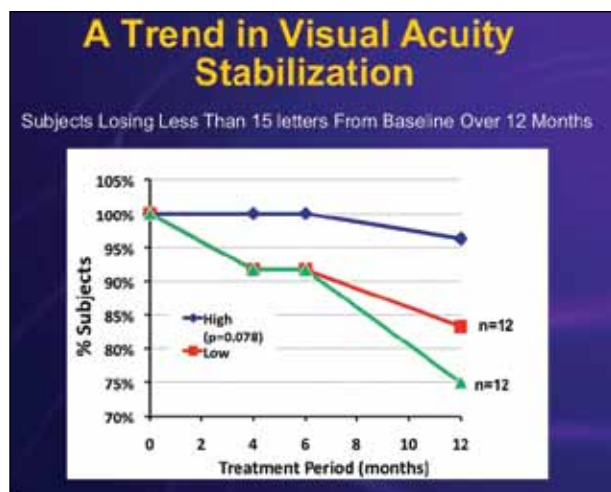


Figure 4. A trend in visual acuity stabilization (loss of less than 15 letters of BCVA) was seen, with 96.3% of those in the high-dose group, compared with 83.3% in the low-dose group and 75% in the sham-treated group, remaining stable at 1 year.

regeneration of cone outer segments. Tao and colleagues¹² investigated delivery of CNTF through ECT in an rcd1 canine model of RP. They found that CNTF delivered directly into the vitreous protected photoreceptors in an apparently dose-dependent manner.

A phase 2 clinical study of CNTF delivered via ECT in patients with GA was recently completed.¹⁷ In this 1-year, randomized, double-masked, controlled dose-ranging study, 48 individuals were randomly assigned to receive a high-dose (n=24) or low-dose (n=12) implant or sham surgery (n=12). The primary endpoint was change in BCVA at 12 months.

The investigators reported that treatment with CNTF resulted in a dose-dependent increase in retinal thickness. Visual acuity stabilization (loss of less than 15 letters of BCVA) was seen in 96.3% of those in the high-dose group, compared with 83.3% in the low-dose group and 75% in the sham-treated group (Figure 4). Among those with baseline BCVA of 20/63 or better, 100% of those in the high-dose group lost less than 15 letters, compared with 55.5% in the combined low-dose and sham groups ($P = .03$).

The change in BCVA was a mean gain of 0.8 letter in the high-dose group compared with a mean 9.7 letter loss in the combined low-dose/sham group ($P = .03$). Both the implant and the implantation procedure were well-tolerated. These findings suggest that CNTF delivered by ECT protects photoreceptors in GA, especially in eyes with 20/63 or better vision at baseline.

Using adaptive optics scanning laser ophthalmoscopy, Talcott et al¹³ monitored cone density over

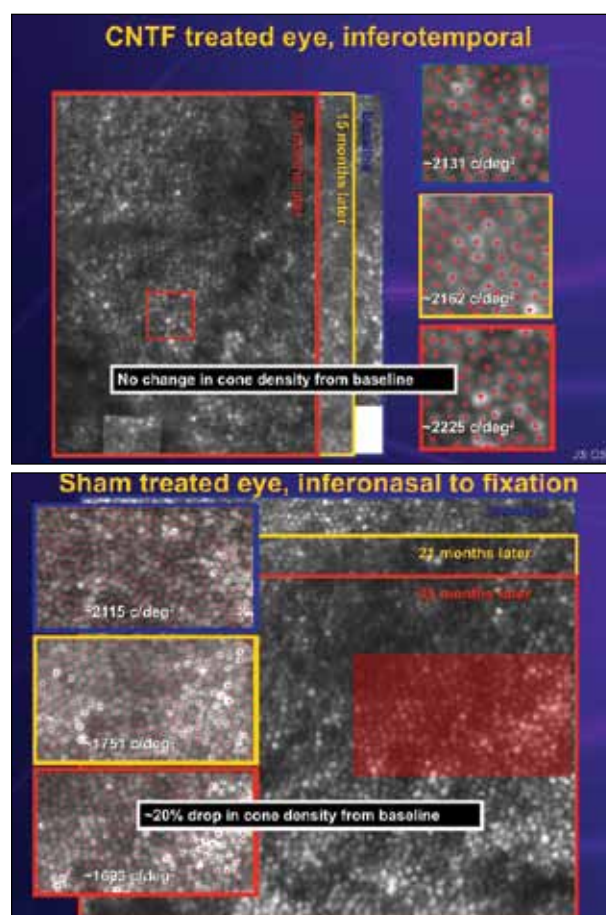


Figure 5. Cone density remained stable in all treated eyes in all locations studied (A), while a decrease of 9% to 24% in cone density was seen in 8 of 9 locations monitored in sham-treated eyes (B).

2 years in 3 patients enrolled in a phase 2 study. In each patient—2 with RP, 1 with Usher syndrome—the CNTF ECT was implanted in 1 eye and the other was sham-treated. Over the 2 years of observation, multiple high-resolution images were obtained. Cone density remained stable in all treated eyes in all locations studied, while a decrease of 9% to 24% in cone density was seen in 8 of 9 locations monitored in sham-treated eyes (Figure 5).

A phase 3 trial of NT-501 in patients with dry AMD has been proposed. The design would include 300 patients, with 200 receiving the high dose ECT implant and 100 receiving sham treatment. The primary endpoint would be stabilization of vision (loss of less than 15 letters of BCVA) at 1 year, with follow-up continuing to 2 years.

Neurotech has received fast track designation for NT-501 for the treatment of visual loss associated with dry AMD from the US Food and Drug Administration.

FLUCINOLONE ACETONIDE

The ability of the glucocorticoid FA to provide neuroprotection to photoreceptors and the RPE has been suggested in animal studies by Glybina and colleagues,^{18,19} who showed that RCS S334-ter rats treated with 0.2 µg/day of FA had less retinal thinning and less reduction of b-wave amplitude on electroretinography than control animals. Sustained-release, low-dose FA reduced retinal neuroinflammation by fivefold in the inner and outer retina, these investigators reported.

A low-dose, sustained-release formulation of FA (Iluvien) is being evaluated in the MAP-GA trial, funded by Alimera Sciences, the developers of the delivery system. The FA implant is a nonbioerodible polyimide tube, 3.5 mm long and 0.37 mm in diameter, which is inserted into the posterior chamber through a self-sealing wound with a 25-gauge inserter in an outpatient procedure. The implant dispenses 0.2 µg/day of FA and is engineered to provide a sustained therapeutic effect over a 2 to 3-year period.

The MAP-GA trial is designed to assess whether low-dose, sustained-release FA can slow the progression of GA in patients with dry AMD. In this randomized, double-masked, fellow-eye comparison study, 40 patients with bilateral GA will receive an implant in 1 eye that releases either 0.2 or 0.5 µg of FA per day. The primary outcome measure at 1 year is change in lesion area on color and fundus autofluorescence photographs, as interpreted by the Digital Angiography Reading Center. Secondary measures include the square root of the lesion area, standard and low-luminance visual acuity, drusen volume, retinal thickness, fluorescein angiography, and number of treatments for choroidal neovascularization.

This trial is currently enrolling patients. Alimera has received marketing authorization for Iluvien in the United Kingdom, Austria, and Portugal for the treatment of diabetic macular edema, and is seeking FDA approval in the United States for the same indication.

CONCLUSIONS

There is significant unmet medical need for neuroprotection in posterior segment eye diseases—not only for GA in dry AMD, but also for diabetic macular ischemia, chronic macular edema, retinal detachment, RP, and other inherited retinal degenerative diseases. Because of the chronic nature of GA in dry AMD, a sustained-delivery method will likely be an important part of any therapeutic approach.

Multiple pathways merit investigation as targets for neuroprotection in GA. Currently, 3 therapeutic entities in 3 distinct delivery systems are being investigated in clinical trials in patients with GA. The ECT method of delivering CNTF has shown benefit in a phase 2 study. A phase 2 trial of the brimonidine bioerodible delivery system is fully

enrolled. A pilot trial of the FA implant is enrolling patients.

There is currently no established treatment to prevent GA or to slow its progression. We look forward to the results of these studies and the potential to therapeutically address this important cause of visual loss in the future. ■

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