Macular Atrophy in Neovascular Age-Related Macular Degeneration Eyes Treated With Monthly or Treat-and-Extend Ranibizumab: TREX-AMD Report No. 2

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OBJECTIVE The incidence, prevalence, and enlargement rate of macular atrophy (ERMA) in neovascular AMD (nAMD) patients enrolled in the prospective, randomized, multicenter treat-and-extend (TREX-AMD) trial.

PURPOSE To follow 60 patients with treatment-naive nAMD treated at one eye with either monthly or TREX ranibizumab, and compare them to fellow control eyes in regard to macular atrophy (MA) presence, development and progression.

METHODS Patients' study and fellow eyes were followed for 18 months using SD-OCT and fundus autofluorescence imaging (FAF). MA was quantified on FAF images using Region Finder software, with suspected areas of atrophy confirmed by SD-OCT and infrared reflectance imaging. For eyes which did not have a baseline (BSL) MA, but developed MA by 18 months, intervening visits were assessed to determine the first visit at which MA appeared in order to allow progression rates to be defined. Foveal choroidal thickness (FCT) at BSL was also measured in all eyes. Eyes were excluded

which did not complete the month-18 visit (n=14), had retinal pigment epithelial rip (n=2) or had poor quality images (n=3).

RESULTS Final cohort included 101 eyes classified into 3 groups: Monthly (n=20), TREX (n=30) and Control (n=51). Mean ERMA by group was: 0.86±1.57 in the Monthly, 0.72±1.26 in the TREX and 0.32±0.65 mm^2/year in the Control groups (p=0.28). Prevalence of MA at BSL in the Monthly, TREX and Control groups was 35% (n=7/20), 57% (n=17/30) and 41% (n=21/51) respectively, and the mean ERMA in these cases was 1.91±2.29, 1.32±1.49 and 0.63±0.76 mm^2/year respectively (p=0.08). The incidence rate of MA in the 3 groups was 46% (n=6/13), 0% (n=0/13) and 7% (n=2/30) respectively. Multinomial logistic regression revealed significantly higher probability for MA development in eyes of the Monthly group than the Control or TREX groups (p<0.01). Mean ERMA in incident cases was 0.64±0.64 in the Monthly and 1.53±1.19 mm^2/year in the Control groups (p=0.2). FCT measurements at BSL by group were 155±52, 122±50 and 146±51 μm respectively, and they could not significantly predict MA development (p=0.27).

CONCLUSION MA was a frequent finding among the nAMD and control eyes studied. There was a trend for greater MA progression in monthly treated eyes compared to TREX –treated and control eyes, but this was not statistically significant. Monthly treatment was significantly associated with an increased probability of MA development.

TAKE HOME MESSAGE Macular atrophy is a frequent finding in neovascular AMD. It has a trend for development and greater progression in monthly treated eyes compared to TREX–treated and control eyes.

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

Genetic Variants Associated With Anti-VEGF Drug Response in Neovascular AMD Patients in the VIEW Trial

- Nancy M. Holekamp, MD

OBJECTIVE To identify genetic variations that are associated with the response to anti-VEGF treatment in neovascular AMD.

PURPOSE To identify genetic variants associated with anti-VEGF drug response as measured by visual acuity, anatomic outcomes and treatment frequency in the VIEW 1 study.

METHODS A genome wide association study (GWAS) was conducted on 362 VIEW 1 patients. DNA samples were genotyped using the Illumina Omni Express Exome Chip. Logistic regression with baseline values was performed to establish the association between genetic variants and efficacy variables. For each SNP, genotypes were coded according to an additive mode of inheritance. Variants associated with gaining ≥15 ETDRS letters at week 52, presence of intraretinal cystoid edema (fluid as measured by time domain optical coherence tomography (TD-OCT)) at week 52 and frequency of treatment at week 96 were evaluated.

RESULTS An X-chromosome SNP (rs2056688) revealed the highest association with anatomical outcome, demonstrating an odds ratio (OR) of 0.2578 and a point-wise association (p-value 7.27×10^{-7}) with presence of intraretinal fluid at week 52. Four neighboring SNPs (rs5962084, rs5962087, rs5915722, rs5962095) revealed similar ORs (0.3151-0.3461) and point-wise associations (5.48×10^{-6} – 8.59×10^{-6}). The rs2056688 SNP was located in a non-coding region, with the closest relevant functional gene (Protein Kinase X-Linked (PRK-X)) mapping ~400kb upstream of the putative variant. Additional SNPs with lower significance were found in association with proportion of

patients with ≥15 ETDRS letters gains in vision at week 52 and frequency of treatment at week 96.

CONCLUSION An association was identified between a genetic variant and the presence of intraretinal fluid at week 52 in neovascular AMD patients undergoing anti-VEGF treatment. The variant was located on chromosome X near the gene for PRK-X, a serine/threonine protein kinase involved in angiogenesis. Given the small number of samples, the findings require validation in additional dataset.

TAKE HOME MESSAGE A GWAS in neovascular AMD patients undergoing anti-VEGF treatment in the View 1 trial identified an association between a genetic variant and the presence of intraretinal fluid at week 52.

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

Baseline Lesion Features are Predictive of Visual Response in Patients With Neovascular AMD Treated With Topical Squalamine and Ranibizumab

- Peter K. Kaiser, MD

OBJECTIVE To determine if lesion characteristics are predictive of visual outcomes in the phase 2 IMPACT study of topical squalamine lactate and ranibizumab in the treatment of neovascular AMD.

PURPOSE To determine if baseline angiographic lesion characteristics are predictive factors for visual outcome in the Phase 2 IMPACT study, which compared combination therapy with topical squalamine lactate ophthalmic solution, 0.2% and PRN ranibizumab (RBZ) to topical placebo and PRN ranibizumab in patients with treatment naïve neovascular AMD

METHODS Treatment naïve patients with CNV due to AMD measuring < 12 disc areas, OCT central subfield > 300 microns with subretinal fluid or cystoid macular edema, any lesion composition, and BCVA of 20/40 to 20/320, received a single RBZ injection at baseline and were randomized 1:1 to topical squalamine 0.2% BID (combination group) or placebo solution BID (RBZ monotherapy group). All patients were followed monthly for 9 months and were treated with PRN RBZ if strict re-treatment criteria were met. Baseline CNV lesion angiographic characteristics were analyzed to determine if they served as predictive factors for visual function outcomes at the month 9 primary endpoint.

RESULTS 128 of the 142 enrolled subjects completed the 9 month study (mITT population) and were analyzed. 44% of subjects with classic containing lesions, who received squalamine combination therapy (n=37) achieved a ≥3 line gain compared to

29% of patients in the RBZ monotherapy arm (n=28) at the 9 month time point. There was an 11 letter mean gain in visual acuity for the squalamine combination arm and a 5 letter gain with RBZ monotherapy. A much larger sub-group of the mITT population, those with occult CNV <10mm^2, regardless of the presence or size of classic CNV, was also analyzed. Subjects who received squalamine combination therapy (n=48) demonstrated a 40% ≥3 line gain in vision compared to 26% in the RBZ monotherapy group (n=46). Mean gains in visual acuity were 11.0 letters for the squalamine combination arm and 5.7 letters with RBZ monotherapy. Additional data on visual acuity outcomes based on lesion size and characteristics will be presented.

CONCLUSION Topically administered squalamine lactate used in combination with RBZ can lead to improved visual function in patients with wet AMD vs RBZ monotherapy. Enhanced visual benefits were seen when the occult component was <10mm^2 (regardless of classic CNV). Lesion size and composition may determine outcomes for topical squalamine combination therapy and potentially for other combination approaches too.

TAKE HOME MESSAGE Occult compnent <10mm^2 led to improved visual outcomes in the phase 2 IMPACT study of topical squalamine lactate and ranibizumab in the treatment of neovascular AMD.

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

A Novel Anti-VEGF/Anti-Angiopoietin2 Bispecific Monoclonal Antibody for Wet Age-Related Macular Degeneration and Diabetic Macular Edema

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- Robert Weikert

OBJECTIVE This presentation will review the design of the novel bispecific antibody RG7716, new preclinical and Phase I data, and the Phase II clinical programs.

PURPOSE Preclinical studies of the bispecific monoclonal anti-VEGF/anti-Angiopoietin-2 antibody RG7716 demonstrated proof-of-principle in animal models of age-related macular degeneration (AMD) and diabetic macular edema (DME). A phase 1 study was conducted to investigate the safety and efficacy of RG7716 in patients with wet AMD with suboptimal therapeutic response following multiple prior anti-VEGF treatments.

METHODS Patients with wet AMD with best corrected visual acuity (BCVA) between 20/40 to 20/400 (Snellen equivalent), with persistent CNV activity despite ≥3 intravitreal anti-VEGF treatments in the preceding 6 months, and last IVT ≥4 weeks prior to day 1 were enrolled. The single ascending dose (SAD) enrolled 4 cohorts each with 3 patients (0.5 to 6 mg RG7716). The multiple ascending dose (MAD) enrolled two cohorts each with 6 patients (3 and 6 mg RG7716) who received a total of 3 treatments

at 4 weekly intervals. Incidence and severity of Medical Dictionary for Regulatory Activities (MedDRA) adverse events (AE) were recorded.

RESULTS SAD and MAD administrations of RG7716 were well tolerated in the 24 patients enrolled. Ocular AEs were reported in 9 study eyes and were generally mild (8); one was classified as moderate severity. Serious systemic AEs were few (1 gastrointestinal hemorrhage was reported 76 days after a single 1.5 mg dose) and 1 patient was withdrawn for elective cardiothoracic surgery; both were deemed to be unrelated to study drug by the principal investigators. In the SAD and 6 mg RG7716 MAD groups, median BCVA increased from baseline by 7 (range: 0 to 18; n=11) and 7.5 letters (range: 3 to 18, n=6), 28 days after the last dose, respectively. Median central subfield thickness (CST) decreased from baseline by -42 μm (range: -101 to 10, n=11) and -117 μm (range: -252 to -7, n=6), 28 days after the last dose in the SAD and 6 mg MAD group, respectively. Following multiple 3 mg RG7716 doses, no changes were observed in median BCVA (-0.5, range: -9 to 8; n=6) or CST (median: -9, range: -188 to -1; n=6).

CONCLUSION The bispecific monoclonal antibody RG7716 was well tolerated with an overall favorable safety profile in patients with wet AMD. In eyes with suboptimal response to anti-VEGF therapy, promising improvements in BCVA and OCT parameters were observed. Phase 2 studies are currently underway to further assess the potential clinical application of RG7716 in patients with both wet AMD and DME.

TAKE HOME MESSAGE In Phase I, the bispecific monoclonal antibody RG7716 showed promising improvements in BCVA and OCT parameters in patients with wet AMD. Phase 2 studies are currently underway in wet AMD and DME.

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