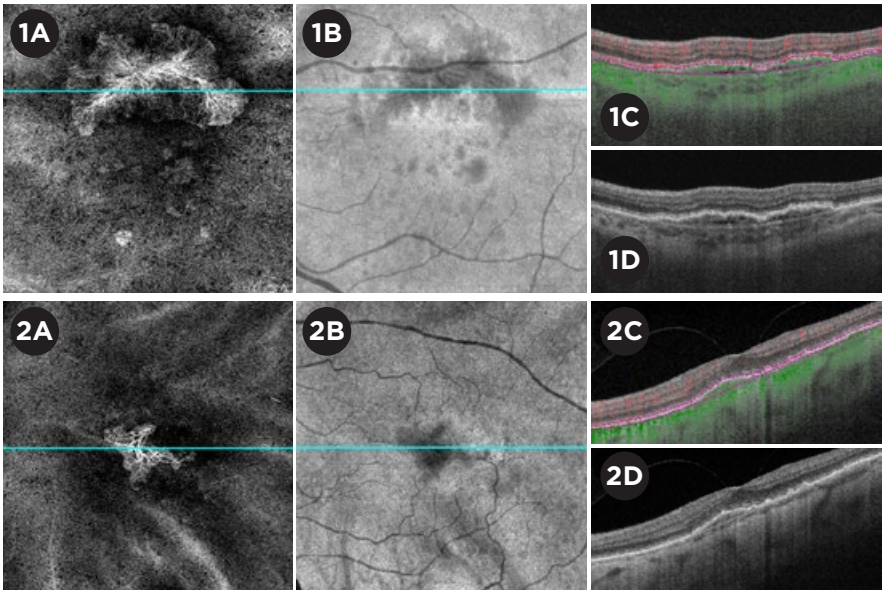
OCT-A: A Path to Earlier Diagnosis of Dry AMD

In 2015, optical coherence tomography angiography (OCT-A) became commercially available as a way to noninvasively image the microvasculature of the retina and choroid. Today, no one disputes that OCT-A produces stunning images. But can it provide new clinical—not just confirmatory—value for the management of dry age-related macular degeneration (AMD)?

That's a question that Philip J. Rosenfeld, MD, PhD, at the Bascom Palmer Eye Institute, frequently fields from his colleagues. Although OCT-A doesn't appear to improve the management of wet AMD, he said, this imaging modality does have the potential to change the way retina specialists manage dry AMD in clinical practice, and it can identify patients who are at high risk of converting to wet AMD.



TWO EXAMPLES. *(A) Subclinical nonexudative type 1 neovascularization detected by SS-OCT-A. 6 x 6 mm en face SS-OCT-A flow image from a slab extending from the retinal pigment epithelium to Bruch's membrane (BM) following removal of the retinal vessel projection artifacts. (B) 6 x 6 mm en face structural image produced from the same slab as A. The area of hyporeflectivity corresponds to the type 1 neovascularization in panel A. (C) SS-OCT-A B-scan with flow corresponding to the horizontal line in A and B, with purple segmentation lines defining the RPE-BM slab. Retinal flow is depicted in red and choroidal flow is in green. (D) SS-OCT-A B-scan as in panel C without superimposed flow or segmentation lines.*

Insights Garnered From OCT-A

"OCT-A, especially swept source, gives you the ability to see subclinical neovascular complexes and the choriocapillaris, the vascular layer under the retinal pigment epithelium (RPE), which couldn't previously be visualized in living humans," said Dr. Rosenfeld. In fact, this technology has allowed retina specialists to identify a whole new category of AMD—nonexudative neovascular AMD, he said.

Loss of the choriocapillaris. These patients "have a loss of the choriocapillaris underlying the atrophy as well in the area surrounding the atrophy," said Nadia K. Waheed, MD, MPH, at Tufts University School of Medicine. "We're still in the preliminary stages of understanding exactly what that means." Dr. Rosenfeld added that it's not known whether the loss of the choriocapillaris precedes loss of vision in AMD or vice versa. "A major focus moving forward is to understand how these changes affect the natural history of AMD."

Subclinical choroidal neovascularization. The ability to visualize subclinical choroidal neovascularization (CNV) in dry AMD patients is important, said Dr. Waheed. She noted that in a recent study[1] by Dr. Rosenfeld's

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Images prepared by Yingying Shi, MD

group, "Patients with subclinical CNV followed for a year were shown to have a 15-fold higher risk of exudation compared with AMD eyes without it."

In this study, swept-source (SS) OCT-A allowed the researchers to monitor disease status in eyes with intermediate dry AMD or geographic atrophy (GA), with wet AMD in the fellow eye. Within a year, wet AMD developed in 24% of eyes with—and in 5.4% of eyes without—subclinical CNV detected by SS-OCT-A.[1]

Being able to spot subclinical CNV long before exudation appears is the most valuable application of OCT-A, said Dr. Rosenfeld. "You need to know who among your dry AMD patients has a ticking time bomb in the back of their eyes."

Eleonora M. Lad, MD, PhD, at the Duke University School of Medicine, also believes that the identification of this subset of patients at high-risk for exudation will lead to improved visual outcomes and a better prognosis through earlier treatment.

SD-OCT-A versus SS-OCT-A. Both spectral-domain (SD) and SS-OCT-A can be used to visualize changes in dry AMD, but SD-OCT-A is slower with a shorter wavelength, and SS-OCT-A is faster with a longer wavelength, said Dr. Waheed, which provides better penetration into the choriocapillaris.

Dr. Lad added that devices using SS-OCT-A are associated with better definition of choroidal vasculature changes, for example, the general decrease in choriocapillaris flow reported in dry AMD that typically extends beyond the borders of areas of atrophy.[2]

If a patient has geographic atrophy, structural SD-OCT-A can provide the volume of drusen and show the area of atrophy, she said. "You can get exactly the same information from the en face OCT as you can from fundus autofluorescence and color fundus photos, and you can additionally check the B-scans for fluid. Although it is not as good as SS-OCT-A in detecting asymptomatic CNV, it still does a reasonably good job."

Although SS-OCT-A is a boutique imaging strategy mostly used for research at a cost approximately twice that of SD-OCT-A, said Dr. Waheed, SS-OCT-A is starting to gain traction now in clinical practices. The cost will likely change as the technology gets cheaper and faster, she said.

Clinical Use of OCT-A for Dry AMD

"OCT-A gives you multimodal imaging using a single imaging modality," said Dr. Rosenfeld. "With a single scan, you can get both structural and flow information, and the 2 types of images can be superimposed." Dr. Waheed added that it's one of the best ways of monitoring the size and direction of GA, both in clinical practice and in clinical trials.

Observe. "OCT-A will change the way we screen patients with dry AMD because it gives us the ability to detect early changes and stratify patients into higher and lower risk groups," said Dr. Waheed. "We can identify patients with subclinical neovascularization and put them into a program with closer observation," said Dr. Rosenfeld. This involves both more frequent clinical observation and home monitoring. "We have always instructed patients on how

Translating AMD Research Into Clinical Benefits

"We still need to demonstrate the clinical usefulness of OCT angiography in improving AMD patient outcomes," said Dr. Rosenfeld, adding that he expects that this technology will be a valuable research tool for helping better understand and diagnose the disease.

Understanding natural history. Two 2-year natural history studies are currently following AMD patients who have a wide range of disease severity, said Dr. Rosenfeld. IMPACT focuses on intermediate AMD, where the main feature is intermediate AMD, primarily with drusen, and SWAGGER focuses on the later form of nonexudative AMD, where the primary manifestation is geographic atrophy. "The researchers are using SS-OCT-A to intensively image patients using different scan patterns repeated multiple times," he said. "We will also average the scans to achieve even better image quality and resolution."

Identifying surrogate endpoints. Researchers also hope to identify clinical study surrogate endpoints that correlate well with endpoints of GA, a slowly developing disease, said Dr. Waheed. This would allow researchers to test whether drugs are effective at an earlier stage and make it possible to run shorter, smaller trials, added Dr. Rosenfeld.

The ongoing Duke natural history trial on early-intermediate AMD, led by Dr. Lad; the upcoming AMD Ryan Initiative Study; and the international MACUSTAR study are all investigating surrogate clinical study endpoints for use in earlier stages of dry AMD.

Improving the OCT-A technology. Under the auspices of the Advanced Retinal Imaging (ARI) Network, which was organized by Zeiss, a global consortium of clinical researchers is testing software and hardware upgrades and sharing cases and testing algorithms via a web portal, said Dr. Rosenfeld. The research program will eventually be expanded to 200 sites.

Developing a risk assessment tool. Studying a patient subset of the Age-Related Eye Disease Study (AREDS) 2, researchers at Duke, led by Cynthia Toth, MD, developed a novel risk-assessment model for progression to color photograph–visible GA over a period up to 5 years.[1] The model is based on age and SD-OCT-A segmentation, drusen characteristics, and retinal pathology. "With future validation, I think it will be very helpful as a clinical tool, as a research tool to simplify SD-OCT-A grading, and to inform industry and pharmaceutical companies on how to design future studies for GA," said Dr. Lad.

1 Sleiman K et al. *Ophthalmology*. 2017;124(12):1764-1777.

to test their vision at home, but now we encourage patients with subclinical neovascularization to increase their vigilance since we can't yet predict whether and when the abnormal neovascularization will leak."

Home monitoring can be done with a phone app called DigiSight or with Notal Vision's ForeseeHome, which is covered by Medicare, said Dr. Rosenfeld. Both technologies allow the doctor to see how often patients check their vision. Although the Amsler grid is unreliable, patients may also check their vision with it every day, he said.

Drs. Rosenfeld, Lad, and Waheed see most patients with dry AMD about every 6 months to a year. But if a patient has subclinical CNV, they scan them every 2-3 months to see how the lesions are progressing.

Treat with caution. Drs. Waheed and Lad do not begin treating these high-risk patients with anti–vascular endothelial growth factor (VEGF) therapy unless they develop subretinal fluid and active exudation, as well as a leak on fluorescein angiography (FA). "Robust data show that treatment helps only once exudation develops," said Dr. Waheed.

Dr. Rosenfeld agrees with this conservative approach—only treating symptomatic exudation. That's because good vision in the presence of CNV may indicate that neovascularization provides beneficial nutritional support to the RPE and photoreceptors, he said. "Although anti-VEGF therapy suppresses exudation and preserves vision," he said, "there's an ongoing controversy about whether anti-VEGF therapy promotes the formation of geographic atrophy. If it does, then it probably accelerates atrophy by accelerating the disappearance of the neovascularization." If you begin treatment as soon as subclinical CNV is detected, he said, it begs the question: How would you know when to stop? Only after atrophy arises?

In other words, the definition of treatable neovascular AMD has not yet been rewritten to incorporate OCT-A's findings of nonexudative neovascularization, added Dr. Lad.

Continue to monitor. Another important point for clinicians to remember? Growth of neovascularization does not correlate with exudation, said Dr. Rosenfeld. "These patients can do well without treatment, and then the disease will usually progress to atrophy. OCT-A can be used to follow the progression to GA. It gives you all the information you need to follow the life cycle of AMD."

OCT-A Scanning Tips

Invest some time. Learning OCT-A requires hands-on training, said Dr. Rosenfeld, as well as time to simply sit and play with the equipment. "There's definitely a learning curve, but once you get the hang of it, it will become second nature," he said.

"An OCT-A scan takes just a few seconds longer, but the real time comes in the interpretation of the scan," he said, adding that this investment of time is outweighed by benefits over dye-based angiography: noninvasiveness, safety, speed, and more valuable information.

Dr. Waheed noted that it really is worth learning OCT-A for your patients, as it can help you figure out the risk of progression, especially for those with atrophy.

Choose the scan size. OCT-A allows you to do different scan sizes, said Dr. Rosenfeld, and you choose the scan size based on the extent of the disease. With a SD instrument, you can do a 3 mm × 3 mm, 6 mm × 6 mm, or 8 mm × 8 mm scan, he said. With SS-OCT-A, there is a choice of scan sizes from 3 mm × 3 mm up to 12 mm × 12 mm or 15 mm × 9 mm. Automated montage capability can extend the field of view out to 60 degrees or larger. "With all these scans, I can see all the pathology in AMD," said Dr. Rosenfeld.

Scrutinize key areas. With OCT-A technology, you can look at various depths, said Dr. Lad, and you must first decide the level where you're most likely to see the pathology. The segmentation levels that are most important to review for AMD are the deep—or avascular—retina and the choriocapillaris, said Dr. Waheed. "If you see something there, you worry about neovascularization."

Look at a structural-flow overlay. "The other thing I always like to look at is the structural B-scan with a flow overlay," said Dr. Waheed. This can help confirm the presence of subclinical neovascularization in patients with nonexudative disease.

Check density. "I also like to look at the overall density of the choriocapillaris, especially on the margins of the geographic atrophy because that tells me how much damage there is," said Dr. Waheed.

Beware of artifacts. Motion artifacts are much less of a problem today due to physical tracking and software-based artifact removal tools, said Dr. Waheed. "However, it can still happen if the patient has poor fixation and a lot of GA," she said. Although projection artifacts have become less common thanks to software designed to remove them, if you see something that looks like neovascularization, double-check that you're not looking at projection artifacts, she said.

Recognize patterns. There is a pathological phenomenon in patients with GA that can sometimes be confusing, said Dr. Waheed. "When patients lose their choriocapillaris, larger vessels migrate upward into the area of the choriocapillaris. These can be confused with CNV." A lot of this interpretation requires pattern recognition, agreed Dr. Lad. "You have to know what the abnormal and normal vessels look like on indocyanine green angiography to identify the suspicious vascular structure."

1 de Oliveira Dias JR et al. *Ophthalmology*. 2018; 125(2):255-266.
2 Choi W et al. *Ophthalmology*. 2015;122(12): 2532-2544.

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