Sunday, August 26

7:35 AM

Age-Related Differences in the Prevalence of Genetic Risk Markers in Patients With Intermediate AMD

- Carl C. Awh, MD

OBJECTIVE To report the prevalence of known genetic risk factors in young and older patients with intermediate and advanced AMD (AREDS categories 3 and 4) in a cohort of over 13,000 patients.

PURPOSE Certain genetic polymorphisms, as well as age and environment, are associated with increased AMD risk. If genetic risk remains constant and the impact of age and environmental risk factors increases over time, we hypothesize that there is a greater prevalence of genetic risk alleles in younger patients with intermediate and advanced AMD.

METHODS We examined genetic risk factors and phenotypes of 13,112 patients who were tested during 2011 and 2012. Individuals were categorized using the simplified AREDS severity scale rating of the more advanced eye. Informed consent was obtained. DNA was analyzed for 5 polymorphic sites in CFH, an insertion/deletion polymorphism in the ARMS2 loci (chromosome 10), the C3 locus and the MT-NADH 2 gene. A risk score was generated using genetics and smoking history in a linear regression model. Five levels of risk of progression to advanced AMD (AREDS 4) were defined. Risk was dichotomized at the 80^{th} percentile and analyzed as a function of age (<60 yrs vs >90 yrs) using a fisher exact test.

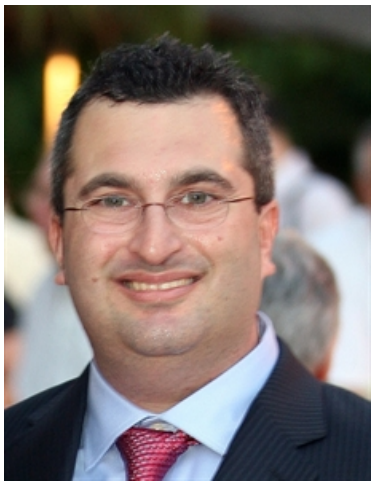
RESULTS Patients were sorted by AREDS phenotype. Of Caucasians (10,073), we identified 1,764 AREDS 3 and 665 ARDS 4 patients. Genotyping was performed in a CLIA/CAP-certified lab. We stratified each phenotypic group by age and examined the frequency of risk scores. Risk was defined for 5 groups relative to the population average risk for progression to advanced AMD. The predicted risk of progression to advanced AMD by age 80 in each group was as follows: "reduced" (2.5%), "average" (9.0 %), "moderate" (25%), "elevated" (45%), and "extreme" (65%). The proportion of individuals with greater than average risk decreased with age. Among AREDS 3 patients the average age of "reduced" risk individuals was 83 yrs, while the average age of those at "extreme" risk was 73 yrs ($p < .05$). For each decade advance in age the proportion of patients in higher risk categories was reduced. This effect was due to differences in CFH risk allele frequency ($p<0.02$). This trend was not observed in AREDS 4 patients.

CONCLUSION Younger patients with intermediate AMD demonstrate more genetic risk compared to older phenotype-matched patients. This is primarily due to differences in CFH risk allele frequency. The impact of age and environment may lead to relatively earlier progression to advanced AMD in younger patients with higher genetic risk. Therefore, more frequent monitoring of these patients may be indicated.

TAKE HOME MESSAGE The impact of genetic risk is more significant in younger patients with intermediate AMD. In older patients, the effects of age and environment become relatively more important.

7:43 AM

Systemic Complement Inhibition With Eculizumab for the Treatment of Geographic Atrophy in AMD: The COMPLETE Study



- Zohar Yehoshua, MD,MHA
- Carlos A de A Garcia-Filho, MD
- Giovanni Gregori, PhD
- Ying Li, PhD
- William J Feuer, MS
- Fernando M. Penha, MD, PhD
- Srinivas Reddy Sadda, MD
- Li Zhang, PhD
- Kang Zhang, MD, PhD
- Philip J. Rosenfeld, MD, PhD

OBJECTIVE To describe the effect of systemically inhibiting complement component 5 (C5) on the growth of geographic atrophy (GA) in eyes with non-exudative age-related macular degeneration (AMD).

PURPOSE The COMPLement Inhibition with Eculizumab for theTreatment of Non-Exudative Age-Related Macular Degeneration (COMPLETE) Study was designed to prospectively evaluate the effect of eculizumab, an FDA-approved systemic inhibitor of complement component 5 (C5), on the growth rate of geographic atrophy (GA) in eyes of patients with non-exudative age-related macular degeneration (AMD).

METHODS Patients with GA were randomized 2:1 to receive intravenous eculizumab or saline.Ten patients randomized to active treatment received 600 mg eculizumab for 4 weeks followed by 900 mg every 2 weeks until week 26, the next 10 patients received 900 mg eculizumab for 4 weeks followed by 1200 mg every two weeks until week 26. After 26 weeks, patients were followed without treatment every 3 months for an additional 6 months. Ophthalmologic exam, normal and low luminance ETDRS visual acuity testing, andimaging studies were performed at baseline and at months 3, 6, 9, 12. All patients were genotyped for the major AMD risk alleles. The primary endpoint was the change in area of GA at 6 months.

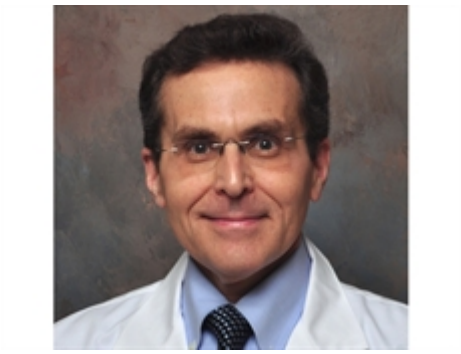
RESULTS Thirty study eyes of 30 patients were enrolled and randomized 1:1:1 to the low dose, high dose, and placebo groups. At baseline, the mean areas of GA (SD) measured by SDOCT were 7.3mm^2 (4.8) and 4.7 (3.6) mm^2 for the eculizumab and placebo groups, respectively (p=0.13). Baseline mean ETDRS visual acuity scores (SD) were71.3 (7.8) and 78.6 (5.2) letters for the eculizumab and placebo groups respectively, (p=0.01). Low and high dose eculizumab groups had similar areas of GA (p=0.44), but the high dose patients read 7 fewer letters (p=0.040). At baseline the mean low luminance visual acuity scores (SD) were48.1 (15.4) and 56.1 (11.7)letters for the eculizumab and placebo groups respectively, (p=0.16). In addition, 19 fellow eyes were found to meet entry criteria and will be evaluated as a secondary endpoint. All patients completed the infusions through 26 weeks and no drug-related adverse events were identified.

CONCLUSION Systemic complement inhibition with FDA-approved C5 inhibitor known as eculizumab was well tolerated through 6 months.The outcome data describing the effect of eculizumab on the growth rates of GA are currently being analyzed and will be presented.

TAKE HOME MESSAGE Treatment with intravenous eculizumab (Soliris) will test whether systemic complement inhibition against C5 can slow the progression of geographic atrophy in age-related macular degeneration

7:51 AM

Systemic Complement Inhibition With Eculizumab for the Treatment of Drusen in AMD: The COMPLETE Study



- Philip J. Rosenfeld, MD, PhD
- Zohar Yehoshua, MD,MHA
- Carlos A de A Garcia-Filho, MD
- Ying Li, PhD
- William J Feuer, MS
- Fernando M. Penha, MD, PhD
- Srinivas Reddy Sadda, MD
- Li Zhang, PhD
- Kang Zhang, MD, PhD
- Giovanni Gregori, PhD

OBJECTIVE To describe the effect of systemically inhibiting complement component 5 (C5) on drusen area and volume in eyes of patients with non-exudative age-related macular degeneration (AMD).

PURPOSE The COMPLement Inhibition with Eculizumab for the Treatment of Non-Exudative Age-Related Macular Degeneration (COMPLETE) Study was designed to prospectively evaluate the effect of eculizumab, an FDA-approved systemic inhibitor of complement component 5 (C5), on drusen area and volume in eyes of patients with non-exudative age-related macular degeneration (AMD).

METHODS Patients with eyes containing drusen were randomized 2:1 to receive intravenous eculizumab or placebo. The drusen volume measured at least 0.03mm^3 within the central 3mm of the macula using SDOCT imaging. The first 10 patients randomized to active treatment received 600mg eculizumab for 4 weeks followed by 900mg every 2 weeks, while the next 10 patients received 900mg eculizumab for 4 weeks followed by 1200mg every two weeks. After 26 weeks, patients were followed without treatment every 3 months for 6 months. Ophthalmologic exam, ETDRS visual

acuity testing, and imaging studies were performed. Primary endpoint was the change in drusen volume at 6 months.

RESULTS Thirty patients (study eyes) were enrolled and randomized 1:1:1 to the low dose, high dose, and placebo groups. At baseline, the mean drusen areas (SD) were 2.1 mm^2 (1.0) and 1.9 mm^2 (0.7) for the eculizumab and placebo groups, respectively (p=0.80). The mean drusen volumes were 0.15 mm^3 (0.17) and 0.12 mm^3 (0.08) for each group respectively (p=0.64). Low and high dose eculizumab groups did not differ significantly in drusen area and volume measurements, p=0.058 and p=0.077 respectively. Baseline mean ETDRS visual acuity scores were 80.9 (5.9) and 78.0 (10.0) letters for the eculizumab and placebo groups. The deficits in the low luminance visual acuity scores at baseline were 14.4 (4.9) and 15.5 (5.4) letters (p=0.58). In addition, 12 fellow eyes were found to meet entry criteria and will be evaluated as a secondary endpoint. Twenty-eight out of 30 patients (93%) completed the follow-up through 26 weeks. No drug-related adverse events were identified through 6 months.

CONCLUSION Systemic complement inhibition with the FDA-approved C5 inhibitor known as eculizumab was well tolerated through 6 months. The outcome data describing the effect of eculizumab on drusen area and volume are currently being analyzed and will be presented.

TAKE HOME MESSAGE Treatment with intravenous eculizumab (Soliris) will test whether systemic complement inhibition of C5 can affect drusen area and volume measurements in eyes with non-exudative AMD.

8:05 AM

Baseline Predictors of Visual Outcomes and Treatment Frequency in Patients With Wet Age-Related Macular Degeneration (AMD) in the First Year of HARBOR

- Brandon G. Busbee, MD
- Linda Yau, MPhil, PhD
- Phil Lai, MD

OBJECTIVE Identify baseline characteristics that are predictive of visual outcomes and treatment frequency in the first 12 months of the HARBOR study.

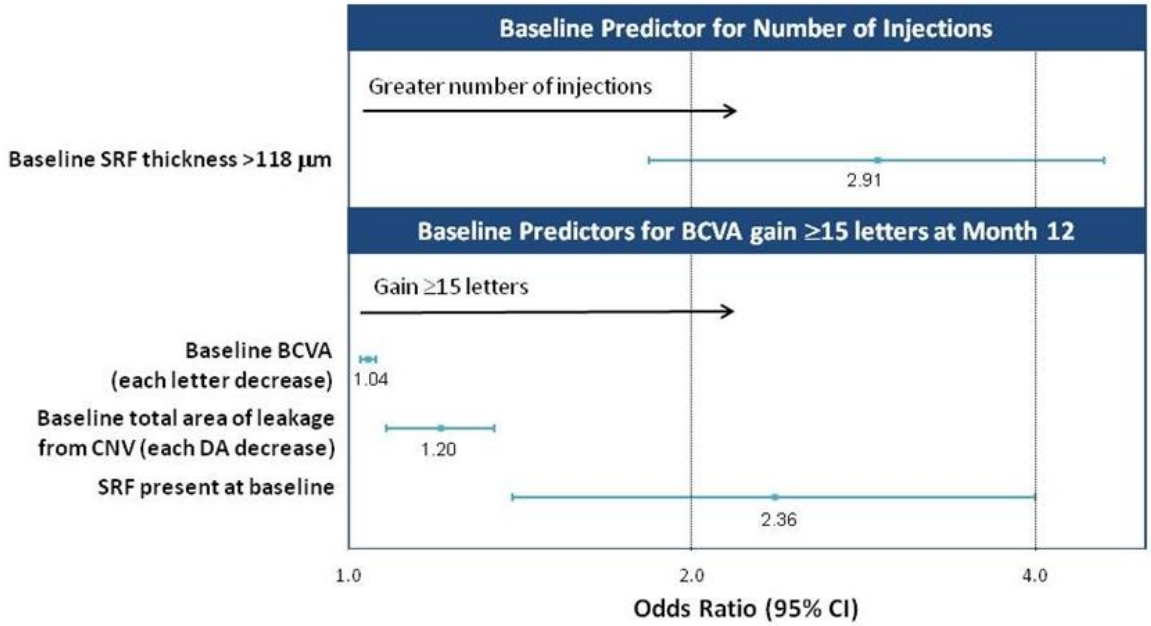
PURPOSE The results of HARBOR demonstrated visual acuity (VA) gains for patients receiving monthly or as-needed (PRN) dosing of ranibizumab for wet AMD. This subanalysis evaluates baseline characteristics in the 0.5 mg cohorts (monthly and PRN) that led to specific visual and injection frequency outcomes. We hypothesize that certain baseline factors may predict outcomes at month 12 in these cohorts.

METHODS HARBOR was a phase III studyfor treatment-naïve, wet AMD. Patients were randomized into 1 of 4 groups. This analysis studied the 0.5 mg monthly (n=275) and 0.5 mg PRN (3 monthly loading doses followed by PRN dosing; n=275) cohorts. Baseline (BL) predictors for gaining ³15 letters and for best-corrected visual acuity (BCVA) change from BL at month 12 (M12) in the 0.5 mg (monthly and PRN) cohorts was explored using logistic and linear regression models, respectively. BL predictors for total number of injections in the 0.5 mg PRN cohort with BL and M12 BCVA were identified by a proportional odds model. Final models included only significant predictors selected by stepwise methods ($P<0.05$).

RESULTS Greater subretinal fluid (SRF) thickness at baseline significantly increased the odds of receiving more total injections in the 0.5 mg PRN cohort. Patients with a baseline SRF thickness >118 mm (measured at its greatest point) had 2.91-times the odds of receiving a greater number of injections than patients whose baseline SRF thickness was £118 mm ($P<0.0001$; **Figure 1**). In the 0.5 mg monthly and 0.5 mg PRN groups, lower baseline BCVA (OR=1.04 for each letter decrease), smaller baseline total area of choroidal neovascularization (CNV) leakage (OR=1.20 for each disc area [DA] decrease), and the presence of SRF at baseline (OR=2.36) significantly increased the odds of gaining ≥15 letters from baseline at month 12. Furthermore, baseline BCVA £44 letters, age £73 years, and total area of CNV leakage ≤5.24 DA with area of occult without classic CNV ≤5.47 DA at baseline were also predictive of significant mean improvements in BCVA at month 12 **(Table 1)**.

CONCLUSION PRN patients with baseline SRF thickness >118 µm were significantly more likely to receive more injections in year 1 of HARBOR, though VA gain was consistent in the entire cohort. Other baseline predictors of better VA outcomes included younger age, smaller CNV leakage area, and lower baseline BCVA. These findings may help clinicians determine an optimal ranibizumab treatment strategy for wet AMD.

TAKE HOME MESSAGE Baseline clinical factors appear to help predict visual and injection frequency outcomes for patients that participated in the HARBOR trial for wet AMD.



Odds ratios are plotted on the natural logarithm scale. Bars are 95% CI on the estimated odds ratio from the proportional odds or logistic regression models.
Proportional odds model with no. of injections categorized by: ≤4 injections, 5 to 6 injections, 7 injections, 8 to 10 injections, and >10 injections as dependent variable was analyzed for predictors of number of injections.
Logistic regression model was analyzed for predictors of BCVA gain ≥15 letters at Month 12.
BCVA=best-corrected visual acuity; CI=confidence interval; CNV=choroidal neovascularization; DA=disc area; SRF=subretinal fluid.

Baseline predictor	Estimated mean difference in BCVA letter score (SE)
BCVA ≤44 letters[1]	+8.1 letters (1.38)
≤73 years of age[2]	+4.5 letters (1.30)
Total CNV leakage area ≤5.24 DA with area of occult w/o classic CNV ≤5.47 DA[3]	+15.8 letters (2.28)
Total CNV leakage area >5.24 DA with area of occult w/o classic CNV >5.47 DA[3]	+14.4 letters (2.79)

[1]Versus BCVA >44 letters.
[2]Versus >73 years of age.
[3]Versus total CNV leakage area >5.24 DA with area of occult w/o classic CNV ≤5.47 DA.

BCVA=best-corrected visual acuity; CNV=choroidal neovascularization; DA=disc areas; SE=standard error; w/o=without.

8:13 AM

Early OCT Responses at Day 7 and Month 1 Post Ranibizumab That Predict Visual Acuity Outcomes and Injection Frequency at Month 12 in the HARBOR Study

- Srinivas Reddy Sadda, MD
- Lisa Tuomi, PharMD
- Linda Yau, MPhil, PhD
- Jeffrey Nau

OBJECTIVE Identify HARBOR patients with early treatment response (favorable OCT outcomes at Day 7 and Month 1 post ranibizumab) that had better anatomic/visual outcomes at Month 12 and required less injections.

PURPOSE Early response to anti-VEGF therapy has been suggested to be predictive of long-term anatomic and visual outcomes in patients with neovascular age-related macular degeneration (wet AMD). Using HARBOR data, we explored spectral domain (SD)-OCT responses at Day 7 and Month 1 following the first ranibizumab injection that may predict BCVA and injection frequency at Month 12 in patients with wet AMD.

METHODS This sub-analysis of the 4-arm, phase III, 24-month HARBOR study included patients randomized to receive intravitreal injections of ranibizumab 0.5 mg or 2.0 mg, on a monthly or as-needed (PRN) schedule after 3 monthly loading doses, who completed Month 12 (M12) and had evaluable BCVA data at M12. Predictors for injection frequency in the 0.5 mg PRN (n=251) and 2.0 mg PRN (n=249) groups were analyzed using separate proportional odds models. Predictors for visual outcomes (n=1000) were explored using a logistic regression model (for BCVA gain of ≥15 letters at M12 from baseline [BL]), and a generalized linear model (for BCVA change at M12 from BL). Observed data were used in these analyses.

RESULTS SD-OCT responses considered in the prediction models were Day 7 and Month 1 (M1) absolute changes from BL in central foveal thickness, central subfield thickness, subretinal fluid (SRF) thickness, pigment epithelial detachment (PED) thickness, total macular volume, and the presence/absence of SRF and PED at Day 7 and M1. Significant predictors ($P<0.05$) for the number of injections in both the 0.5 mg and 2.0 mg PRN arms were presence of SRF at M1 and presence of PED at M1. Presence of SRF at Day 7 was also a significant predictor in the 2.0 mg PRN arm (Table 1). Presence of SRF at Day 7 was the only significant predictor ($P<0.001$) for visual outcomes at M12; patients who had SRF present at Day 7 were more likely (OR=1.8) to achieve a ≥15 letter gain in BCVA at M12 and gained an average of 3.2 letters more in BCVA at M12 than patients who did not have SRF present at Day 7.

CONCLUSION Early persistence of SRF and PED were predictive of requiring more injections in the first year of PRN ranibizumab. Better BCVA gains appeared to be associated with SRF presence at Day 7, but not with early PED presence. Early changes in macular and retinal thickness were not predictive of injection frequency or BCVA at M12. These findings may help clinicians personalize treatment for wet AMD.

TAKE HOME MESSAGE Early response to ranbizumab therapy has predictive value in eyes with neovascular age-related macular degeneration.

	Odds Ratio (95% CI)
Day 7 and Month 1 Anatomic Predictors	**0.5 mg PRN (n=247)***
SRF present at Month 1[1]	4.35 (2.56, 7.40)
PED present at Month 1[2]	1.93 (1.20, 3.11)
	2.0 mg PRN (n=247)*
SRF present & PED present at Month 1[3]	3.67 (1.60, 8.38)
SRF present & PED absent at Month 1[3]	4.02 (1.88, 8.61)
SRF absent & PED present at Month 1[3]	3.17 (1.76, 5.68)
SRF present at Day 7[4]	1.75 (1.02, 3.00)

Proportional odds model with no. of injections categorized by: ≤4 injections, 5 to 6 injections, 7 injections, 8 to 10 injections, and >10 injections as dependent variable was analyzed and stratified by baseline BCVA (<55, ≥55 letters) and baseline CNV class (occult, minimally classic, predominantly classic).
*4 patients in the 0.5 mg PRN arm and 2 patients in the 2.0 mg PRN arm were excluded from the analyses due to missing data.
[1] Versus SRF absent at Month 1.
[2] Versus PED absent at Month 1.
[3] Versus SRF absent & PED absent at Month 1.
[4] Versus SRF absent at Day 7.
CI=confidence interval; PED=pigment epithelial detachment; PRN=pro re nata (as needed); SRF=subretinal fluid.

8:21 AM

Association of Best-Corrected Visual Acuity (BCVA) Gains at Month 12 in the HARBOR Study With Change in Choroidal Neovascularization (CNV) Area

- Karl G. Csaky, MD, PhD
- Linda Yau, MPhil, PhD
- Lisa Tuomi, PharMD

OBJECTIVE Identify changes in the size and anatomic location of choroidal neovascularization (CNV) that may correlate with visual acuity gains at Month 12 in the HARBOR study.

PURPOSE How do changes in CNV size and location correlate with visual outcomes in patients with subfoveal neovascular age-related macular degeneration (wet AMD) administered ranibizumab 0.5 mg or 2.0 mg monthly or as needed (PRN)after 3 monthly loading doses?

METHODS This sub-analysis of the phase III HARBOR study at month 12 included patients =50 years of age with wet AMD who were randomized to receive intravitreal injections of ranibizumab 0.5 mg or 2.0 mg monthly or PRN after 3 monthly loading doses (n=1097). CNV location and change in CNV area (total or classic) over time were evaluated by fluorescein angiography at baseline and at months 3, 6, and 12 (graded by a maskedcentral reading center). At each time point, patients gaining =15 ETDRS letters or gaining <15 ETDRS letters from baseline were classified according to percent change from baseline in CNV area (100% reduction, >0 to 99% reduction, and =0% increase).

RESULTS At baseline, all but 1 patient had subfoveal CNV, and by month 12, extrafoveal, juxtafoveal, or no CNV lesions were observed in nearly half of the patients (Table 1). Compared with the PRN arms, a greater proportion of patients treated monthly showed

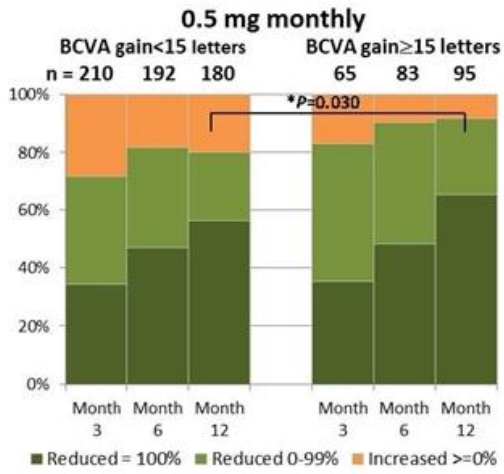
a 100% reduction in total CNV area at Month 12 from baseline (P=0.004). There was no significant association between reduction in classic CNV area from baseline and treatment arm at any time point. At Month 12, area of classic CNV was reduced by 100% in more than 90% of the patients in all treatment arms. After adjusting for study month and treatment, there was a significant association between BCVA gain of =15 ETDRS letters and reduction from baseline in total (P=0.002) or classic (P=0.026) CNV area. In patients who gained =15 letters, the proportion with reduction in the CNV area (total or classic) was greater than that in patients who did not gain =15 letters.

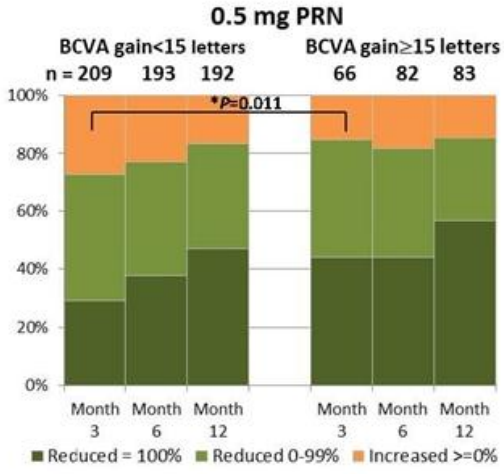
CONCLUSION Ranibizumab treatment (monthly or PRN) induced changes in CNV location and significantly reduced classic CNV area. Monthly treatment was associated with a greater reduction in total CNV area. There appears to be a trend of a positive correlation between reduction in total or classic CNV area from baseline and clinically significant gain in BCVA (=15 ETDRS letters).

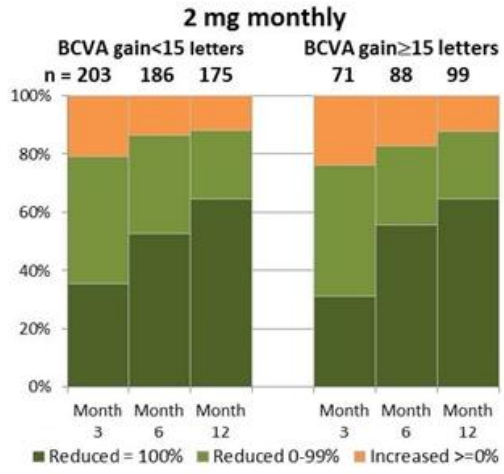
TAKE HOME MESSAGE A large reduction of CNV area may be associated with an improved chance for significant vision improvement (=15 letters) regardless of the dose or frequency of ranibizumab given.

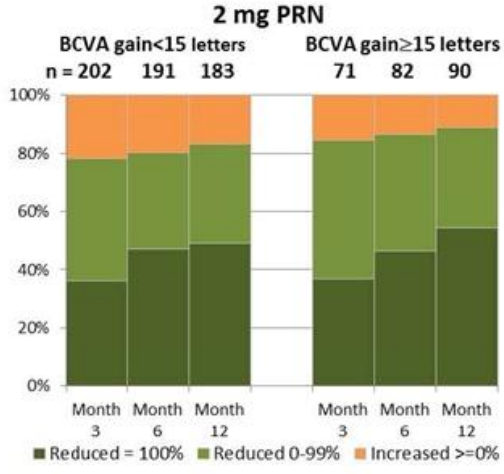
Treatment Group	N	CNV Location, n (row %)			
		Subfoveal	Extrafoveal	Juxtafoveal	None
0.5 mg monthly					
Baseline	275	275 (100)	0 (0)	0 (0)	0 (0)
Month 12	241	117 (49)	43 (18)	13 (5)	68 (28)
0.5 mg PRN					
Baseline	275	275 (100)	0 (0)	0 (0)	0 (0)
Month 12	244	151 (62)	40 (16)	8 (3)	45 (18)
2.0 mg monthly					
Baseline	274	274 (100)	0 (0)	0 (0)	0 (0)
Month 12	239	123 (51)	33 (14)	5 (2)	78 (33)
2.0 mg PRN					
Baseline	273	272 (99.6)	0 (0)	1 (0.4)	0 (0)
Month 12	239	128 (54)	47 (20)	13 (5)	51 (21)

NOTE: percentages may not add up to 100% due to rounding.









8:35 AM

Retinal Pigment Epithelial Cell Loss in Patients With Neovascular Age-Related Macular Degeneration

- Richard F. Spaide, MD
- Nishant Kumar, FRCOphth
- Sarah Mrejen, MD
- Adrian Fung
- Marcela Marsiglia, MD, PhD
- Boon K Loh, MBBS, FRCSEd

OBJECTIVE

To evaluate retinal pigment epithelial cell loss in eyes with neovascular age-related macular degeneration and characterize the consequences of this loss.

PURPOSE

To characterize retinal pigment epithelial (RPE) cell loss as evidenced by autofluorescence imaging in patients with neovascular age-related macular degeneration (AMD).

METHODS

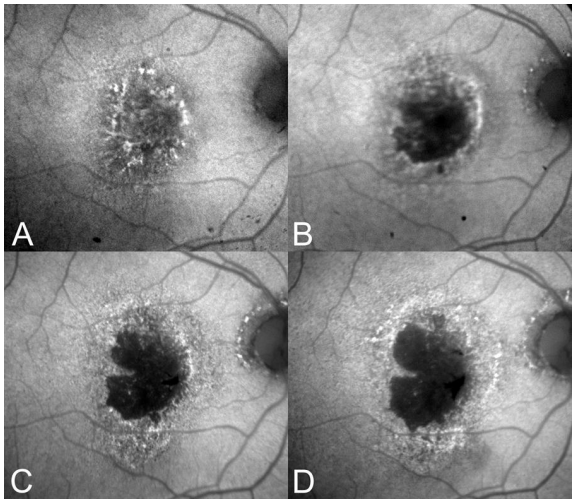
Consecutive patients with neovascular AMD examined in a retinal practice underwent a complete examination including autofluorescence imaging. Areas of confluent absence of autofluorescence signal at least 0.5 mm in greatest linear diameter were measured within the macular area. Patient demographic and examination data were evaluated in relation to the autofluorescence data.

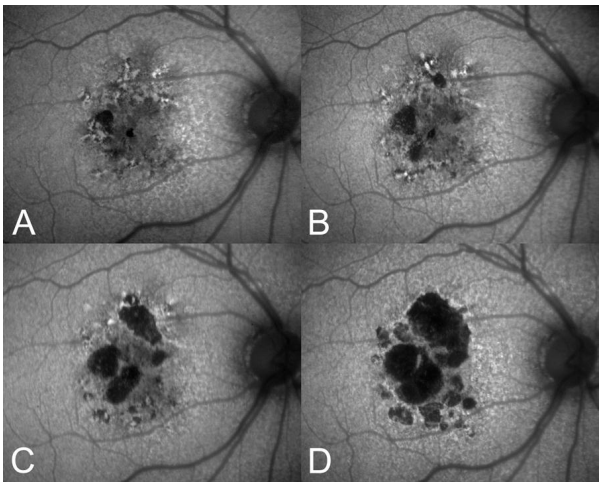
RESULTS There were 162 eyes of 116 patients with a mean age of 82.9 years and the mean visual acuity was 20/71. Confluent loss of autofluorescence was seen in 58.6% of eyes at baseline and the median area of absent autofluorescence among those was 1.57 mm^2 at baseline. Using generalized estimation equation modeling, the significant predictors for area of confluent absent autofluorescence at baseline were duration of disease and any previous treatment with photodynamic therapy. The significant predictor of baseline visual acuity was baseline area of confluent absent autofluorescence. Follow-up was available for 124 (76.5%) eyes with the mean follow-up being 2.9 years. By then the mean visual acuity was 20/90, and 79% of eyes had confluent areas of absent autofluorescence, the large majority of which affected the central macula. The median area of absent autofluorescence was 3.61 mm^2. The best predictor of final visual acuity was the area of absent autofluorescence at the final follow-up.

CONCLUSION

Confluent absence of autofluorescence, a measure signifying RPE loss, was a significant predictor of visual acuity both at baseline and at final follow-up. This is the first study to document the prevalence, rate of progression and factors associated with measures of confluent RPE loss in patients with neovascular AMD.

TAKE HOME MESSAGE Confluent RPE loss in patents with CNV is common, progressive, and is a major determinant of visual acuity in treated patients.





8:43 AM

2 mg Ranibizumab for Fibrovascular Pigment Epithelial Detachments in AMD Refractory to Standard Dosing: The HiPED Study

- Anne E. Fung, MD
- Brandon G. Busbee, MD
- John W. Kitchens, MD
- Richard E Shaw PhD, PhD
- Jan-Kristine Bayabo

OBJECTIVE Patients with fibrovascular PEDs in AMD refractory to at least 6 standard doses of ranibizumab or bevacizumab experienced a mean improvement in vision with monthly 2mg ranibizumab therapy.

PURPOSE AMD with fibrovascular pigment epithelial detachments (PED) that remain after 6 consecutive injections of standard dose ranibizumab and/or bevacizumab are a challenging subtype. The High dose ranibizumab for PED (HiPED) Study is evaluating changes in vision and imaging after dose escalation to 2mg ranibizumab. We hypothesized that the higher dose would control the disease more effectively.

METHODS The HiPED protocol was approved by the CPMC IRB. Consented subjects were enrolled into this randomized, prospective open-label, multi-center, investigator sponsored study for 24 months. Subjects were randomized into 2 groups: Group 1 received 2mg injections monthly, and Group 2 received 2mg for 3 months followed by as needed (PRN) injections for presence of any macular fluid or PED on SD-OCT. At each visit, modified ETDRS protocol visual acuity, dilated fundus exam, and SD-OCT were performed. Fluorescein angiography was obtained at baseline, Months 6, 12 and 24, ICG also at M12 and M24. Changes in ETDRS letters from baseline to Month 3, 6 and 12 were evaluated.

RESULTS 40 patients were enrolled. Patients have completed 6 months (n=34), and 12 months (n=24). Mean visual acuity (VA) at entry was 65 letters (range 25-78, Snellen eq 20/32-20/200). VA improved at 3 months by 4 letters (n=37, p= 0.0001), and at 12 months by 8 letters (n=24, p=0.0001). Mean retinal thickness at baseline, months 6 and 12 were 271, 235 and 245 respectively. Of 24 subjects completing one year (13 in Group 1 and 11 in Group 2), all but two subjects required an injection monthly. Comparison of means from one time point to another was done with Paired t-tests. Comparison of the proportion of patients who did not require injections (Group 2 vs. 1) was done using the Chi-Square statistic using SPSS (version 19.0).

CONCLUSION Subjects with wet AMD and fibrovascular PED refractory to at least 6 months of previous standard therapy who were dose-escalated to 2mg ranibizumab had a mean improvement in visual acuity and reductions in OCT retinal thickness. Despite these improvements, PED were still evident on OCT and monthly injections were required in nearly all patients with this challenging subtype of neovascular AMD.

TAKE HOME MESSAGE Patients with fibrovascular PEDs in AMD refractory to at least 6 standard doses of ranibizumab or bevacizumab experience a mean improvement in vision with monthly 2mg ranibizumab therapy.

8:55 AM

Correlation of Retinal Morphology and Visual Acuity in the Comparisons of Age-Related Macular Degeneration Treatments Trial (CATT)

- Glenn J. Jaffe, MD
- Maureen G Maguire, PhD
- Cynthia Ann Toth, MD
- Gui-Shuang Ying, PhD
- Ebenezer Daniel, MBBS, MS, DO, MPH, PhD
- Juan Grunwald, MD
- Daniel F. Martin, MD

OBJECTIVE To determine the effect of anti-VEGF drug type and regimen on the correlation of visual acuity with OCT and FA-determined retinal morphology in CATT

PURPOSE The morphologic patterns after treatment with anti-VEGF drugs, and the relationship of the morphologic features with VA, and whether it is necessary to eliminate all excess fluid to achieve optimal VA, are not well understood. We describe the effect of different anti-VEGF treatment strategies on lesion activity, as measured by

OCT and FA, and visual acuity outcomes in CATT.

METHODS Stratus OCT, obtained at baseline and at monthly intervals through wk 52, and FA obtained at baseline and wk 52 from 1185 subjects were interpreted by centralized Reading Centers. The frequency of OCT-determined intraretinal fluid (IRF), subretinal fluid (SRF), and subRPE fluid (SRPEF), retinal and subretinal thickness, and FA-determined leakage, stratified by treatment group (L and A, monthly or PRN) was correlated with VA.

RESULTS Fluid of all 3 types (IRF, SRF, SRPEF) and retinal and subretinal tissue thickness, decreased in all 4 treatment groups throughout the study. More eyes treated with L than A had no fluid at 52 wks; however, the majority of eyes still had fluid, most commonly IRF (37-58%), at 1 year. In all treatment groups, average VA increased by wk 52, but at all time points, eyes with residual IRF, and not those with SRF or SRPEF, had worse mean VA (6 to 7 letters). Retinal thickness decreased markedly by 4 weeks, with the greater mean decrease in L eyes (155 u) than A eyes (127 u) and lowest mean thickness at 1 year (266 u) with L monthly than with the other treatments (294-308 u). VA and intraretinal thickness were not related linearly, ie, eyes with abnormally thin (<120 u) or thick (>212u) retinas had worse VA than those with normal thickness (120-212 u). At wk 52, larger CNV lesions had worse VA, (r=-0.25), and eyes with monthly treatment had smaller CNV area than those on PRN treatment.

CONCLUSION Anti-VEGF therapy reduces CNV lesion activity and improves VA in all treatment groups, but at all time points those with residual IRF had worse VA than those with SRF, SRPEF, or no fluid. Abnormally thin or thick retinas had worse VA. These results have important treatment implications in eyes undergoing anti-VEGF therapy for NVAMD.

TAKE HOME MESSAGE Residual intraretinal fluid is associated with worse visual acuity than subretinal fluid or sub-RPE fluid following anti-VEGF therapy.

9:03 AM

Genetic Variants in CFH and CFHR5 Show an Association With Phenotypic Subtypes of Exudative ARMD and With a Response to Anti-VEGF Monotherapy

- Mark H. Nelson, MD, MBA

OBJECTIVE Identify genetic variants associated with the phenotypic subtypes of Choroidal Neovascular Membranes (CNV) in Exudative Age-Related Macular Degeneration and/or the response to anti-VEGF therapy.

PURPOSE This study evaluates the association between genotype and the major sub-types of CNV and the response to anti-VEGF therapy. Additionally, an assessment of risk score, previously validated as a quantitative measure estimating the risk of developing CNV [1] was tested as a proxy to estimate if genetic burden aligned with more aggressive phenotypes and/ or less responsive treatment categories.

METHODS 275 patients with Exudative Age-Related Macular Degeneration were treated with an induction/maintenance protocol consisting of 0.5 mg ranibizumab for a two

year period. Subsequently, each consented genetic specimen was tested across a panel of SNPs previously demonstrated to be associated with CNV.[1] The subjects were classified according to phenotypic subtypes of CNV and to their response to anti-VEGF therapy (Anti-VEGF Sensitive, Anti-VEGF Resistant or Anti-VEGF Dependent). The genetic markers were individually tested for association under an additive genetic model, the mean risk scores were calculated and a t-test performed to compare the means for each pair.

RESULTS The 275 patients included 89 with classic CNV, 171 with occult CNV, 15 with RAP and 105 subjects with bilateral disease. Minor allele frequency estimates were measured - one marker (rs9332739) had minor allele frequency<0.05. Hardy-Weinberg Equilibrium was not assessed due to the known association between the genetic markers and AMD. A total of 374 non-independent association tests were conducted evaluating 11 phenotype-pairs, 13 markers plus 4 haplotypes, with and without adjustment for smoking. Five tests led to $p<0.05$ without adjustment for smoking; all of them, plus one additional had $p<0.05$ with adjustment for smoking. These results are detailed in Table 1. In the comparison of mean risk score for the 12 pairs, 3 pairs had $p < 0.05$ according to the t test. Results for all 12 are given in Table 2 with the 3 p-values below 0.05 highlighted in bold. Mean risk scores were also stratified by smoking status (results not shown).

CONCLUSION These results demonstrate genetic associations ($p <0.05$) between 3 SNPs in CFH and CFHR5 and phenotypic sub-types of Exudative ARMD, the presence of peripapillary subretinal neovascularization, and the response to anti-VEGF monotherapy in CNV subjects. Differences in mean genetic risk score were obtained ($p<0.05$) revealing increased genetic burden in more difficult to treat phenotypes. Testing CNV patients to measure their genetic burden might provide additional information to guide physicians in their therapeutic intervention strategy.

TAKE HOME MESSAGE Phenotypic expressions of Exudative Age-Related Degeneration have associated genotypes that give insight into the response of patients to anti-VEGF monotherapy.

Group1	Group2	Marker	N1	N2	No Adjustment			With Adjustment for Smoking		
					OR	95% CI	p	OR	95% CI	p
RPED	Remainder	rs10490924	31	244	1.81	(1.09, 3.03)	0.0226	1.77	(1.05, 2.96)	0.0311
Polyps	Remainder	rs641153	115	160	2.34	(1.10, 4.95)	0.0267	2.51	(1.17, 5.35)	0.0176
Anti-VEGF Sensitive	Remainder	rs10922153	88	187	0.65	(0.44, 0.96)	0.0287	0.66	(0.45, 0.98)	0.0404
Anti-VEGF Dependent	Remainder	rs403846	58	217	0.63	(0.41, 0.97)	0.0357	0.61	(0.39, 0.96)	0.0308
Anti-VEGF Dependent	Remainder	rs1061170	58	217	0.65	(0.42, 1.00)	0.0493	0.64	(0.41, 0.99)	0.0438
PPP	Remainder	rs10490924	29	246	0.57	(0.32, 1.01)	0.0531	0.56	(0.31, 0.99)	0.0478

Group1	Group2	Mean1	N1	Mean2	N2	95% CI for Difference	T	p
Classic	Occult	0.60	89	0.82	171	(-0.58,0.14)	-1.18	0.2385
Classic	RAP	0.60	89	0.49	15	(-0.65,0.88)	0.32	0.7558
Occult	RAP	0.82	171	0.49	15	(-0.42,1.08)	0.94	0.3626
Polyps	Remainder	0.73	115	0.73	160	(-0.35,0.34)	-0.03	0.9771
Arteriolarization	Remainder	0.66	77	0.76	198	(-0.47,0.28)	-0.50	0.6172
RPED	Remainder	1.36	31	0.65	244	(0.25,1.17)	3.12	**0.0032**
PPP	Remainder	0.29	29	0.78	246	(-1.09,0.10)	-1.70	0.0983
AV Sensitive	Remainder	0.92	88	0.64	187	(-0.06,0.63)	1.63	0.1048
AV Dependent	Remainder	1.04	58	0.65	217	(0.02,0.76)	2.11	**0.0371**
AV Resistant	Remainder	0.59	10	0.74	265	(-1.37,1.08)	-0.26	0.7987
Bilateral	Unilateral	1.02	105	0.59	121	(0.08,0.77)	2.40	**0.0171**
AV Sensitive	AV Dependent	0.92	88	1.04	58	(-0.53,0.29)	-0.57	0.5722

9:11 AM

Flexible Macular Capillary Recruitment in Relative Hypoxia as a Homeostatic Adaptation With Pathologic Implications

- Joseph I. Maguire, MD
- Justis P. Ehlers, MD
- Paul S. Baker, MD

OBJECTIVE To demonstrate the presence of a flexible and inducible macular capillary reserve with longterm pathologic implications.

PURPOSE Oxygen needs of the retina are greater in scotopic than photopic conditions. We postulate that inactive macular capillary bed is “recruited” during times of increased metabolic need, e.g. the scotopic state, as a normal physiologic homeostatic response.

METHODS We developed a standardized indirect method utilizing measurable relative hypoxia and entoptic density (ED) to establish the presence of recruited macular vasculature . Healthy subjects, ages 18 to 40, participated in the study. A blue light entoptoscope with a computer generated entopic field, allowed reproducible recordings of macular ED.Subjects were repeatedly tested in normoxic and hypoxic conditions using the Hypoxico Altitude Training System (Hypoxico Inc, New York, NY).Subjects’ oxygen saturation was monitored by pulse oximetry. Inhaled oxygen percentage was recorded using an in-line oxygen monitor.ED measurements were recorded at room air and in relative hypoxia.

RESULTS Seventeen human subjects participated. Mean baseline oxygen saturation during normoxic conditions was 98.4% (SD: 1.2) and 83.1% (SD: 1.5) with induced hypoxia. When going from induced hypoxia back to normal oxygen saturations, ED decreased by 18.5% [95% CI: (10.6%,25.6%); p=0.0005].

CONCLUSION Increased ED in relative hypoxia implies pre-translational recruitment of inactive macular capillaries. This may serve as a homeostatic mechanism during increased metabolic need. Prolonged activation of aninduciblecapillary network by persistent relative hypoxia, may play a role in ischemic-driven pathologic states, e.g. retinal angiomatous proliferation (RAP).

TAKE HOME MESSAGE Long-term macular capillary recruitment might explain certain macular disease states including age-related macular degeneration, parafoveal telangiectasias, and chorioretinal vascular anastamoses.

9:25 AM

Human Adenovirus Infection Induces RPE Death: Implications for the Pathogenesis of Atrophy

- Lucian V. Del Priore, MD, PhD
- Hui Cai, MD PhD
- Mark A. Fields, PhD, MPH

OBJECTIVE To determine if adenoviruses known to infect humans can cause RPE death, and elucidate the role of complement in this process.

PURPOSE CD46 is a complement regulatory protein located on the basal RPE surface and the complement system has been implicated in the pathogenesis of AMD. Several infectious pathogens are known to use CD46 as a receptor, including measles and adenovirus. Our purpose is to determine whether infection of the RPE with a CD46 specific pathogen in tissue culture can lead to RPE death seen in advanced AMD.

METHODS Human ARPE19 cells were cultured to 70% confluence. Lentiviral-CD46ORF or Lentiviral CD46-shRNAmir was used to over express or knock down the expression level of CD46 in ARPE19 for 72 hours. Non-silencing lentiviral shRNAmir served as a transduction control. Human adenovirus serotype-3 (HAdV3) (dilution from $1:10^{6.2}$ to $10^{13.2}$ from the viral stock with an original titer 10(5.5)TCID[50]/0.2ml) was then introduced into culture dishes. Cell morphology, immunocytochemistry and Western blots were used to monitor HAdV3 infection, and determine the effects of CD46 over expression or knockdown.

RESULTS CD46 protein over expression or knockdown in ARPE19 was confirmed through immunocytochemistry and Western blot using a commercially available anti-CD46 antibody. ARPE19 cells appeared swollen after 96 hour HAdV3 infection; adenovirus infection caused cell death in a dose-dependent fashion. At day 4 the TCID[50] (median tissue culture infective dosage) for ARPE19 without CD46 ove-

rexpression was $1:10^{7.5}$; overexpression of CD46 increased the TCID[50] dilution titer to $1:10^{8.3}$. The same viral load caused 29.8+ 1.3 % more RPE cell death after CD46 overexpression in ARPE19 versus controls. Phase contrast microscopy shows CD46 knockdown protects ARPE19 from HAdV3 induced cell death; CD46 overexpression increases cell death.

CONCLUSION The results suggest that adenovirus-3 infection is capable of inducing RPE cell death in a dose dependent fashion, and that this virus may infect cells using CD46 as a receptor. The potential role of adenoviruses and other infectious pathogens in the death of RPE in disorders such as age-related macular degeneration remains to be elucidated.

TAKE HOME MESSAGE Viral infections can lead to RPE loss in tissue culture

9:29 AM

Subretinal Catheterization Ab Externo as a Method to Deliver Cell Therapy for the Treatment of Advanced Geographic Atrophy

- Tom S. Chang, MD
- Allen C. Ho, MD
- Michael A. Samuel, MD
- Paul Williamson, MD
- Terri Malone, MT(ASCP)

OBJECTIVE To describe a method of sub-retinal catheterization ab-externo for the delivery of biological therapeutics to the peri-macular sub-retinal space.

PURPOSE To describe the surgical method and instrumentation to place and advance a microcatheter into the macular sub-retinal space to administer biological therapeutics

METHODS Eighteen patients with geographic atrophy secondary to dry AMD have been enrolled and 17 subjects treated in a Phase Ib study by administration of a human umbilical tissue-derived cells (CNTO 2476, Janssen R&D) to the macular sub-retinal space.An illuminated microcatheter (iTRACK-275,iScience Interventional) was primed with the cell suspension and inserted into the sub-retinal space through a surgically created sclerotomy and choroidotomy.The microcatheter's illuminated tip was advanced to the macular region, and visualized.Thecell suspension was injected into the sub-retinal space.

RESULTS Seventeen eyes were injected with the cell therapy to the macular sub-retinal space.A sclerotomy was performed andachoroidotomy was created using a 36 gauge viscodissection cannula with a tissue piercing tip (WTC, iScience Interventional).A peripheral sub-retinal bleb was formed by injecting viscoelastic through the choroidotomy.The formation of the peripheral sub-retinal bleb was confirmed by

intraoperative UBM (iUltraSound, iScience Interventional) or, in the last 7 subjects, with an intraocular endoscope (E2 Microprobe, Endo Optiks).Endoscopy demonstrated by direct visualization the creation of the choroidotomy and the peripheral sub-retinal bleb as well as advancement of the catheter and administration of the cell suspension.Twenty seven to fifty microliters of cell suspension was administered, forming a sub-retinal bleb approximately 1.5 -2 disc diameters in size.The microcatheter was retracted and the dissection site closed.

CONCLUSION Sub-retinal catheterization ab-externo is a method in development to administer cell therapy to the sub-retinal space, and has the potential to avoid perforation of the retina.The injected cells may be contained in the sub-retinal space, providing maximal exposure of the retina to trophic factors that may be secreted by the cells.

TAKE HOME MESSAGE To describe the surgical method and instrumentation to place and advance a microcatheter into the macular sub-retinal space to administer biological therapeutics for the treatment of advanced GA.