404 AMD clinical research
Wednesday, May 10, 2017 8:30 AM–10:15 AM
Ballroom 3 Paper Session
Program #/Board # Range: 3762–3767
Organizing Section: Retina

Program Number: 3762
Presentation Time: 8:30 AM–8:45 AM
The impact of the vitreomacular interface (VMI) in neovascular AMD (nAMD) in a treat and extent regimen (TE) with exit strategy
Marion R. Munk, Petra Arendt, Siqing Yu, Andreas Ebneter, Sebastian Wolf, Martin Zinkernagel. Dept of Ophthalmology, Inselspital, University Hospital Bern, Bern, Switzerland.
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 vs. VMA:-1±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; **Siqing Yu**, None; **Andreas Ebneter**, Novartis (R), Bayer (R); **Sebastian Wolf**, Novartis (C), Bayer (C); **Martin Zinkernagel**, Novartis (C), Bayer (C)

Program Number: 3763
Presentation Time: 8:45 AM–9:00 AM
Ranibizumab in pigment epithelial tears secondary to AMD – a prospective, multicenter, investigator-initiated trial (RIP Study)
Tim U. Krohne[1], Petra P. Fang[1], Akio Oishi[1], Seleman Bedar[1], Philipp K. Heymer[1], Christoph R. Clemens[3], Susanna König[2], Nicole Eter[3], Armin Wolf[2], Frank G. Holz[1]. [1]Ophthalmology, University of Bonn, Bonn, Germany; [2]Ophthalmology, Ludwig Maximilian University of Munich, Munich, Germany; [3]Ophthalmology, University of Muenster, Muenster, Germany.
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: Twentyfour 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. Gutfleisch 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), Alimera 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), Gensight (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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Clinical Trial: NCT01914159

Program Number: 3764
Presentation Time: 9:00 AM–9:15 AM
Plasma Mass-spectrometry Metabolomics in Age-related Macular Degeneration
Ines Lains[1, 2], Rachel S. Kelly[5], Jessica Lasky-Su[5], Rufino Silva[2, 3], Joaquim N. Murta[2, 4], John B. Miller[1], Ivana K. Kim[1], Demetrios vavvas[1], Joan W. Miller[1], Deeba Husain[1]. [1]Massachusetts Eye and Ear Infirmary, Boston, MA; [2]Faculty of Medicine, University of Coimbra, Coimbra, Portugal; [3]Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal; [4]Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [5]Systems Genetics and Genomics Unit, Channing Division of Network Medicine Brigham and Women's Hospital and Harvard Medical School, Boston, MA.
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, $p \leq 0.04$), cell membrane (namely phosphatidylcholine, phosphatidyl-ethanolamine and phosphatidyl-inositol, $p \leq 0.04$) 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.
Commercial Relationships: Ines Lains, Allergan (R); **Rachel S. Kelly**, None; **Jessica Lasky-Su**, Metabolon, Inc (C); **Rufino Silva**, Thea (C), Novartis (C), Alimera (C), Bayer (C), Alcon (C), Allergan (C); **Joaquim N. Murta**, None; **John B. Miller**, Allergan (C); **Ivana K. Kim**, None; **Demetrios vavvas**, None; **Joan W. Miller**, Amgen (C), Valeant Pharmaceuticals (P), KalVista Pharmaceuticals Ltd (C), INL Therapeutics, LLC (P), Maculogix, Inc. (C), Alcon (C); **Deeba Husain**, None
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Program Number: 3765
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
Kimberly Cocce, Sandra Stinnett, Lejla Vajzovic, Anupama Horne, Cynthia A. Toth, Scott W. Cousins, Eleonora M. Lad. Ophthalmology, Duke Eye Center, Durham, NC.
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 microperimety 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/m^2), 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 threshhold, 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.
Commercial Relationships: Kimberly Cocce, None; **Sandra Stinnett**, None; **Lejla Vajzovic**, None; **Anupama Horne**, None; **Cynthia A. Toth**, Alcon Laboratories (P), Genentech (F); **Scott W. Cousins**, Maculogix (S), Heidelberg Engineering (C), Theia Biosciences (S), Stealth (R); **Eleonora M. Lad**, Hoffmann La Roche (F)
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Clinical Trial: NCT01822873

Program Number: 3766
Presentation Time: 9:30 AM–9:45 AM
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)
Christine R. Gonzales[1], Gabriela Burian[2]. [1]Retina and Vitreous Center, Ashland, OR; [2]GB Biomed Advisors, Oberwil, Switzerland.
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.
Commercial Relationships: Christine R. Gonzales, Iconic Therapeutics (R), Iconic Therapeutics, Inc. (F); **Gabriela Burian**, Iconic Therapeutics, Inc. (P), Iconic Therapeutics, Inc. (C), Iconic Therapeutics, Inc. (R)
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Clinical Trial: NCT02358889

Program Number: 3767
Presentation Time: 9:45 AM–10:00 AM
Controlled and Extended Release of Bioactive Aflibercept from a Biodegradable Microsphere-Hydrogel Ocular Drug Delivery System
Wenqiang Liu[1], Bao-Shiang Lee[2], William F. Mieler[3], Jennifer J. Kang-Mieler[1]. [1]Biomedical Engineering, Illinois Institute of Technology, Chicago, IL; [2]Research Resource Center, University of Illinois at Chicago, Chicago, IL; [3]Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, IL.
Purpose: Current therapies for chronic posterior segment diseases often require repeated intravitreal bolus injections of anti-vascular endothelial growth factors. The purpose of this study was to validate a composite microsphere-thermoresponsive hydrogel drug delivery system (DDS) capable of releasing bioactive aflibercept in a controlled and extended manner.
Methods: The composite DDS was developed by suspending aflibercept-loaded poly(lactic-*co*-glycolic acid) microspheres within a biodegradable poly(ethylene glycol)-*co*-(L-lactic acid) diacrylate/N-isopropylacrylamide (PEG-PLA-DA/NIPAAm) thermoresponsive hydrogel. Two PEG-PLA-DA concentrations (2mM and 3mM) and two microspheres loading amount (10mg and 20mg) were compared to determine the optimal drug release. The degradation of hydrogel was determined by wet weight changes and normalized to percent degradation. The cytotoxicity from degraded byproducts was investigated by quantifying viability of human umbilical vascular endothelial cells using fluorescent LIVE/DEAD® assay kit. A radioisotope, Iodine-125, was used to label aflibercept and monitor its release from DDS. Finally, a dot blot assay was used to determine the bioactivity of released drug from DDS.
Results: Higher PEG-PLA-DA concentration (3mM) degraded more and faster than the lower concentration (2mM). There was no significant cytotoxicity from degraded DDS byproducts for all investigated time. The amount and rate of aflibercept release can be controlled by both the cross-linker concentration and microspheres load amount. All investigated systems were capable of releasing aflibercept in a controlled manner. The initial burst (release within first 24hr) was 37.35±2.51μg and 74.56±3.14μg (2mM and 3mM hydrogel, each loaded with 10mg and 20mg of microspheres, respectively), followed by a controlled drug release of 0.09μg/day (2mM hydrogel) and 0.19μg/day (3mM hydrogel). A strong binding activity was observed for initial burst samples, which corresponds to a large initial release. The later time point samples also showed bioactivity but lower binding activity, which corresponds to a lower daily release rate.
Conclusions: The results indicate the proposed DDS is safe and can deliver bioactive aflibercept in a controlled manner. The proposed DDS may provide a significant advantage over current bolus injection therapies in the treatment of posterior segment diseases.
Commercial Relationships: Wenqiang Liu; **Bao-Shiang Lee**, None; **William F. Mieler**, None; **Jennifer J. Kang-Mieler**, Microsphere-hydrogel ocular drug delivery (P)
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