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MD Research News

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Drug treatment

J Korean Med Sci. 2013 May;28(5):769-74. doi: 10.3346/jkms.2013.28.5.769. Epub 2013 May 2.

Current smoking is associated with a poor visual acuity improvement after intravitreal ranibizumab therapy in patients with exudative age-related macular degeneration.

Lee S, Song SJ, Yu HG.

Department of Ophthalmology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea.

Abstract: In this study, the risk factors that may influence visual improvement after intravitreal ranibizumab (IVR) treatment for exudative age-related macular degeneration (AMD) were examined. From 2008 to 2012, 420 patients (448 eyes) with exudative AMD were prospectively registered at Seoul National University Hospital. From this group of patients, 125 eyes were included in this study. All patients were treated with 3 consecutive IVR injections. The visual acuity (VA) was evaluated at baseline and 1 month after the third ranibizumab injection. To evaluate the risk factors associated with VA improvement after IVR, patient demographic data and systemic risk factors were analyzed. Patients were divided into a poor VA improvement group and a good VA improvement group, with reference to the median visual improvement in all eyes. Among 125 eyes, 66 eyes (52.8%) were included in the responder group and 59 eyes (47.2%) in the non-responder group. The median VA improvement after 3 monthly ranibizumab injections was -0.05 logMAR. Multivariate analyses revealed that current smoking (adjusted OR, 7.540; 95% CI, 1.732-32.823) was independently associated with poor VA improvement after IVR treatment for exudative AMD. In conclusion, cigarette smoking is an independent risk factor for lower VA gains with IVR treatment for exudative AMD.

PMID: 23678271 [PubMed - in process]

Am J Ophthalmol. 2013 May 8. pii: S0002-9394(13)00136-0. doi: 10.1016/j.ajo.2013.02.009. [Epub ahead of print]

Short-Term Outcomes of Aflibercept for Neovascular Age-Related Macular Degeneration in Eyes Previously Treated With Other Vascular Endothelial Growth Factor Inhibitors.

Ho VY, Yeh S, Olsen TW, Bergstrom CS, Yan J, Cribbs BE, Hubbard GB 3rd.

Section of Vitreoretinal Disease and Surgery, Department of Ophthalmology, Emory Eye Center, Emory University School of Medicine, Atlanta, Georgia.

PURPOSE: To report results of aflibercept therapy in eyes with neovascular age-related macular degeneration previously treated with bevacizumab, ranibizumab, or both.

DESIGN: Retrospective, interventional, noncomparative, consecutive case series.

METHODS: Ninety-six eyes from 85 patients with neovascular age-related macular degeneration who previously had received bevacizumab, ranibizumab, or both were treated with aflibercept monthly for 3 months followed by a fourth injection within 2 months. Outcomes were determined 4 ± 1 months after the first aflibercept dose and included: proportion of patients gaining or losing 2 lines or more of best-corrected visual acuity, proportion remaining within a gain or loss of 1 line, mean change in logarithm of the minimal angle of resolution visual acuity, mean change in central foveal thickness, mean change in macular cube volume, and qualitative anatomic response as assessed by spectral-domain optical coherence tomography.

RESULTS: At baseline, 82 (85%) eyes had signs of active exudation despite a mean of 17 previous anti-vascular endothelial growth factor injections. At final visit, 82 (85%) remained stable within a gain or loss of 1 line, 7 (7%) gained 2 lines or more, and 7 (7%) lost 2 lines or more of best-corrected visual acuity. Mean logarithm of the minimal angle of resolution visual acuity showed minimal change 0.02 (range, -0.46 to 0.70; P = .14). Mean central foveal thickness decreased -18 μm (range, -242 to 198 μm; P = .06). Mean macular volume decreased -0.27 mm3 (95% confidence interval, -0.4 to -0.1 mm3; P = .004). On qualitative analysis, 4 (5%) eyes had complete resolution of exudative fluid, 40 (49%) showed partial resolution, 26 (32%) remained unchanged, and 12 (14%) showed worsened exudative fluid.

CONCLUSIONS: Aflibercept seems to be an effective alternative for neovascular age-related macular degeneration patients previously treated with bevacizumab, ranibizumab, or both at 4 months of follow-up. Most treated eyes demonstrated stable visual acuity and anatomic improvements by spectral-domain optical coherence tomography.

PMID: 23664153 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2013 May 10. pii: S0002-9394(13)00218-3. doi: 10.1016/j.ajo.2013.03.030. [Epub ahead of print]

Conversion to Aflibercept For Chronic Refractory Or Recurrent Neovascular Age-Related Macular Degeneration.

Yonekawa Y, Andreoli C, Miller JB, Loewenstein JI, Sobrin L, Eliott D, Vavvas DG, Miller JW, Kim IK.

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PURPOSE: To explore the visual and anatomic outcomes of patients with refractory or recurrent neovascular age-related macular degeneration (AMD) who were converted from bevacizumab and/or ranibizumab to aflibercept.

DESIGN: Two-center, retrospective chart review.

METHODS: Treatment history, visual acuity (VA), and central macular thickness (CMT) on spectral-domain optical coherence tomography were collected. Patients were divided into "refractory" (persistent exudation despite monthly injections) or "recurrent" (exudation suppressed, but requiring frequent injections).

RESULTS: One hundred and two eyes of 94 patients were included; 68 were refractory and 34 were recurrent. Eyes received a mean of 20.4 prior bevacizumab/ranibizumab injections and a mean of 3.8 aflibercept injections. Mean follow-up was 18 weeks. Mean VA was 20/50-1 before conversion, 20/50-2 after 1 aflibercept injection (P = .723), and 20/50+2 after the final injection (P = .253). Subgroup analysis of refractory and recurrent cases also showed stable VA. Of the refractory cases, mean CMT had improved after 1 injection (P < .001) and the final injection (P < .001). Intraretinal (P < .001) and subretinal (P < .001) fluid de-

creased after 1 injection, and the mean injection interval was extended from 5.2 to 6.2 weeks (P = .003). Of the recurrent cases, mean CMT improved after 1 injection (P < .001) and the final injection (P < .001). Intraretinal (P = .003) and subretinal (P = .046) fluid decreased after 1 injection, and the mean injection interval was extended from 7.2 to 9.5 weeks (P = .001).

CONCLUSIONS: Converting patients with chronic neovascular AMD to aflibercept results in stabilized vision and improved anatomic outcomes, while allowing injection intervals to be extended.

PMID: 23668679 [PubMed - as supplied by publisher]

Ann Pharmacother. 2013 May 14. [Epub ahead of print]

Aflibercept: Newly Approved for the Treatment of Macular Edema Following Central Retinal Vein Occlusion (June).

Evoy KE, Abel SR.

< Purdue University, Lafayette, IN.

OBJECTIVE: To review the pharmacology, efficacy, and safety data available for aflibercept and compare the drug to other therapeutic options for treatment of macular edema following central retinal vein occlusion (CRVO) to determine its likely role in therapy.

DATA SOURCES: A PubMed search using the terms aflibercept and VEGF trap-eye was conducted to identify initial literature sources. No timeframe was used for exclusion of older trials. All trials referenced were published between January 1995 and December 2012.

STUDY SELECTION AND DATA EXTRACTION: Trials pertaining to oncologic use were excluded, as were studies conducted in animals and those written in a language other than English. Abstracts of the remaining trials were evaluated for determination of relevance to this review. Additional information sources were obtained via Internet and PubMed following a review of references.

DATA SYNTHESIS: While previous Phase 1, 2, and 3 trials for other indications (age-related macular degeneration and diabetic macular edema) have shown intravitreal injections of aflibercept to be safe and well tolerated in many patients, preliminary results from the ongoing COPERNICUS and GALILEO trials proved the efficacy of this medication in treating macular edema secondary to CRVO. Of the combined 358 patients studied in COPERNICUS and GALILEO, 56% and 60%, respectively, of the patients receiving aflibercept 2 mg monthly achieved at least a 15-letter improvement in best-corrected visual acuity (BCVA) from baseline over 6 months compared with just 12% and 22% in the control group (p < 0.01 for both). Additionally, in COPERNICUS and GALILEO, patients achieved a 21.3- and 14.7- letter improvement, respectively, in BCVA compared with placebo (p < 0.01 for both).

RESULTS: In September 2012, aflibercept became the second vascular endothelial growth factor (VEGF) inhibitor approved for treatment of macular edema secondary to CRVO. While efficacy and safety appear similar to other anti-VEGF treatments, the higher potency, binding affinity, and duration of action make aflibercept an appealing new option.

PMID: 23673531 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2013 May 8. pii: S0002-9394(13)00139-6. doi: 10.1016/j.ajo.2013.02.012. [Epub ahead of print]

Subfoveal Fibrosis in Eyes With Neovascular Age-Related Macular Degeneration Treated With Intravitreal Ranibizumab.

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PURPOSE: To assess baseline and follow-up characteristics of choroidal neovascularization (CNV) lesions in age-related macular degeneration in relation to the development of subfoveal subretinal fibrosis.

DESIGN: Retrospective, observational case series.

METHODS: settings and study population: One hundred ninety-seven treatment-naïve eyes in 197 patients with CNV in age-related macular degeneration without subfoveal fibrosis at first presentation who were treated with ranibizumab in a pro re nata regimen. main outcome measure: Subfoveal fibrosis at the conclusion follow-up of 24 months or fewer.

RESULTS: The hazard ratio of any subfoveal fibrosis developing in eyes with predominantly classic CNV was 5.95 (95% confidence interval [CI], 3.25 to 10.90) compared with minimally classic and occult CNV, whereas the hazard ratio of fibrosis developing with foveal atrophy was 3.38 (95% CI, 1.47 to 7.81; mean follow-up, 1.80 years; 95% CI, 1.75 to 1.85 years). The hazard ratio of any fibrosis developing was 3.38 (95% CI, 1.10 to 10.38) in eyes with a baseline best-corrected visual acuity of 40 or worse using Early Treatment Diabetic Retinopathy Study letter scores, as compared with eyes with a baseline best-corrected visual acuity of 70 letters or more. An interval between diagnosis and treatment of 15 days or more was associated with a hazard ratio of any fibrosis developing of 2.24 (95% CI, 1.28 to 3.94) as compared with an interval of fewer than 15 days. Compared with eyes in which fibrosis did not develop, eyes in which prominent fibrosis or fibrosis developed with foveal atrophy lost 8.5 more Early Treatment Diabetic Retinopathy Study letters (95% CI, -1.0 to -15.9; P = .0242) and 10.3 more Early Treatment Diabetic Retinopathy Study letters (95% CI, -4.0 to -16.5; P = .0012), respectively.

CONCLUSIONS: The development of subfoveal fibrosis in neovascular age-related macular degeneration was associated with predominantly classic CNV and poorer visual acuity at first presentation, a longer interval between diagnosis and treatment, and approximately 2 lines of additional visual loss at the conclusion follow-up.

PMID: 23664150 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2013 May 9. pii: S0002-9394(13)00228-6. doi: 10.1016/j.ajo.2013.04.001. [Epub ahead of print]

Photodynamic Therapy Versus Combination Therapy in Polypoidal Choroidal Vasculopathy: Changes of Aqueous Vascular Endothelial Growth Factor.

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PURPOSE: To investigate the influence of photodynamic therapy (PDT) and combination of PDT and ranibizumab on aqueous humor levels of vascular endothelial growth factor (VEGF) in polypoidal choroidal vasculopathy (PCV).

DESIGN: Prospective randomized clinical trial.

METHOD: We included 20 eyes with treatment-naïve PCV and 20 eyes undergoing cataract surgery as controls. PCV eyes were randomized to treatment with PDT alone or to a combination of ranibizumab and PDT on the same day. During 3 months, retreatment was not performed. Aqueous humors were collected at baseline and at 1 week, 1 month, and 3 months after treatment in the PCV group and during cataract surgery in the control group. VEGF levels were measured using multiplex bead immunoassay.

RESULTS: At baseline, VEGF levels were significantly increased in PCV eyes compared with control eyes. A significant decrease in VEGF levels was found at 1 week after PDT treatment (n = 8) and at all time points after combination treatment (n = 12). With combination treatment, VEGF levels were decreased to values below the detection limit in all eyes at 1 week and 1 month and in 7 of 12 eyes at 3 months. There was no difference in the clinical profiles among the 2 treatment groups at each time point.

CONCLUSION: Decreased levels of VEGF detected 1 week after PDT for PCV seems to reflect acute damage of vascular endothelial cells, one of the VEGF expression sites in PCV. Concomitant ranibizumab resulted in a further decrease in VEGF to negligible levels, but this result did not affect the clinical results for 3 months.

PMID: 23664208 [PubMed - as supplied by publisher]

Jpn J Ophthalmol. 2013 May 11. [Epub ahead of print]

Treatment results at 1 year of ranibizumab therapy for polypoidal choroidal vasculopathy in eyes with good visual acuity.

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PURPOSE: To evaluate the efficacy of intravitreal ranibizumab (IVR) for subfoveal polypoidal choroidal vasculopathy (PCV) in eyes with a best corrected visual acuity (BCVA) of 0.6 (logMAR 0.22) or better.

METHODS: Fifty eyes with BCVA between 0.6 (logMAR 0.22) and 1.0 (logMAR 0) and subfoveal PCV were treated with IVR for 3 consecutive months. Additional IVR was given at subsequent monthly visits, if needed, up to 11 months after the initial injection. The patients were followed-up prospectively for 12 months, and changes in mean BCVA, central retinal thickness (CRT), serous retinal detachment (SRD), hemorrhage, and number of polypoidal lesions were evaluated.

RESULTS: Mean BCVA improved significantly at the 3-, 6-, 9-, and 12-month follow-up visits and CRT decreased significantly at 1, 2, 3, 6, 9, and 12 months after the initial treatment as compared with the baseline. SRD was observed in 10 and 21 eyes at 3 and 12 months. Hemorrhage was observed in 6 eyes at 3 months and 3 eyes at 12 months. All polypoidal lesions had completely regressed in 19 % and the size of network vessels was either unchanged or enlarged in 98 % of the eyes at 12 months.

CONCLUSION: Based on the maintenance of vision improvement for at least 12 months, IVR for PCV proved useful for eyes with BCVAs of 0.6 (logMAR 0.22) to 1.0 (logMAR 0), despite a low regression rate of polypoidal lesions and minimal network size reduction.

PMID: 23665979 [PubMed - as supplied by publisher]

Ophthalmologe. 2013 May 18. [Epub ahead of print]

[BOON (Bonn ophthalmology online network) : Concept of an integrative databank for monitoring patients under intravitreal therapy.] [Article in German]

Milojcic C, Clemens CR, Fimmers R, Quade G, Alten F, Sarbach P, Eter N.

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BACKGROUND: Previous studies have proven that long-lasting success in the therapy of neovascular age-

related macular degeneration (AMD) and other neovascular retinal diseases depends on monthly follow-up examinations to assess visual acuity and retinal morphology.

MATERIALS AND METHODS: The interactive database Bonn ophthalmology online network (BOON) offers a platform for patient monitoring, increasing control reliability and providing a tool for permanent communication between treating centers and referring ophthalmologists. The BOON data-based project started in 2009 at the department of ophthalmology at Bonn University and ten referring ophthalmology practices. It was programmed to communicate diagnostic findings, images and patient appointments online. In order to react promptly the system gave immediate notice if patients had missed a follow-up appointment or the condition had worsened. Patients were recruited in 2009 and 2010 and were followed for 1 year. Each patient had an electronic master file with several registers in which, besides personal data, precise diagnostic findings, imaging and reports were quickly and easily entered by means of detailed check box and drop-down menus. Each follow-up was registered and an alert email was sent to the referring physician in cases of missed appointments or disease progression.

RESULTS AND CONCLUSIONS: The BOON database supports the requirements for a fast and detailed communication between treating and referring physicians in the treatment of patients with AMD as well as other retinal diseases. It was programmed to support data exchange and monthly control visits and thus a better patient management. Results will show whether this helps to enhance long-term treatment success in neovascular diseases.

PMID: 23681179 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Graefes Arch Clin Exp Ophthalmol. 2013 May 16. [Epub ahead of print]

Characteristics of fundus autofluorescence and drusen in the fellow eyes of Japanese patients with exudative age-related macular degeneration.

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BACKGROUND: The main purpose of this study is to investigate the characteristics of fundus autofluorescence (FAF) and area of soft drusen among the fellow eyes of unilateral typical age-related macular degeneration (typical AMD) and polypoidal choroidal vasculopathy (PCV) in Japanese patients.

METHODS: FAF images were obtained from the fellow eyes of unilateral typical AMD (n = 64), unilateral PCV (n = 95), unilateral retinal angiomatous proliferation (RAP) (n = 4) and 56 control subjects, then classified into normal, minimal-change, and abnormal patterns by two graders. Interobserver variability between two graders and intraobserver variability were assessed for FAF classifications, and cases with inconsistent decisions were finally classified by the third grader. Soft drusen were segmented and their total areas were compared between the fellow eyes of typical AMD and PCV. Area(s) with increased autofluorescence were segmented to assess the relationship with soft drusen area(s).

RESULTS: Assessment for interobserver variability between two graders and intraobserver variability in one grader showed substantial agreement ($\kappa = 0.70$) and almost perfect agreement ($\kappa = 0.85$), respectively. In the final decision mediated by third grader, the proportions of eyes with either minimal-change FAF pattern or abnormal FAF pattern in the fellow eyes of both typical AMD (37 cases, 58 %) and PCV (47 cases, 49 %) were significantly higher than that of the control cases (15 cases, 27 %; $p < 0.01$). The proportion of abnormal FAF pattern in the fellow eyes of typical AMD (20 cases, 31 %) was higher than that of PCV (15 cases, 16 %; $p < 0.05$). Total soft drusen areas in the fellow eyes of typical AMD (0.369 ± 0.718 mm2) were larger than those of PCV (0.173 ± 0.408 mm2; $p < 0.05$), and those in the eyes with abnormal FAF pattern were larger than those with minimal-change FAF pattern or normal FAF pattern ($p < 0.01$). Image analysis

revealed a relationship between increased autofluorescence and soft drusen, especially in the cases with large total soft drusen areas.

CONCLUSIONS: FAF characteristics were different between the fellow eyes of unilateral typical AMD and PCV in Japan, which might be due to the difference of total soft drusen areas between them.

PMID: 23677486 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2013 May 1;44(3):260-7. doi: 10.3928/23258160-20130503-09.

Macular pigment optical density in a central European population.

Pipis A, Touliou E, Augustin AJ.

BACKGROUND AND OBJECTIVE: The purpose of this study is to measure the macular pigment optical density and study its spatial profile as well as identify its determinant factors in a Central European population.

PATIENTS AND METHODS: The macular pigment optical density (MPOD) and its distribution were assessed in 228 eyes of 129 subjects using fundus reflectometry with the Visucam 500 (Carl Zeiss Meditec, Jena, Germany).

RESULTS: A statistically significant positive association between a diet rich in xanthophylls and all MPOD values was found. A positive monotonic relationship was demonstrated between an increasing degree in pigment distribution eccentricity and age, as well as all MPOD values except for area.

CONCLUSION: Assuming that macular pigment is protective against age-related macular degeneration, our study highlights the role of nutritional counseling and intervention in preventing this disease. Furthermore, MPOD appears to increase with age, and the distribution of macular pigment appears to form more eccentric profiles.

PMID: 23676228 [PubMed - in process]

Pathogenesis

Exp Cell Res. 2013 May 10. pii: S0014-4827(13)00199-7. doi: 10.1016/j.yexcr.2013.05.005. [Epub ahead of print]

Retinal Pigment Epithelium (RPE) exosomes contain signaling phosphoproteins affected by oxidative stress.

Biasutto L, Chiechi A, Couch R, Liotta LA, Espina V.

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Abstract: Age-related macular degeneration (AMD) is a leading cause of vision loss and blindness among the elderly population in the industrialized world. One of the typical features of this pathology is the gradual death of retinal pigment epithelial (RPE) cells, which are essential for maintaining photoreceptor functions and survival. The etiology is multifactorial, and oxidative stress is clearly one of the key factors involved in disease pathogenesis (Plafker, Adv Exp Med Biol 2010,664:447-56; Qin, Drug Develop Res 2007,68:213-225). Recent work has revealed the presence of phosphorylated signaling proteins in the vitreous humour of patients affected by AMD or other retinal diseases. While the location of these signaling proteins is typi-

cally the cell membrane or intracellular compartments, vitreous samples were proven to be cell-free (Davuluri et al., Arch Ophthalmol 2009,127:613-21). To gain a better understanding of how these proteins can be shed into the vitreous, we used Reverse Phase Protein Arrays (RPMA) to analyze the protein and phosphoprotein content of exosomes shed by cultured ARPE-19 cells under oxidative stress conditions. 72 proteins were shown to be released by ARPE-19 cells and compartmentalized within exosomes. 41 of them were selectively detected in their post-translationally modified form (i.e., phosphorylated or cleaved) for the first time in exosomes. Sets of these proteins were linked together reflecting activation of pathway units within exosomes. A subset of (phospho)proteins were altered in exosomes secreted by ARPE-19 cells subjected to oxidative stress, compared to that secreted by control/non stressed cells. Stress-altered exosome proteins were found to be involved in pathways regulating apoptosis/survival (i.e, Bak, Smac/Diablo, PDK1 (S241), Akt (T308), Src (Y416), Elk1 (S383), ERK 1/2 (T202/Y204)) and cell metabolism (i.e., AMPKα1 (S485), Acetyl-CoA carboxylase (S79), LDHA). Exosomes may thus represent the conduit through which membrane and intracellular signaling proteins are released into the vitreous. Changes in their (phospho) protein content upon stress conditions suggest their possible role in mediating cell-cell signaling during physio-pathological events; furthermore, exosomes may represent a potential source of biomarkers.

PMID: 23669273 [PubMed - as supplied by publisher]

J Cell Mol Med. 2013 May 11. doi: 10.1111/jcmm.12070. [Epub ahead of print]

Directional protein secretion by the retinal pigment epithelium: roles in retinal health and the development of age-related macular degeneration.

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Abstract: The structural and functional integrity of the retinal pigment epithelium (RPE) is fundamental for maintaining the function of the neuroretina. These specialized cells form a polarized monolayer that acts as the retinal-blood barrier, separating two distinct environments with highly specialized functions: photoreceptors of the neuroretina at the apical side and Bruch's membrane/highly vascularized choriocapillaris at the basal side. The polarized nature of the RPE is essential for the health of these two regions, not only in nutrient and waste transport but also in the synthesis and directional secretion of proteins required in maintaining retinal homoeostasis and function. Although multiple malfunctions within the RPE cells have been associated with development of age-related macular degeneration (AMD), the leading cause of legal blindness, clear causative processes have not yet been conclusively characterized at the molecular and cellular level. This article focuses on the involvement of directionally secreted RPE proteins in normal functioning of the retina and on the potential association of incorrect RPE protein secretion with development of AMD. Understanding the importance of RPE polarity and the correct secretion of essential structural and regulatory components emerge as critical factors for the development of novel therapeutic strategies targeting AMD.

PMID: 23663427 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2013 May 12. [Epub ahead of print]

Intracameral concentrations of the fibrinolytic system components in patients with age-related macular degeneration.

Bertelmann T, Spychalska M, Kohlberger L, Strodthoff S, Witteborn M, Kicova N, Sachs U, Irle S, Mennel S.

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PURPOSE: To detect the intracameral concentrations and activities of plasminogen and other components of the fibrinolytic system, and to investigate whether those concentrations and activities are higher in patients with age-related macular degeneration (AMD) in comparison to healthy controls.

METHODS: Prospective case series of 93 patients scheduled for standard phacoemulsification.

RESULTS: Mean plasminogen activity in patients with non-exsudative AMD (n = 24) revealed to be 0.06 % N, in patients with exudative AMD (n = 7) 0.03 %N and in healthy controls (n = 43) 0.02 %N (p = 0.38, ANOVA). Plasminogen activator inhibitor I (PAI-1) was detected in neither group. Alpha2-antiplasmin activity was 1.61 U/ml in the non-exudative AMD group (n = 27), 0 U/ml in the exudative AMD group (n = 7) and 0.54 U/ml in the control group (n = 48) (p = 0.1, ANOVA). Concentrations of plasmin-a2-antiplasmin complex (PAP) were detected at levels of 17.91 ng/ml in the non-exudative AMD group (n = 11), of 16.6 ng/ml in the exudative AMD group (n = 5), and of 17.43 ng/ml in the control group (n = 14) (p = 0.92, ANOVA).

CONCLUSIONS: Plasminogen is present with a very low activity in aqueous humor. There are no significant differences in aqueous humor concentrations or activities of plasminogen and other components of the fibrinolytic system between patients with non-exudative AMD, exudative AMD, and healthy controls. Further studies should investigate vitreous samples instead of aqueous humor samples. A careful and accurate workup of obtained intraocular fluids is needed to detect the low concentrations and activities of the parameters analyzed.

PMID: 23665864 [PubMed - as supplied by publisher]

J Biol Chem. 2013 May 14. [Epub ahead of print]

Insulin Receptor Signaling in Cones.

Rajala A, Dighe R, Agbaga MP, Anderson RE, Rajala RV.

University of Oklahoma, United States.

Abstract: In humans, age-related macular degeneration and diabetic retinopathy are the most common disorders affecting cones. In retinitis pigmentosa (RP), cone cell death precedes rod cell death. Systemic administration of insulin delays the death of cones in RP mouse models lacking rods. To date there are no studies on the insulin receptor signaling in cones; however, mRNA levels of IR signaling proteins are significantly higher in cone-dominant neural retina leucine zipper (Nrl) knockout mouse retinas compared to wild type rod-dominant retinas. We previously reported that conditional deletion of the p85α subunit of phosphoinositide 3-kinase (PI3K) in cones resulted in age-related cone degeneration and the phenotype was not rescued by healthy rods, raising the question of why cones are not protected by the rod derived cone survival factors. Interestingly, systemic administration of insulin has been shown to delay the death of cones in mouse models of RP lacking rods. These observations led to the hypothesis that cones may have their own endogenous neuroprotective pathway, or rod-derived cone survival factors may be signaled through cone PI3K. To test this hypothesis we generated p85α-/-/Nrl-/- double knockout mice and also rhodopsin mutant mice lacking p85α, and examined the effect of the p85α subunit of PI3K on cone survival. We found that the rate of cone degeneration is significantly faster in both of these models compared to respective mice with competent p85α. These studies suggest that cones may have their own endogenous PI3K-mediated neuroprotective pathway in addition to the cone viability survival signals derived from rods.

PMID: 23673657 [PubMed - as supplied by publisher] Free full text

Epidemiology

Klin Monbl Augenheilkd. 2013 May 13. [Epub ahead of print]

[Choroidal Neovascularisation in Pathological Myopia: Epidemiological Data from a Health Services Research Study Conducted in Germany.] [Article in German]

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Background: Pathological myopia (PM) or high myopia is defined as excessive short-sightedness (more than -6 dioptres) caused by a strong dilation of the bulbus oculi, that can induce the development of new and unstable vessel structures [choroidal neovascularisation (CNV)]. Since there are only limited epidemiological data available on PM, this health services research study was conducted.

Patients and Methods: A health services survey with ophthalmologists throughout Germany was undertaken. Physicians were asked to complete a 51-item questionnaire on CNV in PM as well as on its early stages in their daily practice, diagnosis, control and treatment, patient numbers and evaluation of health care situation. Statistical analyses were entirely descriptive.

Results: Of 7,500 ophthalmologists, a representative sample of 800 was randomly selected; 340 physicians took part. The mean prevalence rates/year/practice were 1,765.5 ± 1,218.1 with myopia, 230.7 ± 278.6 patients with high myopia, subdivided into 129.3 ± 242.8 patients with PM without macular degeneration (MD), 39.6 ± 64.8 patients with PM and MD, and 13.3 ± 30.3 patients with PM and CNV. Data on diagnosis and control show a lack of clearly defined standardisation. With regard to treatment of CNV in PM the data show the current discrepancy of guideline recommendations and approved treatment options.

Conclusion: The prevalence and incidence data collected in this study vary considerably between physicians. This may be explained by the various grades of specialisation as well as to possibly existing uncertainties regarding the definition and nomenclature of PM/high myopia and their different stages of the disease that should be harmonised. A generally accepted definition of severity grades, recommendations on diagnosis as well as detailed information and continuous training programmes on this disease is necessary.

PMID: 23670525 [PubMed - as supplied by publisher]

Diet

J Nutr. 2013 May 15. [Epub ahead of print]

Nutrient Supplementation with n3 Polyunsaturated Fatty Acids, Lutein, and Zeaxanthin Decrease A2E Accumulation and VEGF Expression in the Retinas of Ccl2/Cx3cr1-Deficient Mice on Crb1rd8 Background.

Ramkumar HL, Tuo J, Shen DF, Zhang J, Cao X, Chew EY, Chan CC.

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Abstract: The Age-Related Eye Diseases Study 2 (AREDS2) clinical trial is assessing the effects of higher dietary xanthophyll (lutein and zeaxanthin) and long-chain n3 polyunsaturated fatty acid (LCPUFA) docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) intake on progression to advanced age-related macular degeneration (AMD). This study's purpose was to examine the retinal effects of the AREDS2 formulation on Chemokine (C-C motif) ligand 2 (Ccl2-/-)/CX3C chemokine receptor 1 (Cx3cr1-/-) mice on Crumbs homolog 1 retinal degeneration phenotype 8 (Crb1rd8) background (DKO), which develop focal retinal lesions with certain features similar to AMD. DKO and C57BL/6N rd8 background mice (WT) were bred and randomized into 4 groups. Two groups, WT mice on AREDS2 diet (A-WT) and DKO mice on AREDS2 diet (A-DKO), were supplemented daily with 1.76 μmol of lutein, 35.1 μmol of zeaxanthin, 215 μmol EPA, and 107 μmol of DHA, and 2 control groups, WT mice on control diet (C-WT) and DKO mice on control diet (C-DKO), were fed an isocaloric diet. All mice had monthly fundus photos and were killed after 3 mo for biochemical and histologic analyses. After 3 mo, 81% of A-DKO mice had lesion regression com-

pared with 25% of C-DKO mice ($P < 0.05$). Toxic retinal 2-[2,6-dimethyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1E,3E,5E,7E-octatetra-enyl]-1-(2-hydroxyethyl)-4-[4-methyl-6(2,6,6-trimethyl-1-cyclohexen-1-yl) 1E,3E,5E,7E-hexatrienyl]-pyridinium (A2E) concentrations were significantly lower in A-DKO compared with C-DKO mice. The outer nuclear layer thickness in A-DKO mice was significantly greater than that in C-DKO mice. Retinal expression of inducible nitric oxide synthase (iNos) tumor necrosis factor-α (Tnf-α), Cyclooxygenase-2 (Cox-2), interleukin1beta (IL-1β), and vascular endothelial growth factor (Vegf) was significantly lower in A-DKO compared with C-DKO mice. Xanthophylls and LCPUFAs have antiinflammatory, neuroprotective, and antiangiogenic properties. Our data provide potential mechanisms by which the AREDS2 formula has a protective effect on retinal lesions in DKO mice.

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Zinc and diabetic retinopathy.

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Abstract: Zinc (Zn) is an important nutrient that is involved in various physiological metabolisms. Zn dyshomeostasis is often associated with various pathogeneses of chronic diseases, such as metabolic syndrome, diabetes, and related complications. Zn is present in ocular tissue in high concentrations, particularly in the retina and choroid. Zn deficiencies have been shown to affect ocular development, cataracts, age-related macular degeneration, and even diabetic retinopathy. However, the mechanism by which Zn deficiency increases the prevalence of diabetic retinopathy remains unclear. In addition, due to the negative effect of Zn deficiency on the eye, Zn supplementation should prevent diabetic retinopathy; however, limited available data do not always support this notion. Therefore, the goal of this paper was to summarize these pieces of available information regarding Zn prevention of diabetic retinopathy. Current theories and possible mechanisms underlying the role of Zn in the eye-related diseases are discussed. The possible factors that affect the preventive effect of Zn supplementation on diabetic retinopathy were also discussed.

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Vitamins for age-related macular degeneration demonstrate minimal differences.

Kolber MR, Tennant M, Nickonchuk T.

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