RETINA INTERNATIONAL
Seeking A Cure For
Retinitis Pigmentosa, Macular Degeneration,
Usher Syndrome and Allied Retinal Dystrophies

Investigational GA Therapies

Advancements in the understanding of the processes and pathways involved in the development and progression of GA has led to the development of a several investigational therapies. Potential therapies under investigation in clinical trials include complement cascade inhibitors, anti-inflammatory drugs, neuroprotective drugs, and cell-based therapy.

Complement Inhibitors

Several drugs in clinical development for GA specifically target different components of the alternative complement cascade – this is part of the immune system that helps immune cells and antibodies to clear foreign pathogens and promotes inflammation. In GA, dysregulation of the complement cascade is understood to lead to inflammation resulting in damage to the retinal cells.[1]

Complement inhibitors currently under investigation in clinical studies include:

- APL-2 (Apellis Pharmaceuticals, Inc.): complement 3 (C3) inhibitor currently being investigated in a Phase II study in patients with GA (NCT02503332). On 24 August 2017, it was announced that this study had met is primary endpoint by showing a statistically significant slowing of disease progression compared with sham injection at 12 months. Phase III studies are being planned. [2]
- ARC1905 (Zimura®, Ophthotech Corp.): anti-C5 aptamer targeting C5 has completed a Phase I trial (NCT00950638). Plans to conduct a Phase II/III trial of ARC1905 in patients with GA have been announced.[3]
- Lampalizumab (Roche/Genentech): a humanized monoclonal antibody that inhibits complement factor D, the rate-limiting enzyme in the alternative pathway of the complement cascade. After a Phase Ib/II trial (MAHALO; NCT02288559)[4] showed that lampalizumab slowed the progression of GA, two Phase III trials, Chroma (NCT02247479) and Spectri (NCT02247531), were initiated to evaluate the efficacy and safety of lampalizumab administered every 4 or 6 weeks by intravitreal injection versus sham injections. On 8 September 2017, it was announced that the Spectri study did not meet its primary endpoint of reducing mean change in GA lesion area in

[1] Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. The Pathophysiology of Geographic Atrophy Secondary to Age-Related Macular Degeneration and the Complement Pathway as a Therapeutic Target. Retina. 2017;37(5): 819-835.
[2] Release APIP. Apellis Pharmaceuticals Announces that APL-2 Met its Primary Endpoint in a Phase 2 Study in Patients with Geographic Atrophy, an Advanced Form of Age-Related Macular Degeneration. 2017.
[3] Cooke Bailey JN, Hoffman JD, Sardell RJ, Scott WK, Pericak-Vance MA, Haines JL. The Application of Genetic Risk Scores in Age-Related Macular Degeneration: A Review. Journal of clinical medicine. 2016;5(3).
[4] Yaspan BL, Williams DF, Holz FG, Regillo CD, Li Z, Dressen A, et al. Targeting factor D of the alternative complement pathway reduces geographic atrophy progression secondary to age-related macular degeneration. Science translational medicine. 2017;9(395).

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patients treated with lampalizumab compared with sham treatment. The results from the second Phase III study, Chroma, will be evaluated in November 2017.[5]

- CLG561 (Alcon) and tesidolumab (Novartis/MorphoSys): both drugs target different parts of the complement system. CLG561 inhibits a complement pathway protein called properdin, while LGF316 is complement 5 (C5) inhibitor. A Phase II trial is currently evaluating CLG61 either used alone (monotherapy) or in combination with LGF316 (NCT02515942).

Neuroprotective and anti-inflammatory drugs

Several drugs with neuroprotective properties are being investigated in patients with GA. These agents may be able to prevent death of retinal cells, in order to prevent or delay the progression of the disease.

- Brimonidine (Allergan) is an alpha-2 adrenergic agonist used in ophthalmology for the treatment of glaucoma patients, and there is also evidence from preclinical animal model studies that it has a neuroprotective effect on retinal cells.[6] A Phase II, randomized study (NCT00658619) of brimonidine administered within a 22-gauge intravitreal biodegradable implant appeared to slow the rate of GA progression. During the study, a total of 113 patients with GA were randomized to brimonidine 132 µg, 264 µg or sham treatment at baseline and Month 6. After 12 months, reductions in GA progression rates of 18.8% and 27.5% were observed in the low- and high-dose groups respectively. A follow-up Phase II study (BEACON; NCT02087085) is currently evaluating the safety and efficacy a larger 25-gauge brimonidine implant (400 µg dose) that will be administered once every 3 months during the 36-month study.
- Ciliary neurotrophic factor-501 (CNFT) is a neurotrophic protein naturally produced by neurons and Mueller cells found in the retina. Under conditions of stress, CNFT has been shown to slow the loss of photoreceptor cells during retinal degradation.[7] A double-masked, sham-controlled, Phase II trial (NCT00447954) evaluated low- or high-dose CNTF delivered via an intraocular encapsulated cell technology (ECT) implant (NT-501 ECT; Neurotech Pharmaceuticals). This study reported a slowing progression of visual loss progression after 1 year in patients with GA, as determined by BCVA. It is currently unclear whether future studies of NT-501 ECT in patients with GA are planned.

[5] Release RM. Roche provides update on first lampalizumab phase III study for geographic atrophy, an advanced form of age-related macular degeneration. 2017.
[6] Wheeler L, WoldeMussie E, Lai R. Role of alpha-2 agonists in neuroprotection. Survey of ophthalmology. 2003;48 Suppl 1: S47-51.
[7] Zhang K, Hopkins JJ, Heier JS, Birch DG, Halperin LS, Albini TA, et al. Ciliary neurotrophic factor delivered by encapsulated cell intraocular implants for treatment of geographic atrophy in age-related macular degeneration. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(15): 6241-6245.

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Tetracyclines

Tetracyclines are a class of antibiotics that possess anti-inflammatory and neuroprotective properties. Two tetracycline compounds, minocycline and doxycycline, are currently being investigated in clinical studies involving patients with GA.

- Minocycline - Preclinical studies in mouse models of acute retinal degeneration have demonstrated that minocycline can preserve retinal structure by inhibiting the activation of resident immune cells called microglia.[8] Microglia produce inflammatory factors associated with the development of GA. It is hoped that through reduction of microglia inhibition, minocycline and doxycycline may be able to reduce the rate of GA progression. The efficacy and safety of minocycline is being evaluated in a Phase II trial (NCT02564978) that will enrol around 45 patients. Following a 9-month observational period, participants will receive 100 mg minocycline twice daily for a 3-year period.
- Doxycycline (ORACEA®) is being investigated in a placebo-controlled Phase II/III trial (TOGA; NCT01782989) that plans to recruit 286 patients with GA. Participants will complete a 6-month observation phase before being randomized to either ORACEA® (40 mg doxycycline) once-daily or placebo capsule once-daily for 24 months.

Stem cell therapy

Stem cell therapy is another promising therapeutic approach in age-related macular degeneration. In GA, atrophy primarily affects the retinal pigment epithelium (RPE) and photoreceptors cells of the retina. Replacement of these damaged layers by stem cell transplantation is therefore an attractive treatment option. The use of stem-cell therapy is currently being evaluated in several studies. However, there are number of ethical, regulatory, safety and technical challenges that need to be overcome before stem-cell therapies can be used as standard therapy.[9]

[8] 13 Scholz R, Sobotka M, Caramoy A, Stempfl T, Moehle C, Langmann T. Minocycline counter-regulates pro-inflammatory microglia responses in the retina and protects from degeneration. Journal of neuroinflammation. 2015;12: 209.

[9] Nazari H, Zhang L, Zhu D, Chader GJ, Falabella P, Stefanini F, et al. Stem cell based therapies for age-related macular degeneration: The promises and the challenges. Progress in retinal and eye research. 2015;48: 1-39.