An Investigational Therapy for Geographic Atrophy in Age-Related Macular Degeneration

A monoclonal antibody against amyloid beta (Aβ) may target a novel therapeutic mechanism in dry AMD.

BY BRIAN B. BERGER, MD; IVANA GUNDERSON, BS; CATHERINE BOWES RICKMAN, PHD; JOHN LIN, MD; AND PAMELA GARZONE, PHD

Age-related macular degeneration (AMD) is a major cause of irreversible blindness in the world. Although neovascular AMD garners much attention, the dry form, for which there are few therapeutic options, has become a hot topic of ophthalmic research. Basic science has recently advanced the knowledge base concerning dry AMD, including the identification of several potential targets for intervention.

The late stage of dry AMD, known as geographic atrophy (GA), may be associated with retinal pigment epithelial (RPE) cell death, overlying photoreceptor loss, and underlying choriocapillaris atrophy.[1] Generally, visual acuity loss due to GA progresses slowly; however, foveal involvement in GA may dramatically hasten loss of visual acuity. At the tissue level, AMD is characterized by an accumulation of extracellular lipid- and protein-containing deposits between the RPE and Bruch membrane. These sub-RPE deposits, which contain amyloid beta (Aβ), may be focal (drusen) or diffuse, and they likely contribute to disease onset and progression, as they do in other diseases such as Alzheimer disease.[2]

Associations between Alzheimer disease and AMD have been suggested in the literature. Alzheimer disease is characterized by the presence of plaques composed of amyloid proteins and neurofibrillary tangles, each of which contributes to neural loss. It has been shown that Aβ accumulates and colocalizes with activated complement within drusen.[2,3] Luibl et al detected nonfibrillar oligomeric Aβ in drusen in eyes with AMD, and Yoshida et al demonstrated that Aβ increased VEGF mRNA and VEGF protein levels in human RPE cell cultures.[3-5] Drusen containing nonfibrillar oligomeric Aβ have been demonstrated in a murine model, further suggesting that certain pathologic features of AMD are similar to those of Alzheimer disease.[5,6] Taken together, these data suggest that Aβ may contribute to the pathogenesis of AMD.

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NOVEL TARGET IN DRY AMD: RATIONALE

To date there are no therapies available to treat dry AMD. Current management is restricted to nutritional supplementation and routine monitoring to detect changes in anatomy and/or visual acuity. Recent studies

in a murine model have demonstrated that an antibody against Aβ protected against RPE damage and visual acuity loss.[6-8] Clearance of Aβ from sub-RPE deposits coincided with protection of visual function and structural preservation of the RPE. Administration of anti-Aβ monoclonal antibodies by intraperitoneal injection in this murine model led to decreased AMD-like pathology and increased visual acuity compared with no treatment.[6,8] Delivery of higher doses of antibody was associated with a dose-dependent increase in plasma Aβ concentrations, and with reduced Aβ within deposits and levels of activated complement components in the eye. These results suggest that antibody binding to Aβ while it is circulating in the blood acts as sink for the Aβ, leading to its gradual removal from the eye. This is the first proof-of-principle evidence that anti-amyloid immunotherapy may be a promising strategy for the treatment of human AMD.

RN6G (Rinat Neuroscience Corporation, a research unit of Pfizer) is a monoclonal antibody that has been tested in an AMD murine model. It binds specifically to the C-terminus of Aβ peptides. Known as $A\beta_{1-40}$ and $A\beta_{1-42}$, these peptides result from the sequential cleavage of the amyloid precursor protein by β and γ-secretases. Several monoclonal anti-Aβ antibodies, most notably bapineuzumab (Pfizer/Janssen), solanezumab (Eli Lilly) and ponezumab (PF-04360365, Pfizer), have been evaluated as targets for treatment of Alzheimer disease.

RN6G is different from other monoclonal antibodies in several important aspects: RN6G binds to the C-terminus of the Aβ peptides instead of the N-terminus (as does bapineuzumab) or the central region (as does solanezumab); it binds to both $A\beta_{1-40}$ and $A\beta_{1-42}$ instead of only $A\beta_{1-40}$ like poneuzumab; and RN6G is an IgG2Δa antibody, whereas IgG1 is the antibody isotype for both bapineuzumab and solanezumab. The isotype IgG1 displays strong activities in both complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity.[9] In contrast, IgG2Δa does not elicit these immune effector functions and may, therefore, be much safer than the IgG1 isotype monoclonal anti-Aβ antibodies[9]; however, long-term studies are needed to confirm this hypothesis.

EARLY-STAGE DATA

The first human study with RN6G was an ascending-dose study in 54 adults with dry AMD. The participants were randomized to 6 cohorts with 9 subjects in each group to receive either a single intravenous dose of RN6G (0.3 mg/kg to 40 mg/kg) or placebo in a 2:1 active drug to placebo ratio.

A phase 1 multicenter, randomized, double-masked, placebo-controlled, multidose study in patients with moderate dry AMD (level 3 as defined by the AREDS Group[10]) was initiated in 2010. The study evaluated 6 monthly intravenous doses in 3 cohorts (5 mg/kg, 10 mg/kg, and 15 mg/kg). Following the treatments, there were 5 monthly safety observation visits. The pharmacokinetics and pharmacodynamics of the drug were evaluated through multiple blood draws at various time points during the treatment and observation period. Safety was assessed with electrocardiography and ophthalmic evaluations at almost every visit, as well as with magnetic resonance imaging scans of the brain and complete physical and neurologic examinations. Patients who were taking anticoagulants or who were unable to undergo brain magnetic resonance imaging were excluded. Eight patients with best corrected visual acuity of 20/80 or better in the study eye were enrolled in each cohort for a total of 24 patients randomized to active drug or placebo in a 3:1 ratio. Following 6 intravenous treatments, no safety issues were noted in these 24 patients.

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CONCLUSION

Basic science studies have identified Aβ as functional in the pathogenesis of dry AMD, and, therefore, it may be a potential target for therapy. Early preclinical evaluations of RN6G, an monoclonal anti-Aβ antibody, have shown promising results to date, warranting further evaluation as a potential therapeutic intervention in eyes with dry AMD. The drug has the potential to provide a mechanism of treatment for this blinding form of dry macular degeneration. ■

Brian B. Berger, MD, is the owner of a private retinal practice in Austin, Texas, and is the president and owner of Retina Research Center in Austin, Texas. He has received financial support from Alimera Sciences; Allergan Inc.; Alcon Laboratories; Ampio Pharmaceuticals; Diabetic Retinopathy Clinical Research Network; Glaxo Smith Kline; iCo Therapeutics; Lpath Incorporated; Genentech; Ophthotech; Pfizer; Thrombogenics; and Xoma. He is a consultant to Allergan and Santen. Dr. Berger may be reached at bberger@e-retina.net.

Pamela Garzone, PhD, is the executive director of biotechnology and clinical development at Pfizer WRD. She is an employee of and owns shares of Pfizer. Dr. Garzone may be reached at pamela.garzone@pfizer.com.

Ivana Gunderson, BS, is a clinical research coordinator at Retina Research Center in Austin, Texas. She has no financial relationships with the products or companies mentioned herein. Ms. Gunderson may be reached at igunderson@e-retina.net.

John Lin, MD, is a director at Rinat. He serves as ad hoc reviewer for journals such as Nature Neuroscience *and as a grant reviewer for the Michael J. Fox Foundation for Parkinson's Research. Dr. Lin may be reached at john.lin@pfizer.com.*

Catherine Bowes Rickman, PhD, is an associate professor of ophthalmology and cell biology at Duke University Medical Center in Durham, North Carolina. She has received research funding from Rinat, a research division of Pfizer, but has no financial interests in the products or companies mentioned herein. Dr. Bowes may be reached at bowes007@duke.edu.

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