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PATIENT EXPERIENCE

Correlation of macular sensitivity measures and visual acuity to vision-related quality of life in patients with age-related macular degeneration

BMC Ophthalmol. 2021 Mar 23;21(1):149.

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PMID: 33757447 PMCID: PMC7988949 DOI: 10.1186/s12886-021-01901-x

Background: Visual acuity is commonly used as a functional outcome measure in patients with age-related macular degeneration (AMD), despite having a weak correlation with self-perceived visual quality of life. Microperimetry is a useful method of detecting loss of macular function. We wanted to investigate the relationship between these two objective visual outcome measures and subjective vision-related quality of life, finding out which objective measure is more patient-relevant.

Methods: Fifty-one consecutive patients with AMD were recruited to the study. Participants were required to complete the Visual Function Questionnaire 39, the Early Treatment Diabetic Retinopathy Study visual acuity examination and a microperimetry assessment using the Micro Perimeter 3. One patient withdrew consent and seven patients dropped out due to cooperation difficulties under microperimetry. Forty-three patients with AMD were included in the study: twenty-eight patients with late AMD (exudative AMD) and fifteen patients with early (non-exudative) AMD. The right eye was included as standard, as was the eye with the best-corrected visual acuity.

Results: There was a higher correlation between vision-related quality of life and macular sensitivity ($r = 0.458$; $p = 0.014$) than between vision-related quality of life and visual acuity ($r = 0.446$; $p = 0.018$) in patients with late AMD. There

was a positive correlation between vision-related quality of life and macular sensitivity in patients with early AMD (r = 0.542; p = 0.037) while the correlation between vision-related quality of life and visual acuity in these patients was not statistically significant. Composite score (r = 0.469; p = 0.012) correlated highest with the nasal outer macular sub-region and near-distance activities score (r = 0.652; p < 0.001) correlated highest with the nasal inner macular sub-region in patients with late AMD. Correlations between composite score and macular sub-regions in patients with early AMD were not significant, but near-distance activities score correlated with the nasal outer macular sub-region in these patients (r = 0.469; p = 0.012).

Conclusions: Macular sensitivity as measured using microperimetry correlates with vision-related quality of life in early AMD and in late AMD, showing it to be a patient-relevant outcome measure. Furthermore, the nasal sub-regions of the macula appear to be preferred retinal loci in patients with AMD. (338 words).

COVID-19

Fear Associated with COVID-19 in Patients with Neovascular Age-Related Macular Degeneration

Clin Ophthalmol. 2021 Mar 16;15:1153-1161.

Jean-Philippe Rozon, Mélanie Hébert, Serge Bourgault, Mathieu Caissie, Laurence Letartre, Eric Tourville, Ali Dirani

PMID: 33758498 PMCID: PMC7981158 DOI: 10.2147/OPTH.S300239

Purpose: Since the beginning of the COVID-19 pandemic, news related to the pandemic has created a feeling of fear, particularly among high-risk groups including elderly patients. This study aimed to assess the fear associated with COVID-19 and to evaluate the fear of vision decrease related to the delay of treatment in neovascular age-related macular degeneration patients (nAMD) during the pandemic.

Patients and methods: This is a prospective cross-sectional study of 160 actively treated patients with nAMD enrolled between September and November 2020 at a tertiary hospital in Québec, Canada. For each participant, demographic and clinical data were collected. The anxiety was rated in a questionnaire composed of two sections: the Fear of COVID-19 Scale (FCV-19S) and eight additional questions to assess ophthalmology-related COVID-19 statements.

Results: The mean ± standard deviation level of FCV-19S was 17.05±4.38. In the multivariable analysis, it was significantly higher in women (p<0.001) and lower in patients with a high school education vs elementary school (p=0.009). In the ophthalmology-related statements, 16% feared vision loss because of

difficulties in maintaining regular follow-ups during the pandemic. The female gender was significantly associated with a higher tendency to postpone their appointment (p=0.03). No association was found between the patients' underlying disease characteristics and higher fear of vision loss.

Conclusion: Despite the massive impact of the pandemic, anxiety related to COVID-19 and delaying ophthalmology treatments remained relatively low in nAMD patients. Greater explanations to address this fear may reduce anxiety level, especially among female patients and those with an elementary school education.

Intravitreal injections during COVID-19 outbreak: Protective measures, total duration of care and perceived quality of care in a tertiary retina center

Eur J Ophthalmol. 2021 Mar 22;11206721211003488.

Paul Denys, Alexandra Miere, Donato Colantuono, Camille Jung, Eric H Souied

PMID: 33752454 PMCID: PMC7992096 DOI: 10.1177/11206721211003488

Purpose: To assess patient satisfaction regarding the sudden reorganization of care during the COVID-19 pandemic in the outpatient intravitreal injection (IVI) clinic.

Methods: A survey of patients with ongoing IVIs for retinal diseases was carried out between April 23rd and May 12th, 2020. We designed a questionnaire to assess patient satisfaction concerning: personal protective equipment (PPE), social distancing, the perceived quality of care, and the total time spent in the department, using a Likert scale. We also collected the time spent per patients in the outpatient IVI clinic.

Results: A hundred and twenty-seven eyes of 108 patients were included. The mean time spent in the IVI outpatient clinic was 31.87 +/- 16.61 min. In our survey, 99.1% of the patients were satisfied (highly satisfied or satisfied) with the new type of care provided, 89.8% with the duration of care, and 93.5% with the PPE. Satisfaction was associated with total time spent in hospital (p = 0.005), with dissatisfied patients spending about 50% more time in the hospital than satisfied patients (43.91 min vs 30.50 min).

Conclusion: Despite the crisis-related adjustment, our survey revealed high patient satisfaction with PPE, quality of care, and total time spent in outpatient IVI clinic.

DRUG TREATMENT

Bevacizumab for diabetic macular oedema: one-year treatment outcomes from the Fight Retinal Blindness! Registry

Eye (Lond). 2021 Mar 25.

Sanjeeb Bhandari, David Squirrell, Vuong Nguyen, Nancy Wang, Jane M Wells, Terence Tan, Rachel Barnes, Richard Barry, Daniel Barthelmes, Mark Gillies

PMID: 33767407 DOI: 10.1038/s41433-021-01509-x

Objectives: This study evaluated the 1-year treatment outcomes of bevacizumab for diabetic macular oedema (DMO) in routine clinical practice.

Methods: A retrospective analysis was performed on 298 eyes of 220 patients with DMO that received intra-vitreal bevacizumab between 1 September 2013 and 31 August 2018 that were tracked by a prospectively designed, web-based observational registry-the Fight Retinal Blindness! Registry.

Results: The mean visual acuity (95% confidence interval [CI]) at 1-year was 3 (2, 5) letters better than a mean (SD) of 68 (15) letters at study entry. Nearly a quarter of eyes achieved ≥20/40. Eyes presenting with better vision (≥20/40) tended to maintain that vision during the period of observation, whereas those presenting with worse vision (<20/40) gained a mean (95% CI) of 9 (5, 13) letters. A mean reduction in the macular thickness was observed over the study period with the central subfield improving by 29 µm (95% CI 17, 40) from a mean (SD) of 402 (109) µm at study entry. Eyes that completed 1 year of follow-up received a median (Q1, Q3) of 7 (4, 9) bevacizumab injections. Sixty-two eyes, ~20%, that started with bevacizumab changed to either another VEGF inhibitor or steroid (triamcinolone) during the period of observation. This did not lead to functional improvement for eyes changed to either ranibizumab or aflibercept despite a further reduction in macular thickness. An improvement in vision and reduction in macular thickness was noted in the 13 eyes that subsequently received triamcinolone. Approximately 10% of eyes dropped out over 12 months, even though their mean visual acuity had improved by seven letters from the initial visit.

Conclusions: Bevacizumab is an effective treatment for DMO in unselected populations.

Functional benefits of a chorioretinal anastomosis at 2 years in eyes with a central retinal vein occlusion treated with ranibizumab compared with ranibizumab monotherapy

BMJ Open Ophthalmol. 2021 Mar 8;6(1):e000728.

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PMID: 33768164 PMCID: PMC7942268 DOI: 10.1136/bmjophth-2021-000728

Objective: To evaluate the functional benefits (best corrected visual acuity (BCVA), central subfield thickness, injection loads, central venous pressure (CVP)) of a laser-induced chorioretinal anastomosis (L-CRA) in patients with central retinal vein occlusion (CRVO) treated with ranibizumab compared with ranibizumab monotherapy.

Methods and analysis: This is a post-hoc analysis of the 2-year randomised ranibizumab plus L-CRA for CRVO trial. Twenty-four patients (82.5%) developed a functioning or successful L-CRA; outcome effects were monitored in the monthly as-needed ranibizumab phase from months 7 to 24 and compared with the ranibizumab monotherapy group (n=29).

Results: From months 7 to 24, the mean (95% CI) injection load for the functioning L-CRA group was 2.18 (1.57 to 2.78) compared with 7.07 (6.08 to 8.06) for the control group (p<0.0001). The mean BCVA was averaged across all timepoints between the control and functioning L-CRA groups (average difference=11.46 (3.16 to 19.75) letters, p=0.01). At 2 years, there was an 82.5% reduction in the odds of high CVP (greater or equal to central retinal artery diastolic pressure) for those with a successful L-CRA compared with controls (p<0.0001).

Conclusion: For patients with CRVO, adding L-CRA as a causal-based treatment to conventional therapy reduced CVP and injection loads and offered improved BCVA.Trial registration number ACTRN12612000004864.

High frequency SD-OCT follow-up leading to up to biweekly intravitreal ranibizumab treatment in neovascular age-related macular degeneration

Sci Rep. 2021 Mar 25;11(1):6816.

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PMID: 33767261 PMCID: PMC7994577 DOI: 10.1038/s41598-021-86348-2

A remarkable proportion of neovascular age-related macular degeneration (nAMD) patients respond rather poorly to ranibizumab treatment, in spite of the minimum 4-week follow-up and treatment interval. Usually, retreatments are based on nAMD activity as evaluated by Spectral-domain Optical coherence Tomography (SD-OCT), biomicroscopic fundus examination and visual acuity changes. In this prospective pilot study, we aimed to study SD-OCT changes in a high-frequent follow-up manner (weekly (month 0-6), biweekly (month 7-12)) throughout the first year, which consequently led to intravitreal ranibizumab being administered up to biweekly. Best corrected visual acuity (BCVA) was already significantly improved at week 2. Central

retinal thickness (CRT), intraretinal and subretinal fluid (SRF) were significantly improved from week 1 onwards. Half of the patients showed nAMD activity at week 2 or 3 and received the first retreatment earlier than 4 weeks after baseline injection. In total, 46% of retreatments were already applied 2 or 3 weeks after the previous treatment. Greater range of CRT and SRF fluctuation during follow-up was associated with lower final BCVA. Lower baseline BCVA and better SRF improvement at week 2 was associated with greater BCVA improvement. In conclusion, high-frequency SD-OCT follow-up provided a good option for adapting treatment in nAMD individually.

Short-term outcomes of intravitreal brolucizumab for treatment-naïve neovascular age-related macular degeneration with type 1 choroidal neovascularization including polypoidal choroidal vasculopathy

Sci Rep. 2021 Mar 24;11(1):6759.

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PMID: 33762600 PMCID: PMC7990919 DOI: 10.1038/s41598-021-86014-7

We evaluated the efficacy and safety of loading phase treatment with intravitreal brolucizumab for neovascular age-related macular degeneration (nAMD) with type 1 choroidal neovascularization (CNV). We analyzed consecutive 42 eyes of 40 patients with treatment-naïve nAMD associated with type 1 CNV. Three monthly injections of brolucizumab were completed in 36 eyes (85.7%). In those cases, best-corrected visual acuity (BCVA) was 0.24 ± 0.27 at baseline and improved significantly to 0.12 ± 0.23 after 3 months ($P < 0.001$). Central macular thickness was 301 ± 110 µm at baseline and decreased significantly to 160 ± 49 µm after 3 months ($P < 0.001$). Dry macula was achieved in 34 eyes (94.4%) after the loading phase. Central choroidal thickness was 264 ± 89 µm at baseline and decreased significantly to 223 ± 81 µm after 3 months ($P < 0.001$). Indocyanine green angiography after the loading phase revealed complete regression of polypoidal lesions in 15 of the 19 eyes (78.9%) with polypoidal lesions. Non-infectious intraocular inflammation (IOI) was observed in 8 of 42 eyes (19.0%) during the loading phase, while showing amelioration in response to combination therapy with topical and subtenon injection of steroids. In these eyes, BCVA after 3 months had not deteriorated as compared to that at baseline. These results indicate that loading phase treatment with intravitreal brolucizumab might be effective for improving visual acuity and reducing exudative changes in eyes with nAMD associated with type 1 CNV. Moreover, polypoidal lesions appear to frequently regress after this treatment. However, we must monitor patients carefully for brolucizumab-related IOI, and administer steroid therapy promptly.

Photodynamic therapy combined with anti-vascular endothelial growth factor therapy for pachychoroid neovasculopathy

PLoS One. 2021 Mar 23;16(3):e0248760.

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PMID: 33755678 PMCID: PMC7987186 DOI: 10.1371/journal.pone.0248760

This multicenter retrospective study was conducted to evaluate the 1-year treatment outcome of photodynamic therapy (PDT) combined with anti-vascular endothelial growth factor (VEGF) therapy for pachychoroid neovasculopathy (PNV). A total of 42 eyes of 42 patients with treatment-naïve PNV who were treated with PDT combined with intravitreal injections of an anti-VEGF agent (ranibizumab or aflibercept) for 1 year. All eyes showed exudative and/or hemorrhagic changes that affected the fovea at baseline. After the initial combination therapy, subfoveal choroidal thickness (SCT) and central retinal thickness (CRT) were significantly reduced and were maintained as such for 12 months ($P < 0.01$ in SCT and CRT). The best-corrected visual acuity (BCVA) (0.19 ± 0.30 at baseline) significantly improved at 3 months (0.15 ± 0.29, $P < 0.05$) and further improved at 12 months (0.10 ± 0.30, $P < 0.01$) when compared to that at baseline. After the initial combination therapy, 32 eyes (76.2%) required no additional treatments for 12 months. The mean number of additional PDT and intravitreal injections of anti-VEGF agents was 0.1 ± 0.3 and 0.9 ± 1.9, respectively. Of the 42 eyes included in this study, 22 eyes (52.4%) had polypoidal lesions at baseline. No significant differences in SCT, CRT, or BCVA were observed at any time points between eyes with and without polypoidal lesions. Of 20 eyes without polypoidal lesions, only 1 eye (5.0%) needed additional treatments. PNV, especially without polypoidal lesions, can be treated effectively with PDT combined with anti-VEGF therapy with few sessions.

DIAGNOSIS & IMAGING

Optical Coherence Tomography Signs of Early Atrophy in Age-related Macular Degeneration: Inter-Reader Agreement. CAM Report 6

Ophthalmol Retina. 2021 Mar 22;S2468-6530(21)00093-2.

Zhichao Wu, Maximilian Pfau, Barbara A Blodi, Frank G Holz, Glenn J Jaffe, Sandra Liakopoulos, Srinivas R Sadda, Giovanni Staurenghi, Elvira Bjelopera, Tyler Brown, Petrus Chang, John Choong, Giulia Corradetti, Federico Corvi, Amitha Domalpally, Cynthia Hurtenbach, Muneeswar Gupta Nittala, Anthony Olson, Jeong W Pak, Judith Pappe, Marlene Saßmannshausen, Cindy Skalak, Sarah Thiele, Robyn H Guymer, Steffen Schmitz-Valckenberg

PMID: 33766801 DOI: 10.1016/j.oret.2021.03.008

Objective: To determine the inter-reader agreement for incomplete and complete retinal pigment epithelium and outer retinal atrophy (iRORA and cRORA respectively) and their related features in age-related macular degeneration (AMD).

Design: Inter-reader agreement study.

Participants: Twelve readers from six reading centers.

Methods: Following formal training, readers qualitatively assessed 60 optical coherence tomography (OCT) B-scans from 60 eyes with AMD for nine individual features associated with early atrophy and performed seven different annotations to quantify the spatial extent of OCT features within regions-of-interests. The qualitative and quantitative features were used to derive the presence of iRORA and cRORA, and also in an exploratory analysis to examine if agreement could be improved using different combinations of features to define OCT atrophy.

Main outcome measures: Inter-reader agreement based on Gwet's first-order agreement coefficient (AC1) for qualitatively graded OCT features and classification of iRORA and cRORA, and smallest real difference (SRD) for quantitatively graded OCT features.

Results: Substantial or better inter-reader agreement was observed for all qualitatively graded OCT features associated with atrophy (AC1=0.63-0.87), except for retinal pigment epithelium attenuation (AC1=0.46) and disruption (AC1=0.26). The lowest SRD for the quantitatively graded horizontal features was observed for the zone of choroidal hypertransmission (±190.8μm). There was moderate agreement for a three-category classification of no atrophy, iRORA and cRORA (AC1=0.53). Exploratory analyses suggested a significantly higher level of agreement for a three-category classification using (i) no atrophy, (ii) presence of inner nuclear layer and outer plexiform layer subsidence, or a hyporeflective wedge-shaped band as a less severe atrophic grade and (iii) the latter plus an additional requirement of choroidal hypertransmission ≥250μm for a more severe atrophic grade (AC1=0.68; P=0.013).

Conclusions: Assessment of iRORA and cRORA, and most of their associated features, can be performed relatively consistently and robustly. A refined combination of features to define early atrophy could further improve inter-reader agreement.

Association of Retinal Changes with Alzheimer Disease Neuroimaging Biomarkers in Cognitively Normal Individuals

JAMA Ophthalmol. 2021 Mar 25.

Min Soo Byun, Sung Wook Park, Jun Ho Lee, Dahyun Yi, So Yeon Jeon, Hyo Jung Choi, Haejung Joung, Un Hyung Ghim, Un Chul Park, Yu Kyeong Kim, Seong A Shin, Hyeong Gon Yu, Dong Young Lee, KBASE Research Group

PMID: 33764406 DOI: 10.1001/jamaophthalmol.2021.0320

Importance: Retinal biomarkers reflecting in vivo brain Alzheimer disease (AD) pathologic abnormalities could be a useful tool for screening cognitively normal (CN) individuals at the preclinical stage of AD.

Objectives: To investigate the association of both functional and structural alterations of the retina with in vivo AD pathologic abnormalities in CN older adults and model a screening tool for detection of preclinical AD.

Design, setting, and participants: This cross-sectional study included a total of 49 CN individuals, and all assessment was done at the Seoul National University Hospital, Seoul, South Korea. All participants underwent complete ophthalmic examination, including swept-source optical coherence tomography (SS-OCT) and multifocal electroretinogram as well as amyloid-β (Aβ) positron emission tomography and magnetic resonance imaging. Data were collected from January 1, 2016, through October 31, 2017, and analyzed from February 1, 2018, through June 30, 2020.

Main outcomes and measures: For structural parameters of the retina, the thickness of the macula and layer-specific thicknesses, including peripapillary retinal nerve fiber layer and ganglion cell-inner plexiform layer measured by SS-OCT, were used for analysis. For functional parameters of the retina, implicit time and amplitude of rings 1 to 6 measured by multifocal electroretinogram were used.

Results: Of the 49 participants, 25 were women (51.0%); mean (SD) age was 70.6 (9.4) years. Compared with 33 CN individuals without Aβ deposition (Aβ-CN), the 16 participants with Aβ (Aβ+CN) showed reduced inner nasal macular thickness (mean [SD], 308.9 [18.4] vs 286.1 [22.5] μm; P = .007) and retinal nerve fiber layer thickness, particularly in the inferior quadrant (133.8 [17.9] vs 103.8 [43.5] μm; P = .003). In addition, the Aβ+CN group showed prolonged implicit time compared with the Aβ-CN group, particularly in ring 5 (41.3 [4.0] vs 38.2 [1.3] milliseconds; P = .002). AD-related neurodegeneration was correlated with the thickness of the ganglion cell-inner plexiform layer only (r = 0.41, P = .005). The model to differentiate the Aβ+CN vs Aβ-CN groups derived from the results showed 90% accuracy.

Conclusions and relevance: The findings of this study showing both functional as well as structural changes of retina measured by multifocal electroretinogram and SS-OCT in preclinical AD suggest the potential use of retinal biomarkers as a tool for early detection of in vivo AD pathologic abnormalities in CN older adults.

Assessing the long-term evolution of type 3 neovascularization in age-related macular degeneration using optical coherence tomography angiography

Graefes Arch Clin Exp Ophthalmol. 2021 Mar 21.

Han Joo Cho, Soo Hyun Lim, Jaemin Kim, Jihyun Lee, Dong Won Lee, Jong Woo Kim

PMID: 33744984 DOI: 10.1007/s00417-021-05163-7

Purpose: To analyze the evolution of type 3 neovascularization in eyes with age-related macular degeneration during anti-vascular endothelial growth factor (VEGF) treatment using optical coherence tomography angiography (OCTA) analysis.

Methods: Forty-one treatment-naïve eyes (37 patients) with type 3 neovascularization were retrospectively included in the study. The growth and morphological changes in the type 3 lesions, which were recorded using OCTA, were compared across time.

Results: The high-flow signal of the lesion on OCTA was significantly increased at the sub-retinal pigment epithelium (RPE) and the choriocapillaris during anti-VEGF treatment. The detection rate of the flow signal in the sub-RPE increased from 50.0% at baseline and 51.2% at 12 months to 65.9% at 24 months (P = 0.013). The flow signal extending into the choriocapillaris was detected in 0% of the eyes at baseline, 9.8% of the eyes at 12 months, and 17.1% of the eyes at 24 months (P = 0.018). The presence of subretinal drusenoid deposits (SDD) was significantly more frequent in the group with extension into the choriocapillaris (100%) than in the group without (61.8%, P = 0.036). For the four eyes with extension into the choroid, the morphological feature of the lesion on en face OCTA evolved into a tangled vascular network, similar to type 1 neovascularization.

Conclusion: OCTA analysis revealed that type 3 neovascularization gradually extended downward toward the sub-RPE and choroid during anti-VEGF treatment. The extension of the lesion into the choriocapillaris, suggesting retinal-choroidal anastomosis, was significantly more frequent in eyes with SDD.

PATHOPHYSIOLOGY

Identification of an intraocular microbiota

Cell Discov. 2021 Mar 9;7(1):13.

Yuhua Deng, Xiaofei Ge, Yan Li, Bin Zou, Xiaofeng Wen, Weirong Chen, Lin Lu, Meifen Zhang, Xiaomin Zhang, Chunmei Li, Chan Zhao, Xiaofeng Lin, Xiulan Zhang, Xinhua Huang, Xiaorong Li, Ming Jin, Guang-Hua Peng, Dongni Wang, Xun Wang, Weiyi Lai, Juanran Liang, Jing Jing Li, Qiaoxing Liang, Liu Yang, Qinfen Zhang, Yinyin Li, Ping Lu, Xiao Hu, Xifang Li, Xiuli Deng, Yu Liu, Yanli Zou,

Shixin Guo, Tingting Chen, Yali Qin, Fuhua Yang, Li Miao, Wei Chen, Chi-Chao Chan, Haotian Lin, Yizhi Liu, Richard W J Lee, Lai Wei

PMID: 33750767 PMCID: PMC7943566 DOI: 10.1038/s41421-021-00245-6

The current dogma in ophthalmology and vision research presumes the intraocular environment to be sterile. However, recent evidence of intestinal bacterial translocation into the bloodstream and many other internal organs including the eyes, found in healthy and diseased animal models, suggests that the intraocular cavity may also be inhabited by a microbial community. Here, we tested intraocular samples from over 1000 human eyes. Using quantitative PCR, negative staining transmission electron microscopy, direct culture, and high-throughput sequencing technologies, we demonstrated the presence of intraocular bacteria. The possibility that the microbiome from these low-biomass communities could be a contamination from other tissues and reagents was carefully evaluated and excluded. We also provide preliminary evidence that a disease-specific microbial signature characterized the intraocular environment of patients with age-related macular degeneration and glaucoma, suggesting that either spontaneous or pathogenic bacterial translocation may be associated with these common sight-threatening conditions. Furthermore, we revealed the presence of an intraocular microbiome in normal eyes from non-human mammals and demonstrated that this varied across species (rat, rabbit, pig, and macaque) and was established after birth. These findings represent the first-ever evidence of intraocular microbiota in humans.

Aflibercept Intervention in Experimental Branch Retinal Vein Occlusion Results in Upregulation of DnaJ Homolog Subfamily C Member 17

J Ophthalmol. 2021 Mar 6;2021:6690260.

Lasse Jørgensen Cehofski, Anders Kruse, Alexander Nørgård Alsing, Benn Falch Sejergaard, Jonas Ellegaard Nielsen, Shona Pedersen, Danson Vasanthan Muttuvelu, Svend Kirkeby, Bent Honoré, Henrik Vorum

PMID: 33747556 PMCID: PMC7960061 DOI: 10.1155/2021/6690260

Aflibercept is an inhibitor of vascular endothelial growth factor (VEGF) used to treat macular edema following branch retinal vein occlusion (BRVO). Despite well-documented efficacy, there is limited knowledge about proteome changes following aflibercept intervention in BRVO. Proteome changes may provide insights into mechanisms of action as well as aspects related to safety profile. In seven Danish Landrace pigs, BRVO was induced with a well-established experimental model of argon laser-induced BRVO. BRVO was induced in both eyes. Three days after the induced BRVO, aflibercept was

injected intravitreally in the right eyes, while the left eyes received intravitreal isotonic saline water. Retinas were collected 15 days after the induced BRVO and analyzed with label-free quantification liquid chromatography tandem mass spectrometry (LFQ LC-MS/MS). Fourteen proteins were changed in expression following aflibercept intervention in the BRVO model. LFQ LC-MS/MS identified an upregulation of DnaJ homolog subfamily C member 17 (DNAJC17) (fold change = 6.19) and a modest downregulation of isoform 2 of the protein encoded by N-myc downstream regulated gene 2 (NDRG2) (fold change = 0.40). NDRG2 was unchanged by Western blotting. In the additional significantly regulated proteins, only discrete changes were observed (fold changes 0.52-1.59). Our study is the first to report an association between aflibercept intervention and the heat shock protein DNAJC17. Our results indicate that the role of heat shock proteins in the treatment of BRVO should be further explored.

EPIDEMIOLOGY

Geographic atrophy severity and mortality in age-related macular degeneration

Graefes Arch Clin Exp Ophthalmol. 2021 Mar 19.

Aneesha Ahluwalia, Liangbo L Shen, Evan M Chen, Mengyuan Sun, Michael M Park , Benjamin K Young, Lucian V Del Priore

PMID: 33742280 DOI: 10.1007/s00417-021-05145-9

Purpose: To examine the association between geographic atrophy (GA) disease characteristics and mortality risk.

Methods: We manually delineated color fundus photographs of 209 Age-Related Eye Disease Study (AREDS) participants with GA secondary to age-related macular degeneration to identify total area of atrophy, GA effective radius growth rate, disease laterality, and the presence of foveal center involvement. Associations between GA characteristics and mortality were assessed with Cox proportional hazards models adjusted for health status indicators.

Results: During a median follow-up of 6.8 years, 48 (23.0%) participants with GA died. In adjusted models, accounting for age, sex, and health status, participants with total GA area in the highest quartile had a significantly increased risk of all-cause mortality compared to those with total GA area in the lowest quartile (hazard ratio [HR], 3.42; 95% confidence interval [CI], 1.32-8.86; P = 0.011). GA effective radius growth rate, bilateral disease, and the presence of foveal center involvement were not significantly associated with

mortality. In a multivariable model, including health status indicators and all GA characteristics, total area of atrophy in the highest quartile remained significantly associated with mortality (HR, 4.65; 95% CI, 1.29-16.70; P = 0.019).

Conclusions: More extensive GA, as indicated by a greater total area of atrophy, was associated with an increased risk of all-cause mortality in our cohort. The extent of GA may reflect the extent of underlying disease processes that contribute to greater mortality risk, further suggesting that GA may be part of a systemic rather than purely ocular disease process.

GENETICS

Functional expression of complement factor I following AAV-mediated gene delivery in the retina of mice and human cells

Gene Ther. 2021 Mar 10.

Anna K Dreismann, Michelle E McClements, Alun R Barnard, Elise Orhan, Jane P Hughes, Peter J Lachmann, Robert E MacLaren

PMID: 33750925 DOI: 10.1038/s41434-021-00239-9

Dry age-related macular degeneration (AMD) is characterised by loss of central vision and currently has no approved medical treatment. Dysregulation of the complement system is thought to play an important role in disease pathology and supplementation of Complement Factor I (CFI), a key regulator of the complement system, has the potential to provide a treatment option for AMD. In this study, we demonstrate the generation of AAV constructs carrying the human CFI sequence and expression of CFI in cell lines and in the retina of C57BL/6 J mice. Four codon optimised constructs were compared to the most common human CFI sequence. All constructs expressed CFI protein; however, most codon optimised sequences resulted in significantly reduced CFI secretion compared to the non-optimised CFI sequence. In vivo expression analysis showed that CFI was predominantly expressed in the RPE and photoreceptors. Secreted protein in vitreous humour was demonstrated to be functionally active. The findings presented here have led to the formulation of an AAV-vectored gene therapy product currently being tested in a first-in-human clinical trial in subjects with geographic atrophy secondary to dry AMD (NCT03846193).

Gene polymorphisms associated with an increased risk of exudative age-related macular degeneration in a Spanish population

Eur J Ophthalmol. 2021 Mar 25;11206721211002698.

Pablo Gili, Leyre Lloreda Martín, José-Carlos Martín-Rodrigo, Naon Kim-Yeon, Laura Modamio-Gardeta, Javier L Fernández-García, Ana Belén Rebolledo-Poves, Elena Gómez-Blazquez, Ruth Pazos-Rodriguez, Elia Pérez-Fernández, María Velasco

PMID: 33765843 DOI: 10.1177/11206721211002698

Purpose: To identify the association between single-nucleotide polymorphisms (SNPs) in CFH, ARMS2, HTRA1, CFB, C2, and C3 genes and exudative age-related macular degeneration (AMD) in a Spanish population.

Methods: In 187 exudative AMD patients and 196 healthy controls (61% women, mean age 75 years), 12 SNPs as risk factors for AMD in CFH (rs1410996, rs1061170, r380390), ARMS2 (rs10490924, rs10490923), HTRA1 (rs11200638), CFB (rs641153), C2 (rs547154, rs9332739), and C3 (rs147859257, rs2230199, rs1047286) genes were analyzed.

Results: The G allele was the most frequent in CFH gene (rs1410996) with a 7-fold increased risk of AMD (OR 7.69, 95% CI 3.17-18.69), whereas carriers of C allele in CFH (rs1061170) showed a 3-fold increased risk for AMD (OR 3.22, 95% CI 1.93-5.40). In CFH (rs380390), the presence of G allele increased the risk for AMD by 2-fold (OR 2.52, 95% CI 1.47-4.30). In ARMS2 (rs10490924), the T-allele was associated with an almost 5-fold increased risk (OR 5.49, 95% CI 3.23-9.31). The A allele in HTRA1 (rs11200638) was more prevalent in AMD versus controls (OR 6.44, 95% CI 3.62-11.47). In C2 gene (rs9332739) the presence of C increased risk for AMD by 3-fold (OR 3.10, 95% CI 1.06-9.06).

Conclusion: SNPs in CFH, ARMS2, HTRA1, and C2 genes were associated in our study with an increased risk for exudative AMD in Spanish patients.

STEM CELLS

Low Immunogenicity and Immunosuppressive Properties of Human ESC- and iPSC-Derived Retinas

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ESC- and iPSC-derived retinal transplantation is a promising therapeutic approach for disease with end-stage retinal degeneration, such as retinitis pigmentosa and age-related macular degeneration. We previously showed

medium- to long-term survival, maturation, and light response of transplanted human ESC- and iPSC-retina in mouse, rat, and monkey models of end-stage retinal degeneration. Because the use of patient hiPSC-derived retina with a disease-causing gene mutation is not appropriate for therapeutic use, allogeneic transplantation using retinal tissue/cells differentiated from a stocked hESC and iPSC line would be most practical. Here, we characterize the immunological properties of hESC- and iPSC-retina and present their three major advantages: (1) hESC- and iPSC-retina expressed low levels of human leukocyte antigen (HLA) class I and little HLA class II in vitro, (2) hESC- and iPSC-retina greatly suppressed immune activation of lymphocytes in co-culture, and (3) hESC- and iPSC-retina suppressed activated immune cells partially via transforming growth factor β signaling. These results support the use of allogeneic hESC- and iPSC-retina in future clinical application.

NUTRITION & LIFESTYLE

Outcome of Off-Label AREDS 2 Supplementation for the Treatment of Macular Degeneration in Non-Proliferative Idiopathic Type 2 Macular Telangiectasia

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Purpose: To evaluate if off-label Age-Related Eye Disease Study 2 (AREDS2) supplementation prevents visual and anatomical deterioration in non-proliferative Idiopathic Macular Telangiectasia Type 2 (IMT2).

Patients and methods: This is a single-center retrospective, comparative study of 82 IMT2 eyes treated with AREDS2 from January 1st, 2013 to January 1st, 2018. The study analysis consisted of a non-comparative arm, which included all AREDS2 eyes, and a comparative arm (27 AREDS2 and 42 untreated eyes) that only included eyes with complete follow-up data. Eyes were evaluated at baseline, 12 and 24 months. Better/worse eye sub-analysis was performed in the comparative study arm. Primary outcomes were best corrected visual acuity (BCVA) and optical coherence tomography (OCT) anatomical characteristics including largest cavitation diameter, central macular thickness (CMT), and length of ellipsoid zone (EZ) loss at 24 months.

Results: In the non-comparative arm, AREDS2 eyes showed stable BCVA (0.28 ± 0.18 logMAR at baseline vs 0.26 ± 0.19 logMAR at 24 months; p = 0.35) and

OCT anatomical features after 24 months of supplementation. In the comparative arm, BCVA mean difference was greater for untreated eyes at 24 months (-0.09 ± 0.15 vs 0.03 ± 0.11 logMAR; p = <0.001). AREDS2 eyes had decreased cavitary diameter and EZ loss compared to untreated eyes at the study endpoint (p = 0.01 and p = 0.02, respectively). CMT remained stable for both cohorts throughout the study. For better/worse eye analysis, untreated eyes had worse BCVA at 24 months in both better and worse eyes (both p = 0.01). For anatomical outcomes, increases in both EZ loss (p = 0.04) and cavitary diameter (p = 0.001) among untreated eyes were only significant for eyes with worse baseline BCVA.

Conclusion: Our results suggest that off-label AREDS2 supplementation in non-proliferative IMT2 may prevent anatomical and visual deterioration in a subset of eyes.

Tucumã (Astrocaryum aculeatum) Prevents Oxidative and DNA Damage to Retinal Pigment Epithelium Cells

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Eye diseases have a negative impact on the eyesight quality of the world population. The age-related macular degeneration (AMD) draws special attention since it is a chronic disorder characterized by oxidative and inflammatory damage to the retinal epithelial pigment, which triggers progressive vision loss. In the Brazilian Amazon, Astrocaryum aculeatum is an Amazonian fruit (Tucumã) used by riverside communities in traditional medicine to treat a number of ailments. These communities have recently shown to have increased longevity and reduced prevalence of age-related morbidity. Thus, the aim of this research was to chemically characterize and analyze the in vitro antioxidant effect and molecular damage prevention of the Tucumã ethanolic extract in retinal pigment epithelium (RPE) cells in a model for AMD. The extract was chemically characterized by ultra-high-performance liquid chromatography (HPLC) coupled with diode-array detection and mass spectrophotometry (HPLC-DAD-MS). In vitro protocols were performed, and the cytopreventive effect of Tucumã on RPE cells exposed to high concentrations of superoxide anion, an oxidant and genotoxic molecule, as well as the effect of Tucumã extract on oxidative and molecular makers were assessed. Biochemical and flow cytometry analyses were conducted in these protocols. The extract presents high concentrations

of caffeic acid, gallic acid, catechin, luteolin, quercetin, and rutin. Treatment did not show cytotoxic effects in cells treated only with extract at 50 µg/mL. In fact, it improved cell viability and was able to prevent necrosis and apoptosis, and oxidative and molecular damage was significantly reduced. In summary, Tucumã is an important Amazon fruit, which seems to contribute significantly to improve human health conditions, as our findings suggest that its extract has a relevant chemical matrix rich in antioxidant molecules, and its consumption could improve eye health and contribute to prevention against oxidative stress through cytoprevention, reactive oxygen species reduction, and maintenance of DNA integrity in retinal pigment epithelium (RPE) cells.