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MD Research News

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Drug treatment

Can J Ophthalmol. 2013 Jun;48(3):210-5. doi: 10.1016/j.jcjo.2013.01.023.

Anti-VEGF response in macular hemorrhage and incidence of retinal pigment epithelial tears.

Varshney N, Jain A, Chan V, Yu L, Sarraf D.

Jules Stein Eye Institute, University of California, Los Angeles, Los Angeles;

OBJECTIVE: To study the visual and anatomic outcomes of serial anti-vascular endothelial growth factor (anti-VEGF) therapy for severe macular hemorrhage in eyes with exudative age-related macular degeneration (AMD).

DESIGN: Consecutive retrospective analysis.

PARTICIPANTS: Twenty eyes from 20 patients with severe macular hemorrhage (greater than 50% blockage with formal fluorescein angiography [FA]) secondary to wet AMD were studied.

METHODS: We performed a chart review of patients at a single centre from May 2006 to September 2009. Presenting visual acuity and diameter of hemorrhage were recorded as well as number of injections, time by which no hemorrhage was remaining, and final anatomic outcome. Cardiovascular risk factors and use of antiplatelet medication or anticoagulation were noted.

RESULTS: Average presenting visual acuity was 1.55 (20/710), and number of injections needed for resolution of hemorrhage was 4. Visual acuity significantly improved from 1.55 (20/710) to 0.70 (20/100) after injections. Thirty-five percent of eyes were found to have an associated retinal pigment epithelial (RPE) tear, and these eyes were found to have received more injections. Final visual acuity was not significantly different in eyes with RPE tears compared with nontear eyes. Eighty-one percent of patients had associated cardiovascular risk factors; antiplatelet therapy and anticoagulation were not found to play a role in hemorrhage size.

CONCLUSIONS: RPE tears are found in a significant number of individuals with large macular hemorrhages secondary to exudative macular degeneration, but with continued treatment with anti-VEGF therapy, visual acuity can significantly improve even in the presence of these tears. Eyes with severe macular hemorrhage thus should be considered candidates for anti-VEGF therapy.

PMID: 23769784 [PubMed - in process]

Acta Ophthalmol. 2013 Jun 15. doi: 10.1111/aos.12119. [Epub ahead of print]

Bevacizumab in age-related macular degeneration: a randomized controlled trial on the effect of injections every 4 weeks, 6 weeks and 8 weeks.

Lushchyk T, Amarakoon S, Martinez-Ciriano JP, van den Born LI, Baarsma GS, Missotten T.

Rotterdam Eye Hospital, Rotterdam, The Netherlands Rotterdam Ophthalmic Institute, Rotterdam, The Netherlands.

Purpose: Several clinical trials have established the efficacy of ranibizumab therapy administered every 4 weeks to treat exudative age-related macular degeneration (ARMD). Bevacizumab appears to be a cost-effective alternative to ranibizumab, although an optimal injection schedule has not yet been determined. In this study, we set out to determine whether bevacizumab treatment in exudative ARMD every 6 or 8 weeks is non-inferior to bevacizumab treatment every 4 weeks.

Methods: A total of 191 patients with exudative ARMD were randomly assigned to a 1-year continuous regimen of intravitreal bevacizumab every 4 (n = 64), 6 (n = 63) or 8 weeks (n = 64). The primary outcome was visual acuity change after 1 year of treatment.

Results: In all three treatment groups, visual acuity improved between baseline and 1 year. There was no statistically significant difference in the mean change of visual acuity score at 1 year for bevacizumab administered every 4 (1.96 ± 13.70), 6 (1.60 ± 10.98) or 8 weeks (5.98 ± 8.88). Reduction in central retinal thickness was observed in all three study groups. At 1 year, the mean decrease in central foveal thickness ranged from 86 ± 97 μm in the every 6 weeks group to 109 ± 90 μm in the group every 8 weeks group (p = 0.30).

Conclusion: At 1 year, bevacizumab administered every 6 or 8 weeks was not inferior to therapy administered every 4 weeks.

PMID: 23773796 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2013 Jun 13:0. doi: 10.5301/ejo.5000323. [Epub ahead of print]

Choroidal thickness after treatment for myopic choroidal neovascularization.

Farinha CL, Baltar AS, Nunes SG, Franqueira NF, Figueira JP, Pires IA, Cachulo ML, Silva RM.

Ophthalmology Unit, Centro Hospitalar e Universitário Coimbra, Coimbra - Portugal.

Purpose: To evaluate choroidal thickness in highly myopic eyes with choroidal neovascularization (CNV), 3 or more years after treatment with photodynamic therapy (PDT), intravitreal ranibizumab (IVR), or both (PDT + IVR).

Methods: The medical records of patients with high myopia and CNV treated with PDT or IVR in our department were reviewed. Eyes meeting the inclusion criteria were assigned to 3 groups: PDT, IVR, and PDT + IVR. A fourth group, "dry myopic maculopathy," included the contralateral highly myopic eyes that never developed CNV. All patients performed a cross-sectional evaluation with best-corrected visual acuity (BCVA), measurement of axial length, color fundus photography, and enhanced depth imaging with spectral domain optical coherence tomography.

Results: Forty-two eyes (21 patients) were included: 11 eyes (26.2%) in the PDT group, 8 (19.0%) in the IVR group, 9 (21.4%) in the PDT + IVR group, and 14 (33.3%) in the dry maculopathy group. Subfoveal choroidal thickness showed no significant differences between groups (p>;0.05). Positive correlation was found between BCVA and macular choroidal thickness (r = +0.293, p<;0.001). Regression analysis showed that age (p<0.001), axial length (p<0.001), sex (p = 0.001), and myopic lesions such as tessellated fundus (p = 0.046) and patchy atrophy (p = 0.008) were predictive of choroidal thickness. Type of treatment was

not predictive of choroidal thickness.

Conclusions: Older age and greater axial length are the major factors associated with macular choroidal thinning in highly myopic eyes submitted to CNV treatment. The type of treatment performed for myopic CNV had no predictive contribution for choroidal thickness.

PMID: 23787449 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2013 Jun 21. doi: 10.1111/aos.12111. [Epub ahead of print]

Combination treatment of photodynamic therapy with verteporfin and intravitreal ranibizumab in patients with retinal angiomatous proliferation.

Seidel G, Werner C, Weger M, Steinbrugger I, Haas A.

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

Purpose: To investigate the efficacy and safety of initial photodynamic therapy (PDT) with a ranibizumab loading dose of three monthly intravitreal injections and a subsequent PRN ranibizumab regimen in the treatment of retinal angiomatous proliferation (RAP).

Methods: In this 12-month prospective case series, 15 patients underwent PDT followed by 3 intravitreal ranibizumab injections at monthly intervals. At monthly follow-up examinations, further single ranibizumab injections were given in case of any intra- or subretinal fluid on optical coherence tomography (OCT), visual loss ≥5 letters or signs of activity on fluorescein or indocyanine green angiography.

Results: Best-corrected visual acuity (BCVA) improved from 58.1 ± 13.2 at baseline by 9.2 letters (SD ± 8.5; p = 0.004) at 6 months and by 8.7 letters (SD ± 11.4; p = 0.017) at 12 months. Neither at 6 nor at 12 months, any patient had lost ≥15 letters. The mean number of injections per patient was 4.8 (SD ± 1.4) in the first year of therapy after PDT. The average time to first retreatment was 3.7 months (range 1-7 months). No serious adverse events, such as endophthalmitis or retinal detachment, were noted.

Conclusion: PDT with 3 ranibizumab loading injections and subsequent ranibizumab as needed resulted in a significant gain of 8.7 ± 11.4 letters at month 12. This regimen is safe and efficacious, but even in a population of mostly early stages of RAP, retreatment rates remained high.

PMID: 23786546 [PubMed - as supplied by publisher]

BMJ Case Rep. 2013 Jun 16;2013. pii: bcr2013009697. doi: 10.1136/bcr-2013-009697.

Intravitreal ranibizumab in the management of stage 2B Coats disease in a young adult Malay man.

Teh SS, Ahem A, Bastion ML.

Department of Ophthalmology, Kementerian Kesihatan Malaysia, Selangor, Malaysia.

Abstract: This paper describes a rare case of Coats disease with late presentation in a young adult. The condition improved with a combination of focal photocoagulation, cryotherapy and intravitreal ranibizumab.

PMID: 23774706 [PubMed - in process]

Other treatment & diagnosis

JAMA Ophthalmol. 2013 Jun 20:1-7. doi: 10.1001/jamaophthalmol.2013.4014. [Epub ahead of print]

Quantification of Fundus Autofluorescence to Detect Disease Severity in Nonexudative Age-Related Macular Degeneration.

Schachar IH, Zahid S, Comer GM, Stem M, Schachar AG, Saxe SJ, Gardner TW, Elner VM, Jayasundera T.

IMPORTANCE: Accurate assessment of disease burden and determination of disease progression are challenging in dry age-related macular degeneration (AMD). We assessed the utility of quantified fundus autofluorescence in (FAF) the evaluation and follow-up of dry AMD.

OBJECTIVE: To develop a method for quantitative FAF image analysis that is capable of stratifying severity of nonexudative AMD.

DESIGN, SETTING, AND PARTICIPANTS: A retrospective analysis from 2008 to 2012 at a university eye center of FAF images taken of normal and nonexudative AMD eyes compared the Index of Retinal Autofluorescence (IRA) with retinal specialists' clinical rankings of FAF images and the Age-Related Eye Disease Study (AREDS) grading scheme of corresponding color fundus photographs.

INTERVENTION: Digital files of Heidelberg Spectralis FAF images taken of normal and nonexudative AMD eyes were analyzed. For each image, a unique horizontally oriented FAF signature composed of vertically averaged gray-scale values was generated through the fovea. A pairwise comparison of 2 signatures was performed using a modified difference of squares method, which generated a single quantitative value, the IRA.

MAIN OUTCOMES AND MEASURES: The effects of intersession testing, cataract extraction, pupillary dilation, focal plane, and gain settings on the IRA were assessed.

RESULTS: The FAF images taken of the same subjects at different times demonstrated low intersession variability of the IRA (intraclass coefficient = 0.75; 95% CI, 0.45-0.92). The IRA was affected by cataract severity, cataract extraction, small pupillary diameters (<5.5 mm), defocusing, and excessive high or low camera gain. The IRA values correlated with both subjective clinical rankings by retinal specialists (rs = 0.77). The IRA was positively correlated with AREDS score (rs = 0.73) and could statistically distinguish AREDS grades 3 and 4 ($P < .001$). Serial imaging demonstrated the utility of the method for identifying clinically meaningful disease progression.

CONCLUSIONS AND RELEVANCE: The IRA method applied to FAF digital files can quantify AMD disease severity and may be helpful in identifying AMD progression.

PMID: 23787960 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2013 Jun 13. pii: S0002-9394(13)00312-7. doi: 10.1016/j.ajo.2013.04.036. [Epub ahead of print]

Differential Sensitivity of Choroidal Endothelial, Retinal Ganglion, and Retinal Pigment Epithelial Cells In Vitro to Proton Radiation.

Balaiya S, Murthy RK, Malyapa R, Grover S, Chalam KV.

Department of Ophthalmology, University of Florida College of Medicine, Jacksonville, Florida.

PURPOSE: To evaluate the differential sensitivity of choroidal endothelial, retinal pigment epithelial, and retinal ganglion cells to escalating doses of proton beam radiation and to establish a safe dose range for the management of choroidal neovascularization associated with age-related macular degeneration (AMD).

DESIGN: Laboratory investigation.

METHODS: Proliferating simian choroidal endothelial cells (RF/6A), differentiated rat retinal ganglion cells (RGC-5), and serum-starved human retinal pigment epithelial cells (ARPE-19) were exposed to 2, 4, 8, and 12 cobalt gray equivalent of proton beam radiation and cell viability was quantified on day 9. Reactive oxygen species levels were analyzed.

RESULTS: Significant decline of choroidal endothelial cell viability was noted as dose escalated from 4 to 8 cobalt gray equivalent with maximum effect observed at 12 cobalt gray equivalent. RGC-5 and ARPE-19 cell count decreased to 95% and 62.7% at 8 cobalt gray equivalent, respectively. Sub-analysis between 4 and 8 cobalt gray equivalent radiation revealed significant decrease in choroidal endothelial cell viability (43.1% at 7 cobalt gray equivalent and 32.3% at 8 cobalt gray equivalent of radiation). Correspondingly, RGC-5 and ARPE-19 cells did not show decrease in cell count or viability. Reactive oxygen species levels significantly increased in radiation-treated choroidal endothelial cells (8.3%-11.9%).

CONCLUSIONS: At 6-8 cobalt gray equivalent proton beam radiation, retinal ganglion and retinal pigment epithelial cells are preserved while choroidal endothelial cells are completely inhibited. This dosage offers optimum therapeutic safety window for treatment using proton beam radiation for exudative AMD.

PMID: 23769193 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2013 Jun;48(3):199-203. doi: 10.1016/j.jcjo.2013.01.010.

Impact of colour in the assessment of potential visual acuity in patients with age-related macular degeneration.

Dorrepaal SJ, Markowitz SN.

Department of Ophthalmology, Queen's University, Hotel Dieu Hospital, Kingston. Electronic address: 11sjd1@queensu.ca.

OBJECTIVE: To compare chromatic and achromatic potential visual acuity (PVA) in patients with bilateral low vision caused by age-related macular degeneration (AMD).

DESIGN: Prospective, nonrandomized, observational case series.

PARTICIPANTS: Fifty-five patients, representing a consecutive series of patients all presenting with bilateral AMD.

METHODS: Best-corrected visual acuity of each eye was measured using an Early Treatment in Diabetic Retinopathy Study (ETDRS) chart with appropriate near correction. Included were cases with visual acuity of 0.4 logMAR (20/50) or worse in both eyes. Achromatic and chromatic PVA were measured in each eye using white on black and red on yellow flooding E charts at 50 cm in controlled lighting conditions.

RESULTS: One hundred and seven eyes from 55 patients were included in the analysis. Mean achromatic and chromatic PVA were 0.69±0.26 and 0.65±0.22 logMAR, respectively. Overall, patients had a significantly higher chromatic than achromatic PVA, with a median difference of 0.1 logMAR ($p<0.05$). Patients with ETDRS visual acuity worse than 0.9 logMAR also had a significantly higher chromatic than achromatic PVA, with a median difference of 0.1 logMAR ($p<0.05$). Patients with ETDRS visual acuity between 0.4 and 0.9 logMAR had a trend toward a higher chromatic than achromatic visual acuity that was not significant, with a median difference of 0.1 logMAR ($p = 0.8539$).

CONCLUSIONS: Patients with low vision caused by AMD can discern smaller targets when a red on yellow colour scheme is used than when using achromatic white on black charts.

PMID: 23769782 [PubMed - in process]

Ophthalmologe. 2013 Jun;110(6):555-67. doi: 10.1007/s00347-012-2757-y.

[Atrophic age-related macular degeneration].[Article in German]

von Strachwitz CN.

AugenCentrum Südwest, Hauptstr. 4, 70563, Stuttgart, Deutschland, strachwitz@augencentrum-suedwest.de.

Abstract: Atrophic age-related macular degeneration (AMD) is a degenerative disorder of the central retina that greatly increases with age. This complex disease is mainly based on a genetic background but environmental factors are most likely responsible for modulating the individual course of the disorder. Various mechanisms are thought to underlie this chronic disorder. Besides defective inflammatory control pathways, increased susceptibility to oxidative stress and defective clearing mechanisms of waste products, primary atrophy of photoreceptors and choroidal capillaries may also lead to the typical clinical signs and symptoms of AMD. Therapeutic approaches therefore aim at modulation of the different disease pathways which probably differ from individual to individual. In the future customized therapeutic strategies are expected to be of great value to slow down disease progression or even prevent outbreak of the disorder.

PMID: 23783997 [PubMed - in process]

Acta Ophthalmol. 2013 Jun 20. doi: 10.1111/aos.12214. [Epub ahead of print]

Polypoidal Choroidal Vasculopathy in patients diagnosed with age-related macular degeneration.

Tan CS, Lim LW, Ngo WK, Lim TH.

National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore Fundus Image Reading Center, National Healthcare Group Eye Institute, Singapore.

PMID: 23782725 [PubMed - as supplied by publisher]

Philos Trans A Math Phys Eng Sci. 2013 Jun 17;371(1995):20120371. doi: 10.1098/rsta.2012.0371. Print 2013.

Photodynamic therapy for photochemists.

Bown SG.

National Medical Laser Centre, University College London, , London, UK.

Abstract: Photodynamic therapy (PDT) is an evolving technique for localized control of diseased tissue with light after prior administration of a photosensitizing agent and in the presence of oxygen. The biological effect is quite different from surgery, radiotherapy and chemotherapy. With no temperature change during treatment, connective tissues like collagen are largely unaffected, so maintaining the mechanical integrity of hollow organs. PDT is of particular value for pre-cancer and early cancers of the skin (not melanomas) and mouth as the cosmetic and functional results are so good. Another key indication is for small areas of cancer that are unsuitable for or have persisted or recurred after conventional management. It can be applied in areas already exposed to the maximum safe dose of radiotherapy. Outside cancer, in ophthalmology, it is established for age-related macular degeneration, and has considerable potential in arterial disease for preventing restenosis after balloon angioplasty and in the treatment of infectious diseases, where the responsible organisms are accessible to both the photosensitizer and light. New developments on the horizon include techniques for increasing the selectivity for cancers, such as coupling photosensitizers to antibodies, and for stimulating immunological responses, but many further pre-clinical

and clinical studies are needed to establish PDT's role in routine clinical practice.

PMID: 23776302 [PubMed - in process]

Nihon Ganka Gakkai Zasshi. 2013 Apr;117(4):329-34.

[Background factors of recurrence after remission maintenance with photodynamic therapy for age-related macular degeneration]. [Article in Japanese]

Umeda N, Hokao K, Oyamada T, Hayashi H, Uchio E.

Department of Ophthalmology, School of Medicine, Fukuoka University, 7 45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan. numeda1@fukuoka-u.ac.jp

PURPOSE: To investigate the factors associated with recurrence following remission of at least 12 months after photodynamic therapy in patients with age-related macular degeneration (AMD).

SUBJECTS AND METHODS: We analyzed 42 eyes with AMD in 41 patients who did not require additional treatment within 12 months of their photodynamic therapy (PDT). Additional treatment for recurrence beyond 12 months after the last PDT was required in 20 eyes in the recurrent group (n = 20). The remaining eyes (controls; n = 22) showed no recurrence during this period. We statistically analyzed the factors associated with recurrence by comparing the findings of the 2 groups.

RESULTS: Compared to the controls, the recurrent group showed significantly improved baseline visual acuity (VA) (p = 0.005), but required significantly more PDT applications to achieve remission (p = 0.010). Age (p = 0.026), multiple PDT sessions (p = 0.001), and high baseline VA (p = 0.003) were factors significantly related to the recurrence following remission maintenance with PDT for AMD (R = 0.63; R2 = 0.39; p < 0.0001).

CONCLUSIONS: Age, preoperative VA and number of PDT sessions were associated with a significant risk of recurrence after remission maintenance with PDT.

PMID: 23767188 [PubMed - in process]

Pathogenesis

J Res Health Sci. 2013 May 29;13(1):98-101.

Correlation between Serum Lipids and Age-related Macular Degeneration: A Case-Control Study.

Davari MH, Gheitasi H, Yaghobi G, Heydari B.

Birjand Atherosclerosis and Coronary Artery Research Centre, Department of Ophthalmology, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran. mhd_1337@yahoo.com.

BACKGROUND: Age-related macular degeneration (AMD) is one of the leading causes of visual loss among people aged 65 yr and older. The pathophysiology of AMD is poorly understood. The purpose of this study was to evaluate the relationship between serum lipid concentrations and age-related macular degeneration.

METHODS: In this case-control study, total cholesterol (TCH), low density lipoprotein (LDL), high density lipoprotein (HDL) and triglyceride (TG) of 32 patients with AMD were compared with 32 subjects without AMD that were matched for age. Data were analyzed using Independent t and Chi-Square Tests.

RESULTS: TCH, LDL, and TG serum concentrations were significantly higher in AMD patients compared with control group (P<0.001, P<0.001 and P<0.017 respectively). There was no difference in HDL

concentration between two groups (P=0.781).

CONCLUSION: High level of total cholesterol, TG and LDL were associated with increased risk of AMD. Results of this study suggest further research to better understand the underlying biological mechanisms of AMD related to serum cholesterol.

PMID: 23772022 [PubMed - in process]

J Immunol. 2013 Jun 14. [Epub ahead of print]

An Engineered Construct Combining Complement Regulatory and Surface-Recognition Domains Represents a Minimal-Size Functional Factor H.

Hebecker M, Alba-Domínguez M, Roumenina LT, Reuter S, Hyvärinen S, Dragon-Durey MA, Jokiranta TS, Sánchez-Corral P, Józsi M.

Junior Research Group for Cellular Immunobiology, Leibniz Institute for Natural Product Research and Infection Biology, Hans Knöll Institute, 07745 Jena, Germany;

Abstract: Complement is an essential humoral component of innate immunity; however, its inappropriate activation leads to pathology. Polymorphisms, mutations, and autoantibodies affecting factor H (FH), a major regulator of the alternative complement pathway, are associated with various diseases, including age -related macular degeneration, atypical hemolytic uremic syndrome, and C3 glomerulopathies. Restoring FH function could be a treatment option for such pathologies. In this article, we report on an engineered FH construct that directly combines the two major functional regions of FH: the N-terminal complement regulatory domains and the C-terminal surface-recognition domains. This minimal-size FH (mini-FH) binds C3b and has complement regulatory functions similar to those of the full-length protein. In addition, we demonstrate that mini-FH binds to the FH ligands C-reactive protein, pentraxin 3, and malondialdehyde epitopes. Mini-FH was functionally active when bound to the extracellular matrix and endothelial cells in vitro, and it inhibited C3 deposition on the cells. Furthermore, mini-FH efficiently inhibited complement-mediated lysis of host-like cells caused by a disease-associated FH mutation or by anti-FH autoantibodies. Therefore, mini-FH could potentially be used as a complement inhibitor targeting host surfaces, as well as to replace compromised FH in diseases associated with FH dysfunction.

PMID: 23772024 [PubMed - as supplied by publisher]

Epidemiology

Evid Based Med. 2013 Jun 14. [Epub ahead of print]

Long-term aspirin use and neovascular age-related macular degeneration: association or causation?

Christen WG.

Division of Preventive Medicine, Brigham and Women's Hospital, , Boston, Massachusetts, USA.

PMID: 23771726 [PubMed - as supplied by publisher]

J Am Geriatr Soc. 2013 Jun;61(6):1033-4. doi: 10.1111/jgs.12284.

Guideline-adherent aspirin use in individuals with age-related macular degeneration.

Ramaswamy SG, Greenberg PB, Krzystolik MG.

Section of Ophthalmology, Veterans Affairs Medical Center, Providence, Rhode Island; Division of Ophthalmology, Warren Alpert Medical School, Brown University, Providence, Rhode Island.

PMID: 23772732 [PubMed - in process]

Diet

Can J Ophthalmol. 2013 Jun;48(3):204-9. doi: 10.1016/j.jcjo.2013.01.013.

Survey of patients with age-related macular degeneration: knowledge and adherence to recommendations.

Shah SU, Pilli S, Telander DG, Morse LS, Park SS.

Vitreoretinal Service, Department of Ophthalmology and Vision Science, University of California Davis Eye Center, Sacramento, Calif.

OBJECTIVE: To evaluate the patient's understanding of the importance and adherence to the various lifestyle and Age-Related Eye Disease Study (AREDS) supplement recommendations for age-related macular degeneration (AMD).

DESIGN: Cross-sectional study.

PARTICIPANTS: Patients with AMD treated at the vitreoretinal service clinic.

METHODS: Telephone questionnaire survey was administered to assess knowledge and adherence to various recommendations made to patients with AMD about lifestyle and AREDS supplements in this single -institution study.

RESULTS: Among 92 patients with AMD contacted, dietary modification, exercise and weight reduction, smoking cessation, and AREDS supplementation recommendations were recalled by 47 (51%), 21 (23%), 5 (5%), and 90 (98%) patients, respectively. The necessity of making these interventions was believed by 29 (62%), 16 (76%), 4 (80%), and 67 (74%) patients, respectively. Patient adherence to dietary modification was 81%, to exercise and weight reduction was 76%, to smoking cessation was 0%, and to AREDS supplementation was 88% (71% on correct dose). Financially, 29% of the patients noted a mean increase of $88 per month in expenditure because of making dietary modifications, but most reported such as justified; 61% noted a mean increase of $25 per month in expenditure from consumption of AREDS supplements, and most (96%) believed this was justified.

CONCLUSIONS: Patients with AMD recalled recommendations for AREDS supplementation more often than other lifestyle changes but generally felt recommendations were necessary and affordable. Adherence to smoking cessation recommendation was poor (0%), but to other recommendations was good.

PMID: 23769783 [PubMed - in process]

J Agric Food Chem. 2013 Jun 17. [Epub ahead of print]

Increase in β-ionone, a carotenoid-derived volatile in zeaxanthin-biofortified sweet-corn.

Gallon C, Fuller S, Fanning K, Smyth HE, Pun S, Martin I, O'Hare T.

Abstract: Carotenoids are responsible for the yellow color of sweet-corn (Zea mays var. saccharata), but are also potentially the source of flavor compounds from the cleavage of carotenoid molecules. The carotenoid-derived volatile, β-ionone was identified in both standard yellow sweet-corn ('Hybrix5') and a zeaxanthin-enhanced experimental variety ('HZ') designed for sufferers of macular degeneration. As β-

ionone is highly-perceivable at extremely low concentration by humans, it was important to confirm if alterations in carotenoid profile may also affect flavor volatiles. The concentration of β-ionone was most strongly correlated (r2 > 0.94) with the β-arm carotenoids, β-carotene, β-cryptoxanthin and zeaxanthin, and to a lesser degree (r2 = 0.90) with the α-arm carotenoid, zeinoxanthin. No correlation existed with either lutein (r2 = 0.06) or antheraxanthin (r2 = 0.10). Delaying harvest of cobs resulted in a significant increase of both carotenoid and β-ionone concentrations, producing a six-fold increase of β-ionone in 'HZ', and a two-fold increase in 'Hybrix5', reaching a maximum of 62 µg/kg FW and 24 µg/kg FW, respectively.

PMID: 23767984 [PubMed - as supplied by publisher]