OPEN

Review

RETINAL FLUID AND THICKNESS AS MEASURES OF DISEASE ACTIVITY IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

PETER K. KAISER, MD,* CHARLES C. WYKOFF, MD, PhD,† RISHI P. SINGH, MD,‡ ARSHAD M. KHANANI, MD, MA,§¶ DIANA V. DO, MD,** HERSH PATEL, OD, FAAO,†† NIKHIL PATEL, PharmD††

Purpose: Retinal fluid and thickness are important anatomical features of disease activity in neovascular age-related macular degeneration, as evidenced by clinical trials that have used these features for inclusion criteria, retreatment criteria, and outcome measures of the efficacy of intravitreal injections of anti–vascular endothelial growth factor agents.

Methods: A literature review of anatomical measures of disease activity was conducted.

Results: Treatment goals for neovascular age-related macular degeneration include improving/maintaining vision by drying the retina, and several analyses have evaluated the relationship between visual function and anatomy. The change in retinal thickness has been found to correlate with the change in the visual acuity, and variation in retinal thickness may predict visual acuity outcomes. In addition, specific fluid compartments may have different prognostic values. For example, the presence of intraretinal fluid has been associated with poorer visual acuity, whereas the presence of subretinal fluid has been associated with better visual acuity. Retinal fluid and thickness are important for selecting dosing interval durations in clinical trials and clinical practice.

Conclusion: Retinal thickness and retinal fluid are common anatomical measures of disease activity in neovascular age-related macular degeneration. Further research is required to fully elucidate the relationship between anatomical features and visual outcomes in neovascular age-related macular degeneration.

RETINA 41:1579–1586, 2021

In neovascular age-related macular degeneration (nAMD), new blood vessels emanating from the choroid break through the Bruch membrane and grow within the sub-retinal pigment epithelium (sub-RPE) space and/or the subretinal space. Vessels may also grow within the retina.[1,2] The new vessels leak fluid, lipids, and blood into the retina and surrounding space.[2] This choroidal neovascularization (CNV) is often associated with progressive vision loss, especially if left untreated.[2] Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents are the standard of care for nAMD and result in stabilization or improvements in the visual acuity and anatomical measures of disease activity, such as fluid in and around the retina and retinal thickness.[3–6]

Management of nAMD is associated with a high treatment burden. Reducing burden with less frequent injections may be accomplished with drugs with longer durability delivered at longer fixed intervals or with variable dosing regimens that adjust dosing intervals depending on treatment response. Treatment response is assessed using functional and anatomical measures, including visual acuity, presence of retinal fluid or hemorrhage, size of the CNV, and retinal thickness. The present review focuses on the anatomical measures of retinal fluid and retinal thickness in nAMD. This review describes how these measures relate to the visual acuity and are used to inform treatment decisions.

Retinal Fluid and Thickness as Measures of the Disease Activity

Optical coherence tomography (OCT), used in the diagnosis of nAMD, is the most useful tool in long-

term management of patients with nAMD. Quantitative measurements of retinal thickness and qualitative observation of retinal fluid on OCT are used as the criteria for disease activity and as efficacy outcomes in clinical trials.[3,5,7–19] In practice, clinicians evaluate OCT scans for qualitative evidence of intraretinal fluid (IRF), subretinal fluid (SRF), and irregular elevation of the RPE. Retinal thickness is measured as the distance from the internal limiting membrane of the retina to the RPE or Bruch membrane, depending on the OCT device manufacturer's algorithm. Several measures of retinal thickness are used, including central retinal thickness (CRT) and central subfield thickness (CST), which measure the mean retinal thickness within the 1-mm diameter circular field surrounding the foveola, and central foveal thickness (CFT) and center point thickness, which measure the retinal thickness at the intersection of the six radial scan lines.[20,21] Retinal fluid is a major contributor to retinal thickening on OCT.[7] In the CATT study, at baseline, 82% of patients had fluid involving the fovea, with 30% having fluid in all three compartments (IRF, SRF, or sub-RPE fluid). Subretinal fluid was the most common at baseline (82%), followed by IRF (75%) and then sub-RPE (49%).[22]

The significance of retinal thickness and fluid as anatomical features of nAMD is highlighted by the consistency of clinical trials incorporating these measures as part of the inclusion criteria for enrollment or retreatment. The PrONTO study, evaluating as needed (pro re nata [PRN]) dosing of ranibizumab, was the first study to use OCT guidance for inclusion and retreatment, enrolling patients who had CRT of $\geq$300 μm. An increase in CRT of $\geq$100 μm and persistent fluid were part of the guidelines for retreatment, along with vision (Table 1).[7] Any qualitative change on OCT suggesting recurrent fluid in the macula was later added as retreatment criteria.[23] Aspects of the disease criteria used in PrONTO continue to be used in later trials, including pivotal Phase 3 studies, such as the VIEW 1/2 trials (Week 52–96), in which the criteria for aflibercept retreatment included new/persistent fluid on OCT, an increase in CRT of $\geq$100 μm compared with the lowest previous value, and loss of $\geq$5 ETDRS letters from the best previous score in conjunction with recurrent fluid on OCT.[10] The HAWK and HARRIER trials of brolucizumab used disease activity assessments, including CST, fluid, and vision, to determine dosing interval (q12/q8 weeks). In the HARBOR, LUCAS, TREX-AMD, and TREND clinical trials, among others, the presence of fluid on OCT and disease activity resolution (e.g., no IRF or SRF) affected anti-VEGF treatment intervals.[4,7,14,16,18,19,24–26]

Retinal thickness and retinal fluid are used to evaluate treatment response to anti-VEGF agents (Table 1). From early trials (e.g., PrONTO, PIER, and SAILOR) to more recent trials (e.g., ATLAS, TREND, and HAWK/HARRIER), retinal thickness has been used as 1 efficacy end point,[3,5,7–9,11–19] and anti-VEGF treatment has resulted in reduced retinal fluid and retinal thickness.[3,7,8,13,19] Clinically, the presence/absence and worsening/improvement of fluid on OCT are important determinants of treatment efficacy and durability. Inhibiting leakage from pathologic vasculature and thereby restoring and preserving retinal anatomy is the core objective of anti-VEGF therapy, with the ultimate goal of improving and maintaining visual function long term.

Relationship Between Retinal Fluid or Thickness and Visual Acuity

The relationship between anatomy and visual acuity has been assessed in several studies. Understanding these relationships is important for understanding the anatomical signs that indicate a need for further/more aggressive treatment.

Retinal thickness as measured at a single time point seems to correlate with the visual acuity before treatment. In the EXCITE study, a correlation was found between CRT and visual acuity at baseline but not at any point during the first year of treatment.[6] Notably, the CATT study found that eyes with very high or low retinal thickness at Week 104 had worse visual acuity than eyes with normal thickness; this trend was apparent throughout the first 2 years of treatment.[5,27] The CATT study findings suggest that the relationship between retinal thickness and visual

From the *Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, Ohio; †Retina Consultants of Texas, Retina Consultants of America, Blanton Eye Institute, Houston Methodist Hospital, Houston, Texas; ‡Center for Ophthalmic Bioinformatics, Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, Ohio; §Sierra Eye Associates, Reno, Nevada; ¶University of Nevada, Reno School of Medicine, Reno, Nevada; **Byers Eye Institute, Stanford University, Palo Alto, California; and ††Novartis Pharmaceuticals, East Hanover, New Jersey.

Editorial support was provided by IMPRINT Science, New York, NY and was funded by Novartis Pharmaceuticals.

P. K. Kaiser is a consultant for Novartis, Allergan, Bayer, Regeneron, and Kanghong. C. C. Wykoff, A. M. Khanani, and D. V. Do are consultants for Novartis and receive research funding from Novartis. R. P. Singh is a consultant for Novartis. H. Patel and N. Patel are employees of Novartis.

Reprint requests: Peter K. Kaiser, MD, Cole Eye Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail: kaiserp@ccf.org

Table 1. Anatomical Outcome Measures and Disease Activity Criteria Used in Clinical Trials of anti-VEGF Agents in nAMD

Trial	Drug	Anatomical Outcome Measures	Disease Activity Criteria for the Dosing Regimen
PrONTO[7,23]	Ranibizumab	CRT	PRN: VA loss of ≥5 letters with OCT evidence of fluid (IRF or SRF) in the macula, an increase in OCT CRT of ≥100 μm, new macular hemorrhage, new area of classic CNV, evidence of persistent fluid on OCT, or (according to an amendment) any qualitative change on OCT (eg, retinal cysts, SRF, or PED enlargement), suggesting recurrent fluid in the macula
PIER[11]	Ranibizumab	Foveal CPT,CST, total area of CNV, total area of leakage from CNV, and leakage from CNV plus RPE staining	NA
SAILOR[8]	Ranibizumab	CFT	PRN (cohort 1): >5 letter decrease in VA compared with the highest score or VA (same as above) and/or a 100-μm increase in OCT CFT compared with lowest measurement, with IRF or SRF present
SUSTAIN[9]	Ranibizumab	CRT, total lesion area, and leakage absence	PRN: loss of VA of >5 letters or an increase of >100 μm in CRT. An option of not treating was available if VA ≥79 letters or CRT ≤225 μm
EXCITE[12]	Ranibizumab	CRT, total lesion area, and total area of leakage	NA
CATT[4]	Ranibizumab and bevacizumab	Total thickness at the fovea, retinal thickness plus subfoveal-fluid thickness, fluid presence, dye leakage presence, and area of lesion	PRN: fluid on OCT, new or persistent hemorrhage, decreased VA compared with previous exam, or dye leakage or increased lesion size on FA
VIEW 1 and 2[13]	Aflibercept and ranibizumab	CRT, CNV area, and cystic intraretinal edema and SRF absence	NA
HARBOR[14]	Ranibizumab	CFT, total area of CNV, and total area of CNV leakage	PRN: ≥5-letter decrease in BCVA from the previous visit or any evidence of disease activity on SD-OCT
IVAN[24]	Ranibizumab and bevacizumab	Total thickness at the fovea, retinal plus SRF thickness at the fovea, neuroretinal foveal thickness, maximal retinal thickness, height of PED, active neovascularization presence/area, total lesion presence/area, SRF presence/area, fibrosis presence/area, blood presence, RPE tear presence, dye leakage presence, fluid presence, and geographic atrophy development	PRN: Level 1: SRF presence, increase in IRF, or fresh blood in the lesion. Level 2: persistent IRF and VA dropped by ≥10 letters over the past 3 months. Level 3 (if uncertainty): extension of the CNV or leakage from >25% of the circumference of the CNV

(*continued on next page*)

Table 1. (*Continued*)

Trial	Drug	Anatomical Outcome Measures	Disease Activity Criteria for the Dosing Regimen
LUCAS[16]	Ranibizumab and bevacizumab	CRT, fluid presence, leakage presence, and lesion area	T&E: recurrent disease was any fluid on OCT, new or persistent hemorrhage or dye leakage, or increased lesion size on FA
TREX-AMD[15]	Ranibizumab	CRT	T&E: dry macula: resolution of IRF and SRF on SD-OCT and of subretinal and intraretinal hemorrhage related to exudative activity
ATLAS[17]	Aflibercept	CFT	T&E: extension criteria: absence of macular fluid on OCT (SRF, IRF, or sub-RPE), absence of vision loss of ≥5 letters from the previous visit, absence of new macular hemorrhage, and absence of increased lesion size or leakage on FA
TREND[19]	Ranibizumab	CST, intraretinal cyst presence, SRF presence, CNV leakage presence/area	T&E: IRF or SRF on SD-OCT. The VA was considered for determining the final reduction of the interval size
FLUID[26]	Ranibizumab	CST, SRF presence, and IRF presence	T&E: loss of BCVA ≥5 letters compared with the BCVA since BL, new retinal hemorrhage, or presence of fluid on SD-OCT. Definition of fluid depended on the treatment arm
CANTREAT[25]	Ranibizumab	CRT	T&E: disease stability: gain in VA ≥3 letters from prior month (or no loss >5 letters); no lesion growth, fluid, or blood; and no IRF or SRF on OCT. Disease instability: presence of any fluid, vision loss >5 letters, new hemorrhage, or progression of CNV
HAWK & HARRIER[3]	Brolucizumab and aflibercept	CST, SRF presence, IRF presence, and disease activity presence	q8w versus q12w: decreased BCVA ≥5 letters compared with BL; decreased BCVA ≥3 letters and CST increase ≥75 μm or decrease in BCVA ≥5 letters due to disease activity, compared with Week 12; or new or worse IRF compared with Week 12
CEDAR & SEQUOIA[41]	Abicipar and ranibizumab	CRT, IRF absence, SRF absence, and fluid absence	Participants with persistent IRF and SRF causing loss of BCVA ≥30 letters by OCT could be treated with standard of care

Table 1. (*Continued*)

Trial	Drug	Anatomical Outcome Measures	Disease Activity Criteria for the Dosing Regimen
Archway[44]	Ranibizumab port delivery system	CPT	Supplemental IVI: increase in SD-OCT CST of ≥100 μm from the lowest measurement and decrease of ≥10 letters from the best score, decrease of ≥15 letters from the best score, or increase in SD-OCT CST of ≥150 μm from lowest measurement

BCVA, best-corrected VA; BL, baseline; CPT, center point thickness; FA, fluorescein angiography; IVI: intravitreal injection; NA, not applicable; PED, pigment epithelial detachment; q8w, dosing every 8 weeks; q12w, dosing every 12 weeks; SD-OCT, spectral-domain OCT; T&E, treat-and-extend; VA, visual acuity.

acuity can be nonlinear, which may explain why a correlation between retinal thickness and visual acuity during treatment has not been clearly documented. By contrast, change in retinal thickness from baseline seems to negatively correlate with the change in the visual acuity.[6,7,28] The PrONTO study found correlations at months 2, 3, and 12, although not at Month 1 of treatment.[7] Also, change in CRT at Month 1 correlated with the change in the visual acuity at months 2, 3, and 12, suggesting that early change in CRT is a predictor of later visual acuity.[7] Similarly, a post-hoc analysis of the PIER study found that lower CFT at Month 5 predicted greater visual acuity improvements from baseline to Month 24. Recent post-hoc analyses of the CATT/IVAN and HAWK/HARRIER trials evaluated the effect of fluctuations in retinal thickness on the visual acuity. Greater fluctuations in retinal thickness predicted lower final visual acuity and lower visual acuity gains.[29,30] Greater fluctuations also predicted greater geographic atrophy and fibrosis.[29] These studies suggest that retinal thickness dynamics can be indicators of change in the visual acuity.

The presence of IRF has frequently been associated with poorer visual acuity. In the CATT study, eyes with IRF were found to have poorer visual acuity than eyes without IRF.[5,27] Other post-hoc analyses and retrospective studies found similar associations between IRF and visual acuity and also suggest that the presence of IRF at baseline predicts poorer visual acuity at Year 1.[10,31] Although most studies assessed IRF as present/absent,[5,31] more recent studies measured IRF volume, showing similar correlations,[32,33] suggesting that IRF may be detrimental to anatomical features important to the visual acuity.

The relationship between SRF and visual acuity is less straightforward. In the CATT study, no association was found between the presence of SRF and visual acuity at Week 52.[5] At Week 104, eyes with foveal SRF had better visual acuity than eyes without SRF or with extrafoveal SRF.[27] A post-hoc analysis of the HARBOR study found that residual SRF was associated with greater visual acuity gains at months 12 and 24.[34] When neovascularization types were examined, residual SRF at Month 24 was associated with greater visual acuity gains for Type 2 and mixed Type 1 and 2 lesions.[35] Post-hoc analyses and retrospective studies have also found that SRF at baseline predicts better visual acuity at later timepoints after treatment. Specifically, the presence of SRF at baseline in the VIEW 1/2 and HARBOR studies was associated with greater visual acuity gain at Week 52.[31,36] Similarly, greater SRF volume at baseline has been associated with greater visual acuity at Week 52.[33] Anatomical outcomes are consistent with visual acuity outcomes in that the presence of SRF at baseline or during treatment was associated with a lower rate of macular atrophy at Month 24 in a post-hoc analysis of HARBOR.[37] By contrast, a post-hoc analysis of HAWK/HARRIER found that the visual acuity gain from the end of the loading-dose phase of treatment (Week 12) to Week 96 was lower for eyes with high mean SRF volume during the maintenance phase (weeks 12–96) than for eyes with low mean SRF volume.[38]

The presence of sub-RPE fluid was not associated with the visual acuity at Week 52 of the CATT study, but at Week 104, the visual acuity was greater for eyes with foveal sub-RPE fluid than for eyes with no sub-RPE fluid or with extrafoveal sub-RPE fluid.[5,27] Beyond the CATT study, the relationship between sub-RPE fluid and visual acuity has not been elucidated. Instead, studies have assessed the relationship between visual acuity and pigment epithelial detachment, a condition in which the space between the RPE and Bruch's membrane may be filled with sub-RPE fluid. These studies have found differing results, suggesting that the relationship

between pigment epithelial detachment and visual acuity is not simple.[6,7,22,31,39,40]

Although some studies suggest that SRF may be associated with better visual acuity outcomes, the presence of fluid of any type (IRF, SRF, or sub-RPE fluid) has been negatively associated with visual acuity outcomes. In the CATT study, eyes without fluid of any type at Week 104 were found to have greater visual acuity than eyes with foveal or extrafoveal fluid of any type.[27] Similarly, in a post-hoc analysis of the PIER study, eyes without fluid of any type at months 5 or 8 had greater change from baseline in the visual acuity at Month 24 than eyes with fluid.[28] Notably, this less precise analysis of fluid does not reflect the positive association that has been found between SRF and visual acuity. Overall, these studies suggest the importance of considering anatomical features of disease activity and their impact on visual outcomes.

Disease Activity Measures as Criteria for Retreatment

Clinicians aim to decrease fluid in nAMD while reducing the burden of intravitreal injections. Both variable dosing regimens and anti-VEGF agents with durable efficacy may reduce injection frequency while controlling disease activity. Because there is a risk of disease recurrence with long dosing intervals, these approaches depend on monitoring disease activity, such as retinal fluid, retinal thickness, and vision, to determine appropriate dosing intervals.

Several trials have assessed the efficacy of anti-VEGF agents with PRN regimens, in which eyes are monitored on a regular basis and injections are provided only when there are signs of disease activity (Table 1). In some studies, the visual acuity has increased after 3 monthly loading doses but decreased after the PRN regimen.[8,9] For example, after loading doses in the SAILOR study, eyes were treated with a PRN regimen, in which criteria for retreatment included a >5-letter decrease and/or an increase of >100 μm in CFT with IRF or SRF present.[8] With this regimen, the visual acuity decreased from months 3 to 12 such that at Month 12, the visual acuity gain from baseline was only 2.3 letters, suggesting that the retreatment criteria or the monitoring schedule (every 3 months), allowed too much disease progression.[8] In the HARBOR study, eyes were monitored every month for disease activity and criteria for retreatment included a ≥5-letter decrease or any evidence of disease activity on OCT.[14] At Month 12, the visual acuity gain with ranibizumab 0.5 mg was 8.2 letters for the PRN regimen and 10.1 for the monthly regimen, but the PRN regimen failed to meet 4-letter noninferiority compared with the monthly regimen.[14] In the CATT study, the PRN regimen of ranibizumab met the 5-letter noninferiority margin compared with monthly dosing at Year 1, but noninferiority testing of PRN dosing with bevacizumab was inconclusive. Because PRN regimens only provide treatment as needed, they have the potential to allow for repeated episodes of disease-activity recurrence. Studies that have analyzed fluctuation of retinal thickness over time have attempted to evaluate the impact of such disease instability on visual acuity outcomes and have found negative associations, suggesting the importance of biomarkers that are assessed over extended periods of time.[29,30]

Treat-and-extend (T&E) regimens use signs of disease activity to determine when to readminister treatment. Dosing intervals are usually lengthened by 2 weeks at a time (maximum of 12–16 weeks) when disease activity resolves and shortened when disease activity recurs.[15] Eyes typically receive fewer injections with T&E regimens than with monthly regimens.[18,19,25] T&E regimens can provide similar gains in the visual acuity compared with monthly dosing regimens. In the TREX-AMD study, criteria for extending the dosing interval were resolution of IRF and SRF on OCT and resolution of subretinal/intraretinal hemorrhage.[15] At Month 12, eyes gained 10.5 letters in the T&E arm and 9.2 letters with monthly dosing. At Month 24, eyes gained 8.7 letters in the T&E arm and 10.5 letters with monthly dosing, although noninferiority testing was inconclusive.[15,18] In later studies, the T&E regimens showed noninferiority in visual acuity gains compared with monthly dosing at Month 12.[19,25]

Other methods to reduce treatment burden include fixed 8-week (q8w) or 12-week (q12w) dosing intervals with anti-VEGF agents that produce durable treatment responses.[3,13,41] The VIEW 1/2 studies showed that aflibercept administered q8w after 3 monthly loading doses was noninferior to ranibizumab administered q4w in the proportion of patients maintaining vision at Week 52.[13] The HAWK and HARRIER studies evaluated brolucizumab administered q12w/q8w versus aflibercept administered q8w[3]; after 3 monthly loading doses, brolucizumab was administered q12w unless the disease activity was detected. The disease activity included visual acuity loss, increase in CST, new/worse intraretinal cysts/fluid at Week 16, and visual acuity loss at other visits. At Week 48, brolucizumab met noninferiority to aflibercept for visual acuity gain, and anatomical outcomes (CST and resolution of fluid) showed superiority. Post-hoc analysis demonstrated similar visual acuity gains between brolucizumab and aflibercept in the subgroup with the disease activity at Week

16 (q8w only patients) and the subgroup without disease activity at weeks 16 or 20.[42]

Criteria for determining dosing intervals typically include both change in the visual acuity and signs of anatomical disease activity.[4,16,24] However, different anatomical features have been used to define the disease activity. Increase in retinal thickness has been included as a criterion in some studies,[7–9,43,44] whereas others have excluded retinal thickness but included evidence of retinal fluid.[4,15,16,19,24–26] Furthermore, some studies have included any fluid as a marker of disease activity,[4,14,25] but others have excluded sub-RPE fluid.[7,18,24] The optimal disease activity criteria are presently unknown because few studies have directly compared different criteria. To investigate the effect of including SRF as a criterion in a T&E protocol, the FLUID study randomized patients to two different T&E regimens. This study demonstrated that the visual acuity was noninferior in a T&E regimen in which SRF ($\leq$200 μm in height at the subfoveal center) was tolerated compared with a T&E regimen in which the presence of SRF was not tolerated at Month 24.[26] Indeed, further studies are needed to verify that tolerating SRF is nondetrimental over a longer period of time.

Conclusion

Retinal thickness and fluid as measured through OCT are significant anatomical features in nAMD that are used for inclusion criteria in trials, efficacy outcome measures, and retreatment criteria.[3,5,7–19] The relationship with the visual acuity for both retinal thickness and fluid has been assessed in several studies. The change in retinal thickness negatively correlates with the change in the visual acuity, and early change in retinal thickness may predict change in the visual acuity at Year 1.[6,7,28] The presence of IRF has been associated with poorer visual acuity in several studies,[5,27,31] whereas the presence of SRF has been associated with better visual acuity.[27,31,36] More prospective research is needed to better understand the relationship between specific fluid compartments and vision.

Measures of retinal thickness and fluid are components of disease activity criteria for determining dosing interval duration.[3,4,7–9,15,16,19,24–26] Using variable dosing regimens and anti-VEGF agents that produce durable anatomical and functional responses are efficacious ways to treat nAMD while reducing burden for the patient, caregiver, and physician.[3,19,25] Different criteria have been used for determining dosing interval duration across studies.[3,4,7–9,15,16,19,24–26] Further research is required to understand the optimal disease activity criteria for determining dosing intervals.

Key words: disease activity, dosing, intraretinal fluid, neovascular age-related macular degeneration, retinal thickness, subretinal fluid, subretinal pigment epithelium fluid, visual acuity.

References

1. Spaide RF, Jaffe GJ, Sarraf D, et al. Consensus nomenclature for reporting neovascular age-related macular degeneration data: consensus on neovascular age-related macular degeneration nomenclature study group. Ophthalmology 2020;127:616–636.
2. Keane PA, de Salvo G, Sim DA, et al. Strategies for improving early detection and diagnosis of neovascular age-related macular degeneration. Clin Ophthalmol 2015;9:353–366.
3. Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology 2020;127:72–84.
4. CATT Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897–1908.
5. 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;120:1860–1870.
6. Simader C, Ritter M, Bolz M, et al. Morphologic parameters relevant for visual outcome during anti-angiogenic therapy of neovascular age-related macular degeneration. Ophthalmology 2014;121:1237–1245.
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;143:566–583.
8. Boyer DS, Heier JS, Brown DM, et al. A Phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration. Ophthalmology 2009;116:1731–1739.
9. Holz FG, Amoaku W, Donate J, et al. Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study. Ophthalmology 2011;118:663–671.
10. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology 2014;121:193–201.
11. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 1. Am J Ophthalmol 2008;145:239–248.
12. Schmidt-Erfurth U, Eldem B, Guymer R, et al. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. Ophthalmology 2011;118:831–839.
13. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 2012;119:2537–2548.
14. Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with

subfoveal neovascular age-related macular degeneration. Ophthalmology 2013;120:1046–1056.
15. Wykoff CC, Croft DE, Brown DM, et al. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. Ophthalmology 2015;122:2514–2522.
16. Berg K, Pedersen TR, Sandvik L, Bragadottir R. Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. Ophthalmology 2015;122:146–152.
17. DeCroos FC, Reed D, Adam MK, et al. Treat-and-extend therapy using aflibercept for neovascular age-related macular degeneration: a prospective clinical trial. Am J Ophthalmol 2017;180:142–150.
18. Wykoff CC, Ou WC, Brown DM, et al. Randomized trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: 2-year results of the TREX-AMD study. Ophthalmol Retina 2017;1:314–321.
19. Silva R, Berta A, Larsen M, et al. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration: results with ranibizumab from the TREND study. Ophthalmology 2018;125:57–65.
20. Taban M, Sharma S, Williams DR, et al. Comparing retinal thickness measurements using automated fast macular thickness map versus six-radial line scans with manual measurements. Ophthalmology 2009;116:964–970.
21. Chan A, Duker JS, Ko TH, et al. Normal macular thickness measurements in healthy eyes using Stratus optical coherence tomography. Arch Ophthalmol 2006;124:193–198.
22. Ying GS, Huang J, Maguire MG, et al. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. Ophthalmology 2013;120:122–129.
23. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. Am J Ophthalmol 2009;148:43–58.e1.
24. Chakravarthy U, Harding SP, Rogers CA, et al. A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN). Health Technol Assess 2015;19:1–298.
25. Kertes PJ, Galic IJ, Greve M, et al. Canadian treat-and-extend analysis trial with ranibizumab in patients with neovascular age-related macular disease: one-year results of the randomized Canadian treat-and-extend analysis trial with ranibizumab study. Ophthalmology 2019;126:841–848.
26. Guymer RH, Markey CM, McAllister IL, et al. Tolerating subretinal fluid in neovascular age-related macular degeneration treated with ranibizumab using a treat-and-extend regimen: FLUID study 24 month results. Ophthalmology 2019;126:723–734.
27. Sharma S, Toth CA, Daniel E, et al. Macular morphology and visual acuity in the second year of the comparison of age-related macular degeneration treatments trials. Ophthalmology 2016;123:865–875.
28. Brown DM, Tuomi L, Shapiro H; Pier Study Group. Anatomical measures as predictors of visual outcomes in ranibizumab-treated eyes with neovascular age-related macular degeneration. Retina 2013;33:23–34.
29. Evans RN, Reeves BC, Maguire MG, et al. Associations of variation in retinal thickness with visual acuity and anatomic outcomes in eyes with neovascular age-related macular degeneration lesions treated with anti–vascular endothelial growth factor agents. JAMA Ophthalmol 2020;138:1043–1051.
30. Jhaveri CD, Dugel PU, Wykoff CC, et al. Visual and anatomical outcomes for brolucizumab and aflibercept in patients with nAMD: 96-week data from HAWK and HARRIER. Paper presented at: American Society of Retina Specialists; July 2019; Chicago, IL.
31. Waldstein SM, Simader C, Staurenghi G, et al. Morphology and visual acuity in aflibercept and ranibizumab therapy for neovascular age-related macular degeneration in the VIEW trials. Ophthalmology 2016;123:1521–1529.
32. Waldstein SM, Philip AM, Leitner R, et al. Correlation of 3-dimensionally quantified intraretinal and subretinal fluid with visual acuity in neovascular age-related macular degeneration. JAMA Ophthalmol 2016;134:182–190.
33. Lee H, Jo A, Kim HC. Three-dimensional analysis of morphologic changes and visual outcomes in neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci 2017;58:1337–1345.
34. Holekamp NM. What do the HARBOR data reveal about the relationship between the drying of subretinal and intraretinal fluid and associated vision outcomes? Paper presented at: American Society of Retina Specialists; July 2019; Chicago, IL.
35. Freund KB, Staurenghi G, Jung JJ, et al. Interrelationships between macular neovascularization lesion type, retinal fluid location, and visual outcomes in the HARBOR trial. Paper presented at: Retina Society 2020 VR; September 2020.
36. Regillo CD, Busbee BG, Ho AC, et al. Baseline predictors of 12-month treatment response to ranibizumab in patients with wet age-related macular degeneration. Am J Ophthalmol 2015;160:1014–1023.e1012.
37. Sadda SR, Abdelfattah NS, Lei J, et al. Spectral-domain OCT analysis of risk factors for macular atrophy development in the HARBOR study for neovascular age-related macular degeneration. Ophthalmology 2020;127:1360–1370.
38. Schmidt-Erfurth U, Mulyukov Z, Gerendas BSS, et al. A comparison of the therapeutic response between brolucizumab and aflibercept in the HAWK & HARRIER trials using deep learning-based OCT analysis. Invest Ophthalmol Vis Sci 2020;61:1159.
39. Khanani AM, Eichenbaum D, Schlottmann PG, et al. Optimal management of pigment epithelial detachments in eyes with neovascular age-related macular degeneration. Retina 2018;38:2103–2117.
40. Schmidt-Erfurth U, Waldstein SM, Deak GG, et al. Pigment epithelial detachment followed by retinal cystoid degeneration leads to vision loss in treatment of neovascular age-related macular degeneration. Ophthalmology 2015;122:822–832.
41. Kunimoto D, Yoon YH, Wykoff CC, et al. Efficacy and safety of abicipar in neovascular age-related macular degeneration: 52-week results of phase 3 randomized controlled study. Ophthalmology 2020;127:1331–1344.
42. Kaiser PK, Holz FG, Koh A, et al. Visual and anatomical outcomes by q12w/q8w status in the HAWK and HARRIER studies of brolucizumab versus aflibercept in neovascular age-related macular degeneration. Paper presented at: Retina Society; September 2020; VR 24/7.
43. Campochiaro PA, Marcus DM, Awh CC, et al. The port delivery system with ranibizumab for neovascular age-related macular degeneration: results from the randomized phase 2 ladder clinical trial. Ophthalmology 2019;126:1141–1154.
44. Awh CC, Kaufman D, Kardaztke D, et al. Primary analysis results of the phase 3 Archway trial of the port delivery system with ranibizumab for patients with neovascular AMD. Paper presented at: Retina Society 2020 VR; September 2020.