Prospective Trial Comparing Ranibizumab Monthly to Treat and Extend With and Without Angiography-Guided Laser for DME: TREX-DME 1 Year Outcomes

- John F. Payne, MD
- Charles C. Wykoff, MD, PhD
- W. Lloyd Clark, MD
- Beau Bruce
- David S. Boyer, MD
- David M. Brown, MD

OBJECTIVE Patients with center-involving DME with visual loss treated with this treat & extend strategy are likely to experience similar visual and anatomic benefits at 1 year compared to monthly dosing.

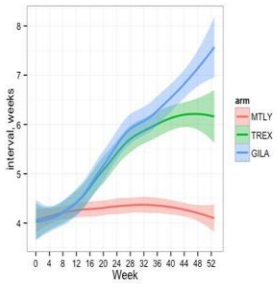
PURPOSE To compare monthly dosing to a treat & extend algorithm using 0.3 mg ranibizumab with and without angiography-guided macular laser photocoagulation for center-involving diabetic macular edema (DME).

METHODS This is a multicenter, prospective, randomized clinical trial of 150 eyes randomized 1:2:2 into one of three cohorts: Monthly (n=30), Treat and Extend without macular laser photocoagulation (TREX; n=60), and treat and extend with angiography-Guided macular Laser photocoagulation (GILA; n=60). In the TREX and GILA cohorts, eyes underwent 4 monthly injections of 0.3 mg ranibizumab followed by a treat & extend algorithm based on disease activity. Eyes in the GILA cohort also received angiography-guided macular laser photocoagulation at month 1 and again every 3 months if microaneurysm-associated leakage was present.

RESULTS Baseline demographics, including diabetes duration, insulin usage, body-mass index, retinopathy severity, best corrected visual acuity (BCVA), and central retinal thickness (CRT), were well balanced between the cohorts. 136 eyes (91%) completed the 1 year end-point visit. At 1 year, BCVA improved by 8.6, 9.6, 9.3 letters in the Monthly, TREX and GILA cohorts, respectively (p=0.8). Likewise, CRT improved by 122, 146 and 165 μm, in the Monthly, TREX, GILA cohorts (p=0.47). The mean number of laser treatments in the GILA cohort was 2.8 (range=1-4). Treatment burden, defined as the number of injections through 1 year, was reduced in TREX (10.7) and GILA (10.2) compared to the Monthly cohort (13.1, p<0.001). There was a trend towards statistical significance in the mean maximum interval at month 12 between the TREX and GILA cohorts (8.1 vs 9.1 weeks, respectively; p=0.105). There were no cases of endophthalmitis; the incidence of serious adverse events from vascular causes was 3.3%.

CONCLUSION In this prospective, randomized trial involving 150 eyes, treat & extend dosing of 0.3 mg ranibizumab with and without angiography-guided macular laser photocoagulation significantly decreased treatment burden while providing similar visual and anatomic outcomes compared to monthly dosing at 1 year.

TAKE HOME MESSAGE This prospective trial found that treat & extend dosing of ranibizumab with & without macular laser reduced treatment burden and provided similar anatomic/visual outcomes compared to monthly dosing.



HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

Vision Gains With Ranibizumab in Eyes With Diabetic Macular Edema and Retinal Nonperfusion at the Macula

- Rahul K. Reddy, MD, MHS
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- Avanti A. Ghanekar, OD
- Na Lu, PhD
- Carlos Quezada, MD

OBJECTIVE To describe the relationship between retinal nonperfusion (RNP) at the macula and visual outcomes in patients with diabetic macular edema (DME) treated with ranibizumab (RBZ) or sham in RIDE/RISE.

PURPOSE Previous analysis of RIDE/RISE data suggested that high levels of intraocular VEGF contribute to RNP progression in patients with DME. The present analysis examines the relationship between baseline (BL) RNP status, changes in RNP status, and best-corrected visual acuity (BCVA) outcomes in patients with DME treated with RBZ or sham in the phase 3 RIDE/RISE trials.

METHODS This was a retrospective subanalysis of data from 2 randomized, controlled phase 3 clinical trials (RIDE, RISE) that evaluated the safety and efficacy of RBZ 0.3 mg or 0.5 mg vs sham for the treatment of DME. Presence and area of RNP were evaluated in study eyes (intent-to-treat population) with valid BCVA and fluorescein angiogram data (pooled RBZ 0.3 mg and 0.5 mg, N=438; sham, N=228). RNP area was calculated as total disc areas (DA) of capillary loss on subfields of the ETDRS grid in field #2 (macula) of 7-field fundus photographs. Changes from BL to Month (M) 12 and M24 in RNP status (worsening, no change, or improvement) and BCVA change by RNP status were evaluated.

RESULTS BL RNP was present in 26.9% (n=118) of RBZ- and 26.3% (n=60) of sham-treated eyes. The proportion of RBZ-treated eyes with RNP remained stable through M24, but increased in sham-treated eyes (RBZ vs sham, M12: 20.1% vs 35.5%, M24: 25.2% vs 43.1%). At M24, RNP status worsened from BL less in RBZ- (15.6%) vs sham-treated eyes (37.6%). Eyes with RNP had lower mean BL BCVA in both treatment arms (present vs absent, RBZ: 53.7 vs 58.0 letters; sham: 56.0 vs 57.9 letters). In the RBZ arm, mean BCVA gain from BL at M12 and M24 was higher in study eyes with vs without RNP (M12, +14.6 vs +10.3 letters, P=0.0004; M24, +16.0 vs +12.1 letters, P=0.008); this was not observed in the sham arm (M12, +3.4 vs +1.8 letters, P=0.43; M24, +4.0 vs +3.5 letters, P=0.86). Change in BCVA from BL was not significantly associated with RNP status change (improved, stable, or worse) from BL in RBZ-treated eyes at M12 (11.2, 10.9, and 13.4, respectively; P=0.38) or M24 (14.3, 13.3, and 13.8, respectively; P=0.90).

CONCLUSION RBZ-treated eyes from DME patients with BL macular RNP had higher vision gains vs eyes without BL RNP. In these eyes, the visual outcomes did not correlate significantly with changes in RNP status (improved, stable or worse). In conclusion, DME patients with RNP at BL may achieve clinically meaningful vision gains with RBZ therapy.

TAKE HOME MESSAGE Data from the RIDE/RISE studies suggest that patients with diabetic macular edema with retinal nonperfusion at the macula may achieve clinically meaningful vision gains with ranibizumab therapy.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

Ranibizumab Induces Regression of Diabetic Retinopathy (DR), Prevents Retinal Nonperfusion in Patients at High Risk of Conversion to Proliferative DR

- Charles C. Wykoff, MD, PhD
- Carlos Quezada, MD
- Lauren Hill, BA, MS
- Zdenka Haskova, MD, PhD

OBJECTIVE To evaluate the effect of ranibizumab (RBZ) on DR and retinal nonperfusion (RNP) in patients with diabetic macular edema (DME) and moderately severe or severe nonproliferative DR (NPDR).

PURPOSE Rates of RNP increase over time in patients with DR/DME, and DR can worsen from NPDR to proliferative DR (PDR) as measured by levels on the Early Treatment Diabetic Retinopathy Study (ETDRS) DR severity scale (DRSS). The effect of RBZ therapy on DR and RNP in patients with DME at high risk of worsening to PDR was evaluated in this analysis of the randomized phase 3 RIDE/RISE trials.

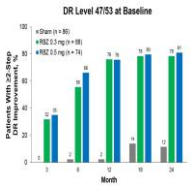
METHODS In the RIDE/RISE core studies, patients with DME (N=759) received monthly RBZ (0.3 mg or 0.5 mg) or sham injections for 24 months. DR severity was graded on the ETDRS-DRSS by masked evaluators at the University of Wisconsin Fundus Photo Reading Center using 7-field fundus photographs taken at baseline and months 3, 6, 12, 18, and 24; RNP was assessed by fluorescein angiography at the same time points. DR

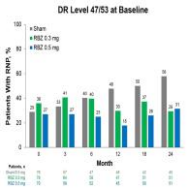
and RNP outcomes by baseline DR severity were retrospectively analyzed from prospectively collected data.

RESULTS At baseline, 33% of patients in RIDE/RISE had moderately severe or severe NPDR (ETDRS-DRSS level 47/53). Among these patients, who were well distributed among the treatment arms, rates of ≥2-step DR improvement were significantly greater with RBZ vs sham at months 12 (76.1%, 75.7%, and 2.3% for RBZ 0.3 mg, RBZ 0.5 mg, and sham, respectively, $P<0.0001$) and 24 (78.4%, 81.1%, and 11.6%, respectively, $P<0.0001$); these improvements were independent of the presence or absence of RNP at baseline. The proportion of patients with RNP at baseline in the DRSS level 47/53 patients was 35.9%, 27.1% and 28.9% for RBZ 0.3 mg, RBZ 0.5 mg and sham, respectively. Subsequently, the proportion of patients with RNP remained stable over time in both RBZ arms while increasing in the sham arm, consistent with the data for the overall RIDE/RISE population; at month 24, RNP was identified in 29.4%, 31.4%, and 57.8% of patients with baseline DR 47/53 for RBZ 0.3 mg, RBZ 0.5 mg, and sham, respectively ($P=0.007$).

CONCLUSION RBZ treatment resulted in statistically significant and clinically meaningful regression of DR to milder severity in >75% of patients at high risk of progression to PDR. RNP remained stable over time in RBZ-treated patients whereas in sham-treated patients rates of RNP increased. RNP analyses support a protective role of RBZ on the development of RNP in diabetic retinopathy.

TAKE HOME MESSAGE Ranibizumab led to stabilization of retinal nonperfusion and improvement in diabetic retinopathy (DR) to milder stages of disease among patients with moderately severe/severe nonproliferative DR.





HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

Optical Coherence Tomography Angiography of Diabetic Macular Edema and its Association With Anti-VEGF Treatment Response

- Young Hee Yoon, MD
- Junyeop Lee, MD, PhD
- Byung Gil Moon, MD
- Ah Ran Cho, MD

OBJECTIVE In DME eyes, a greater damage in deep capillary plexus assessed by OCT angiography and the corresponding OPL disruption in SD-OCT were well correlated with poor-responsiveness to anti-VEGF treatments.

PURPOSE Unlike fluorescein angiography (FA), optical coherence tomography angiography (OCTA) enables closer observation of both superficial and deep retinal capillary layers. We have investigated structural integrity of two different layers in diabetic macular edema (DME) patients and its association with the treatment response to anti-VEGF agents.

METHODS We have conducted a retrospective case-control study on DME patients, using OCTA (AngioVue, 3 x 3 mm). Eyes were divided into anti-VEGF responders and poor-responders. Poor-responder was defined as reduction of less than 50μm, or increase in CRT after 3 consecutive monthly anti-VEGF injections. The *en face* images of superficial capillary plexus (SCP) and deep capillary plexus (DCP) were obtained from each eye. We measured vascular density and foveal avascular zone (FAZ) area, counted the number of microaneurysms in each layer, and compared with FA findings. In addition, spectral domain OCT (SD-OCT) images were compared with OCTA findings.

RESULTS Eighty-three eyes with DME were included along with 20 fellow eyes without DME. Thirty-two eyes were anti-VEGF responders and 51 eyes poor-responders. Compared to the non-DME eyes, the DME eyes presented less vascular density and larger FAZ area in DCP, and more microaneurysms in both layers. While there was no significant difference in SCP between anti-VEGF responders and poor-responders, poor-responders tended to show a greater damage in DCP; much less vascular density (10.62 ± 4.66 vs. 17.39 ± 3.98 %, *p=0.000*), larger FAZ area (2.92 ± 1.14 vs. 2.01 ± 1.50 fold, ratio of deep to superficial FAZ, *p=0.008*), and more microaneurysms in DCP (8.9 ± 4.1 vs. 3.9 ± 1.2, *p=0.000*). Whereas 49 among 51 poor-responders presented a marked disruption of synaptic OPL, only 2 among 32 anti-VEGF responders did (*p=0.000*). The topographic location of disrupted OPL in SD-OCT was exactly matched with non-flow area of DCP in OCTA.

CONCLUSION Compared to anti-VEGF responding DME eyes, poor-responders showed a significant damage in the integrity of DCP, but not in the integrity of SCP. The degree of OPL disruption in SD-OCT was well corresponded to the extent of DCP loss among DME eyes. The extent of DCP loss and the corresponding OPL disruption could be useful predictors for the responsiveness to anti-VEGF treatment.

TAKE HOME MESSAGE In DME eyes, a greater damage in deep capillary plexus assessed by OCT angiography and the corresponding OPL disruption in SD-OCT were well correlated with poor-responsiveness to anti-VEGF treatments.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

Cost-Effectiveness of Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Analysis from a DRCR.net Comparative Effectiveness Trial

- Neil M. Bressler, MD

OBJECTIVE To compare the cost-effectiveness of aflibercept, bevacizumab, or ranibizumab for treatment of diabetic macular edema.

PURPOSE Randomized clinical trial results comparing anti-VEGF agents for DME found at one year, aflibercept (2.0-mg) achieved better visual outcomes than bevacizumab (1.25-mg) or ranibizumab (0.3-mg) for patients with worse starting visual acuity. However, aflibercept and ranibizumab, respectively, are approximately 31 and 20 times as expensive as bevacizumab, warranting this cost-effectiveness analysis.

METHODS Analysis of efficacy, safety, and resource utilization from a Diabetic Retinopathy Clinical Research Network randomized trial was used to compare the cost-effectiveness of aflibercept, bevacizumab repackaged into single use vials, and ranibizumab. The incremental cost-effectiveness ratios (ICERs) of these three agents were assessed for all trial participants and for subgroups of eyes with better baseline vision (approximate Snellen equivalent 20/32 to 20/40) and worse baseline vision (approximate Snellen equivalent 20/50 or worse). One-year trial data were used to calculate cost-effectiveness over one year; mathematical modeling then was used to project 10-year cost-effectiveness results.

RESULTS Over the 1-year study period, the ICERs of aflibercept and ranibizumab compared to bevacizumab were $1,110,000 per quality-adjusted life-year (QALY) and $1,730,000/QALY; over 10 years, these ICERs were $349,000/QALY and $603,000/QALY irrespective of baseline vision. Compared with ranibizumab,

aflibercept's ICER was $648,000/QALY at one year and $203,000/QALY at ten years. For the subgroup with worse baseline visual acuity, the 10-year ICERs of aflibercept and ranibizumab compared to bevacizumab were $287,000/QALY and $817,000/QALY, respectively. To become cost-effective over a 10-year horizon at a commonly accepted threshold of $100,000/QALY, the costs of aflibercept and ranibizumab, respectively, would need to decline by 69% and 80%; for the subgroup with worse baseline visual acuity, the costs would need to decline by 62% and 84%, respectively.

CONCLUSION At current prices, aflibercept 2.0-mg and ranibizumab 0.3-mg would need to decline by 69% and 80%, respectively, over a 10-year horizon to reach a commonly accepted threshold of $100,000/QALY. These results highlight the challenges that emerge when safety and efficacy results are at odds with cost-effectiveness results.

TAKE HOME MESSAGE Aflibercept and ranibizumab are not cost-effective relative to bevacizumab for treating DME, highlighting challenges when safety and efficacy results are at odds with cost-effectiveness results.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

An Exploratory Analysis of Persistent Macular Thickening Following Intravitreous Ranibizumab for Center-Involved DME With Vision Impairment

- Susan B. Bressler, MD

OBJECTIVE Explore 3-year course of DME in eyes with persistent DME following q4week ranibizumab through 24 weeks, subsequently managed with intravitreous ranibizumab and focal/grid laser as needed per protocol.

PURPOSE To assess subsequent vision and anatomic outcomes through 3 years among eyes with center-involved diabetic macular edema (CI-DME) persisting for 24 weeks despite a minimum of 4 intravitreous ranibizumab injections. Eyes continued to receive intravitreous ranibizumab and focal/grid laser as needed per protocol based on visual acuity and central subfield thickness changes.

METHODS In a post-hoc analysis of data from a protocol of the Diabetic Retinopathy Clinical Research Network's randomized trials, 117 (40%) of 296 eyes randomly assigned to ranibizumab (with either prompt or deferred laser) had persistent CI-DME (central subfield thickness [CST] ≥250 μm on time domain optical coherence tomography [OCT]) through the 24-week visit despite at least four intravitreous injections of ranibizumab. Cumulative probabilities of "chronic persistent DME" (failure to achieve CST <250 μm and at least a 10% reduction in CST from the 24-week visit on at least 2 consecutive study visits) were determined by life-table analyses.

RESULTS The cumulative probability of chronic persistent DME among eyes with persistent DME at the 24-week visit decreased from 100% at the 32-week visit to 81% (99% confidence interval [CI]:70% to 89%), 56% (99% CI: 43% to 67%), and 40% (99% CI: 27% to 52%) at the 1-, 2-, and 3-year visits, respectively. At three years, visual acuity

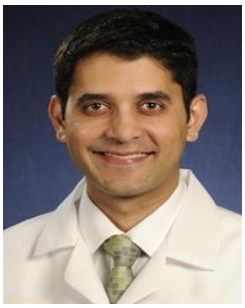
(VA) improved in persistent edema eyes both with and without chronic persistent DME through the follow-up period, respectively, by an average of 7 letters and 13 letters from baseline. Among eyes with chronic persistent edema through 3 years (N=40), 43% (99% CI: 23% to 64%) gained ≥10 letters from baseline while 13% (99% CI: 3% to 32%) lost ≥10 letters from baseline. Median VA letter score (approximate Snellen equivalent) at 3 years was 76 (20/32; 25th, 75th IQR = 80, 57[20/25, 20/80]) in eyes with chronic persistent edema through 3 years compared with 79 (20/25; 25th, 75th IQR = 83, 72 [20/20, 20/40]) in eyes without chronic persistent edema (P = 0.05).

CONCLUSION Less than half of eyes treated for DME with ranibizumab have persistent CI-DME through 24 weeks after initiating treatment. Among the 40% from this subgroup with chronic persistent CI-DME through 3 years, visual acuity appears to be worse than in the 60% without chronic persistent DME. Nevertheless, substantial (≥2 line) vision loss is likely uncommon through 3 years, even when CI-DME persists.

TAKE HOME MESSAGE 40% of eyes with CI-DME thru 24 wks have chronic CI-DME thru 3 years; while most avoid ≥2 line VA loss, using as needed ranibizumab and focal laser based on changes in vision and central thickening.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

Multiplex Vitreous Cytokine Analysis from Office-Based Vitreous Aspiration



- Vaidehi S. Dedania, MD
- Devon Ghodasra, MD
- Thomas W. Gardner, MS, MD
- Jeffrey M. Sundstrom, MD, PhD
- Cagri G. Besirli, MD, PhD
- Steven R. Cohen, MD
- Nieraj Jain, MD
- Kanishka T. Jayasundera, MD,FRANZCO
- Mark W. Johnson, MD
- Partho S. Kalyani, MD
- Rajesh C. Rao, MD
- David N. Zacks, MD, PhD
- Michael Langue, BS
- Leslie M. Niziol, MS
- Ryan J. Fante, MD
- Hakan Demirci, MD

OBJECTIVE The goals of this study were to evaluate the safety of office-based vitreous sampling and determine the utility of these samples with multiplex cytokine analysis.

PURPOSE The vitreous could serve as an important source of biomarkers for the management of vitreoretinal disease. Vitreous cytokine analysis has been limited by practical approaches to sample intraocular fluid and methods to analyze very small volume samples. This report examines the safety of office-based vitreous sampling and the feasibility of using this fluid for multiplexed cytokine analysis.

METHODS Vitreous samples were collected from office-based needle aspiration and the rate of adverse events during follow-up was reviewed. The vitreous cytokine concentrations in a subset of patients with diabetic macular edema (DME) were analyzed using a 42 plex-cytokine bead array. These results were compared to vitreous cytokine concentrations of patients with proliferative diabetic retinopathy (PDR) and

controls (macular hole, epiretinal membrane, symptomatic vitreous floaters) undergoing pars plana vitrectomy.

RESULTS An adequate volume of vitreous fluid (100-200 microliters) was obtained in 52 of 59 (88%) office-based sampling attempts. The average length of follow-up was 300 days (range, 42-926 days). There were no complications such as cataract, retinal tear or detachment, and endophthalmitis. Two patients (3%) had posterior vitreous detachments within 3 months without retinal tear. Vitreous cytokine concentrations were measured in 44 patients: 14 controls, 13 with DME, and 17 with PDR. The concentration of ADAM11, CXCL-10, IL-8, and PDGF-A were significantly higher in PDR compared to controls and DME. The concentration of IL-6 was higher in PDR compared to controls, but not compared to DME.

CONCLUSION Office-based vitreous aspiration is safe and yields high quality samples for multiplex vitreous cytokine analysis. Significant elevations of vitreous cytokines were found in PDR compared to DME and controls, including the novel finding of elevated ADAM11. As such, office-based aspiration is a safe and effective means to identify vitreous factors associated with vitreoretinal disease.

TAKE HOME MESSAGE Multiplex vitreous cytokine analysis from office-based vitreous aspiration may be a safe and effective method to study inflammatory mediators in the human vitreous.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

AKB-9778 in the Treatment of Diabetic Macular Edema: Results From the TIME-2 Study

- Arshad M. Khanani, MD

OBJECTIVE Assess the role of Tie-2 activation, via AKB-9778, in the treatment of patients with diabetic macular edema.

PURPOSE To assess the effect of subcutaneously administered AKB-9778 as monotherapy and in combination with ranibizumab (RBZ) on central subfield thickness (CST) in patients with diabetic macular edema (DME).

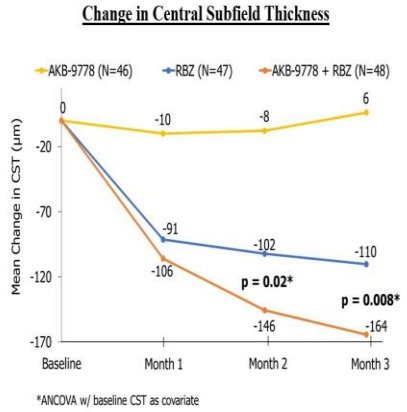
METHODS Patients (n=144) were randomized to 3 months of treatment with AKB-9778 15 mg bid + 0.3 mg RBZ q4 weeks or AKB-9778 15 mg bid + sham q4 weeks or placebo bid + 0.3 mg RBZ q4 weeks. Best-corrected visual acuity (BCVA) and CST were measured at baseline and every 4 weeks.

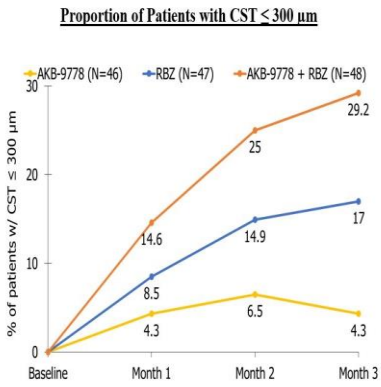
RESULTS At week 12, mean change from baseline CST was significantly greater in the combination group (-164.4±24.2 μm) compared with the ranibizumab monotherapy group (-110.4±17.2 μm; p=0.008), and was 6.2±13.0 μm in the AKB-9778 monotherapy group. Mean CST at week 12 and percent of eyes with resolved edema was 340.0±11.2 μm and 29.2% in the combination group versus 392.1±17.1 μm and 17.0% in the ranibizumab monotherapy group. Mean change from baseline BCVA (letters) was 6.3±1.3 in the combination group, 5.7±1.2 in the ranibizumab monotherapy group, and 1.5±1.2 in the AKB-9778 monotherapy group. The percentage of study eyes that gained

≥10 letters or ≥15 letters was 8.7% and 4.3% in the AKB-9778 monotherapy group, 29.8% and 17.0% in the ranibizumab monotherapy group, and 35.4% and 20.8% in the combination group.

CONCLUSION Activation of Tie2 by subcutaneous injections of AKB-9778 combined with suppression of VEGF causes a significantly greater reduction in DME than that seen with suppression of VEGF alone. Confirmatory studies are planned with longer duration of treatment in patients with diabetic eye disease as well as proof-of-concept studies in other retinopathies, including wAMD.

TAKE HOME MESSAGE Activation of Tie2 by subcutaneous injections of AKB-9778 combined with suppression of VEGF causes a significantly greater reduction in DME than that seen with suppression of VEGF alone.





HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

The Top 10 Insights From the RIDE/RISE Trials of Ranibizumab in Patients With Diabetic Macular Edema

- Rishi P. Singh, MD
- Lisa L. Tuomi, PharmD
- Ivaylo Stoilov, MD

OBJECTIVE To discuss the clinical pearls on the management of diabetic macular edema (DME) and diabetic retinopathy (DR) learned from the RIDE/RISE trials of ranibizumab (RBZ).

PURPOSE To summarize key clinically relevant lessons from 5 years of experience with RBZ in the treatment of DME and DR in the RIDE and RISE phase 3 trials.

METHODS RIDE and RISE were randomized phase 3 trials enrolling patients with DME (N=759) to receive monthly RBZ (0.3 mg or 0.5 mg) or sham injections for 24 months. From month 25 to 36, patients randomized to RBZ continued monthly injections of their original dose, whereas patients in the sham arm crossed over to monthly 0.5 mg RBZ. After month 36, 500 patients elected to enter an open-label extension study in which they received 0.5 mg RBZ pro re nata (PRN) based on prespecified worsening of vision or edema criteria.

RESULTS 1) RBZ resulted in rapid, significant, and sustained improvement of retinal thickness (RT) and vision. 2) Prior laser and/or steroid treatment, baseline HbA1c and posterior retinal nonperfusion did not affect these outcomes. 3) Treatment deferral for 2 years led to less vision gain. 4) RBZ resulted in significant 2- and 3-step improvements in DR as early as months 3 and 12, respectively. 5) Notably, >75% patients with

moderately severe or severe nonproliferative DR experienced ≥2-step improvement as early as month 12 with RBZ. 6) RBZ notably delayed the time to vitreous hemorrhage and panretinal photocoagulation, and 7) significantly reduced the area of hard exudates in eyes with DME. 8) Patients who required cataract surgery during RIDE/RISE experienced a mean of ≥10-letter improvement 1 month after surgery. 9) When patients switched to PRN therapy, mean vision and RT improvements were maintained (mean of 3.8 injections/year). 10) Improvements in DR were also durable with PRN therapy.

CONCLUSION In RIDE and RISE, RBZ treatment resulted in clinically relevant improvements in vision and retinal thickness regardless of baseline characteristics or previous treatment. RBZ also resulted in improvements in DR, particularly in >75% of patients at high risk of progression to proliferative DR. Improvements were maintained with less-than-monthly treatment.

TAKE HOME MESSAGE In the RIDE/RISE trials in DME, RBZ resulted in rapid and long-lasting improvement of vision, along with improvements in DR. These benefits were maintained even with less-than-monthly injections.

HUMAN RESEARCH This study involves human research.
IRB Approval Status: Approved by institutional review board

Real World Data Regarding Initial Visual Acuity in Diabetic Macular Edema (DME)

- Nathan C. Steinle, MD

OBJECTIVE Despite the emphasis in DRCR.net Protocol T results and the common nature of diabetes, there remains a significant paucity of real world data regarding the initial visual acuity in patients with DME.

PURPOSE DRCR.net Protocol T showed that treatment-naive DME patients presenting with ETDRS BCVA ≥20/50 showed better improvement in BCVA when treated with aflibercept compared to those treated with bevacizumab and ranibizumab. In a real world practice setting, the ratio of treatment-naive patients with DME that present with visual acuity of 20/40 or better versus ≥20/50 has not been investigated.

METHODS In a retrospective random sample chart review, we recorded the Snellen visual acuity of patients (n=237) just prior to initiation of Anti-VEGF treatment for DME. Using a published correction factor between Snellen and ETDRS charts, we then calculated the percentage of patients presenting with best corrected ETDRS vision of 20/40 or better (good vision) (n = 124) versus 20/50 or worse (poor vision) (n=113).

RESULTS Patients with initial ETDRS vision ≤20/40 represented 52.3% (124/237), while patients with ≥20/50 represented 47.7% (113/237) in our real world DME patient population.

While DRCR.net Protocol T did not include patients with visual acuity better than 20/32 or worse than 20/320, our analysis included *all* patients presenting with anti-VEGF naive DME regardless of vision. This demonstrates a more representative sample of DME patients in a real world clinical setting and represents the first large published report on this subject.

In DRCR.net Protocol T, 50.8% of patients had baseline ETDRS BCVA of 20/32 to 20/40, and the remaining 49.2% had baseline ≥20/50 (315:305). When comparing the proportion of patients in Group 1 (20/32 to 20/40) to those in Group 2 (20/50 or worse), between the randomized prospective DRCR.net trial and this real world clinical data, we found that the near 50:50 ratio in the randomized trial does accurately represent how patients present in a clinical setting.

CONCLUSION Protocol T concludes anti-VEGF agents improve vision in DME, but the relative effect depends on baseline vision. The application of these study results in a clinic setting is supported as the near 50:50 inclusion of good versus poor initial vision in Protocol T (50.8% versus 49.2%; 315:305) closely mimics the real world where good versus poor initial vision in DME is 52.3% versus 47.7% (124:113).

TAKE HOME MESSAGE This real world study (n=237) revealed 52.3% of DME patients presented with good vision (≤20/40) versus 47.7% who presented with poor vision (≥20/50); this closely mimics Protocol T inclusion data.

HUMAN RESEARCH This study involves human research.

IRB Approval Status: Approved by institutional review board