Patients Ultra-Responsive to Ranibizumab (RBZ): Rates of ≥4-Step Improvement in Diabetic Retinopathy Severity in DRCR.net Protocol S

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OBJECTIVE This study characterized the proportion of patients with diabetic retinopathy (DR) who had ≥4-step improvement in DR severity in response to RBZ therapy, and factors predictive of such improvements.

PURPOSE Improvements in DR severity are commonly reported as 2- or 3-step improvements. Here we characterized the proportion of patients with DR who had ≥4-step improvement on the Early Treatment Diabetic Retinopathy Study (ETDRS) DR Severity Scale (DRSS) from baseline (BL) in response to RBZ 0.5 mg therapy, and the factors predictive of such improvements from the DRCR.net Protocol S dataset.

METHODS Protocol S was a phase 3, randomized, active-controlled clinical trial that compared efficacy of prompt panretinal photocoagulation to RBZ for the treatment of proliferative DR. In this post hoc analysis, DR ultra-responders were defined as eyes with ≥4-step improvement on the ETDRS-DRSS from BL. Frequency of ≥4-step DRSS improvement was analyzed retrospectively at years 1 and 2 in RBZ-treated eyes with gradable BL DRSS of ≥47. Outcomes include best-corrected visual acuity (BCVA). Univariate and multivariate analyses assessed predictors of ≥4-step DR improvement. The data source is DRCR.net, but analyses, content, and conclusions presented herein are solely the responsibility of the authors.

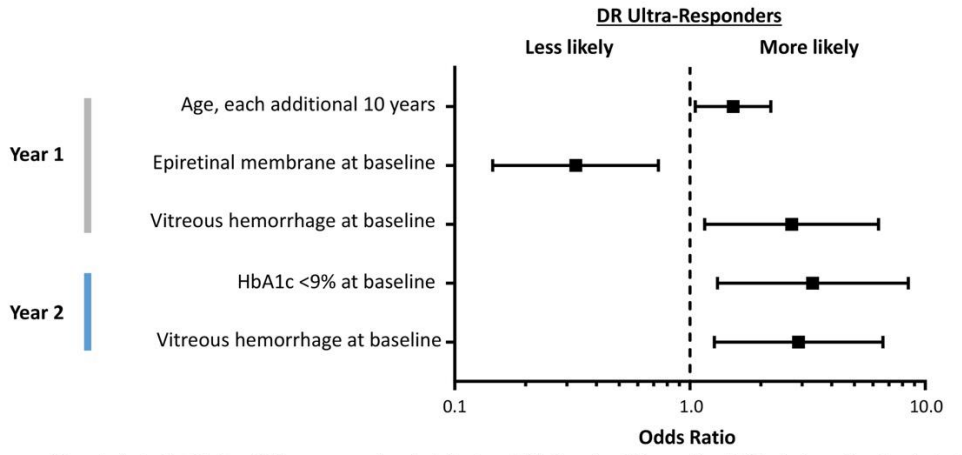
RESULTS The proportion of DR ultra-responders in the RBZ arm at year 1 and 2 was 43/148 (29.1%) and 38/136 (27.9%), respectively. At year 2, BCVA showed better improvements from BL for DR ultra-responders than for those not meeting the ultra-responder criteria (Table). Multivariate analysis further defined eyes with greater or reduced odds of being DR ultra-responders during the 2-year study (Figure). Year 1 DR ultra-responders received a mean (SD) of 7.4 (2.6) RBZ injections in the first year. Year 2 DR ultra-responders received 4.2 (3.4) RBZ injections between year 1 and 2.

CONCLUSION In Protocol S, nearly 30% of RBZ-treated eyes were DR ultra-responders at years 1 and 2. While more studies are needed to further confirm predictors of DR ultra-responsiveness to RBZ, these results indicate that RBZ treatment can dramatically improve DR severity in a subset of patients with proliferative DR. Visual outcomes enhance understanding of treatment impact on this subset of patients.

	DR Ultra-responder	
Year 1	**Yes**	**No**
Number of eyes	43	105
Mean change (95% CI)	5.81 (2.95, 8.68)	6.78 (4.88, 8.69)
Year 2		
Number of eyes	38	98
Mean change (95% CI)	7.63 (4.03, 11.23)	1.77 (–1.51, 5.04)

CI, confidence interval.

Change from BL in BCVA by ETDRS letters



*Eyes included in ≥4-step DR improvement analysis had gradable baseline DR severity of ≥47; study protocol excluded study eyes with prior panretinal photocoagulation. DR, diabetic retinopathy; HbA1c, glycated hemoglobin.

BL factors predictive of ≥4-step DR improvement—multivariate analysis*

HUMAN RESEARCH Yes: Approved by institutional review board

Diabetic Retinopathy Progression in the Absence of Therapy: An Analysis of Untreated Fellow Eyes in RIDE and RISE

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OBJECTIVE To compare the course of diabetic retinopathy (DR) between study (sham- or ranibizumab-treated) and untreated fellow eyes during the first 2 years of RIDE (NCT00473382) and RISE (NCT00473330).

PURPOSE Untreated fellow eyes of RIDE and RISE participants provide a unique opportunity to characterize the natural history of DR. The present analysis sought to examine 2-year DR progression in the absence of therapy, compared against eyes treated with ranibizumab.

METHODS Patients enrolled in RIDE and RISE (N = 759) were randomized to receive monthly intravitreal ranibizumab (0.3 mg or 0.5 mg) or sham for the first 24 months. Color fundus photographs were obtained at baseline and months 3, 6, 12, 18, and 24; DR severity at each time point was prospectively graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) DR Severity Scale. Changes in DR severity over 24 months were compared between study and untreated fellow eyes. New analyses will assess other measures of DR progression with and without ranibizumab treatment, including time to proliferative DR (PDR), and changes in areas of retinal thickening.

RESULTS In total, 709 fellow eyes received no treatment during the study period. In most patients, DR severity in study and fellow eyes was similar at baseline. After excluding eyes that had received prior panretinal photocoagulation, 88.4% of ranibizumab-treated eyes with moderately severe to severe nonproliferative DR (NPDR; ETDRS score 47–53) at baseline

achieved ≥ 2-step DR improvement at month 24, while 1.7% progressed by ≥ 2 steps to PDR (ETDRS score ≥ 60). In comparison, 18.9% of untreated fellow eyes with moderately severe to severe NPDR at baseline achieved ≥ 2-step DR improvement at month 24 (Figure 1), while 28.8% progressed by ≥ 2 steps to PDR (Figure 2). Relative to ranibizumab-treated eyes, median time to PDR was significantly shorter in untreated fellow eyes, while areas of retinal thickening at month 24 were significantly greater. Measures of DR progression among sham-treated eyes were similar to those observed in untreated fellow eyes.

CONCLUSION In the absence of treatment, almost 30% of eyes with moderately severe to severe NPDR progressed to PDR within 2 years, while almost 90% achieved DR severity improvement with monthly ranibizumab therapy. These analyses highlight the importance of prompt intervention to delay DR progression and improve disease severity.

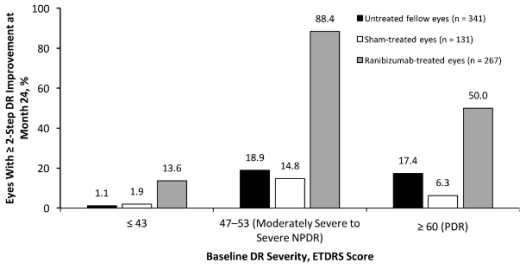

Figure 1. Proportion of eyes with ≥ 2-step DR improvement at month 24 of RIDE/RISE. Excludes eyes with prior panretinal photocoagulation. DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

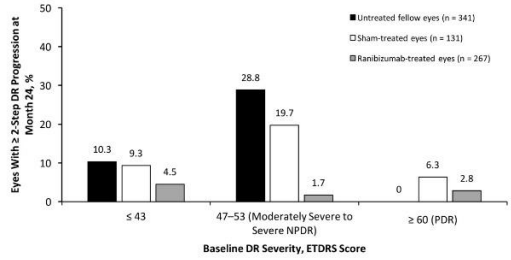

Figure 2. Proportion of eyes with ≥ 2-step DR progression at month 24 of RIDE/RISE. Excludes eyes with prior panretinal photocoagulation. DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

HUMAN RESEARCH Yes: Approved by institutional review board

Simultaneous Inhibition of Ang-2 and VEGF-A With Faricimab in DME: Additional Anatomical and Durability Outcomes From the BOULEVARD Phase 2 Trial

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OBJECTIVE To evaluate key anatomic and durability outcomes from the phase 2 BOULEVARD trial that support the potential for extended faricimab dosing intervals in patients with diabetic macular edema (DME).

PURPOSE Faricimab, the first bispecific antibody designed for intraocular use, binds and neutralizes both angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A). Ang-2 promotes vascular destabilization, leakage, and inflammation. Inhibition of Ang-2 may increase durability of disease response compared with anti-VEGF monotherapy in patients (pts) with DME.

METHODS BOULEVARD (NCT02699450) tested efficacy and durability of faricimab in pts with DME. Anti-VEGF treatment-naïve (TN) pts were randomized 1:1:1 to intravitreal 1.5 mg or 6.0 mg faricimab, or 0.3 mg ranibizumab, and previously anti-VEGF–treated pts were randomized 1:1 to 6.0 mg faricimab or 0.3 mg ranibizumab, given every 4 weeks for 20 weeks. The primary

outcome was mean BCVA change from baseline (BL) at week 24 in TN pts. In a 16-week off-treatment observation period, durability was assessed by time-to-retreatment using prespecified BCVA and optical coherence tomography (OCT) central subfield thickness (CST) criteria. Additional anatomical changes were evaluated on OCT and FFA over time.

RESULTS The phase 2 BOULEVARD trial enrolled 168 TN and 61 previously anti-VEGF–treated pts with center-involving DME on spectral domain OCT. BOULEVARD met its primary outcome. TN pts receiving 6.0 mg faricimab achieved statistically significantly greater BCVA gains over ranibizumab (+3.6 letters, P=0.03) at week 24. CST improved from BL at week 24 in all arms. Macular cube volume reductions from BL at week 24 were observed in both TN (0.3 mg ranibizumab, –1.53 mm^3; 1.5 mg faricimab, –2.83 mm^3; 6.0 mg faricimab, –2.51 mm^3) and previously anti-VEGF–treated (0.3 mg ranibizumab, –1.43 mm^3; 6.0 mg faricimab, –2.46 mm^3) pts. Proportion of pts with macular leakage resolution on FFA was greater among TN pts treated with 6.0 mg faricimab, with a similar trend observed in previously-treated pts. During the observation period, faricimab showed potential for longer time to retreatment compared with ranibizumab. Additional durability analyses from the off-treatment observation period will be presented.

CONCLUSION In BOULEVARD, faricimab treatment led to improved BCVA and CST from BL in all arms. Additional analyses of phase 2 data highlight anatomical benefits and potential for extended durability with faricimab in both pt populations compared with anti-VEGF monotherapy. The ongoing phase 3 YOSEMITE (NCT03622580) and RHINE (NCT03622593) trials are assessing extended interval dosing of faricimab for DME.

HUMAN RESEARCH Yes: Approved by institutional review board

Biomarkers and Predictors for Functional and Anatomical Outcomes for Small Gauge Pars Plana Vitrectomy and Peeling of the ILM in Naïve DME

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- Malgorzata ozimek
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OBJECTIVE To investigate biomarkers and predictive factors for BCVA and anatomical outcome in patients with naïve DME who underwent small gauge PPV and ILM peeling as a first line treatment.

PURPOSE Mostly, PPV was described as a `rescue' procedure when pharmacological treatment did not show efficacy. We aimed to investigate biomarkers and predictive factors for visual and anatomical outcomes in patients with naïve diabetic macular edema (DME) who underwent small gauge pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling as a first line treatment.

METHODS Multicenter, retrospective, interventional study.
Participants: 120 eyes from 120 patients with naïve DME treated with PPV and ILM peeling with a follow up of 24 months.

Change in baseline BCVA and central subfoveal thickness (CST) 1, 6, 12 and 24 months after surgery. Predictive value of baseline BCVA, CST, optical coherence tomography (OCT) features

(presence of subretinal fluid and photoreceptor damage), and time between DME diagnosis and surgery.

Main outcome measures: Correlation between baseline characteristics and BCVA response, mean change from baseline; categorized improvement ≥5 or ≥10; ETDRS 12 and 24 months after surgery

RESULTS Mean BCVA was 0.66 ± 0.14 logMAR, 0.52 ± 0.21 logMAR, and 0.53 ± 0.21 logMAR ($p<0.001$) at baseline, 12 and 24 months, respectively. Shorter time from DME diagnosis until PPV (OR: 0.98, 95% CI: 0.97–0.99, $p<0.001$) was a predictor for good functional treatment response (area under the curve 0.828). For every day PPV is postponed, the patient's chances to gain ≥5 letters at 24 months decrease by 1.8%**.**

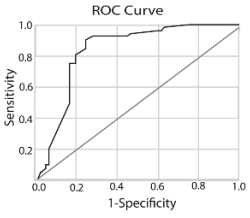
SRF was identified as an anatomical predictor of a better visual outcome, (OR: 6.29, 95% CI: 1.16–34.08, $p = 0.033$). Safety profile was acceptable.
Functional and anatomical outcome

The mean baseline BCVA was 0.66 ± 0.14 logMAR, improved to 0.52 ± 0.21 logMAR after 12 months ($p<0.001$) and remained stable over 24 months (0.53 ± 0.21 logMAR, $p<0.001$,). Fifty-seven (47.5%) and 52 patients (43.3%) gained ≥ 5 letters in vision after 12 and 24 months, respectively. Forty-three (35.8%) and 38 patients (31.7%) gained ≥ 10 letters in vision after 12 and 24 months, respectively.

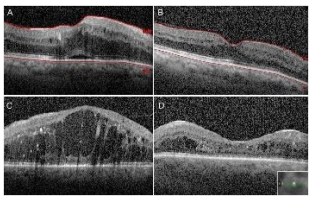
CONCLUSION Our results reveal a significant functional and anatomical improvement of DME 24 months after primary PPV.

In real-life conditions, visual outcome might be comparable using anti-VEGF therapy or PPV with ILM-peeling as a first-line option for the treatment of DME.

For every day PPV is postponed, the patient's chances to gain ≥5 letters at 24 month decrease by 1.8%.



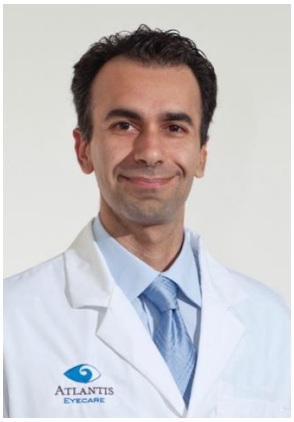
ROC curve for prediction of improvement in visual acuity following PPV with ILM-peeling.The sensitivity and specificity of timing until surgery and the presence of subretinal fluid in predicting the chance of gaining ≥5 letters BCVA 24 months after surgery. The area under the ROC curve was 0.828.



Biomarkers for visual outcome: OCT scans before and 24 months after PPV with ILM peeling.2A-B. Patient presenting with biomarkers for good visual outcome, who had early intervention A. SD-OCT showing diffuse DME with subretinal fluid and intact inter-outer segment layer at baseline. B. 24 months after surgery complete resolution of intra- and subretinal fluid. 2C-D. Patient presenting without biomarkers for good visual outcome, who had late intervention.

HUMAN RESEARCH No: Study does not involve

Anti-VEGF Injections and Risk of Traction Retinal Detachments in Eyes With Proliferative Diabetic Retinopathy: Pooled Analysis of 5 DRCR.net Trials



- Hani Salehi-Had, MD

OBJECTIVE Are anti-VEGF injections associated with an increased rate of traction retinal detachment in eyes with proliferative diabetic retinopathy enrolled in DRCR Network randomized trials?

PURPOSE Published case series suggest that eyes with proliferative diabetic retinopathy (PDR) receiving anti-VEGF prior to vitrectomy have increased risk of traction retinal detachment (TRD). Pooling data from 5 DRCR.net trials evaluated if eyes eligible for these trials not needing prompt vitrectomy had increased risk of TRD when receiving anti-VEGF compared with control groups not receiving anti-VEGF.

METHODS Post hoc analysis of prospectively collected data from 883 eyes enrolled in 5 DRCR.net randomized clinical trials. Participants were adults with type 1 or type 2 diabetes. Eyes had PDR on fundus photography or non-clearing vitreous hemorrhage presumed to be from PDR. Eyes deemed to require prompt vitrectomy or with macular traction were excluded from all trials. The main outcome was the percentage of eyes with investigator-identified TRD in the first year of follow-up. Eyes in the anti-VEGF group were randomized to one of 3 anti-VEGF agents (aflibercept, bevacizumab, or ranibizumab) while eyes in the control group were randomized to laser, sham, or intravitreal saline.

RESULTS In the first year of follow-up, TRD was noted in 6.3% (25 of 396) of eyes in the control group and 4.5% (22 of 487) of eyes in the anti-VEGF group. The corresponding hazard ratio for

eyes randomized to anti-VEGF versus control therapy was 0.69 (95% CI, 0.40-1.22, P = .20). The percentage of eyes undergoing vitrectomy for TRD occurring within the first year of follow-up was 4.0% (16 of 396) in the control group and 1.8% (9 of 487) in the anti-VEGF group. The corresponding hazard ratio for eyes randomized to anti-VEGF versus control therapy was 0.43 (95% CI, 0.20-0.95, P = .04).

CONCLUSION Data from 5 randomized clinical trials do not support the hypothesis that intravitreal anti-VEGF increases the risk of TRD in eyes with PDR not requiring prompt vitrectomy that were eligible for these trials.

HUMAN RESEARCH Yes: Approved by institutional review board