

Profile of a Potential Treatment for Geographic Atrophy

An in-depth look at a complement-targeted therapy.

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In the developed world, age-related macular degeneration (AMD) is a leading cause of blindness in adults older than 55 years. AMD is a multifactorial disease associated with multiple genetic and environmental factors. Age and ethnic background also affect disease susceptibility.

Geographic atrophy (GA) affects more than 5 million people worldwide.¹ Generally, visual function is significantly impaired before visual acuity is affected; however, progressing from no involvement of the center of the macula to foveal involvement may be associated with a dramatic loss of visual acuity over a short period of time. GA was responsible for irreversible, severe vision loss in roughly 20% of patients with AMD prior to the approval of ranibizumab (Lucentis, Genentech), an anti-VEGF treatment for the choroidal neovascular or “wet” form of AMD; in this era of anti-VEGF agents, GA may account for an even larger percentage of cases of severe vision loss from AMD.¹⁻³

There are no approved treatments for GA; therefore, there is a substantial unmet need for a therapy to slow its worsening. This article discusses the genetic component of AMD and describes a promising candidate for the treatment of GA.

GENETIC COMPONENT OF AMD

The pathophysiology of AMD is poorly understood. The complement system is involved in tissue inflammation, cell opsonization, and cytolysis, and its functionality is key to the maintenance of cellular integrity, tissue homeostasis, and temporal modifications of the adaptive and innate immune responses of the organism.⁴ Menno van Lookeren Campagne, PhD, a principal scientist at Genentech, explained that, although correlative evidence for complement, inflammation, and GA pathology has been found

in human tissues, a causative role for complement, or for inflammation in general, can be demonstrated only in appropriate preclinical models of GA.

“As rodents lack a macula,” he said, “such models will likely require higher species that contain a macula combined with appropriate ways to expose the model to environmental risk factors and aging.”

Complement factor (CF) I and CFH are both negative regulators of complement activation, Dr. Campagne said. “Genetic studies on large populations have demonstrated that variation in the genes that encode for these proteins leads to their reduced expression and/or reduced negative regulatory potential,” he explained. “As a consequence, complement will be overactivated and start to affect the health of retinal pigment epithelium [RPE], photoreceptors, and choroid. Complement activation in the retina could result in recruitment of immune cells, coating of RPE and photoreceptors with C3 (making them prey for mononuclear phagocytes) and the generation of holes in the membrane of otherwise healthy cells (through the formation of a membrane attack complex).”

At a Glance

- GA significantly impairs patients’ visual function and quality of life.
- Lampalizumab is an antigen-binding fragment of a humanized monoclonal antibody that binds complement factor D.
- The lampalizumab phase 2 study is the first study to demonstrate positive results in patients with GA.

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Which of these processes contributes to AMD pathology and how, at molecular and cellular levels, complement affects retinal cells are not known and require further investigation, Dr. Campagne said.

INHIBITOR OF FACTOR D

The investigational drug lampalizumab (Genentech/Roche) is an antigen-binding fragment (Fab) of a humanized monoclonal antibody that works against CFD (or, simply, factor D), a rate-limiting enzyme that plays a role in the activation and amplification of the alternative complement pathway (ACP), which functions as a component of the immune system. Dr. Campagne and colleagues at Genentech have been involved in the development of lampalizumab.

For an enzyme to be active, it must bind to its substrate. In this case, Dr. Campagne explained, factor D must bind to factor B in order to generate the active enzyme, factor Bb, required for complement activation.

"Lampalizumab blocks a region on factor D that is an important binding site for factor B," he noted. "As a result, factor B cannot be cleaved, therefore inhibiting the alternate complement pathway."⁵ Dr. Campagne said the affinity of the drug for factor D is 70 000-fold higher than the affinity of factor B for factor D. "Hence," he said, "lampalizumab can break this natural enzyme-substrate (factor D-factor B) interaction and efficiently stop the pathway."

Dr. Campagne's lab developed an interest in the complement pathway after researchers there identified a new macrophage receptor for complement C3b (CRlg) and realized that the extracellular domain of this receptor is a selective inhibitor of the alternative complement pathway.^{6,7}

"Inspired by early work from Greg Hageman, PhD, we decided to develop this reagent for AMD," he explained.⁸ "Our hypothesis was that complement, which was abundant in drusen (precursors of AMD), would switch the local milieu from immunosuppressive (the healthy retina is an immune-privileged site) to immune-promoting, with consequences for the health of the retinal pigment epithelial cells and photoreceptors."

One year into development, Dr. Campagne and his team switched from the extracellular domain of CRlg to an antibody that neutralizes factor D (lampalizumab). He explained that lampalizumab targets a rate-limiting factor in the pathway, whereas other complement proteins that are required for pathway activation are more abundant in the blood as well as in the eye.⁹

CLINICAL TRIAL UPDATE

Several clinical trials evaluating the efficacy and safety of lampalizumab in GA secondary to AMD are under way.

The phase 2 MAHALO study demonstrated a positive treatment effect in GA secondary to AMD.¹⁰ At the 18-month endpoint, a 20% reduction in mean GA area growth was reported for patients treated with lampalizumab monthly compared with sham treatment. Furthermore, data from a subgroup of biomarker-positive patients showed a 44% reduction in disease progression rate at 18 months in those receiving lampalizumab monthly and an 18% reduction in mean GA area progression in those receiving lampalizumab every other month.

Following positive results from MAHALO, Genentech initiated two identically designed phase 3 trials (Chroma [NCT02247479] and Spectri [NCT02247531]) in the fall of 2014 investigating the safety and efficacy of lampalizumab 10 mg as treatment for GA. The phase 3 program will investigate the drug's safety and efficacy in slowing GA growth or worsening. The main outcome measure is mean change in GA lesion area of the study eye from baseline. The trial will also assess whether patients with a genetic biomarker (a mutation in CFI) may benefit more from the drug. Key inclusion criteria include bilateral GA secondary to AMD with no choroidal neovascularization, BCVA 20/100 or better (Snellen equivalent), total lesion size between approximately 1 and 7 disc areas, and, if multifocal, at least one lesion 0.5 disc areas or larger.

Secondary efficacy endpoints will include visual function outcomes potentially relevant to the quality of life of patients with GA (eg, reading speed, low light visual acuity, microperimetry, BCVA, and Visual Function Questionnaire measures).

Estimated enrollment for each study is 936 patients, divided into biomarker-positive and biomarker-negative populations. Study participants who complete the trial will be eligible to enroll in an open-label extension study.

Additionally, Genentech is running two large observational studies, Proxima A (NCT02479386) and Proxima B (NCT02399072), to better understand GA progression and its impact on visual function.

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CONCLUSION

GA is a debilitating, progressive disease that can have profound effects on patients' quality of life. If lampalizumab reaches the market, it would be the first in its class and would provide patients with an opportunity to slow disease progression and preserve vision. "A positive phase 3 trial in GA will almost certainly boost new initiatives both from the basic research and translational side and help us find a cure for this disease that seriously affects a rapidly increasing portion of the aging population," Dr. Campagne said. "Our ultimate goal and desire remains to fully halt progression of the disease and restore lost tissues with regenerative therapy." He said that the human genetics of GA could serve as an important stepping stone for new research initiatives. ■

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