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MD Research News

Issue 129

Tuesday 7 May, 2013

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Drug Treatment

Ophthalmologica. 2013 Apr 30. [Epub ahead of print]

Three-Year Visual Outcome and Injection Frequency of Intravitreal Ranibizumab Therapy for Neovascular Age-Related Macular Degeneration.

Muniraju R, Ramu J, Sivaprasad S.

Laser and Retinal Research Unit, Department of Ophthalmology, King's College Hospital, London, UK.

Background: To assess the 3-year visual outcome and injection frequency for patients on ranibizumab for neovascular age-related macular degeneration (NV-AMD).

Methods: Retrospective case-note review of 174 treatment-naïve eyes of 156 patients with NV-AMD with 3-year follow-up was done at specific time points closest to 12, 24 and 36 months.

Results: The median baseline visual acuity (VA) of 50 Early Treatment Diabetic Retinopathy Study letters (mean 48.2 ± 16.9) improved significantly to 55 (mean 51.2 ± 18.7) by the end of 12 months (p = 0.04). At 24 months, the median letter score remained unchanged at 55 (mean 50.4 ± 20.8; p = 0.14 as compared to baseline) and at 36 months, the median VA was 54 letters (mean 49.1 ± 21.7; p = 0.34 compared to baseline). The mean numbers of injections were 4.8 ± 2.2 at 1 year, 7.8 ± 4.2 at 2 years (2.9 in the second year) and 10.2 ± 6.2 at the end of the third year (2.4 in the third year).

Conclusion: Our study demonstrates the efficacy of a variable dosing regimen of ranibizumab for the treatment of NV-AMD. The mean gain in VA is inversely proportional to the baseline VA and did not correlate with the number of injections.

PMID: 23635665 [PubMed - as supplied by publisher]

Int J Ophthalmol. 2013 Apr 18;6(2):211-5. doi: 10.3980/j.issn.2222-3959.2013.02.20. Print 2013.

Effects of multiple intravitreal anti-VEGF injections on retinal nerve fiber layer and intraocular pressure: a comparative clinical study.

Sobacı G, Güngör R, Ozge G.

Department of Ophthalmology, GATA Medical School, Ankara, Turkey.

AIM: To determine the effect of multiple injections of ranibizumab or bevacizumab on retinal nerve fiber

layer (RNFL) and intraocular pressure (IOP) in patients with age-related macular degeneration (AMD).

METHODS: This retrospective study includes 35 eyes of 35 patients treated with intravitreal bevacizumab (IVB, 1.25mg/0.05mL) and 30 eyes of 30 patients with intravitreal ranibizumab (IVR, 0.5mg/0.05mL) who had Fast RNFL analysis (Stratus™); IOP measurements were taken 30 minutes and 24 hours after each injection.

RESULTS: The mean ages were 68.0±7.5 and 69.1±7.7 years in the IVR and IVB groups, respectively (P=0.55). They underwent (6.3±1.9) and (5.1±1.3) injections (P=0.07) over (13.6±2.1) and (14.05±2.6) months (P=0.45) in the IVR and IVB groups, respectively. Changes in overall and temporal RNFL thickness in IVR-treated eyes (105.3±6.9µm and 74.4±11.2µm) were not different from those in untreated eyes in the IVR group (104.6± 8.4µm and 75.1±12.6µm) (P=0.57 and P=0.41, respectively). Similarly, overall and temporal RNFL thickness in IVB-treated eyes (105.8±8.1µm and 74.5±11.8µm) were not different from those in untreated eyes in the IVB group (104.6±8µm and 74.8±12.9µm) (P=0.42 and P=0.80, respectively). The frequencies of IOP rise (P=0.60) and changes in RNFL thickness from baseline (P=0.16) were comparable between groups.

CONCLUSION: Repeated intravitreal injection of ranibizumab or bevacizumab does not seem have adverse effects on RNFL thickness or IOP in wet AMD patients.

PMID: 23638426 [PubMed]

Klin Monbl Augenheilkd. 2013 Apr;230(4):401-404. Epub 2013 Apr 29.

Three Years Follow-up Results of Ranibizumab Treatment for Choroidal Neovascularization Secondary to Pathologic Myopia.

Hefner L, Riese J, Gerding H.

Department of Retinology, Klinik Pallas, Olten (Head: Prof. Dr. med. Heinrich Gerding).

Background: Choroidal neovascularization (CNV) secondary to pathological myopia (PM) is one of the main causes of severe visual impairment in patients younger than 50 years. In this analysis we want to demonstrate the long-term results of Ranibizumab treating CNV secondary to PM.

Patients and Methods: We retrospectively analysed 15 treatment naive eyes of 13 patients (10 women, 3 men, mean age: 61.5, SD 11.6, range: 41-80) with visual impairment due to CNV secondary to PM, which were treated with ranibizumab. Criteria for re-treatment were reduction of visual acuity and/or activity in OCT or fluorescence angiography.

Results: We applied a mean of 3 injections (standard deviation [SD] 2.5, range: 1-8) ranibizumab during a mean period of 39.6 months (SD 5.3, range: 31-52). The spherical equivalent was - 12.4 diopters ± 4.1 (range - 7.5 to - 20.5 diopters). Before the first injection mean visual acuity (logMAR) was 0.69 ± 0.26. After one month visual acuity improved to 0.39 ± 0.23 (p = 0.002), after 3 months to 0.30 ± 0.22 (p = 0.002) and after 6 months up to 0.30 ± 0.22 (p = 0.002). After 12 months visual acuity was 0.30 ± 0.22 (p = 0.001) and after 24 months 0.30 ± SD 0.24 (p = 0.001). 11 patients reached a follow-up of at least 36 months and visual acuity was 0.30 ± 0.13 (p = 0,001).

Conclusions: Treating CNV secondary to PM with ranibizumab during a follow-up of 36 months, we found considerable improvement of visual acuity. Compared to treatment of CNV secondary to exudative age-related macular degeneration, CNVs secondary to PM seem to respond faster to ranibizumab treatment and less injections are neccessary to reach stabilization.

PMID: 23629791 [PubMed - as supplied by publisher]

Klin Monbl Augenheilkd. 2013 Apr;230(4):392-395. Epub 2013 Apr 29.

Intravitreal Anti-VEGF Therapy for Retinal Macroaneurysm.

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University Hospital Zurich, Department of Ophthalmology, Zurich, Switzerland (Chairman: K. Landau).

Background: We evaluated the effect of intravitreal anti-vascular endothelial growth factor therapy using bevacizumab or ranibizumab for retinal macroaneurysms with macular exudation.

Methods: In a retrospective interventional case series patients with retinal macroaneurysms were treated with either 1.25 mg intravitreal bevacizumab or 0.5 mg ranibizumab as first-line therapy. Patients were imaged by fluorescein angiography and optical coherence tomography. Retreatment was performed in case of persistent intraretinal or subretinal fluid in optical coherence tomography.

Results: Ten patients (10 eyes) with macroaneurysm involving the macula were treated with an average of 3.0 intravitreal anti-vascular endothelial growth factor injections. Mean best corrected visual acuity of all patients improved by 17 letters from baseline to the last follow-up visit. In 7 out of 10 patients, the fovea was affected by a secondary edema. In cases with foveal involvement, central retinal thickness decreased from 366 µm at baseline to 266 µm at the last follow-up visit. In the course of treatment 8 out of 10 patients showed evidence of marked regression of macular exsudation.

Conclusion: Intravitreal anti-vascular endothelial growth factor therapy appears to be a promising treatment alternative to laser treatment in cases of retinal macroaneurysms with macular exudation.

PMID: 23629789 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2013 Apr 26. pii: S0002-9394(13)00133-5. doi: 10.1016/j.ajo.2013.02.006. [Epub ahead of print]

Comparisons of Outcomes With Different Intervals Between Adjunctive Ranibizumab and Photodynamic Therapy for Polypoidal Choroidal Vasculopathy.

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PURPOSE: To determine the optimal time for administration of intravitreal ranibizumab injections before photodynamic therapy (PDT) as combined therapy to treat polypoidal choroidal vasculopathy (PCV).

DESIGN: Retrospective, comparative, interventional case series.

METHODS: The study included 99 eyes (98 patients) with treatment-naïve subfoveal PCV treated with an intravitreal ranibizumab injection followed by PDT. The combination therapy included 1 ranibizumab injection administered 7 days before PDT (7-day group) or 2 days before PDT (2-day group). All eyes were followed for over 12 months.

RESULTS: Intravitreal ranibizumab was administered 7 days before PDT in 59 eyes and 2 days before PDT in 40 eyes. In the 7-day group, the best-corrected visual acuity (BCVA) did not improve significantly at 3 months ($P = .086$) or 12 months ($P = .259$) compared with baseline. In the 2-day group, BCVA improved significantly at 3 months ($P < .001$) and 12 months ($P < .001$). The polypoidal lesions regressed completely in 46 eyes (78.0%) in the 7-day group and in 34 eyes (85.0%) in the 2-day group; 38 eyes (64.4%) and 35 eyes (87.5%), respectively, did not require additional treatment, which differed significantly ($P = .008$) between the 2 groups. Subretinal hemorrhages did not develop in either group within 1 month after the combined therapy.

CONCLUSIONS: Administration of an intravitreal ranibizumab injection 2 days before PDT achieves significantly better visual outcomes and requires fewer additional treatments compared with administration of the injection 7 days before PDT.

PMID: 23628354 [PubMed - as supplied by publisher]

Int J Clin Pharm. 2013 Apr 28. [Epub ahead of print]

Bevacizumab versus ranibizumab: why are we not playing the joker?

Banfi R, Attanasio F, Palazzi N, Colombini S, Falai T, Cecchi M, Virgili G.

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PMID: 23625322 [PubMed - as supplied by publisher]

Expert Opin Investig Drugs. 2013 Apr 30. [Epub ahead of print]

Alprostadil infusion in patients with dry age related macular degeneration: a randomized controlled clinical trial.

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Background: Age-related macular degeneration is the leading cause of blindness among elderly individuals in industrialized countries. New drugs and advanced concepts for the treatment of dry AMD (dAMD) are needed. A new approach is the application of intravenous infusions of prostaglandin E1. Objective: The aim of this study was to assess efficacy and safety of intravenous alprostadil infusion in patients with dAMD.

Methods: This was a prospective, randomized, multi-center study. Patients were treated with intravenous infusion of either 60 µg alprostadil or placebo over 3 weeks. Main efficacy outcomes were mean differences in best corrected visual acuity (BCVA) from baseline assessed in early treatment diabetic retinopathy study (ETDRS) lines immediately, 3 months and 6 months after treatment.

Results: In the full analysis set (FAS) a mean difference of 0.89 ± 0.537 ETDRS lines according to analysis of variance-covariance (ANCOVA) resulted in the alprostadil group (n = 16) and a mean difference of -0.05 ± 0.578 in the placebo group (n = 17) 3 months after end of treatment. Thus, effectiveness of alprostadil infusion was numerically superior to placebo treatment by a mean of 0.94 lines after 3 months (1.51 lines after 6 months). These findings were more pronounced in the per protocol set (PPS). Safety results were in line with the good safety profile of alprostadil.

Conclusion: A numerical treatment effect in favor of alprostadil was visible, which lasted until the end of follow up. These results provide further evidence that alprostadil probably has a therapeutic effect in the treatment of dAMD and justify further clinical studies.

PMID: 23627650 [PubMed - as supplied by publisher]

J Glaucoma. 2013 Apr 29. [Epub ahead of print]

Ocular Decompression With Cotton Swabs Lowers Intraocular Pressure Elevation After Intravitreal Injection.

Gregori NZ, Weiss MJ, Goldhardt R, Schiffman JC, Vega E, Mattis CA, Shi W, Kelley L, Hernandez V, Feuer WJ.

*Miami Veterans Affairs Medical Center †Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL.

OBJECTIVE: To determine the effect of preinjection ocular decompression by cotton swabs on the immediate rise in intraocular pressure (IOP) after intravitreal injections.

METHODS: Forty-eight patients receiving 0.05 mL ranibizumab injections in a retina clinic were randomized to 2 anesthetic methods in each eye on the same day (if bilateral disease) or on consecutive visits (if unilateral disease). One method utilized cotton swabs soaked in 4% lidocaine applied to the globe with moderate pressure and the other 3.5% lidocaine gel applied without pressure. IOPs were recorded at baseline (before injection) and at 0, 5, 10, and 15 minutes after the injection until the IOP was ≤30 mm Hg. The IOP elevations from baseline were compared after the 2 anesthetic methods.

RESULTS: The preinjection mean IOP (SD, mm Hg) was 15.5 (3.3) before the cotton swabs and 15.9 (3.0) before the gel (P=0.28). Mean IOP (SD, mm Hg) change immediately after injection was 25.7 (9.2) after the cotton swabs and 30.9 (9.9) after the gel (P=0.001). Thirty-five percent of gel eyes had IOP≥50 mm Hg compared with only 10% of cotton swab eyes immediately after the injection (P<0.001).

CONCLUSION: Decompressing the eye with cotton swabs during anesthetic preparation before an intravitreal injection produces a significantly lower IOP spike after the injection.

PMID: 23632408 [PubMed - as supplied by publisher]

Klin Monbl Augenheilkd. 2013 Apr;230(4):405-8. doi: 10.1055/s-0032-1328373. Epub 2013 Apr 29.

[Bevacizumab and Ranibizumab for Macular Edema due to Retinal Vein Occlusions]. [Article in German]

Niederhauser N, Valmaggia C.

Augenklinik, Kantonsspital St. Gallen, Schweiz (Chairman: Christophe Valmaggia, MD, MBA).

Background: The effect of Bevacizumab (BE) (Avastin®) or Ranibizumab (RA) (Lucentis®) on the visual acuity (VA) and on the central foveal thickness (CFT) was evaluated in macular edema due to retinal vein occlusion.

Patients and Methods: Eyes with a macular edema due to a central retinal vein occlusion or to a branch retinal vein occlusion were considered if at least 3 intravitreal injections of Bevacizumab (1.25 mg) or Ranibizumab (0.5 mg) had been performed. The visual acuity with ETDRS and the central foveal thickness with spectral optical coherence tomography (OCT) were measured. The 3-months follow-up and, if further injections were necessary, the 6-months follow-up were evaluated.

Results: After 3 months a significant improvement of the visual acuity was measured in both groups ($p < 0.001$) while during the same period the mean central foveal thickness diminished significantly ($p < 0.001$). At the 3-months follow-up there were no significant differences between the two groups for the mean visual acuity and for the mean central foveal thickness. The treatment was continued in 36 eyes and the visual acuity and the central foveal thickness were compared between the 3-months and the 6-months follow-up. No further improvements of the visual acuity or of the central foveal thickness were measured in both groups. A relapse of the macular edema was diagnosed in 30 eyes without a significant difference in the Bevacizumab group compared to the Ranibizumab group.

Conclusion: Intravitreal injections of Bevacizumab and Ranibizumab improved the visual acuity and the central foveal thickness in macular edema due to retinal vein occlusion at 3 months. A further improvement

was not measured if the treatment was prolonged to 6 months. There were no significant differences measured between Bevacizumab and Ranibizumab.The ratio of relapses is important to note.

PMID: 23629792 [PubMed - in process]

J Glaucoma. 2013 Apr 29. [Epub ahead of print]

Does Intravitreal Injections of Bevacizumab for Age-related Macular Degeneration Affect Long-term Intraocular Pressure?

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PURPOSE: To evaluate the long-term intraocular pressure (IOP) changes after intravitreal injection of bevacizumab for age-related macular degeneration.

PATIENTS AND METHODS: A total of 83 eyes that received intravitreal injections of bevacizumab for age-related macular degeneration were enrolled. IOP measurements at baseline, 6, 12, 18, and 24 months, and at the last follow-up after injection were analyzed. On the basis of the median number of injections, the changes in IOP were compared. RESULTS: The mean number of injections was 3.71±1.62. There was no significantly higher elevation than baseline IOP (14.11±2.76 mm Hg) after multiple intravitreal injections of bevacizumab (P>0.05). In the group which had ≥4 injections, mean IOP measurements were not higher compared with the group which had <4 injections during the follow-up period (P>0.05). In the patients with preexisting glaucoma (3 eyes), there were no significant increases of IOP during the follow-up period.

CONCLUSIONS: IOP elevation was not observed during the long-term follow-up period. In addition, the numbers of injection and preexisting glaucoma did not affect IOP changes.

PMID: 23632401 [PubMed - as supplied by publisher]

Int J Ophthalmol. 2013 Apr 18;6(2):169-73. doi: 10.3980/j.issn.2222-3959.2013.02.12. Print 2013.

Bevacizumab vs ranibizumab for neovascular age-related macular degeneration in Chinese patients.

Li J, Zhang H, Sun P, Gu F, Liu ZL.

Department of Ophthalmology, the First Affiliated Hospital of China Medical University, Shenyang 110001, Liaoning Province, China.

AIM: To compare the clinical efficacy of intravitreal injections of bevacizumab and ranibizumab for treating Chinese patients with neovascular age-related macular degeneration (AMD).

METHODS: Among 60 Chinese patients with exudative AMD (60 eyes), 28 received intravitreal bevacizumab injections (1.25mg) and 32 received intravitreal ranibizumab injections (0.5mg), once a month for 3 months and were followed for a total of 6 months. Monthly optical coherence tomography (OCT) was used to determine whether the patients received additional treatments during the follow-up. We compared the baseline and 6-month follow-up values of mean best-corrected visual acuity (BCVA) and central retinal thickness (CRT) in both groups of patients. We also compared the occurrence of adverse events.

RESULTS: At the 6-month follow-up, the mean BCVA (logMAR) of the bevacizumab and ranibizumab treatment groups improved from the baseline measurements of 0.72±0.23 and 0.73±0.22 to 0.47±0.14 and 0.45±0.20, respectively (P<0.05 for both groups). However, the change was not significantly different be-

tween the two groups. As evaluated by OCT, CRT decreased from 366.71±34.72μm and 352±36.9μm at baseline to 250.86±41.51μm and 243.22±41.38μm in the bevacizumab and ranibizumab groups, respectively (P<0.05 for both groups). However, the change was not significantly different between the two groups. There were no severe local adverse reactions or systemic adverse events.

CONCLUSION: Intravitreal bevacizumab and ranibizumab have equivalent effects on BCVA and CRT and appeare safe over the short-term.

PMID: 23638418 [PubMed]

Int J Ophthalmol. 2013 Apr 18;6(2):136-40. doi: 10.3980/j.issn.2222-3959.2013.02.05. Print 2013.

Comparison of subconjunctivally injected bevacizumab, ranibizumab, and pegaptanib for inhibition of corneal neovascularization in a rat model.

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Department of Ophthalmology, Artvin State Hospital, Artvin, Turkey.

AIM: To compare the efficacies of subconjunctival bevacizumab, ranibizumab, and pegaptanib sodium injections for the inhibition of corneal neovascularization in an experimental rat model.

METHODS: Sixteen corneas of 16 rats were chemically cauterized and randomized into four groups: bevacizumab group that treated with 0.05mL/1.25mg bevacizumab, ranibizumab group that treated with 0.05mL/0.5mg ranibizumab, pegaptanib group that treated with 0.05mL/0.15mg pegaptanib sodium, and control group that treated with 0.05mL saline solution. Digital photographs of the corneas were taken and analyzed using an image analysis software program. All corneas were excised and examined histologically on the 15(th) day.

RESULTS: Each treatment group had significantly less neovascularized corneal areas and fewer blood vessels than the control group (all P<0.05). In addition, bevacizumab group had significantly less neovascularized corneal areas and fewer blood vessels than ranibizumab and pegaptanib groups (both P<0.05). However, there was no significant difference between the ranibizumab and pegaptanib groups regarding percentage of neovascularized corneal areas and number of blood vessels (both P>0.05).

CONCLUSION: Subconjunctival bevacizumab, ranibizumab, and pegaptanib sodium were effective with no corneal epitheliopathy for inhibiting corneal neovascularization after corneal burn in rats. Bevacizumab was more effective than ranibizumab and pegaptanib sodium.

PMID: 23638411 [PubMed]

Other treatment & diagnosis

Ophthalmology. 2013 Apr 25. pii: S0161-6420(13)00095-X. doi: 10.1016/j.ophtha.2013.01.049. [Epub ahead of print]

Characteristics of Incident Geographic Atrophy in the Complications of Age-Related Macular Degeneration Prevention Trial.

Brader HS, Ying GS, Martin ER, Maguire MG; Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) Research Group.

Department of Ophthalmology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

OBJECTIVE: To characterize the size, location, conformation, and features of incident geographic atrophy

(GA) as detected by annual stereoscopic color photographs and fluorescein angiograms (FAs).

DESIGN: Retrospective cohort study within a larger clinical trial.

PARTICIPANTS: Patients with bilateral large drusen in whom GA developed during the course of the Complications of Age-related Macular Degeneration Prevention Trial (CAPT).

METHODS: Annual stereoscopic color photographs and FAs were reviewed from 114 CAPT patients in whom GA developed in the untreated eye during 5 to 6 years of follow-up. Geographic atrophy was defined according to the Revised GA Criteria for identifying early GA.23 Color-optimized fundus photographs were viewed concurrently with the FAs during grading.

MAIN OUTCOME MEASURES: Size and distance from the fovea of individual GA lesions, number of areas of atrophy, and change in visual acuity (VA) when GA first developed in an eye.

RESULTS: At presentation, the median total GA area was 0.26 mm2 (0.1 disc area). Geographic atrophy presented as a single lesion in 89 (78%) eyes. The median distance from the fovea was 395 μm. Twenty percent of incident GA lesions were subfoveal and an additional 18% were within 250 μm of the foveal center. Development of GA was associated with a mean decrease of 7 letters from the baseline VA level compared with 1 letter among matched early age-related macular degeneration eyes without GA. Geographic atrophy that formed in areas previously occupied by drusenoid pigment epithelial detachments on average were larger (0.53 vs. 0.20 mm2; P = 0.0001), were more central (50 vs. 500 μm from the center of the fovea; P<0.0001), and were associated with significantly worse visual outcome (20/50 vs. 20/25; P = 0.0003) than GA with other drusen types as precursors.

CONCLUSIONS: Incident GA most often appears on color fundus photographs and FAs as a small, singular, parafoveal lesion, although a large minority of lesions are subfoveal or multifocal at initial detection. The characteristics of incident GA vary with precursor drusen types. These data can facilitate design of future clinical trials of therapies for GA.

PMID: 23622873 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Apr 30. pii: iovs.12-11184v1. doi: 10.1167/iovs.12-11184. [Epub ahead of print]

Noninvasive Investigation of Deep Vascular Pathologies of Exudative Macular Diseases by High Penetration Optical Coherence Angiography.

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PURPOSE: A newly developed high-penetration Doppler optical coherence angiography (HP-OCA) with a 1-μm probe beam for non-invasive investigation of vascular pathology of exudative macular diseases is introduced. A descriptive case series is presented to discuss the clinical utility of HP-OCA.

METHODS: Eleven eyes of 10 subjects with exudative macular disease, including 2 eyes with myopic choroidal neovascularization (mCNV), 4 eyes with age-related macular degeneration (AMD) and 5 eyes with polypoidal choroidal vasculopathy (PCV), were investigated. Two Doppler scanning modes (bi-directional and high-sensitive) of HP-OCA were used for the investigation. HP-OCA provides depth resolved and en face angiograms and a structural OCT noninvasively. The HP-OCA images were compared with fluorescein angiography (FA), indocyanine green angiography (ICGA) and color fundus images.

RESULTS: The abnormal vasculature patterns observed with high-sensitive HP-OCA presented high similarity to the mid-phase of ICGA. Several abnormal Doppler signals were observed in the en face high-sensitive HP-OCA and were co-located with FA leakage. This co-location was found in 1 eye with mCNV, 4

eyes with AMD, and 1 eye with PCV. Doppler tomogram of the bi-directional mode showed abnormal Doppler signals in 3 of 5 PCV cases beneath the pigment epithelium detachment. With the high-sensitive mode, Doppler signals were found beneath the elevated retinal pigment epithelium in all untreated cases.

CONCLUSIONS: HP-OCA revealed depth-resolved abnormal vasculatures in exudative macular diseases. The en face HP-OCA images showed high similarity with FA and ICGA images. These results suggest HP-OCA can be used for non-invasive and three-dimensional angiography in a clinical routine.

PMID: 23633664 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Apr 30. pii: iovs.12-11538v1. doi: 10.1167/iovs.12-11538. [Epub ahead of print]

Longitudinal Analysis of Reticular Drusen Associated With Geographic Atrophy In Age-related Macular Degeneration.

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PURPOSE: To characterize longitudinal changes of reticular drusen (RDR) in subjects with geographic atrophy (GA) secondary to age-related macular degeneration in the multicenter, prospective natural history Geographic Atrophy Progression Study.

METHODS: Three-field confocal scanning laser ophthalmoscopy fundus autofluorescence (FAF, exc=488nm, em 500-800nm, Heidelberg Retina Angiograph/Spectralis, Heidelberg Engineering, Germany) of 44 eyes of 22 patients with RDR (median age 77.6, range 61-90) at baseline were identified in the study population and included for further analysis. Two independent readers determined the presence, topographic distribution and pattern of RDR at baseline and at 18 months. Furthermore, the convex hull of the extent of RDR as the minimum polygon encompassing the entire area of RDR involvement was quantified.

RESULTS: RDR lesion boundaries were clearly detectable in all directions within three-field FAF composite images in 16 eyes of 10 patients at both baseline and final visits. Over time, RDR-affected retinal area and RDR density increased. Quantitative analysis showed a mean average RDR extent of 53.7mm² (95% -confidence interval(95%CI); 40.7;66.8) at baseline. The mean differences for intra-observer agreements were 2.4mm2 (95%CI; -0.1;4.9) for reader1 and -0.6mm2 (95% CI; -2.3;1.1) for reader2. The mean difference of inter-observer agreement was 0.9mm2 (95% CI; -0.8; 2.7). A mean growth rate of the RDR extent within the three-field FAF composite image of 4.4mm2/year (95% CI; 1.9; 6.9) was measured.

CONCLUSIONS: In-vivo cSLO FAF imaging allows for both qualitative and quantitative mapping of longitudinal changes of RDR areas within a relatively short time period. Continuous enlargement of the affected retinal area indicates disease progression with regard to this phenotypic characteristic associated with GA in AMD. Systematic recordings of RDR progression appears warranted in future natural history and interventional studies in dry AMD.

PMID: 23633663 [PubMed - as supplied by publisher]

Retina. 2013 Apr 29. [Epub ahead of print]

RETICULAR MACULAR DISEASE IS ASSOCIATED WITH MULTILOBULAR GEOGRAPHIC ATROPHY IN AGE-RELATED MACULAR DEGENERATION.

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†Department of Ophthalmology and Visual Sciences, John A. Moran Eye Center, University of Utah, Salt Lake City, Utah; and ‡Department of Ophthalmology, New York University Langone Medical Center, New York, New York.

PURPOSE: To investigate the incidence of reticular macular disease (RMD), a subphenotype of age-related macular degeneration, in multilobular geographic atrophy (GA) and its relation to GA progression.

METHODS:: One hundred and fifty-seven eyes of 99 subjects with age-related macular degeneration, primary GA, and good quality autofluorescence, and/or infrared images were classified into unilobular GA (1 lesion) or multilobular GA (≥2 distinct and/or coalescent lesions). Thirty-four subjects (50 eyes) had serial imaging. The authors determined the spatiotemporal relationships of RMD to GA and GA progression rates in five macular fields.

RESULTS:: 91.7% eyes (144 of 157) had multilobular GA, 95.8% of which exhibited RMD. In subjects with serial imaging, the mean GA growth rate significantly differed between the unilobular and multilobular groups (0.40 vs. 1.30 mm/year, P < 0.001). Of the macular fields in these eyes, 77.1% of fields with RMD at baseline showed subsequent GA progression, while 53.4% of fields without RMD showed progression (P < 0.001). Percentage of fields with RMD significantly correlated with GA progression rate (P = 0.01).

CONCLUSION:: Autofluorescence and infrared imaging demonstrates that RMD is nearly always present with multilobular GA in age-related macular degeneration. Furthermore, GA lobules frequently develop in areas of RMD, suggesting progression of a single underlying disease process.

PMID: 23632954 [PubMed - as supplied by publisher]

J Biol Chem. 2013 May 2. [Epub ahead of print]

Lens Epithelium-Derived Growth Factor Fragment (LEDGF1-326), a Novel Therapeutic Protein: Biosynthesis, Characterization, and Efficacy in Retinal Degenerative Diseases.

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Abstract: For vision-threatening retinitis pigmentosa (RP) and dry age related macular degeneration (dry AMD), there are no FDA approved treatments. We identified lens epithelium derived growth factor fragment (LEDGF1-326) as a novel protein therapeutic. We biosynthesized, purified, and characterized LEDGF1-326. LEDGF1-326 was produced at about 20 mg per liter of culture when expressed in E.coli system, with about 95 % purity and aggregate free homogenous population with a mean hydrodynamic diameter of 9 ± 1 nm. The free energy of unfolding of LEDGF1-326 was 3.3 ± 0.5 kcal mol-1 and melting temperature was 44.8 ± 0.2 °C. LEDGF1-326 increased human retinal pigment epithelial cell (RPE) viability from 48.3 ± 5.6 to 119.3 ± 21.1 % in the presence of P23H mutant rhodopsin mediated aggregation stress. LEDGF1-326 also increased RPE FluoSphere uptake to 140 ± 10 %. Eight weeks after single intravitreal injection in Royal College of Surgeon (RCS) rats, LEDGF1-326 increased the b-wave amplitude significantly from 9.4 ± 4.6 to 57.6 ± 8.8 μV for scotopic electroretinogram (ERG) and from 10.9 ± 5.6 to 45.8 ± 15.2 μV for photopic ERG. LEDGF1-326 significantly increased the retinal outer nuclear layer thickness from 6.34 ± 1.6 to 11.7 ± 0.7 μm. LEDGF1-326 is a potential new therapeutic agent for treating retinal degenerative diseases.

PMID: 23640891 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 May 2. pii: iovs.12-11236v1. doi: 10.1167/iovs.12-11236. [Epub ahead of print]

Role of heparin-binding epidermal growth factor-like growth factor (HB-EGF) in light-induced photo-

receptor degeneration in mouse retina.

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PURPOSE: Although heparin-binding epidermal growth factor-like growth factor (HB-EGF) has been reported to have protective effects against various neuronal cell damage, its role in the retina has not been elucidated. Here, we investigated its role in light-induced photoreceptor degeneration using retinas and ventral forebrain specific Hb-egf knockout (KO) mice.

METHODS: Disruption of Hb-egf was confirmed by LacZ staining and RT-PCR. Time-dependent changes in retinal HB-EGF were measured using quantitative RT-PCR and Western blotting. Retinal damage was induced by exposure to light. Recombinant human HB-EGF was injected intravitreally. Electroretinogram (ERG) and histological analyses were performed. To evaluate the effect of HB-EGF against light irradiation-induced cell-death, 661W cells, a transformed mouse cone-cell line, were used.

RESULTS: LacZ-positive cells were observed, and Hb-egf deletion was confirmed in the retinas of Hb-egf KO mice. Hb-egf and pro-HB-EGF levels were increased after light exposure in wild-type (WT) mice. Exposure to light reduced the a- and b-wave amplitudes of the dark-adapted ERG, and also ONL thickness, in Hb-egf KO mice versus WT mice. Treatment with HB-EGF improved both the a- and b-wave amplitudes, and the thickness of the ONL. The 661W cell-death induced by light irradiation was exacerbated by Hb-egf knockdown. HB-EGF also protected against light-induced cell-death and reduced ROS production in 661W cells. HB-EGF treatment improved the a-wave amplitudes, and the thickness of the ONL in Hb-egf KO mice.

CONCLUSIONS: These data suggest that HB-EGF plays a pivotal role in light-induced photoreceptor degeneration. It therefore warrants investigation as a potential therapeutic target for such light-induced retinal diseases as age-related macular degeneration.

PMID: 23640042 [PubMed - as supplied by publisher]

Exp Eye Res. 2013 Apr 27. pii: S0014-4835(13)00102-4. doi: 10.1016/j.exer.2013.04.014. [Epub ahead of print]

A novel ex vivo murine retina angiogenesis (EMRA) assay.

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Abstract: Pathological retinal angiogenesis results from the imbalance of pro-angiogenic and anti-angiogenic factors. In particular, vascular endothelial growth factor (VEGF) plays a pivotal role in retinal neovascularization and various therapeutic VEGF blockers have evolved over time. Nevertheless, new retinal angiogenesis models are crucial for investigating anti-angiogenic therapies and bringing them to patients. Here, we developed a novel ex vivo murine retina angiogenesis (EMRA) assay in which endothelial sprouts originate from mature and quiescent retinal vessels. In this model, retina fragments from adult mice are embedded in a three-dimensional fibrin gel in the presence of human recombinant VEGF. Starting from the 3rd-4th day of incubation, endothelial cell sprouts invading the fibrin gel can be observed under an inverted microscope and measured at different time points thereafter. The effect of VEGF is dose-dependent, maximal stimulation being observed at day 7 for retina fragments stimulated with 25-75 ng/ml of the growth factor. To assess whether the EMRA assay is suitable for testing the activity of anti-angiogenic compounds, retina fragments were incubated with VEGF in the presence of the neutralizing anti-VEGF antibodies bevacizumab and ranibizumab. The results demonstrate that both antibodies inhibit VEGF activity in a dose

-dependent manner. In conclusion, the EMRA assay represents a new ex vivo model of retinal neovascularization suitable for the rapid screening of novel anti-angiogenic therapeutics.

PMID: 23631846 [PubMed - as supplied by publisher]

J Biomed Nanotechnol. 2013 Apr;9(4):621-5.

Multi-channel stimulator IC using a channel sharing method for retinal prostheses.

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Abstract: A retinal stimulator is an implantable device restoring vision by supplying a controlled, stimulating electrical signal to people blinded by retinal diseases such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP). The resolution requirements of artificial retina systems become increasingly significant in their design as well as their usefulness. At least 32 x 32 pixels are required to provide a minimal visual function. However, a retinal stimulator with a high resolution imposes severe constraints on interface electronics. In this paper, a new stimulator IC (integrated chip) using a channel sharing technique is developed to minimize the circuit size, power consumption, as well as overheating of retina tissues. The proposed current-mode stimulator is fabricated by a 0.35 microm 2-poly/4-metal BCDMOS technology. Attention is given to minimizing the silicon area so that higher channel numbers can be implemented. The stimulator for each channel can provide output current in the range of 0-350 muA. The effective chip area excluding the pads is 1.2 mm x 1.2 mm.

PMID: 23621021 [PubMed - in process]

Pathogenesis

Nihon Ganka Gakkai Zasshi. 2013 Mar;117(3):246-68; discussion 269.

[Pupil and melanopsin photoreception]. [Article in Japanese]

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Abstract: The iris is the most anterior portion of the uveal tract. The pupil is round opening near the center of the iris; it is displaced slightly downward and nasally with respect to the center of the cornea. The mammalian iris sphincter is considered to be innervated by cholinergic, and the dilator muscle by adrenergic excitatory nerve fibers, and both miosis and mydriasis are the result of contraction of the iris sphincter and the dilator muscles due to activation of these excitatory nerve fibers. Pharmacological and histological investigations also reveal that the sphincter muscle is innervated in part by inhibitory adrenergic nerve fibers, and that the dilator muscle is also innervated by inhibitory cholinergic nerve fibers. In addition to the release of acetylcholine and norepinephrine by these nerves, the peripheral nerves to the mammalian iris contain various neuropeptides, although the functional role of these pepetides is not clear. It has been known for more than 100 years that two types of photosensitive cells exist in man. However, some totally blind individuals maintain a normal circadian rhythm. Such a phenomenon cannot be explained by the rod and cone functions. Recently, a new photosensitive pigment, melanopsin, was found in the dermal melanophore cells of the frog. In 2002, melanopsin-containing retinal ganglion cells (mRGCs) were discovered and revealed that mRGCs would depolarize without input from the photoreceptors, meaning that these cells are photosensitive. In the human retina, mRGCs comprise only 0.2% of all ganglion cells. Electrophysiological studies

show that light slowly depolarizes mRGCs but rapidly hyperpolarizes rods and cones. The mRGCs innervate the suprachiasmatic nucleus, which is the master circadian pacemaker in mammals, and the olivary pretectal nucleus of the midbrain. In addition to their role in circadian entrainment, the mRGCs mediate the pupillary light reflex. We investigated the mechanism of photoreception by retinal photoreceptor cells, and to evaluate the relative contribution of pupil light response using the control, instigated pharmacological blockade of neurotransmission (PB) model and a transgenic model of retinal degeneration (Tg) rabbit. Although rod and cone photoreceptors disappeared in the PB and Tg models, miosis was still induced during exposure to blue light (470 nm). The greater sustained constriction of pupils to blue light in eyes with outer retinal damage reflects mRGC activation. Our study also indicated that some histologically-identified RGCs were consistent with the characteristics and structures of mRGC. Clinically, in age-related macular degeneration patients, there was no reliable recordable pupil response to red light, even at the brightest intensity but a blue light evoked a sustained pupil constriction. However, in glaucoma patients, there was no reliable recordable pupil response to the brightest intensity of blue light. These preliminary recordings in human subjects demonstrate that changes in the pupil responses to chromatic stimuli are readily detectable and easily quantifiable with standard instruments of clinical testing. We hypothesize that changes in the transient pupil response to red light and low intensity blue light may be more sensitive to cone and rod disease, whereas changes in the sustained pupil response to bright blue light may be more sensitive to optic nerve disease. Ongoing studies of the pupil are aimed at optimizing stimulus conditions that elicit pupil responses that can better localize the site of damage to rods, cones, and RGCs, to quantify the extent of disease.

PMID: 23631256 [PubMed - in process]

Exp Eye Res. 2013 Apr 24. pii: S0014-4835(13)00101-2. doi: 10.1016/j.exer.2013.04.013. [Epub ahead of print]

HtrA1 is induced by oxidative stress and enhances cell senescence through p38 MAPK pathway.

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Abstract: Genetic predisposition and senescence of retinal pigment epithelium induced by oxidative stress are major contributors to age-related macular degeneration (AMD). Single-nucleotide polymorphisms in HTRA1 are strongly linked to the onset of AMD. In this study, we examine the role of HtrA1 in premature senescence and cell death induced by oxidative stress. HtrA1 mRNA and protein were up-regulated during premature senescence induced by H2O2 in both mouse embryonic fibroblasts (MEFs) and ARPE-19 cells. Expression of the senescence markers p21CIP1/WAF1 and p16INK4a, and SA-β-galactosidase activity, were higher in HtrA1+/- MEFs than in HtrA1-/- MEFs. HtrA1+/+ and HtrA1+/- MEFs were more resistant than HtrA1-/- MEFs to H2O2-induced cell death. Activation of p38 MAPK by oxidative stress was quicker in HtrA1+/- MEFs than in HtrA1-/- MEFs. The effects of excess HtrA1 were examined by transient transfection of cells with HtrA1 expression vectors or by addition of recombinant proteins. Excess wild type HtrA1 accelerated premature senescence of MEFs and ARPE-19 cells, while the protease-inactive HtrA1 S328A did not. HtrA1-induced senescence was abrogated by inhibition of p38 MAPK. We conclude that HtrA1 is induced by oxidative stress and promotes premature cell senescence through p38 MAPK in a protease activity-dependent manner.

PMID: 23623979 [PubMed - as supplied by publisher]

ACS Chem Biol. 2013 Apr 26. [Epub ahead of print]

Small molecule mediated proliferation of primary retinal pigment epithelial cells.

Swoboda JG, Elliott J, Deshmukh V, de Lichtervelde L, Shen W, Tremblay MS, Peters EC, Cho CY, Lu B, Girman S, Wang S, Schultz PG.

Abstract: Retinal pigment epithelial (RPE) cells form a monolayer adjacent to the retina and play a critical role in the visual light cycle. Degeneration of this layer results in vision loss, causing retinal disorders such as age-related macular degeneration. Cell transplant therapies exist to restore vision loss; however, risks associated with and an inadequate supply of donor cells have limited their therapeutic success. The identification of factors that proliferate RPE cells ex vivo could provide a renewable source of cells for the treatment of such disorders. We show that a small molecule (WS3) can reversibly proliferate primary RPE cells isolated from fetal and adult human donors. Following withdrawal of WS3, RPE cells differentiate into a functional monolayer, as exhibited by their expression of mature RPE genes and phagocytosis of photoreceptor outer segments. Furthermore, chemically expanded RPE cells preserve vision when transplanted into dystrophic Royal College of Surgeons (RCS) rats, a well-established model of retinal degeneration.

PMID: 23621521 [PubMed - as supplied by publisher]

Genetics

PLoS One. 2013 Apr 18;8(4):e61381. doi: 10.1371/journal.pone.0061381. Print 2013.

Age- and Light-Dependent Development of Localised Retinal Atrophy in CCL2(-/-)CX3CR1(GFP/GFP) Mice.

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Abstract: Previous studies have shown that CCL2/CX3CR1 deficient mice on C57BL/6N background (with rd8 mutation) have an early onset (6 weeks) of spontaneous retinal degeneration. In this study, we generated CCL2(-/-)CX3CR1(GFP/GFP) mice on the C57BL/6J background. Retinal degeneration was not detected in CCL2(-/-)CX3CR1(GFP/GFP) mice younger than 6 months. Patches of whitish/yellowish fundus lesions were observed in 17~60% of 12-month, and 30~100% of 18-month CCL2(-/-)CX3CR1(GFP/GFP) mice. Fluorescein angiography revealed no choroidal neovascularisation in these mice. Patches of retinal pigment epithelium (RPE) and photoreceptor damage were detected in 30% and 50% of 12- and 18-month CCL2(-/-)CX3CR1(GFP/GFP) mice respectively, but not in wild-type mice. All CCL2(-/-)CX3CR1(GFP/GFP) mice exposed to extra-light (~800lux, 6 h/day, 6 months) developed patches of retinal atrophy, and only 20-25% of WT mice which underwent the same light treatment developed atrophic lesions. In addition, synaptophysin expression was detected in the outer nucler layer (ONL) of area related to photoreceptor loss in CCL2(-/-)CX3CR1(GFP/GFP) mice. Markedly increased rhodopsin but reduced cone arrestin expression was observed in retinal outer layers in aged CCL2(-/-)CX3CR1(GFP/GFP) mice. GABA expression was reduced in the inner retina of aged CCL2(-/-)CX3CR1(GFP/GFP) mice. Significantly increased Müller glial and microglial activation was observed in CCL2(-/-)CX3CR1(GFP/GFP) mice compared to age-matched WT mice. Macrophages from CCL2(-/-)CX3CR1(GFP/GFP) mice were less phagocytic, but expressed higher levels of iNOS, IL-1β, IL-12 and TNF-α under hypoxia conditions. Our results suggest that the deletions of CCL2 and CX3CR1 predispose mice to age- and light-mediated retinal damage. The CCL2/CX3CR1 deficient mouse may thus serve as a model for age-related atrophic degeneration of the RPE, including the dry type of macular degeneration, geographic atrophy.

PMID: 23637822 [PubMed - in process]

Diet

JAMA. 2013 May 5:1-11. doi: 10.1001/jama.2013.4997. [Epub ahead of print]

Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration: The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial.

The Age-Related Eye Disease Study 2 (AREDS2) Research Group*.

IMPORTANCE: Oral supplementation with the Age-Related Eye Disease Study (AREDS) formulation (antioxidant vitamins C and E, beta carotene, and zinc) has been shown to reduce the risk of progression to advanced age-related macular degeneration (AMD). Observational data suggest that increased dietary intake of lutein + zeaxanthin (carotenoids), omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] + eicosapentaenoic acid [EPA]), or both might further reduce this risk.

OBJECTIVES: To determine whether adding lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation decreases the risk of developing advanced AMD and to evaluate the effect of eliminating beta carotene, lowering zinc doses, or both in the AREDS formulation.

DESIGN, SETTING, AND PARTICIPANTS: The Age-Related Eye Disease Study 2 (AREDS2), a multicenter, randomized, double-masked, placebo-controlled phase 3 study with a 2 × 2 factorial design, conducted in 2006-2012 and enrolling 4203 participants aged 50 to 85 years at risk for progression to advanced AMD with bilateral large drusen or large drusen in 1 eye and advanced AMD in the fellow eye.

INTERVENTIONS: Participants were randomized to receive lutein (10 mg) + zeaxanthin (2 mg), DHA (350 mg) + EPA (650 mg), lutein + zeaxanthin and DHA + EPA, or placebo. All participants were also asked to take the original AREDS formulation or accept a secondary randomization to 4 variations of the AREDS formulation, including elimination of beta carotene, lowering of zinc dose, or both.

MAIN OUTCOMES AND MEASURES: Development of advanced AMD. The unit of analyses used was by eye.

RESULTS: Median follow-up was 5 years, with 1940 study eyes (1608 participants) progressing to advanced AMD. Kaplan-Meier probabilities of progression to advanced AMD by 5 years were 31% (493 eyes [406 participants]) for placebo, 29% (468 eyes [399 participants]) for lutein + zeaxanthin, 31% (507 eyes [416 participants]) for DHA + EPA, and 30% (472 eyes [387 participants]) for lutein + zeaxanthin and DHA + EPA. Comparison with placebo in the primary analyses demonstrated no statistically significant reduction in progression to advanced AMD (hazard ratio [HR], 0.90 [98.7% CI, 0.76-1.07]; P = .12 for lutein + zeaxanthin; 0.97 [98.7% CI, 0.82-1.16]; P = .70 for DHA + EPA; 0.89 [98.7% CI, 0.75-1.06]; P = .10 for lutein + zeaxanthin and DHA + EPA). There was no apparent effect of beta carotene elimination or lower-dose zinc on progression to advanced AMD. More lung cancers were noted in the beta carotene vs no beta carotene group (23 [2.0%] vs 11 [0.9%], nominal P = .04), mostly in former smokers.

CONCLUSIONS AND RELEVANCE: Addition of lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation in primary analyses did not further reduce risk of progression to advanced AMD. However, because of potential increased incidence of lung cancer in former smokers, lutein + zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation.

PMID: 23644932 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2013 May 5:1-7. doi: 10.1001/jamaophthalmol.2013.4412. [Epub ahead of print]

Lutein/Zeaxanthin for the Treatment of Age-Related Cataract: AREDS2 Randomized Trial Report No. 4.

The Age-Related Eye Disease Study 2 (AREDS2) Research Group*.

IMPORTANCE: Age-related cataract is a leading cause of visual impairment in the United States. The prevalence of age-related cataract is increasing, with an estimated 30.1 million Americans likely to be affected by 2020.

OBJECTIVE: To determine whether daily oral supplementation with lutein/zeaxanthin affects the risk for cataract surgery.

DESIGN, SETTING, AND PATIENTS: The Age-Related Eye Disease Study 2 (AREDS2), a multicenter, double-masked clinical trial, enrolled 4203 participants, aged 50 to 85 years, at risk for progression to advanced age-related macular degeneration.

INTERVENTIONS: Participants were randomly assigned to daily placebo; lutein/zeaxanthin, 10mg/2mg; omega-3 long-chain polyunsaturated fatty acids, 1 g; or a combination to evaluate the effects on the primary outcome of progression to advanced age-related macular degeneration.

MAIN OUTCOMES AND MEASURES: Cataract surgery was documented at annual study examination with the presence of pseudophakia or aphakia, or reported during telephone calls at 6-month intervals between study visits. Annual best-corrected visual acuity testing was performed. A secondary outcome of AREDS2 was to evaluate the effects of lutein/zeaxanthin on the subsequent need for cataract surgery.

RESULTS: A total of 3159 AREDS2 participants were phakic in at least 1 eye and 1389 of 6027 study eyes underwent cataract surgery during the study, with median follow-up of 4.7 years. The 5-year probability of progression to cataract surgery in the no lutein/zeaxanthin group was 24%. For lutein/zeaxanthin vs no lutein/zeaxanthin, the hazard ratios for progression to cataract surgery was 0.96 (95% CI, 0.84-1.10; P = .54). For participants in the lowest quintile of dietary intake of lutein/zeaxanthin, the hazard ratio comparing lutein/zeaxanthin vs no lutein/zeaxanthin for progression to cataract surgery was 0.68 (95% CI, 0.48-0.96; P = .03). The hazard ratio for 3 or more lines of vision loss was 1.03 (95% CI, 0.93-1.13; P = .61 for lutein/zeaxanthin vs no lutein/zeaxanthin).

CONCLUSIONS AND RELEVANCE: Daily supplementation with lutein/zeaxanthin had no statistically significant overall effect on rates of cataract surgery or vision loss.

PMID: 23645227 [PubMed - as supplied by publisher]

Am J Clin Nutr. 2013 May 1. [Epub ahead of print]

Homocysteine, folate, vitamin B-12, and 10-y incidence of age-related macular degeneration.

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BACKGROUND: Epidemiologic evidence of a relation between serum total homocysteine (tHcy), vitamin B-12, and folate and age-related macular degeneration (AMD) is inconsistent and unresolved.

OBJECTIVE: In this cohort study, we aimed to investigate associations between intakes and serum concentrations of folate and vitamin B-12 or serum tHcy and 10-y AMD incidence.

DESIGN: Serum folate, vitamin B-12, and tHcy were determined from blood samples drawn in 1997-1999 from cohort members aged ≥55 y. AMD was assessed in 1760 survivors from retinal photographs taken in 2002-2004 and 2007-2009. Total intakes of folate and vitamin B-12 were assessed by using a food-frequency questionnaire.

RESULTS: After adjustment for age, sex, current smoking, white cell count, and fish consumption, each 1-SD increase in serum tHcy was associated with increased risk of incident early and any AMD [ORs (95% CIs): 1.33 (1.09, 1.63) and 1.33 (1.11, 1.60), respectively]. Participants with a serum vitamin B-12 defi-

ciency (<185 pmol/L) had higher risk of incident early and late AMD [ORs (95% CIs): 1.58 (1.06, 2.36) and 2.56 (1.38, 4.73), respectively. Folate deficiency (<11 nmol/L) was associated with 75% and 89% increased risk of incident early and any AMD, respectively, 10 y later. Participants who reported supplementary vitamin B-12 intake had 47% reduced risk of incident any AMD (OR: 0.53; 95% CI: 0.33, 0.85).

CONCLUSION: Elevated serum tHcy and folate and vitamin B-12 deficiencies predicted increased risk of incident AMD, which suggests a potential role for vitamin B-12 and folate in reducing AMD risk.

PMID: 23636242 [PubMed - as supplied by publisher]