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Editorial

Geographic atrophy- no longer an end game

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Geographic atrophy (GA), the advanced stage of dry age-related macular degeneration (AMD) is characterized by bilateral progressive degeneration of the retinal pigment epithelium (RPE), photoreceptors and choriocapillaris, resulting in irreversible central vision loss. It is an important cause of blindness in the aging population. Till recent times, there were no approved therapies available to modify the course of GA, and its management was limited to low vision aids and rehabilitative services. Cutting edge research has initiated a paradigm shift by introducing the first disease modifying treatments and offering hope to preserve and potentially restore vision.

1. Advances in Complement Inhibition

A new development in GA treatment has been the therapeutic targeting of the complement system which is a critical component of the innate immune response. Chronic overaction of complement pathways contributes significantly to the inflammatory and degenerative processes underlying the pathogenesis of GA.

The United States Food and Drug Administration (FDA) approved pegcetacoplan (Syfovre), a targeted inhibitor of complement component C3 in 2023, based on encouraging results of the OAKS and DERBY clinical trials. These two studies showed that pegcetacoplan reduced GA lesion progression by upto 22% over 24 months compared to the sham treatment.[1] A similar drug, avacincaptad pegol (Izervay) which is a complement C5 inhibitor received FDA approval after the GATHER 1 and GATHER 2 trials, both of which showed statistically significant reductions in lesion enlargement rates.[2]

It is exciting to see such developments, however these agents only slow disease progression, they do not reverse existing atrophic damage, thereby preserving the remaining retinal function. These therapies require frequent intravitreal injections, (monthly or bimonthly). Hence cost and compliance are important considerations. An increased incidence of exudative AMD, has been reported in upto 12% of treated patients.

2. Emerging Strategies-Tyrosine Kinase Inhibitors

Study of the intracellular signalling pathways has shown tyrosine kinase inhibitors (TKIs) as a promising therapy for GA treatment. TKIs regulate multiple cellular functions including proliferation, migration, inflammation and apoptosis. Dysregulation of these pathways contribute to retinal degeneration in AMD.

Promising preclinical studies show that selective tyrosine kinase inhibition can reduce inflammatory signalling and protect the retinal pigment epithelium from degeneration. Several investigational TKIs are currently being developed with the aim of providing a sustained anti-inflammatory and anti-degenerative effect which requires less frequent dosing regimens compared to existing intravitreal therapies.

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3. Regenerative Medicine- CTX-203 and Stem Cell Based Therapies

A novel frontier in GA treatment is regenerative medicine, which not only slows degeneration, but also replaces lost retinal tissue. CTX-203 developed by Cellusion Inc. has corneal endothelial like cells which are derived from pluripotent stem cells (iPSC) and were originally developed for corneal diseases. Adaptations are being explored for retinal diseases like GA, where replacement of the dysfunctional RPE cells may restore structural and functional integrity.[3]

Preclinical studies suggest that transplanted iPSC - derived cells can integrate into host tissue, secrete trophic factors and support the existing retinal cells. If this moves from bench to bedside, CTX 203 could shift the therapeutic focus from preservation of retinal cells to regeneration, offering the hope of visual restoration to patients with advanced GA.

4. Innovations in Therapy- CTX-114

Further expanding the regenerative therapeutic reach is CTX-114, also from Cellusion Inc. It consists of highly purified iPSC derived RPE cells optimized for subretinal delivery. While CTX-203 primarily targets corneal and broader epithelial repair, CTX-114 is being specifically designed for retinal implantation. It can directly replace damaged RPE in geographic atrophy.

Preclinical models have demonstrated that CTX-114 can survive, integrate and functionally support overlying photoreceptors with the potential to restore vision.[4] Clinical trials to evaluate the safety, tolerability and preliminary efficacy of CTX-114 in GA patients are likely to commence shortly. The ability to replace cells and support endogenous repair mechanisms means that CTX-114 is likely to lead the regenerative treatment category. CTX-114 could significantly alter the management paradigm by enabling tissue repair, not merely slowing degeneration.

5. Gene Therapy Approaches

Gene therapy is rapidly emerging as a promising treatment strategy. It aims to achieve a sustained therapeutic protein expression within ocular tissues through a single administration rather than repeated intravitreal injections. One of the promising drugs is GT005 (Gyroscope Therapeutics) which is an Adeno-associated virus (AAV)-based therapy.[5] It is designed to upregulate the complement factor I, a key regulator of the alternative complement pathway. By enhancing the expression of factor I, GT005 seeks to restore the balance to complement activation and reduce retinal inflammation. Early phase clinical trial include FOCUS and EXPLORE studies which have shown encouraging safety profiles and preliminary evidence of biological activity. Gene therapy holds the key to longer durability and also earlier intervention, potentially altering disease progression at a molecular level before substantial atrophy occurs.

6. Neuroprotection and Personalized Medicine

Another promising strategy is neuroprotection, drugs such as brimonidine, which is traditionally used for glaucoma is under evaluation for their potential to protect retinal neurons from apoptosis due to degeneration. A phase 2 trial of brimonidine drug delivery system (Brimo DDS) showed reduced GA lesion enlargement in treated eyes compared to controls, suggestive of a neuroprotective effect which warrants further investigation.

We have reached the era of personalized medicine, advances in genomics have uncovered genetic variants including CFH, ARMS2 and CFI mutations that give different risks for AMD and GA progression.[6] Future therapeutic strategies could leverage individual genetic profiles to stratify patients, predict treatment response and customize interventions. Such precision medicine may maximize the therapeutic efficacy while minimizing adverse outcomes.

7. Conclusion

The introduction of complement inhibitors such as pegcetacoplan and avacincaptad pegol represent a major milestone in the treatment of geographic atrophy, as they are the first disease modifying options for patients with this blinding disease. However their modest efficacy, frequent administration and safety considerations highlight the necessity for further innovation.

Emerging therapies including tyrosine kinase inhibitors, regenerative approaches like CTX-203 and CTX-114, gene therapy such as GT005, neuroprotective agents and personalized treatment strategies offer us a glimpse of the future where GA management extends beyond disease stabilization and towards vision restoration and functional recovery. Over the next decade, these advancements are poised to fundamentally transform the prognosis for individuals with GA, offering hope where previously there was none.

8. Source of Funding

None.

9. Conflict of Interest

None.

References

1. Apellis Pharmaceuticals. SYFOVRE® (pegcetacoplan injection) continued to demonstrate efficacy in geographic atrophy. 2023. Available from: https://investors.apellis.com/news-releases/news-release-details/syfovrer-pegcetacoplan-injection-continued-demonstrate-0

2. Astellas Pharma Inc. Iveric Bio receives U.S. FDA approval for IZERVAY™ (avacincaptad pegol intravitreal solution), a new treatment for geographic atrophy. Astellas Newsroom [Internet]. 2023 Aug 4 [cited 2025 May 31]. Available from: https://newsroom.astellas.us/2023-08-04-Iveric-Bio-Receives-U-S-FDA-Approval-for-IZERVAY-TM-avacincaptad-pegol-intravitreal-solution-,-a-New-Treatment-for-Geographic-Atrophy.
3. Sparrow JR, Hicks D, Hamel CP. The Retinal Pigment Epithelium in Health and Disease. *Curr Mol Med*. 2010;10(9):802–23.
4. Klymenko V, González Martínez OG, Zarbin MA. Recent Progress in Photoreceptor Cell-Based Therapy for Degenerative Retinal Disease. *Stem Cells Transl Med*. 2024;13(4):332–45.
5. Banou L, Sarrafpour S, Teng CC, Liu J. Ocular Gene Therapy: An Overview of Viral Vectors, Immune Responses, and Future Directions. *Yale J Biol Med*. 2024;97(4):491–503.
6. Shughoury A, Sevgi DD, Ciulla TA. Molecular Genetic Mechanisms in Age-Related Macular Degeneration. *Genes (Basel)*. 2022;13(7):1233.

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