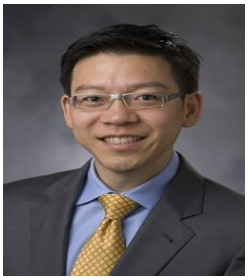
9:50 AM

Ranibizumab Improves Vision in Patients With Myopic Choroidal Neovascularization (mCNV): Results From the Phase III RADIANCE Trial



- Paul Hahn, MD, PhD
- Min Tsuboi, Pharm.D.
- Steven Francom, PhD
- Carlos Quezada-Ruiz, MD
- Zdenka Haskova, MD, PhD

OBJECTIVE The RADIANCE trial compared the efficacy and safety of 2 ranibizumab (RBZ) regimens versus verteporfin photodynamic therapy (vPDT) in patients with vision loss due to mCNV.

PURPOSE Recent analyses of large-scale databases (NHANES, IRIS® Registry, and U.S. Population Census) suggested that mCNV affected >41,000 patients in the US in 2014. Until recently, vPDT was the only approved treatment of mCNV in the US. RADIANCE (NCT01217944) was the first phase III study of anti-VEGF versus this active comparator. Its results led to recent RBZ approval in the US for mCNV.

METHODS RADIANCE was a 12-month, phase III, randomized, double-masked clinical trial conducted in 277 patients with visual impairment due to mCNV. Patients were randomized 2:2:1 to 3 groups: 1) two monthly injections of RBZ 0.5 mg, followed by as-needed (PRN) treatment based on VA stability criteria (RBZ-VA, n = 106), 2) one RBZ 0.5-mg injection followed by PRN treatment based on disease activity

(RBZ-DA, n = 116), or 3) vPDT (n = 55). Starting at month (M) 3, patients in the vPDT arm were allowed to receive rescue RBZ 0.5 mg, vPDT, or both at the investigators' discretion. Superiority of BCVA outcomes was assessed at both M3 and M12.

RESULTS Visual outcomes in the RBZ-VA and RBZ-DA treatment groups were superior to the vPDT arm. Mean BCVA changes from baseline to M3 were +12.1 ETDRS letters in the RBZ-VA group and +12.5 letters in the RBZ-DA group, compared with only +1.4 letters in the vPDT group (both $P < 0.00001$). At M12, patients gained a mean +13.8 (RBZ-VA), +14.4 (RBZ-DA), and +9.3 (vPDT/RBZ) ETDRS letters from baseline. By M12, the majority (n = 38/55, 69.1%) of patients in the vPDT arm had received ≥1 RBZ injections as rescue therapy at the investigators' discretion. The median numbers of RBZ injections by M12 were 4.0 (RBZ-VA), 2.0 (RBZ-DA), and 2.0 (vPDT). The observed RBZ safety profile was consistent with previously established safety profiles in other approved retina indications for RBZ. No deaths or endophthalmitis occurred in any treatment arm by M12.

CONCLUSION Intravitreal RBZ treatment was superior to vPDT at M3, with equivalent improvements in the 2 individualized RBZ treatment regimens. RBZ produced rapid and significant BCVA gains of 12.1 (RBZ-VA) and 12.5 (RBZ-DA) letters at M3, which were sustained at M12 (13.8 and 14.4 letters in RBZ-VA and RBZ-DA, respectively), with patients requiring a median of 2–4 RBZ injections over 12 months.

TAKE HOME MESSAGE The RADIANCE study demonstrated that intravitreal ranibizumab therapy was superior to verteporfin photodynamic therapy for patients with myopic choroidal neovascularization.

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

9:58 AM

Peripheral and Macular Retinal Vascular Dynamics in DME and RVO Following Aflibercept Therapy: The PERMEATE Study 6-Month Results

- Justis P. Ehlers, MD
- Sunil Srivastava, MD
- Rishi P. Singh, MD
- Aleksandra V. Rachitskaya, MD
- Amy S. Babiuch, MD

OBJECTIVE To assess and quantify the impact of aflibercept therapy on retinal vascular features (e.g., leakage, ischemia, microaneurysms) in DME and RVO with quantitative ultra-widefield angiography (UWFA).

PURPOSE Anti-VEGF therapy is a first-line choice for DME and macular edema secondary to RVO but the specific impact of therapy on the underlying panretinal vascular pathophysiology has not been fully explored. The purpose of the PERMEATE study is to evaluate the impact of aflibercept therapy on the peripheral and macular angiographic features utilizing a novel quantitative ultra-widefield analysis tool.

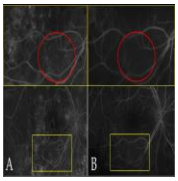
METHODS PERMEATE is an IRB-approved prospective open-label study. Key inclusion criteria were foveal-involving retinal edema secondary to DME or RVO and E-ETDRS visual acuity of 20/25 or worse in the study eye. Key exclusion criteria were prior intravitreal pharmacotherapy or laser photocoagulation in the study eye. All eyes received intravitreal aflibercept monthly for the first 6 visits and then every other month

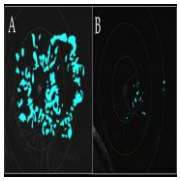
for the next 6 visits. Ultra-widefield angiography (UWFA) and OCT-angiography was performed every 3 months. A novel quantitative assessment tool evaluated changes in ischemia, leakage, and microaneurysms on UWFA.

RESULTS A total of 31 eyes were enrolled. Twenty eyes had completed the 6-month visit at the time of this abstract. We expect the full cohort to be presented at the ASRS meeting. Mean age was 68 years. Mean baseline BCVA was 20/80 and the mean baseline central subfield thickness was 524 microns. DME was the underlying diagnosis in 11 eyes (55%) and RVO in 9 eyes (45%). Mean BCVA improved 3.6 lines to a mean of 20/40 ($p = 0.001$). Mean CST improved to 272 microns ($p < 0.001$). Intraretinal fluid resolved in 55% of eyes and subretinal fluid resolved in 100% of eyes. Presence of leakage improved from 95% at baseline to 65% at month 6. Presence of macular ischemia improved from 35% to 5%. Presence of peripheral ischemia improved from 75% to 40%. Quantitative assessment of microaneurysms demonstrated a 52% reduction in the posterior pole. Quantitative leakage measurement also demonstrated a reduction of 83%. Quantitative ischemia assessment demonstrated a mean reduction of 53%.

CONCLUSION Quantitative assessment of angiographic parameters on UWFA demonstrates significant changes in retinal vascular leakage, retinal ischemia, and microaneurysms in eyes undergoing treatment with intravitreal aflibercept. Further research is needed to better define the role of these quantitative parameters for prognostic assessment, disease burden evaluation, and therapeutic response.

TAKE HOME MESSAGE Quantitative assessment of retinovascular features on ultra-widefield angiography demonstrates significant improvement in leakage and ischemia following treatment with aflibercept for DME and RVO.





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

10:06 AM

Dexamethasone Intravitreal Implant vs Ranibizumab vs Combination for Central Retinal Vein Occlusion (ORION)

- Victor Hugo Gonzalez, MD
- Hamzah Khalaf, MD

OBJECTIVE To compare the effect of dexamethasone implant, ranibizumab, and combination of the two in the treatment of macular edema secondary to central retinal vein occlusion.

PURPOSE The pathophysiology of retinal vein occlusion of this disease includes elevated vascular permeability factors as well as inflammatory cytokines. Therapies include photocoagulation, anti-VEGF agents, corticosteroids, dexamethasone, and surgery. In this study, we compare the outcomes of dexamethasone implant and the combination of ranibizumab and dexamethasone implant with ranibizumab alone.

METHODS This is a multicentered randomized masked clinical trial comparing dexamethasone implant alone every 16 weeks, ranibizumab alone every 4 weeks, and the combination of dexamethasone implant every 16 weeks and ranibizumab according to reinjection parameters assessed monthly through week 20. Sham injections were used to achieve masking of the subject. The primary outcome was change in central retinal thickness using spectral domain OCT and change in ETDRS best corrected visual acuity at 24 weeks. Secondary outcome was the number of injections received during the 24 weeks.

RESULTS As on January 2017, 34 subjects were enrolled with 11 in ranibizumab arm, 14 in dexamethasone implant arm, and 9 in combination arm. Utilizing last observation carried forward, 29 subjects have outcome measurements with 8 in ranibizumab arm, 13 in dexamethasone implant arm, and 8 in combination arm. There was no statistically

significant difference in the change in BCVA between ranibizumab and combination (mean 16.8 vs 18.5, p=0.67) nor dexamethasone implant and combination (mean 13.2 vs 18.5, p=0.36). There was also no statistically significant difference in the change in CRT between ranibizumab and combination (mean -408 vs -486, p=0.56) nor dexamethasone implant and combination (mean -376 vs -486, p=0.50). Regarding the number of injections, the combination group received significantly less injections than ranibizumab only (mean 3.5 vs 6, p<0.01) and the dexamethasone implant group received significantly less injections than the combination group (mean 2 vs 3.5, p<0.001).

CONCLUSION There was no significant difference in structural or functional outcomes between ranibizumab only, dexamethasone implant only, or combination of the two. However, the dexamethasone implant group received significantly less injections than either combination or ranibizumab only.

TAKE HOME MESSAGE There is no difference between ranibizumab, dexamethasone implant, or the combination of both at 24 weeks in the treatment of CME secondary to CRVO while the combination group had less injections.

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

10:14 AM

Role of Per-Operative Anti-VEGF During Vitrectomy For Vitreous Haemorrhage in Relation to Postoperative Nonclearing Vitreous Haemorrhage and Cystoid Macular Oedema

- Manish Nagpal, MD, FRCS (UK)
- Navneet Mehrotra, DNB
- Avijit Vishnoi, MS

OBJECTIVE To assess the role of Per operative anti vegf for non clearing vitreous haemorrhage in reducing the incidence of post operative non clearing vitreous haemorrhage and Cystoid macular oedema (CME).

PURPOSE To assess the role of peroperative anti vascular endothelial growth factor (Anti-VEGF) on the incidence of Postoperative Non clearing vitreous haemorrhage and Cystoid macular oedema in patients undergoing pars plana vitrectomy (PPV) for nonclearing vitreous hemorrhage (VH) due to retinal vascular disorders.

METHODS Patients undergoing vitrectomy for non clearing vitreous haemorrhage (N=312) were assigned to group A (eyes undergoing PPV without AntiVEGF; n= 165) and group B (eyes undergoing PPV with AntiVEGF; n = 147) and were followed up for 6

months. Incidence of Rebleed and DME were noted on follow up. Central foveal thickness was noted postoperatively on OCT for all the cases.

RESULTS The incidence of post-operative vitreous hemorrhage (POVH) in-group A was 21.81%, which was significantly (p value = 0.025) higher than in-group B (12.24%). Mean CFT in-group A (289.24 + 49.47 microns) was higher as compared to group B (263.42 + 94.42 microns).

CONCLUSION This study showed that per operative intravitreal anti-VEGF given at the end of the surgery significantly reduce the incidence of POVH and helped in achieving better CFT post operatively.Hence the incidence of CME was lower in in the eyes given anti vegf along with surgery.

TAKE HOME MESSAGE Giving per operative anti vegf at the end of vitrectomy for vascular conditions helps reduce the incidence of post operative non clearing haemorrhge and Cystoid maculaar oedema macular oedema.

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

10:30 AM

En Face OCT and OCT Angiography to Assess the Spectrum of Perivenular Ischemia and Paracentral Acute Middle Maculopathy in Retinal Vein Occlusion

- David Sarraf, MD
- Khalil Ghasemi Falavarjani, MD
- Nopasak Phasukkijwatana, PhD, MD
- K. Bailey Freund, MD
- Emmett T. Cunningham, MD, PhD, MPH
- Ananda Kalevar, MD, FRCS(C), DABO
- H Richard McDonald, MD
- Rosa Dolz-Marco, MD, PhD
- Philipp Roberts, MD
- Irena Tsui, MD
- Richard B. Rosen, MD, DSc(Hon)
- Lee Jampol, MD
- Srinivas Reddy Sadda, MD

OBJECTIVE To assess the spectrum of perivenular ischemia in eyes with central retinal vein occlusion (CRVO) using en face optical coherence tomography (OCT) and OCT angiography.

PURPOSE To assess the spectrum of perivenular ischemia in eyes with central retinal vein occlusion (CRVO) using en face optical coherence tomography (OCT) and OCT angiography.

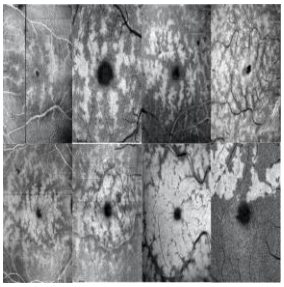
METHODS Eyes with recent retinal vascular obstruction, including CRVO, illustrating paracentral acute middle maculopathy (PAMM) in a perivenular fern-like pattern with en face OCT were evaluated in this study. Multimodal retinal imaging including en face structural OCT and OCT angiography was performed with segmentation of the inner

nuclear layer in all patients. Color fundus photography and fluorescein angiography (FA) images were used to create a vascular overlay of the retinal veins versus the retinal arteries to map the distribution of PAMM lesions with en face OCT analysis.

RESULTS Multimodal retinal imaging was performed in 11 eyes with acute retinal vascular obstruction. While 8 eyes demonstrated obvious findings of retinal vein occlusion (5 with CRVO and 2 with hemicentral RVO), 3 eyes presented with unremarkable retinal examination findings. OCT angiography demonstrated deep retinal capillary plexus (DCP) ischemia corresponding to the PAMM lesions. En face OCT analysis demonstrated a spectrum of perivenular PAMM, illustrating a fern-like, perivenular pattern in the mildest form and diffuse PAMM with periarteriolar sparing in the most severe form. Arterial hypoperfusion secondary to outflow obstruction from a CRVO appears to be the most common cause of this presentation although primary arterial hypoperfusion or insufficiency may also be an etiology.

CONCLUSION This is the first study to illustrate the importance of en face OCT in the diagnosis of CRVO and other forms of central retinal vascular obstruction. En face OCT and OCT angiography are essential imaging modalities to identify ischemia at the level of the deep capillary plexus and in a perivenular pattern, findings that would not be demonstrated with conventional dye based angiography.

TAKE HOME MESSAGE En face OCT and OCT angiography are essential to identify ischemia at the deep capillary plexus level, in a perivenular pattern, in eyes with CRVO and other forms of retinal vascular obstruction.



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

10:38 AM

Disorganization of the Retinal Inner Layers as a Predictor of Visual Acuity in Eyes With Macular Edema Secondary to Vein Occlusion

- Ori Segal, MD
- Or Segev
- Dalia Dori, MD
- Victor A Flores, MD
- Michael Mimouni

OBJECTIVE To investigate whether spectral domain–optical coherence tomography (SD-OCT) parameter disorganization of the retinal inner layers (DRIL) is predictive of VA in eyes with baseline macular edema secondary to vein occlusion (VO-ME).

PURPOSE Biomarkers predicting future best corrected visual acuity (BCVA) in eyes with baseline macular edema secondary to VO-ME may substantively improve risk assessment, management decisions, and selection of eyes for clinical studies. Therefore, the purpose of the study was to determine whether baseline or early change in SD-OCT parameter DRIL is predictive of BCVA in eyes with center-involved VO-ME.

METHODS A retrospective, longitudinal cohort study of patients from two tertiary centers (Meir Medical Center and Rambam Health Care Campus) with VO-ME who were treated with bevacizumab. Data collected included demographics, BCVA, and SD-OCT images from baseline, 4-month, and 8-month visits. Exclusion criteria included cataract surgery within 12 months, and previous retinal pathology affecting BCVA. On SD-OCT,

the 1-mm-wide retinal area centered on the fovea was evaluated by masked graders for DRIL extent, cysts, hyperreflective foci, microaneurysms, cone outer segment tip (COST) visibility, and external limiting membrane or ellipsoid zone disruption.

RESULTS A total of 136 eyes of 136 subjects were included in this study. In univariate analysis greater DRIL extent at baseline correlated with worse baseline BCVA (P=0.003). Also correlated with worse baseline BCVA were increased central subfield thickness (P=0.005), large intraretinal cysts (P=0.04), and extent of COST (P=0.001), ELM (P<0.001) or ellipsoid zone disruption (P<0.001). In multivariate analysis extent of DRIL (P=0.03) and ellipsoid zone disruption (P<0.001) were the only parameters correlated with baseline BCVA. An increase in DRIL during 4 months was associated with BCVA worsening at 8 months (point estimate, 0.02; 95%CI, 0.01-0.04 per 100 μm; P=0.01). Also correlated with BCVA worsening at 8 months were increased central subfield thickness (P=0.005), intraretinal cysts (P=0.02), subretinal fluid width (P=0.009) and external limiting membrane disruption (P=0.03). In stepwise backward multiple regression analysis with 4-month change in BCVA as the dependent variable only DRIL was predictive of an 8-month BCVA change (point estimate, 0.03; 95%CI, 0.01-0.07 per 100 μm; P=0.02).

CONCLUSION Disorganization of the retinal inner layers in the 1-mm foveal area is associated with BCVA, and change in DRIL predicts future change in BCVA in VO-ME. This study supports the use of DRIL as a prognostic sign when interpreting OCT scans in eyes with baseline macular edema secondary to vein occlusion.

TAKE HOME MESSAGE Spectral domain–optical coherence tomography parameter disorganization of the retinal inner layers (DRIL) is predictive of VA in eyes with baseline macular edema secondary to vein occlusion.

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

10:46 AM

Ranibizumab With or Without Verteporfin Photodynamic Therapy for Polypoidal Choroidal Vasculopathy: 12-Month Results of EVEREST II

- Colin S. Tan, MBBS, MMed (Ophth), FRCSEd (Ophth)
- Philippe Margaron, PhD
- Chrystel Feller, PhD

OBJECTIVE EVEREST II compares the long-term functional and anatomical effects of ranibizumab + vPDT combination therapy with ranibizumab monotherapy in a large patient population with symptomatic macular PCV.

PURPOSE EVEREST II is a 24-month, randomized, double-masked phase IV study (NCT01846273) designed to compare the treatment outcomes of ranibizumab 0.5 mg + verteporfin photodynamic therapy (vPDT) versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy (PCV) across 41 Asian sites. Here, we report the Month 12 results.

METHODS PCV patients (N= 322) were randomized 1:1 to receive ranibizumab + vPDT (N=168) or ranibizumab monotherapy (N=154). The eligibility of the study eye was confirmed before randomization by the Central Reading Center using a standardized protocol with well-defined diagnostic criteria. All patients received 3 monthly loading doses of ranibizumab, and then pro re nata (PRN) at intervals of at least 1 month based

on the retreatment algorithm. vPDT (combination arm) or sham PDT (ranibizumab monotherapy arm) was administered on Day 1 and then PRN from Month 3 through Month 11 at intervals of at least 3 months based on the retreatment algorithm. BCVA and polyp regression were assessed at Month 12.

RESULTS Baseline characteristics, including mean BCVA (61.1 letters), were similar between both treatment arms. Combination therapy was superior to ranibizumab monotherapy with respect to BCVA improvement from baseline at Month 12 (LS mean change: +8.3 vs +5.1 letters; p=0.013) and achieving complete polyp regression at Month 12 (69.3% vs 34.7%; p<0.001). At Month 12, 69% and 58.8% of patients had ≥ 69 EDTRS letters in the combination therapy and ranibizumab monotherapy arms, respectively. Median number of ranibizumab injections was 4 in the combination therapy arm and 7 in the monotherapy arm, and 61% of patients in the combination therapy arm only required the first vPDT. In the combination therapy arm, 50.6% of patients needed only 3 or 4 ranibizumab doses. These patients gained 8.7 letters from baseline at Month 12 to reach 70.3 letters and 96.3% were diagnosed by the investigators with no disease activity at Month 11. Safety event rates were similar between both arms.

CONCLUSION The 12-month results of the EVEREST II study demonstrate that ranibizumab monotherapy and ranibizumab + vPDT combination therapy improved visual acuity in PCV patients. The combination of ranibizumab with vPDT resulted in additional visual acuity improvements and higher rates of polyp resolution, with fewer ranibizumab injections than with ranibizumab monotherapy.

TAKE HOME MESSAGE Ranibizumab in combination with verteporfin photodynamic therapy (vPDT) is superior to ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy (PCV).

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

10:54 AM

Types of Strokes Seen in Patients Receiving Intravitreal Anti-VEGF Injections: A Case-Control Study

- Sophie Jane Bakri, MD
- Matthew Starr, MD
- Lauren A. Dalvin, MD
- Jackson Abou Chehade, MD
- Gena M. Damento
- Maria Garcia, BA
- Saumya Shah, BS
- Raymond Iezzi, MD, MS

OBJECTIVE To describe the types of strokes seen in patients receiving intravitreal anti-VEGF injections as compared with control groups

PURPOSE Strokes are currently classified into ischemic, embolic, or hemorrhagic infarcts. The purpose of this study was to identify the differences, if any, in the types of strokes seen in patients receiving intravitreal anti-vascular endothelial growth factor (VEGF) versus a normal control population.

METHODS A retrospective review of patients receiving anti-VEGF from 2004 to 2013 was performed. Using the Rochester Epidemiology Project (REP), records of all patients who received at least 1 anti-VEGF injection for AMD, DME, PDR and RVO were identified. Minimum follow-up for inclusion was 2 years. Two age- and sex-matched control groups were identified: one cohort from the pre-anti-VEGF era (1990-2003), and one concurrent cohort from 2004-2013. Charts were reviewed up to 2015 for demographic data, medical history, thromboembolic events, and mortality data. Data on the location and type of stroke, and age of the patient at the time of the stroke was collected.

RESULTS There were 690 patients identified during the study period as receiving an intravitreal injection for AMD, DME, PDR, and RVO. There were 419 (60.7%) females and 271 (39.3%) males with an average age of 74.1 ± 12.0. Amongst the patients receiving intravitreal injections, 39 patients (5.7%) suffered a stroke after receiving an intravitreal injection. In the era prior to anti-VEGF, 92 patients (14.0%) suffered a stroke, and in the concurrent cohort, 27 (3.2%) suffered a stroke. Of the patients in the study group, 38 had sufficient data to characterize the type of stroke: 27(71.1%) were ischemic, 6 (15.8%) were embolic, and (13.2%) were hemorrhagic. There were no differences in the types of strokes identified amongst the patients receiving intravitreal injections and those in the pre anti-VEGF era as well as the concurrent time period (all p values >0.05).

CONCLUSION Some literature suggests that the mechanism of action of anti-VEGF agents may predispose patients to suffering from hemorrhagic infarcts. Our data suggests that there was no predilection to the development of hemorrhagic infarcts or any other type of stroke amongst those patients receiving intravitreal anti-VEGF compared to control populations.

TAKE HOME MESSAGE There is no predilection to the development of hemorrhagic infarcts or any other type of stroke amongst those patients receiving intravitreal anti-VEGF compared to control populations.

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