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Current advances in multimodal imaging in geographic atrophy secondary to age-related macular degeneration: A review

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Abstract:

As we move toward an era in which there will be treatment options for geographic atrophy (GA) secondary to age-related macular degeneration, the need to accurately understand and interpret multimodal imaging (MMI) for the condition is paramount. This review discusses the evolution of MMI in GA and how it has led to a greater understanding of different phenotypes and risk factors for progression. These advancements have allowed novel imaging biomarkers to be used as end points in large interventional studies exploring new therapies for GA treatment. Due to differences in drug approval timing, ophthalmologists in some jurisdictions are already treating patients with complement inhibiting intravitreal therapies and using MMI to guide management. Cementing knowledge of how GA appears on MMI and evolves over time will be vital for best practice as these interventions become more widely available.

Keywords:

Geographic atrophy, age-related macular degeneration, complement inhibition, imaging, auto-fluorescence

Introduction

Age-related macular degeneration (AMD) is a complex, multifactorial disease with pathogenic contributions from both the environment and genetics. Geographic atrophy (GA) is a progressive, bilateral advanced form of AMD that causes severe vision impairment in 20% of patients.[1] The impact of this vision loss, both on an individual and societal level, is enormous and up until now represented a huge unmet need for intervention. Fortunately, the future of management of GA secondary to AMD is rapidly evolving thanks to recent advancements in therapeutic options. Where once there was little hope that could be offered to patients with this stage of AMD, now there are two FDA approved intravitreal anti-complement factor treatments currently in use in the USA with more jurisdictions likely to follow soon. In addition, there are several other interventions in the late phases of clinical trials with more in the pipeline. Pegcetacoplan (APL-2, Syfovre®, Apellis Pharmaceuticals) and Avacincaptad Pegol (Izervay™, Astellas Pharma) have both been approved in the USA for the treatment of GA following results from the OAKS and DERBY (Syfovre®)[2,3] and GATHER1/GATHER2 (Izervay™)[4,5] studies which showed favorable reduction of disease progression in the treatment arms compared to sham, determined by a slowing of growth of the atrophic lesion on fundus autofluorescence imaging.

Identifying patients who will benefit from GA treatment is dependent firstly on correctly classifying disease and second using standardized nomenclature to discuss imaging findings. The Beckman classification of AMD, based solely on

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clinical examination or color fundus photography (CFP), should be used to grade AMD to permit uniform understanding of disease stage and severity.[6] Under this classification system, early AMD is defined as patients with medium drusen (63–125 μm) without pigmentary change. Intermediate AMD is defined as patients with large drusen (>125 μm) or medium drusen with pigmentary abnormalities. Late AMD is either GA or neovascular AMD (nAMD).[6] The term "dry" AMD is best used only as a lay term to describe GA. Using "dry" AMD to describe all AMD which is non-nAMD, is not helpful when trying to differentiate various stages of the disease.

Color Fundus Photography

Of note, the term "geographic" was initially coined in an era where imaging was confined to CFP. Gass published the first edition of the "Stereoscopic Atlas of Macular Degeneration" in 1970 in which he described the appearance of "sharply circumscribed geographic areas of atrophy of the pigment epithelium at the posterior pole."[7]

The actual term "geographic atrophy" is thought to have been first used in a medical journal by Gass in 1972 when he used it the context of "senile macular degeneration" in an article published in the Transactions of the American Ophthalmological Society.[8] Its use has evolved over time, but it is widely understood in the literature to refer to one form of advanced AMD-the other being nAMD.[9] However, it is important to note that these stages are not mutually exclusive-both forms of advanced AMD can co-exist within the same eye. Outer retinal atrophy is often seen in eyes with neovascular disease,[10] and conversely neovascular complexes can develop in GA, often at the edge of an area of atrophy.[11]

Once the term "geographic atrophy" as a clinical descriptor was introduced into the literature, attempts were made to define it pathologically. The terminology evolved from "GA of the retinal pigment epithelium (and choroid)" or "GA of the retinal pigment epithelium and retina" to simply "geographic atrophy,"[9] indicating an initial lack of understanding of disease pathogenesis. Sarks' in-depth histopathological work broadened the knowledge base further in the 1970s including detailed descriptions of the features of GA both at the edge of and in the base of the lesions.[11] She highlighted the abrupt ending of the retinal pigment epithelium, photoreceptors, and external limiting membrane in areas of GA as well as atrophy of the underlying choroid.

In the 1990s, a definition of GA was stipulated by the Wisconsin Age-related Maculopathy Grading system on the basis of stereoscopic CFP images as a sharply defined area of "drop out of the RPE, exposing choroidal blood vessels."[12] This definition was further expanded for the Age-related Eye Disease Study (AREDS) system for classifying AMD (AREDS report No. 6) which defined GA on stereoscopic CFP as a "sharply demarcated, usually circular zone of partial or complete depigmentation of the retinal pigment epithelium, typically with exposure of underlying large choroidal blood vessels that must be as large as the circle I_1 (1/8 disc diameter or approximately ~ 175 um)."[13]

Fundus Autofluorescence

Major advances in imaging, genetics, and therapeutics since the term was coined have expanded our understanding of GA. In particular, optical coherence tomography (OCT) and fundus autofluorescence (FAF) have led to a greater understanding of how GA lesions behave clinically which have facilitated their use in large interventional studies. This is in part due to the fact while GA lesions are clinically heterogeneous, their behavior over time, when viewed with modern multi-modal imaging (MMI), is generally predictable. While the exact pathogenesis of GA remains unclear, the accumulation of lipofuscin (LF) in the lysosomes of the RPE is thought to be of major importance.[14-17] Under normal circumstances, there is continuous phagocytosis of the outer segments of photoreceptors occurring in the RPE which causes accumulation of LF. Toxic metabolites within LF such as the dominant fluorophore A2-E (N-retinylidene-N-retinylethanol-amine) may disrupt normal lysosomal homeostasis leading to aberrant cell function.[18-20] LF fluorophore accumulation has been identified as a pathogenic mechanism in many retinal diseases through interruption of normal lysosomal protein digestion and acting as a photosensitizer in blue light generating free radicals.[21] Visualization of this process has been dramatically assisted with the advent of autofluorescence imaging in particular with the use of confocal scanning laser ophthalmoscopy (cSLO). This allows for *in vivo* demonstration of normal patterns of FAF. Spectrophotometric analysis has shown the normal FAF signal of the human retina is generated by the RPE LF fluorophores.[22,23] Both blue light (488nM) and green light (514 nM) cSLO machines are commercially available for clinical practice. GA appears in both modalities as a well-demarcated area of reduced FAF intensity.[24] Most commonly blue light cSLO is used (e.g., the Heidelberg Spectralis®) – this wavelength is optimized for macula pigments (MPs) such as xanthophyll. The normal foveal autofluorescence appearance on blue light FAF imaging is a central circular zone of hypofluorescence approximately 0.5 mm in diameter.[25] This normal reduced FAF signal is important as identification of small, GA lesions adjacent to, or involving the fovea, may therefore be hard to identify.[26] As a result, images

obtained with blue-light FAF are often correlated with near-infrared reflectance imaging (NIR) which is not absorbed by MP. Green light cSLO (e.g., Optos®) with the slightly longer wavelength results in less absorption by the MPs. Studies quantifying GA area using FAF comparing blue and green light cSLO suggest the longer green excitation wavelength is superior for distinguishing small islands of preserved retina at the fovea. Misinterpretation of GA lesions at the fovea with the 488 nm wavelength occurs due to MP absorption of the laser light.[26] In one comparative study of the two modalities, the blue-light cSLO was more likely to result in both incorrect measurement of the size of the GA lesion and incorrectly determining whether atrophy at the fovea was present.[26]

However, in both natural history and interventional studies, mostly blue light FAF has been used for lesion quantification, size measurement, location determination and phenotypic characterization.[2,4,5] This includes the GATHER1/2 and OAKS/DERBY studies.[3,5] This has revealed the disease to be phenotypically heterogeneous both between eyes of the same patient and within disease populations. In terms of lesion distribution, it is important to establish if GA is unifocal or multifocal and if they are subfoveal or extrafoveal. Different FAF phenotypic characteristics have been identified that are associated with different growth rates.[27] These are classified into four patterns: focal, banded, patchy, and diffuse (further subdivided into reticular, branching, fine granular, and fine granular with peripheral punctate posts).[27]

The Fundus Autofluorescence Imaging in AREDS (FAM) and the Natural History of Geographic Atrophy Study (GAP) both aimed to use FAF imaging to follow GA progression by serial lesion measurements at 6, 12, and 18 months.[1,28] In the GAP study, mean lesion sizes as measured by FAF were significantly smaller than those measured by CFP at all times points although progression rate was similar for both modalities.[1] Longitudinal progression studies have measured the growth of GA lesions at rates of 1.2–2.8 mm^2/year.[29,30] Several factors identified on MMI predispose to greater GA growth over time. Extrafoveal lesions progress faster than subfoveal lesions [Figure 1].[1] Multifocal lesions grow more rapidly than unifocal GA [Figure 2]. Abnormal FAF patterns in the junctional zone between normal and atrophic retina are also important. Diffuse or banded GA lesions expanded more rapidly than focal lesions or eyes with no abnormality at the junctional zone. In addition, FAF is one imaging modality that can identify reticular pseudodrusen (RPD), which has been associated with faster growth of GA lesions.[31] These biomarkers have become important when considering who to include in treatment trials and in the identification

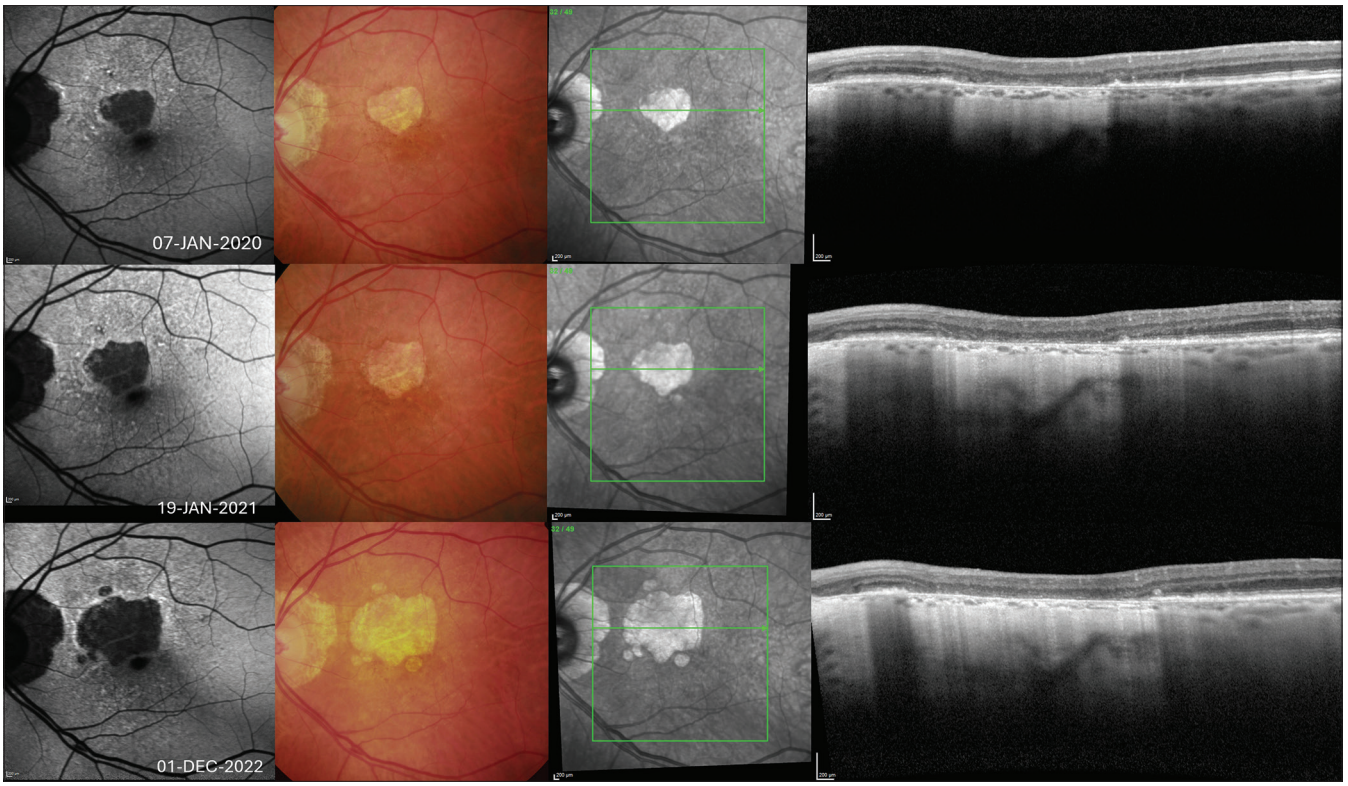

Figure 1: Fundus autofluorescence, color, infra-red reflectance, and optical coherence tomography of the left eye of a patient with geographic atrophy. Initially unifocal geographic atrophy showing progression over follow up. Note the predominance of reticular pseudodrusen

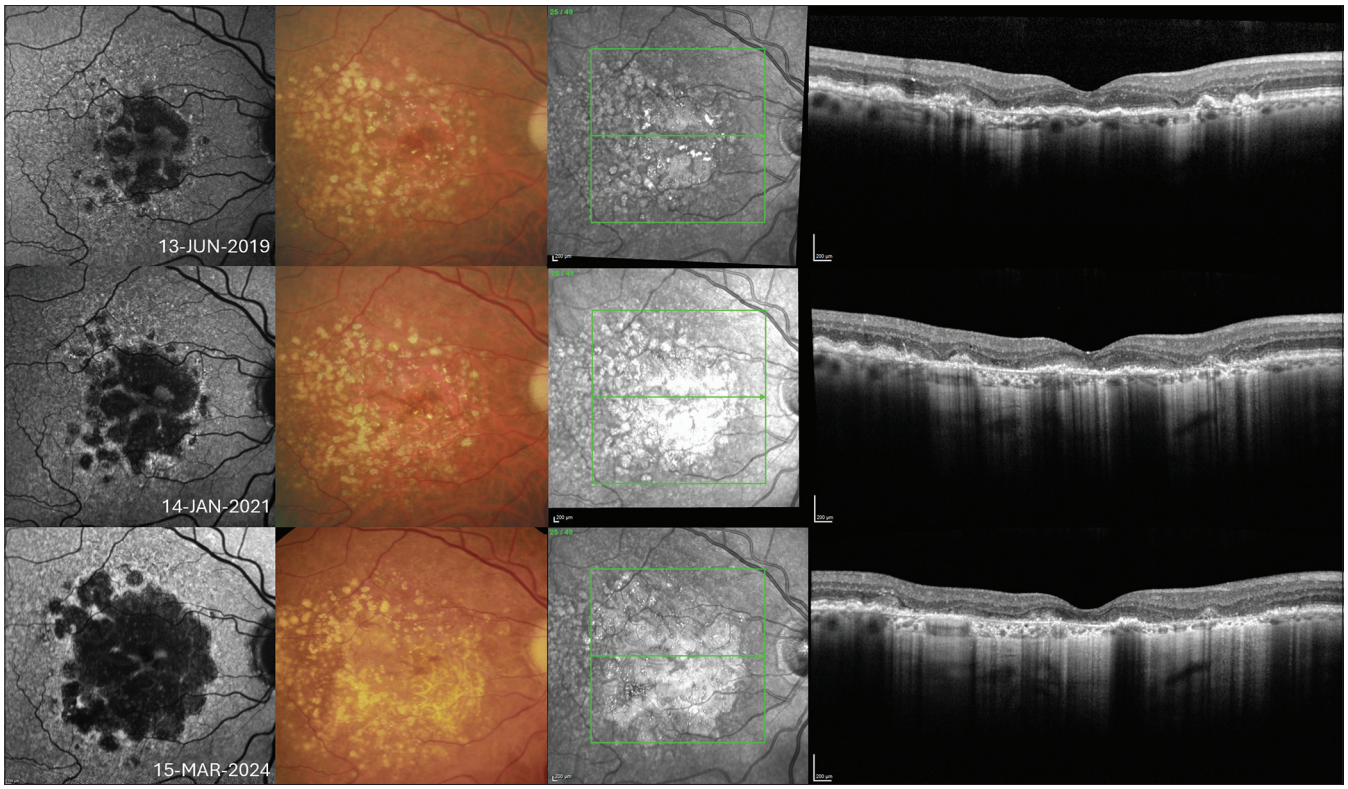

Figure 2: Fundus autofluorescence, color, infrared reflectance, and optical coherence tomography of the right eye of a patient with geographic atrophy. Imaging shows multifocal geographic atrophy initially sparing the fovea with rapid progression to subfoveal involvement

of fast-progressing patients who may gain the most benefit from interventions as they become available.

FAF is being used in pivotal phase 3 studies as a method to measure GA lesion size for inclusion criteria as well as the primary endpoint of change in the rate of growth as the determination of treatment success. The OAKS and DERBY studies examined the safety and efficacy of pegcetacoplan compared with sham in patients with GA using serial FAF over 2 years to monitor progression.[3] In addition, the GATHER1/2 studies randomized patients without foveal involvement from GA to avacincaptad pegol or sham. Both studies had a primary endpoint of the change from baseline to month 12 in slowing the growth of GA lesions as measured on FAF imaging highlighting the widespread adopting of this modality in clinical trials.

Optical Coherence Tomography

Whilst FAF is very useful as an enface imaging technique to measure certain characteristics of the GA lesion, OCT offers additional important information for diagnosing and monitoring GA.[32-36] The high resolution of spectral domain OCT (SD-OCT) images permits modeling of GA in three dimensions and detailed, near histological ability to identify specific loss of the outer retinal layers and choroid. B scans can be correlated with en-face volumetric scans to define the borders of atrophy and document progression.[37] Through the Classification of Atrophy Meeting (CAM) group, there has been an effort to accurately describe the OCT changes seen in the relevant layers on OCT in GA and as the atrophy begins.[37,38] Terms to define SD-OCT findings of atrophy are (1) complete RPE and outer retinal atrophy (cRORA) and (2) incomplete RPE and outer retinal atrophy (iRORA), as long as no RPE rip present. cRORA is defined on OCT by (1) hypertransmission of at least 250 μm in diameter; (2) a zone of corresponding attenuation or disruption of the RPE of at least 250 μm in diameter; and (3) evidence of overlying loss of zones indicative of photoreceptor loss.[37] iRORA is present if these lesions are all present but <250 μm.[38] Given the widespread use of "GA" in the literature, the CAM group proposed to retain its use for when these signs of cRORA are present, but restrict it use to situations without co-existence of nAMD. Therefore, GA can be considered a subtype of cRORA, without neovascularization.[37]

The term nascent geographic atrophy (nGA) was coined a decade ago to define the SD-OCT changes that were often present before the development of GA.[39] Wu *et al*. followed a cohort of patients with large drusen in one eye and late AMD in the fellow eye, or patients with bilateral large drusen. They reported GA in 20 patients and then analyzed their prior serial OCTs before the

development of GA. They found several consistent changes that were nearly always present and termed these "nascent geographic atrophy" (nGA). The nGA OCT characteristics are either the subsidence of the outer plexiform layer (OPL) and inner nuclear layer, or the appearance of a hypo-reflective wedge-shaped band within the OPL, or both.[39] Independent risk factors for the presence of nGA include pigmentary changes and nGA in the fellow eye. In a further study, using a natural history cohort of iAMD, eyes with nGA were found to have a 78-fold increased risk of developing GA.[40] In this same cohort, eyes with iRORA also had an increased risk, (Hazard Ratio of 12) of progression to GA, albeit less than that found for nGA.[41] Other studies have found these lesions to be risk factors for progression, although the exact risk differs, likely in large part due to different grading of these lesions.[42]

There are also recognized even earlier OCT signs that increase the risk of disease progression to GA. Atypical drusen,[43] OCT-reflective drusen substructures,[44] hyperreflective foci (HRF),[45,46] RPD,[31,47] and certain quantitative SD-OCT metrics[48,49] have all been shown to be associated with an increased risk of progression to GA.

Optical Coherence Tomography Angiography

OCT angiography (OCTA) has some utility in both diagnosis and prognostication of GA. An important, unresolved concept in AMD pathogenesis is determining whether a reduction in retinal and choroidal blood flow precedes the death of photoceptors and the RPE or is a secondary phenomenon. OCTA may provide insights into determining whether the primary event in the development of GA is changes in retinal and choroidal perfusion or occurs as a secondary phenomenon. Potential artefacts, for example flow voids from drusen, can often confound OCTA interpretation and must be taken into consideration.[50] Recent studies on GA using OCTA have shown both retinal and choroidal blood flow abnormalities.[51,52] Eyes with GA have been shown to have significantly reduced vessel densities in retinal plexuses compares to healthy eyes.[53] The choriocapillaris (CC) is of particular interest given its close relationship to Bruch's membrane and its vital role in supporting the outer retina, providing nutrient supply and waste removal for the outer retinal layers.[54] While the CC cannot be imaged on OCT, fluorescein angiography, or indocyanine green angiography, it can be differentiated on OCTA with careful segmentation.[55] The analysis of the CC vessel density on OCTA in has identified that flow at the junctional zone of normal retina to an area of GA is impaired.[52] Longitudinal studies have shown that patients with baseline flow deficits associated with GA progress faster over a 1–2-year follow-up compared to patients without flow deficits.[56,57] In recent studies, there is some evidence that this impairment precedes the changes seen on FAF.[52,58]

In addition, a recent report suggests that even before the development of GA, there are already OCTA changes demonstrable in eyes that develop nGA. Greig *et al*. have shown that while there was no significant change in the overall CC flow deficits in eyes that went on to develop nGA compared to eyes that did not, there were detectable difference in specific regions which they called superpixels which allowed pixels to be grouped together to aid analysis.[59,60] Analyzing these superpixels allowed demonstration of differences in flow deficits in the CC of eyes that developed nGA compared to eyes that did not.[59]

OCTA is also a useful tool for identifying eyes with nonexudative macular neovascularization (neMNV) in the setting of AMD with or without GA. neMNV are lesions that demonstrate no exudation on OCT (intraretinal or subretinal fluid) nor leak on fluorescein angiography, and first were described using ICG-A. However, they can be seen on OCTA, which is advantageous as it does not involve the use of intravenous dye.[61] A recent systematic review of neMNV suggested that while the condition is almost certainly a precursor for exudative nAMD, they may be protective in some patients by reducing the risk of developing GA or slow the lesion growth in those already with GA.[62] In their review, Laiginhas *et al*. included 12 studies for the systematic synthesis.[62] Within this, three studies described the prevalence of neMNV in eyes with co-existing GA. de Oliveira Dias *et al*.[63] and Yang *et al*.[64] found the prevalence, incidence, and risk of subsequent exudation of neMNV was the same in eyes with GA as in eyes that had iAMD alone. Capuano *et al*. studied a cohort of 644 eyes in 399 patients with known GA and identified 73 eyes in 71 patients with co-existing neMNV (11%).[65] Nineteen of these eyes were then followed up between 27 and 65 months. The lesion growth rate of GA was 1.38 ± 0.93 mm^2/year which is on the lower end of the longitudinal growth rates quoted in the literature of 1.2–2.8 mm^2/year.[29] In addition, 92% of cases demonstrated the neMNV lesion to be adjacent to an area of GA where there was no documented enlargement.[65] Other smaller studies in eyes with neMNV and GA have shown similarly slower rates of atrophy expansion when compared to eyes without neMNV.[66,67] The common finding of neMNV adjacent to areas GA supports the hypothesis that the lesions arise as a compensatory mechanism due to impairment of blood flow within the CC, with resultant reduction in support to the outer retina.[62] Other authors argue the neMNV lesion arise first and GA develops in the area unable to be metabolically supported by the abnormal neovascular tissue.[62] Regardless of the

sequence of events, it is likely that neMNV provides critical nourishment to areas at risk of GA, potentially slowing its development or growth.[62]

Near-infrared imaging

Confocal NIR can also be used to diagnose and monitor GA.[68] Its utility is not only that is noninvasive, noncontact, and rapid, but also that the images are simultaneously acquired when performing SD-OCT in routine practice. The confocal technology allows minimization of light backscatter which in turn improves image contrast and resolution. Patients often tolerate it better than the intense light of FAF. Due to its longer wavelength (~820 nm), NIR permits excellent visualization of the photoreceptor layer, the RPE, and the choroid.[69] While NIR images often correlate with blue-light FAF, it is more effective at demonstrating sub-RPE lesions. This is largely due to the fact that melanin and LF absorb the shorter (480 nM) wavelengths of blue light FAF but allow passage of the longer monochromatic wavelengths of FAF.[70,71] Studies have sought to correlate the size of GA lesions on both NIR and blue-light FAF. GA appears as an area of hyper-reflectivity on NIR due to the absence of RPE blockage of the long wavelengths and subsequent reflection of light from the underlying sclera.[72] Sadda's group demonstrated good interrater reliability analysis when comparing the FAF and NIR modalities during manual segmentation of the GA lesions on an established dataset.[68] In addition, in 2017, the Classification of Atrophy (CAM) group included NIR as one of the recommended imaging modalities for GA diagnosis and monitoring in natural history studies and interventional clinical trials.[73]

Artificial Intelligence

The use of Artificial intelligence (AI) algorithms in GA assessment has the potential to dramatically assist in disease management. Through improved diagnosis, enhanced understanding of pathogenesis, and identification of biomarkers for use in interventional studies AI will undoubtedly have a significant impact on AMD management. Currently, AI can be used to support the diagnose of GA lesions, provide data to monitor progression, and identify risk factors that are associated with GA development and growth.[74] Using AI in retinal imaging analysis for GA has many advantages including improved accuracy and faster processing.[74] A recent report has shown that AI can support grading of nGA, significantly reducing the burden of a grading center.[75] Ongoing work is being done in an effort to use AI to predict current or future visual function around areas of GA.[76]

Both the risk of progression from iAMD to GA and of worsening GA have been studied using AI. Lad *et al*. looked at patients enrolled in the AREDS2 Ancillary SD-OCT (A2A) study to identify OCT features that could be used for deep learning algorithms to predict progression from iAMD to GA and for subsequent vision loss.[76] The group concluded that individual features in isolation were unable to predict GA over this short term (1 or 2 years). Rather, the combination of SD-OCT biomarkers was associated with GA progression. At 1 year, a combination of high HRF axial distance score, low neurosensory retinal volume, high RPE drusen complex (RPEDC) abnormal thinning volume, and high RPEDC volume resulted in a 75% risk of progression to SD-OCT determined GA. At year 2, there were variable results depending on the combination of risk factors analyzed, leading the authors to recommend further validation.[76]

Bui *et al*. prospectively analyzed SD-OCT and FAF images of 181 eyes of 100 patients with GA for both qualitative and quantitative measures of progression. HRF were quantitatively assessed using a previously validated deep learning algorithm. FAF images were analyzed for predefined FAF patterns (based on the FAM study[28]), presence of RPD, GA lesion configuration, and atrophy enlargement. Factors that were associated with faster GA progression included FAF patterns (diffuse trickling) and higher HRF concentrations.[77]

The utility of AI will also be in patient selection for future GA interventional studies. Until the recent approval of intravitreal complement inhibitors in the USA, failure of previous pharmacological interventions for GA has likely been a combination of poor patient selection and lack of useful earlier endpoints to be used in the place of frank GA to facilitate shorter trials. Using machine learning, the identification of high-risk SD-OCT biomarkers for progression will hopefully mean patients will be eligible for intervention earlier in the disease process and thus less likely to lose vision from GA.[76,78,79]

Conclusion

Advances in MMI have clearly allowed our understanding of GA, its measurement and risk factors associated with its development and progression to continue to evolve. There is no doubt that as imaging improves with such advances as the high-resolution OCTs as well as ongoing development of instruments such as the novel fluorescence lifetime imaging ophthalmoscopy will reveal further biomarkers that improve our ability to manage GA. Without doubt we are on the cusp of an era where we will be able to treat GA, where imaging data will be critical for us to evolve our understanding around who to treat and when to treat and how to measure success of our treatments.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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