Autologous RPE Transplantation in Cases of Long-Standing, Refractory Wet AMD

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OBJECTIVE This study shows the effectiveness of particular surgical approach as a treatment of chronic wet AMD.

PURPOSE To evaluate the effectiveness of the autologous RPE transplantation as an alternative approach of traditional treatment methods in cases where multiple Anti-VEGF therapy becomes ineffective and vision is already significantly reduced.

METHODS Prospective interventional case series. 26 eyes of twenty six patients having longstanding wet-form AMD and low vision (varied from 0.01 to 0.09 in decimals) were. All eyes were evaluated pre-operatively using OCT, FA and ICGA to determine the lesion size, location, scarring amount of CNV and central foveal thickness. All patients were previously treated with multiple intravitreal injection of Anti-VEGF drugs (mean number of injections was14). 23Gauge vitrectomy system was used in all cases. After peripheral 210˚ retinotomy and retinal detachment, CNV lesion was removed and RPE patch taken from infero-temporal quadrant has been re-grafted into the subfoveal zone. Silicone oil tamponade was used in all cases. Recruitment period was 54 months and follow-up period was 60 months.

RESULTS Visual Acuity improved in 3 (12%) cases, varied from 0.1 to 0.15 (mean 0.13 in decimal), unchanged in 18 (69%) cases and worsened in 5 (19%) cases. Intra-operative complications have been observed such as subfoveal hemorrhage at the end of the procedure in 5 (19%) cases, retained subretinal PFCL bubble(s) in 2 (8%) cases, silicone bubble migration into the AC in 2 (8%) cases. Postoperative complications were as follow: patch graft retraction and atrophy in 3 (12%) cases, retinal detachment complicated by PVR in 1 (4%) case, secondary glaucoma in 1 (4%) case and secondary CNV formation and leakage in 1 (4%) case. ICGA revealed RPE graft revascularization in 23 (88%) cases starting at the 4th week and completing by 12 weeks. Neurosensory retina (NSR) thickness of the foveal zone on OCT has not changed post-operatively, but only 2 cases were cystoid macular edema was the cause of NSR thickening.

CONCLUSION Autologous RPE transplantation in cases of long standing wet AMD, refractory to Anti-VEGF treatment may have some clinical value in terms to avoid monthly injections and maintain the stable vision for a long run, but since non-remarkable improvement in visual acuity and serious intraoperative complications due to long learning curve, these cases need to be selected cautiously.

TAKE HOME MESSAGE Autologous RPE transplantation has limited functional outcomes in cases of chronic wet AMD and is associated with significantly high rate of intra- and post-operative complications.

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

Prospective, Randomized, Subject-Masked Evaluation of Intravitreal Sirolimus vs Anti-VEGF in Chronic Neovascular AMD With Persistent Retinal Fluid

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OBJECTIVE Is intravitreal sirolimus superior to standard of care anti-VEGF in chronic neovascular AMD when either subretinal or intraretinal fluid persists despite previous treatment with anti-VEGF agents?

PURPOSE In the CATT trial, at two years, 50% - 85% of subjects had residual fluid (IRF, SRF or sub-RPE fluid). Additionally, the two year results indicated that IRF had a significant negative impact on vision. We thus sought to determine if subjects who had previous chronic treatment with anti-VEGF agents and chronic residual fluid would benefit from a switch to intravitreal sirolimus.

METHODS Six month prospective randomized subject-masked evaluation of sirolimus vs standard of care Anti-VEGF in the treatment of neovascular AMD despite multiple previous treatments. Subjects were randomized in a 1:1 ratio. Key inclusion criteria were (1) BCVA 5-75 in study eye, and (2) persistent fluid despite at least three previous intravitreal anti-VEGF injections in the past five months. Response measures included Heidelberg OCT, FA, and BCVA. The sirolimus group received injections at baseline, month two & four with sham at month one, three and five; the anti-VEGF group was

treated monthly. A reading center was used to analyze the SD-OCT images in a masked manner.

RESULTS 43 subjects were consented with three screen fails (two did not meet VA requirements, 1 had retinal hole). Twelve of the randomized subjects were male. 20 subjects were randomized to sirolimus and of the antiVEGF group 19 received bevecizumab and one received aflibercept. In the sirolimus group the average baseline visual acuity was 47.1 letters and in the Anti-VEGF group 53.9 letters. Previous number of Anti-VEGF injections for the sirolimus group was 29.45 and for the Anti-VEGF group 37.47. To date 21 subjects have completed and 17 are in follow-up. Efficacy measures include 1) Change in intraretinal and subretinal fluid from baseline to month six, as measured by CST on Heidelberg OCT 2) Percent of subjects in each group found to be without intraretinal and/or subretinal fluid at month six 3) Change in BCVA from baseline to month six. Complete results of the study will be presented, including the reading center determined changes in lesion components over the study duration.

CONCLUSION The last subject will finish the trial (month six) in June 2016 and we will present the complete results at the meeting. The analysis plan includes the following: 1) Change in CST from baseline to month six, as determined by a reading center. 2) Change in BCVA from baseline to month six 3) Change in intraretinal and subretinal edema from baseline to month six 4) Change in CNV lesion components

TAKE HOME MESSAGE While Anti-VEGF agents are excellent first line therapy for wet-AMD, additional treatments options for persistent fluid should continue to be investigated. Sirolimus may be one such agent.

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

Comparison of Treatment Outcomes Among Subtypes of Polypoidal Choroidal Vasculopathy in a Multicenter Randomized Controlled Study (EVEREST Study)

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OBJECTIVE Attendees will appreciate the different clinical subtypes of polypoidal choroidal vasculopathy, and the impact of the classification system on prognostication of this disease.

PURPOSE Polypoidal choroidal vasculopathy (PCV) has high prevalence among some populations, and a variable clinical course. We previously described a novel classification of 3 subtypes of PCV. We aimed to describe the frequency and characteristics of PCV subtypes among patients from a multicenter randomized controlled trial, and to determine the impact of PCV subtypes on clinical outcomes.

METHODS We analyzed 60 patients with symptomatic macular PCV from the EVEREST Study. Standardized imaging protocols, including indocyanine green (ICGA) and fluorescein angiography (FA), were used by the Central Reading Center to confirm the diagnosis of PCV. The image sets were subsequently graded to classify PCV into 3 subtypes, and correlated with visual acuity (VA) and central retinal thickness (CRT). Type A PCV had polyps with interconnecting channels only, Type B had branching vascular networks with no leakage on FA, and Type C had branching vascular networks

with significant leakage on FA. VA and retinal thickness on optical coherence tomography were reviewed monthly throughout the study.

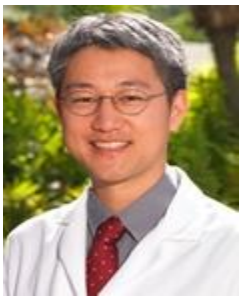
RESULTS Of the 60 patients, 54 were gradeable for PCV subtype. Among these, 8 had Type A PCV (14.8%), 27 had Type B (50%) and 19 had Type C (35.2%). VA and reduction in retinal thickness varied significantly with PCV subtype. At baseline, VA was 65.8 letters for Type A, compared to 57.0 for Type B and 45.6 for Type C ($p<0.001$). At 6 months, the VA was highest among patients with Type A compared to Types B and C (80.1 letters vs. 67.2 vs. 50.4 respectively, $p<0.001$), with the differences among the 3 subtypes statistically significant. Type A PCV gained 13 letters vs. 8.5 (Type B) and 6.9 (Type C) ($p<0.001$). VA ≥20/40 was highest for Type A compared to Types B and C (100% vs. 51.9% vs. 10.5%, $p<0.001$). Retinal thickness improved in all PCV subtypes. At 6 months, the CRT was thickest for Type C PCV followed by Type B and Type A (201.7 μm vs. 188.7 μm vs. 183.8 μm, $p=0.657$).

CONCLUSION The PCV subtype classification shows a good structure-function relationship and also affects the visual outcome following treatment. This PCV subtype classification may be applied to different populations. The distinction in clinical outcomes between the PCV subtypes is observed in the initial months following the start of treatment.

TAKE HOME MESSAGE Polypoidal choroidal vasculopathy consists of subytpes which may be distinguished based on indocyanine green and fluorescein angiography. The subtypes affects the clinicial outcomes

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

High-Dose Ranibizumab Treatment in Polypoidal Choroidal Vasculopathy: PEARL 2 Trial (Polypoidal Choroidal Vasculopathy With Intravitreal Ranibizumab)



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- James C. Lai, MD
- Shannon Kogachi
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OBJECTIVE To prospectively evaluate high dose ranibizumab in Polypoidal Choroidal Vasculopathy (PCV) on stabilization of vision, anatomical changes, and safety on continuous monthly treatment for 2 years.

PURPOSE Polypoidal choroidal vasculopathy is a variant of neovascular age-related macular degeneration (NVAMD). The distinction between PCV and NVAMD is important because PCV has differing clinical phenotypes, reduced response to anti-VEGF therapy, and various treatment algorithms. We evaluated prospectively monthly high dose ranibizumab in PCV for 2 years of monthly therapy.

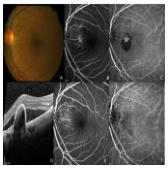
METHODS A prospective open-label clinical trial of high dose ranibizumab was performed on 24 patients diagnosed with PCV. Participants were examined and treated monthly with ranibizumab administered at each visit (2mg/0.5cc or 1mg/0.5cc). Dosing was dependent on drug availability, with discontinuation of the 2mg preparation during the study. Primary outcomes included stabilization of vision (loss ≤15 EDTRS letters) and incidence of ocular and systemic adverse events. Secondary outcomes measured were changes in visual acuity, subretinal hemorrhage, subretinal exudates, central foveal

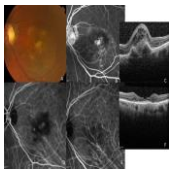
thickness (CFT), choroidal thickness, and polypoidal complex morphology on indocyanine green angiography (ICGA).

RESULTS 24 eyes of 24 subjects entered the PEARL 2 clinical trial with 21 subjects completing the study. 3 subjects lost ≥ 15 EDTRS letters, 1 lost > 5 letters, 6 remained unchanged, 6 gained >5 letters, and 5 gained > 15 EDTRS letters at 2 years. There were no ocular or systemic side effects. Mean EDTRS vision was 57.8 letters at baseline and 64.9 at 2 years (p=0.41). Subretinal fluid increased, decreased, remained stable, and resolved in 1, 2, 1, 15 eyes respectively. Average central foveal thickness was 308 μm at baseline and 216 μm at 2 years (P<0.0001). Choroidal thickness measured at the fovea was on average 206 μm at baseline and 178 μm at 2 years (P=0.001). The BVN of the PCV complex increased, decreased, and remained stable in 3, 1, 18 eyes respectively and the polyps decreased, remained stable, and resolved in 8, 11, and 2 eyes respectively. No increase in disease recurrence was noted with the switch from the 2mg to 1 mg preparation.

CONCLUSION High dose ranibizumab is an effective treatment in hemorrhage and exudation in PCV with improvement in visual acuity and anatomical changes within the retina. The morphology of the PCV complexes have varying response to high dose treatment, with the majority remaining stable. Additional prospective trials involving this therapy are needed to define its role in the current treatment paradigms.

TAKE HOME MESSAGE High dose ranibizumab has good visual results in most subjects but does not result in resolution of the polyps in the majority of cases.





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

Outcomes and Practice Preferences After Anti-VEGF Injection Endophthalmitis

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- Carl D. Regillo, MD, FACS
- J. Michael Jumper, MD
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- Lawrence J. Singerman, MD,FACS
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- Marina Gilca, MD
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- Ryan J. Whitted, MD
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- Vaishali Shah

OBJECTIVE This study is a multicenter review of post-injection endophthalmitis and its effect on subsequent management of neovascular diseases.

PURPOSE Anti-VEGF injections have revolutionized the treatment paradigm of neovascular diseases. To date there have been no large studies evaluating how endophthalmitis after an anti-VEGF injection may change the management of subsequent neovascular disease. This study aims to investigate trends in treatment, medications and injection algorithms after endophthalmitis.

METHODS Retrospective review of medical records from ten major ophthalmic centers identified 147 patients who developed endophthalmitis after an anti-VEGF injection between December 2004 and November 2015. Changes in medication use, treatment

plan and LogMAR visual acuity before and after endophthalmitis were compared using two-tailed Wilcoxon Signed-Ranks tests for matched pairs and McNemar's Test for matched pairs with Yates correction of 0.5.

RESULTS Average age was 77.39. Mean follow up time was 215 weeks with a median of 82. Average LogMAR visual acuity prior to endophthalmitis was 0.59 in the affected eye and 0.57 in the unaffected eye (p=0.81). Mean interval from injection to presentation of endophthalmitis was 4.52 days, with a median of 3 days. 48% were culture positive. Average LogMAR visual acuity at initial presentation and at one, two and three months follow up were 2.15, 1.28, 1.31, 1.23, respectively (p=2.02E-17, 4.34E-15, 5.98E-14, 4.91E-10). Medication used prior to endophthalmitis was bevacizumab 38% of the time, compared to ranibizumab (34%) and aflibercept (29%). There was no significant change in medication choice at one, two or three months follow up (p=0.77, 0.86, 0.85, respectively). Prior to endophthalmitis, regular injections comprised 25% of treatment plans in the affected eye, compared to treat and extend (48%) and PRN (27%). After endophthalmitis, the distribution was 12%, 42%, 46%, respectively (p=0.007).

CONCLUSION This is the largest series with the most extensive follow up to examine the effect of endophthalmitis on anti-VEGF treatment algorithms of the affected and contralateral eyes. The choice of treatment protocol was significantly different after endophthalmitis, with a preference toward treat and extend and PRN.

TAKE HOME MESSAGE An episode of endophthalmitis due to anti-VEGF injection can influence providers to adjust their treatment algorithm of neovascular diseases.

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

Effects of Aflibercept in Patients With Polypoidal Choroidal Vasculopathy: One-Year Results of the VAULT Study

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- Hyun Woong Kim, MD
- Ji Eun Lee, MD, PhD

OBJECTIVE To see efficacy of aflibercept intravitreal injection in patients with polypoidal choroidal vasculopathy (PCV).

PURPOSE To investigate efficacy of aflibercept for treatment-naïve polypoidal choroidal vasculopathy (PCV).

METHODS Three doses of initial monthly intravitreal aflibercept 2.0 mg injections were followed by maintenance injections every two months. The best-corrected visual acuity (BCVA) and central subfield macular thickness(CSMT) were measured at every visit. Fluorescein angiography and indocyanine green angiography (ICGA) were obtained at baseline, month 3, and month 12. The primary outcome measure was the proportion of patients who maintained visual acuity without losing 15 letters or more at month 12. The changes in BCVA, macular appearance on optical coherence tomography (OCT), and polypoidal lesions on ICGA were also evaluated.

RESULTS Of the 48 patients enrolled, 40 completed the follow-up and were included in the final analysis. The mean age was 67.0 years (range: 44-84 years). Thirty-five eyes (87.5%) did not lose visual acuity more than 15 letters at month 12. BCVA was improved significantly from 55.1 letters at baseline to 64.2 letters at month 12 (9.0-letter gain;

p<0.001). The mean CSMT decreased from 365.2µm at baseline to 253.6µm at month 12 (p<0.001). Complete dry-up of the macula was observed in 76.2%, 64.3%, and 60.0% of patients at months 3, 6, and 12, respectively. Reappearance or increase in fluid was noted in 14 patients at month 6 and in 16 patients at month 12. Complete polyp regression was achieved in 61.9% and 66.7% at months 3 and 12, respectively. New polyp formation was noted in 23.1% of patients at month 12.

CONCLUSION Fixed dosing of intravitreal aflibercept showed favorable functional and anatomical outcomes in PCV patients for one year. However, improvements achieved by initial monthly injections were not maintained after extending the treatment interval in some of the patients.

TAKE HOME MESSAGE Aflibercept intravitreal injection showed favorable functional and anatomical outcomes in polypoidal choroidal vasculopathy.

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

Previous Intravitreal Therapy is Associated With Increased Risk of Posterior Capsule Rupture During Cataract Surgery

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OBJECTIVE We sought to determine if previous history of intravitreal injections is associated with intraoperative complications during phacoemulsification cataract extraction.

PURPOSE To investigate if previous intravitreal therapy is a predictor of posterior capsule rupture (PCR) during cataract surgery using a multicenter, national electronic medical record (EMR) database with univariate and multivariate regression modelling.

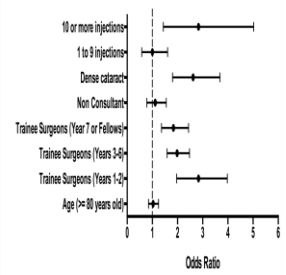
METHODS Anonymized data were extracted for eyes undergoing cataract surgery from 20 hospitals using the same EMR for cases performed between 2004 and 2014. Variables included as possible risk indicators for PCR were age, sex, number of previous intravitreal injections, indication for intravitreal therapy, grade of healthcare professional administering intravitreal therapy and cataract surgeon grade.

RESULTS Data were available on 65,836 cataract operations, of which 1,935 had undergone previous intravitreal therapy (2.99%). In univariate regression analyses, patient age >= 80 years, brunescent cataract, junior cataract surgeon grade and number of previous intravitreal injections were significant predictors of PCR. Considering number of previous intravitreal injections as a continuous variable, the OR for PCR per intravitreal injection was 1.04 (p=0.006) after adjusting for other significant

independent predictors. Repeat analysis considering intravitreal injections as a categorical variable, showed 10 or more previous injections were associated with a 2.83 times higher likelihood of PCR (p=0.001) after again adjusting for other significant independent predictors.

CONCLUSION Previous intravitreal therapy is associated with a higher likelihood of posterior capsule rupture during cataract surgery. This study provides data to help inform surgeons and patients about the risk of complications when undergoing cataract surgery after multiple prior intravitreal injections. Further investigation is required to determine the aetiology behind the increased PCR risk.

TAKE HOME MESSAGE Previous intravitreal therapy may be associated with a higher likelihood of posterior capsule rupture during cataract surgery.



HUMAN RESEARCH This study involves human research.
IRB Approval Status: Exempt from approval

Topical Dorzolamide-Timolol With Intravitreal Anti-Vascular Endothelial Growth Factor for Neovascular Age-Related Macular Degeneration: A Pilot Study

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- Sunir J. Garg, MD
- Marc J. Spirn, MD
- Mitchell S. Fineman, MD
- James F. Vander, MD

OBJECTIVE We found that topical dorzolamide-timolol reduced edema in eyes with neovascular age-related macular degeneration (nAMD) that are incomplete anti-vascular endothelial growth factor (VEGF) responders.

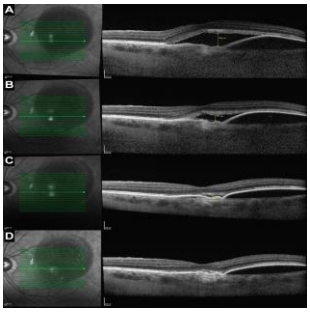
PURPOSE We evaluated the effect of topical dorzolamide-timolol on anatomic and functional outcomes in eyes with nAMD and incomplete response to anti-VEGF therapy.

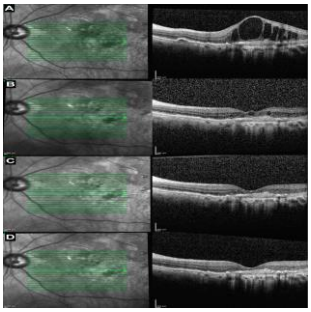
METHODS This was a prospective single-arm interventional study of patients with nAMD and persistent edema despite fixed-interval intravitreal anti-VEGF therapy. Baseline spectral-domain optical coherence tomography (SD-OCT) and clinical data were obtained at enrollment and from one visit before. Enrolled eyes were placed on topical dorzolamide-timolol and continued to receive the same intravitreal anti-VEGF drug at the same interval as prior to enrollment for the study duration. Patients were followed for at least two visits after enrollment. Central subfield thickness (CST), maximum subretinal fluid (SRF) height, and maximum pigment epithelial detachment (PED) height were recorded at each visit.

RESULTS Ten eyes of 10 patients completed the study. 8 eyes received intravitreal aflibercept and 2 eyes received intravitreal ranibizumab. All study eyes had been on chronic anti-VEGF therapy with the same medication prior to study enrollment for an average of 21.9 injections. Comparing the visit before enrollment to the enrollment visit, there was no significant change in mean CST, mean maximum SRF height, or mean maximum PED height. Mean CST decreased from 419.7 μm at enrollment to 334.1 μm at the final visit (p=0.012) with a significant decrease noted at the first visit after enrollment. Mean maximum SRF height decreased from 126.6 μm at enrollment to 49.5 μm at the final visit (p=0.020) with a significant decrease noted at the first visit after enrollment. Mean maximum PED height decreased from 277.4 μm at enrollment to 239.9 μm at the final visit (p=0.12). Mean logarithm of the minimum angle of resolution VA was 0.54 at enrollment and 0.48 at final visit (p=0.62).

CONCLUSION These data suggest that topical dorzolamide-timolol may reduce CST and SRF in eyes with persistent exudation despite consistent fixed-interval intravitreal anti-VEGF treatment for nAMD.

TAKE HOME MESSAGE Topical dorzolamide-timolol may help reduce edema in eyes with neovascular age-related macular degeneration that are incomplete anti-vascular endothelial growth factor responders.





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