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MD Research News

Issue 203

Monday 20 October, 2014

Drug treatment

Ophthalmology. 2014 Oct 11. pii: S0161-6420(14)00790-8. doi: 10.1016/j.ophtha.2014.08.031. [Epub ahead of print]

Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion: The 24-Week Results of the VIBRANT Study.

Campochiaro PA, Clark WL, Boyer DS, Heier JS, Brown DM, Vitti R, Kazmi H, Berliner AJ, Erickson K, Chu KW, Soo Y, Cheng Y, Haller JA.

PURPOSE: To compare the efficacy and safety of intravitreal aflibercept injection (IAI) with macular grid laser photocoagulation for the treatment of macular edema after branch retinal vein occlusion (BRVO).

DESIGN: The VIBRANT study was a double-masked, active-controlled, randomized, phase III trial.

PARTICIPANTS: Treatment-naïve eyes with macular edema after BRVO were included in the study if the occlusion occurred within 12 months and best-corrected visual acuity (BCVA) was between ≤73 and ≥24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/40-20/320 Snellen equivalent).

METHODS: Eyes (1 eye per patient) received either IAI 2 mg every 4 weeks (n = 91) from baseline to week 20 or grid laser (n = 92) at baseline with a single grid laser rescue treatment, if needed, from weeks 12 through 20.

MAIN OUTCOME MEASURES: The primary outcome measure was the proportion of eyes that gained ≥15 ETDRS letters from baseline BCVA at week 24. Secondary end points included mean change from baseline BCVA and central retinal thickness (CRT) at week 24.

RESULTS: The proportion of eyes that gained ≥15 ETDRS letters from baseline at week 24 was 52.7% in the IAI group compared with 26.7% in the laser group (P = 0.0003). The mean improvement from baseline BCVA at week 24 was 17.0 ETDRS letters in the IAI group and 6.9 ETDRS letters in the laser group (P < 0.0001). The mean reduction in CRT from baseline at week 24 was 280.5 μm in the IAI group and 128.0 μm in the laser group (P < 0.0001). Traumatic cataract in an IAI patient was the only ocular serious adverse event (SAE) that occurred. There were no cases of intraocular inflammation or endophthalmitis. The incidence of nonocular SAEs was 8.8% in the IAI group and 9.8% in the laser group. One Anti-Platelet Trialists' Collaboration-defined event of nonfatal stroke (1.1%) and 1 death (1.1%) due to pneumonia occurred during the 24 weeks of the study, both in patients in the laser group.

CONCLUSIONS: Monthly IAI provided significantly greater visual benefit and reduction in CRT at 24 weeks than grid laser photocoagulation in eyes with macular edema after BRVO.

PMID: 25315663 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Oct 9. [Epub ahead of print]

Outcomes of Eyes with Lesions Composed of >50% Blood in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

Altaweel MM, Daniel E, Martin DF, Mittra RA, Grunwald JE, Lai MM, Melamud A, Morse LS, Huang J, Ferris FL 3rd, Fine SL, Maguire MG; Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group.

OBJECTIVE: To compare baseline characteristics, treatment frequency, visual acuity (VA), and morphologic outcomes of eyes with >50% of the lesion composed of blood (B50 group) versus all other eyes (Other group) enrolled in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

DESIGN: Prospective cohort study within a multicenter randomized clinical trial.

PARTICIPANTS: CATT patients with neovascular age-related macular degeneration (AMD).

METHODS: Treatment for the study eye was assigned randomly to either ranibizumab or bevacizumab and to 3 different dosing regimens over a 2-year period. Reading center graders evaluated baseline and follow-up morphology in color fundus photographs, fluorescein angiography (FA), and optical coherence tomography (OCT). Masked examiners tested VA.

MAIN OUTCOME MEASURES: Morphologic features and VA at 1 and 2 years.

RESULTS: The B50 group consisted of 84 of 1185 (7.1%) patients enrolled in CATT. Baseline lesion characteristics differed between groups. In the B50 group, choroidal neovascularization size was smaller (0.73 vs 1.83 disc areas [DA]; P < 0.001), total lesion size was greater (4.55 vs 2.31 DA; P <0.001), total retinal thickness was greater (524 vs 455 μm; P = 0.02), and mean VA was worse (56.0 vs 60.9 letters; P = 0.002). Increases in mean VA were similar in the B50 and Other groups at 1 year (+9.3 vs +7.2 letters; P = 0.22) and at 2 years (9.0 vs 6.1 letters; P = 0.17). Eyes treated PRN received a similar number of injections in the 2 groups (12.2 vs 13.4; P = 0.27). Mean lesion size in the B50 group decreased by 1.2 DA at both 1 and 2 years (primarily owing to resolution of hemorrhage) and increased in the Other group by 0.33 DA at 1 year and 0.91 DA at 2 years (P < 0.001). Leakage on FA and fluid on OCT were similar between groups at 1 and 2 years.

CONCLUSIONS: In CATT, the B50 group had a visual prognosis similar to the Other group. Lesion size decreased markedly through 2 years. Eyes like those enrolled in CATT with neovascular AMD lesions composed of >50% blood can be managed similarly to those with less or no blood.

PMID: 25307130 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 Oct 9. [Epub ahead of print]

Induction with Intravitreal Bevacizumab Every Two Weeks in the Management of Neovascular Age-related Macular Degeneration.

Barikian A, Mahfoud Z, Abdulaal M, Safar A, Bashshur ZF.

PURPOSE: To explore the benefit of rapid induction with intravitreal bevacizumab for neovascular age-related macular degeneration (AMD).

DESIGN: Single institution prospective randomized pilot study.

METHODS: Patients with treatment-naïve neovascular AMD were randomized 1:1:1 into one of 3 groups based on the induction sequence: 1) every 2 weeks for 3 consecutive injections, 2) every 4 weeks for 3 consecutive injections, and 3) immediate pro re nata (prn) after the first injection. Retinal angiomatous

proliferation and polypoidal choroidal vasculopathy were excluded. Best-corrected visual acuity (BCVA) and central retinal thickness using optical coherence tomography (OCT) were measured at baseline and each follow-up. After induction, bevacizumab was administered as-needed based mainly on OCT. Main outcome measure was mean initial fluid-free interval after induction. Secondary outcomes were mean improvement in BCVA and central retinal thickness.

RESULTS: Each group included 30 patients (30 eyes). Mean initial fluid-free interval was 2.4, 3.4 and 3.5 months for biweekly induction, monthly induction and immediate prn groups, respectively (p=0.03). Significance was lost when corrected for age and gender (p=0.073). Mean improvement in BCVA, central retinal thickness and total number of injections were similar among the groups at 12 months. Six eyes in the biweekly induction group developed subretinal fibrosis vs. no eyes in the other 2 groups (p=0.003).

CONCLUSION: Biweekly induction with intravitreal bevacizumab for treatment-naive neovascular AMD does not increase initial fluid-free interval or cause significant anatomical and functional benefit compared to monthly induction or immediate prn. There is also the potential development of subretinal fibrosis with biweekly induction.

PMID: 25308787 [PubMed - as supplied by publisher]

Semin Ophthalmol. 2014 Nov;29(5-6):276-89.

Complications of intravitreal injections in patients with diabetes.

Shikari H, Silva PS, Sun JK.

Abstract: Intravitreal injections for the treatment of retinal disorders and intraocular infection have become a common ophthalmic procedure, and injections of anti-vascular endothelial growth factor agents or steroids are frequently performed for the treatment of diabetic macular edema or other diabetic vascular pathology. Diabetic patients may be at higher risk of adverse events than non-diabetic individuals given frequent systemic co-morbidities, such as cardiovascular and renal disease, susceptibility to infection, and unique ocular pathology that includes fibrovascular proliferation. Fortunately, many associated complications, including endophthalmitis, are related to the injection procedure and can therefore be circumvented by careful attention to injection techniques. This review highlights the safety profile of intravitreal injections in patients with diabetes. Although diabetic patients may theoretically be at higher risk than non-diabetic patients for complications, a comprehensive review of the literature does not demonstrate substantial increased risk of intravitreal injections in patients with diabetes.

PMID: 25325853 [PubMed - in process]

Semin Ophthalmol. 2014 Nov;29(5-6):263-75.

Complications of Subspecialty Ophthalmic Care: Systemic Complications from the Intravitreal Administration of Agents that Target the Vascular Endothelial Growth Factor Pathway.

Ramsey DJ, Haddock LJ, Young LH, Eliott D.

Abstract: The treatment of neovascular age-related macular degeneration (AMD) and other pathologic ocular conditions that overexpress the vascular endothelial growth factor (VEGF) has been revolutionized in the last decade by the introduction of intravitreal agents that target the VEGF pathway. Since treatment trials are designed primarily to assess the prevention of vision loss caused by ocular conditions, they are inadequate for detecting rare, but potentially serious, systemic side effects. The aim of this article is to present what the ophthalmologist needs to know about systemic complications from anti-VEGF therapy and review the likelihood that these side effects occur in the context of small, but often-repeated, intravitreal doses of these potent biological medications. Preferred practice patterns need to be developed that weigh

the ability of these medications to mitigate potentially blinding conditions, while at the same time minimizing the risk of adverse outcomes in specific patient populations that possess multiple and often interrelated medical comorbidities.

PMID: 25325852 [PubMed - in process]

Semin Ophthalmol. 2014 Nov;29(5-6):257-62.

Complications of subspecialty ophthalmic care: endophthalmitis after intravitreal injections of anti-vascular endothelial growth factor medications.

Haddock LJ, Ramsey DJ, Young LH.

Abstract: The use of medications directed against vascular endothelial growth factor (VEGF) signaling has revolutionized the treatment of age-related macular degeneration (AMD) and many other retinal diseases in the last decade. However, the rapidly increasing use of these agents has led to a rise in treatment-associated complications. One of the most feared by patients and ophthalmologists is post-injection endophthalmitis, which can result in severe vision loss and, in rare cases, loss of the eye. The aim of this article is to review the incidence, clinical findings, risk factors, management, and visual outcomes in cases of endophthalmitis following intravitreal injections of anti-VEGF medications.

PMID: 25325851 [PubMed - in process]

Medicine (Baltimore). 2014 Oct;93(18):e116.

Effect of switching therapy to pegaptanib in eyes with the persistent cases of exudative age-related macular degeneration.

Shiragami C, Ono A, Kobayashi M, Manabe S, Yamashita A, Shiraga F.

Abstract: Purpose of this study was to evaluate the efficacy of switching to pegaptanib monotherapy for persistent cases of exudative age-related macular degeneration (AMD).Out of 296 eyes of 296 patients treated with ranibizumab or ranibizumab combined with photodynamic therapy (PDT), 50 eyes of 50 AMD patients were found to be resistant to these treatments. Over a 12-month period, intravitreal pegaptanib (IVP) 0.3 mg was administered at intervals of 6 weeks until the exudation disappeared prospectively. All patients were examined with the following tests: best-corrected visual acuity (BCVA) and central retinal thickness (CRT), determined at the initial visit, before the first IVP (baseline), and at 12 months. The factors responsible for achieving dry macula with IVP were examined statistically.The rate of persistent cases with intravitreal ranibizumab (IVR) and/or PDT was 17.0%. The mean number of IVPs administered was 5.4 (range, 2-9). Logarithm of the minimal angle of resolution BCVA at 12 months was stable or improved by ≥0.3 in 49 eyes (98.0%), with a significant improvement noted between the baseline and final BCVA ($P = 0.01$, paired t test). The CRT (mean ± standard deviation) was 446.9 ± 150.6 μm at the initial visit, 414.5 ± 146.5 μm at baseline, and 318.7 ± 99.0 μm at 12 months. There was a significant decrease in the mean CRT between the measurements at baseline and at 12 months after the first IVP ($P = 0.002$, Bonferroni correction). At 12 months, the exudative change was completely resolved in 27 eyes (54.0%) and reduced in 21 eyes (42.0%). The number of previous IVR treatments was significantly correlated with dry macula at 12 months.After switching therapy to pegaptanib in persistent cases of AMD, most patients maintained or improved their BCVA and exhibited a positive treatment response at 12 months.

PMID: 25319441 [PubMed - in process]

Vestn Oftalmol. 2014 Jul-Aug;130(4):88-96.

[The influence of patient compliance with antiangiogenic therapy on its efficacy for neovascular age -related macular degeneration]. [Article in Russian]

PURPOSE: To study the level of patient compliance with Ranibizumab therapy and affecting factors.

MATERIAL AND METHODS: Medical records of 76 patients aged from 50 to 86 years (mean age 70.7 +/- 9.5 years) who underwent Ranibizumab treatment for neovascular age-related macular degeneration (AMD) during 2010-2014 were used. Demographic data, visual acuity, optical coherence tomography results were analyzed. Surgical interventions, regularity of postoperative follow-up and its outcomes were also taken into consideration.

RESULTS: The results showed high efficacy and safety of Ranibizumab therapy, though patient adherence varied significantly during the treatment course. More than 90% of patients demonstrated strong adherence to treatment in the phase of stabilization. During the follow-up period on a monthly basis and in the phase of maintenance therapy the level of compliance was 48.6% and 63.2% correspondingly. It is found that patient adherence depends on the duration of treatment, visual acuity of the contralateral eye, and functional results of the initial stage of the treatment (phase of stabilization). Four clinical examples are provided to illustrate the correlation between treatment efficacy and compliance.

CONCLUSION: Patient compliance with Ranibizumab antiangiogenic therapy for neovascular AMD improves its efficacy, ensuring maximum increase of visual acuity in the phase of stabilization and functional stability in the phase of maintenance therapy. Monthly performed follow-up allows early detection of disease recurrence and timely recommencement of the treatment.

PMID: 25306730 [PubMed - in process]

Expert Opin Biol Ther. 2014 Oct 4:1-12. [Epub ahead of print]

Bevacizumab for choroidal neovascularization secondary to age-related macular degeneration and pathological myopia.

Hashemi S, Faramarzi MA, Ghasemi Falavarjani K, Abdollahi M.

Introduction: Many retinal specialists have utilized intravitreal bevacizumab as an anti-VEGF to treat choroidal neovascularization (CNV), secondary to age-related macular degeneration (AMD) and pathological myopia, with favorable results. Bevacizumab is currently approved only for the systemic treatment of colon carcinoma, whereas it is widely used off-label for treating ocular neovascular diseases.

Areas covered: In this review, after thorough search, 33 relevant studies conducted in the last 4 years were found. These articles comprised 14 studies about use of bevacizumab alone or in combination with other therapeutic agents to treat exudative AMD, and 19 studies on the use of myopic CNV.

Expert opinion: Although bevacizumab is widely used as an anti-VEGF agent for the treatment of exudative AMD, data on its systemic side effects are limited because of studies' short follow-up periods, absence of appropriate controls, limitation in reporting outcomes, and lack of controlled clinical trials in Phase III. Some safety studies demonstrated no difference between bevacizumab and ranibizumab in occurrence of heart attacks or stroke. Conducting proper randomized clinical trials with long-term follow-up is crucial to make sure about efficacy and safety of bevacizumab.

PMID: 25283631 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Oct 2. [Epub ahead of print]

Vision-Threatening Lesions Developing with Longer-Term Follow-up after Treatment of Neovascular Age-Related Macular Degeneration.

Tanaka E, Chaikitmongkol V, Bressler SB, Bressler NM.

PURPOSE: To assess the development of vision-threatening lesions at least 3.5 years after initiating anti-vascular endothelial growth factor (VEGF) for choroidal neovascularization (CNV) in eyes with age-related macular degeneration (AMD).

DESIGN: Retrospective cohort study.

PARTICIPANTS: A total of 75 patients (81 eyes) with CNV secondary to AMD who received intravitreous anti-VEGF treatment and were followed for at least 3.5 years after initiating treatment.

METHODS: Retrospective record review of patients initiating anti-VEGF treatment between November 2005 and June 2008 at a university-based institution for whom at least 3.5 years of follow-up was available at the same institution.

MAIN OUTCOME MEASURES: Predominantly hemorrhagic lesions or geographic atrophy (GA).

RESULTS: Among 75 patients (81 eyes; 59% were women; median age, 78 years), mean follow-up was 4.9 years and at least 6 years for 40%. Median visual acuity (VA) was 20/80 (interquartile range [IQR], 20/50-20/100) initially, 20/63 (IQR, 20/40-20/160) at 2 years, 20/80 (IQR, 20/40-20/200) at 3.5 years, and 20/63 (IQR 20/32-20/200) at 6 years. Six eyes (7%) had predominantly hemorrhagic lesions initially, whereas this developed in an additional 3 eyes (4%, 95% confidence interval [CI], 1% to 10%) in 3.5 years and in 1 additional eye (1%, 95% CI, 0.03% to 7%) at more than 3.5 years of follow-up. Initially, GA within or overlapping the boundary of the entire CNV was present in 4 eyes (5%) and outside this boundary in 8 eyes (10%). Geographic atrophy enlarged in each eye over time. The only eyes that developed GA outside the CNV boundary were those that had GA outside the lesion at baseline. Additional atrophy within the boundary of CNV defined at baseline, termed "atrophic disciform scars," developed in 5 eyes (6%), all within 4 years of treatment initiation.

CONCLUSIONS: Longer-term follow-up of neovascular AMD managed with anti-VEGF therapy suggests that predominantly hemorrhagic lesions may develop within 3.5 years of initiating therapy and more than 3.5 years after initiating therapy. In contrast, new areas of GA beyond the boundaries of the CNV lesion as defined at initiation of anti-VEGF therapy seem unlikely to develop if there is no GA outside of the CNV lesion initially.

PMID: 25283060 [PubMed - as supplied by publisher]

Cochrane Database Syst Rev. 2014 Sep 15;9:ED000090.

A clearer view of evidence in treating macular degeneration: off-label policies and independent research.

Formoso G1, Marata AM, Magrini N, Bero L.

PMID: 25313417 [PubMed - in process]

Other treatment & diagnosis

Clin Exp Optom. 2014 Oct 12. [Epub ahead of print]

Hyperbaric oxygen therapy and the possibility of ocular complications or contraindications.

McMonnies CW.

Abstract: Hyperbaric oxygen therapy increases oxygen pressure and the concentration of reactive oxygen species in blood and tissues. Increased oxygen pressure may be beneficial in some diseases, such as in the treatment of diabetic leg ulcers and diabetic retinopathy; however, due to their cytotoxic properties, an excess of reactive oxygen species in tissues and/or deficiencies in antioxidant activity, may contribute to complications of hyperbaric oxygen therapy, such as cataract. This review examines the possibility that increased tissue concentrations of reactive oxygen species may also exacerbate other ocular diseases. For example, reactive oxygen species and deficiencies in antioxidant activities contribute to the pathogenetic processes in keratoconus. Such impact may be exacerbated by exposure to additional reactive oxygen species during hyperbaric oxygen therapy. The senescent eye may be particularly prone to oxidative damage as exemplified by conditions such as macular degeneration and cataract. Because of its high consumption of oxygen, the retina is particularly susceptible to oxidative stress, which plays a major role in retinopathy. For example, under normal conditions age-related macular degeneration involves oxidative stress and death of the retinal pigment epithelial cells. Hyperbaric oxygen therapy may exacerbate these processes. In addition to cataract, age-related macular degeneration and keratoconus, there may be other ocular diseases for which exposure to hyperbaric oxygen therapy-related oxidative stress may be significantly adverse. In all such cases, careful pre-examination and evaluation of the potential risk and benefit from this form of therapy appears to be warranted. Unless it could interfere with the benefits of hyperbaric oxygen therapy, antioxidant dietary supplementation may be indicated in conjunction with any hyperbaric oxygen therapy, when there are co-existing diseases for which oxidative stress could have significantly adverse side effects. Delivery of hyperbaric oxygen therapy may need to be modified or it may even be contraindicated in these cases.

PMID: 25308346 [PubMed - as supplied by publisher]

Semin Ophthalmol. 2014 Nov;29(5-6):301-11.

The Impact of Cataract Surgery on AMD Development and Progression.

Qian CX, Young LH.

Abstract: Age-related macular degeneration (AMD) and cataract are two leading causes of visual impairment worldwide which often occur concurrently in the same patient. With more than 1.6 million cataract operations performed per year in the United States, many of which occur in the nearly 1.75 million individuals diagnosed with AMD, there is ample incentive to further explore the interaction between these two conditions. Notably, the role of cataract surgery on AMD development and progression is of particular interest. This review summarizes the major findings from literature focusing on the effect of cataract surgery on AMD.

PMID: 25325855 [PubMed - in process]

Ophthalmology. 2014 Oct 11. [Epub ahead of print]

Outer Retinal Tubulation as a Predictor of the Enlargement Amount of Geographic Atrophy in Age-Related Macular Degeneration.

Hariri A, Nittala MG, Sadda SR.

PURPOSE: To determine the prognostic value of outer retinal tubulation (ORT) in the enlargement amount of geographic atrophy (GA) in eyes with age-related macular degeneration (AMD).

DESIGN: Cohort study.

PARTICIPANTS: One hundred eight fellow untreated eyes of 143 patients with GA resulting from AMD enrolled in the MAHALO study (clinicaltrials.gov identifier, NCT01229215) who completely satisfied the study term and had gradable spectral-domain optical coherence tomography (OCT) images obtained at both baseline and month 18 visits.

METHODS: The MAHALO study enrolled 143 subjects into a phase 1b/2 multicenter, randomized, single-masked, sham-injection controlled clinical trial of the safety, tolerability, and evidence of activity of lampalizumab in patients with GA associated with AMD. Spectral-domain optical coherence tomography images were obtained at multiple time points in both eyes, although only the baseline and month 18 data of the fellow (nonstudy) eyes were considered in this exploratory analysis. The Cirrus HD-OCT review software was used for automatic segmentation and measurement of GA areas, with manual correction of segmentation errors by certified OCT graders. Baseline OCT images also were assessed for the presence of ORT. The enlargement amount of GA in eyes with ORT was compared with that of eyes without ORT.

MAIN OUTCOME MEASURES: Comparison of the enlargement amount of GA in eyes with and without ORT.

RESULTS: Twenty-four of these 108 eyes demonstrated evidence of ORT. The amount of enlargement of GA in eyes with ORT was significantly slower than that of eyes without ORT (1.85±0.78 vs. 2.67±1.61; P = 0.001). This difference remained significant when considering subgroups with unifocal or multifocal GA lesions, because eyes with ORT in both subgroups had a slower enlargement amount of GA than eyes without ORT (2.91±1.70 vs. 2.08±0.88 [P = 0.01], in eyes with multifocal GA lesions; and 2.24±1.40 vs. 1.63±0.57 [P = 0.02], in eyes with unifocal GA lesions).

CONCLUSIONS: In eyes with ORT, GA lesions seem to enlarge at a significantly slower rate than those of eyes without ORT. The presence of ORT may need to be accounted for in longitudinal studies of GA.

PMID: 25315664 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Oct 9. [Epub ahead of print]

Quantitative SD-OCT Imaging Biomarkers as Indicators of Age-Related Macular Degeneration Progression.

de Sisternes L, Simon N, Tibshirani R, Leng T, Rubin DL.

Purpose: We developed a statistical model based on quantitative characteristics of drusen to estimate the likelihood of conversion from early and intermediate age-related macular degeneration (AMD) to its advanced exudative form (AMD progression) in the short term (less than 5 years), a crucial task to enable early intervention and improve outcomes.

Methods: Image features of drusen quantifying their number, morphology, and reflectivity properties, as well as the longitudinal evolution in these characteristics, were automatically extracted from 2146 spectral domain optical coherence tomography (SD-OCT) scans of 330 AMD eyes in 244 patients collected over a period of 5 years, with 36 eyes showing progression during clinical follow-up. We developed and evaluated a statistical model to predict the likelihood of progression at pre-determined times using clinical and image features as predictors.

Results: Area, volume, height, and reflectivity of drusen were informative features distinguishing between progressing and non-progressing cases. Discerning progression at follow-up (mean 6.16 months) resulted in a mean area under the receiver operating characteristic curve (AUC) of 0.74 ((0.58, 0.85) 95% confidence interval (CI)). The maximum predictive performance was observed at 11 months after a patient's first early AMD diagnosis, with mean AUC 0.92 ((0.83, 0.98) 95% CI). Those eyes predicted to progress showed a much higher progression rate than those predicted not to progress at any given time from the

initial visit.

Conclusions: Our results demonstrate the potential ability of our model to identify those AMD patients at risk of progressing to exudative AMD from an early or intermediate stage.

PMID: 25301882 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Oct 9. [Epub ahead of print]

Reliability and Determinants of Retinal Vessel Oximetry Measurements in Healthy Eyes.

Yip W, Siantar R, Perera SA, Milastuti N, Ho K, Tan B, Wong TY, Cheung CY.

Purpose: To assess the reliability and determinants of retinal vessel oximetry measurements using the Oxymap T1 Retinal Oximeter (Oxymap, Reykjavik, Iceland) in normal Asian eyes.

Methods: Subjects, above the age of 40, without a history of stroke and heart disease were recruited from a community-based clinic. Subjects underwent standardized systemic and ocular examinations. Normal eyes were defined as eyes without major eye diseases such as age-related macular degeneration, glaucoma or retinopathy. Retinal vessel oximetry levels were measured using the Oxymap T1 Retinal Oximeter (Oxymap, Reykjavik, Iceland). Intra- and inter grader reliability of retinal vessel oximetry measurements were assessed using 50 images. Intra-visit repeatability of retinal vessel oximetry measurements was assessed using 20 paired images. Univariable linear regression was performed to examine the associations between retinal vessel oximetry measurements and systemic determinants.

Results: 118 retinal oximetry images were included in the final analysis. Intra- (intraclass correlation coefficient [ICC] values ranged from 0.89-0.99) and inter-grader (ICC values ranged from 0.77-0.94) reliability, and intra-visit (ICC values ranged from 0.85-0.96) repeatability were both high. In the linear regression analysis, older age was associated with reduced overall retinal venular oximetry levels (β:-2.61% [95% CI -4.92 to -0.29]) and reduced inferior nasal retinal venular oximetry levels (β: -3.53% 95% CI [-6.07 to -0.99]).

Conclusions: The Oxymap Retinal Oximeter allows reliable and repeatable retinal vessel oximetry measurements. Age is the main factor that influences retinal venular oximetry levels and should be taken into account when retinal oximetry measurements are interpreted.

PMID: 25301879 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Oct 9. [Epub ahead of print]

Clinical characteristics of familial and sporadic age-related macular degeneration: differences and similarities.

Saksens N, Kersten E, Groenewoud JM, van Grinsven MJ, van de Ven JP, Sánchez CI, Schick T, Fauser S, den Hollander A, Hoyng C, Boon CJ.

Purpose: To describe the differences and similarities in clinical characteristics and phenotype of familial and sporadic patients with age-related macular degeneration (AMD).

Methods: We evaluated data of 1828 AMD patients and 1715 controls enrolled in the European Genetic Database. All subjects underwent ophthalmologic examination, including visual acuity testing and fundus photography. Images were graded and fundus photographs were used for automatic drusen quantification by a machine learning algorithm. Data on disease characteristics, family history, medical history and lifestyle habits were obtained by a questionnaire.

Results: The age at first symptoms was significantly lower in AMD patients with a positive family history (68.7 years) than in AMD patients with no family history (71.8 years; P = 1.9x10-5). Risk factors identified in sporadic and familial subjects were increasing age (OR 1.08 per year; P = 3.0x10-51 and OR 1.15; P = 5.3x10-36, respectively) and smoking (OR 1.01 per pack year; P = 1.1x10-6 and OR 1.02; P = 0.005). Physical activity and daily red meat consumption were significantly associated with AMD in sporadic subjects only (OR 0.49; P = 3.7x10-10 and OR 1.81; P = 0.001). With regard to the phenotype, geographic atrophy and cuticular drusen were significantly more prevalent in familial AMD (17.5% and 21.7%, respectively) as compared to sporadic AMD (9.8% and 12.1%).

Conclusions: Familial AMD patients become symptomatic at a younger age. The higher prevalence of geographic atrophy and cuticular drusen in the familial AMD cases may be explained by the contribution of additional genetic factors segregating within families.

PMID: 25301878 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Oct 8. [Epub ahead of print]

Identification of Vinculin as a Potential Plasma Marker for Age-Related Macular Degeneration.

Kim HJ, Woo SJ, Suh EJ, Ahn J, Park JH, Hong HK, Lee JE, Ahn SJ, Hwang DJ, Kim KW, Park KH, Lee C.

Purpose: To identify plasma protein biomarkers for age-related macular degeneration (AMD) using a large-scale quantitative proteomic discovery procedure.

Methods: Plasma proteomes from 20 exudative AMD patients and 20 healthy control patients were comparatively profiled by 4-dimensional liquid chromatography-tandem mass spectrometry (LC-MS/MS). Proteins existing at statistically different levels were validated by enzyme-linked immunosorbent assay (ELISA) and western blotting in 233 case-controlled samples. Newly discovered plasma biomarkers were further confirmed using in vivo and in vitro experiments.

Results: Out of 320 proteins identified, vinculin, protein S100A9, triosephosphateisomerase, protein S100A8, protein z-dependent protease inhibitor, C-X-C motif chemokine 7, and tenascin X showed significantly differential expression in AMD patient plasma compared to control plasma. Among them, the AUC for vinculin was 0.871 for discriminating between exudative AMD and controls (N = 201) and 0.879 for discriminating between AMD and controls (N = 233). A proteo-genomic combination model using vinculin and two known risk genotypes in ARMS2 and CFH genes additionally provided excellent discrimination of AMD from controls (AUC = 0.916). The plasma level of vinculin was not associated with any confounding clinical variables, such as age, smoking, and other comorbidities. Additionally, vinculin was strongly expressed in retinal pigment epithelial cells of human eyes, and its expression was elevated when exposed to oxidative stress in vitro.

Conclusions: Vinculin was identified as a potential plasma biomarker for AMD. The early detection of AMD using novel plasma biomarkers with genetic modeling may enable timely treatment and vision preservation in the elderly.

PMID: 25298412 [PubMed - as supplied by publisher]

Stem Cells Transl Med. 2014 Oct 8. [Epub ahead of print]

Concise Review: Animal Substance-Free Human Embryonic Stem Cells Aiming at Clinical Applications.

Hovatta O, Rodin S, Antonsson L, Tryggvason K.

Abstract: Human embryonic stem cells have been considered the gold standard as a cell source for

regenerative medicine since they were first cultured in 1998. They are pluripotent and can form principally all the cells types in the body. They are obtained from supernumerary human in vitro fertilization embryos that cannot be used for infertility treatment. Following studies on factors regulating pluripotency and differentiation, we now have techniques to establish and effectively expand these cells in animal substance-free conditions, even from single cells biopsied from eight-cell stage embryos in chemically defined feeder-free cultures. The genetic stability and absence of tumorigenic mutations can be determined. There are satisfactory animal tests for functionality and safety. The first clinical trials are ongoing for two indications: age-related macular degeneration and spinal cord injury.

PMID: 25298372 [PubMed - as supplied by publisher]

Pathogenesis

Science. 2014 Oct 17;346(6207):355-9. Epub 2014 Sep 25.

Structure and selectivity in bestrophin ion channels.

Yang T, Liu Q, Kloss B, Bruni R, Kalathur RC, Guo Y, Kloppmann E, Rost B, Colecraft HM, Hendrickson WA.

Abstract: Human bestrophin-1 (hBest1) is a calcium-activated chloride channel from the retinal pigment epithelium, where mutations are associated with vitelliform macular degeneration, or Best disease. We describe the structure of a bacterial homolog (KpBest) of hBest1 and functional characterizations of both channels. KpBest is a pentamer that forms a five-helix transmembrane pore, closed by three rings of conserved hydrophobic residues, and has a cytoplasmic cavern with a restricted exit. From electrophysiological analysis of structure-inspired mutations in KpBest and hBest1, we find a sensitive control of ion selectivity in the bestrophins, including reversal of anion/cation selectivity, and dramatic activation by mutations at the cytoplasmic exit. A homology model of hBest1 shows the locations of disease -causing mutations and suggests possible roles in regulation.

PMID: 25324390 [PubMed - in process]

Mol Ther. 2014 Oct 13. [Epub ahead of print]

AAV2 Delivery of Flt23k Intraceptors Inhibits Murine Choroidal Neovascularization.

Zhang X, Das SK, Passi SF, Uehara H, Bohner A, Chen M, Tiem M, Archer B, Ambati BK.

Abstract: Long-term inhibition of extracellular vascular endothelial growth factor (VEGF) in the treatment of age-related macular degeneration (AMD) may induce retinal neuronal toxicity and risk other side effects. We developed a novel strategy which inhibits retinal pigment epithelium (RPE)-derived VEGF, sparing other highly sensitive retinal tissues. Flt23k, an intraceptor inhibitor of VEGF, was able to inhibit VEGF in vitro. Adeno-associated virus type 2 (AAV2)-mediated expression of Flt23k was maintained for up to 6 months post-subretinal injection in mice. Flt23k was able to effectively inhibit laser-induced murine choroidal neovascularization (CNV). VEGF levels in the RPE/choroid complex decreased significantly in AAV2.Flt23k treated eyes. Neither retinal structure detected by Heidelberg Spectralis nor function measured by electroretinography (ERG) was adversely affected by treatment with AAV2.Flt23k. Hence AAV2.Flt23k can effectively maintain long-term expression and inhibit laser-induced CNV in mice through downregulation of VEGF while maintaining a sound retinal safety profile. These findings suggest a promising novel approach for the treatment of CNV.Molecular Therapy (2014); doi:10.1038/mt.2014.199.

PMID: 25306972 [PubMed - as supplied by publisher]

PLoS One. 2014 Oct 13;9(10):e107551. eCollection 2014.

Angiogenic potential of vitreous from proliferative diabetic retinopathy and eales' disease patients.

Murugeswari P, Shukla D, Kim R, Namperumalsamy P, Stitt AW, Muthukkaruppan V.

PURPOSE: Proliferative Diabetic Retinopathy (PDR) and Eales' Disease (ED) have different aetiologies although they share certain common clinical symptoms including pre-retinal neovascularization. Since there is a need to understand if the shared end-stage angiogenic pathology of PDR and ED is driven by common stimulating factors, we have studied the cytokines contained in vitreous from both patient groups and analyzed the angiogenic potential of these samples in vitro.

MATERIAL AND METHODS: Vitreous samples from patients with PDR (n=13) and ED (n=5) were quantified for various cytokines using a cytokine biochip array and sandwich ELISA. An additional group of patients (n=5) with macular hole (MH) was also studied for comparison. To determine the angiogenic potential of these vitreous samples, they were analyzed for their ability to induce tubulogenesis in human microvascular endothelial cells. Further, the effect of anti-VEGF (Ranibizumab) and anti-IL-6 antibodies were studied on vitreous-mediated vascular tube formation.

RESULTS: Elevated levels of IL-6, IL-8, MCP-1 and VEGF were observed in vitreous of both PDR and ED when compared to MH. PDR and ED vitreous induced greater levels of endothelial cell tube formation compared to controls without vitreous ($P<0.05$). When VEGF in vitreous was neutralized by clinically-relevant concentrations of Ranibizumab, tube length was reduced significantly in 5 of 6 PDR and 3 of 5 ED samples. Moreover, when treated with IL-6 neutralizing antibody, apparent reduction (71.4%) was observed in PDR vitreous samples.

CONCLUSIONS: We have demonstrated that vitreous specimens from PDR and ED patients share common elevations of pro-inflammatory and pro-angiogenic cytokines. This suggests that common cytokine profiles link these two conditions.

PMID: 25310689 [PubMed - in process] PMCID:PMC4195571

Curr Eye Res. 2014 Oct 13:1-10. [Epub ahead of print]

Different Effects of Thrombin on VEGF Secretion, Proliferation, and Permeability in Polarized and Non-polarized Retinal Pigment Epithelial Cells.

Terasaki H, Shirasawa M, Otsuka H, Yamashita T, Uchino E, Hisatomi T, Sonoda S, Sakamoto T.

Abstract: We investigated the effect of thrombin on the secretion of vascular endothelial growth factor (VEGF), on cellular proliferation, and on the integrity of the barrier function of polarized retinal pigment epithelial (RPE) cells. In addition, we compared the responses of polarized to that of non-polarized RPE cells. Porcine polarized RPE cells were established using Transwell membranes. The polarization of the RPE cells was determined by their high transepithelial electrical resistance (TER > 200 Ω cm2) and by their differential secretion of VEGF (basal direction >apical direction by 2.5×). RPE cells were incubated with thrombin (5-20 U/ml) for 24 h. The concentration of VEGF in the culture medium was measured by enzyme-linked immunosorbent assay, and the TER was measured. Cellular proliferation was assessed by Ki-67 immunostaining. The area of laser-induced choroidal naovascularization (CNV) was measured in rat eyes and compare to that of controls with or without thrombin. Our results showed that thrombin significantly increased VEGF secretion both in polarized and non-polarized RPE cells in a dose-dependent way. Thrombin did not significantly affect the TER or the expression of tight-junctional proteins in polarized RPE cells, but decreased it in non-polarized RPE cells by inducing intercellular gaps. Ki-67-positive cells were observed in non-polarized RPE cells but not in polarized RPE cells as controls. After thrombin exposure, the number of Ki-67-positive cells increased significantly in non-polarized RPE cells but not in polarized RPE cells. The area of CNV was larger in thrombin-injected eye than control eyes. Although thrombin

increased VEGF secretion regardless of cell polarity, its effects on proliferation and barrier integrity were dependent upon cell polarity. Cell polarization is an important factor for determining the response of RPE cells to thrombin, and the different responsive patterns to thrombin upon cell polarity might explain the complicated pathology of such diseases as age-related macular degeneration.

PMID: 25310246 [PubMed - as supplied by publisher]

Crit Rev Clin Lab Sci. 2014 Oct 16:1-16. [Epub ahead of print]

Oxidative stress in dry age-related macular degeneration and exfoliation syndrome.

Chiras D, Kitsos G, Petersen MB, Skalidakis I, Kroupis C.

Abstract: Oxidative stress refers to cellular or molecular damage caused by reactive oxygen species, which especially occurs in age-related conditions as a result of an imbalance between the production of reactive oxygen species and the antioxidant defense response. Dry age-related macular degeneration (AMD) and exfoliation syndrome (XFS) are two common and complex age-related conditions that can cause irreversible vision loss. Two subtypes of AMD, which is the leading cause of blindness in the Western world, exist: the most prevalent dry type and the most severe wet type. Early dry AMD is characterized by formation of drusen, which are sub-retinal deposits, in the macular area and may progress to geographic atrophy with more dramatic manifestation. XFS is a systemic disorder of the extracellular matrix characterized by the accumulation of elastic fibrils that leads, in most cases, to glaucoma development with progressive and irreversible vision loss. Due to the aging population, the prevalence of these already-widespread conditions is increasing and is resulting in significant economic and psychological costs for individuals and for society. The exact composition of the abnormal drusen and XFS material as well as the mechanisms responsible for their production and accumulation still remain elusive, and consequently treatment for both diseases is lacking. However, recent epidemiologic, genetic and molecular studies support a major role for oxidative stress in both dry AMD and XFS development. Understanding the early molecular events in their pathogenesis and the exact role of oxidative stress may provide novel opportunities for therapeutic intervention for the prevention of progression to advanced disease.

PMID: 25319011 [PubMed - as supplied by publisher]

J Immunol. 2014 Oct 10. [Epub ahead of print]

Identification of Factor H-like Protein 1 as the Predominant Complement Regulator in Bruch's Membrane: Implications for Age-Related Macular Degeneration.

Clark SJ, Schmidt CQ, White AM, Hakobyan S, Morgan BP, Bishop PN.

Abstract: The tight regulation of innate immunity on extracellular matrix (ECM) is a vital part of immune homeostasis throughout the human body, and disruption to this regulation in the eye is thought to contribute directly to the progression of age-related macular degeneration (AMD). The plasma complement regulator factor H (FH) is thought to be the main regulator that protects ECM against damaging complement activation. However, in the present study we demonstrate that a truncated form of FH, called FH-like protein 1 (FHL-1), is the main regulatory protein in the layer of ECM under human retina, called Bruch's membrane. Bruch's membrane is a major site of AMD disease pathogenesis and where drusen, the hallmark lesions of AMD, form. We show that FHL-1 can passively diffuse through Bruch's membrane, whereas the full sized, glycosylated, FH cannot. FHL-1 is largely bound to Bruch's membrane through interactions with heparan sulfate, and we show that the common Y402H polymorphism in the CFH gene, associated with an increased risk of AMD, reduces the binding of FHL-1 to this heparan sulfate. We also show that FHL-1 is retained in drusen whereas FH coats the periphery of the lesions, perhaps inhibiting their clearance. Our results identify a novel mechanism of complement regulation in the human eye, which highlights potential

new avenues for therapeutic strategies.

PMID: 25305316 [PubMed - as supplied by publisher]

Colloids Surf B Biointerfaces. 2014 Sep 28. [Epub ahead of print]

Physicochemical characterization of epigallocatechin gallate lipid nanoparticles (EGCG-LNs) for ocular instillation.

Fangueiro JF, Andreani T, Fernandes L, Garcia ML, Egea MA, Silva AM, Souto EB.

Abstract: The encapsulation of epigallocatechin gallate (EGCG) in lipid nanoparticles (LNs) could be a suitable approach to avoid drug oxidation and epimerization, which are common processes that lead to low bioavailability of the drug limiting its therapeutic efficacy. The human health benefits of EGCG gained much interest in the pharmaceutical field, and so far there are no studies reporting its encapsulation in LNs. The purpose of this study has been the development of an innovative system for the ocular delivery of EGCG using LNs as carrier for the future treatment of several diseases, such as dry eye, age-related macular degeneration (AMD), glaucoma, diabetic retinopathy and macular oedema. LNs dispersions have been produced by multiple emulsion technique and previously optimized by a factorial design. In order to increase ocular retention time and mucoadhesion by electrostatic attraction, two distinct cationic lipids were used, namely, cetyltrimethylammonium bromide (CTAB) and dimethyldioctadecylammonium bromide (DDAB). EGCG has been successfully loaded in the LNs dispersions and the nanoparticles analysis over 30 days of storage time predicted a good physicochemical stability. The particles were found to be in the nanometer range (<300nm) and all the evaluated parameters, namely pH, osmolarity and viscosity, were compatible to the ocular administration. The evaluation of the cationic lipid used was compared regarding physical and chemical parameters, lipid crystallization and polymorphism, and stability of dispersion during storage. The results show that different lipids lead to different characteristics mainly associated with the acyl chain composition, i.e. double lipid shows to have influence in the crystallization and stability. Despite the recorded differences between DTAB and DDAB, both cationic LNs seem to fit the parameters for ocular drug delivery.

PMID: 25303852 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 Oct 2. [Epub ahead of print]

The reduction of serum soluble Flt-1 in patients with neovascular age-related macular degeneration.

Uehara H, Mamalis C, McFadden M, Taggart M, Stagg B, Passi S, Earle P, Chakravarthy U, Hogg RE, Ambati BK.

PURPOSE: To evaluate serum soluble Flt-1 (sFlt-1) in age-related degeneration (AMD) patients.

DESIGN: Case control study.

METHODS: Fifty-six non-AMD participants, fifty-three early AMD patients and ninety-seven neovascular AMD patients from Belfast in Northern Ireland. Serum samples were collected from each patient. Serum sFlt-1 was measured by human sVEGFR1/sFlt-1 ELISA kit. The results were analyzed by Excel and SPSS.

RESULTS: Serum sFlt-1 concentration of non-AMD, early AMD, and neovascular AMD were 90.8±2.9 pg/mL (±SEM), 88.2±2.6 pg/mL and 79.9±2.2 pg/mL. sFlt-1 from neovascular AMD patients was significantly decreased compared to non-AMD and early AMD patients (ANOVA, $p<0.01$). For each 10 point increase in sFlt-1, the odds for having neovascular AMD compared with non-AMD and neovascular AMD decreases by 27.8% OR=0.722 (95% CI: 0.588-0.888, $p=0.002$) and 27.0% OR=0.730 (95% CI: 0.594-0.898, $p=0.003$), respectively. In patients over 73 years of age, serum sFlt-1 <80 pg/mL was associated with a >6-fold higher

risk of neovascular AMD.

CONCLUSIONS: Reduced serum sFlt-1 differentiates those patients with neovascular AMD from both early AMD and non-AMD participants. In those aged over 73, serum sFlt <80 pg/mL seems to indicate a particularly high risk of neovascular AMD. Our results indicate serum sFlt-1 could be a biomarker for development of neovascular AMD.

PMID: 25284761 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Oct 14. [Epub ahead of print]

Mice that produce ApoB100 lipoproteins in the RPE do not develop drusen yet are still a valuable experimental system.

Fujihara M, Cano MD, Handa JT.

Purpose: Mice typically produce apolipoprotein (apoB) B48 and not apoB100. ApoB100 lipoproteins accumulate in Bruch's membrane prior to basal deposit and drusen formation during the onset of age-related macular degeneration (AMD), raising the possibility that they are a trigger for these Bruch's membrane alterations. The purpose herein, was to determine whether mice that predominantly produce apoB100 develop features of AMD

Methods: The eyes of mice that produce apoB100 were examined for apoB100 synthesis, cholesteryl esterase/filipin labeling for cholesteryl esters, and OTAP transmission electron microscopy for lipid particles and phenotype.

Results: ApoB100 was abundant in the retinal pigment epithelium (RPE)-choroid of apoB100, but not wild-type mice by Western blot analysis. 35S-radiolabeled apoB100 immunoprecipitated from RPE explants confirmed that apoB100 was synthesized by RPE. ApoB100, but not control mice, had cholesteryl esters and lipid particles in Bruch's membrane. ApoB100 immunoreactivity was present in the RPE and Bruch's membrane, but not choroidal endothelium of apoB100 mice. Ultrastructural changes were consistent with aging, but not AMD when aged up to 18 months. The induction of advanced glycation endproducts to alter Bruch's membrane, did not promote basal linear deposit or drusen formation.

Conclusions: Mice that produce apoB100 in the RPE and liver secrete lipoproteins into Bruch's membrane, but not to the extent that distinct features of AMD develop, which suggests that either additional lipoprotein accumulation or additional factors are necessary to initiate their formation.

PMID: 25316721 [PubMed - as supplied by publisher]

Front Neurol. 2014 Sep 29;5:181. doi: 10.3389/fneur.2014.00181. eCollection 2014.

Up-Regulation of miRNA-146a in Progressive, Age-Related Inflammatory Neurodegenerative Disorders of the Human CNS.

Alexandrov PN, Dua P, Lukiw WJ.

PMID: 25324823 [PubMed]

Epidemiology

J Fr Ophtalmol. 2014 Oct 9. [Epub ahead of print]

[Severity of diabetic macular edema (DME) in Seine St Denis among patients treated by anti-VEGF.]

[Article in French]

Stéphan S, Fajnkuchen F, Addou-Regnard M, Grenet T, Nghiem-Buffet S, Chaine G, Giocanti-Auregan A.

INTRODUCTION: DME is the main cause of loss of vision over the course of diabetes. DME incidence is correlated with diabetes duration, high glycemic levels, high blood pressure, and the severity of diabetic retinopathy. To prevent DME, patients need to have access to medical care. In this study, we sought to know whether DME was more severe in Seine-Saint-Denis, a French area, where the poverty is higher than in other french places, and where the number of physicians is lower.

PATIENTS AND METHODS: We enrolled patients suffering from DME and treated by ranibizumab intravitreal injections between November 2012 and April 2013. In order to evaluate the severity of DME and the medical management of diabetes of these patients, we collected the following parameters: central macular thickness measured by SD-OCT, best corrected visual acuity, diabetic retinopathy severity, HbA1c, diabetes duration, type of diabetes, insulinotherapy, previous DME treatment and associated diseases.

RESULTS: We included 25 type 2 diabetic patients (8 women and 17 men), the mean age was 64±8.1 years. Mean central macular thickness was 523±145µm. The best corrected visual acuity was 45 letters at baseline (counting fingers-70 letters). Twenty-two patients (88%) had a severe non-proliferative diabetic retinopathy or a proliferative diabetic retinopathy. Mean HbA1c was 7.8% (±2.3%). For 23 cases (92%), diabetes was associated with high blood pressure. Sixty-four percent were treated by insulin. Diabetes lasted for 13.1 years at baseline.

DISCUSSION AND CONCLUSION: Diabetic patients, in this case series, had a more severe DME regarding macular thickness and visual acuity than patients from large randomized studies found in the literature. This severity could be due to a sub-optimal management of their diabetes. DME may become a tool to identify patients with a limited access to good medical cares.

PMID: 25308789 [PubMed - as supplied by publisher]

Exp Biol Med (Maywood). 2014 Oct 10. [Epub ahead of print]

No evidence of association between variant rs2075650 in lipid metabolism-related locus APOE/TOMM40 and advanced age-related macular degeneration in Han Chinese population.

Kan M, Weng X, Wang T, Liu F, Ye J, Zhang H, Xu M, Zhou D, He L, Liu Y.

Abstract: Age-related macular degeneration (AMD) is a late-onset, neurodegenerative disease. Genes related to lipid metabolism are important in AMD pathogenesis. Recently, a variant rs2075650 located in lipid metabolism-related locus APOE/TOMM40 was identified to be associated with advanced AMD and early AMD, respectively, in two genome-wide association studies with European ancestry, while no association study between rs2075650 and overall advanced AMD in Chinese population has been conducted before. We evaluated the potential effect of this variant on advanced AMD in a Han Chinese cohort with 204 advanced AMD patients and 1536 healthy controls. The results suggested that rs2075650 was neither associated with advanced AMD in allele level (P = 0.348) nor in genotype level (P = 0.890 under additive model with age and sex adjusted). In conclusion, our study did not confirm the impact of rs2075650 on advanced AMD risk, indicating that rs2075650 is unlikely a superior marker for APOE/TOMM40 susceptible region with advanced AMD in Han Chinese population.

PMID: 25304313 [PubMed - as supplied by publisher]

Genetics

J Gene Med. 2014 Oct 17. doi: 10.1002/jgm.2806. [Epub ahead of print]

Angiogenic gene therapy does not cause retinal pathology.

Prokosch V, Stupp T, Spaniol K, Pham E, Nikol S.

Abstract: Potential negative influence of angiogenic gene therapy on the development or progression of retinal pathologies such as diabetic retinopathy (DR) or age-related macular degeneration (AMD) has led to the systematic exclusion of affected patients from trials. We investigated the role of non-viral fibroblast factor 1 (NV1FGF) in two phase II, multinational, double-blind, randomized, placebo-controlled, gene therapy trials (TALISMAN 201 and 211). 152 subjects with critical limb ischemia or claudication were randomized to receive 8 intramuscular injections of 2.5 ml NV1FGF at 0.2 mg/ml or 0.4 mg/dl or placebo. 152 patients received up to 32 mg plasmid dose NV1FGF or placebo. All patients underwent a systematic ophthalmologic examination at baseline and at 3, 6 or 12 months following gene therapy. 26 of these patients (Münster subgroup) received a retinal fluorescence angiography at baseline and at final examination of the studies. Among those 26 pts, 4 of 9 pts with diabetes suffered from non-proliferative DR. Three patients showed non-exudative AMD. No change of retinal morphology or function was observed in Münster subgroup of both TALISMAN trials independent of the intramuscular NV1FGF dosage applied. Angiogenic gene therapy using NV1FGF is safe even in diabetics. PMID: 25322754 [PubMed - as supplied by publisher]

Neurogenetics. 2014 Oct 16. [Epub ahead of print]

A comprehensive clinical and genetic study of a large Mexican population with spinocerebellar ataxia type 7.

Velázquez-Pérez L, Cerecedo-Zapata CM, Hernández-Hernández O, Martínez-Cruz E, Tapia-Guerrero YS, González-Piña R, Salas-Vargas J, Rodríguez-Labrada R, Gurrola-Betancourth R, Leyva-García N, Cisneros B, Magaña JJ.

Abstract: Spinocerebellar ataxia type 7 (SCA7) is an inherited neurodegenerative disorder characterized by progressive cerebellar ataxia associated with macular degeneration. We recently described one of the largest series of patients with SCA7 that originated from a founder effect in a Mexican population, which allowed us to perform herein the first comprehensive clinical, neurophysiological, and genetic characterization of Mexican patients with SCA7. In this study, 50 patients, categorized into adult or early phenotype, were clinically assessed using standard neurological exams and genotyped using fluorescent PCR and capillary electrophoresis. Patients with SCA7 exhibited the classical phenotype of the disease characterized by cerebellar ataxia and visual loss; however, we reported, for the first time, frontal-executive disorders and altered sensory-motor peripheral neuropathy in these patients. Semiquantitative analysis of ataxia-associated symptoms was performed using Scale for the Assessment and Rating of Ataxia (SARA) and the Brief Ataxia Rating Scale (BARS) scores, while extracerebellar features were measured employing the Inventory of Non-ataxia Symptoms (INAS) scale. Ataxia rating scales confirmed the critical role size of cytosine-adenine-guanine (CAG) repeat size on age at onset and disease severity, while analysis of CAG repeat instability showed that paternal rather than maternal transmission led to greater instability.

PMID: 25318446 [PubMed - as supplied by publisher]

Adv Gerontol. 2014;27(2):336-40.

[The senescence-accelerated oxys rats--a genetic model of premature aging and age-dependent degenerative diseases]. [Article in Russian]

Abstract: The genetic model of accelerated senescence and the associated diseases--the OXYS strain of rats--was created using selection and inbreeding of Wistar rats sensitive to cataractogenic effects of galactose. In the first 5 generations, the development of cataract was induced by galactose

overconsumption, and after that, the rats were selected for early spontaneous cataract. Genetically linked with the latter was a set of features of accelerated senescence, which were inherited by the subsequent generations of the animals. At present, we have a 103rd generation of OXYS rats, who at young age develop retinopathy (similar to age-related macular degeneration in humans), osteoporosis, arterial hypertension, accelerated thymus involution, sarcopenia, and neurodegenerative changes in the brain (with the features characteristic of Alzheimer's disease), besides the cataract. This review discusses possible mechanisms of the accelerated senescence: the results of comparison of retinal transcriptomes between OXYS and Wistar(control) rats at different ages, studies of the markers of Alzheimer's disease in the retina and in certain brain regions, and the outcome of the efforts to develop congenic strains of animals via a transfer of several quantitative trait loci (QTLs) of chromosome 1 from OXYS to WAG rats that are associated with the signs of accelerated senescence. The uniqueness of OXYS rats lies in the complex composition of manifestations of the traits; accordingly, this rat model can be used not only for studies of the mechanisms of aging and pathogenesis of the age-related diseases but also for objective evaluation of new methods of treatment and prevention.

PMID: 25306668 [PubMed - in process]

Exp Eye Res. 2014 Oct 9. [Epub ahead of print]

A comparative analysis of C57BL/6J and 6N substrains; chemokine/cytokine expression and susceptibility to laser-induced choroidal neovascularization.

Schnabolk G, Stauffer K, O'Quinn E, Coughlin B, Kunchithapautham K, Rohrer B.

Abstract: Age-related macular degeneration (AMD) is the most prevalent cause of blindness in the elderly. To study potential underlying mechanisms of AMD, animal models are utilized, focusing mostly on mice. Recently, genomic and phenotypic differences between the so-called control substrains, C57BL/6J and C57BL/6N, have been described in models of ocular and non-ocular diseases. In particular, the rd8 mutation of the Crb1 gene present in the C57BL/6N has been shown to impact certain ocular phenotypes and appears to augment phenotypes generally associated with inflammation. Here, we investigated angiogenic factor and cytokine expression using pathway arrays as well as the susceptibility to laser-induced choroidal neovascularization (CNV), a model of wet AMD, in the two substrains. Age-matched 3-month-old C57BL/6J and C57BL/6N animals differed in gene expression levels for angiogenic factors and cytokines, with 6N animals expressing higher levels of inflammatory markers than 6Js. Yet laser-induced CNV was comparable in size between the two substrains. This lack of difference in CNV size was correlated with a gene expression profile that was comparable between the two substrains, due to the fact that the degree of change in gene expression of inflammatory markers after CNV was blunted in 6N mice. In summary, significant gene expression differences exist between C57BL/6J and C57BL/6N animals, reinforcing the notion that appropriate litter-mate controls or genetic background controls need to be used. Contrary to our expectation, CNV was not augmented in 6N animals, suggesting that low chronic inflammation in the RPE might provide a level of pre-conditioning and protection against stress.

PMID: 25305577 [PubMed - as supplied by publisher]

Diet & lifestyle

Ugeskr Laeger. 2014 Sep 8;176(37).

[Physical activity benefits patients with age-related macular degeneration.][Article in Danish]

Subhi Y, Munch IC, Singh A, Sørensen TL1.

Abstract: We have reviewed studies investigating the effect of physical activity on prevention of early age-

related macular degeneration (AMD), progression to late AMD, and risk modulation of morbidity and mortality in patients with AMD. Regular physical activity may lower risk of developing early AMD and progression of early AMD to late AMD at a level comparable with smoking cessation or dietary supplements. Studies suggest that AMD itself is associated with physical inactivity which can result in higher morbidity levels. Patients with AMD may benefit from physical activity counselling at all stages of the disease.

PMID: 25294030 [PubMed - as supplied by publisher]

J Lipid Res. 2014 Oct 7. [Epub ahead of print]

Pathways of cholesterol homeostasis in mouse retina responsive to dietary and pharmacologic treatments.

Zheng W, Mast N, Saadane A, Pikuleva IA.

Abstract: Effects of serum cholesterol on cholesterol content in the retina is currently unknown. It is also unclear how cholesterol levels are controlled in the retina. High cholesterol diet and oral administrations of simvastatin were used to modulate serum cholesterol in mice. These treatments only modestly affected cholesterol content in the retina and had no significant effect on retinal expression of the major cholesterol- and vision-related genes; the SREBP pathway of transcriptional regulation does not seem to be operative in the retina under the experimental conditions used. Evidence is obtained that post-translational mechanisms play a role in the control of retinal cholesterol. Retinal genes were only upregulated by oral administrations of TO901317 activating liver X receptors. Three of the upregulated genes could be of particular importance (apoD, Idol, and Rpe65) and have not yet been considered in the context of cholesterol homeostasis in the retina. Collectively, the data obtained identify specific features of retinal cholesterol maintenance and suggest additional therapies for age-related macular degeneration, a blinding disease characterized by cholesterol and lipid accumulations in chorioretinal tissues.

PMID: 25293590 [PubMed - as supplied by publisher]

Ageing Res Rev. 2014 Oct 8. [Epub ahead of print]

Involvement of oxysterols in age-related diseases and ageing processes.

Zarrouk A, Vejux A, Mackrill J, O'Callaghan Y, Hammami M, O'Brien N, Lizard G.

Abstract: Ageing is accompanied by increasing vulnerability to major pathologies (atherosclerosis, Alzheimer's disease, age-related macular degeneration, cataract, and osteoporosis) which can have similar underlying pathoetiologies. All of these diseases involve oxidative stress, inflammation and/or cell death processes, which are triggered by cholesterol oxide derivatives, also named oxysterols. These oxidized lipids result either from spontaneous and/or enzymatic oxidation of cholesterol on the steroid nucleus or on the side chain. The ability of oxysterols to induce severe dysfunctions in organelles (especially mitochondria) plays key roles in RedOx homeostasis, inflammatory status, lipid metabolism, and in the control of cell death induction, which may at least in part contribute to explain the potential participation of these molecules in ageing processes and in age related diseases. As no efficient treatments are currently available for most of these diseases, which are predicted to become more prevalentdue to the increasing life expectancy and average age, a better knowledge of the biological activities of the different oxysterols is of interest, and constitutes an important step towards identification of pharmacological targets for the development of new therapeutic strategies.

PMID: 25305550 [PubMed - as supplied by publisher]

Clin Lipidol. 2011;6(5):593-613.

Role of long-chain and very-long-chain polyunsaturated fatty acids in macular degenerations and dystrophies.

Liu A, Lin Y, Terry R, Nelson K, Bernstein PS.

Abstract: Macular degeneration is a progressive, bilateral eye disorder that damages the macula of the human eye. The most common form of macular degeneration is age-related macular degeneration (AMD), which is the leading cause of irreversible blindness in people older than 50 years in developed countries. Autosomal dominant Stargardt disease-3 (STGD3) is an inherited macular dystrophy that has clinical features similar to dry AMD, but occurs at a much earlier age. It is caused by a mutation in the elongation of very-long-chain fatty acids-like 4 (ELOVL4) gene, which is responsible for encoding the elongase enzyme that converts shorter chain fatty acids into C28-C38 very long-chain polyunsaturated fatty acids (VLCPUFAs, total number of carbons ≥24). Diets rich in long-chain polyunsaturated fatty acids (LCPUFAs) have inverse associations with the progression of AMD and STGD3, and a deficiency in retinal LCPUFAs and VLCPUFAs has been detected in AMD retinas and STGD3 animal models. This article systematically summarizes the roles of LCPUFAs and VLCPUFAs in AMD and STGD3, and discusses future research directions.

PMID: 25324899 [PubMed]

Brain Connect. 2014 Oct 14. [Epub ahead of print]

Phonemic Fluency and Brain Connectivity in Age-Related Macular Degeneration: A Pilot Study.

Whitson HE, Chou YH, Potter G, Diaz M, Chen NK, Lad E, Johnson M, Cousins S, Zhuang J, Madden D.

Abstract: Age-related macular degeneration (AMD), the leading cause of blindness in developed nations, has been associated with poor performance on tests of phonemic fluency. This pilot study sought to: 1) characterize the relationship between phonemic fluency and resting-state functional brain connectivity in AMD patients and 2) determine whether regional connections associated with phonemic fluency in AMD patients were similarly linked to phonemic fluency in healthy participants. Behavior-based connectivity analysis (BBCA) was applied to resting-state, functional magnetic resonance imaging (fMRI) data from seven patients (mean age 79.9+7.5 years) with bilateral AMD who completed fluency tasks prior to imaging. Phonemic fluency was inversely related to the strength of functional connectivity (FC) among six pairs of brain regions, representing eight nodes: left opercular portion of inferior frontal gyrus (which includes Broca's area), left superior temporal gyrus (which includes part of Wernicke's area), inferior parietal lobe (bilaterally), right superior parietal lobe, right supramarginal gyrus, right supplementary motor area, and right precentral gyrus. The FC of these reference links was not related to phonemic fluency among 32 healthy individuals (16 younger adults, mean age 23.5 + 4.6 years and 16 older adults, mean age 68.3+3.4 years). Compared to healthy individuals, AMD patients exhibited higher mean connectivity within the reference links and within the default mode network (DMN), possibly reflecting compensatory changes to support performance in the setting of reduced vision. These findings are consistent with the hypothesis that phonemic fluency deficits in AMD reflect underlying brain changes that develop in the context of AMD.

PMID: 25313954 [PubMed - as supplied by publisher]

Exp Eye Res. 2014 Oct 7. [Epub ahead of print]

Natural product inhibitors of ocular angiogenesis.

Sulaiman RS, Basavarajappa HD, Corson TW.

Abstract: Natural products are characterized by high chemical diversity and biochemical specificity; therefore, they are appealing as lead compounds for drug discovery. Given the importance of angiogenesis to many pathologies, numerous natural products have been explored as potential anti-angiogenic drugs. Ocular angiogenesis underlies blinding eye diseases such as retinopathy of prematurity (ROP) in children, proliferative diabetic retinopathy (DR) in adults of working age, and age-related macular degeneration (AMD) in the elderly. Despite the presence of effective therapy in many cases, these diseases are still a significant health burden. Anti-VEGF biologics are the standard of care, but may cause ocular or systemic side effects after intraocular administration and patients may be refractory. Many anti-angiogenic compounds inhibit tumor growth and metastasis alone or in combination therapy, but a more select subset of them has been tested in the context of ocular neovascular diseases. Here, we review the promise of natural products as anti-angiogenic agents, with a specific focus on retinal and choroidal neovascularization. The multifunctional curcumin and the chalcone isoliquiritigenin have demonstrated promising anti-angiogenic effects in mouse models of DR and choroidal neovascularization (CNV) respectively. The homoisoflavanone cremastranone and the flavonoid deguelin have been shown to inhibit ocular neovascularization in more than one disease model. The isoflavone genistein and the flavone apigenin on the other hand are showing potential in the prevention of retinal and choroidal angiogenesis with long-term administration. Many other products with anti-angiogenic potential in vitro such as the lactone withaferin A, the flavonol quercetin, and the stilbenoid combretastatin A4 are awaiting investigation in different ocular disease-relevant animal models. These natural products may serve as lead compounds for the design of more specific, efficacious, and affordable drugs with minimal side effects.

PMID: 25304218 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2014 Oct 14. [Epub ahead of print]

Macular response to supplementation with differing xanthophyll formulations in subjects with and without age-related macular degeneration.

Thurnham DI, Nolan JM, Howard AN, Beatty S.

PURPOSE: Our aim was to investigate the macular response to three different supplements containing lutein (L), zeaxanthin (Z) and meso-zeaxanthin (MZ) in normal subjects and those with age-related macular degeneration (AMD).

MATERIALS AND METHODS: Macular pigment optical density (MPOD) and serum xanthophyll concentrations were measured in normal (n = 31) and AMD subjects (n = 32), randomly assigned to: group 1 (20 mg L, 2 mg Z, 0.3 mg MZ), group 2 (10 mg L, 2 mg Z, 10 mg MZ) or group 3 (3 mg L, 2 mg Z, 17 mg MZ). MPOD was measured at baseline, 2, 4, 6 and 8 weeks and at 0.25°, 0.5°, 1.0° and 1.75° of eccentricity using customised heterochromatic flicker photometry and serum xanthophylls by HPLC.

RESULTS: MPOD increased significantly at all eccentricities in each group ($p < 0.05$), except at 1.75° in group 3 ($p = 0.242$). There was no difference in MPOD measurements between AMD and normal subjects, except for group 2, where AMD subjects exhibited a greater response at 1.75° ($p = 0.012$). Final serum concentrations of MZ were positively and significantly related to final MPOD values at each eccentricity in all subjects. Targeted analysis of those subjects receiving the MZ-containing supplements exhibited stronger relationships between serum MZ concentrations and MPOD at 0.25° in group 3 than group 2; in group 2 all associations were positive, but only significant at 1.75°.

CONCLUSIONS: Serum concentrations of MZ were strongly correlated with MPOD after 8 weeks of supplementation with the group 3 formulation, but the inclusion of L in the group 2 formulation may result in greater MPOD augmentation across the spatial profile.

PMID: 25311651 [PubMed - as supplied by publisher]

Vestn Oftalmol. 2014 Jul-Aug;130(4):102-6, 108-9.

[Clinical efficacy of Vitrum Memory in patients with glaucoma and dry form of age-related macular degeneration]. [Article in Russian]

Abstract: The study was conducted to assess clinical efficacy of Vitrum Memory (Ginkgo biloba) in therapeutic dosage for 3 months in patients with glaucoma and dry form of age-related macular degeneration (AMD). Survey data, visual acuity, biomicroscopy, computer perimetry, electrophysiological studies (EPS): visual evoked potentials (VEP) and pattern electroretinogram (pattern ERG), HRT-3 and OCT were evaluated. Subjective improvement, reduction of visual and mental fatigue, increase of light sensitivity, as well as statistically significant improvement in visual functions (at both computer perimetry and EPS) were achieved.

PMID: 25306732 [PubMed - in process]

PLoS One. 2014 Oct 7;9(10):e108536.

The concordance of care for age related macular degeneration with the chronic care model: a multi-centered cross-sectional study.

Markun S, Brändle E, Dishy A, Rosemann T, Frei A.

AIMS: The aim of the study was to assess the concordance of care for age related macular degeneration with the evidence-based framework for care for chronic medical conditions known as the chronic care model. Furthermore we aimed to identify factors associated with the concordance of care with the chronic care model.

METHODS: Multi-centered cross-sectional study. 169 patients beginning medical treatment for age related macular degeneration were recruited and analyzed. Patients completed the Patient Assessment of Chronic Illness Care (PACIC) questionnaire, reflecting accordance to the chronic care model from a patient's perspective, the National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) and Patient Health Questionnaire (PHQ-9). Visual acuity and chronic medical conditions were assessed. Nonparametric tests and correlation analyses were performed, also multivariable regression analysis.

RESULTS: The median PACIC summary score was 2.4 (interquartile range 1.75 to 3.25), the lowest PACIC subscale score was "follow-up/coordination" with a median of 1.8 (interquartile range 1.00 to 2.60). In multivariable regression analysis the presence of diabetes type 2 was strongly associated with low PACIC scores (coefficient=-0.85, p=0.007).

CONCLUSION: Generally, care for patients with age related macular degeneration by ophthalmologists is in moderate concordance with the chronic care model. Concerning follow-up and coordination of health service, large improvements are possible. Future research should answer the question how healthcare delivery can be improved effecting relevant benefits to patients with AMD.

PMID: 25290915 [PubMed - in process] PMCID: PMC4188520

Clin Ophthalmol. 2014 Sep 22;8:1913-7.

Projected changes in age-related macular degeneration and driving license holders in Finland.

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PURPOSE: The aim of the study was to approximate the occurrence of all forms of age-related macular degeneration (AMD) of the retina among the driving license holders aged 80 or more, and to project the changes to 2030 in Finland. AMD, destroying the visual cells in the central part of the retina, is a common

disease of older age: one out of three individuals aged 70 or older shows early signs of AMD progressing later to relentless loss of vision. This eye disease can be detected only by an ophthalmologist. In general, little is known about the prevalence of AMD among driving license holders aged 80 or older.

METHODS: At first the prevalence of individuals with either drusen or AMD in Finland among those 80 or older was approximated. Then the number of license holders in this age group was extracted from the statistics of the Finnish Transport Safety Agency and Eurostat provided us with the demographical data. The changes were projected to 2030.

RESULTS: In Finland, with a population of 5.35 million, the number of those aged 80 or over will increase by 175,000 by 2030. The total number of individuals with either drusen or AMD will increase from 118,000 to 193,000 by the year 2030 and an increasing proportion of them will have a driving license. The proportion of women in 2012 having a driving license in the groups 60 or younger is about 45%, while in those aged 80 or older it is only 20%.

CONCLUSION: The number of people aged 80 years or older will increase in Finland by 2030. The number of those in this age group having a driving license will increase more rapidly as the population ages because the proportion of women with a driving license will increase in this age group. As the prevalence of drusen and AMD among women aged 80 or over is higher than among men at comparable age, this means that AMD will increase even more rapidly among drivers in this age group.

PMID: 25284977 [PubMed] PMCID: PMC4181625