A PROMOTIONAL SUPPLEMENT TO

Ophthalmology Times.



Multimodal Imaging of Geographic Atrophy

PROCEEDINGS FROM A SYMPOSIUM HELD DURING THE EURETINA MEETING OF THE EUROPEAN SOCIETY OF RETINA SPECIALISTS, COPENHAGEN, DENMARK, SEPTEMBER 9, 2016

FACULTY & DISCLOSURES



Professor Giovanni Staurenghi

University of Milan and Luigi Sacco Hospital Milan, Italy

Prof. Staurenghi has been a consultant/advisor for Alcon, Allergan, Bayer, Boehringer, Carl Zeiss Meditec, Genentech, GSK, Heidelberg Engineering, Novartis, Quantel Medical, and Roche. He has received grant support from Centervue, Heidelberg Engineering, Optos, Optovue, and Quantel Medical. He has also received lecture fees from Alcon, Allergan, Bayer, GSK, Novartis, and Roche, and patents/ royalties from Ocular Instruments.

Professor Steffen Schmitz-Valckenberg



The University of Bonn and GRADE Reading Center, Bonn Bonn, Germany

Prof. Schmitz-Valckenberg has received funding for research and clinical trials from Alcon/Novartis, Allergan, Bayer, Bioeq, Carl Zeiss Meditech, Centervue, Genentech/Roche, Heidelberg Engineering, and Optos, as well as consulting fees and honoraria from Alcon/Novartis, Allergan, Bayer, and Heidelberg Engineering.



Professor SriniVas Sadda

UCLA Los Angeles, USA

Prof. Sadda has received research instruments from Carl Zeiss Meditec, Centervue, Heidelberg Engineering, Nidek, Optos, and Topcon. He has received research grants (DIRC) from Allergan, Carl Zeiss Meditec, Genentech, Optos, and Regeneron. He has been a consultant for Allergan, Carl Zeiss Meditec, Centervue, Genentech, Iconic, Novartis, Optos, Regeneron, and Thrombogenics.

Cover photo: Sergey Nivens/shutterstock.com

DISCLAIMER: These symposia proceedings and the symposium itself have been produced and paid for by Heidelberg Engineering. Copyright 2017. No portion of this publication may be reproduced or transmitted in any form, by any means, without the prior written permission of Heidelberg Engineering or UBM Medica. The views and opinions expressed in this supplement do not necessarily reflect the views and opinions of UBM Medica, *Ophthalmology Times Europe*, or *Ophthalmology Times*. Published by UBM.

Multimodal Imaging of Geographic Atrophy



ge-related macular degeneration (AMD) accounts for 8.7% of all blindness worldwide. As populations age, the number of sufferers is expected to rise.¹ The number of people with AMD worldwide is projected to be 196 million by 2020, increasing to 288 million by 2040.1 This can only increase the socioeconomic burden of the disease.² Based on these projections, it seems evident that AMD is going to become too common to be the exclusive preserve of retinal specialists and will have to be diagnosed, monitored, and possibly treated by general ophthalmologists.

Advanced AMD is associated with progressive visual impairment.³ It can be either wet, when neovascularization is involved, or dry (nonexudative), as geographic atrophy (GA), which is retinal pigment epithelium (RPE) atrophy without evident neovascularization. The two types of AMD are not necessarily mutually exclusive and can coexist.⁴

GA patients make up approximately 35% of late AMD patients,⁵ and GA is responsible for approximately 20% of all cases of legal blindness in North America.⁶

The term "geographic areas of atrophy" was first used in 1970 in the context of senile macular degeneration. (The term "AMD" was not introduced in the literature until 1984.) It was used to describe well-defined circular or oval areas of depigmentation showing thinning of underlying tissue, often exposing underlying choroidal vessels.7 The term "geographic" appears to originate from the German word "landkartenartig," which would translate literally as "map-like" in English.7 This terminology is used in medicine in general to describe lesions that resemble the map of a continent or welldefined country borders.8 By the 1980s,

it was well established that the manifestation of nonexudative AMD itself was called geographic atrophy.⁷

The pathway to GA starts with abnormalities at the level of the RPE and depositions of extracellular material, located predominantly between Bruch's membrane and the RPE, that eventually form drusen. The disease progresses to atrophy, involving a gradual degeneration and disappearance of the RPE, photoreceptor cells, and the choriocapillaris layer of the choroid in the central retina.² The fovea itself is typically not involved until later in the course of the disease.9 GA near the foveal center is associated with increased risk of vision loss, but most eyes will maintain normal vision for some time before atrophy expands into the fovea, at which point patients experience increasing loss of visual function. When vision loss does occur, it declines slowly over years.9

Although choroidal neovascularization, which once would have led to scar formation, can now be treated with intravitreal anti-vascular endothelial growth factor (VEGF) therapy, the underlying disease continues to progress.

Average GA area progression rates of about 1.3 to 2.6 mm²/year have been reported around the world.⁹⁻¹² A huge variability in progression rates is seen between patients, some of whom progress very slowly while others progress extremely rapidly.

Although intravitreal anti-VEGF treatment can prevent the progression of neovascular AMD and lead to improvements in vision in some patients, no drugs are currently approved to prevent or slow GA progression and its associated vision loss.^{4,10} Lampalizumab, a complement factor D inhibitor, is under phase 3 development for GA by Roche/

Genentech, with primary endpoint, 1-year results anticipated in late 2017.

Imaging in GA

To highlight innovations in multimodal imaging in GA, Heidelberg Engineering hosted a lunchtime symposium at the 16th European Society of Retina Specialists meeting in Copenhagen, Denmark, on September 9, 2016. "Clinical practice keeps proving the importance of multimodal imaging in comprehensive diagnostics," said Dr. Kester Nahen, managing director. "Which imaging modalities make the most sense for specific patients and pathologies?" he asked.

Prof. Giovanni Staurenghi from the University of Milan and Luigi Sacco Hospital, Italy, confessed to some bias in his presentation, saying "I'm a multimodal imaging supporter," before going on to explain that measuring visual acuity is not a good way to monitor the progression of GA. Imaging is crucial to understand and visualize the anatomy involved. Prof. Steffen Schmitz-Valckenberg from the University of Bonn, Germany, agreed, saying that "imaging plays a key role in understanding the disease and in making the difference between individuals." For Prof. SriniVas Sadda of UCLA, Los Angeles, USA, the important thing is a reliable and efficient endpoint for assessment of therapeutic efficacy.

Until recently, no definition for atrophy had been established to incorporate and take advantage of the power of multimodal imaging, nor were there any guidelines for describing or quantifying atrophy in the setting of neovascular AMD.

Prognostic factors

Prof. Schmitz-Valckenberg explained the difference between prognostic and predictive factors. The former affect disease progression in an untreated individual, whereas the latter term refers to the effect of treatment.¹³ As no treatment for GA is yet available, all factors are prognostic. With the advent of the investigational drug lampalizumab for GA, imaging will soon move from being purely useful for monitoring disease progression to a predictive function.

In the meantime, however, an important outstanding question is which factors affect atrophy progression.

Various potential prognostic factors have been explored. No epidemiologic factors have been found to influence disease progression. Age, sex, blood pressure, smoking and heavy drinking status, body mass index, and sedentary lifestyle were all found to be unrelated to an increase in GA in a populationbased study of 95 subjects.¹⁰ Genetic factors do make a significant contribution to GA progression rate, but explain less than 7% of inter-individual variance in progression rates.² That said, Roche is exploring complement factor I as a predictive genetic factor in its phase 3 trials of lampalizumab, after the subpopulation with this marker in the phase 2 MAHALO study showed a 44% decrease in disease progression compared with a 20% decrease overall.¹⁴

Imaging biomarkers are promising for monitoring the progression of lesion growth, and such biomarkers have been used in different studies. For example, previous rate of progression was found to be the most significant factor in predicting subsequent rate of progression as measured by color fundus photography in a natural history study of 212 eyes, although relying on retrospective quantification of growth is unlikely to be a practical approach in the clinic.^{9,11}

In bilateral cases of GA, progression rate is highly concordant between the two eyes, even when lesion size is very different, with correlation coefficients of approximately 0.8 reported.^{9,11,15}

Other factors relate to the configuration of the GA lesions. Eyes that contain multifocal atrophic lesions at baseline are likely to see more rapid increase in atrophy and decrease in vision than those with a classic single lesion, while calculation of a noncircularity index the ratio of the measured area to the area expected for a given perimeter—revealed that the less circular the lesion, the faster the GA progressed.^{10,16}

Phenotypic patterns of abnormal fundus autofluorescence (FAF) around the GA lesion correlate with disease progression.¹² Some morphologic markers, such as outer retinal tubulation, irregular elevations of the RPE/Bruch's membrane complex, and vitreoretinal interface abnormalities, have become available only with the development of spectral domain optical coherence tomography (SD-OCT) and are associated with faster enlargement rates, larger lesion size, and multifocal patches of atrophy.¹⁷

Of these potentially useful factors, Prof. Schmitz-Valckenberg identified baseline size and circularity as explaining most of the variability in atrophy progression between patients. It is clear that reliable tools are essential to accurately diagnose and assess atrophy, and to follow its course.

Imaging modalities

Until recently, studies to identify new treatment strategies for GA were impeded by reliance on loss of visual acuity as the primary outcome variable. Many eyes with GA will maintain normal vision for some time, and when vision does deteriorate, it does so slowly.⁹ All the speakers at the symposium were very keen on multimodal imaging, and all emphasized its value in transitional, borderline cases in particular. As Prof. Sadda remarked, "We really need that combination [of technologies] to know what's involved and what's not."

Advances in retinal imaging have distinctly improved the detection of atrophy and the morphologic biomarkers associated with disease progression. Validated anatomic endpoints have been accepted by regulatory bodies as primary outcome parameters in interventional clinical trials for GA.⁴

Prof. Staurenghi gave an overview of the different types of imaging useful in GA, concluding that whereas no one type of image is enough to give all the necessary information, combined they can build up a picture of the type of GA or macular atrophy that is present.

Scanning laser ophthalmoscopy (SLO)-based FAF imaging and en-face OCT imaging are the most common techniques used to quantify areas of GA.⁴

Color photography

Retinal imaging began with color photography, which has been used to diagnose and monitor GA for decades. It is still used and will continue to be used in AMD trials to ensure modern studies using new technology are directly comparable with past studies. Color photography allows the detection of many features associated with GA, such as drusen, changes to pigment, and atrophy. It has relatively low contrast compared with other, newer imaging modalities, however, so accurate measuring of atrophic lesions can be a challenge.⁴ Prof. Sadda expanded on the issues with color photography, saying that good stereopsis is essential to determine the lesion's borders and the contrast is not always good. It can be difficult to distinguish atrophy from depigmentation.

Autofluorescence

FAF imaging is a fast technique for studying the RPE that is noninvasive, because injection of dye is not necessary. After more than 10 years of use and with thousands of machines now in operation, FAF imaging is considered the gold standard in retinal imaging of GA. The FAF in AMD and GA progression studies, begun in 2006, led to a paradigm shift toward using FAF to follow progression of AMD. Area of atrophy measured using FAF is now accepted by both the FDA and the EMA as the endpoint of GA studies. One major advantage of FAF compared with some of the other techniques is that the images are fairly easy to take, even for nonspecialists.

A blue light is shone onto the retina, which causes lipofuscin to fluoresce, providing an indicator of the presence of RPE cells. Areas of excess lipofuscin accumulation in a single cell or because of cells overlapping, possibly a sign of early degenerative change, will appear hyperfluorescent, while areas missing from the RPE appear black (Figure 1). Software is available to measure atrophic areas. For example, RegionFinder software from Heidelberg Engineering can not only quantify areas of GA but also track progression over time, producing timelapse movies of lesion growth that can help educate patients about the course of their disease. (Figure 2)

Commercially available FAF systems can be based either on a modified fundus camera or on SLO, which uses a low-power laser beam that sweeps across the fundus in a raster pattern. The SLO produces very high-quality images with high contrast and low background noise and, due to the confocal aperture, can be focused directly on the target tissue of interest, eliminating light from surrounding sources of fluorescence such as the lens. This allows confocal SLO to use blue light, not only the green light used by a conventional fundus camera. Automatic real-time image processing means that images appear instantly on a computer screen and adjustments can be made on the spot.⁵

FAF provides information not only about the area of atrophy but also about the surrounding area. FAF patterns observed in the junctional zone of patients with GA have been classified into phenotypes that correlate strongly with GA progression.⁵ Infrared (IR) and green autofluorescence imaging are often used to supplement blue laser FAF. According to Prof. Sadda, the use of IR in particular can give good contrast and reveal whether there is foveal sparing (*Figure 3*). Reticular pseudodrusen are best visualized using IR and FAF images. The presence of reticular pseudodrusen FIGURE 1. Geographic atrophy shows as a dark patch on a fundus autofluorescence image



FIGURE 2. The RegionFinder software (Heidelberg Engineering) allows the measurement of areas of atrophy for close monitoring of progression.



shows high correlation with the presence of GA, and GA is observed to spread into areas that contain them.¹⁸

Prof. Staurenghi showed images

from the same eye using different types of autofluorescence to demonstrate that it can be difficult to tell whether the fovea is involved in the atrophy using blue light alone, because macular pigment absorbs blue light (*Figure 4*). Green light, with its longer wavelength, can be used to effectively look past the confounding macular pigment and reveal the fovea more clearly.

Prof. Schmitz-Valckenberg showed examples of patients with atrophic lesions resembling GA, only one of which was actually AMD (other conditions often mistaken for GA: central areolar choroidal dystrophy and Stargardt disease). FAF made this clearer than color photography, allowing better detection of lesion boundaries and revealing relevant changes around the lesion.

Optical coherence tomography

Prof. Sadda said that transitional cases sometimes can present a challenge to autofluorescence imaging. "It's not like one day you have no atrophy and the next day you have atrophy; these cases go through an evolution," he explained. Vitality of the RPE is not the only factor of significance in GA. Both color photography and FAF produce planar images, so these cannot reveal whether the photoreceptors are intact.

The beauty of OCT is that it provides 3-dimensional cross-sectional and en-face information and allows detailed inspection of the fine structures of the retina and the RPE.4 Individual retinal layers can be visualized to assess how severely the RPE and photoreceptors are affected, and the impact of atrophy can be quantified. For example, outer and inner segments can be examined. Prof. Schmitz-Valckenberg commented, "Some recent data have shown that the inner nuclear layer is increased in areas of atrophy. This is interesting because the current understanding is that this disease is an outer retinal disease with preservation of inner retinal layers."19 OCT is also a useful method to look at the areas around the atrophy, such as outer retinal tubulation or splitting.

On the other hand, it is more time consuming and labor intensive to interpret SD-OCT output than to examine



FIGURE 3. Infrared imaging can give good contrast and reveal foveal sparing in cases in which the fundus autofluorescence image is unclear, illustrating the benefits of multimodal imaging of geographic atrophy.



FIGURE 4. Using different wavelengths for autofluorescence can provide different information. Here, blue-light autofluorescence makes it more difficult to tell whether the fovea is involved in the atrophy (left), whereas green light, with its longer wavelength, bypasses the macular pigment and clearly reveals the margins of the atrophy (right).

a single image produced by one of the simpler imaging modalities.⁴

In a multimodal approach, cross-sectional OCT scans are reviewed together with, for example, FAF images to fully appreciate the structural and metabolic changes associated with GA (*Figure 5*).

For Prof. Staurenghi, the main advantage of novel OCT angiography is that it can reveal whether choroid capillaries are present or not and that it allows clear differentiation between GA and atrophy secondary to another disease. Prof. Schmitz-Valckenberg believes the most useful applications of OCT angiography in dry AMD are probably for the detection of silent or subclinical choroidal neovascularization and for differential diagnosis (*Figure 6*). "I've seen some beautiful images from Giovanni [Staurenghi] during this conference," he said. "He showed that the detection of the choroid capillaries is changed in patients with other causes of atrophy as compared to patients with AMD."

Classification of Atrophy Meetings

Prof. Sadda gave an extensive overview of the Classification of Atrophy Meetings (CAM), a series of three meetings of a consortium of international experts held in 2015 and 2016 that aimed to produce a consensus approach to the nomenclature and description of atrophy and to evaluate currently available imaging technologies with respect to detection, quantification, and monitoring of atrophy.⁴ Prior to each meeting, exercises comprising multimodal images of particular cases were distributed to more than 60 panel members, who were asked



FIGURE 5. Simultaneous fundus autofluorescence and optical coherence tomography imaging provide a new perspective on structure and metabolic activity within the retina.

to label and diagnose the images. For example: "Is this GA?," "Which of these serial images shows the first evidence of atrophy?," and "Where are the borders of this GA?" The hope was to establish areas of accord and to identify strengths and challenges for the detection of atrophy using each imaging modality.

The main focus of the meetings was a systematic discussion of the role of different imaging modalities in AMD. Prior to the meetings, no definition for atrophy had been established to incorporate and take advantage of the power of multimodal imaging, nor were there any guidelines for describing or quantifying atrophy. It was widely believed that multimodal definitions of atrophy would be necessary, but OCT was chosen as the base modality in the hope that it would allow definition of an early endpoint for atrophy before definitive evidence becomes visible via other modalities.









FIGURE 7. Participants in the second Classification of Atrophy Meeting were asked, without being given any guidance, to move the red line to where they believed the edge of the atrophy was on multimodal images from the same eye. Each red line represents one assessor. In this case, the spread of results from the optical coherence tomography image (left) was wide, whereas the results from fundus autofluorescence (center) and infrared (right) were clearer.

OCT makes it possible to determine whether only the photoreceptors are atrophic or if the RPE is also involved.

CAM-2 focused on trying to classify atrophy at an anatomic level, to determine which retinal layers are involved, using OCT. An interesting exercise asked the faculty to mark where they believed the border of atrophy was on a set of retinal images, initially without any further instructions (*Figure 7*). The lack of criteria to define the boundary of the atrophy and difficulties in pinpoint-

REFERENCES

- Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2(2):e106–e116.
- Grassmann F, Fleckenstein M, Chew EY, et al. Clinical and genetic factors associated with progression of geographic atrophy lesions in age-related macular degeneration. *PLoS One*. 2015;10(5):e0126636.
- Lim LS, Mitchell P, Seddon JM, et al. Age-related macular degeneration. *Lancet*. 2012;379(9827):1728–1738.
- Holz FG, Sadda SR, Staurenghi G, et al; CAM group. Imaging protocols in clinical studies in advanced age-related macular degeneration: recommendations from Classification of Atrophy Consensus Meetings. *Ophthalmology*. 2017;124(4):464–478.
- Blue laser autofluorescence. The fusion of imaging technology for today and tomorrow to assess your patients' retinal health. *Ophthalmol Times Europe*. November 2003;suppl. http://ophthalmologytimes.modernmedicine.com/sites/default/files/ images/OphthalmologyTimesEurope/PDF/ Blue-laser-autofluorescence.pdf. Accessed February 11, 2017.
- Holz FG, Strauss EC, Schmitz-Valckenberg S, et al. Geographic atrophy: clinical features and potential therapeutic approaches. *Ophthalmology*. 2014;121(5):

ing the edge of OCT hypertransmission through the RPE meant that there was a wide variation in opinion. Arbitrary choice of the image that at least 60% of the faculty believed to show atrophy allowed some narrowing of criteria.

One of the outcomes of CAM-2 was an in-depth guidance document setting out which techniques should be included in clinical research and trials for both dry AMD and neovascular AMD.⁴ The recommendation was that for accurate detection, quantification, and monitor-

1079-1091.

 Schmitz-Valckenberg S. The journey of "geographic atrophy" through past, present, and future. Ophthalmologica. 2017;237(1):11–20.

- Schmitz-Valckenberg S, Sadda S, Staurenghi G, et al; CAM (Classification of Atrophy Meeting) Group. Geographic atrophy: semantic considerations and literature review. *Retina*. 2016;36(12):2250–2264.
- AREDS Research Group. Change in area of geographic atrophy in the Age-Related Eye Disease Study. Arch Ophthalmol. 2009;127(9): 1168–1174.
- Klein R, Meuer SM, Knudtson MD, Klein BEK. The epidemiology of progression of pure geographic atrophy: the Beaver Dam Eye Study. Am J Ophthalmol. 2008;146(5):692–699.
- Sunness JS, Margalit E, Srikumaran D, et al. The long-term natural history of geographic atrophy from age-related macular degeneration: enlargement of atrophy and implications for interventional clinical trials. *Ophthalmology*. 2007;114(2):271–277.
- Holz FG, Bindewald-Wittich A, Fleckenstein M, et al; FAM Study Group. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. Am J Ophthalmol. 2007;143(3):463–472.
- Italiano A. Prognostic or predictive? It's time to get back to definitions! J Clin Oncol. 2011;29(35):4718.

ing of GA in a clinical trial, a multimodal approach should be taken, including color photography, confocal FAF (blue light excitation) and nearinfrared reflectance (NIR, 3 field, 30°), and dense SD-OCT or swept-source OCT volume scans ($6 \times 6 \text{ mm or}$ $9 \times 9 \text{ mm}$, maximum distance between scans not >120 µm).⁴

Conclusion

Multimodal imaging is essential to build up a full picture when assessing GA, as different techniques contribute different information. With treatments for GA in the pipeline, monitoring its development will become ever more important.

With an aging population, GA is going to become too common to be the exclusive preserve of retinal specialists and will have to be diagnosed, monitored, and possibly even treated by general ophthalmologists. Every ophthalmologist will need to become familiar with the pathophysiology of GA and recognize its different phenotypes, distinguishing fast-progressing GA from more-indolent disease. Once treatment for GA becomes available, a growing number of general ophthalmologists will probably find it necessary to start performing intravitreal injections.

- Roche. Roche initiates phase III trials for lampalizumab, first potential treatment for geographic atrophy (GA). Investor Update. Basel, Switzerland: Roche; September 15, 2014. http:// www.roche.com/investors/updates/inv-update-2014-09-15.htm. Accessed February 11, 2017.
- Fleckenstein M, Adrion C, Schmitz-Valckenberg S, et al; FAM Study Group. Concordance of disease progression in bilateral geographic atrophy due to AMD. *Invest Ophthalmol Vis Sci.* 2010;51(2):637–642.
- Danis RP, Domalpally A, Hubbard LD, et al. Index of non-circularity of areas of geographic atrophy (GA) is related to progression rate. *Invest Ophthalmol Vis Sci.* 2012;53(14):2054 (abstract).
- Moussa K, Lee JY, Stinnett SS, Jaffe GJ. Spectral domain optical coherence tomography-determined morphologic predictors of age-related macular degeneration-associated geographic atrophy progression. *Retina*. 2013;33(8):1590–1599.
- Marsiglia M, Boddu S, Bearelly S, et al. Association between geographic atrophy progression and reticular pseudodrusen in eyes with dry age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2013;54(12):7362–7369.
- Ebneter A, Jaggi D, Abegg M, et al. Relationship between presumptive inner nuclear layer thickness and geographic atrophy progression in age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2016;57(9):0CT299–306.