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MD Research News

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Drug treatment

Clin Ophthalmol. 2016 Mar 29;10:541-6. eCollection 2016.

Treatment of neovascular age-related macular degeneration with anti-VEGF agents: retrospective analysis of 5-year outcomes.

Pedrosa AC, Reis-Silva A, Pinheiro-Costa J, Beato J, Freitas-da-Costa P, Falcão MS, Falcão-Reis F, Carneiro Â.

PURPOSE: To evaluate the 5-year results obtained in clinical practice in the treatment of neovascular age-related macular degeneration (nAMD) with anti-VEGF agents.

MATERIALS AND METHODS: We retrospectively analyzed all patients with nAMD who initiated anti-VEGF treatment before October 2009. We collected data regarding visual and anatomical outcomes.

RESULTS: A total of 278 patients met the selection criteria. The mean number of intravitreal injections was 5.7 in the first year and 3.7 in the fifth year. A positive mean visual acuity variation of +3.7 Early Treatment Diabetic Retinopathy Study letters occurred in the first year, but no significant differences relative to baseline were observed thereafter. The majority of patients (71%) maintained stable visual acuity throughout follow-up. At 5 years, mean central macular thickness remained substantially inferior to baseline (-96.6 µm), and 56% of patients maintained dry retinas.

CONCLUSION: Anti-VEGF therapy leads to long-term visual stabilization in the great majority of patients.

PMID: 27099460 [PubMed] PMCID: PMC4820212

Ther Clin Risk Manag. 2016 Apr 5;12:527-33. eCollection 2016.

Clinical effects and safety of treating diabetic macular edema with intravitreal injection of ranibizumab combined with retinal photocoagulation.

Yan P, Qian C, Wang W, Dong Y, Wan G, Chen Y.

BACKGROUND: This study was designed to examine the clinical effects of treating diabetic macular edema with an intravitreal injection of ranibizumab in combination with retinal photocoagulation.

METHODS: Sixty-two cases (75 eyes) with confirmed severe proliferative diabetic retinopathy or proliferative diabetic retinopathy in combination with macular edema were randomly divided into the observation group (37 eyes were given an intravitreal injection of ranibizumab combined with retinal photocoagulation) and the control group (38 eyes received retinal photocoagulation only). Vision, fundus condition, central macular thickness, and the macular leakage area were recorded before and after treatment.

RESULTS: The best-corrected visual acuity and macular leakage area were similar between the

observation and control groups (P>0.05). The best-corrected visual acuity in the observation group was higher than that in the control group 3 and 6 months after treatment (P<0.05) and showed a rising tendency. The macular leakage area in the observation group was significantly lower than that in the control group 1 and 3 months after treatment (P<0.05). However, the macular leakage area was similar 6 months after treatment (P>0.05). The central macular thickness of the observation group was lower than that in the control group 1, 3, and 6 months after treatment (P<0.05). The laser energy used in the observation group was also smaller than that in the control group (P<0.05). The intraocular pressure was not significantly different between the groups (P<0.05). No patients in the two groups developed eye or systemic complications, such as glaucoma, cataract, or vitreous hemorrhage during treatment.

CONCLUSION: Intravitreal injection of ranibizumab combined with retinal photocoagulation was proven to be effective in treating diabetic macular edema as it improved vision and resulted in fewer complications.

PMID: 27103811 [PubMed] PMCID: PMC4827417

Am J Ophthalmol. 2016 Apr 16. [Epub ahead of print]

Risk of Myocardial Infarction and Stroke With Single or Repeated Doses of Intravitreal Bevacizumab in Age-Related Macular Degeneration.

Etminan M, Maberley DA, Babiuk DW, Carleton BC.

PMID: 27093892 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2016 Apr;51(2):55-7.

Real-world utilization of ranibizumab in wet age-related macular degeneration patients from Canada.

Devenyi R, Maberley D, Sheidow TG, Tourville E, Brunck L, Berger AR.

Author information

PMID: 27085258 [PubMed - in process]

J Ocul Pharmacol Ther. 2016 Apr 19. [Epub ahead of print]

Combined Intravitreal Ranibizumab and Sub-Tenon Injection of Triamcinolone for the Treatment of Diabetic Macular Edema with Retinal Detachment.

Ercalik NY, Yenerel NM, Imamoglu S, Türkseven Kumral E, Vural ET.

PURPOSE: To evaluate the efficacy of intravitreal ranibizumab (IVR) combined with posterior sub-Tenon injection of triamcinolone acetonide (STTA) for treatment of diabetic macular edema (DME) with serous retinal detachment (SRD).

METHODS: Eighty-five eyes of 65 patients with DME and SRD were enrolled in this retrospective study. Fifty-eight eyes were treated with IVR and STTA (combined group), whereas 27 eyes were treated with pro re nata (PRN) IVR (control group). The combined group patients received a single and the control group patients received mean 1.29 ± 0.46 injections and followed for 3 months. The primary outcome measures were change in central macular thickness (CMT) and best corrected visual acuity (BCVA). The secondary outcome measure was the complication rate.

RESULTS: In the combined group, mean initial CMT was 543.9 ± 133.5 μm. Macular thickness was significantly reduced both after 1 month (334 ± 88 μm; P < 0.001) and after 3 months (387.6 ± 131.9 μm; P < 0.001) of treatment. At the 3-month follow-up, BCVA improved in 37.2% of the eyes. Complications were drug reflux at the time of STTA injection, elevation of intraocular pressure, and migration of hard exudates

to the fovea. The decrease in CMT was statistically significant in the combined group in the first month, but not in the third month compared with the control group. The improvement in BCVA was not statistically significant between the 2 groups both after the first and third months. SRD disappeared with a higher rate with the combined therapy in the first month.

CONCLUSION: IVR and STTA seem to be effective in improving BCVA in DME with SRD.

PMID: 27092435 [PubMed - as supplied by publisher]

ACS Med Chem Lett. 2016 Feb 2;7(4):363-7. eCollection 2016.

Evolution of a New Class of VEGFR-2 Inhibitors from Scaffold Morphing and Redesign.

Mainolfi N, Karki R, Liu F, Anderson K.

Abstract: Anti-VEGF therapy is a clinically validated treatment for age-related macular degeneration (AMD). We have recently reported the discovery of oral VEGFR-2 inhibitors that are selectively distributed to the ocular tissues. Herein we report a further development of those compounds and in particular the validation of the hypothesis that aminoheterocycles such as aminoisoxazoles and aminopyrazoles could also function as effective "hinge" binding moieties leading to a new class of KDR (kinase insert domain containing receptor) inhibitors.

PMID: 27096042 [PubMed] PMCID: PMC4834667

ACS Med Chem Lett. 2016 Mar 16;7(4):357-62. eCollection 2016.

Core Replacements in a Potent Series of VEGFR-2 Inhibitors and Their Impact on Potency, Solubility, and hERG.

Mainolfi N, Powers J, Meredith E, Elliott J, Gunderson KG, Poor S, Liu F, Anderson K.

Abstract: Anti-VEGF therapy has been a clinically validated treatment of age-related macular degeneration (AMD). We have recently reported the discovery of indole based oral VEGFR-2 inhibitors that provide sustained ocular retention and efficacy in models of wet-AMD. We disclose herein the synthesis and the biological evaluation of a series of novel core replacements as an expansion of the reported indole based VEGFR-2 inhibitor series. Addition of heteroatoms to the existing core and/or rearranging the heteroatoms around the 6-5 bicyclic ring structure produced a series of compounds that generally retained good on-target potency and an improved solubility profile. The hERG affinity was proven not be dependent on the change in lipophilicity through alteration of the core structure. A serendipitous discovery led to the identification of a new indole-pyrimidine connectivity: from 5-hydroxy to 6-hydroxyindole with potentially vast implication on the in vitro/in vivo properties of this class of compounds.

PMID: 27096041 [PubMed] PMCID: PMC4834653

Other treatment & diagnosis

Ophthalmologica. 2016 Apr 16. [Epub ahead of print]

Modeling Visual Acuity in Geographic Atrophy Secondary to Age-Related Macular Degeneration.

Schmitz-Valckenberg S, Nadal J, Fimmers R, Lindner M, Holz FG, Schmid M, Fleckenstein M; FAM Study Group.

PURPOSE: To analyze and model visual acuity (VA) in geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

METHODS: The course of VA was analyzed using Turnbull's estimator in 226 eyes with uni- or bilateral GA due to AMD (151 patients; mean age 74.0 ± 7.6 years; mean follow-up time 33.4 ± 23.4 months) from the natural history FAM (Fundus-Autofluorescence Imaging in AMD) study. The variables 'age at baseline', 'gender', 'lesion size', 'diagnosis of the fellow eye', 'status of the fovea', 'focality of the lesion' and 'pattern' were evaluated for effects on predicting VA using linear mixed-effects models.

RESULTS: Mean VA at baseline was 0.6 (Snellen 20/80) ± 0.4 logMAR [range -0.1 to 1.8 (20/17 to hand motions)], showing an estimated mean increase of 0.181 (95% CI 0.152-0.210) and 0.256 (0.214-0.300) after 2 and 4 years of follow-up, respectively. The percentage of eyes with a loss of ≥3 lines was 34% by 2 years and 47% by 4 years. Linear mixed model analysis suggested that 65% of VA variability could be explained by the assessed predictor variables. The strongest effect was found for the 'status of the fovea' (0.69 logMAR units between 'definitively spared fovea' and 'definitive foveal involvement', $p < 0.001$). The second strongest effect was identified for 'total lesion size' (effects between 0.02 and 0.09 logMAR units for each mm depending on foveal involvement, $p < 0.001$, square root transformed values).

CONCLUSIONS:

These findings underscore the importance of GA lesion characteristics as these have the strongest impact on VA. Natural history data and modeling VA to other variables will be helpful for refining outcome parameters and estimating possible benefits of therapeutic interventions.

PMID: 27089126 [PubMed - as supplied by publisher]

Clin Exp Optom. 2016 Apr 17. [Epub ahead of print]

Testing macular letter recognition - reliability and influence of refraction errors.

Eisenbarth W, Richert J, MacKeben M.

PURPOSE: The goal was the validation of the Macular Mapping Test (MMT) for clinical use. We studied its susceptibility to blur caused by refractive errors and its test-retest reliability.

METHODS: We tested letter recognition in 33 target locations in the central visual field (10° radius) at two contrast levels, 10 and 100 per cent. Healthy subjects were either young (mean: 25.7 years) or elderly (mean: 67.0 years). A third group (patients with age-related macular degeneration, mean age: 76.4 years) were tested with their habitual optical correction and subsequently with optimal correction. The influence of refractive errors on performance was measured only for the healthy subgroups. All visual acuities were measured at 6.0 and 0.4 metres. Outcome measure was the 'general field score' (GFS), a single number expressing the overall level of letter recognition performance.

RESULTS: The general field score versus refractive error showed a mean loss of 3.9 points per dioptre and 5.9 points per dioptre in young subjects at 100 and 10 per cent contrast, respectively. In elderly subjects, mean losses were 2.6 points per dioptre and 5.5 points per dioptre for 100 and 10 per cent contrast, respectively. The general field score ratio (GFS at 10 per cent divided by GFS at 100 per cent) shows a decrease of eight per cent for the young group and 11 per cent for the elderly group. Performance increased after improvement of the refractive status in the AMD group: At 100 per cent contrast, the general field score increase from 21.5 to 24.1 ($p < 0.008$) was significant but not at 10 per cent contrast. Mean increase of acuity with the optimal correction was 0.32 to 0.46 decimal for distance ($p = 0.018$) and 0.28 to 0.44 decimal near ($p = 0.018$). Test-retest reliability was good but dependent on contrast.

CONCLUSIONS: At both contrasts, performance declined with increasing blur caused by refractive errors. The slope of this decline is more pronounced at the lower contrast. In healthy subjects, optical blur beyond 1.00 D can cause significant performance losses.

PMID: 27087542 [PubMed - as supplied by publisher]

J Control Release. 2016 Apr 13. [Epub ahead of print]

A sustained release formulation of novel quininib-hyaluronan microneedles inhibits angiogenesis and retinal vascular permeability in vivo.

Galvin O, Srivastava A, Carroll O, Kulkarni R, Dykes S, Vickers S, Dickinson K, Reynolds A, Kilty C, Redmond G, Jones R, Cheetham S, Pandit A, Kennedy BN.

Abstract: Pathologic neovascularisation and ocular permeability are hallmarks of proliferative diabetic retinopathy and age-related macular degeneration. Current pharmacologic interventions targeting VEGF are effective in only 30-60% of patients and require multiple intraocular injections associated with iatrogenic infection. Thus, our goal is to develop novel small molecule drugs that are VEGF-independent are amenable to sustained ocular-release, and which reduce retinal angiogenesis and retinal vascular permeability. Here, the anti-angiogenic drug quininib was formulated into hyaluronan (HA) microneedles whose safety and efficacy was evaluated in vivo. Quininib-HA microneedles were formulated via desolvation from quininib-HA solution and subsequent cross-linking with 4-arm-PEG-amine prior to freeze-drying. Scanning electron microscopy revealed hollow needle-shaped particle ultrastructure, with a zeta potential of -35.5mV determined by electrophoretic light scattering. The incorporation efficiency and pharmacokinetic profile of quininib released in vitro from the microneedles was quantified by HPLC. Quininib incorporation into these microneedles was 90%. In vitro, 20% quininib was released over 4months; or in the presence of increasing concentrations of hyaluronidase, 60% incorporated quininib was released over 4months. Zebrafish hyaloid vasculature assays demonstrated quininib released from these microneedles significantly ($p<0.0001$) inhibited ocular developmental angiogenesis compared to control. Sustained amelioration of retinal vascular permeability (RVP) was demonstrated using a bespoke cysteinyl leukotriene induced rodent model. Quininib-HA microparticles significantly inhibited RVP in Brown Norway rats one month after administration compared to neat quininib control ($p=0.0071$). In summary, quininib-HA microneedles allow for sustained release of quininib; are safe in vivo and quininib released from these microneedles effectively inhibits angiogenesis and RVP in vivo.

PMID: 27086168 [PubMed - as supplied by publisher]

Ophthalmology. 2016 Apr 13. [Epub ahead of print]

Epimacular Brachytherapy for Previously Treated Neovascular Age-Related Macular Degeneration (MERLOT): A Phase 3 Randomized Controlled Trial.

Jackson TL, Desai R, Simpson A, Neffendorf JE, Petrarca R, Smith K, Wittes J, Lewis C, Membrey L, Haynes R, Costen M, Steel DH, Muldrew A, Chakravarthy U; Macular Epiretinal Brachytherapy versus Ranibizumab (Lucentis) Only Treatment (MERLOT) Study Group.

PURPOSE: To assess the safety and efficacy of epimacular brachytherapy (EMB) for patients with chronic, active, neovascular age-related macular degeneration (AMD).

DESIGN: Phase 3 randomized controlled trial.

PARTICIPANTS: Patients (n = 363) with neovascular AMD already receiving intravitreal ranibizumab injections.

INTERVENTION: Either pars plana vitrectomy with 24-gray EMB and ongoing pro re nata (PRN) ranibizumab (n = 224) or ongoing PRN ranibizumab monotherapy (n = 119).

MAIN OUTCOME MEASURES: The coprimary outcomes, at 12 months, were the number of PRN ranibizumab injections and Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (VA). Secondary outcomes included the proportion of participants losing fewer than 15 ETDRS letters, angiographic total lesion size, choroidal neovascularization (CNV) size, and optical coherence tomography (OCT) foveal thickness. A predefined subgroup analysis tested the influence of baseline ocular characteristics on the response to EMB.

RESULTS: The mean number of PRN ranibizumab injections was 4.8 in the EMB arm and 4.1 in the ranibizumab monotherapy arm (P = 0.068). The mean VA change was -4.8 letters in the EMB arm and -0.9 letters in the ranibizumab arm (95% confidence interval of difference between groups, -6.6 to -1.8 letters). The proportion of participants losing fewer than 15 letters was 84% in the EMB arm and 92% in the ranibizumab arm (P = 0.007). In the EMB arm, the mean total lesion size increased by 1.2 mm2 versus 0.4 mm2 in the ranibizumab arm (P = 0.27). The CNV size decreased by 0.5 mm2 in the EMB arm and by 1.3 mm2 in the ranibizumab arm (P = 0.27). The OCT foveal thickness decreased by 1.0 µm in the EMB arm and by 15.7 µm in the ranibizumab arm (P = 0.43). Most subgroups favored ranibizumab monotherapy, some significantly so. One participant showed retinal vascular abnormality attributed to radiation, but otherwise safety was acceptable.

CONCLUSIONS: These results do not support the use of EMB for chronic, active, neovascular AMD. Safety is acceptable out to 12 months, but radiation retinopathy can occur later, so further follow-up is planned.

PMID: 27086023 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2016 Apr 22. [Epub ahead of print]

OCT-Angiography strengthens the theory of a purely serous pigment epithelium detachment in age-related macular degeneration.

Alten F, Clemens CR, Eter N.

PMID: 27106624 [PubMed - as supplied by publisher]

Pathogenesis

Graefes Arch Clin Exp Ophthalmol. 2016 Apr 22. [Epub ahead of print]

Mitochondrial elongation in the macular RPE of aging monkeys, evidence of metabolic stress.

Gouras P, Ivert L, Neuringer M, Nagasaki T.

PURPOSE: This study was conducted to determine whether mitochondria of the macular retinal pigment epithelium (RPE) change with age in rhesus monkeys (Macaca mulatta). Mitochondria are the main instigators of oxidative stress, which has often been considered to play a role in the pathogenesis of age-related macular degeneration (AMD). Any pathological changes in the mitochondria of aging macular RPE, the main target of AMD, would be a clue to the pathogenesis of this common retinal degeneration afflicting both monkey and man.

METHODS: Transmission electron microscopy was used to identify mitochondria and to determine their appearance, their density per unit area of RPE cytoplasm and their length. The eyes of seven monkeys, 1, 2, 6.5, 23, 26, 27 and 35 years of age, were studied. Measurements were kept separate for the basal, middle and apical third of each cell. The basal third of the macular RPE had many more mitochondria than the middle third, and the apical third was almost devoid of mitochondria.

RESULTS: Mitochondrial number decreased and length increased with age. The increase in length was associated with an unusual clustering of mitochondria into parallel arrays of elongated mitochondria, with their long axis orthogonal to the basal membrane of the cell, structures not described before in RPE.

CONCLUSIONS: Mitochondrial elongation is associated with metabolic and/or oxidative stress, which implies that age produces stress in macular RPE. The increased clustering of very elongated mitochondria suggests that pathological changes occur in mitochondrial organization with age. These changes support the hypothesis that age-related mitochondrial dysfunction plays a role in the pathogenesis of AMD.

PMID: 27106622 [PubMed - as supplied by publisher]

Cell Mol Life Sci. 2016 Apr 21. [Epub ahead of print]

Role of Nrf2/HO-1 system in development, oxidative stress response and diseases: an evolutionarily conserved mechanism.

Loboda A, Damulewicz M, Pyza E, Jozkowicz A, Dulak J.

Abstract: The multifunctional regulator nuclear factor erythroid 2-related factor (Nrf2) is considered not only as a cytoprotective factor regulating the expression of genes coding for anti-oxidant, anti-inflammatory and detoxifying proteins, but it is also a powerful modulator of species longevity. The vertebrate Nrf2 belongs to Cap 'n' Collar (Cnc) bZIP family of transcription factors and shares a high homology with SKN-1 from Caenorhabditis elegans or CncC found in Drosophila melanogaster. The major characteristics of Nrf2 are to some extent mimicked by Nrf2-dependent genes and their proteins including heme oxygenase-1 (HO-1), which besides removing toxic heme, produces biliverdin, iron ions and carbon monoxide. HO-1 and their products exert beneficial effects through the protection against oxidative injury, regulation of apoptosis, modulation of inflammation as well as contribution to angiogenesis. On the other hand, the disturbances in the proper HO-1 level are associated with the pathogenesis of some age-dependent disorders, including neurodegeneration, cancer or macular degeneration. This review summarizes our knowledge about Nrf2 and HO-1 across different phyla suggesting their conservative role as stress-protective and anti-aging factors.

PMID: 27100828 [PubMed - as supplied by publisher]

Mol Pharm. 2016 Apr 18. [Epub ahead of print]

Joint anti-angiogenic effect of ATN-161 and anti-VEGF antibody in a rat model of early wet age-related macular degeneration.

Wang W, Wang F, Qin W, Liu H, Lu B, Chung C, Zhu J, Gu Q, Shi W, Wen C, Wu F, Zhang K, Sun X.

Abstract: The wet form of age-related macular degeneration (AMD) is a leading cause of blindness among elderly Americans and is characterized by abnormal vessel growth, termed choroidal neovascularization (CNV). Integrin α5β1 is a transmembrane receptor that binds matrix macromolecules and proteinases to stimulate angiogenesis. We recently demonstrated that integrin α5β1 plays a critical role in the development of choroidal neovascularization. In this study, we determined the role and underlying mechanisms of integrin α5β1 in angiogenesis in human choroidal endothelial cells and evaluated the anti-angiogenic effects of delivering a combination therapy of ATN-161, an integrin α5β1 inhibitor, and an anti-VEGF monoclonal antibody to rats with laser-induced CNV. Vascular endothelial growth factor (VEGF) is a signaling protein that stimulates vasculogenesis and angiogenesis through a pathway that is distinct from the integrin α5β1 signaling pathway. Our results indicate that fibronectin binds to integrin α5β1 and synergizes VEGF-induced angiogenesis via two independent signaling pathways, FN/integrin α5β1/FAK/ERK1/2 and FN/integrin α5β1/FAK/AKT. Integrin α5 knockdown by shRNA inhibits endothelial cell migration, tube formation, and proliferation, while ATN-161 only partially decreases integrin α5 function. Treatment with ATN-161 combined with anti-VEGF antibody showed joint effects in attenuating angiogenesis. In summary, our results provide the first evidence for the mechanisms by which integrin α5β1 is involved in ocular pathological neovascularization in vivo, suggesting that dual inhibition of integrin α5β1 and VEGF may be a promising novel therapeutic strategy for CNV in wet AMD.

PMID: 27089240 [PubMed - as supplied by publisher]

Nat Genet. 2016 Apr 18. [Epub ahead of print]

A missense variant in FGD6 confers increased risk of polypoidal choroidal vasculopathy.

Huang L, Zhang H, Cheng CY, et al

Abstract: Polypoidal choroidal vasculopathy (PCV), a subtype of 'wet' age-related macular degeneration (AMD), constitutes up to 55% of cases of wet AMD in Asian patients. In contrast to the choroidal neovascularization (CNV) subtype, the genetic risk factors for PCV are relatively unknown. Exome sequencing analysis of a Han Chinese cohort followed by replication in four independent cohorts identified a rare c.986A>G (p.Lys329Arg) variant in the FGD6 gene as significantly associated with PCV (P = 2.19 × 10-16, odds ratio (OR) = 2.12) but not with CNV (P = 0.26, OR = 1.13). The intracellular localization of FGD6-Arg329 is distinct from that of FGD6-Lys329. In vitro, FGD6 could regulate proangiogenic activity, and oxidized phospholipids increased expression of FGD6. FGD6-Arg329 promoted more abnormal vessel development in the mouse retina than FGD6-Lys329. Collectively, our data suggest that oxidized phospholipids and FGD6-Arg329 might act synergistically to increase susceptibility to PCV.

PMID: 27089177 [PubMed - as supplied by publisher]

Biochem Pharmacol. 2016 Apr 19. [Epub ahead of print]

Inhibition of BET bromodomains alleviates inflammation in human RPE cells.

Hytti M, Tokarz P, Määttä E, Piippo N, Korhonen E, Suuronen T, Honkakoski P, Kaarniranta K, Lahtela-Kakkonen M, Kauppinen A.

Abstract: Bromodomain-containing proteins are vital for controlling the expression of many pro-inflammatory genes. Consequently, compounds capable of inhibiting specific bromodomain-facilitated protein-protein interactions would be predicted to alleviate inflammation, making them valuable agents in the treatment of diseases caused by dysregulated inflammation, such as age-related macular degeneration. Here, we assessed the ability of known inhibitors JQ-1, PFI-1, and IBET-151 to protect from the inflammation and cell death caused by etoposide exposure in the human retinal pigment epithelial cell line, ARPE-19. The potential anti-inflammatory effects of the bromodomain inhibitors were assessed by ELISA (enzyme-linked immune sorbent assay) profiling. The involvement of NF-κB and SIRT1 in inflammatory signaling was monitored by ELISA and western blotting. Furthermore, SIRT1 was knocked down using a specific siRNA or inhibited by EX-527 to elucidate its role in the inflammatory reaction. The bromodomain inhibitors effectively decreased etoposide-induced release of IL-6 and IL-8. This anti-inflammatory effect was not related to SIRT1 activity, although all bromodomain inhibitors decreased the extent of acetylation of p53 at the SIRT1 deacetylation site. Overall, since bromodomain inhibitors display anti-inflammatory properties in human retinal pigment epithelial cells, these compounds may represent a new way of alleviating the inflammation underlying the onset of age-related macular degeneration.

PMID: 27106081 [PubMed - as supplied by publisher]

Epidemiology

PLoS One. 2016 Apr 20;11(4):e0153624. eCollection 2016.

Association of Serum Ferritin and Kidney Function with Age-Related Macular Degeneration in the General Population.

Oh IH, Choi EY, Park JS, Lee CH.

Abstract: Ferritin is considered to be a marker of the body's iron stores and has a potential relationship with the systemic manifestations of inflammatory reactions. Data on the association between increased levels of serum ferritin and ocular problems are limited, particularly in relation to age-related macular degeneration (AMD). Serum ferritin levels, as a possible clinical parameter for predicting AMD, were analyzed in anthropometric, biochemical, and ophthalmologic data from a nation-wide, population-based, case-control study (KNHNES IV and V). All native Koreans aged ≥ 20 years and who had no medical illness were eligible to participate. Among them, 2.9% had AMD, and its prevalence was found to increase in the higher ferritin quintile groups (Ptrend < 0.0001). In multiple linear regression analysis, serum ferritin level was

closely related to conventional risk factors for AMD. Comparison of early AMD with a control group showed that serum ferritin levels were closely associated with AMD (OR = 1.004, 95% CI = 1.002-1.006), and further adjustment for age, gender, serum iron, and kidney function did not reduce this association (OR = 1.003, 95% CI = 1.001-1.006). Furthermore, the relationship between ferritin quintile and early AMD was dose-dependent. Thus, an increased level of serum ferritin in a healthy person may be a useful indicator of neurodegenerative change in the macula. A large population-based prospective clinical study is needed to confirm these findings.

PMID: 27096155 [PubMed - in process]

Prog Retin Eye Res. 2016 Apr 14. [Epub ahead of print]

Age-related macular degeneration and polypoidal choroidal vasculopathy in Asians.

Wong CW, Yanagi Y, Lee WK, Ogura Y, Yeo I, Wong TY, Cheung CM.

Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in elderly people globally. It is estimated that there will be more Asians with AMD than the rest of the world combined by 2050. In Asian populations, polypoidal choroidal vasculopathy (PCV) is a common subtype of exudative AMD, while choroidal neovascularization secondary to AMD (CNV-AMD) is the typical subtype in Western populations. The two subtypes share many common clinical features and risk factors, but also have different epidemiological and clinical characteristics, natural history and treatment outcomes that point to distinct pathophysiological processes. Recent research in the fields of genetics, proteomics and imaging has provided further clarification of differences between PCV and CNV-AMD. Importantly, these differences have manifested in disparity in response to intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) treatment between PCV and CNV-AMD, emphasizing the need for accurate diagnosis of PCV and in distinguishing PCV from CNV-AMD, particularly in Asian patients. Current clinical trials of PCV of intravitreal anti-VEGF therapy and photodynamic therapy will provide clearer perspectives of evidence-based management of PCV and may lead to paradigm shifts in therapeutic strategies away from those currently employed in the treatment of CNV-AMD. Further research is needed to clarify the relative contribution of specific pathways in inflammation, complement activation, extracellular matrix dysregulation, lipid metabolism and angiogenesis to the pathogenesis of PCV. Findings from this research, together with improved diagnostic technology and new therapeutics, will allow more optimal management of Asian AMD.

PMID: 27094371 [PubMed - as supplied by publisher]

Genetics

J Neuroinflammation. 2016 Apr 18;13(1):81.

Multiallelic copy number variation in the complement component 4A (C4A) gene is associated with late-stage age-related macular degeneration (AMD).

Grassmann F, Cantsilieris S, Schulz-Kuhnt AS, White SJ, Richardson AJ, Hewitt AW, Vote BJ, Schmied D, Guymer RH, Weber BH, Baird PN.

BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of vision loss in Western societies with a strong genetic component. Candidate gene studies as well as genome-wide association studies strongly implicated genetic variations in complement genes to be involved in disease risk. So far, no association of AMD with complement component 4 (C4) was reported probably due to the complex nature of the C4 locus on chromosome 6.

METHODS: We used multiplex ligation-dependent probe amplification (MLPA) to determine the copy number of the C4 gene as well as of both relevant isoforms, C4A and C4B, and assessed their association with AMD using logistic regression models.

RESULTS: Here, we report on the analysis of 2645 individuals (1536 probands and 1109 unaffected controls), across three different centers, for multiallelic copy number variation (CNV) at the C4 locus. We find strong statistical significance for association of increased copy number of C4A (OR 0.81 (0.73; 0.89);P = 4.4 × 10(-5)), with the effect most pronounced in individuals over 78 years (OR 0.67 (0.55; 0.81)) and females (OR 0.77 (0.68; 0.87)). Furthermore, this association is independent of known AMD-associated risk variants in the nearby CFB/C2 locus, particularly in females and in individuals over 78 years.

CONCLUSIONS: Our data strengthen the notion that complement dysregulation plays a crucial role in AMD etiology, an important finding for early intervention strategies and future therapeutics. In addition, for the first time, we provide evidence that multiallelic CNVs are associated with AMD pathology.

PMID: 27090374 [PubMed - in process] PMCID: PMC4835888

JAMA Ophthalmol. 2016 Apr 21. [Epub ahead of print]

Single-Nucleotide Polymorphisms Associated With Age-Related Macular Degeneration and Lesion Phenotypes in the Comparison of Age-Related Macular Degeneration Treatments Trials.

Maguire MG, Ying GS, Jaffe GJ, Toth CA, Daniel E, Grunwald J, Martin DF, Hagstrom SA; CATT Research Group.

IMPORTANCE: Single-nucleotide polymorphisms (SNPs) associated with the CFH, ARMS2, C3, LIPC, CFB, and C2 genes are associated with age-related macular degeneration (AMD); however, the association of these SNPs with angiographic features of neovascular AMD has been inconsistent in previous studies, and to date, no studies have addressed their association with features on optical coherence tomography.

OBJECTIVE: To evaluate the influence of genotype of SNPs previously associated with AMD on the phenotype of neovascular lesions.

DESIGN, SETTING, AND PARTICIPANTS: Participants for this cross-sectional study were recruited from the 1185 patients enrolled in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), a randomized clinical trial. Eligibility criteria for CATT specified that eyes have choroidal neovascularization and visual acuity between 20/25 and 20/320. A subgroup of 835 patients provided blood samples from July 2010 through September 2011 and were genotyped for the SNPs rs1061170 (CFH), rs10490924 (ARMS2),rs2230199 (C3), rs10468017 (LIPC), rs4151667 (CFB), rs547154 (C2) using TaqMan SNP genotyping assays. Data analysis was initiated in November 2013 and completed in January 2016.

MAIN OUTCOMES AND MEASURES: Pretreatment ocular characteristics on fluorescein angiography (lesion type, area of neovascularization and total lesion, retinal angiomatous proliferation) and on time-domain optical coherence tomography (presence of intraretinal, subretinal, and subretinal pigment epithelium fluid; thickness at the foveal center of the retina, subretinal fluid, and subretinal tissue complex), visual acuity, and age.

RESULTS: A total of 835 (73%) of 1150 CATT patients were genotyped. Mean age decreased with the number of risk alleles for CFH (P < .001), ARMS2 (P < .001), and C3 (P = .005). The following results were found as the number of risk alleles increased from 0 to 1 to 2. For CFH, mean total thickness decreased from 476 to 476 to 434 μm (P = .01; adjusted for age, sex, and smoking status). For ARMS2, the mean area of the total lesion increased from 2.0 to 2.8 to 2.4 mm2 (P = .03), the proportion with retinal angiomatous proliferation lesions increased from 8% to 10% to 12% (P = .05), and the proportion with intraretinal fluid increased from 72% to 71% to 82% (P = .008). For C3, the proportion with intraretinal fluid decreased from 78% to 69% to 64% (P = .001), and the mean retinal thickness decreased from 225 to 207 to 197 μm (P = .02).

CONCLUSIONS AND RELEVANCE: CFH, ARMS2, and C3 were associated with specific features of neovascularization at the time patients were enrolled in CATT. Previously identified associations of ARMS2

and CFH with type of choroidal neovascularization on fluorescein angiography were not confirmed. New associations with OCT features identified in CATT need confirmation to establish whether a true association exists.

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Genetics and the Variable Phenotype of Age-Related Macular Degeneration.

Chowers I.

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Stem cells

Int J Mol Sci. 2016 Mar 22;17(3).

Ocular Stem Cell Research from Basic Science to Clinical Application: A Report from Zhongshan Ophthalmic Center Ocular Stem Cell Symposium.

Ouyang H, Goldberg JL, Chen S, Li W, Xu GT, Li W, Zhang K, Nussenblatt RB, Liu Y, Xie T, Chan CC, Zack DJ.

Abstract: Stem cells hold promise for treating a wide variety of diseases, including degenerative disorders of the eye. The eye is an ideal organ for stem cell therapy because of its relative immunological privilege, surgical accessibility, and its being a self-contained system. The eye also has many potential target diseases amenable to stem cell-based treatment, such as corneal limbal stem cell deficiency, glaucoma, age-related macular degeneration (AMD), and retinitis pigmentosa (RP). Among them, AMD and glaucoma are the two most common diseases, affecting over 200 million people worldwide. Recent results on the clinical trial of retinal pigment epithelial (RPE) cells from human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) in treating dry AMD and Stargardt's disease in the US, Japan, England, and China have generated great excitement and hope. This marks the beginning of the ocular stem cell therapy era. The recent Zhongshan Ophthalmic Center Ocular Stem Cell Symposium discussed the potential applications of various stem cell types in stem cell-based therapies, drug discoveries and tissue engineering for treating ocular diseases.

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Diet, lifestyle & low vision

Br J Ophthalmol. 2016 Apr 18. [Epub ahead of print]

Relationship between macular pigment and visual function in subjects with early age-related macular degeneration.

Akuffo KO, Nolan JM, Peto T, Stack J, Leung I, Corcoran L, Beatty S.

PURPOSE: To investigate the relationship between macular pigment (MP) and visual function in subjects with early age-related macular degeneration (AMD).

METHODS: 121 subjects with early AMD enrolled as part of the Central Retinal Enrichment Supplementation Trial (CREST; ISRCTN13894787) were assessed using a range of psychophysical measures of visual function, including best corrected visual acuity (BCVA), letter contrast sensitivity (CS),

mesopic and photopic CS, mesopic and photopic glare disability (GD), photostress recovery time (PRT), reading performance and subjective visual function, using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25). MP was measured using customised heterochromatic flicker photometry.

RESULTS: Letter CS, mesopic and photopic CS, photopic GD and mean reading speed were each significantly ($p<0.05$) associated with MP across a range of retinal eccentricities, and these statistically significant relationships persisted after controlling for age, sex and cataract grade. BCVA, NEI VFQ-25 score, PRT and mesopic GD were unrelated to MP after controlling for age, sex and cataract grade ($p>0.05$, for all).

CONCLUSIONS: MP relates positively to many measures of visual function in unsupplemented subjects with early AMD. The CREST trial will investigate whether enrichment of MP influences visual function among those afflicted with this condition.

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Maturitas. 2016 Jun;88:101-12. Epub 2016 Apr 2.

Circulating vitamin D concentration and age-related macular degeneration: Systematic review and meta-analysis.

Annweiler C, Drouet M, Duval GT, Paré PY, Leruez S, Dinomais M, Milea D.

Abstract: Vitamin D may be involved in ocular function in older adults, but there is no current consensus on a possible association between circulating concentrations of 25-hydroxyvitamin D (25OHD) and the occurrence of age-related macular degeneration (AMD). Our objective was to systematically review and quantitatively assess the association of circulating 25OHD concentration with AMD. A Medline search was conducted in November 2015, with no date limit, using the MeSH terms "Vitamin D" OR "Vitamin D deficiency" OR "Ergocalciferols" OR 'Cholecalciferol' combined with "Age-related macular degeneration" OR "Macular degeneration" OR "Retinal degeneration" OR "Macula lutea" OR "Retina". Fixed and random-effects meta-analyses were performed to compute (i) standard mean difference in 25OHD concentration between AMD and non-AMD patients; (ii) AMD risk according to circulating 25OHD concentration. Of the 243 retrieved studies, 11 observational studies-10 cross-sectional studies and 1 cohort study-met the selection criteria. The number of participants ranged from 65 to 17,045 (52-100% women), and the number with AMD ranged from 31 to 1440. Circulating 25OHD concentration was 15% lower in AMD compared with non-AMD on average. AMD was inversely associated with the highest 25OHD quintile compared with the lowest (summary odds ratio (OR)=0.83 [95%CI:0.71-0.97]), notably late AMD (summary OR=0.47 [95% CI:0.28-0.79]). Circulating 25OHD<50nmol/L was also associated with late-stage AMD (summary OR=2.18 [95%CI:1.34-3.56]), an association that did not persist when all categories of AMD were considered (summary OR=1.26 [95%CI:0.90-1.76]). In conclusion, this meta-analysis provides evidence that high 25OHD concentrations may be protective against AMD, and that 25OHD concentrations below 50nmol/L are associated with late AMD.

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Arch Biochem Biophys. 2016 Apr 1;595:100-8.

The rise, the fall and the renaissance of vitamin E.

Azzi A, Meydani SN, Meydani M, Zingg JM.

Abstract: This review deals with the expectations of vitamin E ability of preventing or curing, as a potent antioxidant, alleged oxidative stress based ailments including cardiovascular disease, cancer, neurodegenerative diseases, cataracts, macular degeneration and more. The results obtained with clinical intervention studies have highly restricted the range of effectiveness of this vitamin. At the same time, new

non-antioxidant mechanisms have been proposed. The new functions of vitamin E have been shown to affect cell signal transduction and gene expression, both in vitro and in vivo. Phosphorylation of vitamin E, which takes place in vivo, results in a molecule provided with functions that are in part stronger and in part different from those of the non-phosphorylate compound. The in vivo documented functions of vitamin E preventing the vitamin E deficiency ataxia (AVED), slowing down the progression of non-alcoholic steato-hepatitis (NASH), decreasing inflammation and potentiating the immune response are apparently based on these new molecular mechanisms. It should be stressed however that vitamin E, when present at higher concentrations in the body, should exert antioxidant properties to the extent that its chromanol ring is unprotected or un-esterified.

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Am J Occup Ther. 2016 May-Jun;70(3):7003270010p1-7.

Health Literacy in Older Adults With and Without Low Vision.

Warren M, DeCarlo DK, Dreer LE.

OBJECTIVE: In this study, we investigated whether older adults with low vision (LV) from age-related macular degeneration (AMD) demonstrated lower functional health literacy than older adults without LV.

METHOD: Fifty adults with AMD were matched with adults without LV on age, gender, education, and income. We measured visual acuity, contrast sensitivity, and reading speed and administered the Test of Functional Health Literacy in Adults (TOFHLA) using two test time conditions, standard and unlimited, to measure health literacy levels.

RESULTS: The group with LV had considerably lower TOFHLA scores for both time conditions ($p < .001$) and took notably longer to complete the test ($p < .001$). Poorer acuity correlated with lower TOFHLA scores in the group with LV.

CONCLUSION: Older adults with LV may take longer to read and understand health information, which has important implications for providing health education to support self-management. Modifying components of the reading task may facilitate reading performance and understanding of health education materials.

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Optom Vis Sci. 2016 May;93(5):558.

Functional Visual Acuity in Age-Related Macular Degeneration: Erratum.

[No authors listed]

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