Loss of central vision from geographic atrophy (GA) is a late stage complication of age-related macular degeneration (AMD) as the central foveal region becomes consumed by the disease. Until recently, GA had not received the attention it deserved from the pharmaceutical industry. Over the years, most of the clinical trial community has been focused on the exudative or neovascular form of AMD due to the rapid and severe vision loss often associated with this form of the disease. With the success of vascular endothelial growth factor inhibitors in slowing and preventing the devastating vision loss from neovascularization in exudative AMD, the development of macular atrophy after anti-vascular endothelial growth factor therapy and growth of GA in nonexudative AMD have become the most common causes of vision loss from AMD. The research by Chakravarthy et al (see http://www.aaojournal.org/article/S0161-6420(17)32513-7/fulltext) in this issue highlights the enormous impact of GA in patients with AMD. Although the loss of visual function is more gradual than in untreated exudative AMD, the resulting visual impairment can be just as devastating.

Although we have always given lip service to the importance of GA in the lives of our patients with AMD, the historical truth is that we underappreciated the impact of this disease until it progressed through the foveal center. In several studies, including the Age-Related Eye Disease Studies, the important outcome measure was the progression of GA through the foveal center rather than the growth of GA. Since these early days of clinical trials studying GA, we have learned so much more about the associations between any GA and visual function impairment. We now know that the earliest signs of GA serve as harbingers for visual function abnormalities and the relentless progression of symptoms long before the fovea becomes involved. Perhaps, the most obvious sign that GA never garnered the respect it deserved can be found in the International Classification of Diseases codes used for many years before the introduction of the International Classification of Diseases 10th revision. As shown in the article by Chakravarthy et al, they wanted to study the impact of GA on patients by performing a retrospective review of the electronic medical records systems from 2000 to 2016 at 10 clinical sites. However, there were no diagnostic categories that could help to easily identify GA and determine whether the disease was in 1 eye or both eyes. To overcome this significant limitation of diagnostic coding, they developed an algorithm based on a list of clinical findings that could identify patients with GA. They systematically categorized these patients as having GA in both eyes, GA in 1 eye and exudative disease in the fellow eye, or GA in 1 eye and intermediate AMD in the fellow eye. For the purposes of this study, they focused on the patients with GA in both eyes (1901 patients), and the study eye was the eye with worse vision. If the visual acuity was the same in both eyes, then the right eye was chosen as the study eye. The validity of their algorithm was confirmed by an exercise that demonstrated impressively high positive predictive values for both the study and fellow eyes in identifying GA.

Their outcome measures focused on various types of vision impairment including progression to legal blindness and loss of driving ability, as well as progression to exudative AMD. For anyone who questions whether preventing the growth of GA is a worthwhile endeavor, these results provide irrefutable evidence that slowing this disease will have a profound societal impact. The vision loss curves shown in Figure 2 in their article summarize the significance of their findings. In the better-seeing eye, they found a loss of 6 letters per year on average, which is a clinically significant outcome given that a line of vision (5 letters) is unequivocally appreciated as an important annual change in vision for patients with AMD, especially when describing the benefits of a therapeutic trial. This loss of vision over a year is just an indirect measure of the relentless progressive growth of GA occurring in all these patients, a growth that will eventually obliterate their central vision. The impact of this result is amplified by the understanding that this only applies to patients with GA close enough to the foveal center so that its growth would have a visual acuity impact. In support of this assumption and as expected, patients not considered legally blind were found to have a loss of at least 10 letters (2 lines) and 15 letters (3 lines) in 40% and 31% of eyes, respectively, over 2 to 3 years. Consistent with this delayed and inevitable loss of vision, they showed that 67% of driving-eligible patients lost the ability to drive over a median of 1.6 years. These results are even more sobering given the fact that their assessment likely represents an underestimate of the true cases with bilateral GA and that visual function impairment involves much more than just reading an eye chart under normal luminance. If there was ever a question about the impact of GA on the real-world
quality of life of our patients, then Chakravarthy et al\textsuperscript{2} have given us an unambiguous answer.

Given that the importance of preventing the growth of GA is now obvious, how can this goal be achieved? When using growth of GA as a clinical trial end point, we have observed numerous treatment failures over the past decade. The most recent failure of the phase 3 trial investigating the complement inhibitor lampalizumab was particularly disappointing.\textsuperscript{5,6} Currently, the only drug entering phase 3 clinical trials over the next year will be APL-2 (Apellis Pharmaceuticals, Crestwood, KY), a complement inhibitor that targets complement component 3, which was shown to slow the enlargement of GA in a phase 2 clinical trial.\textsuperscript{7} As with all the other studies that preceded APL-2, the success of complement component 3 inhibition in Phase 3 trials will depend on its ability to slow the enlargement of GA. If APL-2 fails, then there will be exhaustive speculation as to whether targeting GA may be just too late in the disease process to prevent vision loss. Perhaps an intervention at an earlier stage, such as in intermediate AMD, might succeed in preventing progression to late-stage AMD, which includes both GA and neovascularization.\textsuperscript{8} As with recent developments in clinical trials in Alzheimer disease, the idea of intervening earlier and preventing late-stage disease is gaining momentum. In reality, regardless of whether APL-2 successfully slows the enlargement of GA, early intervention in a disease with a late age of onset will always preserve more vision over the lifetime of the patient. After all, when it comes to our patients with AMD, preserving functional vision is our goal, and failure is not an option.

References


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