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MD Research News

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Drug treatment

Acta Ophthalmol. 2015 Jun 14. [Epub ahead of print]

Visual outcomes in relation to time to treatment in neovascular age-related macular degeneration.

Rasmussen A, Brandi S, Fuchs J, Hansen LH, Lund-Andersen H, Sander B, Larsen M.

PURPOSE: To study the relation between the interval from diagnosis to initiation of intravitreal injection therapy and visual outcome in neovascular age-related macular degeneration (nAMD) and to report changes over time in fellow-eye status.

METHODS: Retrospective chart review. The study included 1185 eyes in 1099 patients who began vascular endothelial growth factor inhibitor treatment for nAMD during four separate periods in 2007, 2009, 2011 and 2012 using a fixed loading-dose regimen of three ranibizumab injections.

RESULTS: Mean best-corrected visual acuity (BCVA) at presentation remained within the range 0.23-0.24 Snellen and the median patient age within 79-80 years, whereas BCVA at first visit after the third injection increased from 0.24 to 0.31 ($p < 0.0001$) in concert with a shift in preferred practice from separate-day injection to same-day injection. This led to a reduction in the median time to treatment from 16 days to 1 day. The proportion of patients with fellow-eye BCVA 0.05 or worse at presentation with newly diagnosed wet AMD in the incident eye decreased from 38% to 22% ($p < 0.0018$). The proportion of bilaterally treated patients increased during the study period.

CONCLUSION: In this study, 2-week-earlier injection was associated with the equivalent of a 5-Early Treatment Diabetic Retinopathy Study letter-gain in mean visual acuity at 3 months after presentation. The difference is larger than expected from the 2-week-longer duration of disease at the study end-point. The study supports that early diagnosis and treatment of nAMD is of value for functional outcomes.

PMID: 26073051 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2015 Jun 5;9:1001-15. eCollection 2015.

Management of neovascular age-related macular degeneration: current state-of-the-art care for optimizing visual outcomes and therapies in development.

Agarwal A, Rhoades WR, Hanout M, Soliman MK, Sarwar S, Sadiq MA, Sepah YJ, Do DV, Nguyen QD.

Abstract: Contemporary management of neovascular age-related macular degeneration (AMD) has evolved significantly over the last few years. The goal of treatment is shifting from merely salvaging vision to maintaining a high quality of life. There have been significant breakthroughs in the identification of viable drug targets and gene therapies. Imaging tools with near-histological precision have enhanced our

knowledge about pathophysiological mechanisms that play a role in vision loss due to AMD. Visual, social, and vocational rehabilitation are all important treatment goals. In this review, evidence from landmark clinical trials is summarized to elucidate the optimum modern-day management of neovascular AMD. Therapeutic strategies currently under development, such as gene therapy and personalized medicine, are also described.

PMID: 26089632 [PubMed] PMCID: PMC4467654

Curr Drug Targets. 2015 Jun 15. [Epub ahead of print]

Anti-VEGF therapy for retinal vein occlusions.

Campa C, Alivernini G, Bolletta E, Battaglia MP, Perri P.

Abstract: Retinal vein occlusion (RVO) is the second most common cause of visual loss in the Western World. RVO is usually classified into branch RVO (BRVO) and central RVO (CRVO) according to the anatomical site of the vascular occlusion. The pathogenesis of RVO is not yet fully understood, however an important event is the intraluminal thrombus formation, which is usually secondary to several conditions such as hypertension, hyperlipidemia, diabetes and thrombophilia. The blockage of venous circulation causes an elevation of intraluminal pressure in the capillaries, leading to hemorrhages and leakage of fluid within the retina, increase of interstitial pressure and a consequent reduction of retinal perfusion. Ischemia may develop resulting in secretion of vascular endothelial growth factor (VEGF) that causes further vascular leakage and retinal oedema. VEGF has therefore a leading role in RVO pathogenesis and symptoms. As a consequence use of anti-VEGF agents by intravitreal injections has become very common with the aim to improve the clinical outcomes in these patients. Currently 2 anti-VEGF agents (ranimizumab and aflibercept) have been FDA (Food and Drug Administration) and EMA (European Medicine Agency) approved for the treatment of RVO, while another VEGF inhibitor (bevacizumab) is often used "off-label" in clinical practice. Many treatment regimens have been suggested in the clinical trials with these drugs, as monthly injections or injections when needed, however the ideal regimen has not been defined yet. We conducted a systematic review searching MEDLINE for the following terms: retinal vein occlusion, ranibizumab, bevacizumab, aflibercept, vascular endothelial growth factor, macular oedema. Data were extracted by one author (AG and BE) and checked by a second (BPM, CC). Aim of this article was to review available data for each drug, focusing on their efficacy and safety trying to compare their advantages and limits.

PMID: 26073857 [PubMed - as supplied by publisher]

Ophthalmologica. 2015 Jun 18. [Epub ahead of print]

Dexamethasone Intravitreal Implant as Adjunctive Therapy to Ranibizumab in Neovascular Age-Related Macular Degeneration: A Multicenter Randomized Controlled Trial.

Kuppermann BD, Goldstein M, Maturi RK, Pollack A, Singer M, Tufail A, Weinberger D, Li XY, Liu CC, Lou J, Whitcup SM.

PURPOSE: To evaluate the efficacy and safety of dexamethasone intravitreal implant 0.7 mg (DEX) as adjunctive therapy to ranibizumab in neovascular age-related macular degeneration (nvAMD).

PROCEDURES: This was a 6-month, single-masked, multicenter study. Patients were randomized to DEX implant (n = 123) or sham procedure (n = 120) and received 2 protocol-mandated intravitreal ranibizumab injections. The main outcome measure was injection-free interval to first as-needed ranibizumab injection.

RESULTS: DEX increased the injection-free interval versus sham (50th percentile, 34 vs. 29 days; 75th percentile, 85 vs. 56 days; p = 0.016). 8.3% of DEX versus 2.5% of sham-treated patients did not require rescue ranibizumab (p = 0.048). Visual acuity and retinal thickness outcomes were similar in DEX and

sham-treated patients. Only reports of conjunctival hemorrhage (18.2 vs. 8.5%) and intraocular pressure elevation (13.2 vs. 4.2%) were significantly different in the DEX versus the sham treatment groups.

CONCLUSION: DEX reduced the need for adjunctive ranibizumab treatment and showed acceptable tolerability in nvAMD patients.

PMID: 26088793 [PubMed - as supplied by publisher]

Expert Opin Biol Ther. 2015 Jun 16:1-10. [Epub ahead of print]

Ranibizumab and aflibercept for the treatment of wet age-related macular degeneration.

Yazdi MH, Faramarzi MA, Nikfar S, Falavarjani KG, Abdollahi M.

INTRODUCTION: Wet age-related macular degeneration (AMD) is a potentially blinding eye disease that causes vision loss among individuals > 50 years old. The main goal in the treatment of wet AMD is to inhibit the choroidal neovascularization (CNV). Currently, ranibizumab and aflibercept are two available anti-VEGF drug for the treatment of wet AMD. Here, we reviewed the clinical outcome of treatment with ranibizumab or aflibercept in patients with wet AMD from recent studies with a special focus on eyes with unusual presentations or treatment resistant and compared these agents with other available wet AMD therapies. Areas covered: For this review, a literature search from 2011 to present was performed using the following terms (or combination of terms): anti-vascular endothelial growth factors, anti-VEGF, age-related macular degeneration, AMD, aflibercept, and ranibizumab. The studies were limited to studies used ranibizumab, and especially those switched from ranibizumab to aflibercept. Also the clinical trial website (www.clinicaltrials.gov) was searched for recently completed trials of aflibercept or ranibizumab for wet AMD treatment. Expert opinion: Ranibizumab and aflibercept are effective for the treatment of wet AMD including those with retinal angiomatous proliferation (RAP) and CNV unresponsive to other anti-VEGF agents. Although high-dose ranibizumab has the potential to treat unresponsive CNV, switching to another anti-VEGF agent may be a preferable option in these eyes.

PMID: 26076760 [PubMed - as supplied by publisher]

J Biol Chem. 2015 Jun 18. [Epub ahead of print]

Deep sequencing-guided design of a high affinity dual-specific antibody to target two angiogenic factors in neovascular age-related macular degeneration.

Koenig P, Lee CV, Sanowar S, Wu P, Stinson J, Harris SF, Fuh G.

Abstract: The development of dual targeting antibodies promises therapies with improved efficacy over mono-specific antibodies. Here, we engineered a Two-in-One vascular endothelial growth factor (VEGF)1 / Angiopoietin 2 (Ang2) antibody with Dual action Fab (DAF) as a potential therapeutic for neovascular age-related macular degeneration (NV AMD). Crystal structures of the VEGF/Ang2 DAF in complex with its two antigens showed highly overlapping binding sites. In order to achieve sufficient affinity of the DAF to block both angiogenic factors, we turned to deep mutational scanning in the complementarity determining regions (CDRs). By mutating all three CDRs of each antibody chain simultaneously, we were able not only to identify affinity improving single mutations but also mutation pairs from different CDRs that synergistically improve both binding functions. Further, insights into the cooperativity between mutations allowed us to identify fold-stabilizing mutations in the CDRs. The data obtained from deep mutational scanning reveal that the majority of the 52 CDR residues are utilized differently for the two antigen binding function and permit, for the first time, the engineering of several DAF variants with sub-nanomolar affinity against two structurally unrelated antigens. The improved variants show similar blocking activity of receptor binding as the high affinity mono-specific antibodies against these two proteins, demonstrating the feasibility of generating a dual specific binding surface with comparable properties to individual high affinity mono-specific antibodies.

PMID: 26088137 [PubMed - as supplied by publisher]

Ophthalmology. 2015 Jun 15. [Epub ahead of print]

One-Year Results of Intravitreal Aflibercept for Polypoidal Choroidal Vasculopathy.

Yamamoto A, Okada AA, Kano M, Koizumi H, Saito M, Maruko I, Sekiryu T, Iida T.

PURPOSE: To investigate 1-year outcomes of intravitreal aflibercept for polypoidal choroidal vasculopathy (PCV).

DESIGN: Retrospective, multicenter, consecutive case series.

PARTICIPANTS: A total of 90 eyes of 87 patients with treatment-naïve PCV followed at 3 tertiary centers.

METHODS: Clinical records were reviewed and imaging studies were analyzed of eyes with PCV that underwent 3 consecutive monthly aflibercept injections followed by injections every 2 months. Additional (rescue) injections were performed for worsening.

MAIN OUTCOME MEASURES: Best-corrected visual acuity (BCVA), optical coherence tomography (OCT), and angiographic findings at 1 year.

RESULTS: The mean BCVA (logarithm of the minimum angle of resolution units) of the 90 eyes improved from 0.31 at baseline to 0.17 at 12 months ($P < 0.001$). The mean central retinal thickness decreased from 315 μm at baseline to 204 μm at 12 months ($P < 0.001$). At 12 months, 64 eyes (71.1%) achieved a dry macula, defined as absence of intraretinal or subretinal fluid on OCT. Of 83 eyes that underwent indocyanine green angiography at both baseline and 12 months, 46 (55.4%) showed complete and 27 (32.5%) showed partial resolution of polypoidal lesions. Eleven of 82 eyes (13.4%) showed decreased size of branching choroidal vascular networks.

CONCLUSIONS: Intravitreal aflibercept administered over 1 year improved both visual acuity and macular morphology in a large number of treatment-naïve eyes with PCV.

PMID: 26088619 [PubMed - as supplied by publisher]

Retina. 2015 Jun 12. [Epub ahead of print]

CORRELATION BETWEEN OPTICAL COHERENCE TOMOGRAPHIC HYPERREFLECTIVE FOCI AND VISUAL OUTCOMES AFTER ANTI-VEGF TREATMENT IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION AND POLYPOIDAL CHOROIDAL VASCULOPATHY.

Lee H, Ji B, Chung H, Kim HC.

PURPOSE: To investigate the correlation between hyperreflective foci (HF) on spectral domain optical coherence tomography at baseline and visual outcomes after intravitreal anti-vascular endothelial growth factor injection in neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV).

METHODS: The authors retrospectively reviewed the medical records of 44 patients with nAMD and 44 patients with PCV. The number of HF was counted according to the location of HF on spectral domain optical coherence tomography: neurosensory retinal layer, outer retinal layer, and subretinal layer. Statistical correlation between final visual acuity and pretreatment and posttreatment optical coherence tomographic parameters including the number of HF, the status of external limiting membrane and inner segment ellipsoid zone was evaluated.

RESULTS: The number of HF in all retinal layers was reduced in nAMD and PCV after treatment. In multivariate regression analysis, final visual acuity was associated with baseline visual acuity ($P = 0.028$), number of subretinal HF ($P = 0.046$), and ellipsoid zone disruption length ($P = 0.009$) in nAMD. In PCV, final visual acuity was associated with baseline visual acuity ($P = 0.001$), number of subretinal HF ($P = 0.001$), and pigment epithelial detachment thickness ($P = 0.034$). The baseline number of subretinal HF was correlated with final foveal thickness and thickness of subretinal fluid and choroidal neovascularization

in nAMD (P = 0.002, P < 0.001, P = 0.009, respectively). In PCV, the baseline number of subretinal HF was correlated with final foveal thickness and ellipsoid zone and external limiting membrane disruption lengths (P = 0.027, P = 0.010, P = 0.020, respectively).

CONCLUSION: The number of HF at subretinal layer on spectral domain optical coherence tomography at baseline might predict the final visual acuity after treatment in nAMD and PCV.

PMID: 26076214 [PubMed - as supplied by publisher]

J Clin Invest. 2015 Jun 15. [Epub ahead of print]

Molecular pharmacodynamics of emixustat in protection against retinal degeneration.

Zhang J, Kiser PD, Badiee M, Palczewska G, Dong Z, Golczak M, Tochtrop GP, Palczewski K.

Abstract: Emixustat is a visual cycle modulator that has entered clinical trials as a treatment for age-related macular degeneration (AMD). This molecule has been proposed to inhibit the visual cycle isomerase RPE65, thereby slowing regeneration of 11-cis-retinal and reducing production of retinaldehyde condensation byproducts that may be involved in AMD pathology. Previously, we reported that all-trans-retinal (atRAL) is directly cytotoxic and that certain primary amine compounds that transiently sequester atRAL via Schiff base formation ameliorate retinal degeneration. Here, we have shown that emixustat stereoselectively inhibits RPE65 by direct active site binding. However, we detected the presence of emixustat-atRAL Schiff base conjugates, indicating that emixustat also acts as a retinal scavenger, which may contribute to its therapeutic effects. Using agents that lack either RPE65 inhibitory activity or the capacity to sequester atRAL, we assessed the relative importance of these 2 modes of action in protection against retinal phototoxicity in mice. The atRAL sequestrant QEA-B-001-NH2 conferred protection against phototoxicity without inhibiting RPE65, whereas an emixustat derivative incapable of atRAL sequestration was minimally protective, despite direct inhibition of RPE65. These data indicate that atRAL sequestration is an essential mechanism underlying the protective effects of emixustat and related compounds against retinal phototoxicity. Moreover, atRAL sequestration should be considered in the design of next-generation visual cycle modulators.

PMID: 26075817 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2015 Jun 11;9:1049-56. eCollection 2015.

Potential role of lampalizumab for treatment of geographic atrophy.

Rhoades W, Dickson D, Do DV.

Abstract: The purpose of this article is to review the pathways underlying age-related macular degeneration and potential therapeutic targets, focusing on the complement pathway and the recent MAHALO Phase II trial of the investigational drug lampalizumab. This trial was the first to have shown positive results for the treatment of geographic atrophy in age-related macular degeneration. It has potential as a future treatment, and is currently undergoing a Phase III trial.

PMID: 26089637 [PubMed] PMCID: PMC4468985

Graefes Arch Clin Exp Ophthalmol. 2015 Jun 20. [Epub ahead of print]

Short-term results of switchback from aflibercept to ranibizumab in neovascular age-related macular degeneration in clinical practice.

Despreaux R, Cohen SY, Semoun O, Zambrowski O, Jung C, Oubraham H, Souied EH.

PURPOSE: This work was undertaken to analyze the efficacy of switchback from aflibercept to ranibizumab in patients with neovascular age-related macular degeneration (nAMD) who had previously switched from ranibizumab to aflibercept.

METHODS: This retrospective double-center study included 45 patients with nAMD who were previously treated with ranibizumab, then aflibercept, and then ranibizumab again, regardless of the number of intravitreal injections received. The primary outcome was change in best-corrected visual acuity (BCVA) measured on the Early Treatment Diabetic Retinopathy Study ETDRS chart before (T0) and after (T1) the switch, and 3 months after the switchback (T2). Secondary outcomes included changes in central foveal thickness (CFT) measured at T0, T1, and T2, as analyzed on spectral-domain optical coherence tomography (SD-OCT), and the percentage of patients gaining five letters or better.

RESULTS: Forty-seven eyes of 45 patients were switched back from aflibercept to ranibizumab. The mean BCVA was 67.4 ± 13.4 at T0, 66.7 ± 14.4 at T1, and 68.2 ± 13.9 at T2. BCVA was significantly improved between T1 and T2 ($p = 0.0230$), but not between T0 and T1 ($p = 0.5153$) or between T0 and T2 ($p = 0.4248$). The mean CFT decreased from 317.8 µm ± 89.6 at T0 to 306.9 µm ±68.0 at T1, and to 291.2 µm ± 76.6 at T2. The decrease in CFT was not statistically significant between either T0 and T1 or T1 and T2, but was significant between T0 and T2, when compared before switch and after switchback ($p = 0.0027$). However, when considering eyes that received three or more consecutive intravitreal injections of aflibercept before switchback, the statistical significance between T1 and T2 was lost, although a trend towards significance remained ($p = 0.06$). Thirteen eyes (27.7 %) gained five letters or more (range, 5-15 letters) after switchback.

CONCLUSIONS: A short-term benefit of switchback from one anti-VEGF agent to another was observed in patients with nAMD who had shown no benefit from the initial switch.

PMID: 26092633 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Retina. 2015 Jun 17. [Epub ahead of print]

PREVALENCE OF RETICULAR PSEUDODRUSEN IN AGE-RELATED MACULAR DEGENERATION USING MULTIMODAL IMAGING.

De Bats F, Mathis T, Mauget-Faÿsse M, Joubert F, Denis P, Kodjikian L.

PURPOSE: To determine the rate of reticular pseudodrusen (RPD) in age-related macular degeneration using multimodal imaging, including color fundus photography, the blue channel image of fundus photography, infrared reflectance, fundus autofluorescence, multicolor imaging, and spectral domain optical coherence tomography, as well as to compare the sensitivities and specificities of these modalities for detecting RPD.

METHODS: This prospective study included 243 eyes from 125 consecutive patients with age-related macular degeneration. They underwent fundus examination including color fundus photography, blue channel, infrared reflectance, fundus autofluorescence, multicolor imaging, and spectral domain optical coherence tomography in both eyes. To be considered as having RPD, eyes had to have reticular patterns on spectral domain optical coherence tomography in a large studied cube of 30° × 25° or on infrared reflectance with at least one other examination.

RESULTS: The mean age of the 125 patients was 81.1 years (±8.1). Eighty-six patients (68.8%) were diagnosed with RPD. Spectral domain optical coherence tomography, infrared reflectance, and multicolor imaging had the highest sensitivity (99.3, 84.6, and 87.1%, respectively) and specificity (100%). The color fundus photography, blue channel, and fundus autofluorescence had lower sensitivity to detect RPD.

CONCLUSION: Reticular pseudodrusen is frequently associated with soft drusen in patients with age-

related macular degeneration. As RPD may be rarely located only in the perifoveal area, spectral domain optical coherence tomography with a larger cube (30 × 25°) than that usually used (20 × 20°) had the highest sensitivity and specificity to detect RPD and is recommended to optimize the rate of detection.

PMID: 26090899 [PubMed - as supplied by publisher]

J Biol Chem. 2015 Jun 19. [Epub ahead of print]

Rescuing trafficking mutants of the ATP binding cassette protein, ABCA4, with small molecule correctors as a treatment for Stargardt eye disease.

Sabirzhanova I, Lopes-Pacheco M, Rapino D, Grover R, Handa JT, Guggino WB, Cebotaru L.

Abstract: Stargardt disease is the most common form of early onset macular degeneration. Mutations in ABCA4, a member of the ATP-binding cassette (ABC) family, are associated with Stargardt disease. Here, we have examined two disease-causing mutations in the NBD1 region of ABCA4, R1108C and R1129C, which occur within regions of high similarity with CFTR, another ABC transporter gene which is associated with cystic fibrosis. We show that R1108C and R1129C are both temperature-sensitive processing mutants that engage the cellular quality control mechanism and show a strong interaction with the chaperone Hsp 27. Both mutant proteins also interact with HDCAC6 and are degraded in the aggresome. We also demonstrate that novel corrector compounds that are being tested as treatment for cystic fibrosis, such as VX-809, can rescue the processing of the ABCA4 mutants, particularly their expression at the cell surface, and can reduce their binding to HDAC6. Thus, our data suggest that VX-809 can potentially be developed as a new therapy for Stargardt disease, for which there is currently no treatment.

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Invest Ophthalmol Vis Sci. 2015 Jun 1;56(6):3976-83.

Ganglion Cell-Inner Plexiform Layer and Peripapillary Retinal Nerve Fiber Layer Thicknesses in Age -Related Macular Degeneration.

Lee EK, Yu HG.

PURPOSE: To investigate changes of inner retinal layers and optic nerve head (ONH) in patients with dry age-related macular degeneration (AMD) and demonstrate the pattern of these changes.

METHODS: A total of 76 eyes classified as having dry AMD and 76 control eyes were included. Ophthalmologic evaluations included best-corrected visual acuity (BCVA) assessment, spectral-domain optical coherence tomography (SD-OCT), and Humphrey visual field (VF) test. The drusen area and volume were determined using the automated algorithm of the SD-OCT software. Macular ganglion cell-inner plexiform layer (mGCIPL) and peripapillary retinal nerve fiber layer (pRNFL) thicknesses and ONH parameters, as well as VF parameters, were compared between groups.

RESULTS: Macular GCIPL thickness was significantly lower in eyes with AMD than in controls (73.83 ± 7.13 vs. 82.00 ± 4.85 μm; $P < 0.001$), and mGCIPL thinning was observed in a ring-shaped pattern around the fovea. The pRNFL thickness was also significantly lower in eyes with AMD than in controls (88.69 ± 6.93 vs. 93.96 ± 8.33 μm; $P < 0.001$), but no significant difference in ONH parameters was found. An inverse correlation between drusen area and average mGCIPL thickness was found ($r = -0.3253$; $P = 0.0064$). Best-corrected visual acuity and VF parameters were worse in AMD eyes than in controls. The pattern of VF defects was mostly consistent with foveal or parafoveal scotoma.

CONCLUSIONS: In eyes with dry AMD, mGCIPL and pRNFL thicknesses were lower than measurements in control eyes, and the average mGCIPL thickness was negatively correlated with the drusen area. However, the pattern of these changes differed from glaucomatous abnormalities.

PMID: 26087362 [PubMed - in process]

Retina. 2015 Jun 15. [Epub ahead of print]

OUTER RETINAL TUBULATION: Characteristics in Patients With Neovascular Age-Related Macular Degeneration.

Iaculli C, Barone A, Scudieri M, Giovanna Palumbo M, Delle Noci N.

PURPOSE: To assess the incidence, characteristics, best-corrected visual acuity (BCVA), central macular thickness (CMT), and retinal sensitivity correlations in patients with and without outer retinal tubulation (ORT) affected by subfoveal choroidal neovascularization due to neovascular age-related macular degeneration.

METHODS: Prospective case series including 78 eyes of 78 consecutive patients with subfoveal choroidal neovascularization due to neovascular age-related macular degeneration. Baseline and follow-up visits included BCVA, intraocular pressure, ophthalmoscopic examination, CMT as measured by spectral domain optical coherence tomography, and retinal sensitivity tested with fundus-related perimetry (MP-1). Fluorescent angiography was performed at baseline.

RESULTS: At the end of the follow-up period, the mean BCVA and CMT of patients with ORT were statistically different from those without ORT (BCVA: 0.61 ± 0.13 vs. 0.37 ± 1.59, P < 0.0001; CMT: 290 ± 26.7 vs. 215.2 ± 33.5 μm; P < 0.0001). Patients with ORT showed a decreased mean retinal sensitivity compared with patients without ORT (6.31 ± 2.5 dB vs. 9.89 ± 5.43 dB; P < 0.0001).

CONCLUSION: The results of this study investigating the BCVA, CMT, and retinal sensitivity detected by MP-1 between patients with and without ORT in neovascular age-related macular degeneration suggest that these parameters are statistically different in patients with ORT; this may be due to the pathogenesis of ORT formation, secondary to retinal pigment epithelial tears or photoreceptor damage. MP-1 microperimeter is a noninvasive instrument that provides useful information to better characterize the functional aspect of ORT in patients with age-related macular degeneration.

PMID: 26079476 [PubMed - as supplied by publisher]

Retina. 2015 Jun 15. [Epub ahead of print]

OPTICAL COHERENCE TOMOGRAPHY FINDINGS AND SURGICAL OUTCOMES OF TISSUE PLASMINOGEN ACTIVATOR-ASSISTED VITRECTOMY FOR SUBMACULAR HEMORRHAGE SECONDARY TO AGE-RELATED MACULAR DEGENERATION.

Hirashima T, Moriya T, Bun T, Utsumi T, Hirose M, Oh H.

PURPOSE: To study the relationship between morphologic findings using spectral domain optical coherence tomography and surgical outcomes in patients with submacular hemorrhage (SMH) secondary to age-related macular degeneration.

METHODS: Medical charts of nine eyes of nine patients who underwent tissue plasminogen activator-assisted vitrectomy for SMH secondary to age-related macular degeneration were retrospectively reviewed. The preoperative height and lateral width of both SMH and pigment epithelial detachment documented with optical coherence tomography, were measured. The status of ellipsoid layers was also analyzed.

RESULTS: Complete displacement of SMH from the fovea was achieved in all nine eyes. The preoperative status of the ellipsoid layer under the fovea was detectable in four eyes and absent in the remaining five eyes. Postoperative best-corrected visual acuity was significantly better in eyes with preoperative detectable ellipsoid layers (P < 0.01). Eyes with preoperative SMH heights <400 μm also exhibited better best-corrected visual acuity (P < 0.05). There was no significant correlation between postoperative best-corrected visual acuity and the specific features of pigment epithelial detachment, including height, lateral width, and number.

CONCLUSION: The preoperative presence of detectable ellipsoid layers and a lower height of SMH may predict good visual prognosis. In contrast, no specific features of pigment epithelial detachment correlated with postoperative best-corrected visual acuity.

PMID: 26079475 [PubMed - as supplied by publisher]

Ophthalmology. 2015 Jun 12. [Epub ahead of print]

Reticular Pseudodrusen in Sorsby Fundus Dystrophy.

Gliem M, Müller PL, Mangold E, Bolz HJ, Stöhr H, Weber BH, Holz FG, Charbel Issa P.

PURPOSE: To investigate the association of reticular pseudodrusen (RPD) with Sorsby fundus dystrophy (SFD).

DESIGN: Prospective, monocenter, cross-sectional case series.

SUBJECTS: Sixteen patients of 4 unrelated families with SFD caused by mutations in TIMP3.

METHODS: All subjects underwent multimodal imaging including near-infrared (NIR) reflectance and fundus autofluorescence with a confocal scanning laser ophthalmoscope and spectral-domain optical coherence tomography (SD OCT).

MAIN OUTCOME MEASURES: Prevalence, topographic distribution, and phenotype of RPD.

RESULTS: Mean age of the investigated patients was 56.8 years (range, 23-78 years). Reticular pseudodrusen were identified frequently in SFD patients in the sixth decade of life (5 of 7 [71%]) and were absent in younger (n = 3) or older (n = 6) patients. They were most abundant in the superior quadrant and spared the foveal region. Reticular pseudodrusen appeared as yellowish round to oval (dot subtype; n = 5) or confluent, wriggled (ribbon subtype; n = 3) lesions, sometimes forming irregular networks. Reticular pseudodrusen were hyporeflective on NIR reflectance and hypofluorescent on fundus autofluorescence imaging. They appeared as subretinal deposits on SD OCT imaging. Other lesions, such as peripheral pseudodrusen and soft drusen, were present less frequently.

CONCLUSIONS: Reticular pseudodrusen are a frequent finding in patients with SFD. Although SFD patients with RPD are younger, distribution and phenotype of RPD are similar to those observed in patients with age-related macular degeneration. The association of RPD with SFD implicates a role of Bruch's membrane, the Bruch's membrane-retinal pigment epithelium interface, or both in the pathogenesis of RPD.

PMID: 26077580 [PubMed - as supplied by publisher]

Vestn Oftalmol. 2015 Mar-Apr;131(2):68-75.

[Diagnostic errors when referring patients for cataract surgery].[Article in Russian]

Egorov VV, Savchenko NV, Sorokin EL, Danilov OV.

AIM: To study the frequency of patients with macular pathology being wrongly diagnosed with cataract and possible reasons for this to occur.

MATERIAL AND METHODS: A total of 1390 patients (1390 eyes), in whom cataract turned out to be not the main cause of visual impairment, were recruited as research subjects. To reveal the reasons for misdiagnosis, we resorted to methods of ophthalmic examination that are available at ambulatory care facilities, i.e. visual acuity measurement, slit lamp biomicroscopy of the anterior and posterior eye segments, direct and indirect ophthalmoscopy.

RESULTS: In most patients (72.6%) visual acuity was decreased due to macular pathology, especially age-

related macular degeneration (AMD)--736 eyes (72.9%). Less common were degenerative myopia (10%), idiopathic macular hole (8.4%), epiretinal macular fibrosis (5.1%), and secondary macular changes of vascular, traumatic, or inflammatory genesis (3.6%). In 76.6% of eyes with macular pathology ophthalmoscopy was perfectly feasible and could be performed by a local ophthalmologist. Only in 23.4% of cases there was a dense posterior capsule opacification or nuclear cataract that impeded visualization of macular structures.

CONCLUSIONS: The main reason for misdiagnosis of macular pathology and referring the patient to cataract surgeon was the neglect of apparent discordance between visual acuity and lens transparency. One should aim at adequate assessment of macular zone by all means, including non-contact ophthalmoscopy with 60 or 90 D aspherical lenses or Hruby lens and red-free examination.

PMID: 26080586 [PubMed - in process]

Pathogenesis

Eye (Lond). 2015 Jun 19. [Epub ahead of print]

Dementia of the eye: the role of amyloid beta in retinal degeneration.

Ratnayaka JA, Serpell LC, Lotery AJ

Abstract: Age-related macular degeneration (AMD) is one of the most common causes of irreversible blindness affecting nearly 50 million individuals globally. The disease is characterised by progressive loss of central vision, which has significant implications for quality of life concerns in an increasingly ageing population. AMD pathology manifests in the macula, a specialised region of the retina, which is responsible for central vision and perception of fine details. The underlying pathology of this complex degenerative disease is incompletely understood but includes both genetic as well as epigenetic risk factors. The recent discovery that amyloid beta (Aβ), a highly toxic and aggregate-prone family of peptides, is elevated in the ageing retina and is associated with AMD has opened up new perspectives on the aetiology of this debilitating blinding disease. Multiple studies now link Aβ with key stages of AMD progression, which is both exciting and potentially insightful, as this identifies a well-established toxic agent that aggressively targets cells in degenerative brains. Here, we review the most recent findings supporting the hypothesis that Aβ may be a key factor in AMD pathology. We describe how multiple Aβ reservoirs, now reported in the ageing eye, may target the cellular physiology of the retina as well as associated layers, and propose a mechanistic pathway of Aβ-mediated degenerative change leading to AMD.

PMID: 26088679 [PubMed - as supplied by publisher]

Cell Rep. 2015 Jun 9. [Epub ahead of print]

Iron Toxicity in the Retina Requires Alu RNA and the NLRP3 Inflammasome.

Gelfand BD, Wright CB, Kim Y, Yasuma T, Yasuma R, Li S, Fowler BJ, Bastos-Carvalho A, Kerur N, Uittenbogaard A, Han YS, Lou D, Kleinman ME, McDonald WH, Núñez G, Georgel P, Dunaief JL, Ambati J.

Abstract: Excess iron induces tissue damage and is implicated in age-related macular degeneration (AMD). Iron toxicity is widely attributed to hydroxyl radical formation through Fenton's reaction. We report that excess iron, but not other Fenton catalytic metals, induces activation of the NLRP3 inflammasome, a pathway also implicated in AMD. Additionally, iron-induced degeneration of the retinal pigmented epithelium (RPE) is suppressed in mice lacking inflammasome components caspase-1/11 or Nlrp3 or by inhibition of caspase-1. Iron overload increases abundance of RNAs transcribed from short interspersed nuclear elements (SINEs): Alu RNAs and the rodent equivalent B1 and B2 RNAs, which are inflammasome agonists. Targeting Alu or B2 RNA prevents iron-induced inflammasome activation and RPE degeneration. Iron-induced SINE RNA accumulation is due to suppression of DICER1 via sequestration of the co-factor

poly(C)-binding protein 2 (PCBP2). These findings reveal an unexpected mechanism of iron toxicity, with implications for AMD and neurodegenerative diseases associated with excess iron.

PMID: 26074074 [PubMed - as supplied by publisher]

Front Immunol. 2015 May 26;6:257. eCollection 2015.

Complement System Part II: Role in Immunity.

Merle NS, Noe R, Halbwachs-Mecarelli L, Fremeaux-Bacchi V, Roumenina LT.

Abstract: The complement system has been considered for a long time as a simple lytic cascade, aimed to kill bacteria infecting the host organism. Nowadays, this vision has changed and it is well accepted that complement is a complex innate immune surveillance system, playing a key role in host homeostasis, inflammation, and in the defense against pathogens. This review discusses recent advances in the understanding of the role of complement in physiology and pathology. It starts with a description of complement contribution to the normal physiology (homeostasis) of a healthy organism, including the silent clearance of apoptotic cells and maintenance of cell survival. In pathology, complement can be a friend or a foe. It acts as a friend in the defense against pathogens, by inducing opsonization and a direct killing by C5b-9 membrane attack complex and by triggering inflammatory responses with the anaphylatoxins C3a and C5a. Opsonization plays also a major role in the mounting of an adaptive immune response, involving antigen presenting cells, T-, and B-lymphocytes. Nevertheless, it can be also an enemy, when pathogens hijack complement regulators to protect themselves from the immune system. Inadequate complement activation becomes a disease cause, as in atypical hemolytic uremic syndrome, C3 glomerulopathies, and systemic lupus erythematosus. Age-related macular degeneration and cancer will be described as examples showing that complement contributes to a large variety of conditions, far exceeding the classical examples of diseases associated with complement deficiencies. Finally, we discuss complement as a therapeutic target.

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Exp Eye Res. 2015 Jun 16. [Epub ahead of print]

Expression of Toll-Like Receptors in Human Retinal and Choroidal Vascular Endothelial Cells.

Stewart EA, Wei R, Branch MJ, Sidney LE, Amoaku WM.

Abstract: Toll-like receptors (TLRs) are a family of proteins that initiate the innate immune response in reaction to invading microbes. Studies confirm the expression of TLRs in a variety of ocular tissues and cells, and it has also been suggested that selected TLRs may be associated with geographic atrophy and neovascularisation in age-related macular degeneration, diabetic retinopathy and other vascular and inflammatory diseases of the ocular posterior segment. However, TLR expression and localisation in the retinal and choroidal vasculature has not been defined. A better understanding of differential TLR expression in the choroid and retina, particularly in endothelial cells would improve our knowledge of vascular and inflammatory diseases in the posterior segment of the eye. In this study the gene (mRNA) expression of TLRs 1-10 was investigated using RT-PCR and comparative qPCR and the protein expression and localisation of selected TLRs (3, 4, 6 and 9) were examined using western blotting, flow cytometry and immunofluorescent staining. PCR showed gene expression of TLR1-6 and 9 in human choroidal endothelial cells (hCEC) and TLR2-6, 9 and 10 in human retinal endothelial cells (hREC). Western blotting detected TLR3, 4 and 9 proteins in both hCEC and hREC with higher levels in hCEC, whilst TLR6 protein was not detectable in either endothelial cell type. Flow cytometry detected all four TLRs (3, 4, 6 and 9) on the cell surface and intracellularly, TLR6 expression was detectable but low. The expression and localisation of TLR3, 4 and 9 were confirmed by immunofluorescent staining in endothelial cells and whole tissue sections and their functionality tested by expression of IL-6 (ELISA) in response to stimulation with specific TLR ligands. This study has, for the first time, identified the differential expression

and localisation of TLRs in intraocular endothelial cells. This profiling will help inform our understanding of different retinal and choroidal vascular diseases, as well as the development of future treatments for intraocular vascular diseases.

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PLoS One. 2015 Jun 19;10(6):e0129945.

Complement Factor H Expressed by Retinal Pigment Epithelium Cells Can Suppress Neovascularization of Human Umbilical Vein Endothelial Cells: An in vitro Study.

Zhang Y, Huang Q, Tang M, Zhang J, Fan W.

Abstract: Complement factor H (CFH) is one of the most important soluble complement regulatory proteins and is closely associated with age-related macular degeneration (AMD), the leading cause of irreversible central vision loss in the elderly population in developed countries. Our study searches to investigate whether CFH expression is changed in oxidative damaged retinal pigment epithelium (RPE) cells and the role of CFH in the in vitro neovascularization. First, it was confirmed by immunofluorescence staining that CFH was expressed by ARPE-19 cells. CFH mRNA and protein in oxidative (H2O2) damaged ARPE-19 cells were both reduced, as determined by Real-time PCR and Western blotting analysis. Enzyme-linked immunosorbent assay (ELISA) also showed that ARPE-19 cells treated with H2O2 caused an increase in C3a content, which indicates complement activation. Then, wound assays were performed to show that CFH expression suppression promoted human umbilical vein endothelial cell (HUVECs) migration. Thereafter, ARPE-19 cells were transfected with CFH-specific siRNA and CFH knockdown was confirmed with the aid of Real-time PCR, immunofluorescence staining and Western blotting. The ELISA results showed that specific CFH knockdown in ARPE-19 cells activated the complement system. Finally, in vitro matrigel tube formation assay was performed to determine whether change of CFH expression in RPE would affect tube formation by HUVECs. More tubes were formed by HUVECs co-cultured with ARPE-19 cells transfected with CFH specific-siRNA when compared with controls. Our results suggested that RPE cells might be the local CFH source, and RPE cell injuries (such as oxidative stress) may cause CFH expression suppression, which in turn may lead to complement activation and promotion of tube formation by HUVECs. This finding is of importance in elucidating the role of complement in the pathogenesis of ocular neovascularization including choroidal neovascularization.

PMID: 26091360 [PubMed - as supplied by publisher]

Gene Ther. 2015 Jun 19. [Epub ahead of print]

Inhibition of pathological brain angiogenesis through systemic delivery of AAV vector expressing soluble FLT1.

Shen F, Mao L, Zhu W, Lawton MT, Pechan P, Colosi P, Wu Z, Scaria A, Su H.

Abstract: The soluble vascular endothelial growth factor (VEGF) receptor 1 (sFLT1) has been tested in both animals and humans for anti-angiogenic therapies, e.g., age-related macular degeneration. We hypothesized that adeno-associated viral vector (AAV)-mediated sFLT1 expression could be used to inhibit abnormal brain angiogenesis. We tested the anti-angiogenic effect of sFLT1 and the feasibility of using AAV serotype 9 to deliver sFLT1 through intravenous injection (IV) to the brain angiogenic region. AAV vectors were packaged in AAV serotypes 1 and 2 (stereotactic injection) and 9 (IV-injection). Brain angiogenesis was induced in adult mice through stereotactic injection of AAV1-VEGF. AAV2-sFLT02 containing sFLT1 VEGF-binding domain (domain 2) was injected into the brain angiogenic region, and AAV9-sFLT1 was injected into the jugular vein at the time of or 4 weeks after AAV1-VEGF injection. We showed that AAV2-sFLT02 inhibited brain angiogenesis at both time points. Intravenous injection of AAV9-sFLT1 inhibited angiogenesis only when the vector was injected 4 weeks after angiogenic induction.

Neither lymphocyte infiltration nor neuron loss was observed in AAV9-sFLT1-treated mice. Our data show that systemically delivered AAV9-sFLT1 inhibits angiogenesis in the mouse brain, which could be utilized to treat brain angiogenic diseases such as brain arteriovenous malformation.Gene Therapy accepted article preview online, 19 June 2015. doi:10.1038/gt.2015.57.

PMID: 26090874 [PubMed - as supplied by publisher]

Int J Ophthalmol. 2015 Jun 18;8(3):585-9. eCollection 2015.

Retinal circulation and its role in macular disorders in patients without systemic disease.

Chandra P, Sudhalkar A, Mandal S, Chhablani J.

AIM: To determine whether retinal circulatory changes play a role in the pathogenesis of macular disorders in patients who are otherwise healthy.

METHODS: Patients with macular disorders that required angiographic imaging were included in this prospective case series. After a complete ocular exam, fluorescein angiography was performed using a standardized technique on the HRA-II (Heidelberg Engineering, Heidelberg, Germany) with special focus on the posterior pole. Only patients with good quality images were included in the analysis. Circulatory parameters recorded included the arm-choroid time, choroid-retinal artery, and finally the retinal artery-vein time. Zonal asymmetry (between the upper and lower zones divided by a line passing through the centre of the fovea) in transit times, if any was also noted. Appropriate statistical analysis was done. Circulation times were compared with age matched historical controls. Changes in retinal dye transit times relative to historical age matched controls, if any, were noted and compared between various disorders.

RESULTS: A total of 156 eyes of 156 patients (120 males) were included in the study. Mean age: 49.14±14.93y. Macular disorders studied were age related degeneration, polypoidal vasculopathy, central serous chorioretinopathy (CSCR) and parafoveal telangiectasia. Delayed circulation time was noted in CSCR patients only.

CONCLUSION: CSCR patients appear to have delayed arterial filling, retinal circulatory disturbances do not seem to contribute to the pathogenesis of other macular disorders.

PMID: 26086013 [PubMed] PMCID: PMC4458668

Int J Ophthalmol. 2015 Jun 18;8(3):556-9. eCollection 2015.

Matrix γ-carboxyglutamate protein and Fetuin-A, in wet type age-related macular degeneration.

Javadzadeh A, Ghorbanihaghjo A, Heidari E, Baharivand N, Sadeghi K, Sorkhabi R, Ahoor MH.

AIM: To evaluate the high sensitivity C-reactive protein (hsCRP), Fetuin-A and matrix γ-carboxyglutamate protein (MGP) as the main factors for vascular calcification and inflammation in serum of patients with advanced age-related macular degeneration (ARMD) in comparison to healthy controls.

METHODS: The subjects were 40 patients with choroidal neovascularization (CNV) having a mean age of 70.9±9.1y and a matched group of 49 apparently healthy control subjects. The ARMD was diagnosed using a slit-lamp with superfield lens, fundus photography and fluorescein angiography. Measurement of hsCRP was done by nephelometry method. Levels of Fetuin-A and MGP were measured by enzyme-linked immunosorbent assay (ELISA) technique.

RESULTS: hsCRP [0.45(0.07-2.63) mg/L vs 0.25(0.03-1.2) mg/L, P=0.02)] and Fetuin-A levels (50.27±5.04 vs 44.99±10.28 ng/mL, P=0.009) were higher in the patients than in the control groups. We could not find significant difference in MGP level between two groups (P=0.08). There was not a significant correlation between MGP with Fetuin-A and hsCRP among the patients (P=0.7, P=0.9 respectively). A significant negative correlation of hsCRP with Fetuin-A was observed in both case and control groups (P=0.004, r=-

0.33 and P=0.001, r=-0.54, respectively).

CONCLUSION: Although our study shows that serum hsCRP and Fetuin-A is increased in CNV patients as well as negatively correlated with both study groups, their direct role on pathogenesis of ARMD required future studies.

PMID: 26086007 [PubMed] PMCID: PMC4458662

Vestn Oftalmol. 2015 Mar-Apr;131(2):50-6, 58.

[Intraocular cytokines imbalance in retinal vein occlusion and its impact on the efficacy of anti-angiogenic therapy].[Article in Russian]

Shchuko AG, Zlobin IV, Yur'eva TN, Ostanin AA, Chernykh ER.

AIM: To study the concentrations of intraocular cytokines in patients with retinal vein occlusion (RVO) before and after intravitreal ranibizumab injection and to compare the results with clinical activity of the disease and treatment efficacy.

MATERIAL AND METHODS: A comprehensive ophthalmological examination of 44 patients with RVO and macular edema was performed. Intraocular fluid was first collected before the intravitreal injection. Cytokines concentrations were measured using Bio-Plex Pro Human Cytokine 27-plex Panel (Bio-Rad Laboratories, USA) for flow cytometry. The test was repeated 1 month after the injection.

RESULTS: A total of 11 cytokines were reliably detected. After ranibizumab injections certain angiogenic (VEGF) and proinflammatory (IL-6, IL-8, IL-13, IL-15, MCP-1) factors appeared to be significantly suppressed. Clinical efficacy of the therapy correlated with the degree of cytokines suppression, which in turn depended on the severity of ocular involvement at baseline.

CONCLUSIONS: Retinal vein occlusion pathogenesis involves a cascade of immune and inflammatory processes, including activation of not only VEGF but also quite a few inflammatory and chemotactic factors, whose activity depends on the extent of ischemic damage in the retina.

PMID: 26080583 [PubMed - in process]

Vestn Oftalmol. 2015 Mar-Apr;131(2):26-31.

[Beta-amyloidopathy as a manifestation of proteinopathy in age-related macular degeneration]. [Article in Russian]

Ermilov VV, Nesterova AA.

AIM: To investigate clinical and morphological features of amyloidogenesis in age-related macular degeneration (AMD), which is thought to be associated with proteinopathy, namely beta-amyloidopathy.

MATERIAL AND METHODS: A total of 111 eyes with morphological signs of AMD as well as brain samples from 56 cadavers (aged at death 60 and over) were assessed with selective methods of amyloid detection.

RESULTS: Amyloid deposits were present in 39% of eyes with dry AMD and 80% of eyes with wet AMD. Combined accumulation of amyloid (that is both in eyes and the brain) was found in 50.6% of cases.

CONCLUSION: The results allow to suggest that common etiopathogenetic and morphological features of AMD and Alzheimer's disease (AD) are due to the same metabolic pathway of the transmembrane amyloid precursor protein (APP) responsible for aggregation of beta-amyloid (Aβ), an abnormal fibrillar protein, and the development of beta-amyloidopathy in eyes and brains. It has been demonstrated that beta-amyloidopathy is the keynote of both AMD and AD pathogenesis leading to cytotoxicity, neurodegeneration and pathological apoptosis. Such views on the problem may promote the development of neuroprotective

and ophthalmic geriatric medications effective at all stages of pathogenesis, including beta-amyloid formation and aggregation.

PMID: 26080579 [PubMed - in process]

Am J Pathol. 2015 Jun 12. [Epub ahead of print]

IL-4 Regulates Specific Arg-1+ Macrophage sFlt-1-Mediated Inhibition of Angiogenesis.

Wu WK, Georgiadis A, Copland DA, Liyanage S, Luhmann UF, Robbie SJ, Liu J, Wu J, Bainbridge JW, Bates DO, Ali RR, Nicholson LB, Dick AD.

Abstract: One of the main drivers for neovascularization in age-related macular degeneration is activation of innate immunity in the presence of macrophages. Here, we demonstrate that T helper cell type 2 cytokines and, in particular, IL-4 condition human and murine monocyte phenotype toward Arg-1+, and their subsequent behavior limits angiogenesis by increasing soluble fms-like tyrosine kinase 1 (sFlt-1) gene expression. We document that T helper cell type 2 cytokine-conditioned murine macrophages neutralize vascular endothelial growth factor-mediated endothelial cell proliferation (human umbilical vein endothelial cell and choroidal vasculature) in a sFlt-1-dependent manner. We demonstrate that in vivo intravitreal administration of IL-4 attenuates laser-induced choroidal neovascularization (L-CNV) due to specific IL-4 conditioning of macrophages. IL-4 induces the expression of sFlt-1 by resident CD11b+ retinal microglia and infiltrating myeloid cells but not from retinal pigment epithelium. IL-4-induced suppression of L-CNV is not prevented when sFlt-1 expression is attenuated in retinal pigment epithelium. IL-4-mediated suppression of L-CNV was abrogated in IL-4R-deficient mice and in bone marrow chimeras reconstituted with myeloid cells that had undergone lentiviral-mediated shRNA silencing of sFlt-1, demonstrating the critical role of this cell population. Together, these data establish how IL-4 directly drives macrophage sFlt-1 production expressing an Arg-1+ phenotype and support the therapeutic potential of targeted IL-4 conditioning within the tissue to regulate disease conditions such as neovascular age-related macular degeneration.

PMID: 26079814 [PubMed - as supplied by publisher]

Autophagy. 2015 Jun 3;11(6):939-53.

Deletion of autophagy inducer RB1CC1 results in degeneration of the retinal pigment epithelium.

Yao J, Jia L, Khan N, Lin C, Mitter SK, Boulton ME, Dunaief JL, Klionsky DJ, Guan JL, Thompson DA, Zacks DN.

Abstract: Autophagy regulates cellular homeostasis and response to environmental stress. Within the retinal pigment epithelium (RPE) of the eye, the level of autophagy can change with both age and disease. The purpose of this study is to determine the relationship between reduced autophagy and age-related degeneration of the RPE. The gene encoding RB1CC1/FIP200 (RB1-inducible coiled-coil 1), a protein essential for induction of autophagy, was selectively knocked out in the RPE by crossing Best1-Cre mice with mice in which the Rb1cc1 gene was flanked with Lox-P sites (Rb1cc1(flox/flox)). Ex vivo and in vivo analyses, including western blot, immunohistochemistry, transmission electron microscopy, fundus photography, optical coherence tomography, fluorescein angiography, and electroretinography were performed to assess the structure and function of the retina as a function of age. Deletion of Rb1cc1 resulted in multiple autophagy defects within the RPE including decreased conversion of LC3-I to LC3-II, accumulation of autophagy-targeted precursors, and increased numbers of mitochondria. Age-dependent degeneration of the RPE occurred, with formation of atrophic patches, subretinal migration of activated microglial cells, subRPE deposition of inflammatory and oxidatively damaged proteins, subretinal drusenoid deposits, and occasional foci of choroidal neovascularization. There was secondary loss of photoreceptors overlying the degenerated RPE and reduction in the electroretinogram. These observations are consistent with a critical role of autophagy in the maintenance of normal homeostasis in the aging RPE, and indicate

that disruption of autophagy leads to retinal phenotypes associated with age-related degeneration.

PMID: 26075877 [PubMed - in process]

Genetics

Ophthalmology. 2015 Jun 13. [Epub ahead of print]

Association of Genetic Variants with Polypoidal Choroidal Vasculopathy: A Systematic Review and Updated Meta-analysis.

Ma L, Li Z, Liu K, Rong SS, Brelen ME, Young AL, Kumaramanickavel G, Pang CP, Chen H, Chen LJ.

TOPIC: A systematic review and meta-analysis of the genetic association with polypoidal choroidal vasculopathy (PCV) and the genetic difference between PCV and neovascular age-related macular degeneration (nAMD).

CLINICAL RELEVANCE: To identify genetic biomarkers that are potentially useful for genetic diagnosis of PCV and for differentiating PCV from nAMD.

METHODS: We performed a literature search in EMBASE, PubMed, Web of Science, and the Chinese Biomedical Database for PCV genetic studies published before February 6, 2015. We then conducted a meta-analysis of all polymorphisms that had sufficient genotype/allele data reported in ≥2 studies and estimated the summary odds ratio (OR) and 95% confidence intervals (CIs) for PCV. We also compared the association profiles between PCV and nAMD, and performed a sensitivity analysis.

RESULTS: A total of 66 studies were included in the meta-analysis, involving 56 polymorphisms in 19 genes/loci. In total, 31 polymorphisms in 10 genes/loci (age-related maculopathy susceptibility 2 [ARMS2], high-temperature requirement factor A1 [HTRA1], complement factor H [CFH], complement component 2 [C2], CFB, RDBP, SKIV2L, CETP, 8p21, and 4q12) were significantly associated with PCV. Another 25 polymorphisms in 13 genes (ARMS2, HTRA1, C2, CFB, ELN, LIPC, LPL, ABCA1, VEGF-A, TLR3, LOXL1, SERPING1, and PEDF) had no significant association. Twelve polymorphisms at the ARMS2-HTRA1 locus showed significant differences between PCV and nAMD. The sensitivity analysis validated the significance of our analysis.

CONCLUSIONS: This study revealed 31 polymorphisms in 10 genes/loci that contribute to PCV susceptibility. Among them, ARMS2-HTRA1 also showed allelic diversity between PCV and nAMD. Our results confirm the gene variants that could affect the phenotypic expressions of PCV and nAMD.

PMID: 26081444 [PubMed - as supplied by publisher]

Hum Gene Ther Clin Dev. 2015 Jun;26(2):97-100.

Transposon-Based, Targeted Ex Vivo Gene Therapy to Treat Age-Related Macular Degeneration (TargetAMD).

[No authors listed]

PMID: 26086761 [PubMed - in process]

Diet, lifestyle and low vision

J Nutr. 2015 Jun 17. [Epub ahead of print]

Vitamin D Deficiency in Community-Dwelling Elderly Is Not Associated with Age-Related Macular Degeneration.

Cougnard-Grégoire A, Merle BM, Korobelnik JF, Rougier MB, Delyfer MN, Féart C, Le Goff M, Dartigues JF, Barberger-Gateau P, Delcourt C.

BACKGROUND: Elderly persons are at elevated risk of vitamin D deficiency which is involved in various health problems. However, its relation with age-related macular degeneration (AMD) is debated.

OBJECTIVES: We investigated factors associated with plasma 25-hydroxyvitamin D [25(OH)D] deficiency and the associations between plasma 25(OH)D concentrations and AMD in elderly subjects.

METHODS: Antioxydants, Lipides Essentiels, Nutrition et maladies OculaiRes (ALIENOR) is a population-based study on eye diseases performed in elderly residents of Bordeaux, France. Plasma 25(OH)D concentrations were assessed from blood samples and categorized as <25 nmol/L (deficiency), 25-49 nmol/L (insufficiency), or ≥50 nmol/L (sufficiency). AMD was graded into: no AMD, early AMD, and late AMD. Associations between baseline characteristics and plasma 25(OH)D status were examined with multinomial logistic regression analysis. Associations between AMD and plasma 25(OH)D status were estimated using generalized estimating equation logistic regressions.

RESULTS: Six hundred ninety-seven subjects with complete data were included. The prevalence of plasma 25(OH)D deficiency and insufficiency were 27.3% and 55.9%, respectively. In multivariate analysis, 25(OH) D deficiency was significantly associated with older age (P = 0.0007), females (P = 0.0007), absence of physical activity (P = 0.01), absence of vitamin D supplementation (P < 0.0001), higher plasma total cholesterol (P = 0.007), use of fibrates (P < 0.0001), lower alcohol consumption (P = 0.02), and season of blood sampling (P < 0.0001). After adjustment for these covariates and dietary omega-3 polyunsaturated fatty acid intake, smoking, and body mass index, no significant associations were found between early AMD and 25(OH)D insufficiency or deficiency (OR: 0.71, P = 0.12; OR: 0.73, P = 0.23, respectively) or with late AMD (OR: 1.04, P = 0.93; OR: 0.74, P = 0.59, respectively).

CONCLUSION: These findings underline the very high prevalence of plasma 25(OH)D deficiency in this elderly population but do not support a specific role for vitamin D in AMD.

PMID: 26084364 [PubMed - as supplied by publisher]

Nutr Rev. 2015 Jul;73(7):448-62. Epub 2015 Apr 28.

Dietary modification and supplementation for the treatment of age-related macular degeneration.

Broadhead GK, Grigg JR, Chang AA, McCluskey P.

Abstract: Age-related macular degeneration (AMD) causes a significant proportion of visual loss in the developed world. Currently, little is known about its pathogenesis, and treatment options are limited. Dietary intake is one of the few modifiable risk factors for this condition. The best-validated therapies remain oral antioxidant supplements based on those investigated in the Age-Related Eye Disease Study (AREDS) and the recently completed Age-Related Eye Disease Study 2 (AREDS2). In this review, current dietary guidelines related to AMD, along with the underlying evidence to support them, are presented in conjunction with current treatment recommendations. Both AREDS and AREDS2 are discussed, as are avenues for further research, including supplementation with vitamin D and saffron. Despite the considerable disease burden of atrophic AMD, few effective therapies are available to treat it, and further research is required.

PMID: 26081455 [PubMed - in process]

PLoS One. 2015 Jun 19;10(6):e0130879.

Age-Related Vitamin D Deficiency Is Associated with Reduced Macular Ganglion Cell Complex: A Cross-Sectional High-Definition Optical Coherence Tomography Study.

Uro M, Beauchet O, Cherif M, Graffe A, Milea D, Annweiler C.

BACKGROUND: Vitamin D deficiency is associated with smaller volume of optic chiasm in older adults, indicating a possible loss of the visual axons and their cellular bodies. Our objective was to determine whether vitamin D deficiency in older adults is associated with reduced thickness of the ganglion cell complex(GCC) and of the retinal nerve fibre layer(RNFL), as measured with high-definition optical coherence tomography(HD-OCT).

METHODS: Eighty-five French older community-dwellers without open-angle glaucoma and patent age-related macular degeneration(mean, 71.1±4.7years; 45.9%female) from the GAIT study were separated into 2 groups according to serum 25OHD level(i.e., deficient≤25nmol/L or sufficient>25nmol/L). Measurements of GCC and RNFL thickness were performed using HD-OCT. Age, gender, body mass index, number of comorbidities, dementia, functional autonomy, intracranial volume, visual acuity, serum calcium concentration and season of testing were considered as potential confounders.

RESULTS: Mean serum 25OHD concentration was 58.4±26.8nmol/L. Mean logMAR visual acuity was 0.03±0.06. Mean visual field mean deviation was -1.25±2.29dB. Patients with vitamin D deficiency(n=11) had a reduced mean GCC thickness compared to those without vitamin D deficiency(72.1±7.4μm versus 77.5±7.5μm, P=0.028). There was no difference of the mean RNFL thickness in these two groups (P=0.133). After adjustment for potential confounders, vitamin D deficiency was associated with reduced GCC thickness(ß=-5.12, P=0.048) but not RNFL thickness(ß=-9.98, P=0.061). Specifically, vitamin D deficiency correlated with the superior medial GCC area(P=0.017) and superior temporal GCC area (P=0.010).

CONCLUSIONS: Vitamin D deficiency in older patients is associated with reduced mean GCC thickness, which can represent an early stage of optic nerve damage, prior to RNFL loss.

PMID: 26090872 [PubMed - as supplied by publisher]

Vestn Oftalmol. 2015 Mar-Apr;131(2):81-6, 88.

[Efficacy of conservative treatment in patients with dry form of age-related macular degeneration]. [Article in Russian]

Kovalevskaya MA, Milyutkina SO.

AIM: To evaluate the efficacy of conservative treatment in dry AMD patients by means of 3D computer-automated threshold Amsler grid testing (3D-CTAG; Fink & Sadun, 2004).

MATERIAL AND METHODS: The study included 90 patients (180 eyes) with dry AMD divided into three groups. Group 1 (n = 30) was prescribed Vitrum Vision forte, 1 tablet b.i.d., group 2 (n = 30)--Vitrum Vision forte, 1 tablet b.i.d. and Vitrum Cardio Omega-3, 1 capsule b.i.d. Group 3 (n = 30), the controls, received Taurine 250 mg, 1 tablet b.i.d. Besides standard ophthalmic examination, all patients underwent 3D-CTAG before and after the treatment. The number of defects per eye (ND) and volume lost relative to the hill-of-vision (VLRH) were chosen as evaluation criteria.

RESULTS: After 3 months of treatment ND decreased from 0.33 ± 0.02 to 0.22 ± 0.01 in group 1 ($p < 0.01$) and from 0.33 ± 0.02 to 0.2 ± 0.01 in group 2 ($p < 0.01$); VLRH decreased from 0.32 ± 0.02% to 0.15 ± 0.01% out of 693,000 [deg2%] in group 1 ($p < 0.01$) and from 0.32 ± 0.03% to 0.15 ± 0.01% out of 693,000 [deg2%] in group 2 ($p < 0.01$). In the controls both indices increased: ND from 0.32 ± 0.02 to 0.37 ± 0.02 and VLRH from 0.35 ± 0.24% to 0.49 ± 0.03% out of 693,000 [deg2%] ($p < 0.01$).

CONCLUSION: The positive effect of Vitrum Vision forte in combination with Vitrum Cardio Omega-3 on

macular function is comparable to that of monotherapy with Vitrum Vision forte. The maximum effect was achieved in patients with small scotomas (VLRH < 1.5% out of 693,000 [deg2%]).

PMID: 26080588 [PubMed - in process]

Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2015 Jun 12. [Epub ahead of print]

Blood levels of antioxidants during age-related macular degeneration treatment by rheohaemapheresis.

Aufartova J, Blaha M, Kasalova E, Honegrova B, Cervinkova B, Kujovska Krcmova L, Plisek J, Lanska M, Sobotka L, Solichova D.

AIMS: Rheohaemapheresis treatment influences rheological markers and most likely improves metabolism in affected retinal areas, resulting not only in absorption of soft drusen but also reduction or complete disappearance of drusenoid retinal pigment epithelium detachments. However, the character of the treatment process has raised suspicion that there is a decrease not only in cholesterol but also in antioxidants, such as vitamin E and vitamin A.

METHODS: Twenty-three patients with the progressive dry form of age-related macular degeneration were each treated with 8 procedures of rheohaemapheresis. We measured levels of vitamin E (α-tocopherol), the vitamin E/cholesterol ratio in serum and lipoproteins (VLDL, LDL, HDL). Vitamin E in erythrocyte membrane and serum vitamin A (retinol) were also measured. These parameters were determined before and after rheohaemapheresis. Erythrocyte superoxide dismutase, erythrocyte glutathione peroxidase and serum malondialdehyde were analysed as markers of antioxidant activity and lipid peroxidation, respectively.

RESULTS: In serum, the VLDL and LDL fraction ratios of vitamin E/cholesterol increased significantly. Additionally, the HDL fraction ratio showed an increase but this was not statistically significant. The patients showed no clinical signs of vitamin E deficiency, and their serum concentrations of vitamin E did not differ from normal values. The results show that rheohaemapheresis in addition to causing a significant reduction in atherogenic LDL cholesterol, may have favourable additive anti-atherogenic effects due to a relative increase in the content of vitamin E in the lipoprotein fractions.

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