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MD Research News

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Drug treatment

Am J Ophthalmol. 2015 Aug 23. [Epub ahead of print]

Randomized Trial to Evaluate Tandosporine in Geographic Atrophy Secondary to Age-Related Macular Degeneration: the GATE Study.

Jaffe GJ, Schmitz-Valckenberg S, Boyer D, Heier J, Wolf-Schnurrbusch U, Staurenghi G, Schmidt-Erfurth U, Holz FG.

PURPOSE: To determine the safety and efficacy of AL-8309B (tandospirone) in the management of patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) and obtain standardized data on GA lesion growth progression.

DESIGN: Prospective, controlled, double-masked, randomized, multicenter phase 3 clinical trial.

METHODS: Setting: 48 clinical sites.

PATIENTS: Patients with GA associated with AMD were enrolled. All patients were followed for a minimum of 30 months, and up to 36 months. Intervention Procedures: Patients were randomized (1:1:1) to receive AL-8309B ophthalmic solution 1.0%, 1.75%, or vehicle, administered as a twice-daily topical ocular drop.

MAIN OUTCOME MEASURES: The primary efficacy endpoint was mean annualized lesion enlargement from baseline as assessed with fundus autofluorescence (FAF) imaging.

RESULTS: A total of 768 eyes of 768 patients were enrolled and treated with AL-8309B 1.0% (N=250), AL-8309B 1.75% (N=258), or vehicle (N= 260). An increase in mean lesion size was observed in both the AL-8309B and vehicle treatment groups, and growth rates were similar in all treatment groups. Annualized lesion growth rates were 1.73, 1.76 and 1.71 mm2 for AL-8309B 1.0%, AL-8309B 1.75%, and vehicle, respectively.

CONCLUSIONS: AL-8309B 1.0% and 1.75% did not affect lesion growth in eyes with GA secondary to AMD. There were no clinically relevant safety issues identified for AL-8309B. The large natural history dataset from this study is a valuable repository for future comparisons.

PMID: 26310670 [PubMed - as supplied by publisher]

J Manag Care Spec Pharm. 2015 Sep;21(9):735-41.

Treatment Patterns of Anti-Vascular Endothelial Growth Factor and Laser Therapy Among Patients with Diabetic Macular Edema.

Jiang S, Barner JC, Park C, Ling YL.

BACKGROUND: Diabetic macular edema (DME) is a form of diabetic retinopathy caused by continued leakage from retinal blood vessels. The use of anti-vascular endothelial growth factor (VEGF) injections has gained in popularity in the treatment of DME due to satisfactory efficacy, while laser photocoagulation is still the first-line therapy. Examining anti-VEGF treatment patterns may improve understanding of real-world medication-taking behaviors.

OBJECTIVES: To (a) compare demographic and clinical characteristics and treatment patterns of anti-VEGF (bevacizumab, ranibizumab, and pegaptanib) and laser therapies among DME patients and (b) determine predictors of switching and anti-VEGF therapy initiation.

METHODS: A retrospective cohort analysis was conducted with Texas Medicaid medical and prescription claims (January 1, 2008-December 31, 2012) for patients who were aged 18-63 years, continuously enrolled 1 year pre- and post-index, diagnosed with DME and treated with anti-VEGF or laser therapies. Treatment patterns included treatment frequency and switching between anti-VEGF and laser therapies. Logistic regression and multinomial analysis were used to determine factors associated with switching and initiation of anti-VEGF therapy, while controlling for demographic and clinical characteristics.

RESULTS: DME patients (N = 2,201) were aged 54.7 (SD ± 7.9) years; 63.1% were female; 59.1% were Hispanic; and 10.3% were visually impaired. CCI mean score was 6.5 (SD ± 3.1), and patients were on 2.6 (SD ± 3.3) unique prescription medications. Anti-VEGF users had significantly (P less than 0.0001) fewer prescriptions compared with laser users (1.9 [SD ± 3.1) vs. 2.8 [SD ± 3.3], respectively). Laser was the most commonly used (84.9%) therapy from 2009 to 2011; however, anti-VEGF use increased from 11.7% in 2009 to 21.8% in 2011 (P less than 0.0001). Patients received 1.5 (SD ± 0.7) laser surgeries compared with 1.7 (SD ± 1.1) anti-VEGF injections per eye annually. Switching from laser to anti-VEGF injections was 9.7%, while switching from anti-VEGF injections to laser surgery was 42.2%. Patients who switched from anti-VEGF injections to laser surgery were more likely to be Hispanic (OR = 1.415, 95% CI = 1.037-1.930); male (OR = 1.341, 95% CI = 1.053-1.709); have fewer prescriptions (OR = 0.944, 95% CI = 0.905-0.985); and less likely to have no visual impairment (OR = 0.641, 95% CI = 0.449-0.915). Multinomial regression results showed anti-VEGF users were more likely to remain on the same therapy if they had more prescriptions (OR = 1.094, 95% CI = 1.029-1.172) or were female (OR = 1.441, 95% CI = 1.024-2.041). Anti-VEGF initiators had fewer prescriptions (OR = 0.917, 95% CI = 0.868-0.947) and initiated in 2011 vs. 2009 (OR = 2.363, 95% CI = 1.777-3.141).

CONCLUSIONS: Although anti-VEGF use is increasing, laser use is still more prevalent. Over 40% of patients who initiated on anti-VEGF injections switched to laser surgery. Additional research should be conducted to determine factors associated with this high rate of switching.

PMID: 26308221 [PubMed - in process]

Asia Pac J Ophthalmol (Phila). 2015 Aug 21. [Epub ahead of print]

Modified Approach in Management of Submacular Hemorrhage Secondary to Wet Age-related Macular Degeneration.

Kumar A, Roy S, Bansal M, Tinwala S, Aron N, Temkar S, Pujari A.

PURPOSE: The aim of this study was to evaluate the surgical outcomes of a modified approach in the management of thick submacular hemorrhage in patients with wet age-related macular degeneration.

DESIGN: This was a retrospective study.

METHODS: A retrospective chart review was performed on 10 eyes of 10 patients with submacular hemorrhage secondary to wet age-related macular degeneration treated with 23-gauge pars plana vitrectomy, followed by submacular injection of recombinant tissue plasminogen activator (12.5 µg/0.1 mL), bevacizumab (2.5 mg/0.1 mL), and air (0.3 mL). Gas tamponade was given with 20% SF6 and postoperative propped-up positioning. Patients were evaluated for displacement of hemorrhage,

preoperative and postoperative best-corrected visual acuity, occurrence of intraoperative and postoperative complications, and recurrence of hemorrhage. All patients were followed up for 6 months.

RESULTS: Displacement of the submacular bleed was achieved in all cases. Improvement of best-corrected visual acuity was seen in 8 of 10 patients. Rebleed was seen in 2 eyes that were retreated with intravitreal injection of recombinant tissue plasminogen activator, bevacizumab, and 20% SF6 gas.

CONCLUSIONS: This modified technique aids in the effective displacement of thick submacular hemorrhage with simultaneous treatment of the underlying choroidal neovascular membrane, which halts the disease progression resulting in significant improvement of visual acuity.

PMID: 26302314 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 Aug 1;56(9):5574-8.

Intraocular Pharmacokinetics of Aflibercept and Vascular Endothelial Growth Factor-A.

Celik N, Scheuerle A, Auffarth GU, Kopitz J, Dithmar S.

PURPOSE: To determine intraocular pharmacokinetics of aflibercept and VEGF-A in patients with neovascular age-related macular degeneration (nAMD) during a treatment period of 6 months.

METHODS: Seven nonvitrectomized patients diagnosed with macular edema secondary to nAMD undergoing intravitreal injections (IVI) of aflibercept. Patients were treatment naïve at least for the last 2 months and received intravitreal injection of 2 mg aflibercept for the first time. Aqueous humor samples were obtained prior to each injection procedure during a 6-month period: three times monthly, then bimonthly. Over all 35 samples were analyzed with ELISA for unbound VEGF-A and a self-developed assay for unbound aflibercept.

RESULTS: In all cases, wet AMD was inactive after IVI. Unbound aflibercept could be detected in all samples. Initial mean concentration of aflibercept was 305.4 ± 43.8 µg/mL and remained stable after the first injection with 0.8 ± 0.5 µg/mL. Initial mean level of unbound VEGF-A was 190.7 ± 26.9 pg/mL. A significant decrease of the concentration to 92.6 ± 10.2 pg/mL ($P < 0.05$, Wilcoxon rank sum test) after the first injection was observed. This level remained stable during further treatment.

CONCLUSIONS: Levels of unbound aflibercept and unbound VEGF-A remained stable after every month and every second month of IVI. The findings of these small case series support suggestions that treatment intervals with bimonthly IVI of aflibercept are sufficient due to a detectable remaining biologic active concentration of aflibercept.

PMID: 26305529 [PubMed - in process]

Vestn Oftalmol. 2015 May-Jun;131(3):27-30, 32-3.

[Evaluating the efficacy of anti-VEGF therapy in patients with exudative age-related macular degeneration and concomitant glaucoma]. [Article in Russian]

Erichev VP, Budzinskaya MV, Karpilova MA, Yulova AG, Smirnova TV, Andreeva IV, Shchegoleva IV, Plyukhova AA.

AIM: To evaluate the efficacy of anti-VEGF therapy in patients with exudative age-related macular degeneration (AMD) and glaucoma.

MATERIAL AND METHODS: The study enrolled 117 patients (117 eyes) with exudative AMD and concomitant non-operated primary open-angle glaucoma (POAG). All patients were divided into several groups depending on their intraocular pressure (IOP) and stage of POAG. Hypotensive therapy included carbonic anhydrase inhibitors, beta-adrenergic antagonists (beta blockers) and alpha(2)-adrenergic

agonists (alpha-2 mimetics). Lucentis (ranibizumab) was intravitreally injected thrice at monthly intervals. All patients underwent a standard ophthalmic examination, fluorescent retinal angiography, and optical coherence tomography. IOP was measured before the first and after the last injection by means of Icare PRO reboud tonometer.

RESULTS: There was no statistically significant difference between groups Ia, IIa, Ib, and IIb in terms of IOP elevation. Glaucoma IIc and IIIa patients showed just a moderate increase in IOP that did not require regimen adjustment. There was, however, a single IIIb case of persistent IOP elevation, in which one-step penetrating trabeculectomy with intravitreal ranibizumab injection was later performed. Resolution of macular edema was achieved in all patients. Visual acuity (VA) varied between the groups demonstrating a tendency toward improvement in glaucoma Ia patients ($p = 0.062$) and stabilization in glaucoma IIa ($p = 0.61$), Ib ($p = 0.07$), and IIb ($p = 0.29$) patients. In some cases of low vision at baseline and subretinal fibrosis, VA changes were of no clinical significance.

CONCLUSIONS: Intravitreal ranibizumab therapy proved effective in exudative age-related macular degeneration with concomitant glaucoma. Timely treatment of both AMD (i.e. before the development of subretinal fibrosis) and glaucoma contributes to therapeutic success in these patients.

PMID: 26310004 [PubMed - in process]

Int J Ophthalmol. 2015 Aug 18;8(4):849-51. eCollection 2015.

Subfoveal choroidal thickness changes after intravitreal bevacizumab therapy for neovascular age-related macular degeneration.

Ünlü C, Erdogan G, Onal Gunay B, Sezgin Akcay BI, Kardes E.

PMID: 26309892 [PubMed] PMCID: PMC4539626

Int J Ophthalmol. 2015 Aug 18;8(4):846-8. eCollection 2015.

Tachyphylaxis during ranibizumab treatment of exudative age-related macular degeneration.

Doguizi S, Ozdek S, Yuksel S.

PMID: 26309891 [PubMed] PMCID: PMC4539654

Other treatment & diagnosis

Prog Retin Eye Res. 2015 Aug 22. [Epub ahead of print]

A paradigm shift in imaging biomarkers in the management of neovascular age-related macular degeneration.

Schmidt-Erfurth U, Waldstein SM.

Abstract: Neovascular age-related macular degeneration (AMD) has undergone substantial break-throughs in diagnostic as well as therapeutic respect, with optical coherence tomography (OCT) allowing to identify disease morphology in great detail, and intravitreal anti-vascular endothelial growth factor therapy providing unprecedented benefit. However, these two paths have yet not been combined in an optimal way, real-world outcomes are inferior to expectations, and disease management is largely inefficient. This dilemma can be solved by the identification of biomarkers relevant for visual function, disease activity and prognosis, which can provide solid guidance for therapeutic management on an individual level as well as on the population base. Qualitative and quantitative morphological features obtained by advanced OCT provide novel insight into exudative and degenerative stages of neovascular AMD. However, conclusions from

structure/function correlations evolve differently from previous paradigms. While central retinal thickness was used as biomarker for guiding retreatment management in clinical trials and practice, fluid localization in different compartments offers superior prognostic value: Intraretinal cystoid fluid has a negative impact on visual acuity and is considered as degenerative when persisting through the initial therapeutic interval. Subretinal fluid is associated with superior visual benefit and a lower rate of progression towards geographic atrophy. Detachment of the retinal pigment epithelium was identified as most pathognomonic biomarker, often irresponsive to therapy and responsible for visual decline during a pro-re-nata regimen. Alterations of the neurosensory tissue are usually associated with irreversible loss of functional elements and a negative prognosis. Novel OCT technologies offer crucial insight into corresponding changes at the level of the photoreceptor - retinal pigment epithelial - choriocapillary unit, identifying the biological limits of therapeutic interventions. To optimally benefit from high-resolution multi-modal imaging, an integrated analysis of all functional and structural features is required involving reliable automated algorithms and computational data analyses. Using innovative analysis methods, retinal biomarkers can be used to provide efficient personalized therapy for the individual patient, predictive disease- and population-based models for large-scale management and identifying promising targets for the development of novel therapeutic strategies.

PMID: 26307399 [PubMed - as supplied by publisher]

Int J Mol Sci. 2015 Aug 20;16(8):19796-19811.

Effect of Factor XIII-A G185T Polymorphism on Visual Prognosis after Photodynamic Therapy for Neovascular Macular Degeneration.

Parmeggiani F, Costagliola C, Semeraro F, Romano MR, Rinaldi M, Gallenga CE, Serino ML, Incorvaia C, D'Angelo S, De Nadai K, Dell'Omo R, Russo A, Gemmati D, Perri P.

Abstract: Macular degenerations represent leading causes of central blindness or low vision in developed countries. Most of these severe visual disabilities are due to age-related macular degeneration (AMD) and pathologic myopia (PM), both of which are frequently complicated by subfoveal choroidal neovascularization (CNV). Photodynamic therapy with verteporfin (PDT-V) is still employed for CNV treatment in selected cases or in combined regimen. In Caucasian patients, the common polymorphism G185T of factor XIII-A gene (FXIII-A-G185T; rs5985) has been described as predictor of poor angiographic CNV responsiveness to PDT-V. Nevertheless, the prognostic implications of this pharmacogenetic determinant on long-term visual outcome after a PDT-V regimen have not been evaluated. We retrospectively selected Caucasian patients presenting with treatment-naive CNV and receiving standardized PDT-V protocol for two years. The study population included patients affected by subfoveal CNV secondary to AMD or PM. We assessed the correlations between the polymorphic allele T of FXIII-A-G185T and: (1) total number of photodynamic treatments; and (2) change in visual acuity from baseline to the end of the follow-up period. Considering a total study population of 412 patients with neovascular AMD or PM, the carriers of 185 T-allele of FXIII-A (GT or TT genotype) received a higher number of photodynamic treatments than patients without it (GG wild-type genotype) ($p < 0.01$; mean number of PDT-V: 5.51 vs. 3.76, respectively). Moreover, patients with 185 T-allele of FXIII-A had a more marked worsening of visual acuity at 24 months than those with the GG-185 wild genotype ($p < 0.01$; mean difference in logMAR visual acuity: 0.22 vs. 0.08, respectively). The present findings show that the G185T polymorphism of the FXIII-A gene is associated with significant differences in the long-term therapeutic outcomes of patients treated with standardized PDT-V protocol. The comprehensive appraisal of both anti-thrombophilic effects due to FXIII-A G185T variant and photo-thrombotic action of PDT-V toward CNV provides several clues about the rationale of this intriguing pharmacogenetic correlation. Further investigations are warranted to outline the appropriate paradigm for guiding PDT-V utilization in the course of the combined therapeutic protocol for neovascular macular degeneration.

PMID: 26307969 [PubMed - as supplied by publisher]

Mol Ther. 2015 Aug 24. [Epub ahead of print]

TAPharmacological modulation of photoreceptor outer segment degradation in a human iPS cell model of inherited macular degeneration.

Singh R, Kuai D, Guziewicz KE, Meyer J, Wilson M, Lu J, Smith M, Clark E, Verhoeven A, Aguirre GD, Gamm DM.

Abstract: Degradation of photoreceptor outer segments (POS) by retinal pigment epithelium (RPE) is essential for vision, and studies have implicated altered POS processing in the pathogenesis of some retinal degenerative diseases. Consistent with this notion, a recently established hiPSC-RPE model of inherited macular degeneration, Best disease (BD), displayed reduced rates of POS breakdown. Herein we utilized this model to determine 1) if disturbances in protein degradation pathways are associated with delayed POS digestion and 2) whether such defect(s) can be pharmacologically targeted. We found that BD hiPSC-RPE cultures possessed increased protein oxidation, decreased free-ubiquitin levels, and altered rates of exosome secretion, consistent with altered POS processing. Application of valproic acid (VPA) with or without rapamycin increased rates of POS degradation in our model, whereas application of bafilomycin-A1 decreased such rates. Importantly, the negative effect of bafilomycin-A1 could be fully reversed by VPA. The utility of hiPSC-RPE for VPA testing was further evident following examination of its efficacy and metabolism in a complementary canine disease model. Our findings suggest that disturbances in protein degradation pathways contribute to the POS processing defect observed in BD hiPSC-RPE, which can be manipulated pharmacologically. These results have therapeutic implications for BD and perhaps other maculopathies.

PMID: 26300224 [PubMed - as supplied by publisher]

Ophthalmology. 2015 Sep;122(9):e53.

Re: Wu et al.: Optical coherence tomography-defined changes preceding the development of drusen-associated atrophy in age-related macular degeneration.

Querques G.

PMID: 26299726 [PubMed - in process]

Cell Stem Cell. 2015 Aug 19. [Epub ahead of print]

Humanized Mice Reveal Differential Immunogenicity of Cells Derived from Autologous Induced Pluripotent Stem Cells.

Zhao T, Zhang ZN, Westenskow PD, Todorova D, Hu Z, Lin T, Rong Z, Kim J, He J, Wang M, Clegg DO, Yang YG, Zhang K, Friedlander M, Xu Y.

Abstract: The breakthrough of induced pluripotent stem cell (iPSC) technology has raised the possibility that patient-specific iPSCs may become a renewable source of autologous cells for cell therapy without the concern of immune rejection. However, the immunogenicity of autologous human iPSC (hiPSC)-derived cells is not well understood. Using a humanized mouse model (denoted Hu-mice) reconstituted with a functional human immune system, we demonstrate that most teratomas formed by autologous integration-free hiPSCs exhibit local infiltration of antigen-specific T cells and associated tissue necrosis, indicating immune rejection of certain hiPSC-derived cells. In this context, autologous hiPSC-derived smooth muscle cells (SMCs) appear to be highly immunogenic, while autologous hiPSC-derived retinal pigment epithelial (RPE) cells are immune tolerated even in non-ocular locations. This differential immunogenicity is due in part to abnormal expression of immunogenic antigens in hiPSC-derived SMCs, but not in hiPSC-derived RPEs. These findings support the feasibility of developing hiPSC-derived RPEs for treating macular degeneration.

PMID: 26299572 [PubMed - as supplied by publisher]

Ophthalmology. 2015 Aug 19. [Epub ahead of print]

The Onion Sign in Neovascular Age-Related Macular Degeneration Represents Cholesterol Crystals.

Pang CE, Messinger JD, Zanzottera EC, Freund KB, Curcio CA.

PURPOSE: To investigate the frequency, natural evolution, and histologic correlates of layered, hyperreflective, subretinal pigment epithelium (sub-RPE) lines, known as the onion sign, in neovascular age -related macular degeneration (AMD).

DESIGN: Retrospective observational cohort study and experimental laboratory study.

PARTICIPANTS: Two hundred thirty eyes of 150 consecutive patients with neovascular AMD and 40 human donor eyes with histopathologic diagnosis of neovascular AMD.

METHODS: Spectral-domain optical coherence tomography (SD OCT), near-infrared reflectance (NIR), color fundus images, and medical charts were reviewed. Donor eyes underwent multimodal ex vivo imaging, including SD OCT, before processing for high-resolution histologic analysis.

MAIN OUTCOME MEASURES: Presence of layered, hyperreflective sub-RPE lines, qualitative analysis of their change in appearance over time with SD OCT, histologic correlates of these lines, and associated findings within surrounding tissues.

RESULTS: Sixteen of 230 eyes of patients (7.0%) and 2 of 40 donor eyes (5.0%) with neovascular AMD had layered, hyperreflective sub-RPE lines on SD OCT imaging. These appeared as refractile, yellow-gray exudates on color imaging and as hyperreflective lesions on NIR. In all 16 patient eyes, the onion sign persisted in follow-up for up to 5 years, with fluctuations in the abundance of lines and association with intraretinal hyperreflective foci. Patients with the onion sign disproportionately were taking cholesterol-lowering medications (P = 0.025). Histologic analysis of 2 donor eyes revealed that the hyperreflective lines correlated with clefts created by extraction of cholesterol crystals during tissue processing. The fluid surrounding the crystals contained lipid, yet was distinct from oily drusen. Intraretinal hyperreflective foci correlated with intraretinal RPE and lipid-filled cells of probable monocytic origin.

CONCLUSIONS: Persistent and dynamic, the onion sign represents sub-RPE cholesterol crystal precipitation in an aqueous environment. The frequency of the onion sign in neovascular AMD in a referral practice and a pathology archive is 5% to 7%. Associations include use of cholesterol-lowering medication and intraretinal hyperreflective foci attributable to RPE cells and lipid-filled cells of monocyte origin.

PMID: 26298717 [PubMed - as supplied by publisher]

Prog Mol Biol Transl Sci. 2015;134:477-90. Epub 2015 Jul 9.

Retinoid Processing in Induced Pluripotent Stem Cell-Derived Retinal Pigment Epithelium Cultures.

Fields MA, Bowrey HE, Gong J, Ablonczy Z, Del Priore LV.

Abstract: Stem cell therapy for retinal degenerative diseases such as age-related macular degeneration is a promising clinical option for the replacement of photoreceptors and retinal pigment epithelium (RPE). Induced pluripotent stem cell technology has emerged as a viable potential source of cells for transplantation in retinal degenerative disorders. Induced pluripotent stem cells have been used to derive RPE and have been tested for their functional behavior. These cells have the ability to express RPE-specific proteins and morphologically resemble native RPE. Induced pluripotent stem cell-derived RPE are also able to contribute to the visual cycle by their ability to metabolize all-trans retinol, a critical function of RPE in maintaining visual function. Advances in induced pluripotent stem cell technology will contribute to the development of clinical therapies for retinal degenerative diseases as well as provide a tool to understand the pathology of these disorders.

PMID: 26310172 [PubMed - in process]

Retina. 2015 Sep;35(9):1715-1718.

Vitreous in Age-Related Macular Degeneration Therapy-The Medium Is the Message.

Sebag J.

PMID: 26312447 [PubMed - as supplied by publisher]

Pathogenesis

Biochim Biophys Acta. 2015 Aug 21. [Epub ahead of print]

Mitochondrial DNA has a pro-inflammatory role in AMD.

Dib B, Lin H, Maidana DE, Tian B, Miller JB, Bouzika P, Miller JW, Vavvas DG.

Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly of industrialized nations, and there is increasing evidence to support a role for chronic inflammation in its pathogenesis. Mitochondrial DNA (mtDNA) has been recently reported to be pro-inflammatory in various diseases such as Alzheimer's and heart failure. Here, we report that intracellular mtDNA induces ARPE-19 cells to secrete IL-6 and IL-8, inflammatory cytokines that have consistently been associated with AMD onset and progression. The induction was dependent on the size of mtDNA, but not on specific sequence. Oxidative stress plays a major role in the development of AMD, and our findings indicate that mtDNA induces IL-6 and IL-8 more potently when oxidized. Cytokine induction was mediated by STING (Stimulator of Interferon Genes) and NF-κB as evidenced by abrogation of the cytokine response with the use of specific inhibitors (siRNA and Bay 11-7082, respectively). Finally, mtDNA primed the NLRP3 inflammasome and weakly activated it as shown by caspase-1 activation and mature IL-1β secretion. This study contributes to our understanding of the potential pro-inflammatory role of mtDNA in the pathogenesis of AMD.

PMID: 26305120 [PubMed - as supplied by publisher]

Lancet. 2015 Feb 26;385 Suppl 1:S97.

Role of interleukin 33/ST2 axis in the immune-mediated pathogenesis of age-related macular degeneration.

Theodoropoulou S, Copland DA, Liu J, Dick AD.

BACKGROUND: Age-related macular degeneration is a leading cause of irreversible blindness. Altered immune responses drive degeneration, in response to oxidative stress and hypoxia-induced regulation of metabolism. We tested the hypothesis that toll-like receptor activation of retinal pigment epithelium and cellular metabolic switch upregulate interleukin 33, which acts through its receptor ST2 to activate both choroidal stromal fibroblasts and mast cells. By such mechanisms, the fibrosis and insidious degeneration, which we observe clinically, is accentuated.

METHODS: Retinal pigment epithelial cells (ARPE-19 and B6-RPE07) were stimulated with toll-like receptor ligands, and energetic pathways were assessed through lactate production and the expression of glycolytic enzymes. Expression profile and secretion of interleukin 33 were determined by RT-PCR and western blots. Function and expression profile of bone-marrow-derived mast cells and human choroidal fibroblasts were also assessed.

FINDINGS: The production of lactate, determining aerobic glycolysis, increased after stimulation of retinal pigment epithelial cells with LPS or poly(I:C), indicating an increase in the glycolytic activity after toll-like receptor stimulation. Increased levels of GLUT1 transcripts, and upregulation of GAPDH expression corroborated this finding. Furthermore, increased expression of interleukin 33 was dependent on a

glycolytic metabolic switch and was enhanced under hypoxic conditions. ST2 was highly expressed in retinal pigment epithelium, choroidal mast cells, and choroidal fibroblasts in mouse and man. ST2+ bone-marrow-derived mast cells generated a spectrum of inflammatory cytokines and PGS2 when cultured with interleukin-33-rich retinal pigment epithelium supernatant. Interleukin-33 treatment impaired fibroblast migration and gel contraction alongside suppression of MMP-2 and MMP-9 expression.

INTERPRETATION: Our data highlight an unrecognised link between retinal pigment epithelium bioenergetic status and tissue remodelling of choroidal stroma. Our findings suggest that the interleukin 33/ST2 axis and changing bioenergetic sources are potential therapeutic targets to inhibit progression of age-related macular degeneration.

PMID: 26312920 [PubMed - as supplied by publisher]

Prog Mol Biol Transl Sci. 2015;134:449-63. Epub 2015 Jul 14.

A2E and Lipofuscin.

Crouch RK, Koutalos Y, Kono M, Schey K, Ablonczy Z.

Abstract: Lipofuscin is highly fluorescent material, formed in several tissues but best studied in the eye. The accumulation of lipofuscin in the retinal pigment epithelium (RPE) is a hallmark of aging in the eye and has been implicated in various retinal degenerations, including age-related macular degeneration. The bis-retinoid N-retinyl-N-retinylidene ethanolamine (A2E), formed from retinal, has been identified as a byproduct of the visual cycle, and numerous in vitro studies have found toxicity associated with this compound. The compound is known to accumulate in the RPE with age and was the first identified compound extracted from lipofuscin. Our studies have correlated the distribution of lipofuscin and A2E across the human and mouse RPE. Lipofuscin fluorescence was imaged in the RPE from human donors of various ages and from assorted mouse models. The spatial distribution of A2E was determined using matrix-assisted laser desorption-ionization imaging mass spectrometry on both flat-mounted and transversally sectioned RPE tissue. Our data support the clinical observations in humans of strong RPE fluorescence, increasing with age, in the central area of the RPE. However, there was no correlation between the distribution of A2E and lipofuscin, as the levels of A2E were highest in the far periphery and decreased toward the central region. Interestingly, in all the mouse models, A2E distribution and lipofuscin fluorescence correlate well. These data demonstrate that the accumulation of A2E is not responsible for the increase in lipofuscin fluorescence observed in the central RPE with aging in humans.

PMID: 26310170 [PubMed - in process]

Prog Mol Biol Transl Sci. 2015;134:415-31. Epub 2015 Jul 14.

Insights into the Molecular Properties of ABCA4 and Its Role in the Visual Cycle and Stargardt Disease.

Molday RS.

Abstract: ABCA4 is a member of the A-subfamily of ATP-binding cassette (ABC) transporters localized in rod and cone outer segment disc membranes. Over 800 mutations in ABCA4 are now known to cause Stargardt macular degeneration and related retinal degenerative diseases. Biochemical studies have shown that ABCA4 transports or flips the 11-cis and all-trans isomers of N-retinylidene-phosphatidylethanolamine across disc membranes, thereby facilitating the removal of retinal from disc membranes through the visual cycle and preventing the accumulation of potentially toxic bisretinoid compounds in photoreceptor and retinal pigment epithelial cells. This chapter summarizes studies which have led to our understanding of the role of ABCA4 in the visual cycle and Stargardt disease.

PMID: 26310168 [PubMed - in process]

Korean J Pediatr. 2015 Jul;58(7):239-44. Epub 2015 Jul 22.

Complement regulation: physiology and disease relevance.

Cho H.

Abstract: The complement system is part of the innate immune response and as such defends against invading pathogens, removes immune complexes and damaged self-cells, aids organ regeneration, confers neuroprotection, and engages with the adaptive immune response via T and B cells. Complement activation can either benefit or harm the host organism; thus, the complement system must maintain a balance between activation on foreign or modified self surfaces and inhibition on intact host cells. Complement regulators are essential for maintaining this balance and are classified as soluble regulators, such as factor H, and membrane-bound regulators. Defective complement regulators can damage the host cell and result in the accumulation of immunological debris. Moreover, defective regulators are associated with several autoimmune diseases such as atypical hemolytic uremic syndrome, dense deposit disease, age-related macular degeneration, and systemic lupus erythematosus. Therefore, understanding the molecular mechanisms by which the complement system is regulated is important for the development of novel therapies for complement-associated diseases.

PMID: 26300937 [PubMed] PMCID: PMC4543182

Hum Mol Genet. 2015 Aug 26. [Epub ahead of print]

Synonymous variants in HTRA1 implicated in AMD susceptibility impair its capacity to regulate TGF -β signaling.

Friedrich U, Datta S, Schubert T, Plössl K, Schneider M, Felix G, Fuchshofer R, Tiefenbach KJ, Längst G, Weber BH.

Abstract: High temperature requirement A1 (HTRA1) is a secreted serine protease reported to play a role in the development of several cancers and neurodegenerative diseases. Still, the mechanism underlying the disease processes largely remain undetermined. In age related macular degeneration (AMD), a common cause of vision impairment and blindness in industrialized societies, two synonymous polymorphisms (rs1049331:C>T, and rs2293870:G>T) in exon 1 of the HTRA1 gene were associated with a high risk to develop disease. Here, we show that the two polymorphisms result in a protein with altered thermophoretic properties upon heat induced unfolding, trypsin accessibility, and secretion behavior, suggesting unique structural features of the AMD risk-associated HTRA1 protein. Applying MicroScale Thermophoresis and protease digestion analysis, we demonstrate direct binding and proteolysis of transforming growth factor β1 (TGF-β1) by normal HTRA1 but not the AMD risk-associated isoform. As a consequence, both HTRA1 isoforms strongly differed in their ability to control TGF-β mediated signaling, as revealed by reporter assays targeting the TGF-β1 induced serpin peptidase inhibitor (SERPINE1, alias PAI-1) promoter. In addition, structurally altered HTRA1 led to an impaired autocrine TGF-β signaling in microglia, as measured by a strong down regulation of downstream effectors of the TGF-β cascade such as phosphorylated SMAD2 and PAI-1 expression. Taken together, our findings demonstrate the effects of two synonymous HTRA1 variants on protein structure and protein interaction with TGF-β1. As a consequence, this leads to an impairment of TGF-β signaling and microglial regulation. Functional implications of the altered properties on AMD pathogenesis remains to be clarified.

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The 11-cis Retinal Origins of Lipofuscin in the Retina.

Adler L 4th, Boyer NP, Chen C, Ablonczy Z, Crouch RK, Koutalos Y.

Abstract: Lipofuscin is a fluorescent mixture of partially digested proteins and lipids that accumulates with age in the lysosomal compartment of the retinal pigment epithelium (RPE) of the eye. Because it has been found to have significant cytotoxic potential, lipofuscin is thought to play a role in retinal degeneration diseases including age-related macular degeneration and Stargardt disease, a form of juvenile macular degeneration. The only known components of lipofuscin are bis-retinoids, the condensation products of two molecules of retinal. The bulk of lipofuscin is thought to originate in the rod photoreceptor outer segments as a by-product of reactions involving the retinal chromophore of rhodopsin. 11-cis retinal flows from the RPE into the rod outer segments, where it combines with opsin to form rhodopsin; all-trans retinal is released into the rod outer segments by photoactivated rhodopsin following its excitation by light. Both 11-cis and all-trans retinal can generate lipofuscin-like fluorophores and bis-retinoids when added to rod outer segment membranes. The levels of lipofuscin precursor fluorophores present in the outer segments of dark-adapted rods are similar in cyclic-light- and dark-reared mice, as are the levels of accumulated lipofuscin in the RPE. Because the retinol dehydrogenase enzyme present in rod outer segments can reduce all-trans but not 11-cis retinal, lipofuscin precursors are more likely to form from 11-cis than all-trans retinal, even under cyclic light conditions. Thus, 11-cis retinal may be the primary source of lipofuscin in the retina.

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Genetics

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Associations Between the T280M and V249I SNPs in CX3CR1 and the Risk of Age-Related Macular Degeneration.

Zhang R, Wang LY, Wang YF, Wu CR, Lei CL, Wang MX, Ma L.

PURPOSE: Two common single nucleotide polymorphisms (SNPs) in the CX3CR1 gene, T280M and V249I, have been reported to affect the risk of age-related macular degeneration (AMD) in several studies. The aim of the present study was to combine all published data on the relationship between these two variants and AMD susceptibility in a meta-analysis to clarify this association.

METHODS: MEDLINE, EMBASE, and ISI Web of Science were searched for all eligible studies on the relationship between AMD and T280M and V249I variants. The pooled odds ratio (OR) with 95% confidence intervals (CIs) for each SNP in the allele frequency, homozygote, second codominant genotype, and dominant genotype models were calculated to evaluate the strength of this association.

RESULTS: A total of 3017 AMD cases and 4096 controls from eight studies were involved in this meta-analysis. Both T280M and V249I SNPs exhibited significant associations with increased risk of AMD in the allele (T versus C: OR = 1.43, 95% CI: 1.06-1.91; A versus G: OR = 1.25, 95% CI: 1.01-1.55) and homozygous models (TT versus CC: OR = 2.11, 95% CI: 1.00-4.43; AA versus GG: OR = 1.27, 95% CI: 1.00-1.61), while no significance association was observed for the codominant genotype model. Moreover, studies showing high linkage disequilibrium between these two variants demonstrated a significantly stronger connection between these SNPs and AMD risk, compared with the moderate linkage disequilibrium group.

CONCLUSIONS: Significant evidence for a relationship between T280M and V249I variants in CX3CR1 in the homozygote state with increased susceptibility to AMD was reported. Further studies are needed to confirm these findings.

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Biomarkers. 2015 Jun;20(4):266-70.

Effects of adiponectin polymorphisms on the risk of advanced age-related macular degeneration.

Cao G, Chen Y, Zhang J, Liu Y, Zhang M, Zhang K, Su Z.

OBJECTIVE: To determine the relationships between variants in adiponectin gene (ADIPOQ) with advanced forms of age-related macular degeneration (AMD) susceptibility.

METHODS: A total of 189 advanced AMD patients and 168 controls were recruited. Seven tagging single-nucleotide polymorphisms in ADIPOQ were genotyped by the SNaPshot method.

RESULTS: Alleles or genotypes of rs822396 distributed significantly differently in advanced AMD patients and controls. The minor allele G at rs822396 was associated with an increased risk of advanced AMD in a dominant model. Furthermore, haplotype analysis revealed that haplotypes AGGACCT and TGACCCC were significantly increased the advanced AMD susceptibility, whereas haplotypes AGAACGC, TGAACGT and TGACAGC had protective effects.

CONCLUSION: ADIPOQ genetic variant rs822396 might affect an individual's susceptibility to AMD, making it efficient genetic biomarkers for early detection of AMD.

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Diet, lifestyle & low vision

JAMA. 2015 Aug 25;314(8):791-801.

Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function: The AREDS2 Randomized Clinical Trial.

Chew EY, Clemons TE, Agrón E, Launer LJ, Grodstein F, Bernstein PS; Age-Related Eye Disease Study 2 (AREDS2) Research Group.

IMPORTANCE: Observational data have suggested that high dietary intake of saturated fat and low intake of vegetables may be associated with increased risk of Alzheimer disease.

OBJECTIVE: To test the effects of oral supplementation with nutrients on cognitive function.

DESIGN, SETTING, AND PARTICIPANTS: In a double-masked randomized clinical trial (the Age-Related Eye Disease Study 2 [AREDS2]), retinal specialists in 82 US academic and community medical centers enrolled and observed participants who were at risk for developing late age-related macular degeneration (AMD) from October 2006 to December 2012. In addition to annual eye examinations, several validated cognitive function tests were administered via telephone by trained personnel at baseline and every 2 years during the 5-year study.

INTERVENTIONS: Long-chain polyunsaturated fatty acids (LCPUFAs) (1 g) and/or lutein (10 mg)/ zeaxanthin (2 mg) vs placebo were tested in a factorial design. All participants were also given varying combinations of vitamins C, E, beta carotene, and zinc.

MAIN OUTCOMES AND MEASURES: The main outcome was the yearly change in composite scores determined from a battery of cognitive function tests from baseline. The analyses, which were adjusted for baseline age, sex, race, history of hypertension, education, cognitive score, and depression score, evaluated the differences in the composite score between the treated vs untreated groups. The composite score provided an overall score for the battery, ranging from -22 to 17, with higher scores representing better function.

RESULTS: A total of 89% (3741/4203) of AREDS2 participants consented to the ancillary cognitive function study and 93.6% (3501/3741) underwent cognitive function testing. The mean (SD) age of the participants was 72.7 (7.7) years and 57.5% were women. There were no statistically significant differences in change of scores for participants randomized to receive supplements vs those who were not. The yearly change in the composite cognitive function score was -0.19 (99% CI, -0.25 to -0.13) for participants randomized to receive LCPUFAs vs -0.18 (99% CI, -0.24 to -0.12) for those randomized to no LCPUFAs (difference in

yearly change, -0.03 [99% CI, -0.20 to 0.13]; P = .63). Similarly, the yearly change in the composite cognitive function score was -0.18 (99% CI, -0.24 to -0.11) for participants randomized to receive lutein/zeaxanthin vs -0.19 (99% CI, -0.25 to -0.13) for those randomized to not receive lutein/zeaxanthin (difference in yearly change, 0.03 [99% CI, -0.14 to 0.19]; P = .66). Analyses were also conducted to assess for potential interactions between LCPUFAs and lutein/zeaxanthin and none were found to be significant.

CONCLUSIONS AND RELEVANCE: Among older persons with AMD, oral supplementation with LCPUFAs or lutein/zeaxanthin had no statistically significant effect on cognitive function.

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PLoS One. 2015 Aug 27;10(8):e0135779.

Structure and Conformation of the Carotenoids in Human Retinal Macular Pigment.

Arteni AA, Fradot M, Galzerano D, Mendes-Pinto MM, Sahel JA, Picaud S, Robert B, Pascal AA.

Abstract: Human retinal macular pigment (MP) is formed by the carotenoids lutein and zeaxanthin (including the isomer meso-zeaxanthin). MP has several functions in improving visual performance and protecting against the damaging effects of light, and MP levels are used as a proxy for macular health-specifically, to predict the likelihood of developing age-related macular degeneration. While the roles of these carotenoids in retinal health have been the object of intense study in recent years, precise mechanistic details of their protective action remain elusive. We have measured the Raman signals originating from MP carotenoids in ex vivo human retinal tissue, in order to assess their structure and conformation. We show that it is possible to distinguish between lutein and zeaxanthin, by their excitation profile (related to their absorption spectra) and the position of their v1 Raman mode. In addition, analysis of the v4 Raman band indicates that these carotenoids are present in a specific, constrained conformation in situ, consistent with their binding to specific proteins as postulated in the literature. We discuss how these conclusions relate to the function of these pigments in macular protection. We also address the possibilities for a more accurate, consistent measurement of MP levels by Raman spectroscopy.

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Association Between Vitamin D Status and Age-Related Macular Degeneration by Genetic Risk.

Millen AE, Meyers KJ, Liu Z, Engelman CD, Wallace RB, LeBlanc ES, Tinker LF, Iyengar SK, Robinson JG, Sarto GE, Mares JA.

Importance: Deficient 25-hydroxyvitamin D (25[OH]D) concentrations have been associated with increased odds of age-related macular degeneration (AMD).

Objective: To examine whether this association is modified by genetic risk for AMD and whether there is an association between AMD and single-nucleotide polymorphisms of genes involved in vitamin D transport, metabolism, and genomic function.

Design, Setting, and Participants: Postmenopausal women (N = 913) who were participants of the Carotenoids in Age-Related Eye Disease Study (CAREDS) (aged 54 to <75 years) with available serum 25 (OH)D concentrations (assessed October 1, 1993, to December 31, 1998), genetic data, and measures of AMD (n = 142) assessed at CAREDS baseline from May 14, 2001, through January 31, 2004, were studied.

Main Outcomes and Measures: Prevalent early or late AMD was determined from graded, stereoscopic fundus photographs. Logistic regression was used to estimate odds ratios (ORs) and 95% CIs for AMD by the joint effects of 25(OH)D (<12, ≥12 to <20, ≥20 to <30, and ≥30 ng/mL) and risk genotype (noncarrier, 1 risk allele, or 2 risk alleles). The referent group was noncarriers with adequate vitamin D status (≥30 ng/

mL). Joint effect ORs were adjusted for age, smoking, iris pigmentation, self-reported cardiovascular disease, self-reported diabetes status, and hormone use. Additive and multiplicative interactions were assessed using the synergy index (SI) and an interaction term, respectively. To examine the association between AMD and variants in vitamin D-related genes, age-adjusted ORs and 95% CIs were estimated using logistic regression.

Results: Among the 913 women, 550 had adequate levels of vitamin D (≥20 ng/mL), 275 had inadequate levels (≥12 to <20 mg/mL), and 88 had deficient levels (<12 ng/mL). A 6.7-fold increased odds of AMD (95% CI, 1.6-28.2) was observed among women with deficient vitamin D status (25[OH]D <12 ng/mL) and 2 risk alleles for CFH Y402H (SI for additive interaction, 1.4; 95% CI, 1.1-1.7; P for multiplicative interaction = .25). Significant additive (SI, 1.4; 95% CI, 1.1-1.7) and multiplicative interactions (P = .02) were observed for deficient women with 2 high-risk CFI (rs10033900) alleles (OR, 6.3; 95% CI, 1.6-24.2). The odds of AMD did not differ by genotype of candidate vitamin D genes.

Conclusions and Relevance: In this study, the odds of AMD were highest in those with deficient vitamin D status and 2 risk alleles for the CFH and CFI genotypes, suggesting a synergistic effect between vitamin D status and complement cascade protein function. Limited sample size led to wide CIs. Findings may be due to chance or explained by residual confounding.

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More than meets the eye: from carotenoid biosynthesis, to new insights into apocarotenoid signaling.

McQuinn RP, Giovannoni JJ, Pogson BJ.

Abstract: Carotenoids are a class of isoprenoids synthesized almost exclusively in plants involved in a myriad of roles including the provision of flower and fruit pigmentation for the attraction of pollinators and seed dispersing organisms. While carotenoids are essential throughout plant development, they are also extremely important in human diets providing necessary nutrition and aiding in the prevention of various cancers, age-related diseases and macular degeneration. Utilization of multiple plant models systems (i.e. Arabidopsis; maize; and tomato) has provided a comprehensive framework detailing the regulation of carotenogenesis throughout plant development covering all levels of genetic regulation from epigenetic to post-translational modifications. That said, the understanding of how carotenoids self-regulate remains fragmented. Recent reports demonstrate the potential influence of carotenoid-cleavage products (apocarotenoids) as signaling molecules regulating carotenoid biosynthesis in addition to various aspects of plants development (i.e. leaf and root development). This review highlights recent advances in carotenogenic regulation and insights into potential roles of novel apocarotenoids in plants.

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Vestn Oftalmol. 2015 May-Jun;131(3):34-40, 42-4.

[Results of the use of antioxidant and angioprotective agents in type 2 diabetes patients with diabetic retinopathy and age-related macular degeneration].[Article in Russian]

Moshetova LK, Vorob'eva IV, Alekseev IB, Mikhaleva LG.

AIM: To investigate changes in clinical, functional, and morphological parameters of the retina in type 2 diabetes patients with diabetic retinopathy (DR) and those with combined fundus pathology (DR plus age-related macular degeneration (AMD)) before and after a course of antioxidants and angioprotectors in the form of mono- or combination therapy.

MATERIAL AND METHODS: The study included 180 patients (180 eyes) with type 2 diabetes divided into 6 groups of 30 each. DR was graded according to E. Kohner and M. Porta classification, AMD--AREDS classification. Thus, group 1 consisted of patients with DRO,; group 2--DR1 without DM, group 3--DR1 with DM, group 4--DRO and "dry" AMD (AREDS 1-3), group 5--DR1 with no DM but with AMD (AREDS 1-3), and group 6--DR1 with DM and AMD (AREDS 1-3). A drug containing lutein 6 mg, zeaxanthin 0.5 mg, vitamin C 60 mg, vitamin E 7 mg, vitamin A 1.5 mg, vitamin B2 1.2 mg, rutin 25 mg, zinc 5 mg, selenium 25 mcg, and bilberry extract 60 mg was used for antioxidative therapy. Ginkgo biloba leaf extract 60 mg was chosen as the angioprotector. In all patients visual acuity, macular thickness and morphology (OCT) as well as light sensitivity (microperimetry) were assessed before and after the treatment course.

RESULTS: Analysis of baseline measurements demonstrated a significant decrease in best corrected visual acuity ($p < 0.05$) in study groups 2-6 as compared with group 1. Macular thickness was increased in all groups, however, the changes were statistically significant only in groups 3 and 6 ($p<0.05$). Light sensitivity of the macula showed a reduction, which was statistically significant in groups 4-6 ($p < 0.05$). After the course of antioxidant and angioprotective therapy, these parameters improved in all groups. The greatest effect was achieved with simultaneous antioxidant and double-dose angioprotective therapy (240 mg per day): visual acuity increased significantly ($p < 0.05$) in all groups except group 1; macular thickness decreased in all groups, however, the changes were statistically significant ($p < 0.05$) only in groups 1-3 and 5; light sensitivity also improved in all groups, significantly ($p < 0.05$) in groups 1-3 and 4.

CONCLUSIONS: Extended analysis of clinical, functional and morphological changes in the retina at the onset of DR in type 2 diabetes patients with concomitant "dry" AMD enables timely diagnosis, prognosis, prevention, and early treatment. Conservative treatment with antioxidant and angioprotective agents has been proved effective in type 2 diabetes patients with preclinical (DRO) and early (DR1) diabetic retinopathy and those with DR and "dry" AMD (AREDS 1-3) in terms of functional and morphological parameters of the retina. From all the regimens, a combined antioxidant and double-dose angioprotective (240 mg) therapy appeared to be the most effective and can be considered not only a preventive, but also a therapeutic measure in type 2 diabetes patients with initial stages of DR (DRO, DR1) or those with DR and DM or combined DR and AMD (AREDS 1-3).

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