The impact of the vitreomacular interface (VMI) in neovascular AMD (nAMD) in a treat and extend regimen (TE) with exit strategy
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Purpose: Evaluate the impact of the VMI in a TE regimen with exit strategy in patients with nAMD

Methods: In this retrospective study, all eyes treated according to a TE regimen with at least 3 intravitreal injections of ranibizumab or aflibercept between 2014 and 2015 were reviewed. Eyes reaching the exit criterion were included. The exit criterion was defined as dry macula during 3 consecutive 16-weekly injection visits. Eyes were regularly monitored, without injections thereafter. The impact of the VMI on mean treatment interval, number of injections, central retinal thickness (CRT) decrease and BCVA improvement as well as CNV recurrences was assessed

Results: 598 eyes of 488 patients were identified. Out of these, 100 eyes (17%) of 95 patients (mean age: 80±9) met the exit criteria and were included in this study. Mean number of administered injections was 23.7±14.7 during a mean treatment duration of 4.5±2.5yrs. At treatment initiation, 74% had a posterior vitreous detachment (PVD). At treatment cessation 86% showed a PVD with a release rate of 48% in eyes with vitreomacular adhesion (VMA) at baseline. Numerical, but no statistical difference in CRT decrease (PVD: -87±18µm vs. VMA: -23±46µm, p=0.1) and BCVA improvement (PVD: +3.2±2 vs. VMA: -1.3±3 letter, p=0.3) between the PVD and the VMA group were noted. There was also no difference in mean injection interval (PVD: 13.2±0.3 vs. VMA: 12.8±0.4weeks, p=0.5), number of injections (PVD: 22.8±1.7 vs. VMA: 26.2±2.8, p=0.3) or absolute treatment duration (PVD: 226±15 vs. VMA: 263±26weeks) until cessation. 15% eyes showed CNV recurrence after a mean of 41±7 weeks. VMA at treatment cessation was significantly associated with disease recurrence (p=0.006): VMA eyes showed in 43% disease recurrence during the observational period, in contrast to 10.5% of eyes with PVD. Additional data from the full 598 eye data set will be presented

Conclusions: There was a high prevalence of PVD and release rates in our patient cohort reaching the TE exit criterion. VMA was associated with significantly higher recurrence rates. This indicates that eyes with VMA reaching TE exit criterion should be very carefully monitored for new disease activity. Even continuation of treatment until VMA release may be considered

Commercial Relationships: Marion R. Munk, Novartis (R), Bayer (R); Petra Arendt, None; Si Qing Yu, None; Andreas Ebmeter, Novartis (R), Bayer (R); Sebastian Wolf, Novartis (C), Bayer (C); Martin Zinkernagel, Novartis (C), Bayer (C)

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Ranibizumab in pigment epithelial tears secondary to AMD – a prospective, multicenter, investigator-initiated trial (RIP Study)
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Purpose: Retinal pigment epithelium (RPE) tears represent a complication of neovascular age-related macular degeneration (AMD), most commonly in association with pigment epithelial detachments. The efficacy of intravitreal anti-VEGF therapy in neovascular AMD has been demonstrated in various prospective large-scale clinical trials, whereby the presence of an RPE tear constituted an exclusion criterion. Thus, the efficacy of anti-VEGF therapy in this AMD subtype is unclear. This study aims to assess efficacy of ranibizumab in RPE tears.

Methods: In a prospective, multicenter, investigator-initiated trial (Ranibizumab In Pigment epithelial tears secondary to AMD - RIP Study, EudraCT no. 2011-005807-33), the morphological and functional effects of monthly intravitreal injections of ranibizumab (0.5 mg) over 12 months in patients diagnosed with an RPE tear secondary to AMD were investigated. Study visits included assessment of best-corrected visual acuity (BCVA) according to ETDRS protocol, color fundus photography, spectral domain optical coherence tomography (OCT), fundus autofluorescence, fluorescein and indocyanin green angiography, and microperimetry. Quality of life was assessed using the NEI-VFQ-25. Paired Student’s t test was employed for statistical analyses.

Results: Twenty-four eyes of 24 patients (mean age 79 ± 2 years, age range 69-94 years) were included in the study. Central retinal thickness (ILM to BM) in OCT decreased from 612 μm (± 202) to 436 μm (± 171; p < 0.0001) over the 12 months study period. Mean BCVA at baseline and at final visit was 50.0 (± 18.8) and 52.9 ETDRS letters (± 19.7; p = 0.39), respectively, thus demonstrating a stabilization of mean BCVA under ranibizumab therapy. One patient (4%) experienced a visual loss of 15 ETDRS letters, 2 patients (8%) gained ≥ 15 letters, and in 21 patients (88%) BCVA remained stable within ± 15 letters. In contrast, a comparable historical control cohort of patients with untreated RPE tears exhibited a progressive and significant decline of mean BCVA over 12 months and beyond (M. Gutleisch et al., Eye 2011:25:1181-6).

Conclusions: The RIP Study provides prospective results of morphological and functional efficacy parameters of ranibizumab therapy in RPE tears, demonstrating BCVA stabilization over 12 months. The results will help to establish treatment recommendations for this understudied AMD subphenotype.

Commercial Relationships: Tim U. Krohne, Petra P. Fang, None; Akio Oishi, Alcon (F), Novartis (R), Bayer (R); Seleman Bedar, None; Philipp K. Heymer, None; Christoph R. Clemens, Novartis (C), Heidelberg Engineering (R), Bayer (C), Novartis (R), Bayer (R), Bayer (F), Novartis (F); Susanna König, None; Nicole Eter, Novartis (C), Roche (C), Bayer (C), Novartis (R), Allmera Sciences (C), Bayer (R), Allergan (F), Novartis (F), Bausch + Lomb (C), Heidelberg Engineering (R), Bayer (F), Allergan (C); Armin Wolf, DORC (R), Novartis (C), Optos (C), Genisight (F), Oertli (R), Novartis (R), Roche (F), Novartis (F), Optos (R), Ophthotech (F), Bayer (F); Frank G. Holz, NightstarX (F), Boehringer-Ingelheim (C), Roche (F), Allergan (F), Thea (C), Allergan (R), Bioeq (C), Optos (F), Zeiss (F), Genentech (F), Acucela (F), Novartis (C), Heidelberg Engineering (F), Roche (C), Novartis (R), Bayer (C),
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Presentation Time: 9:00 AM–9:15 AM

Plasma Mass-spectrometry Metabolomics in Age-related Macular Degeneration

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Purpose: Age-related Macular Degeneration (AMD) is multifactorial, combining environmental and genetic risk factors. Likely due to this complexity, reliable AMD biomarkers in biofluids are still lacking. The metabolome, the global profile of all the small molecules (<1 kDa) comprising a biological system, is the downstream product of the cumulative effects of the genome and environmental exposures. This study performed mass-spectrometry (MS) based metabolomic profiling of plasma to explore the metabolome of AMD and identify potential metabolic AMD biomarkers.

Methods: Prospective, cross-sectional study, including subjects with a diagnosis of AMD and a control group (> 50 years) without any vitreoretinal disease. All participants were imaged with color fundus photographs, used for AMD diagnosis and staging, according to the Age-Related Eye Disease Study (AREDS) classification scheme. Fasting blood samples were collected and analyzed by Metabolon, Inc (Durham, NC), using ultra-performance liquid chromatography (UPLC) and high-resolution MS. Metabolon’s hardware and software were used for peak-identification and quality control. Metabolite variations were quantified through signal integration and significance assessment (ANOVA tests).

Results: We included 90 patients with AMD (30 early, 30 intermediate, 30 late AMD; 64.4% female) and 30 controls (60.0% female), mean age 68.1 ± 10.2 and 71.3 ± 7.5 years, respectively. Using UPLC-MS, 878 biochemicals were identified. The comparison between all AMD patients and controls revealed statistically significant differences in fatty acid metabolites (in particular those related to acyl carnitine, p ≤ 0.04), cell membrane (namely phosphatidylcholine, phosphatidyl-ethanolamine and phosphatidyl-inositol, p ≤ 0.04) and vitamin A metabolites (p ≤ 0.01). Compared to controls, subjects with more severe AMD demonstrated greater differences in plasma metabolites.

Conclusions: Our data suggests that patients with AMD have altered plasma metabolomic profiles compared to controls. As the disease severity increases, an increasing number of changes are evident. These findings support the development of plasma-based metabolomics biomarkers of AMD, which will be the focus of subsequent analyses.

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Presentation Time: 9:15 AM–9:30 AM

Visual function endpoints in early and intermediate dry age-related macular degeneration for use as clinical trial endpoints


Purpose: The ability to effectively treat dry age-related macular degeneration (AMD) is significantly hampered by a lack of reliable functional endpoints for proof of concept clinical trials. The main objective of our study is to evaluate and quantify visual function metrics that can be used as predictors of AMD progression and visual acuity (VA) loss in patients with early and intermediate AMD.

Methods: Observational, cross-sectional, prospective study of 101 patients enrolled at Duke Eye Center: 80 patients with AMD age-related eye disease study (AREDS) stage 2 (N=33) and stage 3 (N=47) and 21 age-matched, normal controls. During baseline examination, a dilated retinal examination, including best-corrected VA (BCVA), mesopic microperimetry with eye tracking (MAIA), dark adaptometry (AdaptDx), low luminance VA (LLVA) (standard using a log 2.0 neutral density filter and a computerized method), and cone contrast test (CCT) (Innova Systems Inc) were performed. Low luminance deficit (LLD) on LLVA testing was defined as the difference in numbers of letters read at standard vs. low luminance. The Research Electronic Data Capture (REDCap) system was used for data entry and management. Group comparisons were performed to evaluate differences between the control group and the AREDS 2 and AREDS 3 groups using two-sided significance tests.

Results: BCVA was similar between control and AMD groups. The functional measures that showed significant differences between the normal and the intermediate AREDS3 AMD groups were LLVA standard and computerized (0.5 cd/m²), percent reduced threshold and average threshold on microperimetry, CCT tests (red, green, and blue), and rod intercept on dark adaptation (p < 0.05). Compared to age-matched controls, patients with early AMD AREDS 2 showed increased rod intercept values (p < 0.05). The AREDS 3 group demonstrated deficits in microperimetry reduced threshold, computerized LLD2 and dark adaptation rod intercept (p < 0.05) relative to AREDS 2. There was no difference between the three groups in standard or computerized LLD.

Conclusions: Our study demonstrates that LLVA, MAIA microperimetry, CCT and dark adaptation may be used as reliable functional measures of disease progression for eyes with early and intermediate AMD and as alternative clinical trial endpoints for future studies of dry AMD.

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A Phase 2 Study (EMERGE) Evaluating Repeated Intravitreal Administration of ICON-1 in Patients With Choroidal Neovascularization (CNV) Secondary to Age-related Macular Degeneration (AMD)
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Purpose: Current anti-VEGF therapies for wetAMD reduce leakage and exudation but do not appear to reverse CNV progression. This study examined the hypothesis that ICON-1, an anti-Tissue Factor (TF) immunoconjugate protein, binds to CNV overexpressing TF and via a new mechanism of action acts to reduce CNV activity alone or in combination with ranibizumab (RBZ).

Methods: EMERGE was a randomized, double masked, active control study in the United States. A total of 88 patients with treatment naïve CNV secondary to AMD were enrolled. Patients were randomized 1:1:1 and received intravitreal injections of ICON-1 0.3mg as monotherapy (n=30), ICON-1 0.3mg in combination with ranibizumab 0.5mg (n=30) or ranibizumab 0.5mg monotherapy (n=28). Patients received 3 initial monthly injections, then remained masked in their respective randomized group for additional 3 possible injections based on protocol retreatment criteria. Safety, BCVA letter score and CNV lesion activity were assessed monthly with optical coherence tomography (sdOCT) and quarterly with fluorescein angiography (FA).

Results: No serious ocular adverse events were reported. The most frequently reported study eye ocular adverse events (AEs) in all groups were conjunctival hemorrhage (13.3-26.7%), vitreous floaters (10.7-13.3%), eye pain (3.3-23.3%) and retinal hemorrhage due to AMD (0-26.7%). After the 3 fixed injections, mean BCVA increased from baseline to Month 3 (primary endpoint) by 0.3 letters with ICON-1 monotherapy, 6.8 letters with ICON-1 in combination with RBZ, and 7.6 letters with RBZ monotherapy and was associated with CRT reduction in all treatment groups. From Month 3 to 6, fewer patients in the ICON-1 combination group (60%) received at least one additional injection compared to ICON-1 (82.8%) and RBZ (85.2%) monotherapy. Mean BCVA and mean CRT between months 3 and 6 were maintained in all treatment groups.

Conclusions: Repeated intravitreal ICON-1 0.3mg injections alone or in combination with RBZ were well tolerated. BCVA gain was comparable in the ICON-1 combination and RBZ groups, although it was maintained with fewer treatments from Month 3 to 6 with ICON-1 combination. Together with signs of reduction in CNV activity (FA and sdOCT), these results provide biological signals of ICON-1 activity on the reduction of CNV progression.

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