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MD Research News

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Drug treatment

Retina. 2015 Jul 10. [Epub ahead of print]

CONVERSION TO AFLIBERCEPT THERAPY VERSUS CONTINUING WITH RANIBIZUMAB THERAPY FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION DEPENDENT ON MONTHLY RANIBIZUMAB TREATMENT.

Mantel I, Gianniou C, Dirani A.

PURPOSE: To compare the effects of converting to aflibercept therapy with continuing ranibizumab therapy in eyes with neovascular age-related macular degeneration requiring monthly ranibizumab treatment.

METHODS: Patients were selected from the 104 patients (115 eyes) already enrolled in an "Observe and Plan" prospective case series that included treating neovascular age-related macular degeneration with ranibizumab for 24 months. Patients who still needed monthly retreatment at the end of a 2-year study were randomized to either continue ranibizumab therapy or to convert to aflibercept therapy. Outcome measures included average interval between treatments, resolution of exudative signs, number of retreatments, and change in visual acuity over 12 months (the third treatment year).

RESULTS: Nineteen patients (21 eyes) met the inclusion criteria. Ten eyes were randomized to receive aflibercept, and 11 eyes remained on ranibizumab. Groups were balanced for baseline characteristics. Outcomes were similar in the 2 groups over a 12-month study duration, with no statistical difference.

CONCLUSION: This comparative pilot study suggests that neovascular age-related macular degeneration requiring monthly retreatment with ranibizumab may respond in similar ways to both ranibizumab and aflibercept treatment. Larger sample sizes would be needed to confirm this observation.

PMID: 26166797 [PubMed - as supplied by publisher]

Expert Opin Pharmacother. 2015 Jul 13:1-13. [Epub ahead of print]

Advances in pharmacotherapy for wet age-related macular degeneration.

Santarelli M, Diplotti L, Samassa F, Veritti D, Kuppermann BD, Lanzetta P.

INTRODUCTION: In developed countries, neovascular age-related macular degeneration (AMD) is the leading cause of irreversible central blindness. Although AMD pathogenesis is complex and still not fully understood, many involved mechanisms are already partially known and could be promising targets for future therapies. Currently, anti-VEGF drugs are the standard care of this condition.

Areas covered: This review summarizes both the current available and the emerging pharmacological therapies for the management of neovascular AMD. At first, we briefly focused on anti-VEGF compounds

that are commonly used. Then, we reviewed the mechanisms of action and potential advantages of new candidate drugs that are being evaluated in clinical trials.

Expert opinion: Although anti-VEGF drugs have shown mild-term good efficacy and safety profile in the treatment of neovascular AMD, they are far away from being a perfect therapy. Pharmacological research should focus on finding new molecular targets in the AMD pathogenetical pathway and on developing longer lasting agents or new drug delivery systems. Besides the development of new drugs, a better characterization of patients is also needed, taking into account variables such as choroidal neovascularization subtypes and genetic factors, in order to identify a tailored treatment for each patient.

PMID: 26165696 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2015 Jul 17. [Epub ahead of print]

Prognostic significance of foveal capillary drop-out and previous panretinal photocoagulation for diabetic macular oedema treated with ranibizumab.

Ebneter A, Wolf S, Zinkernagel MS.

AIMS: To investigate the prognostic significance of macular capillary drop-out and previous panretinal laser photocoagulation in diabetic macular oedema treated with intravitreal ranibizumab.

METHODS: Retrospective observational case series. Treatment-naive patients with diabetic macular oedema that had been treated with intravitreal ranibizumab as per the RESTORE study protocol for at least 12 months were included. Some patients (n=15) had previous panretinal laser photocoagulation. Best-corrected visual acuity and central retina thickness were recorded monthly. The foveal avascular zone and the perifoveal capillaries were quantitatively and qualitatively assessed on fluorescein angiography on two occasions during the observational period.

RESULTS: From the 46 eyes (46 patients) in this study, 13 (28%) had evidence of perifoveal capillary drop-out. Central retinal thickness was significantly thinner at baseline (p=0.02) and throughout the study period in these eyes compared with those with normal perifoveal capillaries. Both groups responded with a significant gain of best-corrected visual acuity to ranibizumab treatment (7.6±3.3 and 6.3±1.3 ETDRS letters, respectively). Eyes with previous panretinal laser photocoagulation displayed a comparable final outcome regarding function and morphology, requiring a similar intensity of intravitreal injections.

CONCLUSIONS: Perifoveal capillary drop-out did not limit the gain of visual acuity from intravitreal ranibizumab treatment. The reduction of central retina thickness was similar to that seen in eyes with normal perifoveal capillaries. Central retinal thickness in eyes with perifoveal capillary drop-out was generally reduced. However, this did not affect their benefit from treatment. Ranibizumab did not increase the amount of perifoveal capillary loss.

PMID: 26187951 [PubMed - as supplied by publisher]

Biomed Rep. 2015 Jul;3(4):503-508. Epub 2015 Apr 16.

Predictors of visual and anatomical outcomes for neovascular age-related macular degeneration treated with bevacizumab.

Ma C, Bai L, Lei C, Wu C, Shi Q, Hu F, Hao Z, Ma LE.

Abstract: The present study aimed to evaluate the predictive factors for visual and anatomical outcomes in neovascular age-related macular degeneration (AMD) patients treated with intravitreal bevacizumab (IVB). A total of 113 patients with neovascular AMD received IVB treatment. The best corrected visual acuity (BCVA), central retinal thickness (CRT) and total macular volume (TMV) were assessed before the injection, and at 1, 2, 3 and 9 months after surgery. Changes in BCVA and these optical coherence

tomography (OCT) outcomes from baseline were compared, and independent predictors were evaluated by logistic regression models. During the treatment, logarithm of the minimum angle of resolution (logMAR) significantly decreased from 1.12 to 0.83, and reductions in OCT parameters were earlier and larger. Baseline BCVA was associated with the changes in BCVA and CRT, whereas baseline OCT features significantly affected their own changes. Larger baseline logMAR and OCT features were more likely to experience a greater proportion of ≥50 μm reduction in CRT (P<0.05). The BCVA decreases were positively associated with the reductions in CRT (r=0.34, P<0.01) and TMV (r=0.41, P<0.01). Among patients with neovascular AMD, IVB resulted in earlier significant decreases in TMV and CRT, suggesting that these OCT anatomical outcomes may be considered as more sensitive responders to evaluate the treatment effects of bevacizumab.

PMID: 26171156 [PubMed] PMCID: PMC4486809

Biomed Res Int. 2015;2015:268796. Epub 2015 Jun 8.

Ganglion Cell Complex Evaluation in Exudative Age-Related Macular Degeneration after Repeated Intravitreal Injections of Ranibizumab.

Perdicchi A, Peluso G, Iacovello D, Balestrieri M, Delle Fave M, Abdolrahimzadeh S, Scuderi GL, Fenicia V, Recupero SM.

Purpose: To detect the effects of intravitreal ranibizumab injections on GCC in patients with wet AMD.

Methods: 32 wet AMD eyes were selected and submitted at three ranibizumab injections. RTVue-OCT GCC and MM5 protocol were performed before treatment and twenty days after each injection.

Results: At baseline mean GCC thickness was 93.9 ± 18.5 μm. Twenty days after each intravitreal injection it was, respectively, 85.8 ± 10.1, 86.5 ± 9.3, and 91.1 ± 11.5 μm, without statistical significance. A significant improvement in visual acuity (P = 0.031) and a reduction of mean foveal (P = 0.001) and macular thickness (P = 0.001) were observed.

Conclusion: The clinical results confirm therapeutic efficacy of intravitreal injections of ranibizumab in wet AMD. A contemporary not statistically significant reduction of GCC thickness suggests that the loading phase of ranibizumab does not have any toxic effects on ganglion cell complex.

PMID: 26167478 [PubMed - in process] PMCID: PMC4475747

Other treatment & diagnosis

Eur J Ophthalmol. 2015 Jul 8:0. [Epub ahead of print]

Visual acuity at presentation in the second eye versus first eye in patients with exudative age-related macular degeneration.

Chevreaud O, Semoun O, Blanco-Garavito R, Kamami-Levy C, Merle B, Jung C, Querques G, Souied EH.

PURPOSE: To assess the difference in best-corrected visual acuity (BCVA) at presentation between the first and second eye in patients with bilateral neovascular age-related macular degeneration (AMD).

METHODS: We reviewed the charts of all patients who had a clinical examination for neovascular AMD at the University Eye Clinic of Creteil in January 2013. We retrospectively analyzed demographic and clinical data for 264 patients.

RESULTS: In the fellow eye, choroidal neovascularization (CNV) developed in 75/264 patients (28.4%) with a time interval between the 2 events of 30.3 months (range 6-145). Data were available on 65 patients: 14/65 (21.5%) were asymptomatic, 24/65 (36.9%) had BCVA >20/40, whereas at the time of CNV

diagnosis in the first eye, no patient was asymptomatic (p<0.0001), and 11/65 (16.9%) eyes had BCVA >20/40 (p<0.0001). The mean BCVA of the first affected eye was 0.68 (±0.41) logarithm of minimum angle of resolution (logMAR) and the mean BCVA for the second eye was 0.36 (±0.29) logMAR (p<0.0001).

CONCLUSIONS: The BCVA at the time of diagnosis of CNV was higher in the second eye than in the first affected eye. This was possibly due to several factors including systematic bilateral examination in follow-up of unilateral exudative AMD that allowed detection of 20% of cases.

PMID: 26165330 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2015 Jul 8. [Epub ahead of print]

Optical Coherence Tomography Angiography of Type 1 Neovascularization in Age-Related Macular Degeneration.

Kuehlewein L, Bansal M, Lenis TL, Iafe NA, Sadda SR, Bonini Filho MA, De Carlo TE, Waheed NK, Duker JS, Sarraf D.

PURPOSE: To analyze type 1 neovascular membranes in age-related macular degeneration (AMD) using optical coherence tomography (OCT) angiography, to correlate morphological characteristics with imaging and clinical criteria, and to analyze structural features of type 1 neovascularization sequentially after anti-vascular endothelial growth factor (VEGF) therapy.

DESIGN: Prospective interventional case series.

METHODS: Macular OCT angiography images were acquired using the RTVue XR Avanti with AngioVue. Distinct morphological patterns and quantifiable features of the neovascular membranes were studied on en face projection images at baseline and follow-up.

RESULTS: Thirty-three eyes of 25 patients were included. In 75% of the eyes, a highly organized vascular complex could be identified. A large main central vessel trunk/feeder vessel could be seen in 72% of these eyes, with vessels radiating in a branching pattern either in all directions from the center of the lesion ('medusa' pattern), or from one side of the lesion ('seafan' pattern). Of the 18 eyes with follow-up OCT angiography, the lesion area and vessel density remained unchanged, even after anti-VEGF therapy, indicating a more mature longstanding neovascular complex resistant to anti-VEGF therapy.

CONCLUSIONS: OCT angiography provides a unique opportunity to study the morphology of occult type 1 neovascular membranes in AMD and allows precise structural and vascular assessment noninvasively. We identified a large mature neovascular complex in approximately 75%, typically consisting of a feeder vessel and large branching vessels resistant to anti-VEGF therapy. OCT angiography may better guide evaluation and treatment of neovascular AMD, and may contribute to the development of improved therapies.

PMID: 26164826 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 Jul 1;56(8):4267-74.

Foveal Sparing of Reticular Drusen in Eyes With Early and Intermediate Age-Related Macular Degeneration.

Steinberg JS, Fleckenstein M, Holz FG, Schmitz-Valckenberg S.

PURPOSE: To analyze the central distribution of reticular drusen (RDR) in eyes with early and intermediate AMD without soft drusen or pigmentary changes within the central subfield using confocal scanning laser ophthalmoscopy (cSLO) and spectral-domain optical coherence tomography (SD-OCT).

METHODS: Fifty-two eyes of 46 subjects (median age: 76.3 years, interquartile range [IQR], 71-80) were

examined by simultaneous combined near-infrared cSLO and raster SD-OCT imaging. The appearance and the topographic distribution of RDR were analyzed within the macula area using the Early Treatment Diabetic Retinopathy Study grid. In addition, longitudinal examinations during an observation period of at least 6 months were included (median observation time: 1.5 years, IQR, 0.9-2.8).

RESULTS: The RDR involvement within the central subfield (46%) was less compared with the surrounding subfields (62%-100%), slices (67%-100%), and zones (94%-100%) ($P < 0.001$). RDR were typically distributed as one continuous zone around the fovea in an incomplete or complete ring-shaped pattern, whereas the fovea itself was either spared or only a few lesions were present. Over time, the RDR density increased and new RDR lesions occurred at the border of the RDR zone toward a closure of the ring-shaped pattern. Within the fovea, development of RDR was observed in 8 of 28 eyes.

CONCLUSIONS: The fovea appears to be less vulnerable to RDR development as compared with peripheral macula areas. Factors for initial sparing of the foveal retina are yet unknown but may relate to topographic differences of choroidal blood flow and/or photoreceptor distribution.

PMID: 26161988 [PubMed - in process]

Transl Vis Sci Technol. 2015 Jun 30;4(3):13. eCollection 2015.

Measurement of Retinal Sensitivity on Tablet Devices in Age-Related Macular Degeneration.

Wu Z, Guymer RH, Jung CJ, Goh JK, Ayton LN, Luu CD, Lawson DJ, Turpin A, McKendrick AM.

PURPOSE: We compared measurements of central retinal sensitivity on a portable, low-cost tablet device to the established method of microperimetry in age-related macular degeneration (AMD).

METHODS: A customized test designed to measure central retinal sensitivity (within the central 1° radius) on a tablet device was developed using an open-source platform called PsyPad. A total of 30 participants with AMD were included in this study, and all participants performed a practice test on PsyPad, followed by four tests of one eye and one test of the other eye. Participants then underwent standardized microperimetry examinations in both eyes.

RESULTS: The average test duration on PsyPad was 53.9 ± 7.5 seconds, and no significant learning effect was observed over the examinations performed ($P = 1.000$). The coefficient of repeatability of central retinal sensitivity between the first two examinations on PsyPad was ±1.76 dB. The mean central retinal sensitivity was not significantly different between PsyPad (25.7 ± 0.4 dB) and microperimetry (26.1 ± 0.4 dB, $P = 0.094$), and the 95% limits of agreement between the two measures were between -4.12 and 4.92 dB.

CONCLUSIONS: The measurements of central retinal sensitivity can be performed effectively using a tablet device, displaying reasonably good agreement with those obtained using the established method of microperimetry.

TRANSLATIONAL RELEVANCE: These findings highlight the potential of tablet devices as low-cost and portable tools for developing and performing visual function measures that can be easily and widely implemented.

PMID: 26175959 [PubMed] PMCID: PMC4497484

Cytokine Growth Factor Rev. 2015 Jul 3. [Epub ahead of print]

Ciliary neurotrophic factor (CNTF): New facets of an old molecule for treating neurodegenerative and metabolic syndrome pathologies.

Pasquin S, Sharma M, Gauchat JF.

Abstract: Ciliary neurotrophic factor (CNTF) is the most extensively studied member of the cytokine family that signal through intracellular chains of the gp130/LIFRβ receptor. The severe phenotype in patients suffering from mutations inactivating LIFRβ indicates that members of this cytokine family play key, non-redundant roles during development. Accordingly, three decades of research has revealed potent and promising trophic and regulatory activities of CNTF in neurons, oligodendrocytes, muscle cells, bone cells, adipocytes and retinal cells. These findings led to clinical trials to test the therapeutic potential of CNTF and CNTF derivatives for treating neurodegenerative and metabolic diseases. Promising results have encouraged continuation of studies for treating retinal degenerative diseases. Results of some clinical trials showed that side-effects may limit the systemically administrated doses of CNTF. Therefore, therapies being currently tested rely on local delivery of CNTF using encapsulated cytokine-secreting implants. Since the side effects of CNTF might be linked to its ability to activate the alternative IL6Rα-LIFRβ-gp130 receptor, CNTFR-specific mutants of CNTF have been developed that bind to the CNTFRα-LIFRβ-gp130 receptor. These developments may prove to be a breakthrough for therapeutic applications of systemically administered CNTF in pathologies such as multiple sclerosis or Alzheimer's disease. The "designer cytokine approach" offers future opportunities to further enhance specificity by conjugating mutant CNTF with modified soluble CNTFRα to target therapeutically relevant cells that express gp130-LIFRβ and a specific cell surface marker.

PMID: 26187860 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2015 Jul 16. [Epub ahead of print]

Polarisation-sensitive OCT is useful for evaluating retinal pigment epithelial lesions in patients with neovascular AMD.

Schütze C, Teleky K, Baumann B, Pircher M, Götzinger E, Hitzenberger CK, Schmidt-Erfurth U.

BACKGROUND/AIMS: To examine the reproducibility of lesion dimensions of the retinal pigment epithelium (RPE) in neovascular age-related macular degeneration (AMD) with polarisation-sensitive optical coherence tomography (PS-OCT), specifically imaging the RPE.

METHODS: Twenty-six patients (28 eyes) with neovascular AMD were included in this study, and examined by a PS-OCT prototype. Each patient was scanned five times at a 1-day visit. The PS-OCT B-scan located closest to the macular centre presenting with RPE atrophy was identified, and the longitudinal diameter of the lesion was quantified manually using AutoCAD 2008. This procedure was followed for the identical B-scan position in all five scans per eye and patient. Reproducibility of qualitative changes in PS-OCT was evaluated. Interobserver variability was assessed. Results were compared with intensity-based spectral-domain OCT (SD-OCT) imaging.

RESULTS: Mean variability of all atrophy lesion dimensions was 0.10 mm (SD±=0.06 mm). Coefficient of variation (SD±/mean) was 0.06 on average (SD±=0.03). Interobserver variability assessment showed a mean difference of 0.02 mm across all patients regarding RPE lesion size evaluation (paired t test: p=0.38). Spearman correlation coefficient was r=0.98, p<0.001. Results revealed a good overall reproducibility of ~90%. PS-OCT specifically detected the RPE in all eyes compared with conventional intensity-based SD-OCT that was not capable to clearly identify RPE atrophy in 25 eyes (89.3%, p<0.01).

CONCLUSIONS: PS-OCT offers good reproducibility of RPE atrophy assessment in neovascular AMD, and may be suitable for precise RPE evaluation in clinical practice. PS-OCT unambiguously identifies RPE changes in choroidal neovascularisation compared with intensity-based SD-OCT that does not identify the RPE status reliably.

PMID: 26183936 [PubMed - as supplied by publisher]

Expert Opin Drug Deliv. 2015 Jul 14:1-16. [Epub ahead of print]

Efficacy and vitreous levels of topical NSAIDs.

Semeraro F, Russo A, Gambicorti E, Duse S, Morescalchi F, Vezzoli S, Costagliola C.

INTRODUCTION: Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed medications and are routinely used for their analgesic, antipyretic, and anti-inflammatory properties. Because of their potent cyclooxygenase-inhibitory activity, they can inhibit pro-inflammatory prostaglandin synthesis, leading to complex inflammatory cascades. NSAIDs have been broadly used systemically for many decades and have recently become commercially available in the form of topical ophthalmic formulations. NSAIDs are weak acids with pKa values mostly between 3.5 and 4.5 and are poorly water-soluble. New, aqueous ophthalmic solutions of NSAIDs that afford better tissue penetration have recently been developed. In ophthalmological practice, topical NSAIDs are mostly used to stabilize pupillary dilation during intraocular surgery, manage postoperative pain and inflammation, and treat pseudophakic cystoid macular edema.

Areas covered: This review focuses on the vitreous penetration of topical NSAIDs and their potential clinical applications in the treatment of retinal diseases.

Expert opinion: A growing body of evidence suggests that NSAIDs may be beneficial in the treatment of age-related macular degeneration, diabetic retinopathy, and ocular tumors. Recent studies from our group and other authors have shown that the vitreous levels of NSAID exceed the median inhibitory concentration, which can significantly decrease vitreous PGE2 levels.

PMID: 26173446 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2015 Jun 1;46(6):604-5.

Letter to the Editor: Outer Retinal Tubulations and Age-Related Macular Degeneration.

Chin EK, Almeida DR, Grant LW, Niles PI, Folk JC.

PMID: 26172060 [PubMed - in process]

Sci China Life Sci. 2015 Jul 17. [Epub ahead of print]

Macular auto-fluorescence is a follow-up parameter for cystoid macular edema.

Zhang X, Gong X, Wang Y, Wang N.

Abstract: This study aimed to evaluate if macular autofluorescence (MAF) is a valuable, non-invasive follow-up parameter for cystoid macular edema. A total of 71 eyes (71 cases) with cystoid macular edema (CME) were included in the study. Macular pigment (MP) was evaluated using HRA2 (infrared) IF and FA models. The density of MP was graded into three categories: without, partial, and normal amount of MP. A comparison was made between the baseline (before the first administration) level and at the fourth month, following three consecutive intravitreal lucentis injections every month. The morphology and distribution of MAF, and the density and distribution of MP were regarded as the main outcome measures. At the baseline visit, all eyes with CME had petaloid/irregular-shaped MAF in the macular area (100%). No MAF was detected in the control eyes (0). There was significant difference in MAF between the CME and normal groups (P=0.000). At the fourth monthly visit, normal levels of MP density without MAF was detected in 68 eyes (95.8%) with the best corrected spectacular visual acuity increasing to at least 1 line accordingly. We conclude that macular MAF can be used as a follow-up parameter for patients with CME. MP and MAF can indirectly reflect the fovea cone function.

PMID: 26187408 [PubMed - as supplied by publisher]

Lancet. 2015 Jul 4;386(9988):30.

Stem cells in age-related macular degeneration and Stargardt's macular dystrophy - Authors' reply.

Schwartz SD, Anglade E, Lanza R; Ocata Macular Disease Investigator Group.

Comment on: Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. [Lancet. 2015]

PMID: 26169867 [PubMed - indexed for MEDLINE]

Lancet. 2015 Jul 4;386(9988):29.

Stem cells in age-related macular degeneration and Stargardt's macular dystrophy.

Sunness JS.

Comment in: Stem cells in age-related macular degeneration and Stargardt's macular dystrophy - Authors' reply. [Lancet. 2015]

PMID: 26169864 [PubMed - indexed for MEDLINE]

Lancet. 2015 Jul 4;386(9988):29-30.

Stem cells in age-related macular degeneration and Stargardt's macular dystrophy.

Zhang GY, Liao T, Fu XB, Li QF.

Comment in: Stem cells in age-related macular degeneration and Stargardt's macular dystrophy - Authors' reply. [Lancet. 2015]

PMID: 26169863 [PubMed - indexed for MEDLINE]

Pathogenesis

J Med Chem. 2015 Jul 16. [Epub ahead of print]

Bicyclic [3.3.0]-Octahydrocyclopenta[c]pyrrolo Antagonists of Retinol Binding Protein 4: Potential Treatment of Atrophic Age-Related Macular Degeneration and Stargardt Disease.

Cioffi CL, Racz B, Freeman EE, Conlon MP, Chen P, Stafford DG, Schwarz DM, Zhu L, Kitchen DB, Barnes KD, Dobri N, Michelotti E, Cywin CL, Martin WH, Pearson PG, Johnson G, Petrukhin K.

Abstract: Antagonists of retinol-binding protein 4 (RBP4) impede ocular uptake of serum all-trans retinol (1) and have been shown to reduce cytotoxic bisretinoid formation in the retinal pigment epithelium (RPE), which is associated with the pathogenesis of both dry AMD and Stargardt disease. Thus, these agents show promise as a potential pharmacotherapy by which to stem further neurodegeneration and concomitant vision loss associated with geographic atrophy of the macula. We previously disclosed the discovery of a novel series of non-retinoid RBP4 antagonists, represented by bicyclic [3.3.0]-octahydrocyclopenta[c]pyrrolo analogue 4. We describe herein utilization of a pyrimidine-4-carboxylic acid fragment as a suitable isostere for the anthranilic acid appendage of 4, which led to the discovery of standout antagonist 33. Analogue 33 possesses exquisite in vitro RBP4 binding affinity and favorable drug-like characteristics and was found to reduce circulating plasma RBP4 levels in vivo in a robust manner (>90%).

PMID: 26181715 [PubMed - as supplied by publisher]

PLoS One. 2015 Jul 15;10(7):e0132800.

Systemic and Ocular Long Pentraxin 3 in Patients with Age-Related Macular Degeneration.

Juel HB, Faber C, Munthe-Fog L, Bastrup-Birk S, Reese-Petersen AL, Falk MK, Singh A, Sørensen TL, Garred P, Nissen MH.

Abstract: Age-related macular degeneration (AMD) has been associated with both systemic and ocular alterations of the immune system. In particular dysfunction of complement factor H (CFH), a soluble regulator of the alternative pathway of the complement system, has been implicated in AMD pathogenesis. One of the ligands for CFH is long pentraxin 3 (PTX3), which is produced locally in the retinal pigment epithelium (RPE). To test the hypothesis that PTX3 is relevant to retinal immunohomeostasis and may be associated with AMD pathogenesis, we measured plasma PTX3 protein concentration and analyzed the RPE/choroid PTX3 gene expression in patients with AMD. To measure the ability of RPE cells to secrete PTX3 in vitro, polarized ARPE-19 cells were treated with activated T cells or cytokines (interferon (IFN)-gamma and/or tumor necrosis factor (TNF)-alpha) from the basolateral side; then PTX3 protein concentration in supernatants and PTX3 gene expression in tissue lysates were quantified. Plasma levels of PTX3 were generally low and did not significantly differ between patients and controls (P=0.307). No statistically significant difference was observed between dry and exudative AMD nor was there any correlation with hsCRP or CFH genotype. The gene expression of PTX3 increased in RPE/choroid with age (P=0.0098 macular; P=0.003 extramacular), but did not differ between aged controls and AMD patients. In vitro, ARPE-19 cells increased expression of the PTX3 gene as well PTX3 apical secretions after stimulation with TNF-alpha or activated T cells (P<0.01). These findings indicate that PTX3 expressed in the eye cannot be detected systemically and systemic PTX3 may have little or no impact on disease progression, but our findings do not exclude that locally produced PTX3 produced in the posterior segment of the eye may be part of the AMD immunopathogenesis.

PMID: 26176960 [PubMed - as supplied by publisher] PMCID: PMC4503310

Cytokine. 2015 Jul 11. pii: S1043-4666(15)30004-1. [Epub ahead of print]

SIRT1 mediated inhibition of VEGF/VEGFR2 signaling by Resveratrol and its relevance to choroidal neovascularization.

Zhang H, He S, Spee C, Ishikawa K, Hinton DR.

Abstract: SIRT1, a NAD+ -dependent histone deacetylase, has been shown to act as a key regulator of angiogenesis. The purpose of this study was to determine the effects of resveratrol (RSV, a SIRT1 activator) on the vascular endothelial growth factor receptor 2 (VEGFR2) signaling pathway and to establish its relevance to choroidal neovascularization (CNV), a blinding complication of age-related macular degeneration. Western blot and ELISA assay showed that RSV inhibited hypoxia-inducible factor (HIF)-1α accumulation and VEGF secretion induced by cobalt chloride (CoCl2) through SIRT1 in human retinal pigment epithelial (hRPE) cells. Furthermore, RSV down-regulated VEGFR2 phosphorylation and activation induced by VEGF in endothelial cells via SIRT1. Thus, the inhibitory effect of RSV on the HIF-1α/VEGF/VEGFR2 signaling axis is mediated, at least in part, through SIRT1. The results suggest that targeting SIRT1 could have therapeutic potential for the treatment of CNV.

PMID: 26174951 [PubMed - as supplied by publisher]

Mol Vis. 2015 Jul 10;21:736-48. eCollection 2015.

Basal and apical regulation of VEGF-A and placenta growth factor in the RPE/choroid and primary RPE.

Klettner A, Kaya L, Flach J, Lassen J, Treumer F, Roider J.

PURPOSE: Members of the vascular endothelial growth factor (VEGF) family are strongly involved in pathological processes in the retina, such as age-related macular degeneration and diabetic retinopathy. Cells of the retinal pigment epithelium (RPE) constitutively secrete VEGF-A, and the secretion of placental growth factor (PlGF) has also been described. RPE cells are strongly polarized cells with different secretome at the apical and basal side. In this study, we evaluated the basal and apical regulation of VEGF -A and PlGF secretion in RPE/choroid explants and primary RPE cells.

METHODS: RPE/choroid tissue explants were prepared from porcine eyes and cultivated in modified Ussing chambers, separating apical (RPE) and basal (choroid) supernatant. Primary RPE cells were also prepared from porcine eyes and cultivated on Transwell plates. Explants and cells were treated with inhibitors for VEGFR-2 (SU1498), p38 (SB203580), and the transcription factors nuclear factor-kappa B (NF-κB) and SP-1 (mithramycin), respectively. VEGF-A and PlGF content was evaluated with enzyme-linked immunosorbent assay (ELISA). In addition, western blots were performed.

RESULTS: In the RPE/choroid, VEGF-A can initially be found on the apical and basal sides with significantly more pronounced secretion on the basal side. VEGF-A secretion is differentially regulated on the apical and basal sides, with the inhibition of SP-1 and NF-κB showing strong effects apically and basally after 24 h and 48 h, the inhibition of p38 displaying its effect mainly on the basal side with some effect apically after 48 h, and the inhibition of VEGFR-2 reducing the secretion of VEGF only on the apical side at 24 h and 48 h. In the RPE cell culture, similar effects were found, with inhibition of NF-κB or SP-1 displaying a strong decrease in VEGF-A on both sides, and p38 inhibition displaying only an inhibitory effect on the basal side. In contrast, an apical effect of VEGFR-2 inhibition was not found. However, the western blot experiments exhibited a significant decrease in the VEGF-A protein under SU1498 treatment. In the RPE/choroid organ cultures, PlGF was initially found mainly on the basal site with only minute amounts of PlGF found apically. NF-κB and SP-1 were strongly involved in PlGF regulation apically and basally, while VEGFR2 and to a lesser degree p38 displayed some regulation at the basal site. In the primary RPE cell culture, PlGF was not found on the apical or basal side.

CONCLUSIONS: VEGF-A and PlGF were constitutively secreted and regulated by the RPE/choroid complex, with PlGF secreted mainly by the choroid. Although the transcription factors NF-κB and SP-1 were involved in apical and basal regulation of both growth factors, VEGFR-2 displayed a strong polarity, with regulation of apical VEGF-A and basal PlGF secretion.

PMID: 26167115 [PubMed - in process] PMCID: PMC4499472

Invest Ophthalmol Vis Sci. 2015 Jul 1;56(8):4231-8.

Nitrite Modification of Extracellular Matrix Alters CD46 Expression and VEGF Release in Human Retinal Pigment Epithelium.

Fields MA, Cai H, Bowrey HE, Moreira EF, Beck Gooz M, Kunchithapautham K, Gong J, Vought E, Del Priore LV.

PURPOSE: Loss of CD46 has recently been implicated in choroidal neovascularization in mice. Herein we investigated the effect of nitrite modification of the extracellular matrix (ECM) as an in vitro model of "aging" and its effect on CD46 expression and vascular endothelial growth factor (VEGF) release in cocultured human retinal pigment epithelium (RPE).

METHODS: ARPE-19 cells were plated onto RPE-derived ECM conditions (untreated; nitrite modified; nitrite modified followed by washing with Triton X-100; or nitrite modified followed by washing with Triton X-100 and coated with extracellular matrix ligands). Cells were cultured for 7 days and CD46 expression was analyzed by immunohistochemistry and Western blot. Additionally, CD46 short interfering RNA (siRNA) was transfected into ARPE-19 cells, and VEGF levels were determined by ELISA. Finally, in the same ECM conditions, ARPE-19 cells were challenged with normal human serum and VEGF levels determined by ELISA.

RESULTS: CD46 is expressed on the basolateral surface of ARPE-19 cells on RPE-derived ECM. Nitrite modification of ECM reduced the expression of CD46 on ARPE-19 cells by 0.5-fold (P = 0.003) and increased VEGF release in ARPE-19 cells by 1.7-fold (P < 0.001). CD46 knockdown also increased release of VEGF on the apical and basal sides of ARPE-19 cells in culture by 1.3- (P = 0.012) and 1.2-fold (P = 0.017), respectively.

CONCLUSIONS: Nitrite modification of the ECM decreased CD46 expression and increased the release of VEGF from ARPE-19 cells. Changes in CD46 expression may lead to changes in VEGF and play a pathologic role in the development of age-related macular degeneration.

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Optimization of an Image-Guided Laser-Induced Choroidal Neovascularization Model in Mice.

Gong Y, Li J, Sun Y, Fu Z, Liu CH, Evans L, Tian K, Saba N, Fredrick T, Morss P, Chen J, Smith LE.

Abstract: The mouse model of laser-induced choroidal neovascularization (CNV) has been used in studies of the exudative form of age-related macular degeneration using both the conventional slit lamp and a new image-guided laser system. A standardized protocol is needed for consistent results using this model, which has been lacking. We optimized details of laser-induced CNV using the image-guided laser photocoagulation system. Four lesions with similar size were consistently applied per eye at approximately double the disc diameter away from the optic nerve, using different laser power levels, and mice of various ages and genders. After 7 days, the mice were sacrificed and retinal pigment epithelium/choroid/sclera was flat-mounted, stained with Isolectin B4, and imaged. Quantification of the area of the laser-induced lesions was performed using an established and constant threshold. Exclusion criteria are described that were necessary for reliable data analysis of the laser-induced CNV lesions. The CNV lesion area was proportional to the laser power levels. Mice at 12-16 weeks of age developed more severe CNV than those at 6-8 weeks of age, and the gender difference was only significant in mice at 12-16 weeks of age, but not in those at 6-8 weeks of age. Dietary intake of omega-3 long-chain polyunsaturated fatty acid reduced laser -induced CNV in mice. Taken together, laser-induced CNV lesions can be easily and consistently applied using the image-guided laser platform. Mice at 6-8 weeks of age are ideal for the laser-induced CNV model.

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The association between neovascular age-related macular degeneration and regulatory T cells in peripheral blood.

Madelung CF, Falk MK, Sørensen TL.

PURPOSE: To investigate regulatory T cells (Tregs) and subsets of the Treg population in patients with neovascular age-related macular degeneration (AMD).

PATIENTS AND METHODS: Twenty-one neovascular AMD cases and 12 age-matched controls without retinal pathology were selected. Patients were recruited from our outpatient retinal clinic. Control individuals were typically spouses. The diagnosis of neovascular AMD was confirmed using fluorescein and indocyaningreen angiography. Fresh venous blood was analyzed by flow cytometry using fluorochrome-conjugated antibodies to the Treg surface antigens CD4, CD25, CD127, CD45RA, and CD31. Main outcome measures were the percentage of CD25(high)CD127(low) Tregs, the percentage of CD45RA(+) naïve Tregs, and the percentage of CD31(+) recent thymic emigrant Tregs.

RESULTS: Comparing patients with neovascular AMD to controls, no significant differences were found in the percentages of CD4(+) lymphocytes, CD25(high)CD127(low) Tregs, CD45RA(+) naïve Tregs, or CD31

(+) recent thymic emigrant Tregs.

CONCLUSION: Our data does not indicate an altered state of systemic Treg cells in neovascular AMD.

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FASEB J. 2015 Jul 17. [Epub ahead of print]

Serum levels of lipid metabolites in age-related macular degeneration.

Orban T, Johnson WM, Dong Z, Maeda T, Maeda A, Sakai T, Tsuneoka H, Mieyal JJ, Palczewski K.

Abstract: Age-related macular degeneration (AMD) is a neurodegenerative disease that causes adult-onset blindness. There are 2 forms of this progressive disease: wet and dry. Currently there is no cure for AMD, but several treatment options have started to emerge making early detection critical for therapeutic success. Analysis of the eyes of Abca4-/-Rdh8-/- mice that display light-induced retinal degeneration indicates that 11-cis-retinal and docosahexaenoic acid (DHA) levels were significantly decreased as compared with the eyes of control dark-adapted C57BL/6J mice. In addition, exposure to intense light correlated with higher levels of prostaglandin G2 in the eyes of Abca4-/-Rdh8-/- mice. Intense light exposure also lowered DHA levels in the eyes of wild-type C57BL/6J mice without discernible retinal degeneration. Analysis of human serum from patients with AMD recapitulated these dysregulated DHA levels and revealed dysregulation of arachidonic acid (AA) levels as well (~32% increase in patients with AMD compared with average levels in healthy individuals). From these observations, we then built a statistical model that included levels of DHA and AA from human serum. This model had a 74% probability of correctly identifying patients with AMD from controls. Addition of a genetic analysis for one of the most prevalent amino acid substitutions in the age-related maculopathy susceptibility 2 gene linked to AMD, Ala69→Ser, did not improve the statistical model. Thus, we have characterized a reliable method with the potential to detect AMD without a genetic component, paving the way for a larger-scale clinical evaluation. Our studies on mouse models along with the analysis of human serum suggest that our small molecule-based model may serve as an effective tool to estimate the risk of developing AMD.

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Novel CCR3 Antagonists Are Effective Mono- and Combination Inhibitors of Choroidal Neovascular Growth and Vascular Permeability.

Nagai N, Ju M, Izumi-Nagai K, Robbie SJ, Bainbridge JW, Gale DC, Pierre E, Krauss AH, Adamson P, Shima DT, Ng YS.

Abstract: Choroidal neovascularization (CNV) is a defining feature of wet age-related macular degeneration. We examined the functional role of CCR3 in the development of CNV in mice and primates. CCR3 was associated with spontaneous CNV lesions in the newly described JR5558 mice, whereas CCR3 ligands localized to CNV-associated macrophages and the retinal pigment epithelium/choroid complex. Intravitreal injection of neutralizing antibodies against endothelial growth factor receptor 2, CCR3, CCR3 ligand 11/eotaxin-1, and CCR3 ligand 24/eotaxin-2 all reduced CNV area and lesion number in these mice. Systemic administration of the CCR3 antagonists GW766994X and GW782415X reduced spontaneous CNV in JR5558 mice and laser-induced CNV in mouse and primate models in a dose-dependent fashion. Combination treatment with antivascular endothelial growth factor receptor 2 antibody and GW766994X yielded additive reductions in CNV area and hyperpermeability in mice. Interestingly, topical GW766994X and intravitreal anti-CCR3 antibody yielded strong systemic effects, reducing CNV in the untreated, contralateral eye. Contrarily, ocular administration of GW782415X in primates failed to substantially elevate plasma drug levels or to reduce the development of grade IV CNV lesions. These findings suggest that CCR3 signaling may be an attractive therapeutic target for CNV, utilizing a pathway that is at least partly

distinct from that of endothelial growth factor receptor. The findings also demonstrate that systemic exposure of CCR3 antagonists may be crucial for CNV-targeted activity.

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Epidemiology

PLoS One. 2015 Jul 15;10(7):e0132565.

Cross Sectional and Longitudinal Associations between Cardiovascular Risk Factors and Age Related Macular Degeneration in the EPIC-Norfolk Eye Study.

Yip JL, Khawaja AP, Chan MP, Broadway DC, Peto T, Tufail A, Luben R, Hayat S, Bhaniani A, Wareham NJ, Khaw KT, Foster PJ.

PURPOSE: To examine the cross sectional and longitudinal relationship between cardiovascular risk factors and age-related macular degeneration (AMD) in a large British cohort study.

METHODS: The EPIC Norfolk Eye study is nested in a larger prospective cohort study. Data on cardiovascular risk factors were collected at baseline (1993-1997) and follow up (2006-2011) via clinical examination, validated lifestyle questionnaires and serum blood samples. AMD was ascertained using standardised grading of fundus photographs at the follow up. Logistic regression was used to examine associations between baseline and follow up risk factors with AMD.

RESULTS: 5,344 pairs (62.0% of total 8623) of fundus photographs were of sufficient quality for grading of AMD in participants with mean age of 67.4 years old (range 44-91) at diagnosis. There were 28 cases of late AMD (0.5%, 95% confidence interval (CI)=0.3-0.8%) and 645 cases of early AMD (12.1%, 95%CI=11.2 -13.0.%). In multivariable analysis, older people with higher levels of baseline high density lipoprotein-cholesterol (HDL-C) and C-reactive protein (CRP) were more likely to have any signs of AMD, after adjusting for sex, education, smoking, and systolic blood pressure. In cross sectional analysis, only older age and higher HDL were significantly associated with AMD.

CONCLUSIONS: We have found that older age and higher levels of CRP and HDL-C were associated with increased odds of AMD in this population in the longitudinal analysis, but older age and HDL-C, not CRP was significantly associated with AMD in the cross sectional analysis. The prevalence of AMD in this cohort was low compared to other cohorts in Europe, the US and Australia, and probably reflects the some selection biases in follow up participation as well as the low rate of smoking among our healthy participants.

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Analysis of Genetic and Environmental Risk Factors and Their Interactions in Korean Patients with Age-Related Macular Degeneration.

Woo SJ, Ahn J, Morrison MA, Ahn SY, Lee J, Kim KW, DeAngelis MM, Park KH.

PURPOSE: To investigate the association of genetic and environmental factors, and their interactions in Korean patients with exudative age-related macular degeneration (AMD).

METHODS: A total of 314 robustly characterized exudative AMD patients, including 111 PCV (polypoidal choroidal vasculopathy) and 154 typical choroidal neovascularization (CNV), and 395 control subjects without any evidence of AMD were enrolled. Full ophthalmologic examinations including fluorescein angiography (FA), indocyanine green angiography (ICG) and optical coherence tomography (OCT) were done, according to which patients were divided into either PCV or typical CNV. Standardized questionnaires were used to collect information regarding underlying systemic diseases, dietary habits, smoking history and body mass index (BMI). A total of 86 SNPs from 31 candidate genes were analyzed.

Genotype association and logistic regression analyses were done and stepwise regression models to best predict disease for each AMD subtype were constructed.

RESULTS: Age, spherical equivalent, myopia, and ever smoking were associated with exudative AMD. Age, hypertension, hyperlipidemia, spherical equivalent, and myopia were risk factors for typical CNV, while increased education and ever smoking were significantly associated with PCV ($p<.05$ for all). Four SNPs, ARMS2/HTRA1 rs10490924, rs11200638, and rs2736911, and CFH rs800292, showed association with exudative AMD. Two of these SNPs, ARMS2/HTRA1 rs10490924 and rs11200638, showed significant association with typical CNV and PCV specifically. There were no significant interactions between environmental and genetic factors. The most predictive disease model for exudative AMD included age, spherical equivalent, smoking, CFH rs800292, and ARMS2 rs10490924 while that for typical CNV included age, hyperlipidemia, spherical equivalent, and ARMS2 rs10490924. Smoking, spherical equivalent, and ARMS2 rs10490924 were the most predictive variables for PCV. When comparing PCV cases to CNV cases, age, BMI, and education were the most predictive risk factors of PCV.

CONCLUSIONS: Only one locus, the ARMS2/HTRA1 was a significant genetic risk factor for Korean exudative AMD, including its subtypes, PCV and typical CNV. Stepwise regression revealed that CFH was important to risk of exudative AMD in general but not to any specific subtype. While increased education was a unique risk factor to PCV when compared to CNV, this association was independent of refractive error in this homogenous population from South Korea. No significant interactions between environmental and genetic risk factors were observed.

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Clin Ophthalmol. 2015 Jun 30;9:1187-93. eCollection 2015.

Prevalence and factors associated with scleral hyaline plaque: clinical study of older adults in southeastern Brazil.

Horowitz S, Damasceno N, Damasceno E.

PURPOSE: To investigate the prevalence of scleral hyaline plaque among older adults in the city of Niterói in southeastern Brazil. A second goal was to assess the correlation between scleral hyaline plaque and several age-related diseases, including eye diseases and systemic diseases.

METHODS: The study sample comprised 667 participants who were followed for 15 months. The study had a prospective, longitudinal, observational design that established inclusion and exclusion criteria. The following variables were selected for correlation with scleral hyaline plaque: sex, age, age range, iris color, ethnicity, presence of cataract, moderate to high myopia, age-related macular degeneration (AMD), diabetes mellitus, systemic arterial hypertension, degenerative arthritis, and osteoporosis. These correlations were assessed by means of the χ (2) test and Student's t-test. Multivariate analysis was performed to exclude factors that were potentially associated with aging exclusively but that did not have a direct relationship with hyaline plaque. Binary logistic regression was used to calculate odds ratios, significance, and confidence intervals.

RESULTS: Scleral hyaline plaques were found in 177 patients (17.54%). There was a statistically significant association between the presence of hyaline plaques and sex (female), age range (≥70 years old), ethnicity (Caucasian), cataract, moderate to high myopia, systemic arterial hypertension, degenerative arthritis, and osteoporosis ($P<0.05$). On multivariate binary logistic regression analysis, only female sex, age range (≥70 years), moderate to high myopia, and degenerative arthritis exhibited significant correlation.

CONCLUSION: The prevalence of scleral hyaline plaque in the present study was higher than in previous reports in the medical literature. Several age-related diseases exhibited a correlation with scleral hyaline plaque. The most significant factors associated with scleral hyaline plaque were advanced age, female sex, moderate to high myopia, and degenerative arthritis.

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Genetics

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Differences in the Genetic Susceptibility to Age-Related Macular Degeneration Clinical Subtypes.

Shen L, Hoffmann TJ, Melles RB, Sakoda LC, Kvale MN, Banda Y, Schaefer C, Risch N, Jorgenson E.

PURPOSE: We compared across age-related macular degeneration (AMD) subtypes the effect of AMD risk variants, their predictive power, and heritability.

METHODS: The prevalence of AMD was estimated among active non-Hispanic white Kaiser Permanente Northern California members who were at least 65 years of age as of June 2013. The genetic analysis included 5,170 overall AMD cases ascertained from electronic health records (EHR), including 1,239 choroidal neovascularization (CNV) cases and 1,060 nonexudative AMD cases without CNV, and 23,130 controls of non-Hispanic white ancestry from the Kaiser Permanente Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. Imputation was based on the 1000 Genomes Project reference panel.

RESULTS: The narrow-sense heritability due to common autosomal single nucleotide polymorphisms (SNPs) was 0.37 for overall AMD, 0.19 for AMD unspecified, 0.20 for nonexudative AMD, and 0.60 for CNV. For the 19 previously reported AMD risk loci, the area under the receiver operating characteristic (ROC) curve was 0.675 for overall AMD, 0.640 for AMD unspecified, 0.678 for nonexudative AMD, and 0.766 for CNV. The individual effects on the risk of AMD for 18 of the 19 SNPs were in a consistent direction with those previously reported, including a protective effect of the APOE ε4 allele. Conversely, the risk of AMD was significantly increased in carriers of the ε2 allele.

CONCLUSIONS: These findings provide an independent confirmation of many of the previously identified AMD risk loci, and support a potentially greater role of genetic factors in the development of CNV. The replication of established associations validates the use of EHR in genetic studies of ophthalmologic traits.

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Identification of Genetic Defects in 33 Probands with Stargardt Disease by WES-Based Bioinformatics Gene Panel Analysis.

Xin W, Xiao X, Li S, Jia X, Guo X, Zhang Q.

Abstract: Stargardt disease (STGD) is the most common hereditary macular degeneration in juveniles, with loss of central vision occurring in the first or second decade of life. The aim of this study is to identify the genetic defects in 33 probands with Stargardt disease. Clinical data and genomic DNA were collected from 33 probands from unrelated families with STGD. Variants in coding genes were initially screened by whole exome sequencing. Candidate variants were selected from all known genes associated with hereditary retinal dystrophy and then confirmed by Sanger sequencing. Putative pathogenic variants were further validated in available family members and controls. Potential pathogenic mutations were identified in 19 of the 33 probands (57.6%). These mutations were all present in ABCA4, but not in the other four STGD-associated genes or in genes responsible for other retinal dystrophies. Of the 19 probands, ABCA4 mutations were homozygous in one proband and compound heterozygous in 18 probands, involving 28 variants (13 novel and 15 known). Analysis of normal controls and available family members in 12 of the 19 families further support the pathogenicity of these variants. Clinical manifestation of all probands met the diagnostic criteria of STGD. This study provides an overview of a genetic basis for STGD in Chinese patients. Mutations in ABCA4 are the most common cause of STGD in this cohort. Genetic defects in approximately 42.4% of STGD patients await identification in future studies.

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Diet, lifestyle and low vision

Crit Rev Food Sci Nutr. 2015 Jul 13:0. [Epub ahead of print]

A Review on Factors Influencing Bioaccessibility and Bioefficacy of Carotenoids.

Priyadarshani AM.

Abstract: Vitamin A deficiency is one of the most prevalent deficiency disorders in the world. As shown by many studies plant food based approaches have a real potential on prevention of vitamin A deficiency in a sustainable way. Carotenoids are important as precursors of vitamin A as well as for prevention of cancers, coronary heart diseases, age-related macular degeneration, cataract etc. Bioaccessibility and bioefficacy of carotenoids are known to be influenced by numerous factors including dietary factors such as fat, fiber, dosage of carotenoid, location of carotenoid in the plant tissue, heat treatment, particle size of food, carotenoid species, interactions among carotenoids, isomeric form and molecular linkage and subject characteristics. Therefore even when carotenoids are found in high quantities in plant foods their utilization may be unsatisfactory because some factors are known to interfere as negative effectors.

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Oxid Med Cell Longev. 2015;2015:340520. Epub 2015 Jun 9.

Polyphenol Stilbenes: Molecular Mechanisms of Defence against Oxidative Stress and Aging-Related Diseases.

Reinisalo M, Kårlund A, Koskela A, Kaarniranta K, Karjalainen RO.

Abstract: Numerous studies have highlighted the key roles of oxidative stress and inflammation in aging-related diseases such as obesity, type 2 diabetes, age-related macular degeneration (AMD), and Alzheimer's disease (AD). In aging cells, the natural antioxidant capacity decreases and the overall efficiency of reparative systems against cell damage becomes impaired. There is convincing data that stilbene compounds, a diverse group of natural defence phenolics, abundant in grapes, berries, and conifer bark waste, may confer a protective effect against aging-related diseases. This review highlights recent data helping to clarify the molecular mechanisms involved in the stilbene-mediated protection against oxidative stress. The impact of stilbenes on the nuclear factor-erythroid-2-related factor-2 (Nrf2) mediated cellular defence against oxidative stress as well as the potential roles of SQSTM1/p62 protein in Nrf2/Keap1 signaling and autophagy will be summarized. The therapeutic potential of stilbene compounds against the most common aging-related diseases is discussed.

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PLoS One. 2015 Jul 14;10(7):e0128119. eCollection 2015.

Similar Sensitivity to Ladder Contours in Macular Degeneration Patients and Controls.

Haun AM, Peli E.

PURPOSE: To determine whether people with central field loss (CFL) from macular degeneration have improved ability to recognize a particularly difficult spatial configuration embedded in noise, the peripherally -viewed 'ladder contour'. The visibility of these configuration has been linked to general contour integration ability and crowding limitations in peripheral vision.

METHODS: We used a trial-based yes-no task. CFL patients and normally-sighted controls performed the task, looking for ladder contours embedded in a field of randomly oriented Gabor patches, at a range of stimulus presentation times (varying stimulus difficulty). Viewing eccentricity in CFL patients was set by

their preferred retinal loci (PRLs) and matched artificially in the control group. The contours were presented so as to be tangent to the CFL region, given a patient's PRL location.

RESULTS: CFL and normally-sighted groups performed similarly on the task. The only significant determinant of performance was the viewing eccentricity.

CONCLUSIONS: CFL patients do not seem to develop any improved ability to recognize ladder contours with their parafoveal retina, which suggests that there is no underlying improvement in contour integration or reduction in crowding limitations in the region of the PRL despite extended daily use.

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