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MD Research News

Issue 251

Wednesday 7 October, 2015

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Drug treatment

Am J Ophthalmol. 2015 Sep 30. [Epub ahead of print]

Retinal Pigment Epithelial Atrophy in Neovascular Age-Related Macular Degeneration After Ranibizumab Treatment.

Kuroda Y, Yamashiro K, Tsujikawa A, Ooto S, Tamura H, Oishi A, Nakanishi H, Miyake M, Yoshikawa M, Yoshimura N.

PURPOSE: To investigate the risk factors for development and progression of retinal pigment epithelial (RPE) atrophy during ranibizumab treatment for neovascular age-related macular degeneration (AMD) in Japanese patients.

DESIGN: Retrospective interventional case series.

METHODS: This study included 195 eyes with treatment-naïve subfoveal neovascular AMD. All patients were treated with an as-needed regimen after 3 monthly ranibizumab treatments. Color fundus photography, spectral-domain optical coherence tomography, and fundus autofluorescence were evaluated for RPE atrophy diagnosis. Baseline characteristics and ARMS2 A69S and CFH I62V polymorphisms were analyzed for their association with development and progression of RPE atrophy.

RESULTS: Ten (5.1%) of 195 eyes had RPE atrophy at baseline; 3 had typical AMD and 7 had polypoidal choroidal vasculopathy (PCV). Among 185 eyes without preexisting RPE atrophy at baseline, 7 (3.8%) developed RPE atrophy at 12 months, and 10 (5.4%) during the mean follow-up of 26.7 months. The incidence of newly developed RPE atrophy was lower in PCV than in typical AMD (P=.036), while the progression of the RPE atrophy area was faster in typical AMD than in PCV (0.57±0.35 and 0.31±0.13 mm/year, respectively; P=.018). The ARMS2 A69S and CFH I62V polymorphisms were significantly associated with the baseline RPE atrophy (P=.014 and P=.009, respectively).

CONCLUSIONS: The RPE atrophy developed in 5.4% of eyes with neovascular AMD during the 26.7 months of ranibizumab treatment. When compared with Caucasian individuals, RPE atrophy developed less frequently in Japanese patients, but the progression rate was similar. The subtype of AMD thus affects the development of RPE atrophy.

PMID: 26432927 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2015 Sep 1;46(8):844-50.

Bevacizumab Versus Ranibizumab in the Treatment of Macular Edema Due to Retinal Vein Occlusion: 6-Month Results of the CRAVE Study.

Rajagopal R, Shah GK, Blinder KJ, Altaweel M, Eliott D, Wee R, Cooper B, Walia H, Smith B, Joseph DP.

BACKGROUND AND OBJECTIVE: To compare efficacy of monthly treatment with bevacizumab or ranibizumab for macular edema due to retinal vein occlusion.

PATIENTS AND METHODS: Randomized, multicenter, comparative trial (ClinicalTrials.gov identifier: NCT01428388). Participants were randomized 1:1 to receive monthly treatment with bevacizumab or ranibizumab. The primary outcome was change in central foveal thickness at 6 months compared to baseline.

RESULTS: The trial randomized 98 patients to treatment with bevacizumab or ranibizumab. At 6 months, there were no differences in change in central foveal thickness between groups (bevacizumab: mean reduction of 212.6 µm, 95% confidence interval [CI], -288.3 to -137.0; ranibizumab: mean reduction of 243.8 µm, 95% CI, -309.6 to -178.0; P = .72, analysis of variance [ANOVA]). Both groups showed similar functional outcomes (bevacizumab: 0.33 logMAR gain, 95% CI, -0.47 to -0.18; ranibizumab: 0.34 logMAR gain, 95% CI, -0.45 to -0.23; P = .38, ANOVA).

CONCLUSION: In the treatment of retinal vein occlusion, bevacizumab and ranibizumab have similar effects on reducing macular thickness and improving visual acuity.

PMID: 26431300 [PubMed - in process]

Ophthalmic Surg Lasers Imaging Retina. 2015 Sep 1;46(8):824-30.

SLO-Microperimetry in Wet Age-Related Macular Degeneration During Anti-VEGF Therapy.

Hartmann K, Oster SF, Amini P, Bartsch DU, Cheng L, Freeman WR.

BACKGROUND AND OBJECTIVE: To evaluate the morphological and functional outcome of wet age-related macular degeneration (AMD) during antivascular endothelial growth factor therapy with bevacizumab using SLO microperimetry (SLO-MP) with eye tracking.

PATIENTS AND METHODS: First, reproducibility was tested over the choroidal neovascularization (CNV) in 21 eyes of 19 patients with wet AMD. Second, 21 eyes of 19 patients with active CNV were studied longitudinally during bevacizumab therapy. Best-corrected visual acuity, SLO-MP, spectral-domain optical coherence tomography and fluorescein angiography were performed.

RESULTS: There was good reproducibility with a concordance correlation coefficient of 0.85. In the longitudinal study, eyes with anatomical response demonstrated a significant increase of retinal sensitivity. Non-responders showed no change in SLO-MP. Retinal sensitivity at baseline had a significant predictive value for the change in retinal sensitivity during therapy with bevacizumab (P = .032).

CONCLUSION: SLO-MP is able to analyze retinal function overlying lesions in wet AMD and can be a useful tool to monitor therapy in patients with macular diseases.

PMID: 26431297 [PubMed - in process]

Pharmacogenet Genomics. 2015 Sep 29. [Epub ahead of print]

A genetic variant in NRP1 is associated with worse response to ranibizumab treatment in neovascular age-related macular degeneration.

Lorés-Motta L, van Asten F, Muether PS, Smailhodzic D, Groenewoud JM, Omar A, Chen J, Koenekoop RK, Fauser S, Hoyng CB, den Hollander AI, de Jong EK.

OBJECTIVE: The aim of the study was to investigate the role of single-nucleotide polymorphisms (SNPs) located in the neuropilin-1 (NRP1) gene in treatment response to antivascular endothelial growth factor (VEGF) therapy for neovascular age-related macular degeneration (nvAMD).

METHODS: Four SNPs in the NRP1 gene (rs2229935, rs2247383, rs2070296, and rs2804495) were

genotyped in a study cohort of 377 nvAMD patients who received the loading dose of three monthly ranibizumab injections. Treatment response was assessed as the change in visual acuity after three monthly loading injections compared with baseline.

RESULTS: SNP rs2070296 was associated with change in visual acuity after 3 months of treatment. Patients carrying the GA or AA genotypes performed significantly worse than individuals carrying the GG genotype (P=0.01). A cumulative effect of rs2070296 in the NRP1 gene and rs4576072 located in the VEGF receptor 2 (VEGFR2 or KDR) gene, previously associated with treatment response, was observed. Patients carrying two risk alleles performed significantly worse than patients carrying zero or one risk allele (P=0.03), and patients with more than two risk alleles responded even worse to the therapy (P=3×10). The combined effect of these two SNPs on the response was also seen after 6 and 12 months of treatment.

CONCLUSION: This study suggests that genetic variation in NRP1, a key molecule in VEGFA-driven neovascularization, influences treatment response to ranibizumab in nvAMD patients. The results of this study may be used to generate prediction models for treatment response, which in the future may help tailor medical care to individual needs.

PMID: 26426212 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2015 Sep 30. [Epub ahead of print]

Outer retinal tubulations response to anti-VEGF treatment.

Espina M, Arcinue CA, Ma F, Camacho N, Barteselli G, Mendoza N, Ferrara N, Freeman WR.

AIM: To review the longitudinal changes of outer retinal tubulations (ORTs) in wet age-related macular degeneration (AMD) and their response to anti-vascular endothelial growth factor (VEGF) therapy by spectral-domain optical coherence tomography (SD-OCT), and to correlate these observations with disease activity, presence or absence of fluid, and patients' demographics.

METHODS: Retrospective study of wet AMD eyes treated with anti-VEGF agents and showing ORTs on SD-OCT, and the patients' fellow eye with wet AMD but without ORTs.

RESULTS: Fifty-one wet AMD eyes from 31 patients diagnosed and treated for wet AMD were included in the review and analysis of data; 33 eyes showed ORTs at baseline, while 18 fellow eyes had no ORTs. During a median follow-up treatment period of 11 months, 23 eyes had stable ORTs and 10 eyes had ORT changes. Among the 10 eyes with ORTs changes, ORTs collapsed during anti-VEGF treatment in 5 eyes but then reappeared within 12 months after stopping treatment. In two eyes, ORTs increased in size during anti-VEGF treatment, while in two other eyes ORTs collapsed without any treatment. In a single eye, ORTs collapsed within 10 months of no treatment and did not reappear upon recurrence of fluid. Eyes with ORTs tended to have lower visual acuity than eyes with no ORTs due to greater disruption of the external limiting membrane in the fovea.

CONCLUSIONS: ORTs documented by SD-OCT may exhibit multiple types of longitudinal changes, such as collapse, recurrence or enlargement, which could be associated with anti-VEGF treatment or spontaneous. Some ORTs may have a vascular component or may be vascular in nature, considering their response to anti-VEGF treatment, while other ORTs are likely composed only of degenerating photoreceptor cells and may collapse independently from anti-VEGF treatments.

PMID: 26423451 [PubMed - as supplied by publisher]

Retina. 2015 Sep 28. [Epub ahead of print]

VOLUMETRIC ASSESSMENT OF THE RESPONSIVENESS OF PIGMENT EPITHELIAL DETACHMENTS IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TO INTRAVITREAL BEVACIZUMAB.

Or C, Chui L, Fallah N, Forooghian F.

PURPOSE: To determine baseline factors that can predict the response of pigment epithelial detachments (PEDs) in neovascular age-related macular degeneration to treatment with intravitreal bevacizumab (IVB).

METHODS: Patients with newly diagnosed neovascular age-related macular degeneration and PED who were treated exclusively with IVB were included. Response to treatment was defined by change in PED volume (determined using spectral-domain optical coherence tomography). PEDs were classified as either predominantly serous or fibrovascular. Multivariable regression and receiver operating characteristic analyses were performed.

RESULTS: A total of 48 eyes were identified (mean follow-up time 73 weeks). Overall, the response to the first IVB treatment was predictive of the response to treatment at the final visit (P = 0.015). Serous PEDs had a greater decrease in volume at the final visit (P = 0.008). With respect to both PED types, a decrease in PED volume of 21% after the first IVB treatment was predictive of an overall decrease in volume of 30% at the final visit (sensitivity 83%, specificity 76%).

CONCLUSION: In neovascular age-related macular degeneration, serous PEDs respond more favorably to IVB than fibrovascular PEDs. Overall, for both types of PED, the response to the first treatment is predictive of the final response to treatment. Taken together, the results would suggest that if there is less than 21% reduction in PED volume after the first IVB treatment, and/or the PED is predominantly fibrovascular, then switching to another antivascular endothelial growth factor agent should be considered.

PMID: 26418445 [PubMed - as supplied by publisher]

Ophthalmic Res. 2015 Sep 29;54(3):150-156. [Epub ahead of print]

Clinical Outcome after Switching Therapy from Ranibizumab and/or Bevacizumab to Aflibercept in Central Retinal Vein Occlusion.

Pfau M, Fassnacht-Riederle H, Becker MD, Graf N, Michels S.

PURPOSE: After 48 months, unresolved macular edema secondary to central retinal vein occlusion (CRVO) is present in more than half of the patients treated with ranibizumab/bevacizumab. Switching therapy to aflibercept, a more recent vascular endothelial growth factor-A (VEGF-A) inhibitor, as well as VEGF-B and placental growth factor inhibitor, might improve the clinical outcome in patients with CRVO who respond insufficiently to ranibizumab/bevacizumab.

METHODS: The presented study is a retrospective analysis of CRVO patients (n = 13) responding insufficiently to ranibizumab and/or bevacizumab (requiring treatment every 6 weeks or more frequently). Treatment in these patients was switched to aflibercept, which was administered based on a 'treat and extend' regime. The injection interval, relapse-free interval, central retinal thickness, central retinal volume, visual acuity, and intraocular pressure (IOP) were evaluated prior to switching to aflibercept and at month 6 and year 1 after switching therapy.

RESULTS: From baseline to year 1 after switching therapy to aflibercept, the mean injection interval (primary end point) increased by 0.51 months (p = 0.023) and the relapse-free interval by 3.02 weeks (p = 0.003). The mean central retinal thickness decreased by 195.84 µm and the mean central retinal volume (6 mm diameter) by -1.81 mm3 (p = 0.007). Correspondingly, the mean ETDRS score increased from 66.15 at baseline to 76.54 letters at year 1 after switching therapy to aflibercept (+10.38 letters, p = 0.021). The IOP was not statistically significantly affected (-1.2 mm Hg, p = 0.196).

CONCLUSION: Switching therapy from intravitreal ranibizumab/bevacizumab to aflibercept in insufficiently responding macular edema secondary to CRVO elongates the injection interval and the relapse-free interval and provides an improved anatomical as well as functional outcome.

PMID: 26413794 [PubMed - as supplied by publisher]

Sci Rep. 2015 Sep 28;5:14517.

Pharmacogenetics of Complement Factor H Y402H Polymorphism and Treatment of Neovascular AMD with Anti-VEGF Agents: A Meta-Analysis.

Chen G, Tzekov R, Li W, Jiang F, Mao S, Tong Y.

Abstract: The purpose of this study is to investigate whether the Y402H polymorphism (rs1061170, a T-to-C transition at amino acid position 402) in the complement factor H (CFH) gene have a pharmacogenetics effect on the anti-vascular endothelial growth factor (VEGF) treatment for neovascular age-related macular degeneration (AMD). We performed a meta-analysis using databases including PubMed and EMBASE to find relevant studies. 13 published association studies were selected for this meta-analysis, including 2704 patients. For the CFH Y402H polymorphism, anti-VEGF treatment was much less effective in AMD patients with the CFH CC genotype (CC versus TT: odds ratio (OR) = 55, 95% confidence interval (CI), 0.31 to 0.95, P = 0.03; CC versus CT: OR = 0.60, 95% CI, 0.40 to 0.91, P = 0.02; and CC versus CT + TT: OR = 0.59, 95% CI, 0.38 to 0.90, P = 0.02, respectively). In subgroup analysis, CFH Y402H polymorphism was more likely to be a predictor of response for Caucasians (CC versus CT+TT: OR = 0.63, 95% CI, 0.42 to 0.95, P = 0.03). In conclusion, pharmacogenetics of CFH Y402H polymorphism may play a role in response to anti-VEGF treatment for neovascular AMD, especially for Caucasians.

PMID: 26411831 [PubMed - in process] PMCID: PMC4585967

Curr Drug Metab. 2015 Oct 1. [Epub ahead of print]

Pharmacokinetic and Pharmacodynamic Properties of Anti-VEGF Drugs after Intravitreal Injection.

Semeraro F, Morescalchi F, Duse S1, Gambicorti E, Cancarini A, Costagliola C.

Abstract: Subretinal neovascularization and pathologic ocular angiogenesis are common causes of progressive, irreversible impairment of central vision, and dramatically affect quality of life. Anti-vascular endothelial growth factor (anti-VEGF) therapy has improved the quality of life for many patients with age-related macular degeneration, diabetic retinopathy, and other ocular diseases involving neovascularization and edema. In these pathologies, the inhibition of intraocular VEGF is the only therapy that can preserve vision. Four anti-VEGF drugs are currently used to treat ocular neovascularization; pegaptanib, ranibizumab, and aflibercept have been approved for this condition, while bevacizumab can be used off-label. Anti-VEGF therapy is administered regularly for many months or years because its suspension or discontinuation may cause recurrence of neovascularization. On the other hand, VEGF is necessary for the survival of retinal and choroidal endothelial cells. Experimental studies in animal models have shown that local inhibition of VEGF causes thinning and atrophy of the choriocapillaris and degeneration of photoreceptors, primarily cones. These studies combined with clinical experience indicated that prolonged VEGF inhibition could impair retinal function. Moreover, anti-VEGF compounds can cross the blood-retina barrier, enter the systemic circulation, and inhibit serum VEGF. Since circulating VEGF protects blood vessel integrity, prolonged anti-VEGF treatment could induce thromboembolic adverse events from vascular causes such as heart attack and stroke, and even death. The ocular dosing regimen and systemic toxicity of anti-VEGF compounds are therefore central concerns. A better understanding of this topic requires knowledge of the metabolism, tissue distribution, and clearance of anti-VEGF compounds. This manuscript reviews the properties of anti-VEGF compounds following intravitreal administration.

PMID: 26424177 [PubMed - as supplied by publisher]

Diabetes Metab Syndr Obes. 2015 Sep 18;8:473-82. eCollection 2015.

The clinical utility of aflibercept for diabetic macular edema.

Stewart MW.

Abstract: The treatment of center-involving diabetic macular edema (DME) has improved because of the proven efficacy of drugs that inhibit the effects of vascular endothelial growth factor (VEGF). The newest

anti-VEGF drug, aflibercept, has recently been approved by the United States Food and Drug Administration for the treatment of center-involving DME and for diabetic retinopathy in eyes with DME. In the pivotal Phase III VISTA and VIVID trials, intravitreal aflibercept 2 mg injections every 4 or 8 weeks (after 5 monthly loading doses) produced superior gains in BCVA compared to laser/sham injections. In the Diabetic Retinopathy Clinical Research Network Protocol T trial, which featured monthly anti-VEGF monotherapy for 6 months, followed by monthly pro re nata anti-VEGF injections with laser rescue therapy from months 6 through 12, aflibercept 2 mg monthly was superior to bevacizumab 1.25 mg and ranibizumab 0.5 mg in eyes with BCVA of 20/50 or worse (aflibercept versus bevacizumab: P<0.001; aflibercept versus ranibizumab: P=0.003), but the three regimens were comparable for eyes with VA of 20/40 or better. Only in the 20/50 or worse subgroup did aflibercept achieve clinical superiority (>5 letter difference) to bevacizumab. Each treatment regimen led to significant macular thinning, with aflibercept being superior to bevacizumab in both visual acuity subgroups (P<0.001 for each), but it was not statistically superior to ranibizumab in either group. In diabetic patients, aflibercept has an excellent safety profile that does not appear to differ from laser/sham or other VEGF inhibitory drugs.

PMID: 26425104 [PubMed] PMCID: PMC4583120

Pak J Pharm Sci. 2015 Jul;28(4 Suppl):1481-4.

Clinical research on intravitreal injection of bevacizumab in the treatment of macula lutea and retinal edema of ocular fundus disease.

Yan Y, Wang T, CaO J, Wang M, Li F.

Abstract: This paper aimed to explore clinically curative effect of intravitreal injection of bevacizumab in the treatment of macula lutea and retinal edema of ocular fundus disease. The number of 300 patients (390 eyes) with ocular fundus diseases including retinal vein occlusion (RVO), diabetic retinopathy (DR), age-related macular degeneration (ARMD), central serous chorioretinopathy (CSC), choridal new vessel (CNV) received and cured in the hospital from February 2010 to February 2014 were given intravitreal injection of bevacizumab (1.5mg) with once per month and a total of 2-3 times. Results of patients' vision and fluorescence fundus angiography (FFA), optical coherence tomography (OCT) before and after treatment were compared and curative effects were evaluated. Vision of 349 eyes (89.49%) improved obviously with the average of more than 2 lines, patient's intraocular pressure (IOP) was normal and all indexes were clearly better; vision of 26 eyes (6.67%) was stable before the treatment and without any changes after the treatment, the situation of fundus got better without increased IOP; vision of 15 eyes (3.85%) decreased to some extent, and the symptoms eased slightly after symptomatic treatment. In the 1st day after intravitreal injection, best-corrected visual acuity increased to 0.239±0.175, best-corrected visual acuity in 1 m was 0.315±0.182, in 3m continuously climbed to 0.350±0.270, and in 6 m was 0.362±0.282. Compared with vision before injection, t value was t=3.184, t=7.213, t=9.274 and t=9.970 (P=0.002, P=0.000, P=0.000 and P=0.000) respectively, and all P were less than 0.01. Furthermore, the difference was significant if a=0.01, which could confirm that 1m best corrected visual acuity of patients after intravitreal injection improved clearly in combination with before injection and 3m and 6 m visions enhanced constantly after injection. To sum up, intravitreal injection of bevacizumab in treating ocular fundus disease improves patient's vision effectively, also relieves macula lutea, retinal edema and other symptoms obviously, and promotes the hemorrhage absorption of vitreous body and retina.

PMID: 26431660 [PubMed - in process]

Other treatment & diagnosis

Lancet. 2015 Sep 29. [Epub ahead of print]

Gene therapy with recombinant adeno-associated vectors for neovascular age-related macular degeneration: 1 year follow-up of a phase 1 randomised clinical trial.

Rakoczy EP, Lai CM, Magno AL, Wikstrom ME, French MA, Pierce CM, Schwartz SD, Blumenkranz MS,

Chalberg TW, Degli-Esposti MA, Constable IJ.

BACKGROUND: Neovascular, or wet, age-related macular degeneration causes central vision loss and represents a major health problem in elderly people, and is currently treated with frequent intraocular injections of anti-VEGF protein. Gene therapy might enable long-term anti-VEGF therapy from a single treatment. We tested the safety of rAAV.sFLT-1 in treatment of wet age-related macular degeneration with a single subretinal injection.

METHODS: In this single-centre, phase 1, randomised controlled trial, we enrolled patients with wet age-related macular degeneration at the Lions Eye Institute and the Sir Charles Gairdner Hospital (Nedlands, WA, Australia). Eligible patients had to be aged 65 years or older, have age-related macular degeneration secondary to active subfoveal choroidal neovascularisation, with best corrected visual acuity (BCVA) of 3/60-6/24 and 6/60 or better in the other eye. Patients were randomly assigned (3:1) to receive either 1 × 1010 vector genomes (vg; low-dose rAAV.sFLT-1 group) or 1 × 1011 vg (high-dose rAAV.sFLT-1 group), or no gene-therapy treatment (control group). Randomisation was done by sequential group assignment. All patients and investigators were unmasked. Staff doing the assessments were masked to the study group at study visits. All patients received ranibizumab at baseline and week 4, and rescue treatment during follow-up based on prespecified criteria including BCVA measured on the Early Treatment Diabetic Retinopathy Study (EDTRS) scale, optical coherence tomography, and fluorescein angiography. The primary endpoint was ocular and systemic safety. This trial is registered with ClinicalTrials.gov, number NCT01494805.

FINDINGS: From Dec 16, 2011, to April 5, 2012, we enrolled nine patients of whom eight were randomly assigned to receive either intervention (three patients in the low-dose rAAV.sFLT-1 group and three patients in the high-dose rAAV.sFLT-1 group) or no treatment (two patients in the control group). Subretinal injection of rAAV.sFLT-1 was highly reproducible. No drug-related adverse events were noted; procedure-related adverse events (subconjunctival or subretinal haemorrhage and mild cell debris in the anterior vitreous) were generally mild and self-resolving. There was no evidence of chorioretinal atrophy. Clinical laboratory assessments generally remained unchanged from baseline. Four (67%) of six patients in the treatment group required zero rescue injections, and the other two (33%) required only one rescue injection each.

INTERPRETATION: rAAV.sFLT-1 was safe and well tolerated. These results support ocular gene therapy as a potential long-term treatment option for wet age-related macular degeneration.

PMID: 26431823 [PubMed - as supplied by publisher]

Lancet. 2015 Sep 29. [Epub ahead of print]

Gene therapy for age-related macular degeneration.

MacLaren RE.

PMID: 26431822 [PubMed - as supplied by publisher]

Retina. 2015 Sep 29. [Epub ahead of print]

DISTINGUISHING POLYPOIDAL CHOROIDAL VASCULOPATHY FROM TYPICAL NEOVASCULAR AGE-RELATED MACULAR DEGENERATION BASED ON SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY.

Liu R, Li J, Li Z, Yu S, Yang Y, Yan H, Zeng J, Tang S, Ding X.

PURPOSE: To investigate the sensitivity and specificity of spectral domain optical coherence tomography in distinguishing polypoidal choroidal vasculopathy (PCV) from typical neovascular age-related macular degeneration (nAMD).

METHODS: One hundred and eighty-eight eyes in 156 patients with active PCV or typical nAMD were enrolled prospectively. Three spectral domain optical coherence tomography manifestations, pigment

epithelium detachment, double-layer sign, and thumb-like polyps were estimated in all the eyes. A diagnostic test to differentiate PCV from nAMD based on spectral domain optical coherence tomography was performed. Furthermore, the sensitivity and specificity was validated in a retrospective series of patients.

RESULTS: Pigment epithelium detachment, double-layer sign, and thumb-like polyps were more common in PCV eyes than in nAMD eyes. When the cutoff point was set as at least 2 positive signs out of 3 in the diagnostic test, the sensitivity was 89.4% and specificity was 85.3%. The results of the validation test further confirmed the strategy, with satisfying sensitivity (87.5%) and specificity (86.2%).

CONCLUSION: Spectral domain optical coherence tomography is sensitive and specific in distinguishing PCV from nAMD. From these results, the presence of at least two out three signs (pigment epithelium detachment, double-layer sign, and thumb-like polyps) indicates a positive test and is therefore suggested to be the screening strategy for PCV.

PMID: 26428604 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2015 Sep 1;46(8):814-22.

Choroidal Thickness in Eyes With Central Geographic Atrophy Secondary to Stargardt Disease and Age-Related Macular Degeneration.

Nunes RP, Rosa PR, Giani A, Goldhardt R, Thomas B, Filho CA, Gregori G, Feuer W, Lam BL, Staurenghi G, Rosenfeld PJ.

BACKGROUND AND OBJECTIVE: Choroidal thickness (CT) measurements from eyes with similar areas of macular geographic atrophy (GA) secondary to age-related macular degeneration (AMD) and Stargardt disease (STGD) were compared to determine whether GA from different diseases had a similar or different effect on the underlying subfoveal choroid.

PATIENTS AND METHODS: Eyes with the diagnosis of central GA secondary to STGD and AMD were matched, with subfoveal CT measurements obtained from the central B-scan using an enhanced depth imaging protocol. The area of GA was measured using fundus autofluorescence (FAF) imaging. AMD eyes were divided into those with and without reticular pseudodrusen.

RESULTS: A total of 22 eyes of 22 patients were included in the STGD and AMD groups and were matched with respect to the area of GA. The mean age of the STGD patients was 48.9 years (standard deviation [SD] = 17.1), and the mean age was 81.8 years (SD = 6.2) for the AMD patients. Mean area measurements of GA for the STGD and AMD groups were 5.4 mm(2) (SD = 4.1) and 5.1 mm(2) (SD = 4.0), respectively (P = .83). After adjusting for age and axial length, eyes with STGD had a mean CT measurement greater than the AMD eyes (336.1 µm vs. 198.1 µm, respectively; P = .039). However, this difference was driven by AMD eyes with reticular pseudodrusen (RPD) and by a single Stargardt case with a very thick choroid. Eyes with RPD had statistically thinner subfoveal CT measurements when compared with all other groups.

CONCLUSION: A small but statistically significant increase in the CT of STGD eyes was observed when compared with normal controls and AMD eyes without RPD. However, this small increase in CT was driven by a single case with a markedly thicker choroid within the STGD group, so it is unlikely that a clinically significant difference exists. However, AMD eyes with GA and RPD had significantly thinner subfoveal CT measurements.

PMID: 26431296 [PubMed - in process]

J Ophthalmol. 2015;2015:865083. Epub 2015 Sep 3.

Effects of Vitreomacular Adhesion on Age-Related Macular Degeneration.

Kang EC, Koh HJ.

Abstract: Herein, we review the association between vitreomacular adhesion (VMA) and neovascular age-related macular degeneration (AMD). Meta-analyses have shown that eyes with neovascular AMD are twice as likely to have VMA as normal eyes. VMA in neovascular AMD may induce inflammation, macular traction, decrease in oxygenation, sequestering of vascular endothelial growth factor (VEGF), and other cytokines or may directly stimulate VEGF production. VMA may also interfere with the treatment effects of anti-VEGF therapy, which is the standard treatment for neovascular AMD, and releasing VMA can improve the treatment response to anti-VEGF treatment in neovascular AMD. We also reviewed currently available methods of relieving VMA.

PMID: 26425354 [PubMed] PMCID: PMC4573628 Free PMC Article

Ophthalmic Surg Lasers Imaging Retina. 2015 Sep 1;46(8):872-9.

Image Scaling Difference Between a Confocal Scanning Laser Ophthalmoscope and a Flash Fundus Camera.

Nittala MG, Hariri A, Wong WT, Chew EY, Ferris FL, Sadda SR.

BACKGROUND AND OBJECTIVE: To evaluate scaling and measurement differences between flash and scanning laser fundus images.

PATIENTS AND METHODS: The authors analyzed fundus autofluorescence images of patients with geographic atrophy secondary to age-related macular degeneration imaged with both 30º confocal scanning laser ophthalmoscope (cSLO) and 50º flash fundus camera (FFC). Multiple vessel-crossing points served as landmarks.

RESULTS: The mean (± SD; range) scaling factor between cSLO and FFC images (by GRADOR) for the horizontal dimension was 1.217 (± 0.0487; 1.0474-1.272) versus 1.138 (± 0.0311; 1.0841-1.193) for the vertical dimension. The mean percentage difference between horizontal and vertical scaling factors was 7.48 (± 2.29; 2.30-10.70). Refractive error (focus) and aperture size (or field of view of the image) were positively correlated and aspect ratio was negatively correlated with landmark pair measurements.

CONCLUSION: Inherent image-scaling differences between fundus autofluorescence imaging systems are not restricted to simple pixel-to-millimeter calibration variances, but appear to vary depending on measurement orientation. Differences should be considered when comparing measurements obtained using different imaging systems, particularly for clinical trials.

PMID: 26431304 [PubMed - in process]

Eur J Ophthalmol. 2015 Oct 1:0. [Epub ahead of print]

Intravitreal injection of recombinant tissue plasminogen activator in submacular hemorrhage: case series.

Araújo J, Sousa C, Faria PA, Carneiro Â, Rocha-Sousa A, Falcão-Reis F.

PURPOSE: To report the safety and efficacy of intravitreal recombinant tissue plasminogen activator (rtPA) with gas for managing submacular hemorrhage.

METHODS: Patients with submacular hemorrhage centered in or close to the fovea underwent hemorrhage displacement with intravitreal injection of rtPA (50 µg/0.05 mL) followed by gas injection (0.3 mL SF6). Anatomic and visual outcomes are described.

RESULTS: Exudative age-related macular degeneration (AMD) (n = 4) and blunt trauma (n = 2) were the etiologies of submacular hemorrhage in this sample. Intravitreal injection of rtPA decreased the extent of submacular hemorrhage in all eyes, with complete hemorrhage displacement in 2 and partial displacement in 4. Visual acuity remained stable (n = 4) or improved (n = 2) after the procedure. Improvements in anatomic and visual outcomes were less evident in exudative AMD cases, which also had longer

hemorrhage duration. Recurrence occurred only in 1 eye. No evident rtPA-associated retinal toxicity was observed.

CONCLUSIONS: Untreated submacular hemorrhage has poor visual prognosis. Our results suggest that rtPA injection is a minimally invasive, simple, inexpensive procedure with few related complications. Cost-benefit of this injection seems acceptable.

PMID: 26428222 [PubMed - as supplied by publisher]

Curr Mol Pharmacol. 2015 Sep 28. [Epub ahead of print]

Stem Cell Therapy and Immunological Rejection in animal models.

Jin X, Lin T, Xu Y.

Abstract: With their capability to undergo unlimited self-renew and to differentiate into various functional cells, human pluripotent stem cells, including embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs), hold great promise in regenerative medicine to treat currently incurable diseases. Significant progress has been achieved in differentiating pluripotent stem cells into various functional cells, such as pancreatic □ cells, neural cells, hepatocytes, and cardiomyocytes. In addition, three hESC-based therapies to treat spinal cord injury, macular degeneration and type I diabetes have entered clinical trial. However, there remain several major bottlenecks that hinder the clinical trial of stem cell based therapy. One such key challenge is the immune rejection of cells derived from allogeneic hESCs. The challenge of immune rejection is mitigated by recent discovery of iPSCs, raising the hope that patient-specific hiPSCs can be differentiated into autologous cells for transplantation into the same patient without the concern of immune rejection. However, due to the oncogenic potential of the reprogramming factors and the reprogramming-induced DNA damage, there remains safety concerns about the cancer risk and immunogenicity of hiPSC-derived cells. This review discusses recent progress in our understanding of the immunogenicity of pluripotent stem cells and the development of new strategies to resolve this challenge.

PMID: 26415913 [PubMed - as supplied by publisher]

Expert Opin Biol Ther. 2015 Sep 28:1-8. [Epub ahead of print]

Stem cells in clinical trials for treatment of retinal degeneration.

Klassen H.

INTRODUCTION: After decades of basic science research involving the testing of regenerative strategies in animal models of retinal degenerative diseases, a number of clinical trials are now underway, with additional trials set to begin shortly. These efforts will evaluate the safety and preliminary efficacy of cell-based products in the eyes of patients with a number of retinal conditions, notably including age-related macular degeneration, retinitis pigmentosa and Stargardt's disease. Areas covered: This review considers the scientific work and early trials with fetal cells and tissues that set the stage for the current clinical investigatory work, as well the trials themselves, specifically those either now completed, underway or close to initiation. The cells of interest include retinal pigment epithelial cells derived from embryonic stem or induced pluripotent stem cells, undifferentiated neural or retinal progenitors or cells from the vascular/bone marrow compartment or umbilical cord tissue. Expert opinion: Degenerative diseases of the retina represent a popular target for emerging cell-based therapeutics and initial data from early stage clinical trials suggest that short-term safety objectives can be met in at least some cases. The question of efficacy will require additional time and testing to be adequately resolved.

PMID: 26414165 [PubMed - as supplied by publisher]

Retin Cases Brief Rep. 2015 Sep 28. [Epub ahead of print]

RECURRENCE OF VITELLIFORM LESIONS ASSOCIATED WITH TEMPORARY VISION LOSS IN BEST VITELLIFORM MACULAR DYSTROPHY.

Wang YT, Tadarati M, Scholl HP, Bressler NM.

PURPOSE: To describe visual acuity changes associated with several cycles of accumulation, disappearance, and reaccumulation of vitelliform material in Best disease, with fundus photographs, fluorescein angiograms, and optical coherence tomography images documenting these stages.

METHODS: Case report with 70 months of follow-up using fundus photography, fluorescein angiography, and optical coherence tomography to image the retina. A non-Hispanic white 33-year-old man with Best disease (positive for a mutation in the BEST1 gene, namely p.Tyr167Cys:c.500A>G).

RESULTS: The patient had a history of choroidal neovascularization (CNV) followed by scarring of the macula with sustained vision loss of ~20/250 in the left eye when he was in his twenties. He subsequently presented in his thirties with acute vision loss in the right eye 3 times during a 70-month follow-up period. Each episode of vision loss in the right eye was preceded by several months of reaccumulation of vitelliform material in the macula apparent on fundus photographs, fluorescein angiograms, and optical coherence tomography, but no evidence of CNV on presentation. Each of the three episodes of vision loss in the right eye was followed by spontaneous gradual improvement in visual acuity over the next several months, correlating with decreasing amounts of the vitelliform material on clinical examination and fundus photographs. After the third documented recovery of visual acuity, at a time of stable vision, the patient developed CNV in the right eye, treated with intravitreal ranibizumab.

CONCLUSION: This case demonstrates that vitelliform material can reaccumulate and resorb several times in Best disease, with temporary visual acuity decline after each episode of vitelliform material accumulation. There is a need for continued vigilance for the development of CNV in patients presenting with acute vision loss, although this patient developed CNV at a time of stable vision.

PMID: 26418331 [PubMed - as supplied by publisher]

Biomed Opt Express. 2015 Aug 25;6(9):3564-76. eCollection 2015.

Automated choroidal neovascularization detection algorithm for optical coherence tomography angiography.

Liu L, Gao SS, Bailey ST, Huang D, Li D, Jia Y.

Abstract: Optical coherence tomography angiography has recently been used to visualize choroidal neovascularization (CNV) in participants with age-related macular degeneration. Identification and quantification of CNV area is important clinically for disease assessment. An automated algorithm for CNV area detection is presented in this article. It relies on denoising and a saliency detection model to overcome issues such as projection artifacts and the heterogeneity of CNV. Qualitative and quantitative evaluations were performed on scans of 7 participants. Results from the algorithm agreed well with manual delineation of CNV area.

PMID: 26417524 [PubMed] PMCID: PMC4574680

Am J Ophthalmol. 2015 Sep 27. [Epub ahead of print]

The Effects of Cataract Surgery on Patients With Wet Macular Degeneration.

Kim JH.

PMID: 26422829 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2015 Sep 24. [Epub ahead of print]

The Effects of Cataract Surgery on Patients With Wet Macular Degeneration.

Saraf SS, Ryu CL, Ober MD.

PMID: 26411632 [PubMed - as supplied by publisher]

Pathogenesis

J Ophthalmic Vis Res. 2015 Apr-Jun;10(2):151-4.

Endothelin-1 and Nitric Oxide Levels in Exudative Age-Related Macular Degeneration.

Totan Y, Koca C, Erdurmuş M, Keskin U, Yiğitoğlu R.

PURPOSE: To evaluate plasma levels of endothelin-1 (ET-1) and nitric oxide (NO) in patients with exudative age-related macular degeneration (AMD).

METHODS: In this study, ET-1 levels, as well as nitrite plus nitrate concentrations as an indicator of plasma NO level, were measured in the plasma of 20 subjects with exudative AMD and compared with 20 healthy age and sex matched controls.

RESULTS: Mean plasma ET-1 level was significantly higher in exudative AMD patients as compared to control subjects (0.35 ± 0.06 fmol/ml versus 0.17 ± 0.03 fmol/ml, P = 0.015). Patients with exudative AMD also showed significantly lower mean plasma levels of nitrite plus nitrate as compared to the controls (58.9 ± 2.7 µmol/l versus 82.6 ± 5.9 µmol/l, P = 0.001).

CONCLUSION: Increased concentrations of ET-1 and reduced levels of NO in the plasma may suggest an imbalance between vasoconstrictor and vasodilator agents, respectively, as a reflection of endothelial dysfunction in the pathogenesis of AMD. These findings may also imply the role of vasoconstriction in exudative AMD.

PMID: 26425317 [PubMed] PMCID: PMC4568612

Invest Ophthalmol Vis Sci. 2015 Oct 1;56(11):6265-74.

Effects of Cytokine Activation and Oxidative Stress on the Function of the Human Embryonic Stem Cell-Derived Retinal Pigment Epithelial Cells.

Juuti-Uusitalo K, Nieminen M, Treumer F, Ampuja M, Kallioniemi A, Klettner A, Skottman H.

PURPOSE: In several retinal complications, such as age-dependent macular degeneration (AMD), oxidative stress is increased and cytokine level is elevated. These are shown to alter the activation and expression of matrix metalloproteinase (MMP) both in human primary and immortalized retinal pigment epithelial (RPE) cells. However, the effects on human embryonic stem cell (hESC)-derived RPE cells remain to be elucidated.

METHODS: The mature hESC-RPE cells were exposed to inflammatory cytokines (IFN-γ or TNF-α) for 24 hours or oxidative stress (H2O2) for 1 hour. Effects on barrier properties were analyzed with transepithelial electrical resistance (TEER), the expression of MMP-1, MMP-2, MMP-3, MMP-9, collagen I, and collagen IV genes with quantitative RT-PCR, and the expression of MMP-1 and MMP-3 proteins with Western blot or ELISA, respectively. Also, activation and secretion of MMP-2 and -9 proteins were analyzed with zymography.

RESULTS: In normal state, mature hESC-RPE cells expressed MMP-1, -2, -3, and -9 genes in low levels, respectively. Tumor necrosis factor-α increased MMP-1 and -2 gene expression, and H2O2 increased MMP -3 and -9 gene expression. Zymography revealed IFN-γ- and TNF-α-induced secretion of MMP-2 and high-

molecular-weight species of MMP (HMW MMP), but H2O2 decreased their secretion. Furthermore, TNF-α and H2O2 significantly decreased barrier properties.

CONCLUSIONS: Here, cytokines induced the MMP-1 and -2 gene and protein expression. Also, H2O2 induced MMP-3 and -9 gene expression, but not their protein secretion. These data propose that under oxidative stress and cytokine stimuli, mature hESC-RPE cells resemble their native counterpart in the human eye in regard to MMP secretion and expression and could be used to model retinal disorders involving alterations in MMP activity such as AMD, diabetic retinopathy, or proliferative vitreoretinopathy in vitro.

PMID: 26431480 [PubMed - in process]

Exp Eye Res. 2015 Sep 30. [Epub ahead of print]

Illumination from light-emitting diodes (LEDs) disrupts pathological cytokines expression and activates relevant signal pathways in primary human retinal pigment epithelial cells.

Shen Y, Xie C, Gu Y, Li X, Tong J.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the aged people. The latest systemic review of epidemiological investigations revealed that excessive light exposure increases the risk of AMD. With the drastically increasing use of high-energy light-emitting diodes (LEDs) light in our domestic environment nowadays, it is supposed to pose a potential oxidative threat to ocular health. Retinal pigment epithelium (RPE) is the major ocular source of pathological cytokines, which regulate local inflammation and angiogenesis. We hypothesized that high-energy LED light might disrupt the pathological cytokine expression of retinal pigment epithelium (RPE), contributing to the pathogenesis of AMD. Primary human RPE cells were isolated from eyecups of normal eye donors and seeded into plate wells for growing to confluence. Two widely used multichromatic white light-emitting diodes (LEDs) with correlated color temperatures (CCTs) of 2954 and 7378 K were used in this experiment. The confluent primary RPE cells were under white LEDs light exposure until 24 hours. VEGF-A, IL-6, IL-8 and MCP-1 proteins and mRNAs were measured using an ELISA kit and RT-PCR, respectively. Activation of mitogen-activated protein kinases (MAPKs), Akt, Janus kinase (JAK)2 and Nuclear factor (NF)-κB signal pathways after LEDs illumination were evaluated by western blotting analysis. The level of reactive oxygen species (ROS) using chloromethyl- 2',7'-dichlorodihydrofluorescein diacetate. Inhibitors of relevant signal pathways and anti-oxidants were added to the primary RPE cells before LEDs illumination to evaluate their biological functions. We found that 7378 K light, but not 2954 K upregulated the VEGF-A, IL-6, IL-8 and downregulated MCP-1 proteins and mRNAs levels in a time-dependent manner. In parallel, initial activation of MAPKs and NF-κB signal pathways were also observed after 7378 K light exposure. Mechanistically, antioxidants for eliminating reactive oxygen species (ROS) and targeted inhibitors of MAPKs and NF-κB significantly blocked 7378 K light-induced changes of specific cytokines, respectively. Our findings suggest that 7378 K light, not 2954 K induced upregulation of VEGF-A, IL-6, IL-8 and downregulation of MCP-1 via ROS accumulation, activating MAPKs and NF-κB signal pathways.

PMID: 26432918 [PubMed - as supplied by publisher]

Carbohydr Polym. 2015 Dec 10;134:590-7. Epub 2015 Aug 18.

Review on complement analysis method and the roles of glycosaminoglycans in the complement system.

Li L, Li Y, Ijaz M, Shahbaz M, Lian Q, Wang F.

Abstract: Complement system is composed of over 30 proteins and it plays important roles in self-defence and inflammation. There are three activation pathways, including classical pathway, alternative pathway and lectin pathway, in complement system, and they are associated with many diseases such as osteoarthritis and age-related macular degeneration. Modulation of the complement system may be a promising strategy in the treatment of related diseases. Glycosaminoglycans are anionic linear

polysaccharides without branches. They are one kind of multi-functional macromolecules which have great potential in regulating complement system. This review is organized around two aspects between the introduction of complement system and the interaction of glycosaminoglycans with complement system. Three complement activation pathways and the biological significance were introduced first. Then functional analysis methods were compared to provide a strategy for potential glycosaminoglycans screen. Finally, the roles of glycosaminoglycans played in the complement system were summed up.

PMID: 26428162 [PubMed - in process]

Prog Retin Eye Res. 2015 Sep 30. [Epub ahead of print]

Connexin43 in retinal injury and disease.

Danesh-Meyer HV, Zhang J, Acosta ML, Rupenthal ID, Green CR.

Abstract: Gap junctions are specialized cell-to-cell contacts that allow the direct transfer of small molecules between cells. A single gap junction channel consists of two hemichannels, or connexons, each of which is composed of six connexin protein subunits. Connexin43 is the most ubiquitously expressed isoform of the connexin family and in the retina it is prevalent in astrocytes, Muller cells, microglia, retinal pigment epithelium and endothelial cells. Prior to docking with a neighboring cell, Connexin43 hemichannels have a low open probability as open channels constitute a large, relatively non-specific membrane pore. However, with injury and disease Connexin43 upregulation and hemichannel opening has been implicated in all aspects of secondary damage, especially glial cell activation, edema and loss of vascular integrity, leading to neuronal death. We here review gap junctions and their roles in the retina, and then focus in on Connexin43 gap junction channels in injury and disease. In particular, the effect of pathological opening of gap junction hemichannels is described, and hemichannel mediated loss of vascular integrity explained. This latter phenomenon underlies retinal pigment epithelium loss and is a common feature in several retinal diseases. Finally, Connexin43 channel roles in a number of retinal diseases including macular degeneration, glaucoma and diabetic retinopathy are considered, along with results from related animal models. A final section describes gap junction channel modulation and the ocular delivery of potential therapeutic molecules.

PMID: 26432657 [PubMed - as supplied by publisher]

Oncotarget. 2015 Sep 29. [Epub ahead of print]

RAGE mediated intracellular Aβ uptake contributes to the breakdown of tight junction in retinal pigment epithelium.

Park SW, Kim JH, Park SM, Moon M, Lee K, Park KH, Park WJ, Kim JH.

Abstract: Intracellular amyloid beta (Aβ) has been implicated in neuronal cell death in Alzheimer's disease (AD). Intracellular Aβ also contributes to tight junction breakdown of retinal pigment epithelium (RPE) in age -related macular degeneration (AMD). Although Aβ is predominantly secreted from neuronal cells, the mechanism of Aβ transport into RPE remains to be fully elucidated. In this study, we demonstrated that intracellular Aβ was found concomitantly with the breakdown of tight junction in RPE after subretinal injection of Aβ into the mouse eye. We also presented evidence that receptor for advanced glycation end products (RAGE) contributed to endocytosis of Aβ in RPE. siRNA-mediated knockdown of RAGE prevented intracellular Aβ accumulation as well as subsequent tight junction breakdown in RPE. In addition, we found that RAGE-mediated p38 MAPK signaling contributed to endocytosis of Aβ. Blockade of RAGE/p38 MAPK signaling inhibited Aβ endocytosis, thereby preventing tight junction breakdown in RPE. These results implicate that intracellular Aβ contributes to the breakdown of tight junction in RPE via the RAGE/p38 MAPK-mediated endocytosis. Thus, we suggest that RAGE could be a potential therapeutic target for intracellular Aβ induced outer BRB breakdown in AMD.

PMID: 26431165 [PubMed - as supplied by publisher]

Exp Eye Res. 2015 Sep 28. [Epub ahead of print]

An easy, rapid method to isolate RPE cell protein from the mouse eye.

Wei H, Xun Z, Granado H, Wu A, Handa JT.

Abstract: The retinal pigment epithelium (RPE) is essential for maintaining the health of the neural retina. RPE cell dysfunction plays a critical role in many common blinding diseases including age-related macular degeneration (AMD), diabetic retinopathy, retinal dystrophies. Mouse models of ocular disease are commonly used to study these blinding diseases. Since isolating the RPE from the choroid has been challenging, most techniques separate the RPE from the retina, but not the choroid. As a result, the protein signature actually represents a heterogeneous population of cells that may not accurately represent the RPE response. Herein, we describe a method for separating proteins from the RPE that is free from retinal and choroidal contamination. After removing the anterior segment and retina from enucleated mouse eyes, protein from the RPE was extracted separately from the choroid by incubating the posterior eyecup with a protein lysis buffer for 10 min. Western blot analysis identified RPE65, an RPE specific protein in the RPE lysates, but not in choroidal lysates. The RPE lysates were devoid of rhodopsin and collagen VI, which are abundant in the retina and choroid, respectively. This technique will be very helpful for measuring the protein signal from the RPE without retinal or choroidal contamination.

PMID: 26424220 [PubMed - as supplied by publisher]

Yakugaku Zasshi. 2015;135(10):1135-40.

Carrier-mediated Transport of Cationic Drugs across the Blood-Tissue Barrier.

Kubo Y.

Abstract: Studies of neurological dysfunction have revealed the neuroprotective effect of several cationic drugs, suggesting their usefulness in the treatment of neurological diseases. In the brain and retina, blood-tissue barriers such as blood-brain barrier (BBB) and blood-retinal barrier (BRB) are formed to restrict nonspecific solute transport between the circulating blood and neural tissues. Therefore study of cationic drug transport at these barriers is essential to achieve systemic delivery of neuroprotective agents into the neural tissues. In the retina, severe diseases such as diabetic retinopathy and macular degeneration can cause neurological dysfunction that dramatically affects patients' QOL. The BRB is formed by retinal capillary endothelial cells (inner BRB) and retinal pigment epithelial cells (outer BRB). Blood-to-retina transport of cationic drugs was investigated at the inner BRB, which is known to nourish two thirds of the retina. Blood-to-retinal transport of verapamil suggested that the barrier function of the BRB differs from that of the BBB. Moreover, carrier-mediated transport of verapamil and pyrilamine revealed the involvement of novel organic cation transporters at the inner BRB. The identified transport systems for cationic drugs are sensitive to several cationic neuroprotective and anti-angiogenic agents such as clonidine and propranolol, and the involvement of novel transporters was also suggested in their blood-to-retina transport across the inner BRB.

PMID: 26423869 [PubMed - in process]

Hum Mol Genet. 2015 Sep 29. [Epub ahead of print]

Improved dual AAV vectors with reduced expression of truncated proteins are safe and effective in the retina of a mouse model of Stargardt disease.

Trapani I, Toriello E, de Simone S, Colella P, Iodice C, Polishchuk EV, Sommella A, Colecchi L, Rossi S, Simonelli F, Giunti M, Bacci ML, Polishchuk RS, Auricchio A.

Abstract: Stargardt disease (STGD1) due to mutations in the large ABCA4 gene is the most common inherited macular degeneration in humans. We have shown that dual AAV vectors effectively transfer ABCA4 to the retina of Abca4-/- mice. However, they express both lower levels of transgene compared to a

single AAV and truncated proteins. To increase productive dual AAV concatemerization, which would overcome these limitations, we have explored the use of either various regions of homology or heterologous inverted terminal repeats (ITR). In addition, we tested the ability of various degradation signals to decrease the expression of truncated proteins.We found the highest levels of transgene expression using regions of homology based on either alkaline phosphatase or the F1 phage (AK). The use of heterologous ITR does not decrease the levels of truncated proteins relative to full-length ABCA4 and impairs AAV vector production. Conversely, the inclusion of the CL1 degradation signal results in the selective degradation of truncated proteins from the 5'-half without affecting full-length protein production. Therefore, we developed dual AAV hybrid ABCA4 vectors including homologous ITR2, the photoreceptor-specific GRK1 promoter, the AK region of homology and the CL1 degradation signal. We show that upon subretinal administration these vectors are both safe in pigs and effective in Abca4-/- mice. Our data support the use of improved dual AAV vectors for gene therapy of STGD1.

PMID: 26420842 [PubMed - as supplied by publisher]

Epidemiology

Am J Ophthalmol. 2015 Sep 30. [Epub ahead of print]

Geo-epidemiology of age-related macular degeneration: new clues into the pathogenesis.

Reibaldi M, Longo A, Pulvirenti A, Avitabile T, Russo A, Cillino S, Mariotti C, Casuccio A.

PURPOSE: To evaluate the demographic, geographical, and race-related variables that account for geographical variability in prevalence rates of Age-related macular degeneration (AMD).

DESIGN: Systematic review, metaregression, and decision-tree analysis.

METHODS: A systematic literature review of PubMed, Medline, Web of Science, and Embase databases identified population-based studies on the prevalence of AMD published before May 2014. Only population-based studies that took place in a spatially explicit geographic area that could be geolocalised, and used retinal photographs and standardised grading classifications were included. Latitude and longitude data (geolocalisation) and the mean annual insolation for the area where survey took place were obtained. Age-standardised prevalence rates across studies were estimated using the direct standardisation method. Correlations between the prevalence of AMD and longitude and latitude were obtained by regression analysis. A hierarchical Bayesian meta-regression approach was used to assess the association between the prevalence of AMD and other relevant factors. We further investigated the interplay between location and these factors on the prevalence of AMD using regression based on conditional-inference decision trees.

RESULTS: We observed significant inverse correlations between latitude or longitude, and crude or age-standardised prevalence rates of early and late AMD (P<0.001). Metaregression analysis showed that insolation, latitude, longitude, age, and race have a significant effects on the prevalence rates of early and late AMD (P<0.001). Decision-tree analysis identified that the most important predictive variable was race for early AMD (P=0.002) and insolation for late AMD (P=0.001).

CONCLUSIONS: Geographical position and insolation are key factors in the prevalence of AMD.

PMID: 26432929 [PubMed - as supplied by publisher]

Genetics

Am J Geriatr Psychiatry. 2015 Jun 24. [Epub ahead of print]

Age-Related Macular Degeneration-Associated Genes in Alzheimer Disease.

Williams MA, McKay GJ, Carson R, Craig D, Silvestri G, Passmore P.

OBJECTIVES: Given the clinical and pathological similarities between age-related macular degeneration (AMD) and Alzheimer disease (AD), to assess whether AMD-associated single nucleotide polymorphisms (SNPs), including those from complement-related genes, are associated with AD.

DESIGN: A case-control association study-type design.

SETTING: A UK tertiary care dementia clinic.

PARTICIPANTS: 322 cognitively normal participants and 258 cases with a clinical diagnosis of AD.

MEASUREMENTS: Polymorphisms in the following genes were studied: CFH, ARMS2, C2/CFB, C3, CFI/PLA2G12a, SERPING1, TLR3, TLR4, CRP, APOE, and TOMM40. Haplotypes were analysed for CFH, TOMM40, and APOE. Univariate analysis was performed for each genetic change and case-comparator status, and then correction for multiple testing performed.

RESULTS: The presence of an ε4 APOE allele was significantly associated with AD. No association was evident between CFH SNPs or haplotypes, or other AMD-associated SNPs tested, and AD. The exceptions were TOMM40 SNPs, which were associated with AD even after correction for multiple comparisons. The associations disappeared, however, when entered into a regression model including APOE genotypes.

CONCLUSIONS: The results for most SNPs tested, as well as CFH haplotypes, are novel. The functional effects of abnormal complement activity in AD's pathogenesis may be contradictory, but methodological reasons may underlie the lack of association-for example, genetic changes other than SNPs being involved.

PMID: 26419733 [PubMed - as supplied by publisher]

J Ophthalmic Vis Res. 2015 Apr-Jun;10(2):155-9.

Tumor Necrosis Factor Gene Polymorphisms in Advanced Non-exudative Age-related Macular Degeneration.

Bonyadi MH, Bonyadi M, Ahmadieh H, Fotuhi N, Shoeibi N, Saadat S, Yagubi Z.

PURPOSE: To investigate tumor necrosis factor (TNF)-α gene polymorphisms in advanced dry-type age-related macular degeneration (AMD) in a population from Northeastern Iran.

METHODS: In this case-control study, 50 patients with geographic macular atrophy and 73 gender-matched controls were enrolled. Genomic deoxyribonucleic acid (DNA) was extracted from the peripheral blood. Polymerase chain reaction was performed to analyze 2 candidate single nucleotide polymorphisms in the TNF-α gene, namely -1031 thymine (T)/cytosine (C) and -308 guanine (G)/adenine (A).

RESULTS: The distribution of the - 1031 T/C genotype was TT, 62%; TC, 36%; CC, 2% in the patients and TT, 60%; TC, 36%; CC, 4% in the controls (P = 0.94). Genotype analysis of TNF-α -308 also revealed no significant difference in distribution between patients (G, 78%; GA, 22%; AA, 0%) and controls (GG, 74%; GA, 23%; AA, 3%) (P = 0.51). None of the haplotypes nor alleles of studied TNF-α polymorphisms were significantly associated with advanced dry-type AMD.

CONCLUSION: The findings of this study show that polymorphisms in the TNF-α gene, do not play an important role in dry-type AMD in the studied population.

PMID: 26425318 [PubMed] PMCID: PMC4568613 Free PMC Article

Diet, lifestyle & low vision

J Cataract Refract Surg. 2015 Aug;41(8):1559-63.

New add-on intraocular lens for patients with age-related macular degeneration.

Scharioth GB.

Abstract: We present a new option for visual rehabilitation of patients with advanced macular degeneration and evaluate the outcomes in the first 8 patients who had implantation of the ciliary sulcus-fixated macular add-on intraocular lens (IOL) (Scharioth Macula Lens) at our institute. The surgical technique for implantation of the add-on IOL is described. Near vision improved in 7 eyes and was stable in 1 eye. The corrected near visual acuity improved by 4.4 lines with the macular add-on IOL at 15 cm versus with glasses at 40 cm; it improved by 2.1 lines with the macular add-on IOL at 15 cm versus with glasses at 15 cm. Distance vision was stable in all eyes. No intraoperative or postoperative complication occurred. The macular add-on IOL has the potential of improving near vision and reading ability in patients with advanced age-related macular degeneration.

PMID: 26432110 [PubMed - in process]

Retina. 2015 Sep 29. [Epub ahead of print]

SOCIETAL COSTS ASSOCIATED WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION IN THE UNITED STATES.

Brown MM, Brown GC, Lieske HB, Tran I, Turpcu A, Colman S.

PURPOSE: The purpose of this study was to use a cross-sectional prevalence-based health care economic survey to ascertain the annual, incremental, societal ophthalmic costs associated with neovascular age-related macular degeneration.

METHODS: Consecutive patients (n = 200) with neovascular age-related macular degeneration were studied. A Control Cohort included patients with good (20/20-20/25) vision, while Study Cohort vision levels included Subcohort 1: 20/30 to 20/50, Subcohort 2: 20/60 to 20/100, Subcohort 3: 20/200 to 20/400, and Subcohort 4: 20/800 to no light perception. An interviewer-administered, standardized, written survey assessed 1) direct ophthalmic medical, 2) direct nonophthalmic medical, 3) direct nonmedical, and 4) indirect medical costs accrued due solely to neovascular age-related macular degeneration.

RESULTS: The mean annual societal cost for the Control Cohort was $6,116 and for the Study Cohort averaged $39,910 ($P < 0.001$). Study Subcohort 1 costs averaged $20,339, while Subcohort 4 costs averaged $82,984. Direct ophthalmic medical costs comprised 17.9% of Study Cohort societal ophthalmic costs, versus 74.1% of Control Cohort societal ophthalmic costs ($P < 0.001$) and 10.4% of 20/800 to no light perception subcohort costs. Direct nonmedical costs, primarily caregiver, comprised 67.1% of Study Cohort societal ophthalmic costs, versus 21.3% ($1,302/$6,116) of Control Cohort costs ($P < 0.001$) and 74.1% of 20/800 to no light perception subcohort costs.

CONCLUSION: Total societal ophthalmic costs associated with neovascular age-related macular degeneration dramatically increase as vision in the better-seeing eye decreases.

PMID: 26428606 [PubMed - as supplied by publisher]