Geographic Atrophy (GA): A Guide for Clinicians

Geographic Atrophy (GA) is the advanced atrophic form of Age-related Macular Degeneration (AMD). GA is a leading cause of visual impairment among older people, affecting 5 million people worldwide, including 29% of people over 50 years old. While there are no approved treatments currently available, recent advances in our understanding of AMD mechanisms and risk factors provide a host of potential targets for drug development.

Symptoms

GA progression causes a gradual loss of visual function in patients. Symptoms include the presence of scotomas (large dark or blind spots in the visual field), difficulty recognizing faces, decreased reading speed measured in words per minute, impaired dark adaptation, impaired contrast sensitivity, and difficulty driving at night.

Risk Factors

Risk factors for GA include:
- Advanced age (especially over 80)
- Early AMD or GA present in fellow eye
- Smoking
- Genetic polymorphisms

Generic Risk Factors:
Most of the genetic risk for AMD and GA is linked to polymorphisms in complement genes C3, C4, CFB, and CCF.

Age-Related Changes in the Retina

The high metabolic demands of the photoreceptors combined with their photoregeneration processes account for the age-related degenerative changes in the retinal environment. Lipoprotein deposits called drusen accumulate under the RPE.

Pathogenesis of AMD

It is thought that excessive accumulation of lipid peroxidation products in the photoreceptors leads to self-complement attack, resulting in increased inflammation that can contribute to AMD progression.

Progression of AMD

The usual inflammatory microenvironment and dysregulation of the alternative complement pathway may lead to cell death and increased inflammatory processes. Lipid peroxidation deposits (LIPD) form between the RPE and photoreceptors, Bruch’s membrane, Bruch’s membrane, and photoreceptors. RPE dysfunction occurs.

Potential therapy: alternative pathway inhibitors

Clinical Trials

Phase II and III clinical trials for GA therapies are ongoing, employing strategies such as complement pathway inhibitors and cell replacement therapy.

References

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Bressler NM, Bressler SB, Baier M, et al. “Materials for Clinical Trials.” GA. Use reasonably strong and lasting evidence for significant improvements in outcomes. Changes in alternative complement pathway leads to cell death and increased inflammatory processes. Lipid peroxidation deposits (LIPD) form between the RPE and photoreceptors, Bruch’s membrane, Bruch’s membrane, and photoreceptors. RPE dysfunction occurs.

Pathways & Potential Targets for Future Therapies

Visual Cycle Toxic Byproducts, Impaired Lipid Metabolism

Inflammation and Immune Attack

Inflammatory amplification of immune processes at the level of the retina, the RPE, and the photoreceptors appear to contribute to AMD. Retinal inflammation can lead to immune attack, which is linked to cellular damage and GA progression.

Potential therapy: anti-inflammatory agents

Alternative Complement Pathway Dysregulation

A loss of control of complement activation is necessary for immune surveillance in the eye. Dysregulation of the alternative complement pathway leads to self-complement attack, resulting in increased inflammation that can contribute to AMD progression.

Potential therapy: alternative complement pathway inhibitors

Clinical Diagnosis

Several imaging methods are used, often in combination, to assess and diagnose geographic atrophy cases. Atrophic lesions are characterized by confluent areas of RPE atrophy (RPE/AMD) and photoreceptor cell loss. Implantation of subretinal gene therapy or FAF imaging is possible. FA allows one to map out these areas and helps one to identify GA with a minimum of these processes. GA most commonly starts around the center of the macula. As the lesion expands into the fovea, visual function may become worse.

Color Fundus Fluorescein Imaging (FFI)

The OCT scan correlates with the green line on the optical coherence imaging (OCT) scan.