MEETING AN UNMET NEED: GEOGRAPHIC ATROPHY

Could retina be on the verge of a treatment for GA?

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Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD) that causes progressive, irreversible vision loss. It affects more than 5 million people worldwide. To clarify the impact of GA, it is worth noting that the number of patients with GA is essentially equal to the number of patients with neovascular, or wet, AMD. It surprises many retina specialists that the prevalence of GA is so high. In addition, the burden of GA is likely to increase over time as the population ages. It is projected that the numbers of patients with GA and with wet AMD are going to increase in parallel over time, with both numbers almost doubling during the next 25 years, culminating in approximately 8 million to 9 million people with each condition globally. Given these epidemiologic data, GA is likely one of the most significant unmet medical needs in any discipline.

WHEN VITAMINS WORK, AND WHEN THEY DO NOT

There is a variety of treatment options available for wet AMD. The combination of vitamins and nutrients commonly known as the AREDS formulation has been shown to reduce the rate of advance from intermediate dry AMD to wet AMD. It is important to note that the AREDS Research Group has also used its study database to analyze the impact of antioxidant micronutrients on progression to GA. There has been no evidence that the AREDS formulation protects against or accelerates progression from intermediate dry AMD to GA. It is fair to conclude that, to date, no effective therapy for GA is available.

COMPLEMENT PATHWAYS

The complement system is part of the innate human immune system. The complement system consists of three pathways: the classical pathway, the mannose-binding lectin pathway, and the alternative pathway. The alternative complement pathway, in particular, has been implicated in the pathogenesis of AMD. Complement byproducts are found in drusen, and genetic polymorphisms for certain complement factors have been shown on fundus autofluorescence (FAF) to contribute to the progression of GA. Tissue samples from human postmortem maculas with advanced AMD have also been shown to have elevated levels of complement proteins. The preponderance of data suggests that targeting complement may be a reasonable strategy in the treatment of GA.

Lampalizumab (Genentech) is an antigen-binding fragment of a humanized monoclonal antibody designed to bind to complement factor D. Complement factor D is required for the initiation and amplification of the alternative complement pathway.

GOING TO TRIAL

A phase 1a clinical investigation was performed to determine the safety and tolerability of administration of a single dose of intravitreal lampalizumab in patients with GA. Eighteen patients received escalating doses of intravitreal
lampalizumab. All patients completed the study with no
dose-limiting toxicities or ocular or systemic adverse effects.
The maximum tolerated dose in the study was 10 mg, the
highest dose tested. This then became the treating dose for
future trials. Based on the elimination half-life of the drug,
it is predicted that it takes approximately 2 months after
administration of a 10-mg intravitreal dose for the vitreous
concentration to fall below the estimated minimum con-
centration required for biologic activity. Therefore, it was
concluded that it was therapeutically plausible to achieve a
sustained biologic effect with intravitreal administration.
The observed safety and tolerability of single-dose admin-
istrations of intravitreal lampalizumab led to the initiation of
a phase 2 multidose study, MAHALO, to investigate the bio-
logical activity of the drug in preventing progression of GA.
The MAHALO trial compared monthly lampalizumab with
placebo. Trial data showed a positive treatment effect at
18 months. On average, patients in the treatment arm had a
20% reduction in the rate of enlargement of the area of GA.

In subpopulations identified by exploratory biomarkers, the
GA progression rate on FAF decreased by as much as 54% (
P < 0.05). Further details of this study will be presented in
a forthcoming publication by the study investigators.

These promising results encouraged the development
of the lampalizumab clinical trial program. The four stud-
ies comprising the lampalizumab clinical trial program will
enroll more than 2,400 patients with GA at more than
275 sites in more than 20 countries. Proxima A and B are
a pair of prospective natural history studies of visual func-
tion and genetics in a broad population of GA patients.
Patients in Proxima A and Proxima B will be followed every
6 months. Researchers will gather anatomic and functional
data to better understand the relationship between anat-
omic changes and visual function metrics.
The other two studies comprising the lampalizumab
clinical trial program are the phase 3 trials Chroma and
Spectri. These are two parallel trials each enrolling approxi-
mately 936 patients randomly assigned to receive 10 mg of

**STUDYING THE STUDIES**

Lampalizumab has undergone and will undergo a number of trials. Here’s a cheat sheet.

**PHASE 1A**
- **Name:** FCFD5414S
- **Design:** 18 patients received escalating doses of intravitreal lampalizumab.
- **Investigating:** safety and tolerability of single-dose administration of intravitreal lampalizumab in patients with GA
- **Findings:** No dose-limiting toxicities or ocular or systemic adverse effects were seen; patients tolerated the highest tested dose (10 mg).

**PHASE 2**
- **Name:** MAHALO
- **Design:** monthly intravitreal lampalizumab versus placebo for 18 months
- **Investigating:** whether lampalizumab therapy curbs GA progression
- **Findings:** Patients in the treatment arm had a 20% reduction in the rate of GA area enlargement. Data analysis of subpopulations identified by exploratory biomarkers showed that the GA progression rate on FAF decreased significantly in lampalizumab groups.

**PHASE 3**
- **Name:** Chroma and Spectri
- **Design:** parallel trials, each enrolling more than 900 patients randomly assigned to receive one of the following: 10 mg lampalizumab every 4 weeks, 10 mg sham every 4 weeks, 10 mg lampalizumab every 6 weeks, or sham every 6 weeks
- **Investigating:** primary outcome measurement: change in GA assessed by FAF imaging at 1 year; secondary outcomes: BCVA, reading speed, and low-luminance visual acuity
- **Findings:** scheduled for completion October 2018

**Name:** Proxima A and Proxima B
- **Design:** pair of prospective, natural history studies that will follow patients every 6 months for imaging and functional measurement
- **Investigating:** the relationship between anatomy and function in patients with GA untreated with lampalizumab
- **Findings:** Proxima A scheduled for completion May 2021; Proxima B scheduled for completion May 2022
intravitreal lampalizumab or sham injection every 4 weeks or every 6 weeks. The trial includes patients who are at least 50 years old and have well-demarcated GA in both eyes but do not have choroidal neovascularization in either eye. Patients must have baseline BCVA of 20/100 or greater. GA can be a single lesion from approximately 1 to 7 disc areas (DA) in size or multifocal with a least one lesion greater than or equal to 0.5 DA. Patients with significant comorbid retinal vascular disease are excluded.

The primary outcome is change in GA assessed by FAF imaging at 1 year. Secondary outcomes include BCVA and metrics to assess changes in visual function (eg, reading speed, low-luminance visual acuity, visual function questionnaire, microperimetry) that often precede changes in BCVA and also significantly affect quality of life.

The estimated study completion date for Chroma and Spectri is October 2018. The retina community and the patients with GA we treat will be eager to see whether lampalizumab will be the first safe and effective approved therapy for this sight-threatening condition.


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