What Happens to Diabetic Retinopathy Severity Scores With Less Aggressive Treatment? A Post Hoc Analysis of the RISE and RIDE Open Label Extension Study

- Roger A. Goldberg, MD, , MBA
- Lauren Hill, BA, MS
- Tatiana Ecoiffier Davis, PhD
- Ivaylo Stoilov, MD

OBJECTIVE The aim of this study is to understand how patients' diabetic retinopathy severity scores respond to less-than-monthly ranibizumab treatment and to identify factors that may predict patient outcomes.

PURPOSE To characterize what happens to diabetic retinopathy severity score (DRSS) when less-than-monthly treatment is initiated after a period of monthly ranibizumab. The present analysis compares patients from the RISE/RIDE (NCT00473330/NCT00473382) open-label extension (OLE) who experienced DRSS stability or improvement over the course of OLE, compared with those who did not.

METHODS The 500 patients from the RISE and RIDE phase 3 clinical trials who enrolled in OLE and received ranibizumab (RBZ) 0.5 mg as-needed (PRN) treatment were analyzed through month (M)48. PRN criteria during OLE included diabetic macular edema (DME) on ocular coherence tomography (OCT) and best-corrected visual acuity (BCVA) worsening of ≥ 5 ETDRS letters from M36. DRSS response was defined as ≥ 0 step improvement from M36 to M48 (stable/improved) or ≥ 1 step DRSS worsening from M36 to M48 (worsening). The analysis examined the association between baseline/M36 ocular and demographic characteristics and DRSS response as well as injection frequency in OLE (M36-M48).

RESULTS Of the 500 patients from RISE/RIDE OLE, 367 had evaluable DRSS data at M36 and M48. Of these 367 patients, 72% (263/367) improved or maintained their DRSS from M36 to

M48 while receiving PRN treatment. On average, patients who improved or maintained their DRSS from M36-48 received 4.4 (95%CI, 3.9, 4.9) (median: 4) injections during the PRN period, while those whose DRSS worsened received 2.3 (95%CI, 1.8, 2.9) (median: 1) injections. M36 BCVA and CFT were comparable for those whose DRSS worsened during OLE and those whose DRSS remained stable or improved. Randomization to ranibizumab 0.3 mg, 0.5 mg, or "sham/crossover" (12 monthly ranibizumab 0.5 mg injections) prior to OLE showed similar treatment effects on DRSS during OLE. Of the 198 patients whose DRSS improved 1 or more steps from baseline to M36, 108 (55%) had stable/improved DRSS with less-than-monthly treatment during OLE.

CONCLUSION Most patients were able to maintain their DRSS with less-than-monthly injections. Those whose DRSS stabilized or improved received a median of 4 injections over the course of 1 year, compared to 1 in those whose DRSS worsened, suggesting that some minimum treatment may be necessary to maintain DRSS stability. BCVA and CFT at the time PRN therapy was initiated were not indicative of DRSS outcomes.

HUMAN RESEARCH Yes: Approved by institutional review board

Sustained Diabetic Retinopathy Severity Improvement With Intravitreal Aflibercept in Diabetic Macular Edema: Post Hoc Analysis of VISTA and VIVID

- Rishi P. Singh, MD

OBJECTIVE To characterize sustained Diabetic Retinopathy Severity Scale score improvement in diabetic macular edema patients treated with intravitreal aflibercept injection or macular laser photocoagulation.

PURPOSE To characterize sustained Diabetic Retinopathy Severity Scale (DRSS) score improvement in patients with diabetic macular edema (DME) who were treated with intravitreal aflibercept injection (IAI) or macular laser photocoagulation (laser control) in the VISTA and VIVID trials.

METHODS VISTA and VIVID randomized 862 patients with DME to IAI 2 mg every 4 weeks (2q4; n=290), IAI 2 mg every 8 weeks following 5 initial monthly doses (2q8; n=286), or laser photocoagulation (laser control; n=286). In this post hoc analysis, hazard ratios (HR) comparing the relative risk of achieving a sustained (2 or more consecutive DRSS evaluation visits) ≥2-step DRSS improvement with IAI and laser control were estimated using Cox proportional hazards analysis. Time to event and cumulative incidences of improvements were calculated using Kaplan-Meier analysis; For patients who received rescue treatment, data were censored from the time of rescue treatment.

RESULTS Patients treated with IAI were significantly more likely to achieve ≥2-step DRSS improvement than those treated with laser control (HR [95% confidence interval [CI]]: 2q4, 2.735 [1.878, 3.985]; 2q8, 2.556 [1.751, 3.732]; $p<0.0001$ for both). Patients treated with IAI were also significantly more likely to achieve sustained ≥2-step DRSS improvement than those

treated with laser control (HR [95% CI]: 2q4, 3.820 [2.242–6.504]; 2q8, 3.674 [2.158–6.258]; p<0.0001 for both). The cumulative incidences of first sustained ≥2-step DRSS improvement from baseline through week 100 were significantly higher with IAI 2q4 and IAI 2q8 versus laser (40.0% and 42.8% versus 15.5%, respectively; p<0.0001 for both). The estimated 25th percentile of time [95% CI] to achieve first sustained ≥2-step DRSS improvement was 369 [365, 526] days with IAI 2q4, 499 [367, 512] days with IAI 2q8, and not achieved over the entire study with laser control.

CONCLUSION These results suggest that greater proportions of patients treated with IAI achieve a sustained ≥2-step DRSS improvement compared to those treated with laser control. The time to sustained improvement was hastened with a greater frequency of IAI treatment.

HUMAN RESEARCH Yes: Approved by institutional review board

Suprachoroidal CLS-TA Plus Aflibercept Compared With Aflibercept Monotherapy for Diabetic Macular Edema (DME): Results of a Phase 2 Trial

- Michael S. Ip, MD

OBJECTIVE To present the results of a Phase 2 trial, which evaluated suprachoroidal CLS-TA in combination with aflibercept compared to aflibercept monotherapy for the treatment of DME.

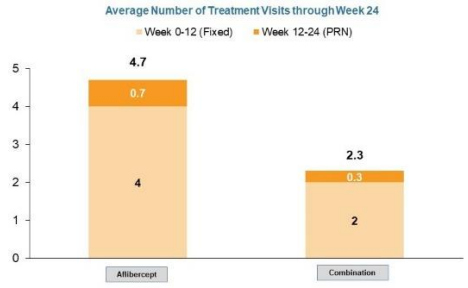
PURPOSE The Phase 2 trial was a 24-week study evaluating suprachoroidal (SC) injections of CLS-TA plus IVT aflibercept given every 12 weeks versus aflibercept alone given every 4 weeks up to 12 weeks. SC injections target chorioretinal tissues more directly than intravitreal injections while limiting exposure to the anterior chamber, thereby offering potential safety, efficacy, and durability advantages.

METHODS TYBEE was a prospective, randomized, controlled, double-masked study in treatment-naïve DME subjects randomized 1:1 to CLS-TA + aflibercept combination or aflibercept monotherapy. Inclusion was based on BCVA 20-70 letters read and CST > 300 µm. Subjects in the combination arm (n=36) received CLS-TA + aflibercept at Baseline and W12. Subjects in the monotherapy arm (n=35) received aflibercept at Baseline, W 4, W8, and W12. All subjects were eligible to receive aflibercept as needed (PRN) at W16 and W20 per re-treatment criteria: presence of macular edema (CST ≥ 340 µm); decrease in BCVA (≥6 letters) from previous visit or decrease in BCVA (≥10 letters) from best measurement.

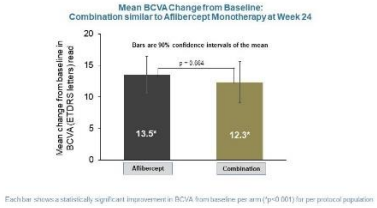
RESULTS The primary endpoint, mean change in BCVA from baseline at W24 (+12.3 & +13.5 letters in the combination and monotherapy per protocol arms) was not statistically different

(p=.288). Eyes in the combination arm received an average of 2.3 treatments: 2 fixed combination treatments at baseline & W12 and a mean 0.3 PRN aflibercept treatments at W16 & W20. Eyes in the aflibercept monotherapy arm received an average of 4.7 treatments: 4 fixed monthly aflibercept treatments from baseline to W12 and a mean 0.7 PRN aflibercept treatments at W16 and W20. Mean CST change was similar between the arms at W24 (combination: -208 µm, aflibercept: -177 µm; p>0.05). No treatment-related serious AEs were observed. Elevated IOP was observed in 8.3% in the combination arm and 2.9% in the monotherapy arm. Cataract was observed in 5.6% of the combination arm and 2.9% of the aflibercept arm.

CONCLUSION Combination suprachoroidal CLS-TA plus IVT aflibercept given every 12 weeks for up to 24 weeks showed similar efficacy outcomes as aflibercept monotherapy given monthly for up to 12 weeks and assesessed up to 24 weeks in DME. The combination arm was associated with a reduction in treatment burden throughout 24-weeks, as well as during the PRN phase. Ocular adverse events were low for both arms.



SC injections of CLS-TA in combination with IVT aflibercept was compared to IVT aflibercept monotherapy for the treatment of DME in a 24-week Phase 2 trial. Combination arm eyes received an average of 2.3 treatments whereas aflibercept monotherapy arm eyes received an average of 4.7 treatments. Mean PRN treatments in the combination arm was 0.3 PRN and 0.7 in the aflibercept monotherapy arm.



SC injections of CLS-TA in combination with IVT aflibercept was compared to IVT aflibercept monotherapy for the treatment of DME in a 24-week Phase 2 trial. Mean change from baseline in BCVA at Week 24 was similar between DME subjects in the combination arm as subjects in the aflibercept monotherapy arm.

HUMAN RESEARCH Yes: Approved by institutional review board

Randomized Trial of Initiating Therapy With Aflibercept, Laser, or Observation for Eyes With Good Vision and Center-Involved Diabetic Macular Edema

- Jennifer K. Sun, MD
- Carl W. Baker, MD

OBJECTIVE What is the best treatment strategy for eyes with center-involved DME and good vision: start with anti-VEGF therapy or start with observation or laser and initiate anti-VEGF therapy if vision worsens?

PURPOSE For eyes with center-involved diabetic macular edema (CI-DME) and visual acuity (VA) loss (20/32 or worse), anti-VEGF therapy provides superior VA outcomes compared with laser or observation. However, for eyes with CI-DME and good VA (>20/25), it is unknown whether the best approach is prompt anti-VEGF therapy vs initiating with laser or observation and treating with anti-VEGF only if VA worsens.

METHODS Randomized trial of 702 eyes with VA of 20/25 or better and CI-DME confirmed on optical coherence tomography (OCT). Participants were adults with type 1 or 2 diabetes. One eye per participant was randomized to initial treatment with 2-mg intravitreous aflibercept, focal/grid laser, or observation. Eyes randomized to laser or observation received aflibercept during follow-up if VA worsened by 5-9 letters (1-2 lines) at two consecutive visits or by 10 or more letters (2 or more lines) at any visit. Once aflibercept was initiated, the retreatment algorithm for aflibercept therapy was the same across all three groups. Best corrected VA and OCT scans were obtained by masked technicians.

RESULTS The primary outcome is the percentage of eyes losing 5 or more letters (one line) of VA from baseline at 2 years. Additional outcomes include mean change in VA, mean change in OCT central subfield thickness, and 2-step change in diabetic retinopathy severity level. The results of this clinical trial will be presented; however because of the potential public health

impact of these results, the DRCR Network requests that the results be made available only after the primary manuscript is published, which is expected to occur prior to the 2019 ASRS annual meeting.

CONCLUSION Conclusions will follow from the results presented.

HUMAN RESEARCH Yes: Approved by institutional review board

Treatment of Moderately Severe to Severe Nonproliferative Diabetic Retinopathy With Intravitreal Aflibercept Injection: 52-Week Results From PANORAMA

- W. Lloyd Clark, MD

OBJECTIVE To investigate efficacy and safety of treatment with IAI vs sham in patients with moderately severe to severe nonproliferative diabetic retinopathy (NPDR) and without DME, enrolled in PANORAMA.

PURPOSE In VISTA/VIVID, more patients with diabetic macular edema (DME) who received intravitreal aflibercept injection (IAI) had a ≥2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) score vs laser photocoagulation. PANORAMA investigated the efficacy and safety of IAI versus sham in patients with moderately severe to severe nonproliferative diabetic retinopathy (NPDR) without DME.

METHODS PANORAMA is a phase 3, double-masked, randomized study (ClinicalTrials.gov NCT02718326). Patients ≥18 yrs old with diabetes mellitus type 1/2 were eligible to enroll if they had moderately severe to severe NPDR (DRSS levels 47 or 53), absence of center-involved - DME, and baseline best-corrected visual acuity (BCVA) of ≥69 letters (approximately ≥20/40) in study eye. 402 patients were randomized to receive IAI 2 mg every 8 weeks (wk) following 5 monthly doses (2q8, n=134), IAI 2 mg every 16 wks following 3 monthly doses and 1 8-wk interval (2q16, n=135), or sham (n=133) through wk 52. The primary endpoint was proportion of patients with ≥2-step improvement in DRSS score at wk 52.

RESULTS Overall, 44.0% of patients were female, with a mean (SD) age of 55.7 (10.5) years and a mean (SD) BCVA of 82.4 (6.0) letters at baseline. IAI 2q8 and IAI 2q16 patients received a mean of 8.6 and 5.5 injections through week 52, respectively. The proportion of patients with a

≥2-step improvement in DRSS score was significantly greater with IAI 2q8 and IAI 2q16 versus sham at week 52 (80% and 65% versus 15%, P<0.0001 for both). The proportion of patients who developed vision-threatening complications (proliferative diabetic retinopathy/anterior segment neovascularization) was significantly lower with IAI 2q8 and IAI 2q16 compared with sham (3% and 4% versus 20%, P<0.001 for both). The incidence of center-involved DME was also significantly lower with IAI 2q8 and IAI 2q16 compared with sham (8% and 7% versus 26%, P<0.001 for both). No new safety signals were identified with IAI.

CONCLUSION These findings suggest that treatment with IAI may reverse disease progression in patients diagnosed with moderately severe to severe NPDR.

HUMAN RESEARCH Yes: Approved by institutional review board

Quantification of Capillary Nonperfusion in Diabetic Retinopathy Using Ultra-widefield Optical Coherence Tomography Angiography

- Kasra Rezaei, M.D.
- Steven S. Saraf, MD
- Qinqin Zhang
- FuPeng Wang, PhD
- Wang Ruikang, PhD

OBJECTIVE The UW-OCTA can be used to quantify capillary nonperfusion in patients with different grades of diabeticretinopathy (DR).

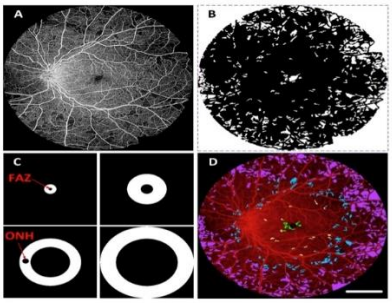
PURPOSE To quantify and compare retinal capillary nonperfusion in patients with different grades of diabetic retinopathy (DR) using ultra-widefield optical coherence tomography angiography (UW-OCTA). To assess the performance of capillary nonperfusion in varying field of view (FOV) sectors in determining the clinical severity of DR.

METHODS UW-OCTA images were obtained from 45 patients . Eyes were classified clinically into three groups: diabetes without retinopathy (DWR), NPDR and PDR. Scans of 21 x 21 mm (100 degree FOV) were constructed by montaging five individual 12 x 12 mm scans. The ratio of nonperfusion (RNP) was expressed as the percent area of capillary nonperfusion within the total FOV. RNP was calculated for the entire 100 degree image. In addition, concentric sectors of FOV encompassing 10 (excluding the foveal avascular zone), 10-30, 30-50 and 50-100 degrees were similarly assessed.

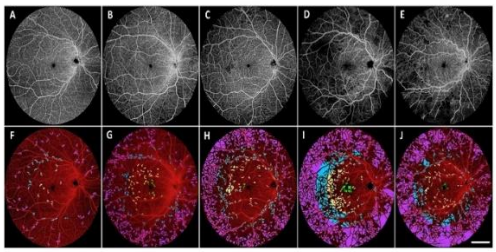
RESULTS The ultra-widefield image (FOV 100) showed a significant difference in RNP between all three severities of DR (DWR: 11.1 ± 4.2%, NPDR: 18.3 ± 7.1%, PDR: 29.2 ± 16.2%, $p<0.05$).

Within each DR group, FOV 50-100 measured significantly higher RNP than FOV 10, FOV 10-30, FOV 30-50, and FOV 100 ($p<0.01$). There was also a significantly higher RNP in the FOV 50-100 region in NPDR eyes compared to DWR eyes ($p<0.001$) and PDR eyes compared to NPDR eyes ($p<0.01$). FOV 50-100 gave the best optimal sensitivity and specificity to distinguish between NPDR and DWR (84% and 94%, AUC=0.944) and PDR from NPDR (90% and 79%, AUC=0.879) compared to all other FOV sectors, including FOV 100.

CONCLUSION Our findings suggest capillary nonperfusion is higher in more severe grades of DR. RNP is on average higher in the retinal periphery, where it also has better diagnostic utility in determining DR severity.



Ultra-widefield OCTA image of the whole retina layer in gray (A). The nonperfusion area map of the OCTA image (B). Analysis of the OCTA image to delineate areas of nonperfusion within concentric sectors centered on the fovea, including 10 , 10-30, 30-50 and 50-100 degrees (C). The areas of nonperfusion in the concentric FOV zones are coded with green, yellow, blue and purple colors, respectively (D).



Representative ultra-widefield OCTA images with different severities of diabetic retinopathy.DWR (A), mild NPDR (B), moderate NPDR (C), severe NPDR (D) and PDR (E). The images (F-J) were analyzed as described in Figure 1. Bar = 4 mm. DWR: diabetes without retinopathy, NPDR: nonproliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy

HUMAN RESEARCH Yes: Approved by institutional review board

Widefield Fluorescein Angiographic-Guided Aflibercept (WFFAGA) Monotherapy for Proliferative Diabetic Retinopathy (PDR)

- Dennis M. Marcus, MD
- Robert A. Lalane, MD
- Harinderjit Singh, MD
- Davis C. Starnes, BS
- Caitlen Taylor, Bachelor of Science in Biology
- Lindsay Williamson, BSBA
- Rachel Levy
- Priscilla Rex
- Venkatkrish Manohar Kasetty, BS

OBJECTIVE To assess injection burden, visual, anatomic and safety outcomes in PDR eyes after aflibercept monotherapy using wide-field Optos fluorescein angiographic guided therapy.

PURPOSE The DRCR S and Clarity trials established anti-VEGF therapy as an alternative to PRP for PDR eyes not requiring vitrectomy. After baseline anti-VEGF, these trials used clinical examination as the primary determinant of neovascularization status and need for additional dosing. WFFAGA monotherapy may allow for better neovascularization and PDR assessment resulting in optimal dosing.

METHODS The LASERLESS trial enrolled 40 study eyes with PDR-related vitreous hemorrhage and is evaluating endolaserless vitrectomy with aflibercept monotherapy in a 3-year study. We retrospectively, evaluated 17 non-study fellow LASERLESS trial PDR eyes not requiring vitrectomy that received WFFAGA monotherapy. Fellow eyes, in the trial, prospectively underwent monthly BCVA, OCT, and ocular examinations with quarterly WFFA. After baseline

aflibercept, PRN aflibercept dosing was administered for PDR progression based on clinical examination and WFFA evaluation.

RESULTS We report 52-week follow-up results in 17 eyes from 17 adult diabetics (9 female; average age 55; 6 Caucasians, 11 African Americans; 15 NIDDM; 15 phakic, 2 pseudophakic) with PDR. At baseline, average visual acuity (VA) was 76 letters (20/32) and average OCT CSF was 279um. At baseline, all eyes demonstrated active PDR and 4 eyes demonstrated diabetic macular edema (DME) (OCT CSF>300um). At baseline, 9, 8 and 6 eyes demonstrated PDR with high risk characteristics (HRC), PDR without HRC, and mild vitreous hemorrhage or preretinal hemorrhage, respectively. Through 52 weeks, 17 eyes received an average of 5.7 injections. At 52 weeks, average VA was 80 letters (20/25) with average gain of 5 letters. Average OCT CSF was 261um with average thinning of 18um. At 52 weeks, 0 eyes demonstrated OCT CSF>300um. Ocular adverse events through 52 weeks included 3 eyes with progression or new VH, 1 with new DME, 1 with 30 letter loss and 0 needing vitrectomy or PRP for PDR complications.

CONCLUSION Optos wide-field fluorescein angiographic monitoring of neovascularization helps guide clinicians to optimally assess PDR status and may lead to optimal aflibercept monotherapy dosing with excellent visual acuity, OCT and safety outcomes for PDR eyes, while avoiding PRP-related side effects.

HUMAN RESEARCH Yes: Approved by institutional review board

Intravitreal Aflibercept for Retinal Nonperfusion in Proliferative Diabetic Retinopathy: One-Year Primary Outcomes From the Randomized RECOVERY Trial

- Charles C. Wykoff, MD, PhD
- Muneeswar Nittala, MS
- Brenda Zhou, BS
- Swetha Velaga, BS
- Alexander Michael Rusakevich, BA
- Michael S. Ip, MD
- Srinivas Reddy Sadda, MD

OBJECTIVE To evaluate the impact of intravitreal aflibercept on retinal non-perfusion in eyes with proliferative diabetic retinopathy with no macular edema.

PURPOSE Diabetic retinopathy (DR) is characterized by progressive retinal vascular damage manifest as retinal non-perfusion (RNP). Large prospective series have reported that vascular endothelial growth factor inhibition can slow RNP development among eyes with diabetic macular edema (DME). This study evaluated the impact of intravitreal aflibercept on RNP in eyes with proliferative DR (PDR) without DME.

METHODS Forty eyes with PDR & substantial RNP (>20-disc areas) with best corrected visual acuity (BCVA) 20/400 or better without DME were randomized to receive intravitreal 2 mg aflibercept every 4 weeks (Monthly) or every 12 weeks (Quarterly) (RECOVERY, NCT02863354). All subjects underwent ultra-wide field (UWF) fluorescence angiography at baseline and 1 year. After stereographic projection, RNP area was delineated at an external reading center that was blinded to patient-specific data, including randomized arm. The primary outcome was change in

total area of RNP (in mm^2) from baseline to 1 year; secondary outcomes included ischemic index (ISI) and change in DR severity scale (DRSS) scores.

RESULTS At baseline, mean age was 48 years & mean BCVA was 20/32. Through 1 year, the Monthly & Quarterly cohorts received 10.9 & 3.9 mean aflibercept injections & DRSS scores improved ≥2 steps in 73.7% & 66.7% respectively. Among all patients, the ISI increased significantly through 1 year (26% ± 4.7% to 32% ± 4.2%; p=0.003) while mean total area of RNP increased numerically compared to baseline (235 ± 50.8 mm^2 to 266 ± 35.8 mm^2; p=0.18). While most eyes demonstrated increased areas of RNP longitudinally, rare eyes did demonstrate localized areas of apparent reperfusion of non-perfused retina. All RNP outcomes favored monthly-dosing, with more substantial RNP increases observed with quarterly dosing (p=0.049). Among the Quarterly cohort, mean total RNP increased from 207 to 268 mm^2 (p=0.012) & ISI increased from 23.4% to 31.1% (p=0.009). Among the Monthly cohort, mean total RNP remained stable, and an ISI increase from 28.2% to 32.7% was not statistically significant.

CONCLUSION RECOVERY found no evidence of wide-spread retinal reperfusion with aflibercept dosing in PDR eyes. To the contrary, significant, progressive worsening of RNP was observed. Nevertheless, aflibercept did impact RNP in a dose-dependent fashion; eyes dosed monthly demonstrated less RNP accumulation while receiving nearly 3 times the cumulative aflibercept dose compared to eyes dosed quarterly.

HUMAN RESEARCH Yes: Approved by institutional review board