



TACKLING GEOGRAPHIC ATROPHY WITH GENE THERAPY

Stopping atrophy at the source—our genes—may one day be an effective treatment approach.

BY REBECCA HEPP, EDITOR-IN-CHIEF

The era of geographic atrophy (GA) therapy is upon us with the approval of pegcetacoplan (Syfovre, Apellis Pharmaceuticals) for patients with GA secondary to AMD and Iveric Bio hot on their heels with an FDA Prescription Drug User Fee Act goal date in August for avacincaptad pegol (Zimura). Within 1 year, a population that formerly had no treatment options may have two to choose from. Despite the excitement surrounding these therapies, many clinicians are already looking forward to further advances that may be able to do more than slow the progression of GA. Gene and cell therapies may be able to do just that. Here's a look at the research underway.

GENE THERAPY

GT005 (Gyroscope/Novartis) is a one-time gene therapy that uses an adeno-associated viral vector and encodes for complement factor I (CFI), which is a natural break in the system. The therapy is delivered using one of two methods: a vitrectomy with subretinal delivery or the Orbit subretinal delivery system (Gyroscope/Novartis).

The phase 1/2 FOCUS trial enrolled 56 patients and is designed to evaluate the safety, dose response, and efficacy of three different doses of GT005.¹ Interim safety data suggested that GT005 was safe and well tolerated with no treatment-related serious adverse events.² One patient experienced a possible GT005-related adverse event of suspected choroidal neovascularization at 6 months. The researchers noted that 11 of 13 patients treated with GT005 had increased CFI levels (an average increase of 122% compared with baseline) that was sustained at week 29 and beyond.

The phase 2 HORIZON trial has completed enrollment of 255 patients who are randomized to receive either a medium or high dose of GT005 or control.³ Patients are followed for 96 weeks, with a primary endpoint being the change in GA area from baseline to week 72. Key secondary endpoints include the change in GA area at week 96, frequency of adverse events, changes in retinal morphology, change in BCVA, and change in quality of life as measured by the Visual Function Questionnaire-25.³ As part of this study, participants are also undergoing genotyping to help the researchers

identify those who have a CFI rare variant genotype, which will determine eligibility for certain stages of the study. The estimated completion date of the trial is September 2023.

The phase 2 EXPLORE trial, like HORIZON, is evaluating the safety and efficacy of two different doses of GT005 in approximately 75 patients.⁴ The primary endpoint is the change in GA area from baseline to week 48. Unlike HORIZON, the inclusion criteria do not include genotyping to identify the CFI variant genotype. Patients will receive one of two doses of GT005 or sham via subretinal injection. The trial's estimated completion date is in November 2024.⁴

Some patients treated in HORIZON and EXPLORE will be invited to participate in the long-term follow-up trial for GT005, ORACLE.⁵ Patients will participate in five study visits within 3 years, providing a total of 5 years of follow-up post-treatment.

CELL THERAPY

HMR59 (Hemera Biosciences/Janssen) is in clinical trials with a completed phase 1 study.⁶ HMR59 is administered via intravitreal injection with the goal of increasing the expression of the soluble form of CD59. This product is intended to protect retinal cells by inhibiting MAC formation, the terminal step of complement-mediated cell lysis. The trial

AT A GLANCE

- ▶ Gene and cell therapies are under investigation to treat geographic atrophy and potentially stop disease progression.
- ▶ GT005 (Gyroscope/Novartis) is currently in several phase 2 trials.
- ▶ HMR59 (Hemera Biosciences/Janssen) has completed a phase 1 study.
- ▶ RG6501 (OpRegen, Lineage Cell Therapeutics/Genentech/Roche) is in phase 2 trials.

GENE THERAPY ADVANCES IN WET AMD

Regenxbio is forging ahead with its gene therapy candidate, RGX-314, for wet AMD with several clinical trials:

- The phase 1/2 safety and tolerability study of RGX-314 (NCT03066258) in 42 patients with wet AMD remains active with up to 5 years of follow-up.
- The phase 2 AAVIATE (NCT04514653) trial is evaluating suprachoroidal delivery of RGX-314 and is enrolling approximately 115 patients with wet AMD.
- The phase 3 ASCENT (NCT05407636) and ATMOSPHERE (NCT04704921) trials are enrolling approximately 300 patients each with wet AMD who will be randomized to one of two RGX-314 doses or a control arm treated with aflibercept (Eylea, Regeneron) or ranibizumab (Lucentis, Genentech/Roche), respectively.

Adverum Biotechnologies initiated a phase 2 trial (NCT05536973) of ixoberogene soroparvovec (Ixo-vec [formerly ADVM-022]), which is enrolling approximately 72 wet AMD patients randomized to receive one of two doses of the study drug.

4D Molecular Therapeutics has a gene therapy candidate, 4D-150, currently in a phase 1/2 trial (NCT05197270) that is recruiting approximately 65 patients who will be randomized into one of four treatment arms.

enrolled 17 patients who were treated with one of three doses of HMR59, and the primary endpoint was the number of patients experiencing adverse events through week 26. Secondary endpoints included the change in GA area from baseline, GA growth rate, incidence of conversion to wet AMD, and the prevention of visual acuity loss of 15 or more letters.⁶ Completed study data is pending.

RG6501 (OpRegen, Lineage Cell Therapeutics/Genentech/Roche), an allogeneic retinal pigment epithelial cell therapy, is under investigation for the treatment of GA secondary to AMD. Preliminary results of the phase 1/2 study suggest that treatment with RG6501 can lead to improvements in outer retinal structure and visual function.⁷ For example, patients in cohort 4 of the study experienced an average gain of 7.6 letters in visual acuity at 12 months in the study eye—three patients experienced a gain of at least 15 letters

AN ORAL APPROACH

ALK-001 (Alkeus Pharmaceuticals) isn't a gene therapy, but it proposes a very different approach to standard GA therapy. This modified form of vitamin A is a once-daily oral medication designed to replace natural vitamin A with a form that creates dimers more slowly. The accumulation of vitamin A dimers in the retinal pigment epithelium and Bruch membrane has been implicated in the aging and degeneration of the retina. The active phase 2 trial enrolled 300 patients with a primary endpoint of GA growth rate from baseline to 24 months. Secondary endpoints include safety, tolerability, pharmacokinetics, incidences of conversion to wet AMD, and changes in visual acuity, and reading speed. The estimated completion date is August.¹

1. Phase 3 study of ALK-001 in geographic atrophy (SAGA). Accessed April 25, 2023. bit.ly/42KlQyS

at 12 months.⁷ The phase 2 study is recruiting at least 30 patients (up to 60) with GA who will receive subretinal delivery of an RG6501 dose of approximately 200,000 cells.⁸ While the main focus of the study is to assess the safety and feasibility of the subretinal delivery method, the researchers are also evaluating the improvement in retinal structure (determined via OCT imaging) 3 months post-surgery.⁸ The estimated completion date is September 2029.

Astellas is investigating human embryonic stem cell-derived RPE cells to treat GA. The phase 1b clinical trial of ASP7317 is recruiting 18 patients with GA who will receive one of three doses (low, medium, or high cells/dose) via vitrectomy with subretinal injection, along with immunosuppressive therapy. The primary outcomes are safety and tolerability at 52 weeks, and secondary endpoints include change in GA lesion area and BCVA at week 52 compared with baseline.⁹ ■

1. FOCUS: first in human study to evaluate the safety and efficacy of GT005 administered in subjects with dry AMD. Accessed April 3, 2023. clinicaltrials.gov/ct2/show/NCT03846193

2. Gyroscope Therapeutics announces presentation of positive interim phase I/II data for investigational gene therapy GT005 at Retina Society Annual Scientific Meeting [press release]. September 30, 2021. Accessed April 25, 2023. bit.ly/3pASIMH

3. HORIZON: A phase II study to evaluate the safety and efficacy of two doses of GT005. Accessed April 25, 2023. bit.ly/3UV17lu

4. EXPLORE: A phase II study to evaluate the safety and efficacy of two doses of GT005. Accessed April 3, 2023. bit.ly/43PNazL

5. ORACLE: A long-term follow-up study to evaluate the safety and durability of GT005 in a Gyroscope-sponsored antecedent study. Accessed April 3, 2023. clinicaltrials.gov/ct2/show/NCT05481827

6. Treatment of advanced dry age related macular degeneration with AAVCAGsCDS9. Accessed April 3, 2023. bit.ly/3UZy0SK

7. RG6501 (OpRegen) phase 1/2a clinical results support the potential for OpRegen to slow, stop or reverse disease progression in GA [press release]. Eyewire+. April 27, 2023. Accessed April 27, 2023. bit.ly/3pyl5Kt

8. A study to optimize subretinal surgical delivery and to evaluate safety and activity of OpRegen in participants with geographic atrophy secondary to age-related macular degeneration. Accessed April 26, 2023. clinicaltrials.gov/ct2/show/NCT05626114

9. A study of the safety and tolerability of ASP7317 in adults who are losing their clear, sharp central vision due to geographic atrophy secondary to dry age-related macular degeneration. Accessed May 3, 2023. clinicaltrials.gov/ct2/show/NCT03781449