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Editorial

Local Complement Inhibition for Geographic Atrophy in Age-Related Macular Degeneration: Prospects, Challenges, and Unanswered Questions

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Geographic atrophy (GA) in age-related macular degeneration (AMD) represents a common, blinding condition that typically is bilateral and relentlessly progressive.[1,2] It affects more than 5 million people, with a global prevalence of 0.44%.[2] If the fovea is involved, visual acuity typically is very poor. It represents a substantial public health problem because no drugs are approved to slow GA enlargement or to restore vision.

The Prospect of Local Complement Inhibition: A Novel Therapeutic Approach

If local complement inhibition obtains approval, the prospect of the first therapy to slow GA enlargement will be highly welcome. In the FILLY phase 2 trial (NCT02503332),[3] the C3 inhibitor pegcetacoplan met its primary end point. Geographic atrophy enlargement over 12 months was decreased by 29% (monthly treatment) or 20% (every-other-month treatment). The results of the phase 3 trials DERBY (NCT03525613) and OAKS (NCT03525600) are expected in late 2021. In the GATHER 1 (NCT02686658) phase 2/3 trial, the C5 inhibitor avacincaptad pegol, given monthly, met its primary end point.[4] Geographic atrophy enlargement over 12 months was decreased by 27% (2 mg) or 28% (4 mg). Currently, a second phase 3 trial, GATHER 2 (NCT04435366), is enrolling patients. It involves 2-mg treatment only (monthly), with a second randomization at 12 months to monthly or every-other-month treatment.

Potential Challenges

However, several challenges present themselves. This degree of slower enlargement will be meaningful clinically over long periods only. This makes the risk-to-benefit balance more nuanced for each patient. Delivery requires intravitreal injection, and monthly dosing seems to be required. Because GA typically is bilateral, many patients will need 2 injections per month.

One important risk-to-benefit consideration is the increased risk of neovascular AMD (nAMD). In both trials, treatment caused a dose-dependent increase in exudative disease (17-fold with monthly C3 inhibition and 3-fold with monthly C5 inhibition).[3,4] The eligibility criteria may explain this variation partially: in FILLY, but not in GATHER 1, fellow-eye nAMD was permitted (comprising 39%). In FILLY, with monthly treatment, the rate of nAMD was 33% in those with fellow-eye neovascularization, but 12% in those without (i.e., similar to the GATHER 1 rate of 9%−10%). Overall, the highest nAMD rates seem to occur with the combination of propensity (fellow-eye nAMD) and stimulus (higher dose or frequency). Some patients therefore might be discouraged from treatment for this reason.

Will the risk of nAMD be altered in subsequent years of treatment? In FILLY, progression to exudation seemed to be relatively monotonic over 18 months,[5] which suggests some ongoing risk in subsequent years. Understanding nAMD behavior after complement inhibition is important. In FILLY, where fluorescein angiography detected neovascularization, all incident cases were type 1 lesions.[5] Over a mean follow-up of 7 months, the mean number of injections was 5. This seems partially distinct from neovascularization occurring naturally after GA, where most lesions are type 2 and few injections are required.[6] However, it may relate to the high rate of nonexudative type 1 lesions present at baseline in FILLY: the double-layer sign was present in 73% of converting eyes.[5]

What is the mechanism for increased risk of nAMD? If the same mechanism were responsible for both neovascularization and slower GA enlargement, increased risk would be inseparable from efficacy. If not, future complement inhibitors might be refined to avoid this risk. The FILLY authors suggested that decreased C3b deposition on choriocapillaris endothelial cells may cause decreased phagocytosis, causing vessel regrowth.[3] However, this would not explain why the phenomenon is observed with C5 inhibition also. Some have suggested that pegylation may be responsible.[7] However, in this case, one would expect higher risk in the 4-mg than 2-mg GATHER 1 arms. Knowing the location of the neovascularization would indicate whether it occurs in areas where otherwise atrophy would have developed (i.e., tipping the balance from atrophy toward neovascularization) or elsewhere de novo.[8]

Unanswered Questions

Regarding the practicalities of service provision in routine clinical practice, how many eligible patients are there, and how many will pursue treatment? Many with noncentral GA may be highly motivated to slow progression to central involvement, whereas some with central GA may not. Of note, one-third of eyes show central involvement at onset; of the remainder, the proportion progressing to central involvement is approximately 57% over 4 years.[1] The level of motivation may differ by scenario:

1. Bilateral noncentral GA: many patients may be highly motivated for treatment in both eyes;

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2. Central GA and noncentral GA in the fellow eye: many may be motivated (especially regarding the latter eye);
3. Noncentral GA and intermediate AMD: many may be motivated (although perhaps less strongly); and
4. Noncentral GA and nAMD (with or without GA): treatment in the former eye would carry a high risk of nAMD (although motivation might be higher with poor acuity in the fellow eye).

In all scenarios, a detailed assessment for nAMD is recommended, including OCT angiography for non-exudative neovascularization.

How long will treatment be required? Median time from noncentral GA onset to central involvement is estimated at 3.1 years.[1] If treatment slows enlargement by 28%, median time to central involvement might be approximately 4 years. Hence, treatment for 4 years would delay central involvement by 1 year (assuming treatment is commenced early, efficacy in clinical practice is similar, and treatment affects foveal and extrafoveal areas similarly). Will treatment effects persist over years, or could tachyphylaxis occur?

Indeed, how can physicians assess whether treatment is working? In nAMD, treatment responses are assessed rapidly and easily by OCT. In GA, treatment effects must be inferred by a partial slowing in already slow and variable enlargement rates. Several paradigms may be imagined. One simple approach is to initiate treatment, assume efficacy, and continue injecting. Are patients and physicians willing to proceed agnostically?

Another approach, particularly for early GA, is to obtain natural history data on enlargement, perhaps over 6 months, before treatment. Several months later, again, enlargement is calculated. Given that the square root of enlargement is relatively monotonic,[1,9,10] this enables a response rate to be calculated. In previous analyses, 6-month enlargement rates were predictive of subsequent 12-month rates, explaining 37% of variability (Friesenhahn M, et al. *Invest Ophthalmol Vis Sci.* 61 [ARVO E-Abstract 2988], 2020). Disadvantages include suboptimal accuracy and vision lost through delaying treatment. This would require imaging software advances, ideally with automated GA area measurements in real time. Such approaches exist,[11] but most are still at the proof-of-principle stage.

A third approach is to treat immediately and to compare the actual enlargement rate with a predicted rate. Again, such algorithms exist.[10–12] One deep learning model predicts enlargement rates from imaging data and can explain 52% (fundus autofluorescence), 48% (OCT), or 56% (fundus autofluorescence and OCT) of variability (Yang Q, et al. *Invest Ophthalmol Vis Sci.* 62 [ARVO E-Abstract 235], 2021). This approach would avoid delaying treatment, but accuracy remains suboptimal. An alternative approach might be possible if biomarkers of treatment response were available. OCT characteristics of the photoreceptor layer might be candidates (Schmidt-Erfurth U, et al. *Invest Ophthalmol Vis Sci.* 62 [ARVO E-Abstract 236], 2021),[13] but require further research.

How are physicians to choose between C3 and C5 inhibitors? The response rate seemed to be similar in FILLY and GATHER 1, despite important mechanistic differences.[7] The FILLY authors suggested reasons why C3 might be preferable: C3 being upstream of all major effectors, protecting cell surfaces from phagocytosis by decreased C3b deposition, and modulation of microglia and macrophages.[3] The GATHER 1 authors suggested that, because C5 inhibition preserves C3 activity, it may offer safety advantages, while still preventing C5a and C5b formation.[4] Ultimately, we must learn more about the relative involvement of the 3 effector mechanisms: (1) chemotaxis and immunomodulation by anaphylatoxins C3a and C5a, (2) cell lysis and sublytic effects by membrane attack complex, and (3) opsonization and immunomodulation by C3b and breakdown fragments. Similar treatment responses with C3 and C5 inhibition may argue for the relative importance of the membrane attack complex and C5a over C3a and C3b.

Finally, could complement inhibition delay GA onset? Post hoc FILLY analyses examined macular lesions larger than 500 μm beyond GA margins at baseline (Chakravarthy U, et al. *Invest Ophthalmol Vis Sci.* 62 [ARVO E-Abstract 1213], 2021). Monthly pegcetacoplan treatment decreased progression from incomplete to complete retinal pigment epithelium and outer retinal atrophy, whereas progression from large drusen to retinal pigment epithelium and outer retinal atrophy was decreased numerically. However, if some of this contributes to lower GA area measurements at later time points, this effectively downgrades the treatment effect related to slower enlargement at GA margins. Indeed, for the FILLY and GATHER 1 treatment effects, it would be helpful to know the relative contributions of preventing incident atrophy at nonconfluent sites versus slowing the enlargement of established GA at its margins.[8] Importantly, if the main contribution were from the former, it would suggest that complement inhibition's principal role should be earlier in AMD, while additional therapeutic strategies would be required at the GA stage.

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