Review

ASRS American Society of Retina Specialists

Journal of VitreoRetinal Diseases
1-5

DOI: 10.1177/2474126419834702
jvrd.sagepub.com
SAGE

Best Clinical Practice for Age-Related Macular Degeneration Imaging

K. Bailey Freund, MD[1], Cynthia Toth, MD[2], and Marco Zarbin, MD, PhD, FACS[3]

Abstract

Purpose: To identify best clinical practices for macular degeneration imaging. **Methods:** We reviewed best clinical practices for imaging patients with age-related macular degeneration. These recommendations are based on different levels of evidence (I-III). **Results:** The type of imaging needed depends to some degree on the clinical scenario: first visit vs follow-up visit vs poorly responsive patient. **Conclusions:** Imaging technologies that may be useful include optical coherence tomography, fundus photography, fundus autofluorescence imaging, fluorescein angiography, indocyanine green angiography, and optical coherence tomography angiography.

Keywords

age-related macular degeneration, fluorescein angiography, fundus autofluorescence, fundus photography, imaging, indocyanine green angiography, optical coherence tomography, optical coherence tomography angiography

Introduction

Ideally, validation of clinical practice is based on results of randomized clinical trials, ie, level I evidence.[1] However, level I evidence does not exist for all aspects of clinical practice, and even when available, certain real-world obstacles make its application challenging.[2] While treatment for neovascular age-related macular degeneration (nAMD) has evolved, so has the range of retinal imaging modalities used to establish a diagnosis, assess neovascular lesion characteristics, and guide treatment decisions.

In some cases, the use of imaging in this setting has been validated in randomized trials. For example, fluorescein angiography (FA) provided critical information in the randomized clinical trials evaluating laser photocoagulation[3] and verteporfin photodynamic therapy.[4] By contrast, although patients underwent optical coherence tomography (OCT) during the initial randomized trials assessing intravitreal anti-VEGF therapy for nAMD,[5,6] its value in guiding treatment decisions was established later in a relatively small case series (ie, level II evidence).[7] This was followed by OCT-based determination of presence of fluid for treatment decisions in the first large randomized clinical trial of comparative efficacy of intravitreal anti-VEGF therapies.[8-10]

There are a number of other imaging modalities that, in the proper setting, provide important information enabling clinicians to optimize therapy for patients with nAMD. Although the level of evidence supporting their usefulness ranges from level I to level III (ie, opinion of respected authorities), that variability is a boundary condition that is typical of clinical practice and does not per se invalidate the value of recommendations so derived. With these caveats in mind, our goal is to provide guidelines for best clinical practice regarding the use of imaging studies in the management of patients with nAMD. Image analysis of non-neovascular AMD has been reviewed elsewhere.[11-15]

Clinical Scenarios

First Visit

When a patient with suspected nAMD first presents for evaluation, some or all of the following imaging tests may be useful for establishing a correct diagnosis, making decisions regarding management, and for educating the patient regarding the treatment plan.

OCT. Because current OCT devices are more sensitive than clinical ophthalmoscopy using a contact lens in detecting certain subtle alterations in retinal structure, ophthalmologists often perform OCT in patients reporting changes in central vision, even when no exudative findings are detected on

[1] Vitreous-Retina-Macula Consultants of New York, New York, NY, USA
[2] Department of Ophthalmology, Duke University Medical Center, Duke Eye Center, Durham, NC, USA
[3] Institute of Ophthalmology and Visual Science, Rutgers-New Jersey Medical School, Rutgers University, Newark, NJ, USA

Corresponding Author:
Marco Zarbin, MD, PhD, FACS, Rutgers University, Rutgers-New Jersey Medical School, Institute of Ophthalmology and Visual Science, Doctors Office Center, Room 6156, 90 Bergen St, Chatham, NJ 07103, USA.
Email: zarbin@earthlink.net

clinical examination. OCT may also detect retinal fluid in patients lacking symptoms. Some clinicians use OCT to help direct their clinical examination, and since OCT does not require dilation, patients can be imaged while their pupils are dilating. OCT allows one to identify and document the extent of subretinal fluid, intraretinal fluid, subretinal hyperreflective material (SRHM), and/or pigment epithelial detachment (PED), which will be used to assess the response to therapy as well as to identify areas of retinal pigment epithelium (RPE) and photoreceptor loss.

Certain characteristic OCT findings may suggest specific neovascular lesion types that may warrant additional imaging. For example, identifying intraretinal fluid surrounding a hyperreflective focus in the outer retina anterior to a PED can help detect cases of type 3 (intraretinal) macular neovascularization (MNV).[7,16-22] The presence of "peaked" PEDs found in association with an adjacent shallow, irregular splitting of the RPE/Bruch membrane complex (double-layer sign) is suggestive of polypoidal choroidal vasculopathy (PCV) also known as aneurysmal type 1 (sub-RPE) MNV.[23]

It is important to recognize that SHRM may represent different types of exudative material, including hemorrhage, so clinical examination and/or additional imaging is often required to completely evaluate its presence. Not infrequently, patients with no fluid and normal vision may harbor nonexudative MNV that can be seen with OCT. These patients warrant close follow-up so treatment can be initiated if fluid develops.

Fundus photographs. Color (including multicolor) photographs may be useful to document the extent of geographic atrophy (GA) and/or fibrosis, extent of subretinal hemorrhage (eg, for comparison at the next visit), as well as for patient education.[11,21]

Fundus autofluorescence imaging. Fundus autofluorescence (FAF) may be useful to document the extent of associated GA, which may progress and may contribute to changes in visual acuity not attributable to CNV activation.[21,24,25] FAF imaging also can help clinicians distinguish GA from other similar entities such as acquired vitelliform lesions.[26]

FA (rate of anaphylaxis: ~ 1/222 000[27]). An FA, unless contraindicated, may be useful to assist in distinguishing masquerade conditions such as choroiditis or central serous chorioretinopathy (CSC) from MNV.[21]

Indocyanine green angiography (rate of anaphylaxis: ~ 1/200 000[28,29]). An indocyanine green angiogram (ICGA) may be useful for detecting MNV beneath areas of macular hemorrhage and for identifying PCV (ie, aneurysmal type 1 [sub-RPE] MNV[23]). If OCT/FA are not diagnostic, ICGA may also help distinguish MNV related to AMD vs CSC or other non-AMD entities.[21,30]

OCT angiography. An OCT angiogram (OCTA) may substitute for an FA, provided one recognizes its limitations such as limited ability to image flow beneath PEDs. Also, with OCTA, there is a need for reasonably clear media and steady fixation.[31-34] OCTA also can identify occult, nonexudative type 1 MNV in cases of intermediate AMD. This finding may have a predictive value in patients at higher risk for progressing to clinically active MNV.[35,36]

Follow-Up Visit

Routine follow-up visits usually require less-extensive imaging than the first visit. If a patient has unexplained visual loss or appears refractory to therapy, more-extensive imaging may be indicated.

OCT. OCT imaging is important for most follow-up visits, as reactivation or persistent activity of MNV may not be evident on clinical examination alone, even with contact lens biomicroscopy. Clinicians should not rely solely on thickness maps and should check for segmentation errors by reviewing structural B-scans.[37] Changes in OCT thickness >10% of the previous value (eg, increased retinal thickness from 300 μ to 335 μ) that do not arise from imaging artifacts are probably clinically significant.[18]

Additional imaging is appropriate to document changes from baseline or to evaluate unexplained clinically significant changes in visual acuity or uncertain anatomic findings on OCT. Depending on the circumstances, these additional studies may include FA, ICGA, FAF, and color photographs.

OCTA may provide information not available with FA or OCT and may be useful if there is an unexplained change in visual acuity or if OCT findings are not clear.[38-40]

Poorly Responsive Patient

If a patient responds poorly to intravitreal anti-VEGF therapy, it may be prudent to consider alternative diagnoses including CSC, large drusenoid PED, or an acquired vitelliform lesion for which additional imaging may be needed to correctly identify the condition. If the patient previously responded to anti-VEGF therapy and no longer seems responsive, then more extensive imaging is undertaken both to ascertain possible changes in disease anatomy (eg, development of foveal atrophy causing visual loss in the absence of CNV activity) as well as to confirm the correct diagnosis. Repeat imaging at times earlier than 1 month following the previous anti-VEGF injection can help identify patients who respond to therapy but require more-intensive treatment than monthly injections.[41]

OCT. Consider enhanced-depth imaging OCT or swept-source OCT to identify choroidal thickening typical of CSC.[42,43]

ICGA. Consider ICGA to identify PCV or choroidal hyperpermeability consistent with CSC.[30]

FA. Repeat FA may be useful.

OCTA or FAF. OCTA or FAF may be useful in identifying masquerade entities.

Conclusions

Given the variable presentations of nAMD and the variable clinical response to therapy, it is not appropriate to provide rigid guidelines regarding the use of retinal imaging in evaluating a patient with AMD. Fortunately, a wide array of imaging technologies is now available to assist physicians in diagnosing and guiding treatment decisions for these patients. These technologies should be deployed on an as-needed basis. With the evolution of machine learning,[44-46] it is likely that physicians will become increasingly reliant on image analysis to make treatment decisions for patients with exudative manifestations of nAMD.

Ethical Approval

Not applicable.

Statement of Informed Consent

Not applicable.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Freund serves as a paid consultant for Heidelberg Engineering, Zeiss, Optovue, Novartis, Genentech, and Allergan. Dr Toth receives royalties from Alcon for surgical technology licensed through Duke University and royalties from HemoSonics. Dr Toth also serves as a paid consultant to the EMMES Corporation for service on a data safety and monitoring board. Dr Zarbin serves as a paid consultant for Cell Cure, Chengdu Kanghong Biotechnology, Coherus BioSciences, Daiichi Sankyo, Frequency Therapeutics, Genentech/Roche, Healios KK, Iridex, Isarna Therapeutics, Makindus, Novartis Pharma AG, Ophthotech, and Percept Corp.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported in part by Genentech/Roche (Freund), an unrestricted grant from Research to Prevent Blindness (Toth), the Eng Family Foundation (Zarbin), the Joseph J and Marguerite DiSepio Retina Research Fund (Zarbin), and the New Jersey Lions Eye Research Foundation (Zarbin).

References

1. The periodic health examination. Canadian task force on the periodic health examination. *Can Med Assoc J*. 1979;121(9):1193-1254.
2. Zarbin MA. Challenges in applying the results of clinical trials to clinical practice. *JAMA Ophthalmol*. 2016;134(8):928-933. doi:10.1001/jamaophthalmol.2016.1266
3. Laser photocoagulation of subfoveal neovascular lesions in age-related macular degeneration. Results of a randomized clinical trial. Macular Photocoagulation Study Group. *Arch Ophthalmol*. 1991;109(9):1220-1231. doi:10.1001/archopht.1991.01080090044025
4. Blinder KJ, Bradley S, Bressler NM, et al. Effect of lesion size, visual acuity, and lesion composition on visual acuity change with and without verteporfin therapy for choroidal neovascularization secondary to age-related macular degeneration: TAP and VIP report no. 1. *Am J Ophthalmol*. 2003;136(3):407-418. doi:10.1016/S0002-9394(03)00223-X
5. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419-1431. doi:10.1056/NEJMoa054481
6. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1432-1444. doi:10.1056/NEJMoa062655
7. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol*. 2007;143(4):566-583. doi:10.1016/j.ajo.2007.01.028
8. Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364(20):1897-1908. doi:10.1056/NEJMoa1102673
9. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012;119(7):1388-1398. doi:10.1016/j.ophtha.2012.03.053
10. Jaffe GJ, Martin DF, Toth CA, et al. Macular morphology and visual acuity in the Comparison of Age-related Macular Degeneration Treatments Trials. *Ophthalmology*. 2013;120(9):1860-1870. doi:10.1016/j.ophtha.2013.01.073
11. Ben Moussa N, Georges A, Capuano V, Merle B, Souied EH, Querques G. MultiColor imaging in the evaluation of geographic atrophy due to age-related macular degeneration. *Br J Ophthalmol*. 2015;99(6):842-847. doi:10.1136/bjophthalmol-2014-305643
12. Spaide RF, Curcio CA. Drusen characterization with multimodal imaging. *Retina*. 2010;30(9):1441-1454. doi:10.1097/IAE.0b013e3181ee5ce8
13. Zarbin MA, Casaroli-Marano RP, Rosenfeld PJ. Age-related macular degeneration: clinical findings, histopathology, imaging techniques. In: Casaroli-Marano RP, Zarbin MA, eds. *Cell-Based Therapy for Retinal Degenerative Disease*. Basel, Switzerland: Karger Medical and Scientific Publishers; 2014:1-32. doi:10.1159/000358536
14. Sleiman K, Veerappan M, Winter KP, et al. Optical coherence tomography predictors of risk for progression to non-neovascular atrophic age-related macular degeneration. *Ophthalmology*. 2017;124(12):1764-1777. doi:10.1016/j.ophtha.2017.06.032
15. Farsiu S, Chiu SJ, O'Connell RV, et al. Quantitative classification of eyes with and without intermediate age-related macular degeneration using optical coherence tomography. *Ophthalmology*. 2014;121(1):162-172. doi:10.1016/j.ophtha.2013.07.013
16. Fleckenstein M, Schmitz-Valckenberg S, Adrion C, et al. Tracking progression with spectral-domain optical coherence tomography in geographic atrophy caused by age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2010;51(8):3846-3852. doi:10.1167/iovs.09-4533
17. Nunes RP, Gregori G, Yehoshua Z, et al. Predicting the progression of geographic atrophy in age-related macular degeneration

with SD-OCT en face imaging of the outer retina. *Ophthalmic Surg Lasers Imaging Retina*. 2013;44(4):344-359. doi:10.3928/23258160-20130715-06

18. Nagiel A, Sarraf D, Sadda SR, et al. Type 3 neovascularization: evolution, association with pigment epithelial detachment, and treatment response as revealed by spectral domain optical coherence tomography. *Retina*. 2015;35(4):638-647. doi:10.1097/IAE.0000000000000488
19. Querques G, Souied EH, Freund KB. How has high-resolution multimodal imaging refined our understanding of the vasogenic process in type 3 neovascularization? *Retina*. 2015;35(4):603-613. doi:10.1097/IAE.0000000000000487
20. Sadda SR, Guymer R, Holz FG, et al. Consensus definition for atrophy associated with age-related macular degeneration on OCT: classification of atrophy report 3. *Ophthalmology*. 2018;125(4):537-548. doi:10.1016/j.ophtha.2017.09.028
21. Holz FG, Sadda SR, Staurenghi G, et al. Imaging protocols in clinical studies in advanced age-related macular degeneration: recommendations from classification of atrophy consensus meetings. *Ophthalmology*. 2017;124(4):464-478. doi:10.1016/j.ophtha.2016.12.002
22. Freund KB, Zweifel SA, Engelbert M. Do we need a new classification for choroidal neovascularization in age-related macular degeneration? *Retina*. 2010;30(9):1333-1349. doi:10.1097/IAE.0b013e3181e7976b
23. Dansingani KK, Gal-Or O, Sadda SR, Yannuzzi LA, Freund KB. Understanding aneurysmal type 1 neovascularization (polypoidal choroidal vasculopathy): a lesson in the taxonomy of 'expanded spectra'—a review. *Clin Exp Ophthalmol*. 2018;46(2):189-200. doi:10.1111/ceo.13114
24. Holz FG, Bindewald-Wittich A, Fleckenstein M, Dreyhaupt J, Scholl HP, Schmitz-Valckenberg S. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. *Am J Ophthalmol*. 2007;143(3):463-472. doi:10.1016/j.ajo.2006.11.041
25. Forte R, Querques G, Querques L, Massamba N, Le Tien V, Souied EH. Multimodal imaging of dry age-related macular degeneration. *Acta Ophthalmol*. 2012;90(4):e281-e287. doi:10.1111/j.1755-3768.2011.02331.x
26. Freund KB, Laud K, Lima LH, Spaide RF, Zweifel S, Yannuzzi LA. Acquired vitelliform lesions: correlation of clinical findings and multiple imaging analyses. *Retina*. 2011;31(1):13-25. doi:10.1097/IAE.0b013e3181ea48ba
27. Yannuzzi LA, Rohrer KT, Tindel LJ, et al. Fluorescein angiography complication survey. *Ophthalmology*. 1986;93(5):611-617. doi:10.1016/S0161-6420(86)33697-2
28. Hope-Ross M, Yannuzzi LA, Gragoudas ES, et al. Adverse reactions due to indocyanine green. *Ophthalmology*. 1994;101(3):529-533. doi:10.1016/S0161-6420(94)31303-0
29. Olsen TW, Lim JI, Capone A Jr, Myles RA, Gilman JP. Anaphylactic shock following indocyanine green angiography. *Arch Ophthalmol*. 1996;114(1):97. doi:10.1001/archopht.1996.01100130093018
30. Guyer DR, Yannuzzi LA, Slakter JS, et al. Classification of choroidal neovascularization by digital indocyanine green videoangiography. *Ophthalmology*. 1996;103(12):2054-2060. doi:10.1016/S0161-6420(96)30388-6
31. Jia Y, Bailey ST, Wilson DJ, et al. Quantitative optical coherence tomography angiography of choroidal neovascularization in age-related macular degeneration. *Ophthalmology*. 2014;121(7):1435-1444. doi:10.1016/j.ophtha.2014.01.034
32. Kuehlewein L, Bansal M, Lenis TL, et al. Optical coherence tomography angiography of type 1 neovascularization in age-related macular degeneration. *Am J Ophthalmol*. 2015;160(4):739-748.e2. doi:10.1016/j.ajo.2015.06.030
33. Kuehlewein L, Sadda SR, Sarraf D. OCT angiography and sequential quantitative analysis of type 2 neovascularization after ranibizumab therapy. *Eye (Lond)*. 2015;29(7):932-935. doi:10.1038/eye.2015.80
34. El Ameen A, Cohen SY, Semoun O, et al. Type 2 neovascularization secondary to age-related macular degeneration imaged by optical coherence tomography angiography. *Retina*. 2015;35(11):2212-2218. doi:10.1097/IAE.0000000000000773
35. de Oliveira Dias JR, Zhang Q, Garcia JMB, et al. Natural history of subclinical neovascularization in nonexudative age-related macular degeneration using swept-source OCT angiography. *Ophthalmology*. 2018;125(2):255-266. doi:10.1016/j.ophtha.2017.08.030
36. Faridi A, Jia Y, Gao SS, et al. Sensitivity and specificity of OCT angiography to detect choroidal neovascularization. *Ophthalmol Retina*. 2017;1(4):294-303. doi:10.1016/j.oret.2017.02.007
37. Toth CA, Decroos FC, Ying GS, et al. Identification of fluid on optical coherence tomography by treating ophthalmologists versus a reading center in the Comparison of Age-related Macular Degeneration Treatments Trials. *Retina*. 2015;35(7):1303-1314. doi:10.1097/IAE.0000000000000483
38. Lumbroso B, Rispoli M, Savastano MC, Jia Y, Tan O, Huang D. Optical coherence tomography angiography study of choroidal neovascularization early response after treatment. *Dev Ophthalmol*. 2016;56:77-85. doi:10.1159/000442782
39. Spaide RF. Optical coherence tomography angiography signs of vascular abnormalization with antiangiogenic therapy for choroidal neovascularization. *Am J Ophthalmol*. 2015;160(1):6-16. doi:10.1016/j.ajo.2015.04.012
40. Muakkassa NW, Chin AT, de Carlo T, et al. Characterizing the effect of anti-vascular endothelial growth factor therapy on treatment-naive choroidal neovascularization using optical coherence tomography angiography. *Retina*. 2015;35(11):2252-2259. doi:10.1097/IAE.0000000000000836
41. Stewart MW, Rosenfeld PJ, Penha FM, et al. Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor Trap-eye). *Retina*. 2012;32(3):434-457. doi:10.1097/IAE.0B013E31822C290F
42. Imamura Y, Fujiwara T, Margolis R, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in central serous chorioretinopathy. *Retina*. 2009;29(10):1469-1473. doi:10.1097/IAE.0b013e3181be0a83

43. Ferrara D, Mohler KJ, Waheed N, et al. En face enhanced-depth swept-source optical coherence tomography features of chronic central serous chorioretinopathy. *Ophthalmology*. 2014;121(3): 719-726. doi:10.1016/j.ophtha.2013.10.014
44. De Fauw J, Keane P, Tomasev N, et al. Automated analysis of retinal imaging using machine learning techniques for computer vision. *F1000Res*. 2016;5:1573 [revised June 22, 2017]. doi:10.12688/f1000research.8996.2
45. Poplin R, Varadarajan AV, Blumer K, et al. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. *Nat Biomed Eng*. 2018;2:158-164. doi:10.1038/s41551-018-0195-0
46. Bogunović H, Waldstein SM, Schlegl T, et al. Prediction of anti-VEGF treatment requirements in neovascular AMD using a machine learning approach. *Invest Ophthalmol Vis Sci*. 2017; 58(7):3240-3248. doi:10.1167/iovs.16-21053