Severity of Diabetic Retinopathy as an Independent Risk Factor for Cerebral Vascular Accidents, Myocardial Infarctions, and All-Cause Mortality



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OBJECTIVE To determine if diabetic retinopathy severity is independently associated with the risk of future cerebral vascular accidents (CVAs), myocardial infarctions (MIs), or death.

PURPOSE Diabetic retinopathy severity may provide a personalized assessment of patients' risk of morbidity and mortality beyond traditional risk factors. If patients' degree of diabetic retinopathy is independently associated with the risk of future morbidity and mortality, then retinopathy grading may play a role in the mangement of diabetic patients' risk of future CVA, MI, and death.

METHODS A retrospective study of patients with type 2 diabetes mellitus was performed after attaining Institutional Review Board approval. New incidents of CVA, MI, or all-cause mortality within five years of retinal evaluation were examined. Patients with previously diagnosed congestive heart failure, CVA, and/or MI were excluded. Age, gender, race, smoking status, hypertension history, lipid profiles, estimated glomerular filtration rate, insulin use, glitazone use, body mass index, hemoglobin A1c (HbA1c), and degree of retinopathy (based on fundus photographs) were included in the analysis. Multivariate Cox proportional-hazards models were performed. 68,206 patients met inclusion criteria.

RESULTS Of the 68,206 patients who were included, 1,680 (2.5%) suffered a MI, 2,269 (3.3%) suffered a CVA, and 3,756 (5.5%) died within 5 years of retinal evaluation. Severity of diabetic retinopathy was independently associated with the risk of future CVA, MI, and death after controlling for the variables listed in the methods, with higher degrees of

retinopathy being statistically significantly associated with an increased risk of each outcome when compared to patients with no retinopathy. Patients with mild retinopathy had a higher risk of CVA [Hazard ratio (HR)=1.40, 95% Confidence Interval (CI)=1.26-1.55, p<0.0001), MI (HR=1.30, 95% CI=1.13-1.47, p<0.0001), and death (HR=1.20, 95% CI=1.10-1.30, p<0.0001). Those with moderate retinopathy had a higher risk of CVA (HR=1.76, 95% CI=1.45-2.13, p<0.0001), MI (HR=2.13, 95% CI=1.78-2.59, p<0.0001), and death (HR=1.62, 95% CI=1.38-1.89, p<0.0001). Similarly, patients with severe retinopathy had a higher risk CVA (HR=2.34, 95% CI=1.64-3.29, p<0.001), MI (HR=2.08, 95% CI=1.39-3.12, p=0.0003), and death (HR=1.72, 95% CI=1.25-2.98, p<0.0001). Figure 1 provides adjusted five-year cumulative hazards for each outcome.

CONCLUSION The five-year risk of CVA, MI, and death are independently associated with patients' degree of diabetic retinopathy, even after adjusting for traditional risk factors such as HbA1c, hypertension, smoking history, and lipid profiles. These findings highlight the importance of retinal exam findings as retinopathy severity may help identify patients at heightened risk for morbidity and mortality.



Adjusted five-year cumulative hazards for cerebral vascular accident (CVA), myocardial infarction (MI) and death based on degree of diabetic retinopathy.

Longitudinal Panretinal Microaneurysm and Leakage Index Evaluation in Proliferative Diabetic Retinopathy in the RECOVERY Study: 2-Year Results



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OBJECTIVE To determine if leakage index and microaneurysm count on ultra-widefield fluorescein angiography improve following intravitreal aflibercept treatment in eyes with proliferative diabetic retinopathy.

PURPOSE To assess the longitudinal change in panretinal leakage index and microaneurysm (MA) counts on ultra-widefield fluorescein angiography (UWFA) in eyes with proliferative diabetic retinopathy (PDR) following intravitreal aflibercept (IAI) in the RECOVERY Study (NCT02863354).

METHODS RECOVERY is a prospective study enrolling 40 subjects with PDR without vitreous hemorrhage or prior panretinal photocoagulation. Subjects were randomized 1:1 to receive 2mg IAI every 4-weeks (2q4) or every 12-weeks (2q12) for the first 52 weeks. At 52-weeks the 2q4 group switched to IAI every 12-weeks and the 2q12 group to IAI every 4-weeks. UWFA images were obtained at baseline, 24, 48, 72, and 96 weeks. UWFA were analyzed using automated segmentation to detect and quantify MAs and panretinal leakage index (percentage of leaking retinal area divided by total analyzable retinal area), and assessed for change over time.

RESULTS Forty eyes of 40 subjects were enrolled with a mean age 48±12.1 years. At baseline, the mean panretinal leakage index in the 2q4 and 2q12 groups was 6.4% and 4.4%, respectively (p=0.28). At week 48, the 2q4 group improved to 1.5% (p<0.001); but

following cross-over to q12 dosing, increased by week 96 to 3.7%, a 43% decrease from baseline (p=0.03), but a significant increase from week 48 (p=0.04). In the 2q12 group, leakage improved to 2.5% (p=0.01) at week 48 with additional improvement with cross-over to q4 dosing to 1.7% at week 96, a 31% decrease from week 48 (p=0.06). Following the treatment crossover, the 2q12 group with q4 dosing during year 2 resulted in a greater reduction in leakage index compared to the 2q4 group with q12 dosing (3.7% vs 1.7%; p=0.007). Both cohorts demonstrated significant declines in MAs at baseline to 48-weeks and 96-weeks, but only the 2q12 cohort following cross-over to q4 dosing demonstrated significant declines in MAs in year 2.

CONCLUSION IAI resulted in dramatic reductions in MA counts and panretinal leakage index in eyes with PDR. 2q4 dosing provided more rapid reduction in leakage index compared to 2q12, but regression of leakage improvement was noted in the 2q4 group when cross-over to q12 dosing occurred. Future research will focus on the impact of MAs and leakage index dynamics and the potential indicator for treatment.



Representative case demonstrating microaneurysm quantification on ultra-widefield angiography: at baseline (A) with segmentation overlay (B), at 24 weeks (C) with segmentation overlay (D), and at 48 weeks (E) with segmentation overlay (F). Macula centered concentric rings in B,D,F outline zones where microaneurysms were defined.



Representative case demonstrating leakage quantification on ultra-widefield angiography: at baseline (A) with leakage overlay (B), at 24 weeks (C) with leakage overlay (D), and at 48 weeks (E) with leakage overlay (F). Macula centered concentric rings seen in B,D,F outline the zones where leakage was defined.

Five-Year Outcomes After Initial Aflibercept, Bevacizumab, or Ranibizumab Treatment for Diabetic Macular Edema (Protocol T)



• Dante Joseph Pieramici, MD

OBJECTIVE To assess treatment patterns and long-term outcomes in eyes with centerinvolved diabetic macular edema that had treatment with anti-vascular endothelial growth factor therapy.

PURPOSE Anti-vascular endothelial growth factor (anti-VEGF) therapy is an effective treatment to improve visual acuity (VA) in eyes with visual impairment from center-involved diabetic macular edema (CI-DME). However, limited data exist on the need for more treatment once study participants discontinue protocol-defined visit and retreatment regimens and enter routine clinical care.

METHODS Participants were enrolled 5-years after initial randomization in a 2-year multicenter clinical trial comparing aflibercept, bevacizumab and ranibizumab anti-VEGF treatments for DME in eyes with baseline VA of 20/32 to 20/320 (Protocol T). Routine clinical care practices were assessed among participants by retrospectively collecting data on clinical visits and retina treatments in the study eye occurring between the 2 and 5-year extension period. Five-year outcomes of VA and central subfield thickness (CST) change from baseline and 2-years are reported.

RESULTS Sixty-eight percent (317/463) of the eligible participants completed a 5-year visit. Between 2 and 5 years, the median number of visits with a retina specialist was 12 (interquartile range [IQR]: 5, 21) and the median number of anti-VEGF injections was 4 (IQR: 0, 12) with 68% receiving at least one injection. VA at 5-years was an average of +7.4 letters (95% CI: +5.9, +9.0) higher than baseline VA but -4.7 letters (95% CI: -3.3, -6.0) lower than 2-year VA. Among participants with baseline VA 20/50 to 20/320, mean VA at 5-years was +11.9 letters (95% CI: +9.3, +14.5) higher than baseline but -4.8 letters (95% CI: -2.5, -7.0) lower than 2 years. For participants with baseline VA 20/32 to 20/40, mean VA at 5-years was +3.2 letters (95% CI: +1.4, +5.0) higher than baseline but -4.6 letters (95% CI: -3.1, -6.1) lower than 2 years. CST at 5-years was on average -154 μ m (95% CI: -142, -166) thinner than baseline and showed no substantial changes (-1 μ m, 95% CI: -12, +9) from CST at 2-years.

CONCLUSION Of the two-thirds of Protocol T participants who completed a 5-year visit, mean VA maintained improvement relative to baseline. However, VA decreased from 2 to 5 years, although there was no associated change in retinal thickening. Whether other management strategies could have better maintained VA is unknown, however these findings suggest that methods to improve long-term visual outcomes in eyes with DME are needed.

Switching to Combination OPT-302 With Aflibercept From Prior Anti-VEGF-A Monotherapy in Eyes With Persistent Diabetic Macula Edema (DME)



• David S. Boyer, MD

OBJECTIVE To evaluate safety, visual function and anatomic outcomes of switching patients with persistent diabetic macula edema from anti-VEGF-A monotherapy to combination therapy of OPT-302 with aflibercept.

PURPOSE OPT-302 inhibits VEGF-C/-D, which may contribute to treatment resistance with VEGF-A suppression. This study assessed safety, vision and anatomic outcomes of switching from anti-VEGF-A monotherapy to combination OPT-302 and aflibercept for persistent DME.

METHODS In the Phase 1b patients receive escalating doses of OPT-302 (0.3, 1 or 2 mg) + aflibercept (2mg) in 3 cohorts. In the Phase 2a ~ 108 patients are randomized (2:1) to either aflibercept + OPT-302 (2mg) or aflibercept alone. Intravitreal injections of aflibercept \pm OPT-302 are given once every 4 weeks (total of 3 doses), and patients followed at week 12 to 24, during which aflibercept retreatment is available as needed if there is a \geq 5 letter decline in best-corrected visual acuity (BCVA) or a \geq 10% increase in retinal thickness. Outcomes included safety, effects on BCVA and anatomical changes.

RESULTS Interim analysis from the Phase 1b dose escalation included 9 patients who had a mean of 6.3 (SD 2.4) injections of prior anti-VEGF-A monotherapy, with the last one given a mean 36 (SD 6) days prior to switching to combination therapy. Multiple dosing of IVT aflibercept + OPT-302 was well tolerated at all 3 dose levels with no dose limiting toxicities. For whole group analysis, mean change in BCVA at week 12 increased by + 7.7 letters (95% CI: 2, 13.3) from baseline (65 letters [SD 5.5]) and a dose response relationship of improved BCVA was observed with increasing doses of OPT-302 + aflibercept. There was also a reduction in central subfield thickness at week 12 of -71 μ m (95% CI -117, -26) from

baseline (434 μ m [SD 58]) and 6 of 9 (67%) patients had a \geq 50% reduction in excess foveal thickness as measured on SD-OCT.

CONCLUSION Conversion to combination OPT-302 with aflibercept was well tolerated with improved visual and anatomic outcomes in patients with persistent DME despite prior anti-VEGF-A monotherapy. Thus, dual-targeted inhibition of VEGF-C/-D and VEGF-A may hold promise in the management of DME.

Intravitreal Liposome-Encapsulated Bromfenac for the Treatment of Refractory Diabetic Macular Edema



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OBJECTIVE To evaluate the safety and efficacy of intravitreal liposome-encapsulated bromfenac in eyes with end-stage DME refractory to anti-VEGF and steroids.

PURPOSE There is a need to develop new therapies for diabetic macular edema (DME), mainly for eyes refractory to anti –VEGF treatment, which can be up to 40%. This therapy should ideally have a similar effect and offer a good safety profile. Liposome-encapsulated bromfenac has been proven to be safe in animal models, we conducted a pilot study to observe safety and efficacy in patients with end-stage DME.

METHODS We conducted a prospective, non-randomized pilot study in 10 patients with refractory diabetic macular edema to evaluate the safety and efficacy of our treatment based on liposome-encapsulated bromfenac. This study was based on our previous work where we demonstrated non-toxicity of these liposomes in a rabbit model. All patients had received more than 3 Anti-VEGF injections with unsatisfactory clinical response. After signing informed consent, basal central macular thickness was measured with OCT scan, and a basal ETDRS score was recorded. Follow-up time was one month. Consecutive central macular thickness measures, ETDRS scores and ophthalmologic evaluation were performed weekly.

RESULTS A total of 70% of patients showed improvement in the final OCT with a mean 118.4 micron decrease in central macular thickness. Visual acuity improved in 50% of patients, with a 2 line mean improvement in ETDRS score. 30% of patients had no significant changes in their central macular thickness. 40% of patients showed some degree of inflammation after treatment. 10% of them resolved with topical prednisolone treatment, and 30% required intraseptal betamethasone administration as well. One of the patients required two intraseptal betamethasone applications, whom visual acuity decreased despite having improved OCT.

CONCLUSION Intravitreal liposome-encapsulated bromfenac may be an alternative treatment to anti-VEGF and steroid treatment in non-responders. However, a large, randomized, double-blind clinical trial must be conducted, and intravitreal inflammation must be addressed, probably by purifying phospholipids in the liposome membrane.

Current United States Treatment Patterns for the Treatment of Proliferative Diabetic Retinopathy in the IRIS Registry



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- Flora Lum, MD
- Scott P Kelly, PhD
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OBJECTIVE To understand how treatment patterns for proliferative diabetic retinopathy have evolved with the advent of anti-VEGF medications.

PURPOSE To investigate the use of anti-VEGF (anti-vascular endothelial growth factor) medications in patients with proliferative diabetic retinopathy (PDR) for 1 year using the American Academy of Ophthalmology (AAO) Intelligent Research in Sight (IRIS) Registry.

METHODS In a retrospective, nonrandomized, comparative study, the rate of use of anti-VEGF medications, panretinal photocoagulation (PRP), and vitrectomy surgery were calculated in patients with PDR and new onset vitreous hemorrhage. The group was stratified based on the presence or absence of diabetic macular edema. The visual acuity at 6 months was compared between patients receiving anti-VEGF medications compared to those not receiving this treatment. Thirty-three thousand four hundred and fifty-two patients were identified.

RESULTS Eighty-three percent (n=22,484) of patients who had PDR plus diabetic macular edema (DME) had treatment with anti-VEGF medication and 68.7% (n=4,511) of patients without DME had treatment with anti-VEGF medication. PRP alone was performed in 31% (n=8320) of patients without DME and in 35% (n-2317) of patients with DME. Twenty-two percent of patients (n=7246) had vitrectomy surgery. Anti-VEGF medication was used in 49.1% (n=3571) of the patients receiving vitrectomy. Visual acuity results were similar in patients regardless of anti-VEGF use. Sixty-three percent (n=3,092) of patients receiving

PRP plus anti-VEGF medication achieved visual acuity of 0.4 log MAR (20/50) or better, while 65% (n=6,344) of patients receiving PRP alone achieved this level of visual acuity. Fifty-one percent (n=2,430) of patients treated with vitrectomy alone achieved visual acuity of 0.4 log MAR or better compared to 49% (n=1,145) of patients treated with vitrectomy plus anti-VEGF medication.

CONCLUSION The treatment patterns for patients with proliferative diabetic retinopathy have changed significantly with a prominent role for anti-VEGF therapy. Visual acuity results were similar regardless of anti-VEGF use.



HUMAN RESEARCH Yes: Exempt from approval

Diabetic Retinopathy Progression in Anti-VEGF Versus Fluocinolone Acetonide Implant Treated Eyes Who Are Lost to Follow-up



• Caesar K. Luo, MD

OBJECTIVE Compare outcomes in patients with high risk diabetic retinopathy (DR) who are lost to followup (LTFU) and have been treated with anti-VEGF monotherapy or fluocinolone acetonide implant (Iluvien).

PURPOSE Data suggest the risk of progression of DR and visually threatening sequelae in patients who are LTFU are greater in anti-VEGF vs. panretinal photocoagulation (PRP) treated eyes. Subanalysis of the FAME trial showed retinopathy regression in Iluvien treated eyes. This report aimed to evaluate the risk of progression in anti-VEGF vs. fluocinolone treated eyes who were LTFU >6 months.

METHODS This is a retrospective, time-matched series collected from the Vestrum database. Patients with moderate or severe nonproliferative DR, or proliferative DR with macular edema treated with anti-VEGF or Iluvien and were LTFU >6 months were evaluated. Eyes with panretinal photocoagulation at any time prior to or during the evaluation period were excluded. 344 Iluvien treated eyes and 15,510 anti-VEGF treated eyes were included for analysis. Visual acuity, central subfield thickness, intraocular pressure changes were recorded. Incidence of vitreous hemorrhage, tractional retinal detachment, rubeosis were also reported.

RESULTS Mean visual acuity score of Iluvien group improved from 79.6 to 80.6 letters, and worsened in the anti-VEGF group from 76.8 to 72.5 letters. The mean central foveal thickness (microns) in the Iluvien group improved from 335 to 312, but increased in the anti-VEGF group from 345 to 352. The mean IOP was stable for the Iluvien group at 15 index and 16 return, and stable for the anti-VEGF group at 16 index and 16 return. Rates of

tractional retinal detachment were 2/344 (1%) in the Iluvien group and 649/15,510 (4%) in the anti-VEGF group. Rates of rubeosis were 2/344 (1%) in the Iluvien group and 775/15,510 (5%) in the anti-VEGF group. Rates of vitreous hemorrhage were 23/344 (7%) Iluvien group and 5295/15,510 (34%) in the anti-VEGF group.

CONCLUSION In eyes with high risk DR that are lost to followup without panretinal photocoagulation, eyes treated with Iluvien have improved vision and central foveal thickness as compared to anti-VEGF treated eyes. Moreover, rates of visually threatening sequelae of proliferative DR were lower in Iluvien treated eyes as compared to anti-VEGF treated eyes.

HUMAN RESEARCH Yes: Exempt from approval

Intravitreal Aflibercept Injection for Nonproliferative Diabetic Retinopathy: Results From the PANORAMA Study



• W. Lloyd Clark, MD

OBJECTIVE To investigate efficacy and safety of treatment with IAI versus sham in patients with moderately severe-to-severe NPDR and without diabetic macular edema (DME), enrolled in PANORAMA.

PURPOSE The PANORAMA study investigated efficacy and safety of IAI vs sham in moderately severe to severe nonproliferative diabetic retinopathy (NPDR) in patients without DME.

METHODS Eligible patients were ≥ 18 years with type 1 or 2 diabetes mellitus and moderately severe to severe NPDR (DRSS score 47 or 53), absence of center-involved DME (CI-DME), and baseline best-corrected visual acuity (BCVA) score of ≥ 69 letters (approximately $\geq 20/40$) in the study eye. A total of 402 eyes were randomized to IAI 2 mg q16 weeks after 3 monthly doses and one q8 interval (2q16, n=135), IAI 2 mg q8 weeks after 5 monthly doses (2q8, n=134), or sham (n=133). The primary endpoint was the proportion of eyes with a ≥ 2 -step improvement in DRSS score at week 52. Secondary endpoints included proportion of eyes that developed a vision.threatening complication (VTC) and/or CI-DME.

RESULTS Overall, 44.0% of patients were women, with a mean (SD) age of 55.7 (10.5) years. Mean (SD) baseline BCVA was 82.4 (6.0) letters. At week 52, 65% and 80% of 2q16 and 2q8 eyes, respectively, versus 15% of sham eyes had a \geq 2-step improvement in DRSS score (P<0.0001 for both). Through week 52, 4% of 2q16 eyes and 3% of 2q8 eyes versus 20% of sham eyes (P<0.0001 for both) developed a VTC (proliferative diabetic retinopathy or anterior segment neovascularization), and IAI significantly reduced the risk of developing a VTC by 85% and 88% compared to sham (2q16 and 2q8 groups, respectively). The incidence of CI-DME was lower in the 2q16 (7%) and 2q8 (8%) groups versus the sham group (26%, P<0.001 for both), and IAI significantly reduced the risk of developing CI-DME

by 79% and 73% in the 2q16 and 2q8 groups, respectively. No new safety signals were identified with IAI. 100-week results will be presented.

CONCLUSION IAI improved diabetic retinopathy and prevented disease progression in eyes with moderately severe to severe NPDR in patients without DME.

Artificial Intelligence Screening for Diabetic Retinopathy: Subgroup Comparison of the EyeArt System with Ophthalmologists' Dilated Exams



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OBJECTIVE How do the EyeArt artificial intelligence (AI) system and dilated ophthalmoscopy (by general ophthalmologists and retina specialists) for diabetic retinopathy (DR) screening compare with graded reference standard fundus photographs?

PURPOSE To compare general ophthalmologists, retina specialists and an artificial intelligence (AI) screening system for detection of referable diabetic retinopathy (rDR; defined as moderate or higher NPDR and/or CSDME) using fundus photo standards for comparison.

METHODS DR gradings of a subgroup of diabetic patients, enrolled in a prospective AI screening study, who also underwent dilated ophthalmoscopy (retina, non-retina) were analyzed. Subjects underwent undilated 2-field, 45-degrees, fundus photography (macula centered, disk centered) using the EyeArt AI System, dilated 4-wide field stereoscopic fundus photography and dilated ophthalmoscopy. AI provided automatic eye level results regarding rDR. Wisconsin Fundus Photograph Reading Center (FPRC) gradings of dilated 4-wide field stereo photographs were the reference standard. Statistical comparisons of AI, retina and non-retina specialist gradings with the reference standard were performed.

RESULTS 521 of 893 subjects (999 eyes) at 10 centers underwent dilated ophthalmoscopy: 406 by non-retina and 115 by retina specialists. FPRC found 207 positive (190 moderate NPDR, 1 severe NPDR, 15 PDR, 37 CSDME) and 792 eyes were negative for rDR (684 no

DR, 108 mild NPDR). For undilated images, AI sensitivity was 96.1% [95% CI: 92.5-99.7%], specificity 87.5% [95% CI: 94.5-90.5%], gradability rate 85.3% [95% CI: 82.2-88.4%]. Dilated photos were required for 147 eyes of which 26 (2.6%) remained ungradable by AI. Gradability rate improved to 97.4% [95% CI: 96.0% - 98.8%]; sensitivity 96.4% [95% CI: 93.1% - 99.8%], specificity 88.4% [95% CI: 85.8% - 91.1%]. Ophthalmoscopy sensitivity was 27.7% [95% CI: 20.1% - 35.2%], specificity 99.6% [95% CI: 99.1% - 100.0%]: retina specialists: sensitivity 59.5% [95% CI: 40.2%-78.7%] with specificity 98.9% [95% CI: 97.1% - 100%], non-retina: sensitivity 20.7% [95% CI: 13.2%-28.2%] and specificity 99.8% [95% CI: 99.5% - 100%].

CONCLUSION This AI system's sensitivity for detection of referable DR was much higher than a general ophthalmologist or even retina specialist as compared to the clinical reference standard.

Incidence of New Diabetic Macular Edema in Fellow Eyes of Patients in the VISTA and VIVID Studies



• Sumit Sharma, MD

OBJECTIVE To evaluate incidence, time to development, and baseline factors predicting occurrence of diabetic macular edema (DME) in fellow eyes of patients treated for DME in the study eye in VISTA and VIVID

PURPOSE To evaluate the incidence, time to development as well as baseline characteristics that predict occurrence of DME in fellow eyes of patients treated for DME in the study eye in VISTA and VIVID.

METHODS VISTA and VIVID randomized 872 DME patients to receive either intravitreal aflibercept injection (IAI) 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 monthly doses (2q8), or macular laser photocoagulation (laser control) through week 100. This post hoc analysis evaluated 755 fellow eyes (laser control, n=252; 2q4, n=245; and 2q8, n=258) without DME at baseline (defined as between 6 weeks before and 4 weeks after first study eye dose) for DME development determined by reported adverse events (DME) and the use of treatments for DME (intravitreal agents, laser). The effect of select baseline factors on incidence of DME in fellow eyes was evaluated by Cox regression model.

RESULTS Over 100 weeks, 44.9%, 44.2%, and 42.9% of fellow eyes developed DME in the 2q4, 2q8, and laser control groups, respectively. No significant differences were observed in the mean time to development of DME across treatment groups. The mean time to DME development in all treatment groups combined was 199 days. Univariate analysis identified worse Diabetic Retinopathy Severity Scale score, and worse best-corrected visual acuity (BCVA) in study eye, shorter duration of diabetes, and lack of insulin usage as baseline factors associated with higher rate of DME development in the fellow eye. Multivariate regression analysis confirmed that patients with shorter duration of diabetes (hazard ratio (HR) [95% CI] per 10 years: 0.850 [0.755, 0.957], P=0.0074) and worse baseline BCVA in the study eye (HR [95% CI] per 10 letters: 0.876 [0.789,0.973], P=0.0131) were at higher

risk of developing DME in fellow eye.

CONCLUSION Almost half of patients with DME in one eye only at baseline, developed DME in the fellow eye with a mean time to onset of approximately 6 months over 2 years of follow-up. Shorter duration of diabetes and worse baseline BCVA in the study eye were predictors for DME development in the fellow eye.

Baseline Diabetic Retinopathy Severity Affects Time to Clinically Meaningful Improvements in Diabetic Retinopathy During Ranibizumab Treatment

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- Karen N Colbert, PhD
- Ivaylo Stoilov, MD
- David W. Faber, MD

OBJECTIVE To determine the relationship between baseline diabetic retinopathy (DR) severity and the rate of disease improvement with ranibizumab treatment.

PURPOSE In previous analyses, patients in RIDE/RISE with moderately severe/severe nonproliferative DR (NPDR) at baseline were more likely to achieve clinically meaningful improvements in DR severity with ranibizumab than patients with either less or more severe baseline DR. This new analysis evaluated the relationship between baseline DR severity and time to DR improvement in RIDE/RISE.

METHODS RIDE (NCT00473382) and RISE (NCT00473330) were identical phase 3 trials of monthly ranibizumab (0.3 mg and 0.5 mg) in patients with DR and vision loss due to diabetic macular edema. DR severity was prospectively graded from color fundus photographs by masked reading center evaluators using the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS). In this ad hoc analysis, the main outcome evaluated was time to improvement by \geq 2 steps in DR severity on the ETDRS-DRSS. Data from the ranibizumab 0.3 mg and 0.5 mg treatment groups were pooled. Eyes with baseline ETDRS-DRSS severity < 35 (mild NPDR) were excluded.

RESULTS A total of 443 eyes were evaluated. The time to ≥ 2 -step DR improvement was significantly shorter among eyes with moderately severe or severe NPDR (ETDRS-DRSS 47/53) at baseline than among eyes with either mild/moderate NPDR (ETDRS-DRSS 35/43) or proliferative DR (PDR; ETDRS-DRSS 60–75 with or without prior panretinal photocoagulation [PRP]) at baseline (P < 0.01; Figure). Very few eyes with PDR and a history of PRP achieved ≥ 2 -step DR improvement; among those that did, the time to ≥ 2 -step DR improvement was significantly longer than in eyes with no prior PRP (Figure). As has been reported previously, the proportion of patients achieving ≥ 2 -step DR improvement at month 6 was greater in eyes with moderately severe or severe NPDR at baseline than in eyes with either less or more severe baseline DR.

CONCLUSION Eyes with moderately severe or severe NPDR at baseline achieved more rapid improvements in DR severity during ranibizumab treatment than did eyes with either milder or more severe DR at baseline. These findings support treating eyes with moderately severe or severe NPDR before they progress to PDR.

HUMAN RESEARCH Yes: Approved by institutional review board



Time to ≥ 2-Step DR Improvement by Baseline DR Severity (Ranibizumab-Treated Study Eyes, Pooled 0.3- and 0.5-mg Arms; Kaplan-Meier Plot)

Figure: Time to \geq 2-step improvement in ETDRS-DRSS by baseline DR severity (Kaplan-Meier plot).

Progression to Proliferative Diabetic Retinopathy in Nonproliferative Diabetic Retinopathy Eyes Without Diabetic Macular Edema in the United States



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OBJECTIVE To evaluate the natural history of disease progression from nonproliferative Diabetic Retinopathy to proliferative diabetic retinopathy in routine clinical practice in the United States.

PURPOSE To evaluate the natural history of disease progression from nonproliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy in routine clinical practice in the United States, in patients with NPDR without diabetic macular edema (DME).

METHODS This retrospective analysis evaluated electronic medical records (Vestrum Health Retina Research Dataset; Naperville, IL) during January 2013 through June 2019 from adult eyes diagnosed with NPDR without DME and prior intravitreal anti.vascular endothelial growth factor treatment. Eyes were excluded if they converted to PDR or DME within 1 week of index NPDR diagnosis or showed evidence of age-related macular degeneration or retinal vein occlusion during the study period. Time to PDR conversion was analyzed by Kaplan–Meier estimation. Cox multivariable regression was used for adjusted analyses. Data were censored from the time of DME development.

RESULTS Of 135,324 eyes included in the study, 52% had mild NPDR, 29% had moderate

NPDR, 8% had severe NPDR, and 11% had unspecified NPDR. Median baseline visual acuity (VA) was the same across NPDR severity groups, 76 letters (20/32 Snellen equivalent). Patients with severe NPDR were slightly younger (median age: 60 years vs 64–67 across mild, moderate, and unspecified severities), and less likely to have been diagnosed with hypertension (60% vs 64–79% across mild, moderate, and unspecified severities). The 4-year risk (95% CI) of progression to PDR was 14.9% (14.5%, 15.4%) in overall patient population. This risk increased with higher NPDR severity (mild: 7.7% [7.2, 8.2], moderate: 21.4% [20.3, 22.4], severe: 48.1% [45.2, 50.9], unspecified: 13.1% [12.2, 14.0]). This relationship persisted when adjusting for baseline characteristics. Additional baseline factors associated with increased risk of progression to PDR included younger age, type 1 diabetes, and worse VA.

CONCLUSION Baseline NPDR severity was a strong predictor of progression to PDR. When left untreated, nearly half of eyes with severe NPDR progressed to PDR within 4 years in routine clinical practice in the United States.

Treatment Effect of Intravitreal Aflibercept Injection by Baseline Factors in Moderately Severe-to-Severe NPDR in PANORAMA



• Nathan C. Steinle, MD

OBJECTIVE To evaluate the difference in treatment effect between intravitreal aflibercept injection and sham by baseline factors at week 52.

PURPOSE To evaluate the difference in treatment effect between intravitreal aflibercept injection (IAI) and sham by baseline factors for the proportions with ≥ 2 -step improvement in Diabetic Retinopathy Severity Scale (DRSS) score in eyes with moderately severe-to-severe nonproliferative diabetic retinopathy (NPDR) without diabetic macular edema (DME).

METHODS Phase 3 PANORAMA trial (NCT02718326) randomized eyes with DRSS levels 47 or 53 without DME to receive either IAI 2 mg every 16 weeks (2q16) following 3 monthly doses and one 8-week interval (2q16, n=135), IAI 2 mg every 8 weeks (2q8) following 5 monthly doses (2q8, n=134), or sham (n=133) through week 52. Adjusted Mantel-Haenszel weighting scheme was used to evaluate differences between treatment groups across baseline factors. Treatment-by-subgroup interactions were evaluated by logistic regression. Missing data were imputed using the last observation carried forward method. Data from patients receiving rescue treatment were censored from the time of rescue treatment.

RESULTS At week 52, the adjusted differences between IAI 2q16 and sham and IAI 2q8 and sham for the proportions of eyes with ≥ 2 -step improvement in DRSS score were greater across age tertiles (≤ 52 years: 41.4% and 60.0%; $>52 - \leq 61$ years: 56.6% and 70.3%; and >61 years: 52.6% and 60.5%, respectively), Hispanic ethnicity (Yes: 60.0% and 65.9%; No: 43.8% and 62.2%, respectively), body mass index (BMI) groups (≤ 30 kg/m2: 52.2% and 62.7%; >30 to ≤ 35 kg/m2: 42.6% and 61.6%; and >35 kg/m2: 53.3% and 68.7%, respectively), hemoglobin A1c tertiles (\leq 7.6%: 38.9% and 56.6%; >7.6% – \leq 9.1%: 57.9% and 64.1%; >9.1%: 57.5% and 72.7%, respectively), diabetes duration tertiles (\leq 10.3 years: 38.6% and 63.6%; >10.3 – \leq 17.6 years: 63.1% and 68.3%; >17.6 years: 50.8% and 56.2%, respectively), and DRSS severity (level 47: 45.3% and 61.1%; level 53: 63.6 and 75.8%, respectively). For all comparisons versus sham, P \leq 0.0004. Treatment effect was not impacted in any of the selected baseline subgroups.

CONCLUSION Significantly greater proportions of eyes treated with IAI had a \geq 2-step improvement in DRSS score compared with sham, across all selected baseline factors (age, Hispanic ethnicity, BMI, hemoglobin A1c, diabetes duration, and DRSS severity) in eyes with moderately severe-to-severe NPDR. No treatment-by-subgroup interactions across selected baseline factors were found.

Diabetic Retinal Telescreening Program in a High-Risk Population Highlights Significant Rates of Retinal Pathology



• Matthew P. Ohr, MD

OBJECTIVE The objective of this study is to evaluate the rates of retinal pathology identified during a diabetic retinal telescreening program in a high risk population.

PURPOSE Despite referral by primary care physicians and other providers for dilated fundus examination in diabetic patients, many patients fail to complete eye exams. Telescreening programs have been shown to improve compliance. The purpose of this study is to evaluate effectiveness and report outcomes of a diabetic telescreening program in a high risk population.

METHODS The medical records of all patients who underwent OSUWMC Diabetic Telescreening retinal imaging. The retinal imaging took place from May 7, 2019 to August 12, 2019. During the study period, the imaging was deployed at 2 sites. These sites were selected based on a high risk patient population identified as having many patients of lower socioeconomic status and higher rates of disease. The patients at these sites had the lowest compliance for recommended diabetic eye exams. All imaging was performed on an ultrawide field camera (UWF Primary) (Optos, Fife, U.K.). The non-mydriatic imaging was performed by medical assistants in the primary care office and read by a retinal specialist.

RESULTS 200 eyes of 100 patients were imaged and evaluated. There were 64 Females and 36 Males. (Table 1) There were 98 patients with Type II Diabetes Mellitus (DM) and 2 patients with Type I DM. The mean age of the patients imaged was 56 (+/- 11 standard deviation). 196 of 200 (98%) eyes imaged were high enough quality to be graded. Of the patients imaged 68 of 100 (68%) of the patients imaged had identifiable pathology. 85 of 200 (42.5%) eyes were found to have no diabetic retinopathy (Graph 1). 88 (44%) had mild nonproliferative diabetic retinopathy (NPDR). 11 (5.5%) were noted to have moderate NPDR. 6 (3%) had Severe NPDR. 1 (0.5%) patient was found to have undiagnosed high risk proliferative diabetic retinopathy (PDR). 5 (2.5%) of eyes had quiescent PDR. 4 (2%) of eyes

were unreadable. 8 (4%) of eyes were noted to have clinically significant diabetic macular edema. 36 patients were referred to an ophthalmologist for further evaluation.

CONCLUSION With minimal training, non-ophthalmic medical assistants can be trained to capture high quality non-mydriatic ultra wide field fundus photos for diabetic screening. In high risk populations, the rates of retinal pathology are significantly higher. Diabetic telescreening is an effective strategy to identify patients that need intervention and reduces the barriers associated with noncompliance.



HUMAN RESEARCH Yes: Approved by institutional review board

Rates of diabetic retinopathy in diabetic telescreening program for high risk population.

Table 1. Patient Demographic Characteristics	
Ultrawide Field Imaging	
(n = 100 Patients)	
Mean age ±SD	56 ± 11.5
Female gender, no. (%)	64 (64)
Male gender, no. (%)	36 (36)
Type I DM, no. (%)	2 (2)
Type II DM, no. (%)	98 (98)
SD = standard deviation; DM = Diabetes Mellitus	

Demographics

Insights Into the Progression of Diabetic Retinopathy Severity Among Primary Care Patients With Diabetes in the United States



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- Chin-Yu Lin
- Verena Steffen
- Zdenka Haskova, MD, PhD

OBJECTIVE To assess the risk of diabetic retinopathy (DR) progression among real-world patients with diabetes in a large, US primary care setting.

PURPOSE To explore the natural progression of DR in eyes from patients with diabetes screened at primary care centers across the United States. We report changes in DR severity and progression to vision-threatening forms of DR (clinically significant macular edema [CSME] or proliferative DR [PDR]) in the overall population and among eyes with moderate to severe nonproliferative DR (NPDR) at baseline.

METHODS Eyes of 22,116 patients with diabetes were analyzed using data and images collected from 1999–2016 (Source: Inoveon Corporation, Oklahoma City, OK). DR severity and CSME were assessed from 7-field color fundus photographs by professional graders at a centralized reading center. DR severity was graded using the Early Treatment Diabetic Retinopathy Study (ETDRS) DR Severity Scale (DRSS); analyses included eyes with valid baseline and postbaseline DRSS values (42,011 eyes). Occurrence of \geq 2-step DR worsening was assessed in the overall population and by DRSS at baseline. Development of CSME (using ETDRS criteria) or PDR was analyzed among eyes with no CSME and no PDR, respectively, at baseline.

RESULTS For all eyes evaluated, the Kaplan-Meier rate for time to first \geq 2-step worsening was 2.7% at year 2 and 7.1% at year 4. Consistent with expectations, the rate of DRSS

worsening by ≥ 2 steps was greatest among eyes with baseline DRSS severity of 43–53 (moderate to severe NPDR; Figure 1). When all eyes with baseline DRSS severity of 43–53 were analyzed together, the Kaplan-Meier rate for time to first ≥ 2 -step worsening was 11.6% at year 2 and 26.4% at year 4. The development of CSME or PDR was analyzed in all eyes and in the group of eyes with baseline DRSS of 43–53. The time to development of CSME, PDR, or either CSME or PDR among eyes with baseline DRSS 43–53 is shown in Figure 2 (the number of eyes at risk over time is shown below the graph). Both analyses suggest that eyes with worsening DR fall into distinct clinical subtypes, one progressing to CSME, the other progressing to PDR, and a small subset experiencing progression to both vision-threatening forms of DR.

CONCLUSION Consistent with the design of the ETDRS-DRSS, the results from this population show that eyes with moderate to severe NPDR were at greatest risk of progression to vision-threatening forms of DR. These data also suggest the existence of 3 clinical subtypes among eyes with DR: one at increased risk of CSME, one at increased risk of PDR, and one at increased risk of developing both.



HUMAN RESEARCH No: Study does not involve human research

Figure 1. Percentage of eyes with \geq 2-step DR worsening at year 2 by baseline DR severity (2-year Kaplan-Meier rate).



Figure 2. Time to development of CSME, PDR, or either CSME or PDR among eyes with baseline DRSS 43–53. The shaded areas represent the 95% CIs. Number at risk refers to the number of eyes at risk of developing CSME, PDR, or either CSME or PDR, at each year.

Adjunctive Focal Laser Following Central Fluid Resolution After Bevacizumab, Ranibizumab, or Aflibercept Injection: A Secondary Analysis of Protocol T



- Jennifer R Gallagher, MD
- Hamzah Khalaf, MD
- Ansel Hoang, MS

OBJECTIVE The objective of our study is to determine if patients who have central fluid resolution at six months received fewer injections at 1 and 2 years by augmenting their treatment with focal laser.

PURPOSE The use of anti-VEGF agents has transformed the way we approach and treat diabetic eye disease; however, monthly visits and injections prove burdensome for patients and is likely a factor in the higher rate of loss to follow up we see in this patient population. The purpose of our study is to determine if focal laser reduced the number of injections patients received at 1 and 2 years.

METHODS Of the 660 eyes that were randomized to aflibercept (n=224), bevacizumab (n=218), or ranibizumab (n=218), 452 eyes (68%) were excluded. Subjects included (n=208) in this secondary post hoc analysis had a CST \leq 250 um on Zeiss (or equivalent) at 24 weeks. Of the 208 eyes, 46 received FGLT between 24-40 weeks and 162 did not receive FGLT between 24-40 weeks. Primary outcome was the number of injections at 1 year. Secondary outcomes were changes in BCVA and CRT at 1 year and 2 years as well as number of injections at 2 years.

RESULTS The mean number of anti-VEGF injections at 1 year was 9.74 for FGLT group and 9.03 for the control group (p=0.0468). The mean number of anti-VEGF injections at 2 years was 15.7 for FGLT group and 13.9 for control group (p=0.045). Mean BCVA at baseline was lower for the FGLT group (58.4 vs 63.6, p=0.031) but no significant difference was found at 24 weeks (74.7 vs 75.2, p=0.116). At 1 year, the mean BCVA was worse in FGLT group at 74.8 letters compared to 78 letters for the control group (p=0.006). At 2 years, the

same trend continued with mean BCVA higher in the control group (73.7 vs 77.4, p=0.049) [Figure 1]. Mean CRT at baseline and 24 weeks showed no significant differences between the two groups. At 1 year, there was no difference in mean CRT (268 for FGLT vs 264 for control, p=0.812). At 2 years, the mean CRT was lower in FGLT group but not statistically significant (258 vs 269, p=0.239) [Figure 2].

CONCLUSION Our analysis showed that patients who responded well to injections and had FGLT between weeks 24 and 40 weeks received more intravitreal injections at 1 and 2 years. However, mean BCVA was worse in the FGLT group at 1 and 2 years. The data demonstrates that adjunctive FGLT does not reduce the number of injections nor does it protect BCVA long term.

HUMAN RESEARCH Yes: Exempt from approval







Figure 2. Comparison of changes in Visual Acuity from baseline at 1 and 2 years in the control and treatment groups.

Complications, Compliance, and 2-Year Outcomes After Endolaserless Vitrectomy With Aflibercept Monotherapy for PDR-Related Vitreous Hemorrhage



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OBJECTIVE To determine the 2-year outcomes, complications, and compliance after endolaserless vitrectomy with intravitreal aflibercept injection (IAI) monotherapy for PDR-related vitreous hemorrhage (VH).

PURPOSE Anti-VEGF monotherapy is a demonstrated alternative to panretinal photocoagulation (PRP) for PDR eyes not requiring vitrectomy. For PDR-related VH requiring vitrectomy, IAI monotherapy without endolaser PRP (endolaserless) may be a viable approach. We report the 2-year visual and anatomic outcomes, safety, and compliance for patients undergoing endolaserless vitrectomy with IAI for PDR-related VH.

METHODS Phase I/II open label, randomized, prospective, single center interventional study. Randomized eyes underwent endolaserless vitrectomy and 2mg IAI. Eyes received one preoperative and intraoperative IAI followed by randomization to a q8week group receiving 4 post-operative q4week IAI followed by q8week IAI or q16week group receiving 2 post-operative q4week IAI followed by q16week IAI. Mandatory ocular examination and OCT were performed monthly in year 1 and every two months in year 2. Additional IAI for PDR progression or DME was administered as needed. Non-compliance was defined as

missing >3 consecutive or >4 mandatory appointments in 1 year.

RESULTS Thirty-one of 40 eyes were randomized (14 and 17 eyes in q8week and q16week groups, respectively) with 22 eyes completing the week 104 visit (3 eyes pending week 104 visit). Through 104 weeks, 10/13(77%) and 9/15(60%) eyes met compliance criteria in the q8 and q16week groups, respectively. Q8 and q16week eyes received an average of 14.3 and 8.6 IAI, respectively. Visual acuity(VA) improvements favored the q8week eyes with a 37 letter increase from 38 to 74 letters (20/160 to 20/32) (p=0.0026) versus a 14 letter increase from 51 to 65 letters (20/100 to 20/50) in the q16week eyes (p=0.167). At week 104, 0 and 3 eyes in the q8 and q16week groups, respectively, observed a decrease in VA from baseline (range: -19 to -2 letters). Significant adverse ocular events were more common in q16week eyes with worsening VA > 30 letters (4 q8week eyes, 7 q16week eyes) and VH (2 q8week eyes, 7 q16week eyes). NVG was seen in 1 q16week eye and 1 RRD was seen in both groups.

CONCLUSION Endolaserless vitrectomy with aflibercept monotherapy for PDR-related VH results in significant visual gains. The greater rates of proliferative consequences in the q16week group, poor compliance rate in both groups, and greater q8week VA gains indicate that persistent and frequent postoperative anti-VEGF therapy is necessary to optimize visual outcomes and reduce complications.