

To Treat or Not to Treat Geographic Atrophy – That is the Question

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To treat or not to treat — that is the question for patients with geographic atrophy and the physicians entrusted with their care. This is a timely question because our profession finds itself enmeshed in a legitimate debate about the role of complement inhibition in the treatment of geographic atrophy.^{1–3} This debate arises from our own success, as 2 complement inhibitory drugs have been recently approved by the U.S. Food and Drug Administration, pegcetacoplan and avacincaptad pegol.^{4–6} Monthly intravitreal avacincaptad pegol reduced the mean square-root-transformed geographic atrophy area growth rate by 14% at 1 year (2 mg dose) and by 28.1% (2 mg cohort) and 30.0% (4 mg cohort) at 18 months versus sham.^{7–9} Intravitreal pegcetacoplan (15 mg/0.1 mL) monthly or every other month slowed geographic atrophy lesion growth by 21% and 16%, respectively, at 12 months.¹⁰ In DERBY, pegcetacoplan monthly or every other month slowed geographic atrophy lesion growth by 19% and 16% versus sham by 24 months.¹⁰ New-onset exudative age-related macular degeneration was more frequent in treated eyes in all studies, ranging from 11.9% to 15.7% versus 2.4% to 2.7% in sham groups in GATHER1, and was reported as 20.9% and 8.9% in monthly and every other month groups versus 1.2% in sham in GATHER2.^{7,8} The rate of new-onset exudation was reported as 8% to 11% versus 2% in sham eyes in OAKS, and was reported in 27 (13%), 12 (6%), and 9 (4%) patients in DERBY receiving pegcetacoplan monthly, every other month, or sham, respectively, at 24 months.¹⁰ None of the trials demonstrated differences in key secondary visual function end points. This progress has generated much excitement in the field, as evidenced by the recent acquisition of Iveric Bio by Astellas for the staggering sum of \$5.9 billion. And yet the treatment question remains in the minds of many patients and their physicians because the treatment burden, including cost and potential complications, is sobering while the effect of both drugs is limited to slowing the growth rate of geographic atrophy with no detectable effect in visual function at 2 years.^{1–3}

It is critical to ask exactly how we are going to apply the data that have been published on complement inhibition for geographic atrophy to the care of patients. Recently, Spaide and Vavvas^{1,3} have adopted the valid and important stance that the potential costs to the patient outweigh the benefits because the treatment effect is small and many patients eligible for and receiving regular intravitreal injections of complement inhibitors would never experience visual loss in

their lifetime even without treatment. There is an enormous treatment burden with regular intravitreal injections that do not result in any visual benefit over the 2 year period of time of the study. However, there is a thoughtful opposing point of view, in which the argument can be made that limiting progression of geographic atrophy is an important addition to our treatment armamentarium despite the lack of visual acuity benefit.² The argument here goes that enlargement of geographic atrophy is a bad thing and we should do whatever we can to limit progression, because a visual benefit may be seen over a longer period of time. Herein lies the essential question—is there any point in treating when there is a risk associated with treatment, when there is significant treatment burden, and when the visual loss associated with the disease may or may not occur during a patient's lifetime? The data so far show that complement inhibition will lead to slowing of disease progression and some treatment may be better than no treatment. Whether this is worth the treatment burden and cost, as well as the complications at this point (including choroidal neovascularization, occlusive retinal vasculitis, etc.)¹¹ is quite another matter.

There is an analogy to be made to our current treatment of glaucoma, where we have little difficulty intervening when we see a disastrous potential outcome for untreated patients. Significant ganglion cell loss occurs before visual field changes occur in glaucoma patients, and early visual loss occurs in the periphery without symptoms.^{12,13} Central vision loss, which occurs late in the disease, is devastating. Yet in glaucoma, we intervene well before symptoms and visual loss develop.^{12,13} We are willing to treat glaucoma patients with essentially lifelong eye drops for elevated eye pressure in the absence of changes on perimetry or nerve fiber layer changes on OCT if the pressure is high enough. Our judgment of whether to treat, and how aggressively to treat, is often modulated by risk factors weighed in a subjective and qualitative (rather than a quantitative) fashion. Physicians often perform the mental calculation of the risk-benefit ratio of a possible treatment versus the disease course, and act on the basis of this quick mental calculation. Thus, we may readily initiate topical therapy in a 30 or 40 year old glaucoma suspect with a strong family history and elevated intraocular pressure, but are less likely to initiate treatment in a patient with identical risk factors (except for age) in their ninth decade of life as the elderly patient is less likely to experience

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visual loss during their lifetime. The invasiveness of the treatment also enters into our treatment decision. Intervention with eye drops is one thing; intervention with laser treatment is not much more invasive and can be applied very early in disease course, but trabeculectomy and tube surgery are quite something else. In glaucoma, we readily accept topical eye drop therapy, and perhaps even laser to mitigate risk in early stages, but reserve surgical interventions for advanced disease. There is some analogy here in the management of geographic atrophy in age-related macular degeneration, where we would readily accept topical therapy for the prevention of geographic atrophy, but unfortunately no such topical therapy is approved by the U.S. Food and Drug Administration. Accepting intravitreal injections at a rate of every 1 or 2 months is something else, particularly because many of the patients being treated will not experience visual loss during their lifetime. Therein lies the conundrum.

In macular degeneration management, we find ourselves in a healthy, important, and timely debate about whether and how aggressively we should treat our patients with geographic atrophy. Our decisions are tied to the question of how to interpret the results on complement inhibition, our first major therapeutic option for geographic atrophy. Such a debate is necessary because the dilemma of how and when to use these drugs has been thrust upon us by the remarkable advances in our field. The depth of the quagmire is evident from the fact that extremely competent, intelligent and thoughtful people, leaders in our field, are reaching quite different conclusions based upon the same data. On the one hand, we are seeing posts on social media with physicians being proud to deliver intravitreal injections of complement inhibitors in patients with geographic atrophy. Finally, we have a drug to treat non exudative age-related macular degeneration! Simultaneously, others are writing and speaking about the fact that they see no role for these drugs. Who would we treat and why, they ask? Most patients will not develop vision loss; many patients will need to be treated to benefit the few; there is an enormous fiscal and practical treatment burden associated with monthly or bimonthly intravitreal injections, with many patients needing bilateral treatment. Not to mention that some patients will develop neovascularization, which then must be treated with even more injections of drugs targeting VEGF, or retinal vasculitis that cannot be treated.^{7,8,10,11}

This vociferous debate exists because we are missing the right tools to make an informed decision as to whether it is best to treat or to observe individual patients with geographic atrophy. Physicians often make clinical judgments in the

absence of complete data, based upon their own experience, their collective memory of how patients with and without treatment have fared in the past, and numerous other soft factors. In addition, selective memory comes into play. No complications in the last 15 years of anti-VEGF therapy will make a physician more likely to treat; on the other hand, caring for a patient who started with relatively good vision and then lost it to intravitreal injection complications such as endophthalmitis can be a sobering experience that will temper the enthusiasm of the most vocal among us for future injections.

The reality is that the data will not change until we get studies with longer follow-up, but we need to move forward now as a profession aligned with the best interests of our patients. To do so we need a risk calculator to predict the probability of meaningful vision loss without treatment and the impact of treatment on disease natural history. Concretely, we need to understand the risk to an individual patient of doing nothing—are they likely to suffer loss of function and decreased quality of life during their lifetime without intervention, or will they simply have no change in function despite some enlargement of the atrophic lesion on imaging? And most importantly, will intravitreal injections reduce this risk in an impactful way? During my last visit to my internist, he sat at a computer terminal (will bedside manner ever return to medicine?) and calmly calculated my 10 year risk of a stroke with and without a statin—and I chose the drug despite a normal cholesterol and lipid panel. Such a risk calculator is clearly needed in geographic atrophy. Do we really care if geographic atrophy enlarges in a particular patient? I would say only if that enlargement will lead to a calculable risk of decreased vision and quality of life during a patient's lifetime. To counsel patients correctly, we need an online tool similar to what internists use for calculating cardiovascular risk¹⁴; a tool that can be used by physicians in real time in the patient office that adjusts for location of geographic atrophy, patient age and general health, and possibly incorporates other systemic risk factors and data from imaging modalities such as OCT to determine the effect of complement inhibition on other variables such as the photoreceptor/retinal pigment epithelium thickness ratio.^{15–17} With these data in hand, the physician can determine in an actuarial fashion the patient's risk of vision loss without versus with treatment during their lifetime. The availability of such a risk calculator could lead to a convergence of opinion on geographic atrophy treatment. In its absence, confusion and divergence of opinion may continue unabated.

Footnotes and Disclosures

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