Macular Disease Foundation AUSTRALIA
Our focus is your vision

MD Research News

Issue 151

Tuesday 9 October, 2013

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term “macular degeneration”.

If you have not already subscribed, please email Rob Cummins at **research@mdfoundation.com.au** with ‘Subscribe to MD Research News’ in the subject line, and your name and address in the body of the email.

You may unsubscribe at any time by an email to the above address with your ‘unsubscribe’ request.

Drug treatment

Ophthalmology. 2013 Sep 28. pii: S0161-6420(13)00729-X. doi: 10.1016/j.ophtha.2013.08.011. [Epub ahead of print]

Intravitreal Aflibercept Injection for Neovascular Age-Related Macular Degeneration: Ninety-Six-Week Results of the VIEW Studies.

Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, Brown DM, Chong V, Nguyen QD, Ho AC, Ogura Y, Simader C, Jaffe GJ, Slakter JS, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Soo Y, Anderesi M, Sowade O, Zeitz O, Norenberg C, Sandbrink R, Heier JS.

Department of Ophthalmology, Medical University of Vienna, Vienna, Austria.

PURPOSE: To determine efficacy and safety of intravitreal aflibercept in patients with neovascular age-related macular degeneration (AMD) during a second year of variable dosing after a first-year fixed-dosing period.

DESIGN: Two randomized, double-masked, active-controlled, phase 3 trials.

PARTICIPANTS: Two thousand four hundred fifty-seven patients with neovascular AMD.

METHODS: From baseline to week 52, patients received 0.5 mg intravitreal ranibizumab every 4 weeks (Rq4), 2 mg aflibercept every 4 weeks (2q4), 0.5 mg aflibercept every 4 weeks (0.5q4), or 2 mg aflibercept every 8 weeks (2q8) after 3 monthly injections. During weeks 52 through 96, patients received their original dosing assignment using an as-needed regimen with defined retreatment criteria and mandatory dosing at least every 12 weeks.

MAIN OUTCOME MEASURES: Proportion of eyes at week 96 that maintained best-corrected visual acuity (BCVA; lost <15 letters from baseline); change from baseline in BCVA.

RESULTS: Proportions of eyes maintaining BCVA across treatments were 94.4% to 96.1% at week 52 and 91.5% to 92.4% at week 96. Mean BCVA gains were 8.3 to 9.3 letters at week 52 and 6.6 to 7.9 letters at week 96. Proportions of eyes without retinal fluid decreased from week 52 (60.3% to 72.4%) to week 96 (44.6% to 54.4%), and more 2q4 eyes were without fluid at weeks 52 and 96 than Rq4 eyes (difference of 10.4% [95% confidence interval {CI}, 4.9-15.9] and 9.0% [95% CI, 3.0-15.1]). Patients received on average 16.5, 16.0, 16.2, and 11.2 injections over 96 weeks and 4.7, 4.1, 4.6, and 4.2 injections during weeks 52 through 96 in the Rq4, 2q4, 0.5q4, and 2q8 groups, respectively. The number of injections during weeks 52 through 96 was lower in the 2q4 and 2q8 groups versus the Rq4 group (differences of -0.64 [95% CI, -0.89 to -0.40] and -0.55 [95% CI, -0.79 to -0.30]; P < 0.0001, post hoc analysis). Incidences of Antiplatelet

Trialists' Collaboration-defined arterial thromboembolic events were similar across group (2.4% to 3.8%) from baseline to week 96.

CONCLUSIONS: All aflibercept and ranibizumab group were equally effective in improving BCVA and preventing BCVA loss at 96 weeks. The 2q8 aflibercept group was similar to ranibizumab in visual acuity outcomes during 96 weeks, but with an average of 5 fewer injections. Small losses at 96 weeks in the visual and anatomic gains seen at 52 weeks in all arms were in the range of losses commonly observed with variable dosing.

PMID: 24084500 [PubMed - as supplied by publisher]

Ophthalmology. 2013 Sep 28. pii: S0161-6420(13)00759-8. doi: 10.1016/j.ophtha.2013.08.015. [Epub ahead of print]

Risk of Geographic Atrophy in the Comparison of Age-related Macular Degeneration Treatments Trials.

Grunwald JE, Daniel E, Huang J, Ying GS, Maguire MG, Toth CA, Jaffe GJ, Fine SL, Blodi B, Klein ML, Martin AA, Hagstrom SA, Martin DF; CATT Research Group.

Department of Ophthalmology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania. Electronic address: juangrun@mail.med.upenn.edu.

PURPOSE: To describe risk factors for geographic atrophy (GA) in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).

DESIGN: Cohort within a randomized clinical trial.

PARTICIPANTS: We analyzed 1024 CATT patients with no GA visible on color fundus photographs (CFPs) and/or fluorescein angiograms (FAs) at enrollment.

METHODS: Eyes were assigned to ranibizumab (0.5 mg) or bevacizumab (1.25 mg) treatment and to a 2-year monthly or pro re nata (PRN) injection regimen, or monthly injections for 1 year and PRN for 1 year. Demographic, genetic, and baseline ocular characteristics and lesion features of CFP/FA and optical coherence tomography (OCT) were evaluated as risk factors for GA through 2 years of follow-up. Time-dependent Cox proportional hazard models were used to estimate adjusted hazard ratios (aHRs).

MAIN OUTCOME MEASURES: Development of GA.

RESULTS: By 2 years, GA developed in 187 of 1024 patients (18.3%). Baseline risk factors for GA development included baseline visual acuity (VA) ≤20/200 (aHR, 2.65; 95% confidence interval [CI], 1.43-4.93), retinal angiomatous proliferation (RAP; aHR, 1.69; 95% CI, 1.16-2.47), GA in the fellow eye (aHR, 2.07; 95% CI, 1.40-3.08), and intraretinal fluid at the foveal center (aHR, 2.10; 95% CI, 1.34-3.31). Baseline factors associated with lower risk for GA development included blocked fluorescence (aHR, 0.49; 95% CI, 0.29-0.82), OCT measurements of subretinal fluid thickness of >25 μ (aHR, 0.52; 95% CI, 0.35-0.78), subretinal tissue complex thickness of >275 compared with ≤75 μ (aHR, 0.31; 95% CI, 0.19-0.50), and vitreomacular attachment (aHR, 0.55; 95% CI, 0.31-0.97). Ranibizumab compared with bevacizumab had a higher risk (aHR, 1.43; 95% CI, 1.06-1.93), and monthly dosing had a higher risk (aHR, 1.59; 95% CI, 1.17-2.16) than PRN dosing. There were no strong associations between development of GA and the presence of risk alleles for CFH, ARMS 2, HTRA1, C3, or TLR3.

CONCLUSIONS: Approximately one fifth of CATT patients developed GA within 2 years of treatment. Independent baseline risk factors included poor VA, RAP, foveal intraretinal fluid, monthly dosing, and treatment with ranibizumab. Anti-vascular endothelial growth factor therapy may have a role in the development of GA.

PMID: 24084496 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2013;7:1849-1858. Epub 2013 Sep 19.

Real-world variability in ranibizumab treatment and associated clinical, quality of life, and safety outcomes over 24 months in patients with neovascular age-related macular degeneration: the HELIOS study.

Rakic JM, Leys A, Brié H, Denhaerynck K, Pacheco C, Vancayzeele S, Hermans C, Macdonald K, Abraham I.

Department of Ophthalmology, Centre Hospitalier Universitaire de Liège, Site du Sart Tilman, Liège, Belgium.

INTRODUCTION: The aim of this study was to examine ranibizumab treatment patterns in "real-world" practice and clinical settings, as well as to assess quality of life outcomes over a 24-month period.

MATERIALS AND METHODS: This was a prospective, observational, multicenter, open-label study of 0.5 mg of ranibizumab administered intravitreally. Patients were followed over 24 ± 3 months with intermediate data points at 6 ± 2 months and 12 ± 2 months, and a limited data point at 2.5 ± 1 month that coincided with the end of the loading phase. Outcomes included visual acuity (Early Treatment Diabetic Retinopathy Study), visual function (National Eye Institute Visual Function Questionnaire-25 [NEI VFQ-25]), quality of life (Health Utilities Index Mark III [HUI3]), and safety.

RESULTS: A total of 267 patients with wet age-related macular degeneration (mean ± standard deviation [SD] age = 78.5 ± 7.3 years; 62.4% were female; 34.5% with dual eye involvement; 74.9% were treatment-naïve) were treated (309 eyes were treated). The mean ± SD Early Treatment Diabetic Retinopathy Study score at baseline was 56.3 ± 14.3 letters. The mean ± SD number of injections over 24 months was 7.6 ± 4.1, including 2.5 ± 0.7 and 5.9 ± 3.6 during the loading and maintenance phases, respectively, with corresponding treatment intervals of 4.8 ± 1.4 weeks and 11.5 ± 9.5 weeks, respectively. Improvements in visual acuity over baseline were reached at 2.5 months and maintained at 6 months (both $P < 0.0001$). The mean visual acuity increase over baseline at 12 months was not significant ($P = 0.08$); the decline over baseline at 24 months statistically significant ($P = 0.02$). Overall, 94.3% of patients showed stable or improved disease at 6 months and 81.5% of patients showed stable or improved disease at 24 months. At 6 months, improvements over baseline were significant for VFQ-25 ($P = 0.03$) and HUI3 ($P = 0.02$), but not at 12 months and 24 months. Improvements in VFQ-25 and HUI3 were maintained at 24 months in 38% and 34% of patients, respectively. In total 78 serious adverse events were reported in 40 patients and 77 nonserious adverse events in 34 patients. Nine serious adverse events and nine nonserious adverse events in 14 patients were suspected to be related to ranibizumab treatment.

CONCLUSION: The "real-world" clinical effectiveness of ranibizumab was evidenced by the initial improvements over baseline in visual acuity and quality of life, as well as the maintenance of these outcomes at baseline levels at 24 months, and this was observed under variable treatment conditions. The findings underscore the need for individualized treatment with regular monitoring to achieve optimal vision and quality of life outcomes.

PMID: 24092964 [PubMed - as supplied by publisher]

Ophthalmology. 2013 Sep 28. pii: S0161-6420(13)00730-6. doi: 10.1016/j.ophtha.2013.08.012. [Epub ahead of print]

Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study.

Korobelnik JF, Holz FG, Roider J, Ogura Y, Simader C, Schmidt-Erfurth U, Lorenz K, Honda M, Vitti R, Berliner AJ, Hiemeyer F, Stemper B, Zeitz O, Sandbrink R; GALILEO Study Group.

Service d'ophtalmologie, Hopital Pellegrin, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France;

Université Bordeaux Segalen, Bordeaux, France; INSERM, L'Institut de Santé Publique, d'Épidémiologie et de Développement (ISPED), Centre INSERM U897-Epidemiologie-Biostatistique, Bordeaux, France. Electronic address: jean-francois.korobelnik@chu-bordeaux.fr.

PURPOSE: To evaluate the efficacy and safety of intravitreal aflibercept injections for treatment of macular edema secondary to central retinal vein occlusion (CRVO).

DESIGN: A randomized, multicenter, double-masked phase 3 study.

PARTICIPANTS: A total of 177 treatment-naive patients with macular edema secondary to CRVO were randomized in a 3:2 ratio.

METHODS: Patients received either 2-mg intravitreal aflibercept or sham injections every 4 weeks for 20 weeks. From week 24 to 48, the aflibercept group received aflibercept as needed (pro re nata [PRN]), and the sham group continued receiving sham injections.

MAIN OUTCOME MEASURES: The primary efficacy end point was the proportion of patients who gained 15 letters or more in best-corrected visual acuity (BCVA) at week 24. This study reports week 52 results including the proportion of patients who gained 15 letters or more in BCVA and the mean change from baseline BCVA and central retinal thickness. Efficacy end points at week 52 were all exploratory.

RESULTS: At week 52, the mean percentage of patients gaining 15 letters or more was 60.2% in the aflibercept group and 32.4% in the sham group (P = 0.0004). Aflibercept patients, compared with sham patients, had a significantly higher mean improvement in BCVA (+16.9 letters vs. +3.8 letters, respectively) and reduction in central retinal thickness (-423.5 μm vs. -219.3 μm, respectively) at week 52 (P < 0.0001 for both). Aflibercept patients received a mean of 2.5 injections (standard deviation, 1.7 injections) during PRN dosing. The most common ocular adverse events in the aflibercept group were related to the injection procedure or the underlying disease, and included macular edema (33.7%), increased intraocular pressure (17.3%), and eye pain (14.4%).

CONCLUSIONS: Treatment with intravitreal aflibercept provided significant functional and anatomic benefits after 52 weeks as compared with sham. The improvements achieved after 6 monthly doses at week 24 largely were maintained until week 52 with as-needed dosing. Intravitreal aflibercept generally was well tolerated.

PMID: 24084497 [PubMed - as supplied by publisher]

Ophthalmologica. 2013 Sep 25. [Epub ahead of print]

Genetic Association with Response to Intravitreal Ranibizumab for Neovascular Age-Related Macular Degeneration in the Han Chinese Population.

Yuan D, Yuan D, Liu X, Yuan S, Xie P, Liu Q.

Department of Ophthalmology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, PR China.

Purpose: To investigate a possible association between gene variants and patient response to treatment with intravitreal ranibizumab for neovascular age-related macular degeneration (AMD).

Methods: Visual acuity score (VAS) was recorded at baseline and a subsequent visit at 6 months. Genotypes of 3 polymorphisms in known AMD susceptibility loci (rs1061170 in complement factor H (CFH), rs11200638 in HTRA1 and rs1413711 in VEGF) were determined. Central retinal thickness and maximum thickness of the lesion were also measured.

Results: A total of 168 neovascular AMD patients treated with intravitreal ranibizumab were included in our study. For HTRA1 rs11200638, mean VAS changes were 3.5, 9.4 and 10.6 letters for the AA, AG and GG

genotypes, respectively (p = 0.022). In contrast, for CFH rs1061170 and VEGF rs1413711, mean VAS changes were not significant. However, there was no significant difference in the changes in central retinal thickness and maximum lesion thickness among the genotypes of the tested single-nucleotide polymorphisms.

Conclusions: HTRA1 gene polymorphism may influence patient response to treatment with intravitreal ranibizumab for neovascular AMD. © 2013 S. Karger AG, Basel.

PMID: 24080590 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2013 Oct 1. pii: iovs.13-11665v1. doi: 10.1167/iovs.13-11665. [Epub ahead of print]

Functional characterization and multimodal imaging of treatment-naive "quiescent" choroidal neovascularization.

Querques G, Srour M, Massamba N, Georges A, Ben Moussa N, Rafaeli O, Souied E.

Department of Ophthalmology, University Paris Est Creteil, 40 Av de Verdun, Creteil, 94000, France.

Purpose: To investigate the multimodal morphological and functional characteristics of treatment-naïve "quiescent" choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

Methods: Eleven patients with treatment-naïve "quiescent" CNV that consecutively presented over a six-month period, underwent multimodal morphological and functional assessment (including indocyanine green angiography [ICGA], spectral-domain optical coherence tomography [SD-OCT], microperimetry and preferential hyperacuity perimeter [PHP]). For the purpose of this study, asymptomatic previously untreated CNVs showing absence of intraretinal/subretinal exudation in 2 consecutive visits (at least 6 months apart) were defined as treatment-naïve "quiescent" CNV.

Results: Eleven eyes of 11 patients (9 females; mean age 76.5±8.5 years) were included. On FA, "quiescent" CNVs appeared as late speckled hyperfluorescent lesions lacking well-demarcated borders. Mid-late phase ICGA allowed visualizing the hyperfluorescent "quiescent" CNV network and delineating the plaque. Mean lesion area (mid-late phase ICGA) appeared larger compared to earliest previous examination performed 23.8±16.0 months before (3.24±2.51mm2 vs 3.52±2.46 mm2, respectively; p=0.01). SD-OCT revealed, at the site of "quiescent" CNV, an irregularly slightly elevated retinal pigment epithelium (RPE), without hyporeflective intraretinal/subretinal fluid, showing a major axis in the horizontal plane, which was characterized by collections of moderately reflective material in the sub-RPE space and clear visualization of the hypereflective Bruch's membrane. Hypergeometric distribution revealed a significant correlation between microperimetry and PHP with respect to locations of "affected areas" (p=0.001).

Conclusions: "Quiescent" CNVs are sub-RPE CNVs secondary to AMD, showing absence of intraretinal/subretinal exudation on repeated OCT. "Quiescent" CNVs enlarge over time and may contribute to local reduced retinal sensitivity and metamorphopsia.

PMID: 24084095 [PubMed - as supplied by publisher]

Korean J Ophthalmol. 2013 Oct;27(5):351-360. Epub 2013 Sep 10.

Characteristic Findings of Optical Coherence Tomography in Retinal Angiomatous Proliferation.

Lim EH, Han JI, Kim CG, Cho SW, Lee TG.

Myung-Gok Eye Research Institute, Konyang University Kim's Eye Hospital, Seoul, Korea.

PURPOSE: To identify the unique pathologic findings of retinal angiomatous proliferation (RAP) in optical coherence tomography (OCT).

METHODS: Retrospectively, 29 eyes of 25 patients with age-related macular degeneration and complicated RAP were analyzed. All 29 eyes had choroidal neovascularization (CNV) in the area of pigment epithelial detachment (PED) or adjacent to it, which was visible with fluorescein angiography or indocyanine green angiography. Cross-sectional images were obtained by OCT scanning through the CNV lesions.

RESULTS: Six distinctive findings of OCT included drusen (100%), inner retinal cyst (80%), outer retinal cyst (68%), fibrovascular PED (84%), serous retinal detachment (40%), and PED (68%).

CONCLUSIONS: Through analysis of OCT findings, we revealed six different types of lesions distinctive of RAP which may provide helpful diagnostic information for subsequent treatment and predicting the prognosis of RAP.

PMID: 24082773 [PubMed - as supplied by publisher] PMCID: PMC3782581

Pathogenesis

J Clin Invest. 2013 Oct 1. pii: 70230. doi: 10.1172/JCI70230. [Epub ahead of print]

Ras pathway inhibition prevents neovascularization by repressing endothelial cell sprouting.

Westenskow PD, Kurihara T, Aguilar E, Scheppke EL, Moreno SK, Wittgrove C, Marchetti V, Michael IP, Anand S, Nagy A, Cheresh D, Friedlander M.

Abstract: Vascular networks develop from a growing vascular front that responds to VEGF and other guidance cues. Angiogenesis is required for normal tissue function, but, under conditions of stress, inappropriate vascularization can lead to disease. Therefore, inhibition of angiogenic sprouting may prevent neovascularization in patients with blinding neovascular eye diseases, including macular degeneration. VEGF antagonists have therapeutic benefits but also can elicit off-target effects. Here, we found that the Ras pathway, which functions downstream of a wide range of cytokines including VEGF, is active in the growing vascular front of developing and pathological vascular networks. The endogenous Ras inhibitor p120RasGAP was expressed predominately in quiescent VEGF-insensitive endothelial cells and was ectopically downregulated in multiple neovascular models. MicroRNA-132 negatively regulated p120RasGAP expression. Experimental delivery of α-miR-132 to developing mouse eyes disrupted tip cell Ras activity and prevented angiogenic sprouting. This strategy prevented ocular neovascularization in multiple rodent models even more potently than the VEGF antagonist, VEGF-trap. Targeting microRNA-132 as a therapeutic strategy may prove useful for treating multiple neovascular diseases of the eye and for preventing vision loss regardless of the neovascular stimulus.

PMID: 24084735 [PubMed - as supplied by publisher]

Ophthalmic Genet. 2013 Sep 30. [Epub ahead of print]

The Role of Matrix Metalloproteinases Polymorphisms in Age-Related Macular Degeneration.

Liutkeviciene R, Lesauskaite V, Sinkunaite-Marsalkiene G, Zaliuniene D, Zaliaduonyte-Peksiene D, Mizariene V, Gustiene O, Jasinskas V, Jariene G, Tamosiunas A.

Department of Ophthalmology, Neuroscience Institute, Lithuanian University of Health Sciences, Medical Academy , Kaunas , Lithuania .

Abstract Background: Matrix metalloproteinases (MMP) are responsible for the degradation of extracellular matrix components and play an important role in the physiological and pathological remodeling of tissues. Purpose: To assess the impact of MMP-2 Rs2285053 (C -> T), MMP-3 Rs3025039 (5A -> 6A), and MMP-9 Rs3918242 (C -> T) single nucleotide polymorphism on the development of early age-related macular degeneration (AMD).

Methods: The study group comprised 148 patients with AMD, and the control group enrolled 526 randomly selected persons. The genotyping of MMP-3 Rs3025039, MMP-2 Rs2285053, and MMP-9 Rs3918242 was performed by using the real-time PCR method.

Results: The frequency of the MMP-2 (-735) C/T and MMP-3 (-1171) 5A/6A genotypes did not differ significantly between the patients with AMD and the control group, while the MMP-9 (-1562) C/C genotype was more frequently detected in patients with AMD than the control group (73.7% vs. 64.6%, p = 0.048). Logistic regression analysis showed that the MMP-9 (-1562) C/C genotype increased the likelihood of developing early AMD (OR = 1.51, 95% CI: 1.01-2.21; p = 0.046). After the subdivision into the groups by age, a significant difference only in the frequency of the MMP-9 (-1562) C/C genotype was found comparing the AMD patients and the control group younger than 65 years (79.7% vs. 66.4%, p = 0.039).

Conclusions: Only MMP-9 Rs3918242 (C -> T) single nucleotide polymorphism was found to play a significant role in the development of AMD, and the effect was more pronounced at the age of less than 65 years.

PMID: 24079541 [PubMed - as supplied by publisher]

Genetics

Clin Med Res. 2013 Sep;11(3):146-147.

B4-4: Genome-Wide Association Study of Macular Degeneration: Early Results from the Kaiser Permanente Research Program on Genes, Environment, and Health (RPGEH).

Jorgenson E, Sciortino S, Shen L, Ranatunga D, Hoffmann T, Kvale M, Banda Y, Kwok PY, Walter L, Risch N, Schaefer C.

Background/Aims: Age-related macular degeneration (AMD) is the most common cause of vision loss in individuals over the age of 50 in the United States. Genetic factors explain a large portion of the risk of developing AMD, and genetic variants at the CFH, HTRA1/ARMS2, C2/CFB, and C3 gene loci have previously been associated with the disease.

Methods: We conducted a genome-wide association study (GWAS) of AMD in the Kaiser Permanente Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. The GERA cohort includes 110,266 subjects with extensive electronic medical record information on eye examinations, diagnoses and treatment of vision disorders, and dense genome-wide genotype information on more than 675,000 genetic markers generated using Affymetrix Axiom arrays. The cohort is ethnically diverse, with 7.5% Asian, 7% Latino, 3.5% African American, and 81% non-Hispanic white subjects. We identified a total of 2,147 AMD cases (46 Asian, 125 Latino, 11 African American, and 1,965 non-Hispanic whites) and 37,521 controls (2,013 Asian, 3,201 Latino, 1,168 African American, and 31,139 non-Hispanic whites) for analysis. Analyses were conducted separately for each race/ethnicity group.

Results: In the largest group, non-Hispanic whites, we identified highly significant associations with variants in the CFH and HTRA1/ARMS2 gene regions, and genome-wide significant associations in the C2/CFB and C3 gene regions.

Conclusions: These results confirm those of previous studies and demonstrate the power of the GERA cohort for combining information from electronic medical records with extensive genotype data. This

approach can be applied to additional vision disorder phenotypes, including response to treatment and disease progression.

PMID: 24085932 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2013 Sep 28. pii: S0002-9394(13)00534-5. doi: 10.1016/j.ajo.2013.08.003. [Epub ahead of print]

Relationship between Systemic Cytokines and Complement Factor H Y402H Polymorphism in Patients With Dry Age-Related Macular Degeneration.

Cao S, Ko A, Partanen M, Pakzad-Vaezi K, Merkur AB, Albiani DA, Kirker AW, Wang A, Cui JZ, Forooghian F, Matsubara JA.

Department of Ophthalmology and Visual Sciences, Eye Care Centre, University of British Columbia, Vancouver, Canada.

PURPOSE: To investigate the relationship between systemic cytokines, the complement factor H (CFH) Y402H polymorphism, drusen load, and subfoveal choroidal thickness in patients with dry age-related macular degeneration (AMD).

DESIGN: Cross-sectional study.

METHODS: Forty-four dry AMD patients under care of the Retina Service at the University of British Columbia were enrolled. Drusen load was measured with an automated software algorithm in spectral-domain optical coherence tomography; subfoveal choroidal thickness was measured manually using enhanced depth imaging. Bio-Plex suspension assays (Bio-Rad Laboratories) were used to analyze cytokines in plasma and CFH Y402H was genotyped. Statistical analyses included analysis of covariance and Pearson correlation, corrected for multiple comparisons.

RESULTS: The levels of 3 of 4 studied cytokines were significantly different among patients with CC, CT, or TT variants of the CFH Y402H polymorphism ($P < .01$). Patients with the at-risk CC variant had higher systemic levels of interleukin-6, interleukin-18, and tumor necrosis factor α than those with the CT variants, the TT variant, or both ($P < .01$). Interleukin-1β did not reach significance ($P = .02$), but did demonstrate a consistent trend. No correlation was found between plasma cytokines and drusen load or choroidal thickness (all $P > .15$).

CONCLUSIONS: The elevated systemic levels of selected proinflammatory cytokines, including those representing products of inflammasome activation, were associated with the CC at-risk variant of the Y402H polymorphism and suggest that genetic factors regulate the inflammatory status in dry AMD patients. Our data support the central role of inflammation in the pathogenesis of AMD and provide further evidence of a systemic involvement in AMD etiology.

PMID: 24083687 [PubMed - as supplied by publisher]

DNA Cell Biol. 2013 Oct 1. [Epub ahead of print]

Effect of Soluble Inducible Costimulator Level and Its Polymorphisms on Age-Related Macular Degeneration.

Yu H, Zou X, Peng L, Wang Y, Zhang C, Chen B, Zou Y.

Department of Ophthalmology, General Hospital of Guangzhou Military Command of PLA , Guangzhou, China .

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly population. Evidence has shown that the human immune system may play critical roles in this disease. Inducible costimulator (ICOS) promotes T-cell activation, differentiation, and T:B-cell interactions. The aim of the study was to understand the effect of ICOS on the development of AMD from genetic polymorphism perspective and serum level perspective. Two ICOS polymorphisms, rs10183087A/C and rs10932037C/T, were tested in 223 AMD cases and 262 healthy controls. The serum level of soluble ICOS (sICOS) was compared among subjects with different genotypes, as well as between AMD patients and controls. Data showed that prevalence of rs10183087CC genotype was significantly increased in AMD than in controls ($p=0.001$). Function analysis revealed that subjects carrying rs10183087CC genotype had higher serum levels of sICOS than those with AA or AC genotypes ($p<0.05$). When we compared serum levels of sICOS between cases and controls, results showed that AMD patients had significantly increased sICOS levels than healthy donors ($p<0.05$). Also, wet type cases were observed to have higher sICOS levels than cases with dry type ($p<0.05$). These data suggested ICOS polymorphism could affect the susceptibility to AMD by elevating protein expression, and serum levels of sICOS may be closed correlated with the development and progression of this disease.

PMID: 24083358 [PubMed - as supplied by publisher]

Exp Eye Res. 2013 Sep 27. pii: S0014-4835(13)00278-9. doi: 10.1016/j.exer.2013.09.012. [Epub ahead of print]

1,25-Dihydroxyvitamin D decreases HTRA1 promoter activity in the rhesus monkey - A plausible explanation for the influence of vitamin D on age-related macular degeneration?

Pahl L, Schubert S, Skawran B, Sandbothe M, Schmidtke J, Stuhrmann M.

Institute of Human Genetics, Hannover Medical School, Hannover, Germany. Electronic address: pahl.lisa@mh-hannover.de.

Abstract: Age-related macular degeneration is the major cause of blindness in the elderly worldwide and the risk is influenced by both environmental and genetic risk factors. One important disease-associated region in humans is located on 10q26 and includes the two candidate genes ARMS2 and HTRA1. However, determination of the causative gene has not yet been possible and examining the situation in the rhesus monkey may help understand the situation in humans. In a recent paper, we characterized the rhesus monkey 10q26-orthologue region on chromosome 9 in detail and identified the drusen-associated HTRA1 promoter SNP rs196357513 as a putative risk factor. In this study, we predicted 9 binding sites for the vitamin D-dependent transcription factor vitamin D receptor in the rhesus HTRA1 promoter, one of which is destroyed by the rs196357513-risk allele. As patients with vitamin D deficit are at increased risk for age-related macular degeneration, a luciferase assay in transiently transfected ARPE19-cells was performed to evaluate the influence of the SNP rs196357513 and of 1,25-dihydroxyvitamin D on the rhesus monkey HTRA1 promoter activity. This revealed that the luciferase activity of the promoter construct containing the rs196357513 wild type allele was significantly reduced after vitamin D stimulation. An in silico analysis and literature search imply that this regulation could also play a role in human HTRA1 expression. Moreover, HTRA1 promoter activity of the construct containing the rs196357513 risk allele appeared diminished in comparison to the construct with the wild type allele, albeit this difference was not significant. The lower promoter activity due to the rhesus monkey rs196357513 risk allele apparently contradicts the common hypothesis for the human HTRA1 promoter risk allele of SNP rs11200638, for which a higher promoter activity has been observed. Our data point to a yet unexpected effect of decreased HTRA1 expression on drusen pathogenesis. Thus not only a higher HTRA1 expression, but an imbalance of HTRA1 might be disease-relevant. Both findings require closer analysis, but if relevance for humans proves true, it would impact current age-related macular degeneration research and treatment.

PMID: 24076413 [PubMed - as supplied by publisher]

Diet & lifestyle

Invest Ophthalmol Vis Sci. 2013 Oct 1. pii: iovs.13-12149v1. doi: 10.1167/iovs.13-12149. [Epub ahead of print]

VEGF rescues Cigarette Smoking induced Human Retinal Pigment Epithelial cell death through increasing Autophagic Flux.

Chu YK, Lee SC, Byeon SH.

Ophthalmology, Siloam Eye Hospital, 512, Deungchon 2-dong, Gangseo-gu, Seoul, 157-386, Korea (South), Republic of.

Purpose: Cigarette smoking (CS) is the most consistent risk factor for advanced age-related macular degeneration (AMD). To verify the molecular basis for CS-induced RPE alterations, cell survival rates against CS in relation with VEGF expressions and autophagic flux were evaluated.

Methods: Cigarette smoking extract (CSE) was added to the ARPE-19 cells and hydrogen-peroxide (HP) was used as a pure oxidant control. Cell death was measured by flow cytometry with annexin V-fluorescein isothiocyanate. Survival analysis was performed with pretreatment of anti-VEGF or recombinant VEGF. The expression of VEGF-A, -R1, -R2, and soluble VEGF-R1 was determined by semi-quantitative RT-PCR. LC3B-I (microtubule-associated protein-1 inhibitors), LC3B-II, and phosphorylation of Akt or Erk were measured with Western blot. Autophagic flux was determined with further increased LC3B-II levels with inhibitors of lysosomal proteases.

Results: Incubation with 5% CSE for 16 hours induced about 30 % cell death, which was similar to concentrations of 200μM HP. Pretreatment with anti-VEGF did not affect cell survival rates under CSE, contrary to that of HP. However, supplementation with VEGF rescued CSE-induced RPE cell death. CSE increased autophagic flux, which was augumented with pretreatment of rhVEGF. CSE degraded the total amount of Akt and VEGF blunted CSE induced phosphorylation of Erk.

Conclusions: CSE, similar to HP, affects cell viabilities and induces expression of VEGF and its receptors. Increased autophagic flux accelerated by treatment of exogenous VEGF, may have a role in rescuing CSE-induced RPE cell death.

PMID: 24084092 [PubMed - as supplied by publisher]