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OPTIMIZING TREATMENT OF nAMD

Do Fluid Subtypes Matter?

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This continuing medical education activity is jointly provided by **New York Eye and Ear Infirmary of Mount Sinai** and **MedEdicus LLC**.



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ACTIVITY DESCRIPTION

The rising incidence of neovascular (wet) age-related macular degeneration (nAMD) as a cause of vision loss necessitates updated treatment paradigms and innovative therapies that reduce the burden of treatment while preserving optimal visual outcomes. A growing body of research shows that treat-and-extend approaches using approved anti-vascular endothelial growth factor agents for nAMD are feasible, achieving visual outcomes comparable to those of on-label treatment while reducing the number of injections over time. Importantly, this approach must be tailored to each individual patient, using careful analysis of optical coherence tomography (OCT) images collected at regular intervals. Recent analyses suggest that treat-and-extend approaches could be further individualized by assessing intraretinal fluid—a negative prognosticator—and subretinal fluid, which might have neutral or even positive clinical relevance. Several investigational therapies in late-stage development also have the potential to greatly reduce treatment burden if they are approved. The desired outcome of this activity is for retina specialists and other ophthalmologists to better appraise recent research on the clinical relevance of fluid on OCT and to apply the evidence to evaluate current and emerging treatment strategies and therapies.

TARGET AUDIENCE

This educational activity is intended for retina specialists and other ophthalmologists caring for patients with nAMD.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Describe the clinical relevance of retinal fluid type and location as they pertain to visual acuity outcomes
- Adapt retreatment plans for patients with nAMD according to OCT findings
- Interpret the implications for practice of recent data on treatment durability for established and emerging treatments for nAMD

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OPTIMIZING TREATMENT OF nAMD: Do Fluid Subtypes Matter?

INTRODUCTION: UNMET NEEDS IN THE TREATMENT OF AGE-RELATED MACULAR DEGENERATION

Vision loss resulting from neovascular (wet) age-related macular degeneration (nAMD) is a growing public health problem, with 3.7 million people in the United States projected to have advanced forms of age-related macular degeneration, including nAMD and geographic atrophy, by 2030.¹ Hallmark trials for nAMD support indefinite monthly or bimonthly injections of anti-vascular endothelial growth factor (VEGF) therapy to maintain vision.²⁻⁴ This treatment regimen is challenging for patients to adhere to, as reflected in several real-world treatment studies in which fewer injections were given and visual acuity (VA) gains were significantly reduced compared with pivotal anti-VEGF therapy clinical trials.^{5,6} Thus, patients with nAMD are inherently at risk of progressive vision loss and require treatment strategies that balance efficacy and treatment burden in an individualized manner. This review, based on a recent roundtable discussion, will discuss treatment strategies using the current generation of anti-VEGF treatments, recent analyses that might shape the way we treat various types of retinal fluid, and investigational therapies that aim to alleviate treatment burden.

—Michael Singer, MD

TREATMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: PAST, PRESENT, AND FUTURE

Hallmark Trials: Frequent Anti-Vascular Endothelial Growth Factor Injections

Gaining perspective into how nAMD has historically been treated can be instructive when considering new approaches. In the ANCHOR and MARINA US Food and Drug Administration registration trials of ranibizumab to treat nAMD, participants in the 0.5-mg ranibizumab groups ($n = 140$ and 240 , respectively) had rapid VA improvement of between 6 and 10 letters within the first 3 months of treatment, whereas participants in the verteporfin photodynamic therapy ($n = 143$) and sham ($n = 238$) groups progressively lost vision over 2 years.^{2,3} Ranibizumab was also shown to be safe, with presumed endophthalmitis observed following 0.05% of injections and a low rate ($< 1\%$) of retinal tears and vitreous hemorrhages. Similar trials comparing aflibercept with ranibizumab were conducted several years later, and formed the basis of US Food and Drug Administration approval of aflibercept to treat nAMD. In the VIEW 1 and VIEW 2 studies, aflibercept (2 mg given monthly [$n = 559$], 0.5 mg given monthly [$n = 538$], or 2 mg given every 8 weeks [$n = 535$]) was shown to be noninferior to monthly ranibizumab 0.5 mg ($n = 538$) for maintenance of vision, thereby expanding treatment options to include an efficacious agent that can be dosed less frequently (Figure 1).⁴ The safety of aflibercept was comparable to that of ranibizumab, with rates of ocular injection-related, treatment-emergent serious adverse events between 0.1 and 1.1/1000 injections for all groups.

Evolving Treatment Paradigms: Optical Coherence Tomography–Guided Retreatment

Recent analyses suggest that developing individualized retreatment strategies for patients with nAMD can provide an optimal balance between treatment burden and efficacy. A 2016 post hoc analysis of data from the VIEW 1 and VIEW 2 studies found a higher proportion of patients without retinal fluid through 52 weeks in the monthly 2-mg aflibercept group than in the monthly ranibizumab group (Figure 2A).⁷ Although patients *without* early persistent retinal fluid had similar visual outcomes across treatment arms (Figure 2B), those who had retinal fluid that persisted through the first 12 weeks of treatment achieved significantly better VA at 52 weeks if receiving monthly aflibercept rather than ranibizumab ($P = .049$) or aflibercept every 8 weeks ($P = .006$) (Figure 2C). These data suggest that 1 goal in the treatment of nAMD is to resolve fluid as quickly as possible.

CATT (Comparison of Age-Related Macular Degeneration Treatments Trials) compared the ability of ranibizumab to resolve retinal fluid with that of bevacizumab using several retreatment strategies.⁸ Subfoveal intraretinal, subretinal, and sub-retinal pigment epithelium (RPE) fluid were evaluated throughout the 2-year study and an additional 3-year follow-up period.^{8,9} Monthly ranibizumab was best able to resolve all types of fluid at 2 years (Figure 3).⁸

Visual acuity gains were not significantly different among treatments, and only marginally different between as-needed and monthly regimens ($P = .046$), indicating a need for a better retreatment strategy.¹⁰ Ocular adverse events were similar between the bevacizumab and ranibizumab groups, but in year 2, an elevated risk of systemic serious adverse events was observed in the bevacizumab group (risk ratio 1.30 [95% confidence interval, 1.07-1.57]; $P = .009$) after adjusting for demographic features and baseline coexisting illness.

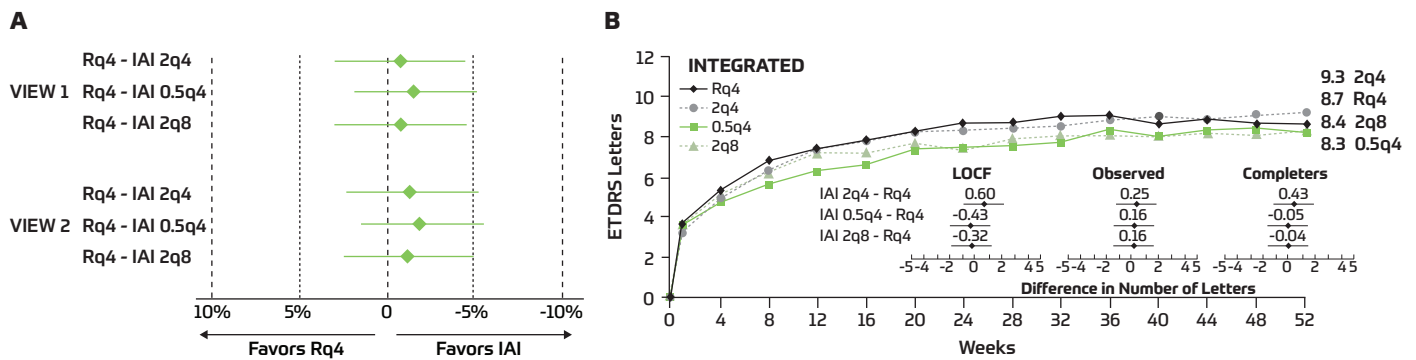


Figure 1. (A) Difference in the proportion of patients in the VIEW 1 and VIEW 2 studies who lost < 15 ETDRS letters at week 52.⁴ Diamonds denote the difference among treatment arms, and horizontal bars denote 95% confidence interval. (B) Mean change in best-corrected visual acuity over 52 weeks in the integrated VIEW 1 and VIEW 2 data analysis. Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; IAI, intravitreal aflibercept injection; LOCF, last observation carried forward; Rq4, monthly 0.5-mg intravitreal ranibizumab; 0.5q4, monthly 0.5-mg intravitreal aflibercept injection; 2q4, monthly 2-mg intravitreal aflibercept injection; 2q8, 2-mg intravitreal aflibercept injection every 2 months after 3 initial monthly doses. Reprinted from *Ophthalmology*, 119, Heier JS, Brown DM, Chong V, et al, Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration, 2537-2548, Copyright 2012, with permission from Elsevier.

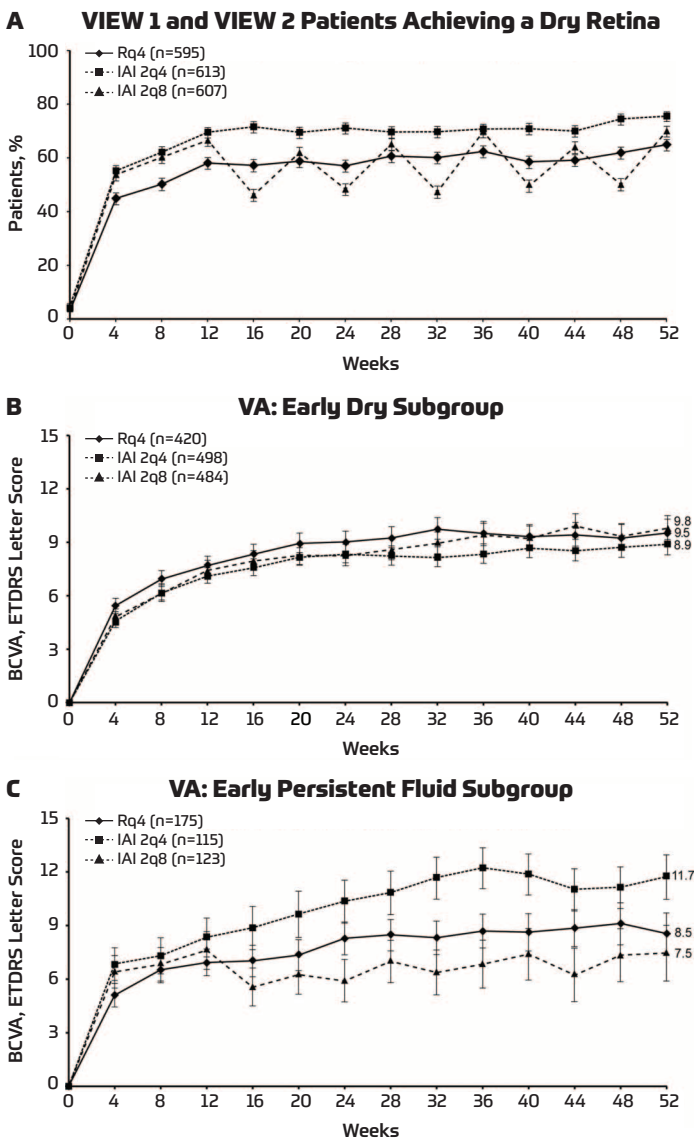


Figure 2. (A) Proportion of patients in the VIEW 1 and VIEW 2 studies without retinal fluid over 52 weeks.⁷ Least-squares mean change BCVA from baseline of patients without (B) and with (C) persistent retinal fluid through 12 weeks of treatment. Abbreviations: BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; IAI, intravitreal aflibercept injection; Rq4, 0.5 mg of intravitreal ranibizumab every 4 weeks; VA, visual acuity; 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks. Reproduced from Jaffe GJ, Kaiser PK, Thompson D, et al. Differential responses to anti-VEGF regimens in age-related macular degeneration patients with early persistent retinal fluid. *Ophthalmology*. 2016;123(9):1856-1864. Copyright 2016 by the American Academy of Ophthalmology. Reprinted with permission.

In the years that followed, optical coherence tomography (OCT)-guided or “treat-and-extend” (TAE) approaches were explored. One observation that has shaped the development of the TAE approach is the linear relationship between number of injections received in various clinical trials and VA gain, regardless of treatment regimen.⁵ Although the goal of TAE is a reduction in treatment burden, avoidance of undertreatment and undetected fluid recurrence is a central tenet of any TAE treatment regimen. Several published studies have now formally investigated whether TAE regimens for nAMD can deliver significantly reduced injection burden without sacrificing VA gains compared with standard treatment regimens (Table 1).¹¹⁻¹⁵

In the TREX-AMD (Treat-and-Extend Protocol in Patients With Wet Age-Related Macular Degeneration) study, ranibizumab 0.5 mg TAE performed comparably to monthly ranibizumab, with a significant reduction in injection burden (18.6 vs 25.5 injections over 24 months, respectively; $P < .0001$).¹¹ The mean maximum extension interval of TAE patients was 8.5 weeks. The 2-year noninferiority LUCAS (Lucentis Compared to Avastin Study) compared bevacizumab with ranibizumab using identical TAE strategies.¹² Although VA was comparable in both groups at 2 years, significantly fewer injections were given in the ranibizumab group (16.0 vs 18.2, respectively [95% confidence interval of mean difference, -3.4 to -1.0]; $P < .001$). Notably, when disease activity necessitated shortening the treatment interval, 2-week reductions were effective for maintaining vision, except among patients at 12-week intervals. This finding suggests a maximum treatment interval of 10 weeks when using ranibizumab or bevacizumab or consideration of a more drastic interval reduction for patients with disease recurrence during a 12-week interval.

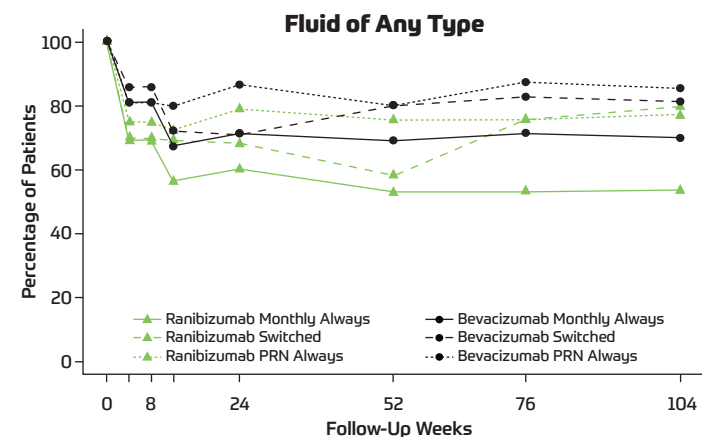


Figure 3. Fluid resolution by medication and treatment algorithm in CATT (Comparison of Age-Related Macular Degeneration Treatments Trials)⁸ Abbreviation: PRN, as needed.

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Table 1. Findings From Published Treat-and-Extend Neovascular Age-Related Macular Degeneration Treatment Trials

Study	Treatment Arm	n	Mean BCVA Gain (ETDRS Letters)	Mean Number of Injections	Retreatment Criteria
TRES-AMD (Treat-and-Extend Protocol in Patients With Wet Age-Related Macular Degeneration) ¹¹	Ranibizumab 0.5 mg monthly	18	10.5	25.5	When macula was dry on OCT, interval extended in 2-week increments
	Ranibizumab 0.5 mg TAE	23	8.7	18.6	
			P = .64	P < .0001	
LUCAS (Lucentis Compared to Avastin Study) ¹²	Ranibizumab 0.5 mg TAE	172	6.6	16.0	When no sign of active disease was observed on OCT and bimicroscopic fundus examination, interval extended in 2-week increments
	Bevacizumab 1.25 mg TAE	167	7.4	18.2	
			P = .634	P < .0001	
TREND (Treat and Extend) ¹³	Ranibizumab 0.5 mg TAE	320	6.2	8.7*	When disease activity had resolved by spectral-domain OCT and VA criteria, interval extended in 2-week increments
	Ranibizumab 0.5 mg monthly	323	8.1	11.1*	
			P < .001 for noninferiority	Not tested	
CANTREAT (Canadian Treat-and-Extend Analysis Trial With Ranibizumab) ¹⁴	Ranibizumab 0.5 mg TAE	287	8.4	9.4*	When VA had stably improved, no disease activity, and no intraretinal or subretinal fluid on OCT, interval extended in 2-week increments
	Ranibizumab 0.5 mg monthly	293	6.0	11.8*	
			P = .017 for noninferiority	P < .001	
ATLAS (Aflibercept Treat and Extend for Less Frequent Administration Study) ¹⁵	Aflibercept 2 mg TAE	40	7.2 at 1 year 2.4 at 2 years	14.5	When fluid had resolved by OCT, treatment interval extended in 2-week increments

Abbreviations: BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography; TAE, treat-and-extend; VA, visual acuity.

* Over 1 year of study

TREND (Treat and Extend) was a 1-year study that was statistically powered to assess noninferiority, which was achieved for ranibizumab TAE vs monthly ranibizumab ($P < .001$ for noninferiority of mean difference in best-corrected VA [BCVA] at 12 months).¹³ CANTREAT (Canadian Treat-and-Extend Analysis Trial With Ranibizumab) was similar to TREND, and also demonstrated noninferiority of ranibizumab TAE to monthly ranibizumab.¹⁴ In the TREND and CANTREAT studies, 62% and 69% of patients, respectively, were able to extend to 8 weeks and beyond. In ATLAS (Aflibercept Treat and Extend for Less Frequent Administration Study), a small single-arm study evaluating aflibercept TAE over 2 years, 75% of patients were able to extend treatment to every 8 weeks or longer, with 38% extending to 12 weeks or longer.¹⁵

The recently completed ALTAIR study ($n = 246$) evaluated 2 TAE regimens for aflibercept: one with 2-week interval adjustments and one with 4-week adjustments up to a maximum of 16 weeks.¹⁶ The mean change in BCVA in the 4-week and 2-week groups was 6.1 and 7.6 ETDRS letters, respectively, at 96 weeks. Over half of participants in both groups were able to extend to 12-week intervals or longer, and the proportion of patients in both groups who extended to 16-week intervals without shortening was similar (42.3% vs 41.1% in the 4-week and 2-week adjustment groups, respectively). Together, these results provide a rationale for using TAE in clinical practice and also reinforce the importance of close follow-up and individualized management of nAMD.

PANEL DISCUSSION: TREAT-AND-EXTEND IN THE REAL WORLD

Dr Singer: Dr Kiss, how has your practice changed according to the data presented? Do you still use TAE? How do you extend your treatment interval?

Dr Kiss: I think we have all been trying to reduce the treatment burden since anti-VEGF therapies first became available. On initial diagnosis, I tend to treat monthly until the patient's retina is dry, regardless of the number of injections required to achieve this; then, I extend the interval 1 to 2 weeks at a time. I err toward resolution of fluid and make sure to couple this conservative treatment regimen with effective patient and family education on the importance of follow-up and treatment adherence. For nearly all my patients, I tend to not extend beyond a quarterly evaluation and dosing interval, meaning that my patients are seeing me and getting injected a minimum of 4 times a year.

Dr Singer: Dr Singh, you and your colleagues at Cleveland Clinic perform excellent imaging studies for nAMD. How do you use imaging to approach treatment-naïve patient education and presentation of what must initially seem like a daunting treatment plan? Does your strategy change as treatment becomes successful—or unsuccessful?

Dr Singh: We first use imaging as our gold standard for assessing disease activity. We discuss treatment goals with our patients and the importance of obtaining a dry retina. I think all of us can admit that we do tolerate some amount of fluid, whether it is a little intraretinal, subretinal, or sub-RPE fluid, so long as it is not in the fovea. Long-term management of nAMD requires an individualized approach that also relies on whether or not the VA is improved and stable. One of the biggest challenges in nAMD treatment is patient retention over time, as demonstrated in both clinical trials and real-world studies.^{17,18} Therefore, it is important to acknowledge that encouraging patient adherence to treatment might necessitate some tolerance of residual fluid.

Dr Singer: Dr Khanani, your practice in Reno, Nevada, draws upon a very large geographic area. How do you balance the logistic challenges your patients face with your preferred treatment algorithm?

Dr Khanani: I agree with the other panelists that communication with patients about treatment goals and tailoring treatment on the basis of OCT images and VA are critical. Unlike Dr Kiss, I still use 3 loading doses per the label.^{19,20} In my practice, we extend treatment 2 weeks at a time according to disease activity on OCT. I counsel patients that nAMD is a chronic disease like diabetes or hypertension, and the consequence of missed treatments is recurrent active disease that can cause permanent vision loss. I do tolerate some subretinal fluid (SRF) when VA is stable in order to maximize the treatment interval. I usually try to extend patients' treatment intervals to 12 weeks, but not longer. Most patients are willing to come in every 12 weeks so long as they have been educated about the chronicity of nAMD.

Dr Singer: Dr Hariprasad, how do you apply TAE? Does your practice have any particular challenges?

Dr Hariprasad: The main difference between my preferred TAE regimen and that of the other panelists is that I have a very stringent treatment regimen, particularly during the first year. I do 3 monthly injections of anti-VEGF therapy, then gingerly extend the interval similarly to how Dr Kiss does during year 1. According to the VIEW 1/VIEW 2 post hoc analysis and my clinical experience, I counsel my patients that if we treat aggressively during year 1, outcomes during year 2 and beyond will be maximized.⁷ I begin extending the treatment interval more aggressively in year 2. As does Dr Khanani, I do not extend beyond 12 weeks. I like to see my patients at least every 12 weeks, if possible, to (1) make sure there is no breakthrough exudation or bleeding and (2) ensure that the fellow eye is still dry. It is also important to remember that fixed dosing is not necessarily bad. In patients who have persistent fluid after 3 monthly doses of aflibercept, it is sensible to continue monthly dosing until the retina is dry in order to capture vision gains earlier in the first year of therapy.

Treat-and-extend regimens have some important limitations as well. Some patients might find that a TAE regimen puts them on an emotional rollercoaster, in which they feel a sense of achievement from having an extended treatment regimen only to later experience disappointment when the treatment interval must be scaled back because of disease activity.

Exploring the Clinical Relevance of Retinal Fluid Subtypes

The shift from time-domain to spectral-domain OCT has made it possible to evaluate and treat minute amounts of fluid found in discrete compartments of the retina. In the TAE studies discussed previously, fluid was not tolerated and the treatment interval was not extended until all retinal fluid had resolved (**Table 1**).¹¹⁻¹⁵ This treatment paradigm fits the current dogma that complete resolution of fluid is required for optimal visual outcomes. A challenge to this paradigm came from the observed absence of correlation between total retinal fluid and VA gain in the CATT and VIEW trials.⁷⁸ Recently, post hoc analyses of hallmark nAMD trials evaluated a potential link between different types of retinal fluid and VA outcomes. These studies, discussed in the sections that follow, suggest that some types of retinal fluid have a particularly detrimental effect on visual outcomes, whereas others might actually be protective.

A recent post hoc analysis of CATT performed by Jaffe and colleagues demonstrated that fluid subtypes can have differential effects on visual outcomes. Although total fluid did not correlate with VA at any timepoint up to 5 years, the presence of intraretinal fluid (IRF) predicted poorer VA compared with eyes without IRF at all timepoints (**Figure 4**).⁹ In particular, foveal IRF at year 5 was associated with poorer VA (44 vs 68 letters, respectively; $P < .001$) (**Figure 4**). Conversely, the presence of SRF and sub-RPE fluid correlated with better VA at 5 years, suggesting a protective role or a marker for retinal healing. These data challenge the original conclusions of CATT, which suggested an unclear role of persistent fluid in long-term visual outcomes.¹⁷

A recent analysis of the relationship between retinal fluid and visual outcomes in the HARBOR study similarly demonstrated that eyes with residual SRF had a comparable likelihood of achieving a BCVA ≥ 69 letters as did eyes with resolved SRF (odds ratio 1.07 [95% CI, 0.72-1.59] and 1.14 [95% CI, 0.77-1.68] at 12 and 24 months, respectively, after adjustment for baseline BCVA).²¹ Eyes with residual SRF also had a better mean baseline BCVA than those with resolved SRF. Importantly, this analysis does not suggest that SRF should not be treated, but rather provides prognostic information that can be shared with patients and suggests that residual SRF might not prevent achievement of optimal VA outcomes.

A recent post hoc analysis of the VIEW 1 and VIEW 2 studies also evaluated retinal fluid and any correlation with BCVA at several timepoints. In this study, aflibercept 2 mg given either monthly or every 8 weeks resulted in a higher proportion of patients with persistently dry retinas ($P = .0065$ and $P = .0140$ for every-4-week and every-8-week treatment, respectively, vs monthly ranibizumab 0.5 mg).²² Consistent with the CATT analysis, foveal IRF was associated with significantly poorer BCVA at all timepoints examined, whereas foveal SRF was associated with better BCVA (**Table 2**).²² Total retinal fluid did not show an association with BCVA at any timepoint beyond baseline.

When change in BCVA was examined in patients with or without persistent IRF by treatment group, a clinically relevant difference emerged: in the ranibizumab group, the consequence of not resolving IRF was a > 3 -letter reduction in BCVA change at 24 weeks (7.1 vs 10.5 letters, respectively; $P = .0002$). Conversely, there was no difference in change in BCVA between patients in the monthly aflibercept group who had persistent IRF and those who were persistently dry (**Figure 5**).²² Persistent drying from baseline was also significantly correlated with improved functional visual outcomes, such as driving and role difficulty. These data suggest that clinicians and payers evaluating first-line anti-VEGF therapy for treatment-naïve patients should consider the value of robust drying in the first few months for long-term VA and functional outcomes.

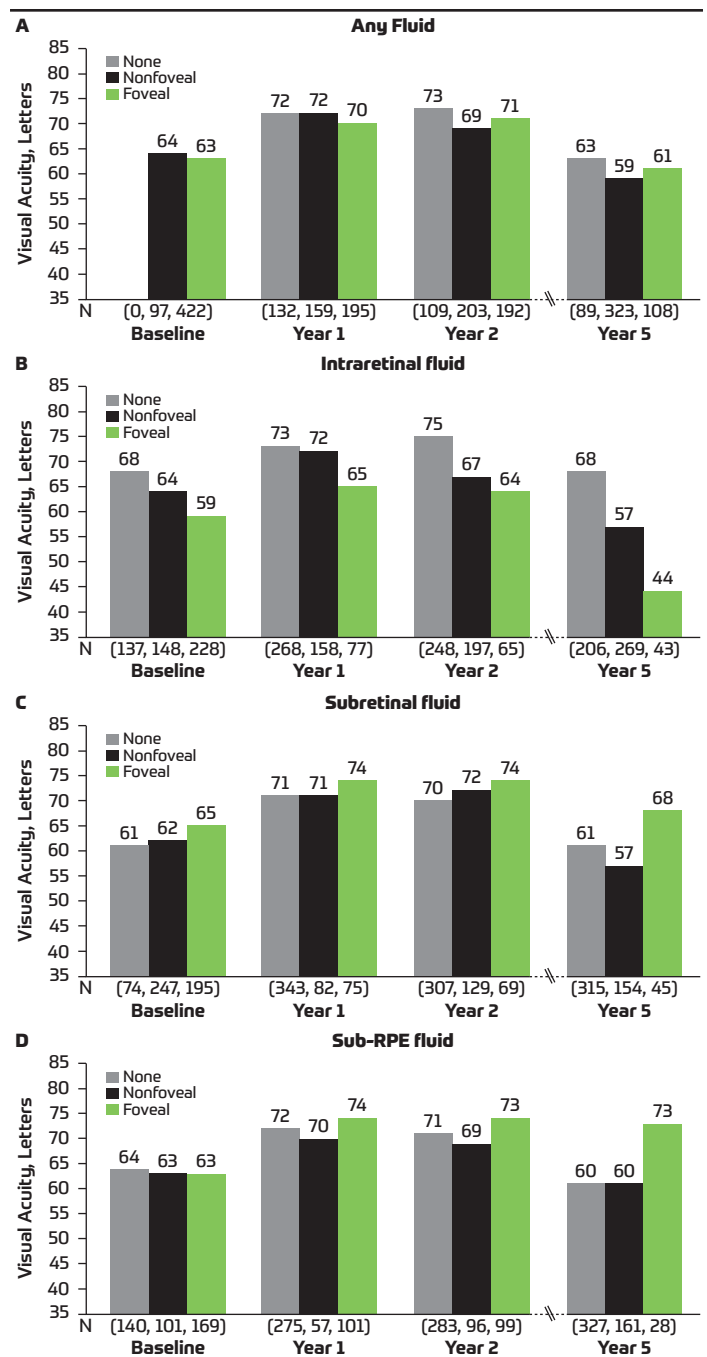


Figure 4. Correlation between total and different types of retinal fluid with visual acuity at different timepoints in CATT (Comparison of Age-Related Macular Degeneration Treatments Trials)⁹

Abbreviation: RPE, retinal pigment epithelium.

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Table 2. Comparison of BCVA Between Eyes With Different Foveal Fluid Types vs No Fluid in the VIEW 1 and VIEW 2 Studies²²

Fluid Type	Mean Difference in BCVA, Letters (95% CI)				
	Baseline	Week 4	Week 12	Week 24	Week 52
Overall retinal fluid	-3.4 (-6.2 to -0.6) $P = .0159$	0.5 (-0.7 to 1.8) NS	-1.1 (-2.5 to 0.3) NS	-1.1 (-2.6 to 0.4) NS	-0.9 (-2.6 to 0.9) NS
Intraretinal fluid	-5.8 (-7.0 to -4.6) $P < .0001$	-4.1 (-5.5 to -2.7) $P < .0001$	-4.5 (-6.1 to -2.9) $P < .0001$	-5.0 (-6.6 to -3.3) $P < .0001$	-4.2 (-6.1 to -2.2) $P < .0001$
Subretinal fluid	5.4 (3.6-7.3) $P < .0001$	5.9 (4.6-7.3) $P < .0001$	4.9 (3.3-6.4) $P < .0001$	6.9 (5.3-8.5) $P < .0001$	7.7 (5.6-9.8) $P < .0001$

Abbreviations: BCVA, best-corrected visual acuity; CI, confidence interval; NS, not stated.

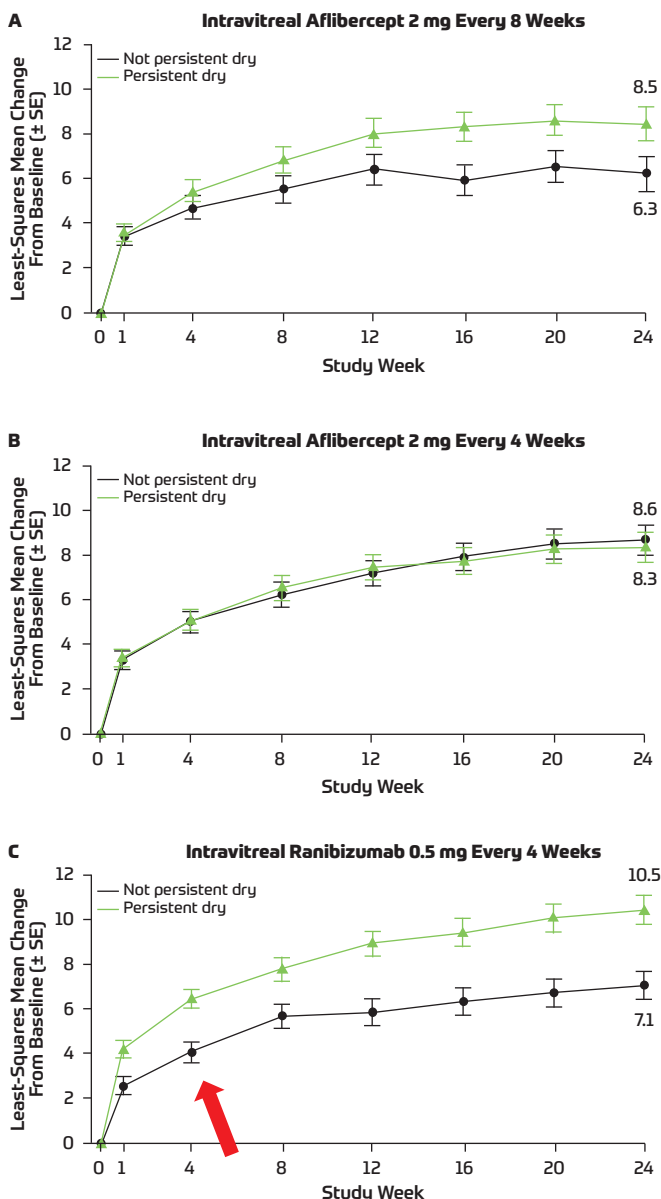


Figure 5. Change in best-corrected visual acuity among treatment groups when persistent intraretinal fluid was present (black line) or when retinas were persistently free of intraretinal fluid (green line)²²
Abbreviation: SE, standard error.

PANEL DISCUSSION: INCORPORATING FLUID DATA INTO PRACTICE

Dr Singer: Dr Singh, have these data changed how you use OCT or how you educate your patients?

Dr Singh: Some patients become concerned about any residual fluid they see on their OCT image. These data have allowed me to alleviate some of that anxiety by treating residual SRF, but not necessarily reducing their treatment interval when I see it. I also let patients know that there are some data suggesting that patients with residual SRF can still have a good visual outcome. Residual SRF might be a sign of choroidal vascular membrane and photoreceptor survival, which might in turn prevent fibrosis and associated long-term effects.

Dr Singer: Dr Kiss, when you see residual IRF after the first anti-VEGF injection, do you consider changing the dosing strategy or the anti-VEGF agent?

Dr Kiss: I am still incorporating these data into practice. My overall philosophy remains that fluid is bad. Although not all fluid is created equal, I am still going to treat significant amounts of fluid. I do not often switch agents, but I am updating my practice with regard to changing the treatment interval. For example, if a patient last treated 6 to 8 weeks ago presents with IRF and visual symptoms, I will reduce the treatment interval. If, however, a patient has a small amount of persistent SRF and is asymptomatic, I might not shorten the interval.

Dr Singer: Dr Khanani, have you had to use step therapy with your patients? Do you think that these data support or argue against step therapy?

Dr Khanani: I have not had to use step therapy yet, but I think it might happen soon. I still use a dry retina as my end point. As does Dr Kiss, I try to initially dry the retina as much as possible using between 3 to 6 monthly injections. These new data guide our response to persistent SRF or IRF when VA is good. I extend the treatment interval for patients with SRF and monitor them closely. If their VA does not change and their OCT image does not worsen, I usually continue to extend the interval. I will not extend the treatment interval if I see IRF so long as I am sure it is not an atrophic cyst.

Dr Singer: Dr Hariprasad, how have these data changed your practice? Have you changed your preferred therapy?

Dr Hariprasad: I agree that these data are very important, but the clinical relevance to my practice is minimal. There are few patients whom I have either treated or not treated on the basis of these data. If a patient has fluid, I treat it. As I previously mentioned, I treat aggressively in year 1 and then might pull back in year 2 and beyond, similar to the new dosing recommendations for aflibercept that were approved in 2018.¹⁹

Dr Singer: When we did some of these analyses, it was very eye-opening. I have had some patients with residual SRF who did not respond to a switch in anti-VEGF therapy, a change in interval, or even to treatment every 2 weeks. I now feel a little more comfortable extending the treatment interval later in the treatment course for these patients. I am much more open to extending the treatment interval for patients with SRF as opposed to those with IRF because untreated IRF negatively affects vision over time. Earlier in the treatment course, I also ask patients if they think the injection is making a difference in their activities of daily living, thus eliciting some information on functional outcomes. Until newer therapies that show comparable fluid resolution with a reduced treatment interval are developed, we must still rely on individualized TAE strategies according to the latest evidence.

Future Directions: Emerging Therapies Aimed at Reducing Treatment Burden While Maximizing Retinal Drying

Treatment burden continues to be a leading barrier to optimal VA improvement in the real world. Ranibizumab (dosed every 4 weeks) and aflibercept (dosed every 4, 8, or 12 weeks) are the only 2 treatments currently approved to treat nAMD.^{19,20} Several agents and delivery systems in development show a promising ability to dry retinal fluid, which might translate to an enhanced ability to extend treatment intervals beyond what is currently possible. These are reviewed subsequently in order of those that are furthest along in development to those that are in earlier-stage trials.

Brolucizumab is a VEGF-A-inhibiting single-chain antibody fragment. It is smaller (26 kDa) than other anti-VEGF molecules, meaning it can be dosed at a higher amount (6.0 vs 0.5–2.0 mg), which translates into a higher molar concentration.^{23–26} These attributes, in turn, might contribute to a greater durability of response and better drying effect. In the phase 3 HAWK and HARRIER trials, 3 monthly loading doses of either brolucizumab (3 or 6 mg) or aflibercept (2 mg) were given, followed by extension to 12 weeks for patients randomized to brolucizumab, with the option to reduce the interval to 8 weeks if disease activity was observed.²⁷ Patients randomized to aflibercept received on-label treatment every 8 weeks. The primary end point of noninferiority of change in BCVA from baseline to week 48 was met, with change in BCVA ranging from 6.1 to 7.6 letters across treatment arms ($P < .001$ for each comparison) (Table 3).²⁷

In both studies, patients treated with brolucizumab had less fluid than those treated with aflibercept.²⁷ Significantly fewer patients treated with brolucizumab had IRF/SRF fluid at week 48 (**Table 3**).²⁷ These findings were consistent with those at week 16 and reaffirmed at week 96.²⁸

Abicipar pegol (abicipar) is a small (34-kDa) VEGF-antagonizing designed ankyrin repeat protein (DARPin), with binding affinity for VEGF that is claimed to be equal or higher than that of ranibizumab.²⁹ The half-life of abicipar is approximately 2 weeks in human eyes with diabetic macular edema,³⁰ which suggests that the agent might have extended treatment durability for nAMD compared with traditional anti-VEGF therapies. In the phase 3 CEDAR and SEQUOIA trials, patients were randomized to receive abicipar 2 mg every 8 or 12 weeks or ranibizumab 0.5 mg every 4 weeks (**Table 4**).³¹

The proportion of patients with stable vision at week 52 was similar, indicating noninferiority of abicipar to ranibizumab for maintenance of vision. Reductions in central retinal thickness were comparable between groups, ranging from -141 to -150 µm, despite fixed dosing, with no adjustment according to fluid recurrence.

Ocular adverse events were similar between groups, with the notable exception of intraocular inflammation, which was observed in approximately 15% of abicipar-treated eyes. The manufacturing process of abicipar was subsequently modified and tested in the recent open-label MAPLE trial.³² Ocular inflammation was observed in 8.9% of abicipar-treated patients, a decrease of approximately 40% from the prior studies.

The **Port Delivery System (PDS)** is a surgically implanted device that continually releases concentrated ranibizumab into the vitreous. In the phase 2 LADDER study, patients who had previously responded to ranibizumab were randomized to receive either a monthly ranibizumab injection or the PDS filled with 3 different concentrations of ranibizumab (**Table 5**).³³ Visual acuity improvement was comparable with high-dose ranibizumab PDS and monthly ranibizumab injection, and patients in the high-dose group were able to go 15 months (median) before needing a refill. Safety was comparable with PDS and monthly ranibizumab injection, with procedure-related exceptions, such as vitreous hemorrhage, conjunctival erosion, retinal detachment, and endophthalmitis. Refinements to the surgical procedure are being made which

Table 3. Brolucizumab Phase 3 HAWK and HARRIER Trial Design and Key Results²⁷

Trial	Treatment	n	Least-Squares Mean BCVA Change at 48 Weeks	Patients Maintained on 12-Week Dosing at 48 Weeks, %	Patients With SRF/IRF at 48 Weeks, %
HAWK	Brolucizumab 3 mg	358	6.1*	49	34†
	Brolucizumab 6 mg	360	6.6*	56	31‡
	Aflibercept 2 mg	360	6.8	–	45
HARRIER	Brolucizumab 6 mg	370	6.9*	51	26‡
	Aflibercept 2 mg	369	7.6	–	44

Abbreviations: BCVA, best-corrected visual acuity; IRF, intraretinal fluid; SRF, subretinal fluid.
* P < .001 for noninferiority
† P = .002 for treatment difference
‡ P < .001 for treatment difference

Table 4. Primary Outcome Data in the Phase 3 CEDAR and SEQUOIA Trials³¹

Trial	Treatment	n	Patients With Stable Vision* at Week 52, %
CEDAR	Abicipar 2 mg every 8 weeks	265	91.7
	Abicipar 2 mg every 12 weeks	262	91.2
	Ranibizumab 0.5 mg every 4 weeks	290	95.5
SEQUOIA	Abicipar 2 mg every 8 weeks	267	94.6
	Abicipar 2 mg every 12 weeks	265	91.3
	Ranibizumab 0.5 mg every 4 weeks	299	96.0

* Stable vision defined as a loss of < 15 Early Treatment Diabetic Retinopathy Study letters compared with baseline

Table 5. Key Data From the Phase 2 LADDER Trial³³

Treatment	n	Median Time to First Required Refill, Months	Mean Change in BCVA From Randomization to 9 Months, ETDRS Letters
Ranibizumab PDS 10 mg/mL	58	8.7	-3.2
Ranibizumab PDS 40 mg/mL	62	13.0	-0.5
Ranibizumab PDS 100 mg/mL	59	15.0	+5.0
Ranibizumab 0.5 mg every 4 weeks	41	–	+3.9

Abbreviations: BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PDS, port delivery system.

significantly reduce the incidence of vitreous hemorrhage.^{34,35} Importantly, some retinal fluid was tolerated in this trial before a refill was required because of continuous release of ranibizumab, with an increase in foveal thickness of > 75 µm vs last 2 visits or ≥ 100 µm vs the lowest on-study measurement triggering refill. The phase 3 Archway study is under way.³⁶

Faricimab is a bispecific antibody targeting both VEGF-A and angiopoietin-2, leading to vascular stabilization and decreased permeability and inflammation.³⁷ Modifications to the Fc region suppress effector function to reduce potential for inflammation and to facilitate systemic clearance for improved safety.³⁸ In the phase 2 AVENUE and STAIRWAY trials, noninferiority of faricimab dosed every 4 or 8 weeks in AVENUE and every 12 or 16 weeks in STAIRWAY to monthly ranibizumab was demonstrated for VA and central retinal thickness.^{39,40} The safety of faricimab was comparable to that of ranibizumab.⁴¹ Two phase 3 studies (TENAYA and LUCERNE) are currently ongoing.^{42,43}

PANEL DISCUSSION: PRACTICE IMPLICATIONS OF RECENT TRIALS

Dr Singer: What are your thoughts on investigational agents currently in late-stage trials?

Dr Khanani: We use OCT to evaluate disease activity in the clinic. With the goal of better retinal drying and enhanced durability in mind, brolucizumab has shown encouraging results. Aflibercept dries better than ranibizumab, which translates to a decreased treatment burden via the ability to extend the treatment interval further. Brolucizumab treatment might be able to be extended even further because it dries the retina even better than aflibercept. Abicipar also seems to dry better than ranibizumab, but a higher rate of inflammation in the phase 3 studies might limit its use until this issue is addressed. Faricimab and the PDS do not have phase 3 data yet, but according to phase 2 data, they seem promising for significantly reducing treatment burden.^{33,39,40}

Dr Hariprasad: I am always an early adopter, and I would love to try these new agents, particularly for the small number of patients that I encounter who have persistent fluid, even when they are treated with aflibercept. The PDS was developed to overcome the frequent dosing thought to be required before the TAE studies were published. Now we can achieve every-12-week dosing, so the need is less pronounced, except among patients with severe recurrent disease. It is also important to consider that the PDS will require surgery to implant, which in itself is not without risk.

Dr Singh: One consideration for TAE dosing is the potential for repeated fluid recurrence on the retina, which could damage vision over time. Also, some patients travel long distances for visits. For patients who cannot come in frequently or who have recalcitrant disease, the PDS could provide a much-needed solution.

Dr Kiss: I think an important limitation of these current trials is that they all address the same pathophysiologic pathway. Faricimab targets 2 pathways, but the main finding was still a lessening of treatment burden, not necessarily improved efficacy in terms of VA. I see a potential place in practice for the PDS, particularly for patients who require frequent injections, but the risks of surgery

and the risk of having an implant need to be weighed relative to the potential benefit of fewer injections. Another pressing question relates to the long-term effects of tolerating fluid prior to a PDS refill. Several therapies that address additional pathways or that use gene therapy for innovative drug delivery are in early-stage clinical trials.⁴⁴

CASE 1: TREATMENT-NAÏVE NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

From the Files of Seenu M. Hariprasad, MD

An 84-year-old female presented with treatment-naïve nAMD in her right eye and VA of 20/60. Her left eye had changes consistent with dry macular degeneration. Fluorescein angiography showed a minimally classic occult lesion (**Figure 6**).

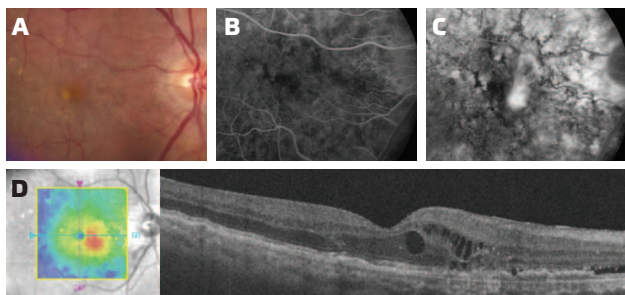


Figure 6. Color fundus photograph (A), early (B) and late (C) fluorescein angiography images, and optical coherence tomography image (D) of the patient in Case 1 at presentation

The patient was treated with aflibercept on presentation and returned 4 weeks later for follow-up. Minimal improvement was noted at that time, but this was not concerning given the short treatment duration. The patient began a regimen of monthly aflibercept. At the next visit 4 weeks later, some restoration of the foveal contour was noted. By the 12th week of treatment, IRF had largely resolved and the patient's VA had improved to 20/30. At 16 weeks of treatment, small intraretinal cystic changes were observed on OCT, despite normal fluorescein angiography images (**Figure 7**).

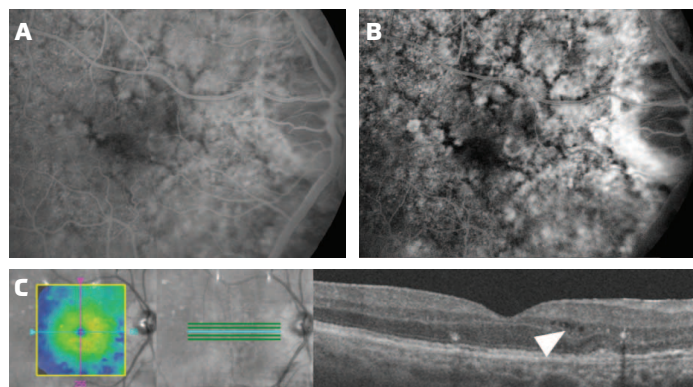


Figure 7. Early (A) and late (B) fluorescein angiography and optical coherence tomography (C) images of the patient in Case 1, showing minor intraretinal fluid recurrence (white arrowhead) after 16 weeks of monthly aflibercept treatment

Commentary

Dr Hariprasad: When can this patient's treatment interval be extended, according to these findings? What should the interval be? How should OCT be used to monitor this patient?

Dr Kiss: I would continue monthly treatment until all IRF has resolved if the patient and family are willing. Looking at the retinal structure, it seems this patient has the potential to achieve 20/20 vision. Given that you have seen improvement after every injection, you might get there with a few more.

Dr Khanani: I agree with Dr Kiss. I would continue monthly injections until the IRF has resolved.

Dr Singh: The amount of residual fluid here is quite minimal. An interesting comparison of time-domain OCT and spectral-domain OCT in year 2 of CATT showed little difference in visual outcomes.⁸ Therefore, I would begin the extension of this patient's treatment interval.

Dr Hariprasad: According to the data, Drs Kiss and Khanani are correct. In the VIEW 1 and VIEW 2 post hoc analysis, early retinal dryness predicted better visual outcomes, and monthly aflibercept was associated with good visual outcomes if early persistent fluid was present. I agree that continuing monthly treatment at this stage is the most appropriate step according to the data. Dr Singh's approach, however, might be more reasonable in the real world given demands on patient and caregiver time. This is where the art of retina comes into play—translating clinical trial data into the real-world setting.

Take-Home Points

- According to the VIEW 1 and VIEW 2 post hoc analysis, early retinal dryness predicted better visual outcome
- If fluid is present after 3 monthly doses, it is sensible to continue monthly dosing rather than extending to every-8-week dosing

CASE 2: PERSISTENT FLUID AFTER ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT

From the Files of Arshad M. Khanani, MD, MA

A 70-year-old male presented with distorted vision OS. He had a history of dry AMD and cataract, and was currently taking lisinopril to treat hypertension. Cataracts were visible on examination OU, but his VA was 20/25 OD and 20/20 OS. OCT performed at baseline revealed SRF as well as a small pigment epithelial detachment (PED) (**Figure 8**). The patient received 3 monthly loading doses of ranibizumab. After 12 weeks of treatment, the patient's VA was 20/25 OS, but the SRF and PED remained unchanged. The patient was then switched to monthly aflibercept, but after 3 monthly injections, both SRF and the PED remained. After an additional 4 monthly injections, SRF began to resolve, but PED did not. His VA was 20/25 OS at week 40.

Treatment Week	Monthly Ranibizumab	Treatment Week	Monthly Aflibercept
Baseline		24	
12		40	
		52	

Figure 8. Optical coherence tomography images after the specified number of weeks of monthly treatment with ranibizumab (left) and continuing after switching to aflibercept (right)

Commentary

Dr Khanani: After 40 weeks of treatment with monthly injections, would you consider TAE or would you continue monthly treatment, knowing that this patient has severe disease and still has some SRF?

Dr Singh: I do not typically reduce the interval for aflibercept below 8 weeks because that is what the label recommends.¹⁹ I think you have done a nice job using an extended loading period to resolve fluid for this patient, but I would not treat more frequently than every 8 weeks moving forward. The recent CATT analysis supports this because patients with persistent SRF actually achieved better VA outcomes than those with other fluid types.⁹

Dr Kiss: Dr Singh, your rationale brings up an important question. In the retrospective analyses mentioned previously, patients were treated regardless of the type of fluid observed on OCT. What happens when treatment can be adjusted according to the type of fluid?

Dr Singer: The FLUID study did just this. Patients were randomized to receive monthly ranibizumab until resolution of SRF and IRF (intensive arm) or until resolution of IRF with some tolerance of SRF (relaxed arm) before the treatment interval was extended. The mean BCVA change from baseline to month 24 was comparable between groups (3.0 letters in the intensive arm vs 2.6 letters in the relaxed arm; $P = .99$).⁴⁵ Obviously, additional similar studies are needed to better understand how to treat and when to tolerate different types of fluid on OCT.

“Although BCVA has been shown to be comparable among anti-VEGF agents in many nAMD clinical trials, the ability to dry the retina is not equal. Intraretinal fluid persistence seems to lead to poorer vision. Intensely administered potent on-label anti-VEGF treatments might be the only way to maintain vision gains in this difficult-to-treat patient population. The results of achieving a dry retina might be reflected more in improved visual function and quality of life than in BCVA as measured in a physician’s office.

—Michael Singer, MD

Take-Home Points

- Monthly anti-VEGF treatment is required in some patients past the loading period
- Patients with mild SRF can maintain good vision even with fluid
- PED can persist even with monthly anti-VEGF treatment; the goal of treatment is to address fluid and not the size of PED

CASE 3: NONRESPONSE TO BEVACIZUMAB

From the Files of Rishi P. Singh, MD

A male with a prior diagnosis of nAMD in the left eye presented after having received 5 monthly bevacizumab injections (used off-label for nAMD) over a 6-month period, with minimal improvement in central subfield thickness (CST) (545-535 μm). On examination, occult choroidal neovascularization was visible on the fundus photograph and fluorescein angiography, with retinal fluid evident on OCT (Figure 9). His VA was 20/125.

The patient decided to enroll in the single-arm ASSESS study, which evaluated switching between 2 different anti-VEGF therapies.⁴⁶ Patients previously treated with bevacizumab or ranibizumab but with recurrent fluid on OCT were switched to 2 mg of monthly aflibercept for 3 months and then every 2 months. Significant

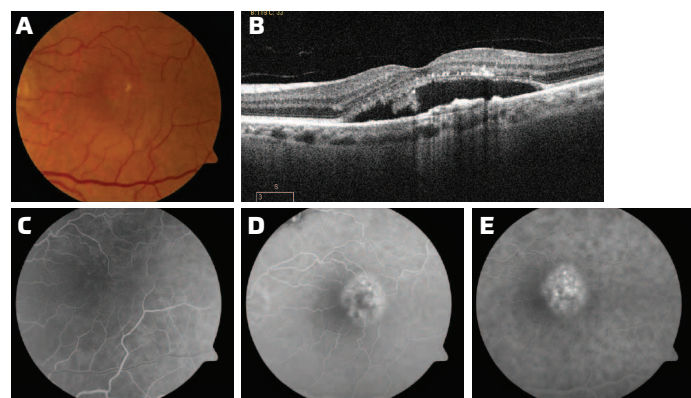


Figure 9. Color fundus photograph (A), optical coherence tomography image (B), and fluorescein angiography images (C-E) of the left eye of the patient presented in Case 3. Early stippled hyperfluorescence (C) with late leakage (E) that is consistent with an occult neovascular membrane is visible by fluorescein angiography.

improvement was seen in BCVA and CST at all timepoints from 2 to 12 months, suggesting that switching to aflibercept is a worthwhile option when minimal improvement in CST is observed during treatment with ranibizumab or bevacizumab. For the patient introduced in this case, retinal fluid resolved completely 8 months after switching. By month 24, he had achieved 20/40 vision.

Commentary

Dr Singer: This case illustrates the concept that treatment with only 1 anti-VEGF therapy might not be best for every patient. The ASSESS study is interesting in that it disputes some previous research, suggesting limited value in switching treatment.⁴⁶ A recent review of several switching studies concluded that although data are mixed with regard to BCVA improvement, most studies showed significant, sustained improvement in anatomic outcomes after switching.⁴⁷

Dr Hariprasad: If a patient is suboptimally responding to a certain course of therapy, rather than continuing, I would consider increasing the frequency of injections or switching the anti-VEGF agent being used.

Dr Khanani: This case clearly highlights that aflibercept dries better than bevacizumab. I usually switch treatments after 3 injections if I do not see a significant improvement in fluid, as in this case—and if there are no insurance barriers.

Dr Kiss: This is an outstanding case that raises 3 important points. (1) Confirmation that the patient does indeed have neovascular AMD: I recently evaluated a patient who was thought to be resistant to anti-VEGF therapy and presented for a second opinion. He had a metastatic choroidal lesion in the macula (rather than nAMD) causing the persistent SRF. Performing the proper evaluation (using OCT, fluorescein angiography, indocyanine green angiography, or even ultrasound) is essential for making the correct diagnosis. (2) The concept of switching agents once the diagnosis of nAMD is confirmed: although in aggregate, the 3 most commonly used agents are all very effective, patients often respond to 1 agent more robustly than to the others. (3) Persistence with treatment: As in this case, some patients simply require frequent injections to control their disease. We have to keep in mind that most patients do not fall into a “one-injection-and-done” treatment paradigm.

Take-Home Points

- Moving a patient to fixed dosing (as frequently as every 2 months) can improve VA and anatomic outcomes
- Aflibercept has been shown to have a superior anatomic result after 3 loading doses compared with ranibizumab, as seen in the VIEW 1 and VIEW 2 studies; therefore, a change in anti-VEGF agent can sometimes be beneficial in improving the clinical outcome

CASE 4: VISUAL DISTORTION FOLLOWING PREMIUM INTRAOCULAR LENS PLACEMENT

From the Files of Szilárd Kiss, MD

A 72-year-old male presented with metamorphopsia following cataract surgery with placement of a premium intraocular lens in the right eye. His VA was 20/40 OD and 20/20 OS, with SRF visible on the OCT image (Figure 10). The patient began a monthly aflibercept injection regimen for the right eye, which he maintained with the exception of a few trial extensions resulting in a return of his original metamorphopsia. His left eye was 20/20 at presentation, but

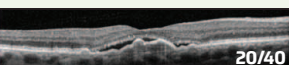
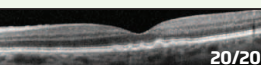
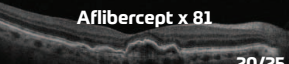

	Right Eye	Left Eye
Baseline	 20/40	 20/20
Last Follow-Up	 20/25	 20/20

Figure 10. Optical coherence tomography images of the right and left eye of the patient in Case 4 at baseline and following an extended regimen of monthly aflibercept injections

32 months later, converted to wet AMD and behaved similarly to his right eye in that his fluid and metamorphopsia returned if the treatment interval exceeded every 4 weeks. This patient has been managed successfully on monthly aflibercept OU ever since and has maintained VA of 20/25 OD and 20/20 OS.

Commentary

Dr Singer: This patient has a very large treatment burden. His SRF accumulation does correlate with his metamorphopsia and decreased vision. He is a patient who will likely benefit from the newer anti-VEGF agents (brolucizumab or abicipar) that are in development, which seem to show greater duration of action. In addition, he would be a good candidate for the investigational PDS because sustained release would keep his OCT fluid under control.

Dr Hariprasad: This case reminds us that vision IS important. Despite changes on OCT, the patient has excellent vision; therefore, I would consider the treatment paradigm to be a success so long as his current VA can be stably maintained. Although it can be worrisome to see OCT changes, in this case they are secondary to excellent vision.

Dr Singh: Clearly, for this patient, a small amount of SRF mattered. This is interesting because it is not the norm in most patients. This case highlights the individualized decisions we must make with our patients with nAMD.

Dr Khanani: This case shows that aggressive monthly treatment with aflibercept can lead to better drying long term. We do not know if this patient would have had a similar visual outcome if some SRF had been tolerated, but according to the FLUID study mentioned by Dr Singer, it could have been possible.

Dr Kiss: Despite our best efforts, we could not extend this patient beyond the monthly injection interval. Because his visual function is being maintained so well, he actually does not consider the visits and injections as burdens, but rather he sees them as opportunities to continue to retain his eyesight.

Take-Home Points

- Some patients require monthly injections even in the era of trying to reduce treatment burden
- Because nAMD tends to be a bilateral disease, monitoring the contralateral eye is important for catching the disease conversion
- With ongoing treatment and close monitoring, patients can maintain excellent visual function even years into their anti-VEGF treatments

SUMMARY

- Recent analyses of large clinical trials have suggested distinct outcomes resulting from persistent retinal fluid, depending on which anti-VEGF treatment is used and if the persistent fluid is subretinal or intraretinal
- Aflibercept, when used monthly, results in a greater proportion of patients with persistently dry retinas and good visual outcome regardless of persistent fluid
- Both aflibercept and ranibizumab can be used in a TAE fashion, with outcomes comparable to those of fixed-interval dosing using fewer injections, but retreatment should be individualized according to vigilant OCT monitoring and thoughtful assessment
- Emerging treatments for nAMD can achieve outcomes comparable to those of established anti-VEGF therapies, with fewer treatments. Caution should be exercised when interpreting the clinical relevance of studies because tolerance of fluid varies among clinical trials.

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1. According to the VIEW 1 and VIEW 2 post hoc analysis, which of the following observations during treatment for nAMD translates to improved long-term VA and functional visual outcomes?
 - a. Larger VA gains in the first 3 months of treatment
 - b. Better drying in the first 3 months of treatment
 - c. Better control of total retinal fluid
 - d. Better control of sub-RPE fluid
2. A 79-year-old male treated with monthly ranibizumab for nAMD for 4 months reports difficulty arranging travel and would like to skip his next scheduled injection. Currently, his VA is 20/40 and his central retinal thickness was reduced by 60% from baseline, with a small amount of IRF remaining. According to the design of recent TAE studies in nAMD, when can the interval of treatment for this patient be extended?
 - a. After 4 months of continuous anti-VEGF treatment
 - b. After 1 year of continuous anti-VEGF treatment
 - c. After evaluating the outcome of switching treatment
 - d. Once all retinal fluid has resolved
3. In the post hoc analysis of the VIEW 1 and VIEW 2 studies, which treatment arm had the highest proportion of patients achieving a dry retina?
 - a. Bevacizumab 1.25 mg dosed monthly
 - b. Ranibizumab 0.5 mg dosed monthly
 - c. Aflibercept 2 mg dosed monthly
 - d. Aflibercept 2 mg dosed every 8 weeks
4. By which mechanism is abicipar theorized to increase the durability of response vs traditional anti-VEGF agents?
 - a. Higher molar concentration
 - b. Continuous drug delivery
 - c. Extended half-life
 - d. Targeting multiple pathways
5. According to recent studies evaluating the significance of retinal fluid subtypes on long-term visual outcomes, which of the following scenarios should prompt a reduction in treatment interval?
 - a. Recurrence of IRF
 - b. Recurrence of SRF
 - c. Recurrence of sub-RPE fluid
 - d. Recurrence of any retinal fluid
6. Which of the following fluid types was associated with BETTER long-term VA in the CATT post hoc analysis?
 - a. IRF
 - b. SRF
 - c. Sub-RPE fluid
 - d. Total fluid
7. A patient who has been maintained successfully on every-12-week dosing of ranibizumab develops a recurrence of fluid, with slightly reduced VA. According to the LUCAS TAE study, which is the best treatment strategy for this patient?
 - a. Continue every-12-week dosing
 - b. Reduce the treatment interval by 2 weeks
 - c. Switch to a different anti-VEGF treatment
 - d. Reduce the treatment interval by 4 weeks