Drug treatment


Evaluation of intraocular pressure elevation after multiple injections of intravitreal ranibizumab.

Yu AL, Seidensticker F, Schaumberger M, Welge-Lussen U, Wolf A.

BACKGROUND: We wanted to determine whether multiple injections of intravitreal ranibizumab was associated with an elevated intraocular pressure (IOP) in patients treated for neovascular age-related macular degeneration (AMD).

METHODS: This retrospective study examined 53 patients with neovascular AMD treated with multiple injections of intravitreal ranibizumab. The main outcome measure was the difference in IOP between the frequently-treated study eyes (≥15 injections) and the unfrequently-treated fellow control eyes (≤ five injections). Patients were divided into three study groups: group I (35 patients with 15 to 19 injections); group II (15 patients with 20 to 29 injections); and group III (three patients with ≥30 injections). The IOP was measured by Goldmann applanation tonometry 4 weeks after the last injection of intravitreal ranibizumab. For statistical analysis, the IOP was then correlated with the number of ranibizumab injections.

RESULTS: Among the frequently-treated study eyes, the mean IOP was 13.68±2.91 mmHg (range, 8 to 20 mmHg). The unfrequently-treated fellow control eyes had a mean IOP of 13.45±3.09 mmHg (range, 9 to 25 mmHg). There was no significant correlation of the IOP difference between the study and control eyes with the number of ranibizumab injections (correlation coefficient 0.77; P=0.583). For each of groups I, II, and III, the difference in mean IOP between the study and control eyes was nonsignificant (P>0.05). There was also no significant association of the IOP difference between the study and control eyes with the number of ranibizumab injections for each group (P=0.391).

CONCLUSION: Our study did not find an increased IOP in frequently-ranibizumab-treated eyes when compared to unfrequently-treated fellow control eyes. Further studies with a greater sample size are needed to evaluate whether an increased number of ranibizumab injections is associated with IOP changes.

PMID: 24748769 [PubMed] PMCID: PMC3990463


Bilateral visual outcomes and service utilization of patients treated for 3 years with ranibizumab for neovascular age-related macular degeneration.
Chavan R, Panneerselvam S, Adhana P, Narendran N, Yang Y.

BACKGROUND: The aim of this study was to describe bilateral visual outcomes and the effect of incomplete follow-up after 3 years of ranibizumab therapy for neovascular age-related macular degeneration. Secondly, the demands on service provision over a 3-year period were described.

METHODS: Data on visual acuity, hospital visits, and injections were collected over 36 months on consecutive patients commencing treatment over a 9-month period. Visual outcome was determined for 1) all patients, using last observation carried forward for missed visits due to early discontinuation and 2) only those patients completing full 36-month follow-up.

RESULTS: Over 3 years, 120 patients cumulatively attended hospital for 1,823 noninjection visits and 1,365 injection visits. A visual acuity loss of <15 letters (L) was experienced by 78.2% of patients. For all patients (n=120), there was a mean loss of 1.68 L using last observation carried forward for missing values. Excluding five patients who died and 30 who discontinued follow-up, mean gain was 1.47 L. In bilateral cases, final acuity was on average 9 L better in second eyes compared to first eyes. Also, 91% of better-seeing eyes continued to be the better-seeing eye.

CONCLUSION: We have demonstrated our approach to describing the long-term service provision and visual outcomes of ranibizumab therapy for neovascular age-related macular degeneration in a consecutive cohort of patients. Although there was a heavy burden with very frequent injections and clinic visits, patients can expect a good level of visual stability and a very high chance of maintaining their better-seeing eye for up to 3 years.

PMID: 24748766 [PubMed] PMCID: PMC3986417


Results of intravitreal ranibizumab with a prn regimen in the treatment of extrafoveal and juxtafoveal neovascular membranes in age-related macular degeneration.


PURPOSE: To evaluate the efficacy of intravitreal ranibizumab with a "pro re nata" regimen in the treatment of nonsubfoveal neovascular membranes secondary to age-related macular degeneration.

METHODS: Retrospective noncomparative case series. Thirty-one eyes with naive nonsubfoveal neovascularization secondary to age-related macular degeneration were consecutively enrolled and treated with ranibizumab intravitreal injections according to a pro re nata regimen. The follow-up was performed monthly up to 6 months and quarterly up to 2 years (25 patients). Early treatment diabetic retinopathy study best-corrected visual acuity and lesion size analysis with fluorescein angiography were recorded.

RESULTS: The mean baseline early treatment diabetic retinopathy study best-corrected visual acuity worsened from 20/40 (0.28 logMAR) at baseline to 20/50 (0.42 logMAR) at 1-year follow-up and 20/60 (0.53 logMAR) at 2-year follow-up. The mean lesions size nearly doubled from baseline at the 2-year follow up (1.19-2.47 mm). Twenty-two patients had one or more recurrences at 1-year follow-up. All 25 patients developed a recurrence at 2 years with 7 cases developing a recurrence by 12 months. Twelve cases progressed to subfoveal lesions by the 24-month visit.

CONCLUSION: Other regimens described in the literature might result in a more the satisfactory outcome using more frequent follow-up and more frequent intravitreal injections.

PMID: 24756034 [PubMed - in process]

Consequences of long-term discontinuation of vascular endothelial growth factor inhibitor therapy in the patients with neovascular age-related macular degeneration.

Vaze A, Fraser-Bell S, Gillies M.

PMID: 24750589 [PubMed - as supplied by publisher]


Age-related macular degeneration: vision challenge of old age.

Wang F, Sun X.

PMID: 24762578 [PubMed - in process]

Other treatment & diagnosis


Mini-cognitive testing in patients with age-related macular degeneration.

Al-Salem KM, Schaal S.

PURPOSE: To compare Mini-Cognitive (Mini-Cog) Screening test results between patients with age-related macular degeneration (AMD) and age-matched controls.

PARTICIPANTS: Two hundred and twenty-nine patients were included in the study. Patients were divided into 3 groups: 56 patients with exudative AMD, mean age of 76 ± 8 years; 82 patients with dry AMD, mean age of 77 ± 9 years; and 91 controls, mean age of 75 ± 8 years.

METHODS: The Mini-Cog test, used to screen patients with early cognitive impairment, was introduced to the three groups of patients at the settings of an ophthalmology outpatient clinic. Test scores were compared between the groups.

RESULTS: The mean for the Mini-Cog test scores was 3.5 (95% confidence interval, 3.15-3.85) for the dry AMD group, 3.95 (95% confidence interval, 3.51-4.39) for the exudative AMD group, and 4.63 (95% confidence interval, 4.45-4.80) for the control group. There was no statistically significant difference between the scores of AMD groups, however, both AMD groups received significantly lower scores than controls (P < 0.0001).

CONCLUSION: Patients with age-related macular degeneration in this study demonstrated lower mean scores in the Mini-Cog test than age-matched controls. The Mini-Cog test may be easily applied at an office setting of ophthalmology outpatient clinics, and may help in the early diagnosis of cognitive impairment in the patients with AMD.

PMID: 24756035 [PubMed - in process]


Synthesis and mechanistic studies of a novel homoisoflavanone inhibitor of endothelial cell growth.

TW.

Abstract: Preventing pathological ocular angiogenesis is key to treating retinopathy of prematurity, diabetic retinopathy and age-related macular degeneration. At present there is no small molecule drug on the market to target this process and hence there is a pressing need for developing novel small molecules that can replace or complement the present surgical and biologic therapies for these neovascular eye diseases. Previously, an antiangiogenic homoisoflavanone was isolated from the bulb of a medicinal orchid, Cremastra appendiculata. In this study, we present the synthesis of a novel homoisoflavanone isomer of this compound. Our compound, SH-11052, has antiproliferative activity against human umbilical vein endothelial cells, and also against more ocular disease-relevant human retinal microvascular endothelial cells (HRECs). Tube formation and cell cycle progression of HRECs were inhibited by SH-11052, but the compound did not induce apoptosis at effective concentrations. SH-11052 also decreased TNF-α induced p38 MAPK phosphorylation in these cells. Intriguingly, SH-11052 blocked TNF-α induced IkB-α degradation, and therefore decreased NF-κB nuclear translocation. It decreased the expression of NF-κB target genes and the pro-angiogenic or pro-inflammatory markers VCAM-1, CCL2, IL8, and PTGS2. In addition SH-11052 inhibited VEGF induced activation of Akt but not VEGF receptor autophosphorylation. Based on these results we propose that SH-11052 inhibits inflammation induced angiogenesis by blocking both TNF-α and VEGF mediated pathways, two major pathways involved in pathological angiogenesis. Synthesis of this novel homoisoflavanone opens the door to structure-activity relationship studies of this class of compound and further evaluation of its mechanism and potential to complement existing antiangiogenic drugs.

PMID: 24752613 [PubMed - in process]

Optom Vis Sci. 2014 Apr 17. [Epub ahead of print]

Color Vision Deficits in Intermediate Age-Related Macular Degeneration.

Downie LE, Cheng AS, Vingrys AJ.

PURPOSE: To assess the effect of intermediate age-related macular degeneration (AMD) on foveal cone-contrast thresholds.

METHODS: We measured L-M and S-cone-contrast thresholds in subjects with intermediate AMD (n = 10) and age-matched control subjects (n = 10). Monocular, foveal 3-degree Gaussian blobs (600-millisecond raised cosine) were presented at 16 cone ratios throughout L-, M-, and S-cone space, and threshold contours were modeled with probability summation between two independent detection mechanisms. The role that preretinal absorption plays in aging was also evaluated by simulation with FG15 and neutral-density filters.

RESULTS: Aging results in loss of neural sensitivity, not explained by lens changes. On average, intermediate AMD was associated with reduced sensitivity in both color and luminance channels (p < 0.05) that appeared to indicate greater involvement of S-cones. When data were normalized to age-expected values, the changes to cone sensitivity were shown to be consistent (~200% loss) across L-M, M-L, and S-cone mechanisms. In comparison, the luminance (L + M) mechanism showed relative sparing (155% loss, p < 0.05).

CONCLUSIONS: Eyes with the same phenotype of intermediate AMD can have varying degrees of color threshold loss. Functional markers enhance the clinical definition of disease expression in AMD.

PMID: 24748029 [PubMed - as supplied by publisher]
Pathogenesis


Adeno-associated virus type 8 vector-mediated expression of siRNA targeting vascular endothelial growth factor efficiently inhibits neovascularization in a murine choroidal neovascularization model.


PURPOSE: To assess the feasibility of a gene therapeutic approach to treating choroidal neovascularization (CNV), we generated an adeno-associated virus type 8 vector (AAV2/8) encoding an siRNA targeting vascular endothelial growth factor (VEGF), and determined the AAV2/8 vector's ability to inhibit angiogenesis.

METHODS: We initially transfected 3T3 cells expressing VEGF with the AAV2/8 plasmid vector psiRNA-VEGF using the H1 promoter and found that VEGF expression was significantly diminished in the transfectants. We next injected 1 μl (3 x 10(14) vg/ml) of AAV2/8 vector encoding siRNA targeting VEGF (AAV2/8/SmVEGF-2; n = 12) or control vector encoding green fluorescent protein (GFP) (AAV2/8/GFP; n = 14) into the subretinal space in C57BL/6 mice. One week later, CNV was induced by using a diode laser to make four separate choroidal burns around the optic nerve in each eye. After an additional 2 weeks, the eyes were removed for flat mount analysis of the CNV surface area.

RESULTS: Subretinal delivery of AAV2/8/SmVEGF-2 significantly diminished CNV at the laser lesions, compared to AAV8/GFP (1597.3 ± 2077.2 versus 5039.5 ± 4055.9 µm²; p<0.05). Using an enzyme-linked immunosorbent assay, we found that VEGF levels were reduced by approximately half in the AAV2/8/SmVEGF-2 treated eyes.

CONCLUSIONS: These results suggest that siRNA-VEGF can be expressed across the retina and that long-term suppression of CNV is possible through the use of stable AAV2/8-mediated siRNA-VEGF expression. In vivo gene therapy may thus be a feasible approach to the clinical management of CNV in conditions such as age-related macular degeneration.

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Epidemiology

Curr Eye Res. 2014 Apr 22. [Epub ahead of print]


La TY, Cho E, Kim EC, Kang S, Jee D.

Purpose: To evaluate the prevalence of and risk factors for age-related macular degeneration (AMD) in a representative Korean population.

Materials and Methods: A nationwide population-based cross-sectional study was conducted among the civilian, noninstitutionalized Korean population aged 40 and older (mean age, 55.7 years; 95% confidence interval [CI], 55.4-56.0). A total of 16,109 older (≥40 years of age) subjects participated in the Korean National Health and Nutrition Survey 2008-2011. All participants underwent standardized interviews and comprehensive ophthalmic examinations. Using physiologic mydriasis, a 45° digital fundus photograph was taken of both eyes of each participant. All fundus photographs were graded according to an international classification and grading system. Main outcome measures consisted of prevalence of early- and late-AMD.

Results: Of the 16,109 subjects, fundus photographs were gradable for 14,352 (89.1%). The prevalence of
early- and late-AMD in the Korean population was 6.0 and 0.6%, respectively. The prevalence of early-AMD increased from 1.5% in those aged 40-49 years to 16.2% in those aged ≥70 years. After adjusting for confounders, the prevalence of early-AMD increased with increasing age (odds ratio [OR], 1.08; CI, 1.06-1.09). For late-AMD, old age (OR, 1.09; CI, 1.04-1.14), male gender (OR, 2.45; CI, 1.11-5.37), high systolic blood pressure (OR, 1.03; CI, 1.00-1.06) and high fasting glucose level (OR, 0.97; CI, 0.94-0.99) were significant risk factors. Smoking was not associated with either early- or late-AMD in this Korean population.

Conclusions: The present study provides the first population-based data on the prevalence of and risk factors for AMD in a representative Korean population. The prevalences of early- and late-AMD in this population were 6.0 and 0.6%, respectively. The prevalence of AMD in Koreans is higher than for those in other Asian countries and similar to that of Caucasians in Western countries.

PMID: 24754248 [PubMed - as supplied by publisher]

Genetics


Metabolism of Very Long-Chain Fatty Acids: Genes and Pathophysiology.

Sassa T, Kihara A.

Abstract: Fatty acids (FAs) are highly diverse in terms of carbon (C) chain-length and number of double bonds. FAs with C>20 are called very long-chain fatty acids (VLCFAs). VLCFAs are found not only as constituents of cellular lipids such as sphingolipids and glycerophospholipids but also as precursors of lipid mediators. Our understanding on the function of VLCFAs is growing in parallel with the identification of enzymes involved in VLCFA synthesis or degradation. A variety of inherited diseases, such as ichthyosis, macular degeneration, myopathy, mental retardation, and demyelination, are caused by mutations in the genes encoding VLCFA metabolizing enzymes. In this review, we describe mammalian VLCFAs by highlighting their tissue distribution and metabolic pathways, and we discuss responsible genes and enzymes with reference to their roles in pathophysiology.

PMID: 24753812 [PubMed - as supplied by publisher] PMCID: PMC3975470


Molecular diagnosis of putative Stargardt disease by capture next generation sequencing.


Abstract: Stargardt Disease (STGD) is the commonest genetic form of juvenile or early adult onset macular degeneration, which is a genetically heterogeneous disease. Molecular diagnosis of STGD remains a challenge in a significant proportion of cases. To address this, seven patients from five putative STGD families were recruited. We performed capture next generation sequencing (CNGS) of the probands and searched for potentially disease-causing genetic variants in previously identified retinal or macular dystrophy genes. Seven disease-causing mutations in ABCA4 and two in PROM1 were identified by CNGS, which provides a confident genetic diagnosis in these five families. We also provided a genetic basis to explain the differences among putative STGD due to various mutations in different genes. Meanwhile, we show for the first time that compound heterozygous mutations in PROM1 gene could cause cone-rod dystrophy. Our findings support the enormous potential of CNGS in putative STGD molecular diagnosis.

PMID: 24763286 [PubMed - in process]

Expression of a single prominin homolog in the embryo of the model chordate Ciona intestinalis.

Russo MT, Racioppi C, Zanetti L, Ristoratore F.

Abstract: Prominins are a family of pentaspan transmembrane glycoproteins, expressed in various types of cells, including stem and cancer stem cells in mammals. Prominin-1 is critical in generating and maintaining the structure of the photoreceptors in the eye since mutations in the PROM1 gene are associated with retinal and macular degeneration in human. In this study, we identified a single prominin homolog, Ci-prom1/2, in the model chordate the ascidian C. intestinalis and characterized Ci-prom1/2 expression profile in relation to photoreceptor differentiation during Ciona embryonic development. In situ hybridization experiments show Ci-prom1/2 transcripts localized in the developing central nervous system, predominantly in photoreceptor cell precursors as early as neurula stage and expression is maintained through larva stage in photoreceptor cells around the simple eye. We also isolated the regulatory region responsible for the specific spatio-temporal expression of the Ci-prom1/2 in photoreceptor cell lineage. Collectively, we report that Ci-prom1/2 is a novel molecular marker for ascidian photoreceptor cells and might represent a potential source to enlarge the knowledge about the function of prominin family in photoreceptor cell evolution and development.

PMID: 24755348 [PubMed - as supplied by publisher]


Longitudinal clinical course of three Japanese patients with Leber congenital amaurosis/early-onset retinal dystrophy with RDH12 mutation.


PURPOSE: To report the longitudinal clinical course of three Japanese patients from two families with Leber congenital amaurosis/early-onset retinal dystrophy (LCA/EORD), and the results of next-generation DNA sequences on them.

PATIENTS AND METHODS: The patients were three Japanese children: a 4-year-old girl, a 6-year-old boy, and a 3-year-old girl. Patients 1 and 2 were siblings, and patient 3 was from an unrelated family. Standard ophthalmic examinations including perimetry, electroretinography, optical coherence tomography, and ultrasonography were performed on each patient. The patients were observed for 28, 16, and 10 years. Whole exomes of the patients and their non-symptomatic parents were analyzed using a next-generation sequence technique.

RESULTS: The decimal visual acuity varied between 0.07 and 0.6 at the initial visit and decreased to counting finger to hand motion in their teens. Funduscopy showed diffuse retinal and macular degeneration. During the follow-up period, a posterior staphyloma developed and the macular area became atrophic. Patient 1 developed cataracts in her early twenties. Genetic analysis revealed a homozygous A126V substitution in the RDH12 gene in all patients.

CONCLUSIONS: The three patients with LCA/EORD had a progressive decrease of their vision with the formation of a posterior staphyloma. This is the first report of Japanese patients with LCA/EORD with a RDH12 mutation.

PMID: 24752437 [PubMed - as supplied by publisher]
Diet & lifestyle


Factors Influencing Self-Reported Use of Antioxidant Supplements in Patients with Age-Related Macular Degeneration.

Yu AL, Paul T, Schaumberger M, Welge-Lussen U.

Aim: The goals of the present study were to evaluate the current use and accuracy of dose-taking prescription among patients with age-related macular degeneration (AMD) and to detect potential factors influencing the use or non-use of oral antioxidant supplements.

Materials and methods: This is a cross-sectional questionnaire-based study of 65 patients with AMD of Age-Related Eye Disease Study (AREDS) category 3 (intermediate AMD) or category 4 (unilateral advanced AMD). Self-report data were obtained from a structural clinical interview in clinic. The patients were asked questions regarding their demographic, ophthalmologic and systemic data, their source of recommendation for antioxidant supplement use and/or their reasons for non-use. Afterwards, this information was correlated with the use or non-use of antioxidant supplements. Statistical analyses were conducted using a series of Mann-Whitney U-tests and Fisher's exact tests.

Results: There were 55.4% (36 of 65) of the patients reporting antioxidant supplement use for AMD and 44.6% (29 of 65) with no supplement use. However, only 56.7% (17 of 30) took the recommended dose on label. There were significantly more female patients taking supplements than male patients (p = 0.010). A statistically significant correlation was also found between supplement use and the number of visits to an ophthalmologist per year (p = 0.037). The main reason for antioxidant supplement non-use was the missing awareness of the availability of antioxidant supplements.

Conclusions: Despite the recommendation of oral antioxidant supplements in the ARED Study for patients with AMD of category 3 or 4, only about half of these patients took the supplements in this study. Identifying the factors, which influenced the decision against supplement use, may help to better support patients in the prevention of severe vision loss caused by AMD.

PMID: 24749547 [PubMed - as supplied by publisher]


Oxidative stress and its downstream signaling in aging eyes.


BACKGROUND: Oxidative stress (OS) and its biomarkers are the biochemical end point of the imbalance between reactive oxygen species (ROS) production and the ability of the antioxidant (AOX) biological systems to fight against oxidative injury.

OBJECTIVE: We reviewed the role of OS and its downstream signaling in aging eyes.

METHODS: A search of the literature and current knowledge on the physiological and pathological mechanisms of OS were revisited in relation to the eyes and the aging process. Most prevalent ocular diseases have been analyzed herein in relation to OS and nutraceutic supplements, such as dry-eye disorders, glaucoma, age-related macular degeneration, and diabetic retinopathy.

RESULTS: Clinical, biochemical, and molecular data from anterior and posterior eye segment diseases point to OS as the common pathogenic mechanism in the majority of these ocular disorders, many of which are pathologies causing visual impairment, blindness, and subsequent loss of life quality. Studies with
nutraceutic supplements in aging eye-related pathologies have also been reviewed.

CONCLUSION: OS, nutritional status, and nutraceutic supplements have to be considered within the standards of care of older ophthalmologic patients. OS biomarkers and surrogate end points may help in managing the aging population with ocular diseases.

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[Comparison of daily intake of lutein+zeaxanthin, serum concentration of lutein/zeaxanthin and lipids profile between age-related macular degeneration patients and controls].[Article in Chinese]

Huang FF, Lin XM.

OBJECTIVE: To compare the daily intake of lutein+zeaxanthin, serum concentrations of lutein, zeaxanthin and serum lipids between age-related macular degeneration (AMD) patients and controls.

METHODS: AMD was diagnosed and graded according to the fundus morphology and the standard of age-related eye disease study (AREDS). In the study, 51 subjects with early AMD, 51 with medium AMD and 51 without AMD as controls were recruited. Food frequency questionnaires were used to calculate the daily intake of lutein and zeaxanthin. The concentrations of serum lutein and zeaxanthin were measured by HPLC and the concentrations of serum lipids including serum total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL) were measured by Roche full-automatic biochemical analyzer.

RESULTS: The daily intake of lutein+zeaxanthin, the concentrations of serum lutein and serum zeaxanthin of the subjects with medium AMD were 7 870.458 μg/d, 0.180 μmol/L, 0.029 μmol/L respectively, which were all significantly lower than those of the controls (11 297.959 μg/d, 0.285 μmol/L, 0.044 μmol/L, P<0.05); The concentrations of serum HDL of the subjects with early and medium AMD were (1.29±0.27) mmol/L and (1.16±0.30) mmol/L respectively, both of which were significantly lower than that of the controls [(1.45±0.35) mmol/L, P<0.001].

CONCLUSION: The development of AMD might be affected by the daily intake of lutein+zeaxanthin and the serum concentrations of lutein and zeaxanthin. The concentration of serum HDL might be related to the occurrence of AMD.

PMID: 24743813 [PubMed - in process]