The ability to identify ideal treatment candidates could speed clinical trials.

BY THEODORE LENG, MD, MS

Approximately half of eyes with advanced age-related macular degeneration (AMD) have geographic atrophy (GA). In patients older than 75 years, GA is the principal cause of severe vision loss. Fortunately, GA often begins outside of the fovea, and central functional areas of vision are often not affected until late in the disease process.

Given the slowly progressive nature of dry AMD with GA, ophthalmologists have an opportunity to preserve vision in these patients. If we could prevent the spread of GA to the center of the fovea, many patients would ultimately end up happier. With the recent success of early clinical trials of pharmacologic agents and cell-based therapies, the ability to intervene may not be too far in the future. So, if we will soon have the power to prevent the growth of GA, to whom should we offer treatment?

IDENTIFYING IDEAL CANDIDATES

When a new treatment emerges, one should select a few ideal candidates—patients whom one is sure will benefit from the treatment—before casting a wider net and trying it on everyone who might benefit from the therapy. There are two reasons for this. First, if there are unknown side effects of a new treatment that were not uncovered during clinical trials, it would be undesirable for many or all of your patients with GA to be affected by them. Second, you want to have a few “wins” early on to boost your confidence in the efficacy of a new product, so you can continue to use it when indicated. In addition, if you can identify those most likely to benefit—in this case, those most likely to experience GA progression and loss of vision—then you can use that information to help counsel potential treatment candidates and explain to them why they might benefit from the therapy.

Lampalizumab (Genentech) is an antigen-binding fragment of a humanized monoclonal antibody directed against complement factor D. This large molecule is currently being evaluated in two identical phase 3 trials in patients with GA: Spectri (NCT02247531) and Chroma (NCT02247479). The completion date is November 2017 for Spectri and September 2018 for Chroma. If approved, lampalizumab would potentially be the first treatment for GA approved by the US Food and Drug Administration.

When that day comes, to whom should we first administer treatment? I believe that the ideal candidate would be someone we think is at high risk of losing central vision due to the spread and growth of GA. This patient would be the most likely to benefit from this intravitreal therapy and the most likely to agree to a treatment meant to be preventive in nature.

QUANTITATIVE IMAGING ANALYSIS

Previous studies have shown that the presence of drusen, hyperpigmentation, and reticular pseudodrusen on infrared reflectance images are qualitative risk factors for GA progression. Spectral-domain optical coherence tomography (SD-OCT) studies have also shown that subretinal drusenoid deposits and abnormalities in the retinal pigment epithelium (RPE) and photoreceptors at the margins of GA may be associated with GA growth. While these imaging studies...
have given us helpful insights into the progression of dry AMD with GA, none of them describe a method to reliably predict where GA is likely to spread and what the pattern of growth will be over a specified time span.

In a recent study,\textsuperscript{10} we harnessed the massive amount of data contained in volume SD-OCT scans of the macula (more than 67 million voxels per scan) to create a fully automated algorithm that can quantitatively and accurately identify macular regions where GA is likely to grow. Moreover, the computer model was able to predict if and when the foveal center was likely to be affected by GA—an important clinical issue, as involvement of the foveal center often leads to a precipitous drop in visual acuity and visual function.

**A PREDICTIVE MODEL**

In our study, 118 longitudinal SD-OCT volume scans from 38 eyes with GA were used to develop a computer algorithm. A fully automated pipeline was developed to segment the scans, extract imaging features, create a predictive model for GA progression, and test that model using a machine learning approach.

We fed the ground truth about 19 imaging features and regions of GA growth into the model to train it in a pixel-by-pixel fashion. We then tested the ability of the model to predict areas of GA growth in a separate set of data in which the truth was hidden from the model.

We created a two-class classification problem for the artificial intelligence model, asking it to predict whether each pixel in a topographic image was a future GA or non-GA region.

**INFLUENTIAL FEATURES**

When the 19 quantitative SD-OCT features were ranked on their predictive ability to identify regions of future GA growth, we found that the most important features were regions of photoreceptor loss, lower reflectivity of OCT band 11, and the height of reticular pseudodrusen. Other influential features included intensity of the GA projection image, retinal thickness between the outer boundary of OCT band 5 and inner boundary of OCT band 11, average intensity between outer boundary of OCT band 7 and inner boundary of OCT band 11, and eccentricity of the existing GA.

Using these features, we were able to predict regions of future GA growth in several testing scenarios with sensitivity ranging from 0.81 to 0.90 and specificity ranging from 0.95 to 0.97, depending on which one of three testing scenarios was used. The area under the receiver operating curve for GA classification was 0.97, with positive predictive values ranging from 0.83 to 0.86 and negative predictive values from 0.96 to 0.97. Correlation coefficients of future GA areas to predictions ranged from 0.97 to 0.99.

Importantly, the ability of our automated algorithm to predict foveal GA involvement had a high level of performance, with correlation coefficients ranging from 0.94 to 0.95 in the various testing scenarios.

Overall, we found the computer model to be quite robust in predicting areas of future GA growth and whether that growth would involve the foveal center (Figure).

**PUTTING IT ALL TOGETHER**

Our algorithm potentially gives us the ability to identify patients who are at high risk of GA progression and of movement of that GA into the foveal center. These patients at risk for vision loss would be ideal candidates for emerging therapies for GA.

Moreover, future GA trials could be designed around these features. If high-risk patients can be recruited into clinical trials, that could potentially shorten trial times and decrease the sample sizes necessary to reach statistical significance in demonstrating the efficacy and safety of a fledgling investigational product. Ultimately, our patients will benefit.


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also for neurodegenerative and cardiovascular diseases, cancers, diabetes, and obesity. Mitochondria are becoming the targets for an entire new field of drug development. The future will likely include clinical trials using mitochondria-targeting drugs for retinal diseases, and this will be an exciting, novel area of research with great therapeutic potential.


For patients with advanced AMD (neovascular AMD or GA involving the center of the macula) in one eye, the risk of progression to an advanced stage in the fellow eye ranged from 35% to 50% at 5 years.2

Of patients with GA, 42% are legally blind.13


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GA BY THE NUMBERS

GA affects more than 5 million people worldwide, including almost 1 million Americans.2

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1 million

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