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Visual Outcomes Associated With Patterns of Macular Edema Resolution in Central Retinal Vein Occlusion Treated With Anti–Vascular Endothelial Growth Factor Therapy

A Post Hoc Analysis of the Lucentis, Eylea, Avastin in Vein Occlusion (LEAVO) Trial

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IMPORTANCE It is unclear how visual outcomes vary between patterns of macular edema (ME) resolution in eyes with central retinal vein occlusion (CRVO).

OBJECTIVE To assess best-corrected visual acuity (BCVA) outcomes at 100 weeks based on macular fluid resolution patterns by 52 and 100 weeks among patients receiving anti–vascular endothelial growth factor therapy for CRVO-related ME.

DESIGN, SETTING, AND PARTICIPANTS Post hoc analysis of the prospective, 3-arm, double-masked, randomized noninferiority trial Lucentis, Eylea, Avastin in Vein Occlusion (LEAVO), which evaluated intravitreal aflibercept (2.0 mg/0.05 mL), bevacizumab (1.25-mg/0.05 mL), or ranibizumab (0.5 mg/0.05 mL) over 100 weeks in adult patients (18 years and older) with CRVO-related ME with BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 19 to 78 in the study eye (approximate Snellen equivalent, 20/400 to 20/32, respectively) from December 2014 to December 2016 at 44 UK National Health Service ophthalmology departments. A total of 140 of 154 eyes were randomized to aflibercept, 144 of 154 randomized to bevacizumab, and 141 of 155 randomized to ranibizumab. Data were analyzed from January 2019 to March 2019.

EXPOSURES Persistent ME included eyes with central subfield thickness (CST) 320 µm or greater, and persistently dry macula (no ME) included eyes with CST less than 320 µm at 52 and 100 weeks. Recurrent ME included eyes that did not meet the criteria for persistently dry or wet. If CST was missing, the closest intervening visit was carried forward.

MAIN OUTCOMES AND MEASURES Adjusted mean BCVA at 100 weeks.

RESULTS The mean (SD) age of the 425 included participants was 69.2 (12.7) years, and 243 participants (57.2%) were men. A total of 425 eyes from 425 participants were included. By 100 weeks, 117 eyes (28.5%) were persistently dry, 44 (10.7%) were persistently wet (with ME), and 250 (60.8%) had recurrent ME. Persistent ME at 100 weeks was associated with worse VA compared with dry macula (adjusted difference, −10.98 ETDRS letters; 95% CI, −16.19 to −5.76; $P < .001$) and recurrent ME (adjusted difference, −5.39 letters; 95% CI, −10.15 to −0.64; $P = .03$). By 52 weeks, individuals with persistent ME also had poorer 100-week BCVA compared with individuals with dry macula (adjusted difference, −7.39; 95% CI, −11.72 to −3.05; $P < .001$) and recurrent ME (adjusted difference, −3.92; 95% CI, −8.05 to 0.20; $P = .06$). By 100 weeks, more eyes treated with bevacizumab had persistently wet macula than those treated with aflibercept (26 of 140 [18.6%] vs 7 of 134 [5.2%]; difference, 13.3%; 95% CI, 5.9 to 20.8; $P < .001$) or ranibizumab (11 of 137 [8%]; difference, 10.5%; 95% CI, 2.7 to 18.4; $P = .01$).

CONCLUSIONS AND RELEVANCE These findings suggest that attempts should be made to maintain persistently fluid-free macula for optimal visual acuity outcomes.

Invited Commentary

Supplemental content

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Macular edema (ME) is a major cause of visual impairment in patients with central retinal vein occlusion (CRVO).[1] Anti-vascular endothelial growth factor (VEGF) agents have been shown to be effective in improving vision and resolving ME.[2]

The noninferiority Lucentis, Eylea, Avastin in Vein Occlusion (LEAVO) trial compared best-corrected visual acuity (BCVA) among 3 anti-VEGF agents—aflibercept, bevacizumab, and ranibizumab—in patients with ME due to CRVO. The noninferiority limit was 5 letters. At 100 weeks, aflibercept was found to be noninferior to ranibizumab and bevacizumab was not noninferior to ranibizumab. Younger age, higher baseline BCVA, and a definitely intact baseline subfoveal ellipsoid zone were independent predictors of final BCVA in Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores after adjusting for randomized treatment arm at baseline.[3] Baseline central subfield thickness (CST) on spectral-domain optical coherence tomography (OCT) was not found to be a predictor for final BCVA score.

In the LEAVO trial, after the loading phase of 4 injections, participants were monitored every 4 to 8 weeks for changes in visual acuity (VA) and CST and treated based on predefined retreatment criteria. While most eyes responded well to anti-VEGF agents, patterns of resolution of ME varied, with most experiencing recurrences over the 100-week period (recurrent ME). A small proportion of patients experienced complete resolution of fluid and ME through 100 weeks (persistently dry) and another group had persistent CST of 320 µm or greater at all visits (persistent ME or persistently wet). It is unclear how VA outcomes varied among these patterns of ME resolution.[4]

In the LEAVO trial, baseline and weeks 12, 24, 52, 76, and 100 were mandated study visits. Refracted VA was recorded, providing an opportunity to explore VA patterns based on ME resolution. We evaluated the association of recurrent, persistently dry, and persistence of ME on VA outcomes. We also examined possible determinants of these CST responses.

Key Points

Question Does persistent macular edema (ME) in eyes with central retinal vein occlusion (CRVO) undergoing anti–vascular endothelial growth factor (VEGF) therapy lead to poorer visual acuity (VA) outcomes than in those with recurrent ME or persistently dry macula (no ME)?

Findings In this study, the persistence of fluid by 52 and 100 weeks was associated with worse VA at 100 weeks compared with eyes with recurrent ME or persistently dry macula in 425 participants from the Lucentis, Eylea, Avastin in Vein Occlusion (LEAVO) trial.

Meaning These findings suggest that avoiding persistent and, where possible, recurrent ME in patients with CRVO undergoing anti-VEGF therapy may improve VA outcomes.

Methods

The LEAVO study was a multicenter, prospective, 3-arm, double-masked, randomized, noninferiority trial approved by the UK National Research Ethics Committee Service. Each patient provided written informed consent, and the study followed the Declaration of Helsinki. This post hoc analysis was conducted using fully anonymized data collected in the study, and the Moorfields Research Management Committee approved that no further ethics approval or consent was required.

Participants

Patients were eligible for the LEAVO study if the BCVA ETDRS letter score in the study eye was between 78 and 19 (approximate Snellen equivalent, 20/32 to 20/400, respectively) and CST was 320 µm or greater due to ME secondary to CRVO of less than 12 months duration. Key study eye exclusion criteria included coexistent ocular pathologies affecting VA. Each participant was randomized 1:1:1 to receive 1 of the 3 anti-VEGF agents in the study eye: aflibercept (2.0 mg/0.05 mL), bevacizumab (1.25 mg/0.05 mL), or ranibizumab (0.5 mg/0.05 mL).

Treatment Regimen

Randomized participants had mandated injections at baseline and at weeks 4, 8, and 12. From week 16 to 96, treatment was given if 1 or more retreatment criteria were met, which included a decrease in BCVA letter score of more than 5 between the current and most recent visit attributed to an increase in CST, an increase in BCVA letter score of more than 5 between the current and most recent visit, CST of 320 µm or greater (Heidelberg, Spectralis, or >300 µm for alternatives) because of intraretinal or subretinal fluid, and CST increase more than 50 µm from the lowest previous measurement. Visits at weeks 16 and 20 were mandated; from week 24, the visit interval could be increased from 4 to 8 weekly if retreatment criteria were not met at 3 consecutive visits. Retreatment was withheld if BCVA letter score was more than 83 letters (approximate Snellen equivalent, 20/25). The refracted ETDRS BCVA at 4 m was done at baseline; at 12, 24, 52, 76, and 100 weeks; and at withdrawal.

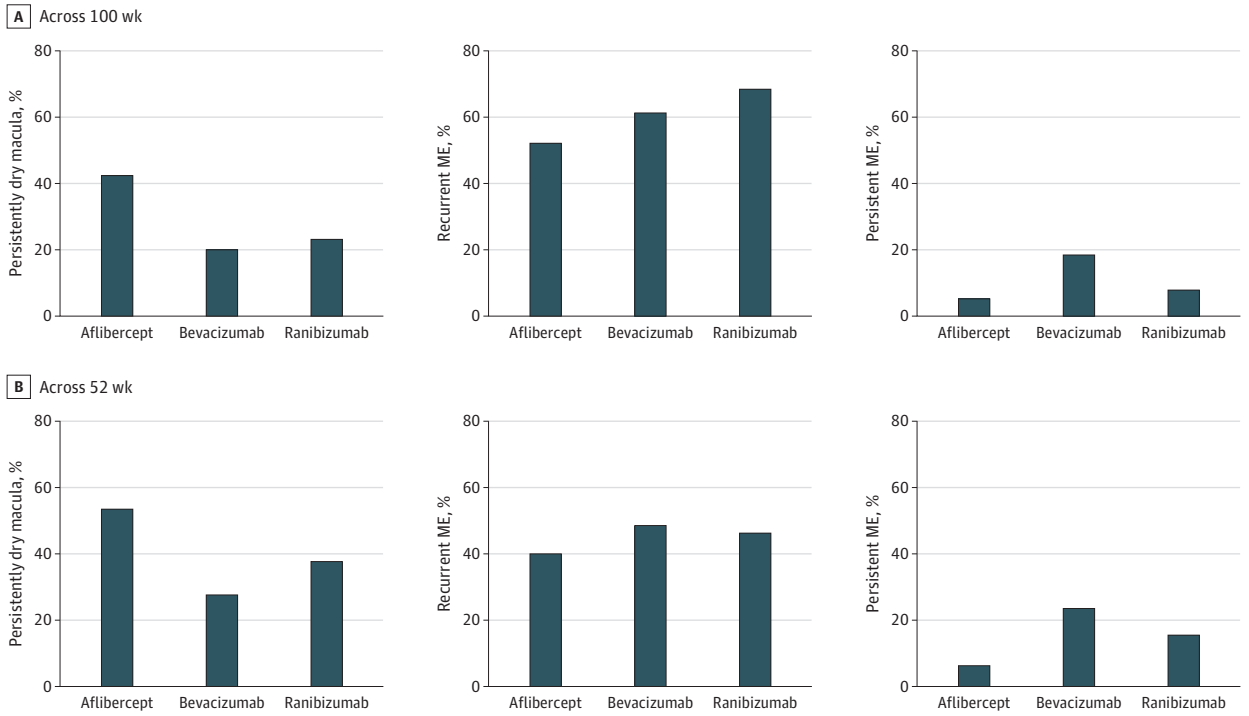
Data Collection and Study Variables

Baseline characteristics, the anti-VEGF agent, and the number of injections received up to 100 weeks were compared across CST resolution groups. Participants who achieved CST less than 320 µm across all milestone visits were defined as having persistently dry macula (no ME), those who had no visits with CST less than 320 µm were defined as having persistent ME, and those who intermittently achieved CST less than 320 µm at 12, 24, 52 76, or 100 weeks postbaseline were grouped as having recurrent ME. If CST was missing, the closest measurement taken during intervening visits was carried forward. Resolution patterns up to week 52 were also assessed.

Outcomes

The main outcome was BCVA change from baseline to 100 weeks. Categorical VA gains of at least 15 letters and at least 10 letters and those achieving a letter score of at least 70 (approximate Snellen equivalent 20/40) were also assessed.

Figure. Resolution in Central Subfield Thickness Across Mandated Visits by Treatment Arm



Resolution patterns based on eyes with recurrent macular edema (ME), persistent ME, and persistently dry macula by treatment arm at 100 weeks and 52 weeks.

Statistical Analysis

Demographic and clinical features were summarized for the whole cohort and by CST response. Generalized estimating equation models were used to study the association between CST response by 52 and 100 weeks and BCVA at 100 weeks. The models assumed an unstructured variance-covariance matrix, which incorporated refracted BCVA outcome data assessed at the milestone visits. The adjusted difference (95% CI) in 100-week BCVA between CST resolution groups was reported, adjusting for age, disease duration, baseline BCVA, baseline CST, treatment arm, and the interactions between all covariates with time. Categorical VA outcomes (proportion of those who gained 10 letters, those who gained 15 letters, and those who achieved a letter score of at least 70 [approximate Snellen equivalent, 20/40] by 100 weeks) by resolution group were compared using Pearson χ^2 test and descriptive risk difference (95% CI). The baseline factors associated with each resolution group were assessed using multinomial logistic regression, adjusting for treatment arm. *P* values were 2-sided with a significance threshold of .05, and there was no adjustment for multiple analyses. Statistical analysis was carried out using Stata version 15 (StataCorp).

Results

Clinical Characteristics

A total of 425 of 463 participants (91.8%) were included in this post hoc analysis (eFigure in the Supplement) after excluding participants that were not in the per protocol population, were unable to be classified in any CST resolution group by 52 or 100 weeks, or with potential outliers in BCVA (>4 SD lower than mean) at each time point. The mean (SD) age of the 425 included participants was 69.2 (12.7) years, and 243 participants (57.2%) were men. A total of 117 eyes achieved resolution across all milestone visits by 100 weeks, 250 eyes were recurrent (among these, 39 were dry, 191 recurrent, 19 persistently wet, and 1 not classified at 52 weeks), and 44 were persistently wet (**Figure**). **Table 1** describes the demographic, treatment, clinical, and ocular characteristics of the study cohort randomized to receive aflibercept (n = 140), bevacizumab (n = 144), or ranibizumab (n = 141). A comparison of baseline characteristics for each treatment group by those included in the final analyses separately by 52 and 100 weeks compared with those randomized is presented in eTable 1 in the Supplement.

Association Between Resolution Patterns and BCVA at Week 100

Mean (SD) visual gains by 100 weeks in ETDRS letters was 16.8 (16.2) for persistently dry eyes, 13.1 (19.6) for eyes with recurrent ME, and 6.4 (21.2) for persistently wet eyes by 100 weeks. The adjusted difference in 100-week BCVA in eyes with persistently wet macula compared with those with recurrent ME was −5.39 ETDRS letters (95% CI, −10.15 to −0.64; *P* = .03) and those with persistently dry macula was −10.98 ETDRS letters (95% CI, −16.19 to −5.76; *P* < .001) (**Table 2**). Eyes that had recurrent ME by 100 weeks were 5.58 letters (95% CI, 2.22 to 8.95; *P* = .001) lower than those that were persistently dry.

Table 1. Demographic, Treatment, and Clinical Characteristics of the Study Cohort

Characteristic (N = 350)	No. (%)
Total	425 (100)
Age, mean (SD), y	69.2 (12.7)
Female	182 (42.8)
Male	243 (57.2)
Systolic blood pressure, mean (SD), mm Hg	142.7 (16.3)
Diastolic blood pressure, mean (SD), mm Hg	79.8 (10.3)
Pseudophakia	60 (14.1)
Cataract	117 (27.7)
Ischemic CRVO	49 (11.5)
Duration of CRVO, median (IQR), mo	0.9 (0.4-1.7)
<3	362 (85.2)
3-6	41 (9.7)
>6	22 (5.2)
Total No. of injections by week 100, mean (SD)	11.5 (4.9)
Total No. of injections by week 52, mean (SD)	8.0 (2.5)
Treatment arm	
Ranibizumab	141 (33.2)
Aflibercept	140 (32.9)
Bevacizumab	144 (33.9)
BCVA ETDRS letter score, mean (SD) (approximate Snellen equivalent)	54.4 (14.4) [20/100]
BCVA ETDRS letter score (approximate Snellen equivalent)[a]	
78-59 (20/32-20/80)	198 (46.7)
58-39 (20/80-20/200)	152 (35.9)
38-19 (20/200-20/400)	74 (17.5)
CST, mean (SD), µm	694.9 (209.7)
Total volume, mean (SD), mm^3[b]	12.7 (2.7)

Abbreviations: BCVA, best-corrected visual acuity; CRVO, central retinal vein occlusion; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study.

[a] The baseline BCVA test was incomplete and not recorded for 1 participant randomized to bevacizumab.

[b] Total volume data were missing for 1 participant randomized to bevacizumab and 2 participants randomized to ranibizumab.

Mean (SD) visual gain by 100 weeks in ETDRS letters was 15.6 (15.8) for eyes persistently dry by 52 weeks, 13.3 (20.6) in eyes with recurrent ME by 52 weeks, and 8.6 (21.2) for those with persistently wet macula by 52 weeks. The adjusted difference in BCVA at 100 weeks for recurrent ME compared with persistently dry by 52 weeks was −3.47 ETDRS letters (95% CI, −6.60 to −0.33; $P = .03$). Eyes persistently wet by 52 weeks were 7.39 letters (95% CI, 3.05 to 11.72; $P < .001$) lower than those who remained dry and 3.92 letters (95% CI, 0.2 to 8.05; $P = .06$) lower than those that were recurrent.

By 100 weeks, persistently dry eyes had a higher proportion of eyes that gained at least 10 BCVA letters compared with recurrent ME (89 of 117 [76.1%] vs 148 of 231 [64.1%]; difference, 12.0%; 95% CI, 2.1 to 21.9; $P = .02$) or persistently wet (89 [76.1%] vs 22 [50.0%]; difference, 26.1%; 95% CI, 9.4 to 42.7; $P = .001$). This difference was preset on comparing recurrent ME with persistently wet macula by 100 weeks (14.1%; 95% CI, −1.9 to 30.1; $P = .08$). Similar associations were found in eyes that achieved 15 ETDRS letters by 100 weeks (eTable 2 in the Supplement). Eyes that achieved an ETDRS letter score of at least 70 (approximate Snellen equivalent, 20/40) at 100 weeks was more frequent in persistently dry macula compared with persistent or recurrent ME.

In eTable 3 in the Supplement, VA was compared with different definitions for ischemic CRVO (iCRVO) in the main study cohort (N = 463) and our study sample for comparison.

Differences in Resolution Patterns in CST Between Drugs

By 100 weeks, persistently dry macula was most frequent in aflibercept-treated eyes than those treated with ranibizumab (57 of 134 eyes [42.5%] vs 32 of 137 [23.4%]; difference, 19.2%; 95% CI, 8.2 to 30.1; $P < .001$) (eTable 4 in the Supplement) or bevacizumab (57 [42.5%] vs 28 [20.0%]; difference, 22.5%; 95% CI, 11.9 to 33.2; $P < .001$). By 100 weeks, more bevacizumab-treated eyes had persistently wet macula than those treated with aflibercept (26 [18.6%] vs 7 [5.2%]; difference, 13.3%; 95% CI, 5.9 to 20.8; $P < .001$) or ranibizumab (26 [18.6%] vs 11 [8%]; difference, 10.5%; 95% CI, 2.7 to 18.4; $P = .01$). A higher proportion of ranibizumab-treated eyes showed recurrence by 100 weeks than those treated with aflibercept (94 [68.6%] vs 70 [52.5%]; difference, 16.4%; 95% CI, 4.9 to 27.9; $P = .006$).

Determinants of Recurrent ME, Persistently Dry Macula, and Persistently Wet Macula

Study characteristics across groups by 52 and 100 weeks are summarized in **Table 3**, and determinants of ME patterns are shown in **Table 4**. Bevacizumab-treated eyes relative to aflibercept-treated eyes were found to be associated with recurrent and wet ME relative to persistently dry by weeks 52 and 100. Moreover, there were more persistently wet ME compared with recurrent by both 100 and 52 weeks. Additionally, ranibizumab relative to aflibercept was associated with recurrent ME relative to persistently dry macula by 100 weeks (relative risk [RR], 2.39; 95% CI, 1.40-4.07; $P = .001$), and similar associations were found for comparisons between recurrent ME vs dry by 52 weeks and wet vs dry by 52 and 100 weeks. Bevacizumab-treated eyes relative to ranibizumab-treated eyes (RR, 2.70; 95% CI, 1.13-6.44; $P = .03$) and ranibizumab relative to aflibercept (RR, 2.80; 95% CI, 0.99-7.93; $P = .05$) were associated with being persistently wet relative to dry by 100 weeks, with similar associations at 52 weeks. Bevacizumab-treated eyes relative to ranibizumab-treated eyes was associated with persistently wet vs recurrent by 100 weeks (RR, 2.58; 95% CI, 1.20-5.54; $P = .02$). Ranibizumab-treated eyes (RR, 2.11; 95% CI, 0.90-4.95; $P = .09$) relative to aflibercept-treated eyes were associated with persistently wet macula relative to recurrent ME by 52 weeks.

Following adjustment for treatment arm, younger age at baseline (RR, 0.88/5-year increase in age; 95% CI, 0.77 to 1.01; $P = .08$) and higher baseline CST (1.23/100-µm increase; 95% CI, 1.02-1.49; $P = .03$) were associated with wet macula compared with persistently dry across 100 weeks and similar factors were identified across 52 weeks. Additionally, longer disease duration at baseline was associated with being persistently wet relative to dry by 52 weeks (RR, 1.63/1-unit increase in $\log_e$ duration; 95% CI, 0.97-2.73; $P = .06$). For recurrent ME rela-

Table 2. Generalized Estimating Equation Model Results for Best-Corrected Visual Acuity (BCVA) at 100 Weeks[a]

	BCVA at 100 wk in ETDRS letters		
CST resolution	Estimate	95% CI	*P* value
By 100 wk[b]			
Dry	Reference	NA	NA
Recurrent ME	−5.58	−8.95 to −2.22	.001
Wet	−10.98	−16.19 to −5.76	<.001
By 52 wk[c]			
Dry	Reference	NA	NA
Recurrent ME	−3.47	−6.60 to −0.33	.03
Wet	−7.39	−11.72 to −3.05	<.001

Abbreviations: CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; ME, macular edema; NA, not applicable.

[a] Two generalized estimating equation models were fitted with an unstructured variance-covariance matrix that incorporated all postbaseline measurements of refracted BCVA at mandated visits. The models were adjusted for age, disease duration (log), baseline BCVA, baseline CST, treatment arm, and interactions with time. The interaction between time and each variable was estimated and the outcome at 100 weeks was presented. The adjusted difference in BCVA at 100 weeks between participants with persistently wet macula relative to recurrent ME by 100 weeks was −5.39 ETDRS letters (95% CI, −10.15 to −0.64; *P* = .03) and by 52 weeks was −3.92 (95% CI, −8.05 to 0.20; *P* = .06).

[b] Generalized estimating equation model incorporated 410 participants as there was 1 patient with missing baseline BCVA.

[c] Generalized estimating equation model incorporated 423 participants as there was 1 patient with missing baseline BCVA.

tive to dry macula by 100 weeks, associated variables included lower baseline VA (RR, 0.83/10-letter increase; 95% CI, 0.70-0.97; *P* = .02), longer disease duration (RR, 1.51; 95% CI, 0.98-2.31; *P* = .06), higher baseline CST (RR, 1.34; 95% CI, 1.18 to 1.52; *P* < .001), and higher systolic blood pressure (RR, 1.06; 95% CI, 0.99-1.14; *P* = .08). Higher baseline CST (RR, 1.24; 95% CI, 1.11-1.38; *P* < .001) was associated with recurrent ME relative to dry by 52 weeks. Younger age (RR, 0.87; 95% CI, 0.77-0.98; *P* = .03) was associated with persistently wet relative to recurrent ME by 100 weeks.

Discussion

Although anti-VEGF therapy generally results in resolution of macular fluid and gain in VA in people with ME related to CRVO, there is marked heterogeneity in treatment response. Approximately 50% to 60% of eyes gain 10 letters or more and 30% gain 15 or more.[2,5] In this study, differences in patterns of macular fluid resolution were associated with VA outcomes at 100 weeks. Approximately 30% of the study cohort achieved complete resolution of macular fluid at all mandated visits after baseline, 60% had recurrent edema, and 10% had persistent macular fluid up to 100 weeks. This suggests that intraocular VEGF concentrations differ considerably between eyes with CRVO. There are several reports showing that response to anti-VEGF is associated with aqueous VEGF levels.[4]

In addition, Shchuko et al[6] showed that eyes with CRVO and branch retinal vein occlusion with insufficient response to ranibizumab had high concentrations of a number of cytokines including VEGF, interleukin 8, monocyte chemoattractant protein-1, interleukin 10, and interleukin 13. In our study, eyes that persistently achieved a fluid-free status may have had intraocular VEGF levels that could be sufficiently suppressed by anti-VEGF therapy based on the LEAVO retreatment criteria. In contrast, although the VEGF drive in eyes with recurrent ME is intermittently suppressible, these eyes may have entered a self-perpetuating cycle of VEGF-induced retinal vascular permeability, probably from retinal ischemia. In this study cohort, 10% of eyes had clinical evidence of iCRVO while 60% had recurrent ME, indicating that lower VEGF concentrations are required to trigger recurrent ME compared with that required for developing iCRVO. Moreover, 10% of eyes did not respond to anti-VEGF therapy at all, and VEGF may not be the predominant cytokine in these eyes. It is interesting to note that younger age was associated with increased likelihood of a wet macula, suggesting that inflammatory cytokines may play a more prominent role in this age group compared with their older counterparts.

The retreatment criteria used in the LEAVO study were a pro re nata regimen, which was dependent on changes in CST and VA. All eyes with CST 320 µm or greater or with a 50 µm increase or greater in CST from lowest recorded reading had to be retreated, explaining the increased number of injections in the recurrent ME and persistently wet groups. Our study results may also suggest that the pro re nata regimen that relies on VA and CST changes are not sufficiently robust to suppress sustained high levels of VEGF in some cases of CRVO.

When we compare the 3 anti-VEGF agents, participants allocated to aflibercept therapy had the greatest proportion of persistently dry macula, the least recurrence (those who went from CST ≥320 µm to CST <320 µm), and the least persistent ME, while bevacizumab had the greatest proportion of persistently wet maculae. Younger age, higher baseline CST, and receiving bevacizumab relative to aflibercept or ranibizumab were associated with being persistently wet relative to dry macula by 52 and 100 weeks. Lower baseline VA, longer disease duration, higher baseline CST, higher systolic blood pressure, and the use of ranibizumab and bevacizumab compared with aflibercept were associated with recurrent ME relative to remaining dry by 100 weeks. These observations suggest that aflibercept may be a better choice in terms of avoiding persistent ME. However, recurrences were high even with

Table 3. Demographic, Treatment, and Clinical Characteristics Summarized Across Central Subfield Thickness (CST) Resolution Groups by 100 Weeks[a]

Characteristic	Mean (SD)					
	100 wk			52 wk		
Total (N = 350)	Persistently dry (n = 117)	Recurrent ME (n = 250)	Persistently wet (n = 44)	Persistently dry (n = 168)	Recurrent ME (n = 191)	Persistently wet (n = 65)
Age, y	68.9 (11.8)	69.8 (12.6)	65.8 (14.3)	70.4 (11.6)	68.9 (13.3)	66.6 (13.3)
Female, No. (%)	52 (44.4)	108 (43.2)	18 (40.9)	74 (44.0)	81 (42.4)	27 (41.5)
Male, No. (%)	65 (55.6)	142 (56.8)	26 (59.1)	94 (56.0)	110 (57.6)	38 (58.5)
Systolic blood pressure, mm Hg	140.1 (18.6)	143.6 (15.4)	142.1 (15.3)	141.5 (17.9)	143.3 (14.9)	144.4 (15.9)
Diastolic blood pressure, mm Hg	79.6 (10.9)	80.1 (9.7)	79.6 (10.8)	79.4 (11.0)	79.7 (9.4)	81.3 (11.0)
Pseudophakia, No. (%)	13 (11.1)	40 (16.0)	5 (11.4)	21 (12.5)	28 (14.7)	11 (16.9)
Cataract, No. (%)	31 (26.7)	72 (28.9)	10 (22.7)	50 (29.9)	51 (26.7)	16 (25.0)
Ischemic CRVO, No. (%)[b]	17 (14.5)	29 (11.6)	3 (6.8)	22 (13.1)	22(11.5)	4(6.2)
Duration, median (IQR), mo	0.7 (0.3-1.3)	0.9 (0.4-2.0)	0.9 (0.4-1.8)	0.9 (0.4-1.6)	0.9 (0.4-1.8)	1.1 (0.4-1.9)
Total No. of injections by wk 100	8.4 (4.2)	12.7 (4.0)	15.0 (6.3)	NA	NA	NA
Total No. of injections by wk 52	6.3 (2.1)	8.6 (2.0)	10.1 (2.9)	6.8 (2.3)	8.4 (1.9)	10.3 (2.6)
Treatment arm, No. (%)						
Aflibercept	57 (48.7)	70 (28.0)	7 (15.9)	75 (44.6)	56 (29.3)	9 (13.9)
Bevacizumab	28 (23.9)	86 (34.0)	26 (59.1)	40 (23.8)	70 (36.7)	34 (52.3)
Ranibizumab	32 (27.4)	94 (37.6)	11 (25.0)	53 (31.6)	65 (34.0)	22 (33.9)
BCVA ETDRS letter score [approximate Snellen equivalent] at baseline[c]	56.8 (13.8) [20/80]	52.9 (14.8) [20/100]	56.8 (13.7) [20/80]	55.2 (14.9) [20/80]	53.6 (14.3) [20/100]	55.0 (13.9) [20/80]
100-wk BCVA, ETDRS letter score [approximate Snellen equivalent][d]	73.3 (15.3) [20/40]	65.8 (17.6) [20/50]	63.2 (17.8) [20/63]	70.4 (15.8) [20/40]	66.8 (18.2) [20/50]	63.6 (17.3) [20/63]
Change in BCVA at 100 wk, ETDRS letters	16.8 (16.2)	13.1 (19.6)	6.4 (21.2)	15.6 (15.8)	13.3 (20.6)	8.6 (21.2)
CST, μm at baseline	619.1 (169.7)	732.7 (214.7)	689.6 (229.0)	646.7 (191.3)	732.4 (214.5)	707.2 (220.2)
100-wk CST, μm[e]	248.9 (32.9)	331.3 (124.2)	471.6 (146.3)	283.1 (99.6)	322.2 (117.9)	420.7 (153.3)
Change in CST at 100 wk, μm	−370.2 (179.0)	−401.0 (247.1)	−218.0 (238.2)	−359.4 (207.3)	−409.6 (240.0)	−286.4 (262.2)
Total volume, mm^3 at baseline[f]	11.9 (2.1)	13.0 (2.9)	13.1 (2.9)	12.3 (2.6)	12.8 (2.8)	13.2 (2.9)
100-wk Total volume, mm^3[g]	11.9 (2.1)	8.9 (1.6)	13.0 (2.9)	8.4 (1.2)	8.8 (1.6)	10.2 (2.6)
Change in total volume at 100 wk, mm^3	−3.8 (2.1)	−4.1 (3.2)	−2.3 (3.8)	−3.9 (2.6)	−4.0 (3.0)	−2.9 (3.8)

Abbreviations: BCVA, best-corrected visual acuity; CRVO, central retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; ME, macular edema; NA, not applicable.

[a] Numbers may not add up to column totals owing to missing data, and proportions were summarized on available data.

[b] Clinician-defined iCRVO. For the comparison of BCVA for different definitions of iCRVO, refer to eTable 3 in the Supplement.

[c] The baseline BCVA test was incomplete and not recorded for 1 participant who had recurrent ME by 52 and 100 weeks.

[d] One hundred–week BCVA was not recorded in 11 participants who had dry macula by 52 weeks (these were all unclassifiable by 100 weeks) and 18 participants who had recurrent ME by 52 and 100 weeks.

[e] Original 100-week CST was summarized (not the imputed CST used for classification of subgroups) and the same participant as for the 100-week BCVA measurements were not recorded.

[f] For total volume at baseline, data were missing for 1 participant with dry macula by 52 weeks and 2 patients with recurrent dry macula by 52 weeks (who remained in their respective groups by 100 weeks).

[g] For 100-week total volume, the same participants as for the 100-week BCVA and 100-week CST measurements were not recorded.

aflibercept, highlighting the continual production of VEGF in these eyes.

VA gain was lower in eyes with persistent macular fluid compared with those with persistently dry macula or recurrent edema. We have previously reported that baseline CST or intraretinal fluid are not predictors of VA outcomes at 100 weeks.[3] Therefore, it may be the persistence of fluid that triggers secondary effects on the neuronal cells.

These findings may also explain the differences in VA outcomes between the Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE-2)[5] and LEAVO trials.[2] The SCORE-2 trial compared aflibercept with bevacizumab in CRVO and hemiretinal vein occlusion and showed that macular fluid resolution was significantly less with bevacizumab compared with aflibercept but it did not translate to poorer visual outcomes at 6 months.[5] This may be because the impact

Table 4. Multinomial Logistic Regression Results Adjusted for Treatment Arm Only, Identifying Determinants of Recurrent Macular Edema (ME), Persistently Wet ME, and Persistently Dry ME[a,b]

	CST resolution across 100 wk		CST resolution across 52 wk	
Determinants	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Recurrent ME vs dry (reference)				
Treatment arm				
Ranibizumab	1 [Reference]	NA	1 [Reference]	NA
Aflibercept	0.42 (0.25-0.71)	.001	0.61 (0.37-1.01)	.05
Bevacizumab	1.05 (0.58-1.88)	.88	1.43 (0.84-2.43)	.19
Baseline VA, ETDRS (per 10-letter increase)[c]	0.83 (0.70-0.97)	.02	0.93 (0.80-1.08)	.33
Age (per 5-y increase), y	1.02 (0.93-1.11)	.70	0.94 (0.86-1.02)	.15
Disease duration, y (log)[d]	1.51 (0.98-2.31)	.06	1.17 (0.80-1.73)	.42
Baseline CST, µm (per 100-µm increase)	1.34 (1.18-1.52)	<.001	1.24 (1.11-1.38)	<.001
Systolic blood pressure, mm Hg (per 5-mm Hg increase)	1.06 (0.99-1.14)	.08	1.03 (0.97-1.10)	.35
Persistently wet vs dry (reference)				
Treatment arm				
Ranibizumab	1 [Reference]	NA	1 [Reference]	NA
Aflibercept	0.36 (0.13-1.01)	.05	0.29 (0.12-0.68)	.004
Bevacizumab	2.70 (1.13-6.44)	.03	2.05 (1.04-4.02)	.04
Baseline VA, ETDRS (per 10-letter increase)[c]	1.00 (0.77-1.31)	>.99	1.00 (0.81-1.23)	.99
Age (per 5-y increase), y	0.88 (0.77-1.01)	.08	0.86 (0.77-0.97)	.01
Disease duration, y (log)[d]	1.56 (0.81-2.99)	.19	1.63 (0.97-2.73)	.06
Baseline CST, µm (per 100-µm increase)	1.23 (1.02-1.49)	.03	1.17 (1.01-1.36)	.04
Systolic blood pressure, mm Hg (per 5-mm Hg increase)	1.03 (0.92-1.15)	.59	1.05 (0.96-1.16)	.27
Persistently wet vs recurrent ME (reference)				
Treatment arm				
Ranibizumab	1 [Reference]	NA	1 [Reference]	NA
Aflibercept	0.85 (0.32-2.32)	.76	0.48 (0.20-1.12)	.09
Bevacizumab	2.58 (1.20-5.54)	.02	1.44 (0.76-2.70)	.26
Baseline VA, ETDRS (per 10-letter increase)[c]	1.21 (0.95-1.55)	.12	1.07 (0.88-1.31)	.49
Age (per 5-y increase), y	0.87 (0.77-0.98)	.03	0.92 (0.82-1.02)	.13
Disease duration, y (log)[d]	1.03 (0.58-1.84)	.91	1.39 (0.85-2.26)	.19
Baseline CST, µm (per 100-µm increase)	0.92 (0.78-1.08)	.31	0.95 (0.83-1.08)	.43
Systolic blood pressure, mm Hg (per 5 mm-Hg increase)	0.97 (0.88-1.07)	.53	1.02 (0.93-1.12)	.64

Abbreviations: CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; NA, not applicable; RR, relative risk; VA, visual acuity.

[a] All variables have been adjusted for treatment arm only.

[b] For recurrent vs dry (reference) by 100 weeks (RR, 2.50; 95% CI, 1.44-4.34; *P* = .001), for wet vs persistently dry (reference) by 100 weeks (RR, 7.56; 95% CI, 2.93-19.54; *P* < .001), for persistently wet vs recurrent (reference) by 100 weeks (RR, 3.02; 95%, 1.24-7.38; *P* = .02), for recurrent vs dry (reference) by 52 weeks (RR, 2.34; 95% CI, 1.39-3.94; *P* = .001), for wet vs persistently dry (reference) by 52 weeks (RR, 7.08; 95% CI, 3.09-16.23; *P* < .001), persistently wet vs recurrent (reference) by 52 weeks (RR, 3.02; 95% CI, 1.34-6.82; *P* = .008).

[c] The baseline BCVA test was incomplete and not recorded for 1 participant who had recurrent ME by 52 and 100 weeks, and so multinomial logistic regression models for baseline VA incorporated 410 participants for 100-week analysis and 423 participants for 52-week analysis.

[d] RR interpreted per 1-integer unit increase for continuous covariates unless otherwise indicated. Natural log transformation was applied to disease duration; the coefficient of the covariate can be approximately interpreted as a 1-unit increase in log-disease duration multiplied by the RR of the outcome (compared with the base) by exp(β) or β percentage increase in the odds per 1% increase in disease duration, where β is the $\log_e$ (RR).

of persistent ME on VA outcome takes time and may only manifest by 52 weeks. In contrast, the LEAVO study showed bevacizumab to be less effective at resolving ME compared with aflibercept but was not noninferior to aflibercept in terms of VA outcomes at 52 and 100 weeks.[2]

Previous studies have shown that larger fluctuations of fluid may be associated with poorer VA outcomes[7-9] because of repeated impact on retinal cells, leading to potential mechanical stress to retinal photoreceptor layers and decreased visual function.[10] It may be that eyes with recurrent ME are more prone to vision loss if the fluctuations result in high standard deviations. In other words, if an eye can achieve CST less than 320 µm after initiating therapy and the eye develops recurrent ME, if the ME does not result in intermittent high CST, VA gains can be sustained. This may be better achieved with treat-and-extend rather than a pro re nata regimen. However, this hypothesis must be proven in future studies.

Strengths and Limitations

A study strength is that we were able to evaluate the effect of CST resolution in mandated visits across the full study period of 100 weeks and within a shorter period of 52 weeks under a clinical trial design setting. However, we were unable to assess the role of capillary nonperfusion in causing recurrent or persistent ME in CRVO. For example, local increases in areas of capillary nonperfusion at the macula may contribute to recurrent ME.[11,12] Further studies using OCT-angiography are required to explore other causes of

recurrent ME. In addition, because of limited sample size in the persistently wet group, we were unable to study multivariable associations of the determinants of CST resolution against one another. Also, misclassification bias may have occurred, as the definitions were based on 5 data points over the course of 2 years. Furthermore, approximately 10% of participants from the original cohort were excluded and therefore our groups were no longer randomized. Also, one cannot determine whether approaches other than that used in LEAVO, such as withholding treatment compared with treatment, would have led to different outcomes. Most importantly, these findings represent a post hoc analysis, which may lead to inherent bias toward evaluating data in a way that supports our hypothesis regarding the association of persistent ME with VA outcomes following different anti-VEGF agents for CRVO-related ME. Further investigations would be needed to determine the magnitude, if any, of fluctuating (recurrent) ME on VA outcomes.

Conclusions

In conclusion, this post hoc analysis showed that VA outcomes in CRVO may be dependent on the ME resolution profile over time, and our 100-week data in a clinical trial setting support the hypothesis that persistent ME across 100 weeks and even 52 weeks should be avoided. Those with recurrent ME by 100 weeks had poorer VA outcomes than those who remained dry. Younger participants, those with higher baseline CST, and bevacizumab-treated eyes were also more likely to be persistently wet than dry by 100 weeks. These findings, if confirmed, may help guide management of ME in CRVO.

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