7/14/2022 10:10 am

Diabetic Retinopathy 1 Symposium

Aflibercept Monotherapy vs Initial Bevacizumab Followed by Aflibercept if Needed for Treatment of Center-Involved Diabetic Macular Edema

- Chirag Jhaveri, MD, FASRS

Objective:
For eyes with center-involved diabetic macular edema (CI-DME) and visual acuity 20/50 or worse, do vision outcomes differ between treatment with aflibercept only versus initial bevacizumab followed by switching to aflibercept if there is an unsatisfactory response?

Purpose:
Intravitreal injections of anti-VEGF agents are highly effective in improving visual acuity (VA) for eyes with DME. In DRCR Retina Network Protocol T, vision outcomes were similar among anti-VEGF agents when baseline VA was ≥20/40, but in eyes with VA ≤20/50, the aflibercept group had better vision through 2 years compared with the bevacizumab group. The cost difference between anti-VEGF agents has led many insurance companies to require “step therapy” where treatment is initiated with bevacizumab and switching to another agent is allowed if a patient has an unsatisfactory response. Vision outcomes withstep therapy compared to aflibercept only are unknown.

Methods:
Study eyes had best corrected E-ETDRS VA of 20/50 to 20/320and CI-DME. 312 eyes of 270 adults were randomized to receive 2.0 mg intravitreous aflibercept or 1.25 mg intravitreousbevacizumab. Starting from 12 weeks, eyes assigned to bevacizumab were switched to aflibercept if prespecified criteria for suboptimal response were met. Follow-up visits occurred every 4 weeks in the first year and every 4 to 16 weeks in the second year depending on treatment course. Best corrected VA and OCT scans were obtained by masked technicians.

Results:
The primary outcome is the mean change in VA from baseline over 104 weeks calculated using area under the curve. Secondary outcomes included changes in VA, retinal thickening, and diabetic retinopathy severity from baseline at 24, 52, and 104 weeks; number of intravitreal injections; number of visits; frequency of complications of diabetic retinopathy; and adverse events. The results of this clinical trial will be presented; however, because of the potential public health impact of these results, the DRCR Retina Network requests that the results be made available only after the primary manuscript is published, which is expected to occur prior to the 2022 ASRS annual meeting.

Conclusion:
Conclusions will follow from results presented.

IRB APPROVAL Yes

7/14/2022 10:16 am

Diabetic Retinopathy 1 Symposium

Efficacy, Durability, and Safety of Faricimab in Diabetic Macular Edema: 2-Year Results of the Phase 3 YOSEMITE and RHINE Trials

- David Eichenbaum, MD, FASRS
- John Wells, MD, FACS
- Jennifer Lim, MD, FARVO, FASRS
- Carl Danzig, MD
- Kemal Asik, PhD
- Zdenka Haskova, MD, PhD
- Shaun Mohan, MD
- David Silverman, MSc, MBChB
- Yannan Tang
- Hugh Lin, MD

Objective:
Year 2 of the phase 3 YOSEMITE/RHINE trials will evaluate the longer-term efficacy, durability, and safety of faricimab in patients with diabetic macular edema (DME).

Purpose:
Faricimab is a dual angiopoietin-2/vascular endothelial growth factor (VEGF)-A pathway inhibitor and the first bispecific antibody designed for intraocular use. Year 1 data from the phase 3 YOSEMITE/RHINE trials support the hypothesis that dual angiopoietin-2/VEGF-A blockade with faricimab may promote vascular stability and durable efficacy beyond current anti-VEGF therapies for DME.

Methods:
YOSEMITE (NCT03622580) and RHINE (NCT03622593) were randomized, double-masked, active comparator–controlled trials of faricimab in patients with center-involving DME. Patients were randomized 1:1:1 to faricimab 6.0 mg every 8 weeks (Q8W) after 6 initial Q4W doses, faricimab 6.0 mg per personalized treatment interval (PTI) after 4 initial Q4W doses, or aflibercept 2.0 mg Q8W after 5 initial Q4W doses. The PTI algorithm was a protocol-driven treat-and-extend regimen, with dosing intervals extended, maintained, or reduced (from Q4W up to Q16W) based on central subfield thickness (CST) and best-corrected visual acuity (BCVA) change at active dosing visits. The primary efficacy endpoint was mean BCVA change from baseline at 1 year, averaged over weeks 48, 52, and 56. Other efficacy and safety endpoints were assessed through week 100.

Results:
In total, 1891 patients with DME were enrolled in YOSEMITE (N = 940) and RHINE (N = 951). At 1 year, faricimab Q8W or per PTI offered durable vision gains that were noninferior to aflibercept Q8W and were achieved with Q16W dosing in > 50% of patients in the PTI arms. Faricimab Q8W or per PTI demonstrated anatomic improvements versus aflibercept Q8W and was well tolerated, with low rates of intraocular inflammation. Year 2 outcomes will be presented at the meeting, including mean BCVA change from baseline averaged over weeks 92, 96, and 100; the proportion of patients in the faricimab PTI arm who achieved Q4W, Q8W, Q12W, or Q16W dosing at week 96; mean CST change from baseline over 2 years; the proportion of patients with ≥ 2-step Diabetic Retinopathy Severity Scale improvement from baseline at week 96; and the incidence and severity of adverse events through study end.

Conclusion:
Following positive 1-year results, YOSEMITE/RHINE will examine whether early vision gains, anatomic improvements, and extended (up to Q16W) dosing with faricimab are maintained over 2 years.

IRB APPROVAL Yes

7/14/2022 10:22 am

Diabetic Retinopathy 1 Symposium

Randomized Phase 1 Trials of RZ402, a Novel Orally Administered Plasma Kallikrein Inhibitor Targeting Diabetic Macular Edema

- Robert Bhisitkul, MD, PhD
- Quan Nguyen, MD, MSc, FARVO, FASRS
- Brian Roberts, MD
- Rajat Agrawal, MD, MS

Objective:
Two Phase 1 clinical trials to assess the safety and systemic pharmacokinetics of RZ402, a novel orally administered plasma kallikrein inhibitor.

Purpose:
Plasma kallikrein-kinin system (KKS) promotes vascular inflammation and permeability through bradykinin and related mediators and is implicated in a number of vascular diseases, including retinal diseases such as diabetic macular edema (DME). RZ402 is a novel, orally administered PKI that has demonstrated reduction in retinal vascular leakage in animal models of DME. Phase 1, first-in-human studies were conducted to assess the safety and pharmacokinetics (systemic exposure) of oral RZ402 in a clinical development program for the treatment of DME.

Methods:
Two randomized, double-masked, placebo-controlled Phase 1 studies were conducted. The first was a single-ascending-dose (SAD) study of RZ402 oral solution in 30 healthy adult subjects in three ascending dose cohorts of 10 subjects each at doses of 25mg, 100mg and 250 mg. The second study was a multiple-ascending-dose (MAD) study of RZ402 oral solution in 40 healthy adult subjects in 4 ascending dose cohorts of 10 subjects each, at doses of 25mg, 100mg, 250mg and 500mg, administered once-daily over 14 days. Safety assessments included systemic and ophthalmic evaluations. Serial plasma RZ402 concentrations by LC/MS/MS supported the pharmacokinetic evaluation. In the MAD study, plasma kallikrein activity was measured as a biomarker of RZ402 activity.

Results:
All 30 subjects in the SAD study completed the study, with a single dose of RZ402 found to be generally safe across all dose levels. Overall, 13 subjects (54%) who received RZ402 experienced a total of 18 adverse events (AEs), compared to 2 subjects (33%; 5 AEs) who received placebo. Many of the AEs in subjects were procedure-related (eg. ECG electrode irritation), with only 3 AEs (diarrhea, nausea and headache; all grade 1/mild) in 3 subjects judged by the Investigator as possibly related to the study drug. There were no grade 2 or 3 AEs and no serious AEs (SAEs). No clinically meaningful changes in laboratory values, vital signs, or ECG results were observed, and physical and ophthalmic examinations were unremarkable. There were no observed dose-limiting toxicities. Dose-dependent plasma RZ402 concentrations were observed with peak levels at 3 to 4 hours after dose and elimination half-life at 20.2 to 25.6 hours across the dose groups. Based on animal models, the systemic RZ402 concentration required for 50-90% inhibition of retinal vascular permeability is 3-6 ng/mL. In the single-dose study, these pharmacologically-relevant plasma concentrations were exceeded throughout the intended 24-hour dosing interval. The MAD study results will be available and reported at the time of the presentation.

Conclusion:
RZ402, a novel, orally administered PKI that counteracts retinal vascular permeability and inflammation, was found to have a good safety profile and was well tolerated in healthy subjects. It yielded target systemic concentrations over 24 hours that support the potential for a once daily oral therapy for patients with DME. A phase 2 study in patients with DME will be initiated later this year.

IRB APPROVAL Yes

7/14/2022 10:26 am

Diabetic Retinopathy 1 Symposium
Angiopoietin-2 Signaling and Vascular Stability With Faricimab in Diabetic Macular Edema

- Karl Csaky, MD, PhD
- Yasha Modi, MD
- Veeral Sheth, MD, MBA, FASRS, FACS
- Jeffrey Willis, MD/PhD
- Zdenka Haskova, MD, PhD
- Peter Westenskow, PhD

Objective:
To explore the effect of dual angiopoietin (Ang)-2 and vascular endothelial growth factor (VEGF)-A inhibition compared with anti-VEGF alone on vascular stability in diabetic macular edema (DME) using preclinical and phase 2/3 data.

Purpose:
Real-world treatment outcomes with anti-VEGF therapy for DME are frequently suboptimal and there is a need for novel targets that promote vascular stability beyond the VEGF pathway. The Ang/Tie signaling pathway is a key regulator of vascular stability, and as such, dual pathway inhibition via Ang-2/VEGF-A blockade may promote vascular stability and improve patient outcomes over anti-VEGF alone.

Methods:
In JR5558 mice (spontaneous choroidal neovascularization [CNV] model), the effects of anti−Ang-2, anti−VEGF-A, dual anti–Ang-2/anti–VEGF-A (VA2), or none/immunoglobulin G (IgG; control) on vascular stability (neovascular leakage and inflammation [Iba1+, CD11b+, CD45+]) were evaluated at baseline and 1 week (1W), 3W, and 5W posttreatment. In the phase 2 BOULEVARD trial (NCT02699450), the effect of faricimab, a bispecific Ang-2/VEGF-A neutralizing antibody, on retinal stability over time (achievement and maintenance [< 10% worsening] of central subfield thickness [CST] ≤ 325 mm to W24) was assessed. Vascular stability with faricimab was also evaluated in the phase 3 YOSEMITE/RHINE trials (NCT03622580/NCT03622593) with endpoints including mean CST change from baseline; proportions of patients with absence of DME, absence of intraretinal fluid (IRF), and absence of subretinal fluid; and proportion of patients in the personalized treatment interval (PTI) arms receiving every-4-week (Q4W), Q8W, Q12W, or Q16W dosing over 2 years.

Results:
In JR5558 mice, CNV lesion leakage was reduced at 1W with anti−Ang-2, anti−VEGF-A, and VA2 compared with controls ($P < 0.05$ to $P < 0.001$); at 3W and 5W, CNV leakage reduction was maintained in the anti−Ang-2 and VA2 treatment groups only ($P < 0.05$ to $P < 0.0001$). Compared with IgG, VA2 treatment reduced Iba1+, CD11b+, and CD45+ cell infiltration at 1W ($P < 0.05$); at 5W, only anti−Ang-2 and VA2 reduced Iba1+ infiltration ($P < 0.0001$). In a post hoc analysis of BOULEVARD, retinal stability over time was achieved by > 50% of patients receiving faricimab 6.0 mg and 1.5 mg at W8 and W16, respectively, compared with W20 for patients receiving ranibizumab. During year 1 of YOSEMITE/RHINE, change in CST from baseline consistently favored faricimab over aflibercept and absence of DME and IRF were achieved by higher proportions of patients treated with faricimab versus aflibercept. In the faricimab PTI arms, these anatomic improvements were achieved with Q16W dosing in > 50% of patients at week 52. Year 2 efficacy and durability data from YOSEMITE/RHINE will be presented.

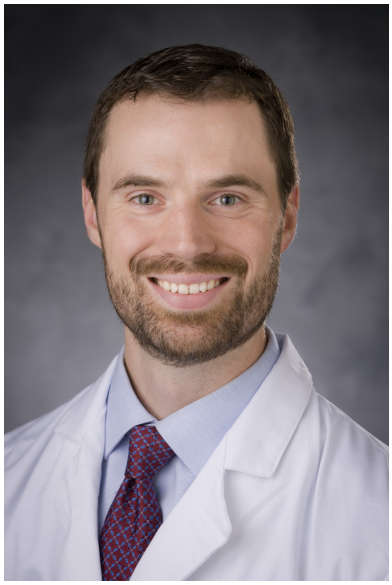
Conclusion:
Preclinical and clinical data suggest that dual inhibition of Ang-2/VEGF-A with faricimab improves vascular stability and reduces inflammation, resulting in greater anatomic outcomes and improved durability over anti-VEGF alone in patients with DME.

IRB APPROVAL Yes

7/14/2022 10:42 am

Diabetic Retinopathy 1 Symposium

Masked Safety Data from ZETA-1, an Ongoing 24-Week Phase 2 Clinical Trial of APX3330, an Oral Therapeutic Being Developed for the Treatment of Diabetic Retinopathy



- Michael Allingham, MD, PhD
- Mitchell Brigell, PhD
- Barbara Withers, PhD
- Ajay Kolli, MPH
- Kavon Rahmani
- Mina Sooch, MBA
- Eliot Lazar, MD
- Ronil Patel, MS
- Mark Kelley, PhD
- Daniel Su, MD
- Peter Kaiser, MD FASRS
- David Boyer, MD

Objective:
To evaluate safety and tolerability of APX3330 dosed at 600mg per day in subjects with diabetic retinopathy (DR) in a Phase 2 clinical trial.

Purpose:
APX3330 is a novel, small molecule inhibitor of Ref-1, a transcriptional regulator of both angiogenic and inflammatory signaling pathways relevant to diabetic eye disease.?Oral treatment with APX3330 has demonstrated a favorable?safety and tolerability profile with doses up to 600 mg in over 300 subjects across 11 prior Phase 1 and Phase 2 clinical trials in healthy volunteers and in subjects with hepatitis or solid tumors. The few related adverse events (AEs) were diarrhea or soft stool (4% with APX3330, 2% with placebo) and rash or pruritis (4% with APX3330, 1% with placebo). Here we report the masked safety and tolerability of APX3330 in the ongoing 24-week ZETA-1 Phase 2 clinical trial in subjects with DR.

Methods:
ZETA-1 is a randomized, placebo-controlled, double-masked, multi-center, phase 2 study designed to evaluate the efficacy and safety of oral APX3330, dosed at 600 mg daily for 24 weeks in subjects with DR. Masked safety data for 68 enrolled subjects through January 12, 2022, comprising over 3,700 subject days of exposure, randomized to APX3330 or placebo are summarized.

Results:
Across both treatment arms, there were 52 AEs reported in 28 (41%) subjects. Of the 6 (9%) AEs that were thought to be possibly or probably related to study medication, 4 were mild (frequent bowel movements, rash, pruritis, vertigo) and 2 were moderate (diarrhea, diabetic retinal edema). Six serious AEs have been reported in 6 subjects, all thought to be unrelated to study medication, APX3330 or placebo (1 cellulitis, 1 abnormal involuntary movement, 1 COVID-19; before dosing: 1 coronary artery disease, 1 cholecystitis and 1 osteomyelitis). Two subjects have withdrawn from the trial due to non-serious AEs (vasovagal near syncope in the subject with diarrhea; worsening diabetic macular edema). No major organ toxicities (liver, heart, kidney, brain, lung) and no vital sign abnormalities (blood pressure or heart rate) have been observed.

Conclusion:

APX3330 600mg oral dosing has demonstrated a favorable safety and tolerability profile in subjects with diabetes and DR. These results confirm prior safety findings in subjects with hepatitis, solid tumors, and healthy subjects.

IRB APPROVAL Yes

7/14/2022 10:46 am

Diabetic Retinopathy 1 Symposium

Three-Year Outcomes of the PALADIN Phase IV Study: Comparison of Anatomical Metrics, Efficacy, and Treatment Burden Post FAc

- Christopher Riemann, MD

Objective:
Do additional anatomical measures (RTA, RTSD, CST-AUC) correlate to efficacy and treatment burden post-0.19mg fluocinolone acetonide implant treatment?

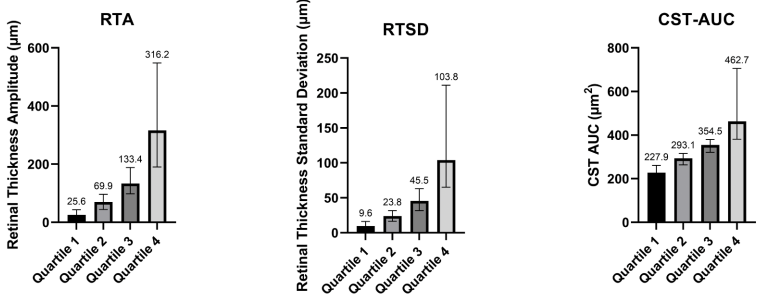
Purpose:
Recently, additional anatomical metrics have been identified that correlate with prognostic outcomes in patients with diabetic macular edema. These include retinal thickness amplitude (RTA), retinal thickness standard deviation (RTSD), and CST area under the curve (CST-AUC). Here, patients from the 36-month PALADIN study were separated into quartiles based on their RTA, RTSD, and CST-AUC post-0.19mg fluocinolone acetonide implant (FAc) treatment to determine the relationship between visual acuity, CST, and treatment burden outcomes.

Methods:
Full analysis population includes 202 eyes from 159 patients enrolled with CI-DME that received FAc and were followed for up to 36 months. 181 eyes met the criteria for RTA and RTSD analysis with 94 meeting the criteria for CST-AUC. Subjects were followed at day 1, week 1, month 2, and quarterly from month 3 up to month 36. RTA was calculated as the max minus min CST measure, RTSD was defined as the standard deviation of CST determinations, and CST-AUC was computed as the area under the curve of CST values.

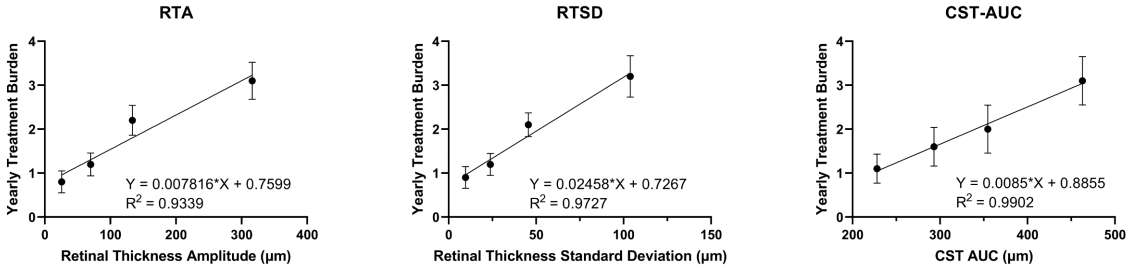
Results:
The quartiles of each subgroup displayed a significant, positive linear relationship to treatment burden with goodness of fit R^2values of 0.9339, 0.9727, and 0.9902 for RTA, RTSD, and CST-AUC respectively. In nearly all groups, each quartile gained vision from baseline to 36 months post-FAc with the largest gain being +8.45 letters in quartile 2 of the RTA subgroup apart from quartile 4 of the CST-AUC subgroup that lost -4.8 letters (NS). CST also improved from baseline to 36 months in all quartiles of each group with the largest reduction in edema found in quartile 4 of the RTA subgroup at -132.5 µm ($p<0.0005$) except for quartile 3 of the RTA subgroup which saw an increase in CST of 13.9 µm (NS).

Conclusion:
Post-FAc, RTA, RTSD, and CST-AUC were all positively, linearly related to treatment burden suggesting patients whose edema is under consistent control will see the greatest benefit in treatment reduction post-FAc. With few exceptions, most eyes benefited from FAc treatment after 36 months with gains in visual acuity and reductions in edema compared to baseline measures. These data again support the efficacy of FAc in the treatment of DME and suggest consistent edema control, and stable CST as positive prognostic indicators of future treatment need.

IRB APPROVAL Yes



Anatomical Quartiles: Means ± Max and Min



Treatment Burden is Linearly Related to Disease Control Post-FAc

7/14/2022 10:50 am

Diabetic Retinopathy 1 Symposium

Investigating the Utility of Near-Infrared Reflectance Imaging for Diabetic Retinopathy Screening

- Mina Naguib, MD
- Archana Nair, MD, MS
- Saagar Pandit, MD
- Ravi Parikh, MD MPH
- Rachel Vardi
- Vikram Modi
- Nitish Mehta, MD
- Yasha Modi, MD

Objective:
The quantity of discrete hyporeflective foci on near infrared imaging can be used as an adjuntive tool in diabetic retinopathy screening.

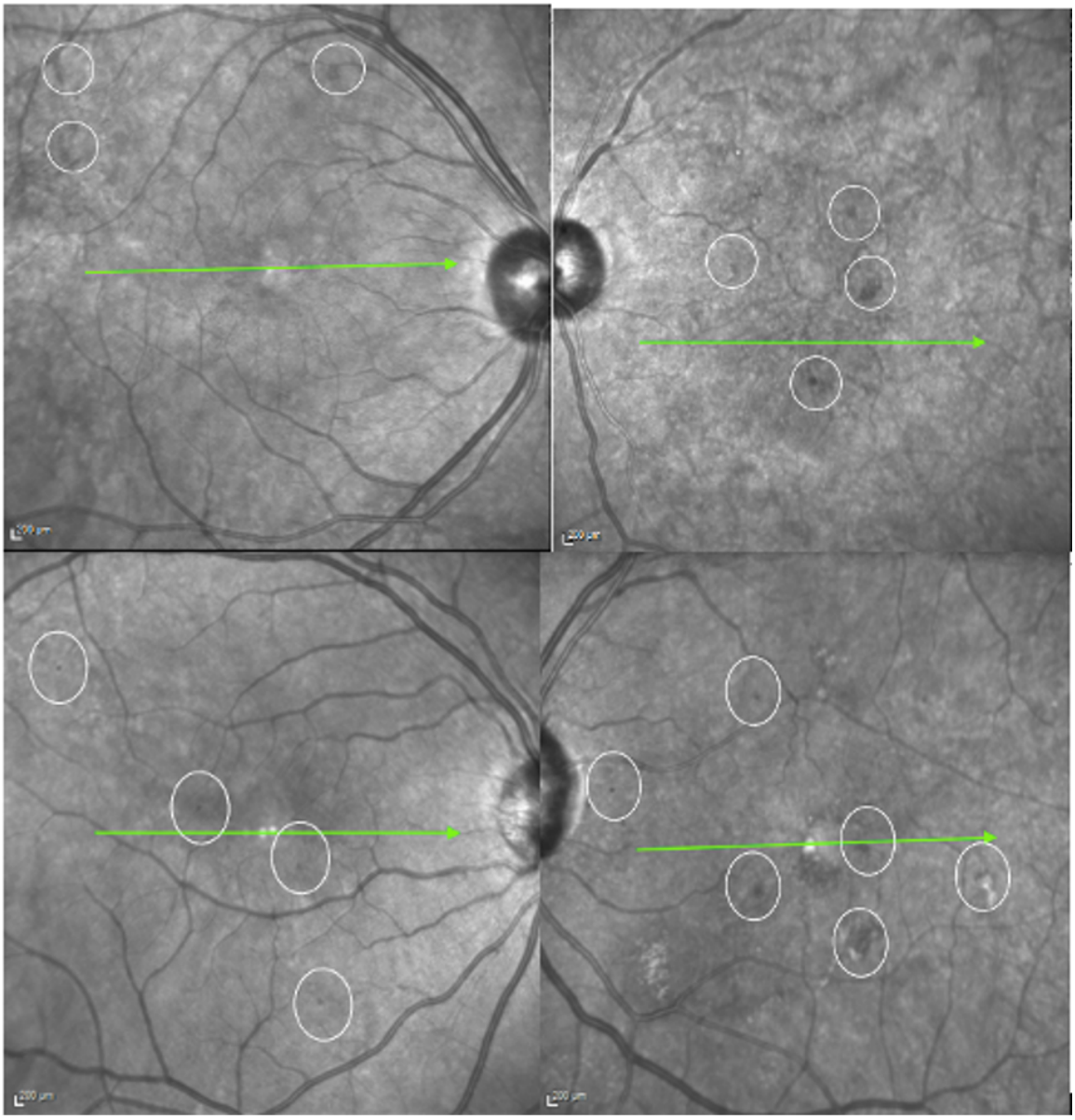
Purpose:
Near infrared reflectence (NIR) is a widely used, non-invasive imaging modality that can highlight intraretinal and preretinal pathology which is useful in diabetic retinopathy screening. Discrete hyporefletive foci on NIR can indicate the presence of intraretinal hemorrhage, microanyeurisms and neovascularization. This study aimed to determine if the quanitity of discrete hyporeflective foci can correlate with traditional diabetic retinopathy severity staging and thus provide clincians with a potential biomarker for assessing patients with diabetic retinopathy.

Methods:
A retrospective chart review was conducted to identify patients with type 1 and type 2 diabetes with and without diabetic retinopathy (DR). Random sampling was performed to generate matched cohorts of patients with all stages of DR. 697 patients were identified that underwent optical coherence tomography using the Heidelberg Spectralis imaging platform. A masked clinician aggregated all DR diagnoses and their respective NIR imaging. This was then shown to two masked ophthalmologists who graded each image with the number of discrete hyporeflective foci. Only hyporeflective foci with discrete margins were included to avoid mislabeling of signals from RPE changes. Images with descrepencies of greater than 10 hyporeflective foci were re-graded by a third masked ophthalmologist. Analysis of variance with appropriate post-hoc tests were conducted to compare means between severity groups. Post-hoc Tukey tests were conducted to determine differences between subgroups of severity. Statistical significance was determined by an alpha level of 0.05. Multiple Receiver operative characteristic (ROC) curves were generated. The area under the ROC (AUROC) was compared to determine the thresholds for hypo- reflective foci for moderate or worse diabetic retinopathy.

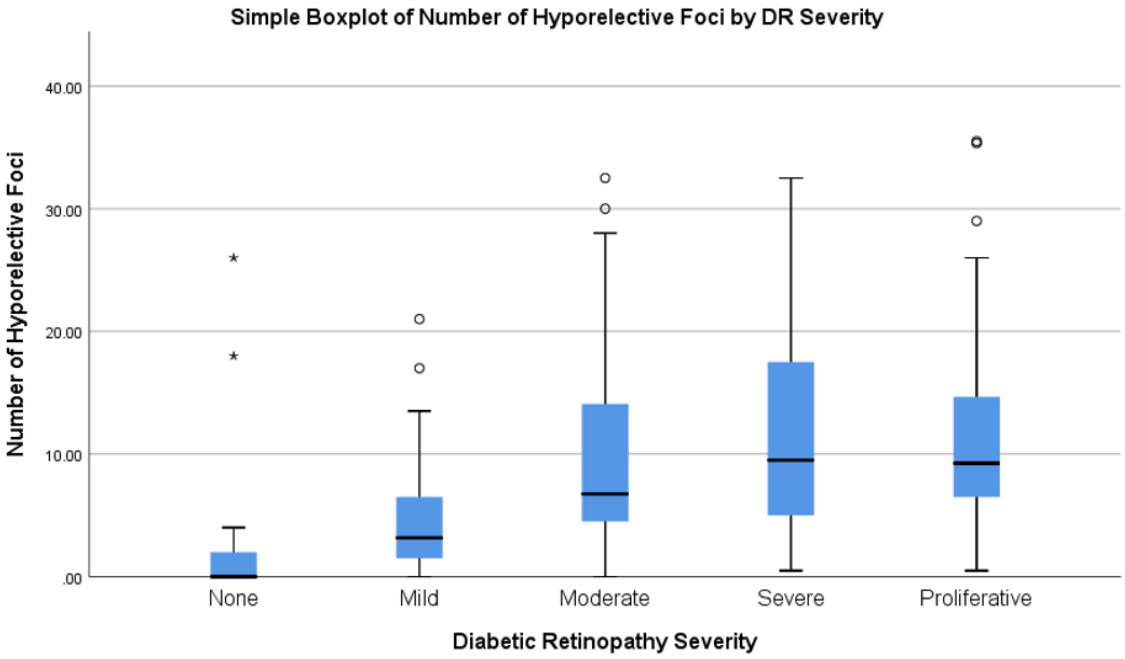
Results:
A statistically significant difference in mean number of hyporeflective foci was found between none and moderate NPDR ($p<0.0001$), none and severe NPDR ($p<0.0001$), none and PDR ($p<0.0001$), mild and moderate NPDR ($p=0.008$), mild and severe NPDR ($p<0.001$), mild NPDR and PDR ($p<0.001$). A statistically significant difference did not exist between moderate to severe, moderate and proliferative disease, or between severe and proliferative disease. Upon creation of the receiver operating characteristic curve, the area under this curve was 0.849 (CI: 0.792, 0.905). Based on this curve, the ideal threshold for detection of moderate nonproliferative diabetic retinopathy or worse was 4.75 hyporeflective foci, with a sensitivity of 79% and a false positive rate of 20%.

Conclusion:
Near infrared imaging may be a useful adjunct tool in screening for DR. Our results indicate that hyporeflective foci differ in number depending of DR disease severity, and that a potential threshold value can be established indicating a high probability of having moderate NPDR or higher.

IRB APPROVAL Yes



Representative photos with white circles indicating hyporeflective foci

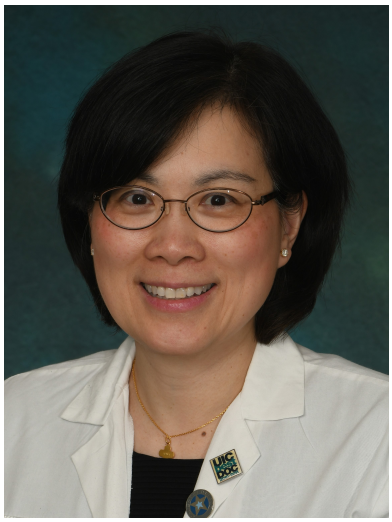


Boxplot of Number of Hyporeflective Foci by severity of DR

7/14/2022 10:54 am

Diabetic Retinopathy 1 Symposium

Progressive Quantitative Outer Retinal Optical Coherence Tomography Abnormalities in Early Diabetic Retinopathy Compared with Controls



- Jennifer Lim, MD, FARVO, FASRS
- David Le, BS
- Tae Yun Son, PhD
- Xincheng Yao, PhD

Objective:
Can quantitative analysis of OCT features differentiate between early stages of diabetic retinopathy?

Purpose:
To investigate whether OCT quantitative feature analysis of photoreceptor abnormalities can serve as a biomarker to distinguish between stages of early diabetic retinopathy (DR).

Methods:
We performed a prospective, cross-sectional OCT study evaluating DR biomarkers in patients 18 years of age or older with type 2 diabetes mellitus and no DR (NoDR) or mild non-proliferative DR (NPDR). Patients without prior or current macular edema and no prior ocular surgery were eligible. Patients were excluded for any other ocular diseases except for cataracts or mild refractive error. All patients underwent a complete anterior segment slit lamp examination, dilated ophthalmoscopy and 6 × 6 mm volumetric, macula-centered, OCT scans (ANGIOVUE spectral domain OCTA system; Optovue, Fremont, CA). OCT images with severe motion or signal loss were also excluded. OCT volumes were exported into a custom developed MATLAB (Mathworks, Natick, MA) software for further outer retinal analysis.

Results:
14 control subjects (21 eyes) and 31 diabetic patients (20 NoDR eyes and 21 mild NPDR eyes) underwent OCT imaging. There were no significant differences between the groups regarding age, gender, hypertension or duration of diabetes (ANOVA, P=0.69, Chi-square test, P=0.85). OCT images were analyzed for 11 outer retinal features: 6 length features (distance from external limiting membrane (ELM) to photoreceptor inner segment ellipsoid (ISe), distance from ISe to interdigitation zone (IZ), distance from IZ to retinal pigment epithelium (RPE), distance from ELM to IZ, distance from ELM to the first and second hyporeflective troughs) and 5 intensity features of the ELM, ISe, IZ, RPE, and ISe/RPE ratio. ISe intensity features differed between mild NPDR and control eyes (Student's t-test, $p<0.001$) and between mild NPDR and NoDR eyes (Student's ttest, $p<0.05$). Overall, ISe intensity trended to decrease with DR progression, whereas RPE intensity trended to increase with DR progression. ISe/RPE ratio decreased with DR progression. There were statistically significant differences between all stages in the perifovea region (Student's t-test, $p<0.05$).

Conclusion:
Quantitative OCT analysis consistently revealed photoreceptor abnormalities in diabetic patients with NoDR and mild NPDR; ISe/RPE intensity ratio of perifoveal OCT was the

most sensitive biomarker to differentiate all three cohorts.

IRB APPROVAL Yes