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MD Research News

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Drug treatment

Br J Ophthalmol. 2015 May 8. [Epub ahead of print]

A model of the ocular pharmacokinetics involved in the therapy of neovascular age-related macular degeneration with ranibizumab.

Saunders DJ, Muether PS, Fauser S.

BACKGROUND: To develop a model of the pharmacokinetics of vascular endothelial growth factor (VEGF-A) determined in samples of aqueous humour from patients with neovascular age-related macular degeneration (AMD) treated with ranibizumab (Lucentis).

METHODS: Post hoc analysis of data from 31 eyes of 31 patients with AMD treated with ranibizumab gathered in a non-randomised, prospective clinical study. VEGF-A concentrations were measured in 440 aqueous humour samples by Luminex multiplex bead analysis (Luminex, Austin, Texas, USA).

RESULTS: The kinetics of recovery of VEGF-A from suppression by ranibizumab were well described by a simple model: VEGF-A is produced at a constant individual rate; VEGF-A and ranibizumab disperse rapidly within the vitreous chamber and bind with a known affinity; both are eliminated at identical rates from the vitreous chamber in a constant but individual flow into the anterior chamber, and are finally cleared by draining into the peripheral circulation. Average rates of VEGF-A production were predicted to be 5.8 fmol/day (range: 2.7-10.1 fmol), and elimination half-times predicted to be 3.5 days (range: 2.3-5.5 days). The duration of complete VEGF-A suppression in the aqueous humour averaged 41 days (range: 28-67 days).

CONCLUSIONS: The ocular pharmacokinetics of VEGF-A and ranibizumab have been linked for the first time in a simple and plausible model which suggests that it might be possible to anticipate individual VEGF-A suppression times.

PMID: 25957377 [PubMed - as supplied by publisher]

Eye (Lond). 2015 May 15. [Epub ahead of print]

OCT angiography and sequential quantitative analysis of type 2 neovascularization after ranibizumab therapy.

Kuehlewein L, Sadda SR, Sarraf D.

Purpose: To study the precise structural aspects of a type 2 neovascular membrane in a patient with age-related macular degeneration (AMD) using optical coherence tomography (OCT) angiography and perform sequential quantitative analysis of the membrane after ranibizumab therapy.

Patients and methods: Split-spectrum amplitude-decorrelation (SSADA) OCT angiography macular cubes (3 × 3 mm) were acquired with a light source centered at 840 nm, a bandwidth of 45 nm, and an A-scan-rate of 70 000 scans per second. Visible pathologic vessels were outlined manually on average intensity projection en face images, and the area of the lesion and the vessel density were measured at baseline and follow-up.

Results: At baseline, the neovascular lesion measured 4.12 mm2 and the vessel density was 19.83 mm-1. Four weeks after the first, and 2 and 4 weeks after the second ranibizumab injection, OCT angiography revealed a progressively smaller vascular lesion (2.32, 1.77 and 1.64 mm2), and vessel density (10.24, 8.52 and 7.57 mm-1), although the large central trunks of the lesion were unchanged.

Conclusions: In this study, an obvious reduction in size and vessel density of the neovascular lesion was noted after treatment with ranibizumab using SSADA OCT angiography technology. Microvascular components can be delineated with precision, suggesting that this technique may be useful for the management of patients with neovascular AMD in a clinical setting as well as for future clinical trials.

PMID: 25976641 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2015 May 15;15(1):52. [Epub ahead of print]

Systematic review and mixed treatment comparison of intravitreal aflibercept with other therapies for diabetic macular edema (DME).

Korobelnik JF, Kleijnen J, Lang SH, Birnie R, Leadley RM, Misso K, Worthy G, Muston D, Do DV.

BACKGROUND: This was an indirect comparison of the effectiveness of intravitreal aflibercept (IVT-AFL) 2 mg every 8 weeks after 5 initial monthly doses (or if different periods, after an initial monthly dosing period) (2q8) and other diabetic macular edema (DME) therapies at doses licensed outside the USA.

METHODS: A comprehensive search was undertaken to source relevant studies. Feasibility networks were prepared to identify viable comparisons of 12-month outcomes between IVT-AFL 2q8 and therapies licensed outside the USA, which were assessed for clinical and statistical homogeneity. Pooled effect sizes (mean difference [MD] and relative risk [RR]) were calculated using fixed- and random-effects models. Indirect comparisons were performed using Bucher analysis. If at least one 'head-to-head' study was found then a mixed treatment comparison (MTC) was performed using Bayesian methods. Two 12-month comparisons could be undertaken based on indirect analyses: IVT-AFL 2 mg every 8 weeks (2q8) versus intravitreal ranibizumab (IVR) 0.5 mg as needed (PRN) (10 studies) and IVT-AFL 2q8 versus dexamethasone 0.7 mg implants (three studies).

RESULTS: There was an increase in mean best corrected visual acuity (BCVA) with IVT-AFL 2q8 over IVR 0.5 mg PRN by 4.67 letters [95% credible interval (CrI): 2.45-6.87] in the fixed-effect MTC model (10 studies) and by 4.82 letters [95% confidence interval (CI): 2.52-7.11] in the Bucher indirect analysis (four studies). IVT-AFL 2q8 doubled the proportion of patients gaining ≥ 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at 12 months compared with dexamethasone 0.7 mg implants (RR = 2.10 [95% CI: 1.29-3.40]) in the fixed-effect model. There were no significant differences in safety outcomes between IVT-AFL 2q8 and IVR 0.5 mg PRN or dexamethasone 0.7 mg implants.

CONCLUSIONS: Studies of IVT-AFL 2q8 showed improved 12-month visual acuity measures compared with studies of IVR 0.5 mg PRN and dexamethasone 0.7 mg implants based on indirect comparisons. These analyses are subject to a number of limitations which are inherent in indirect data comparisons.

PMID: 25975823 [PubMed - as supplied by publisher]

Risk Manag Healthc Policy. 2015 Apr 21;8:55-62. eCollection 2015.

Anti-VEGF treatment patterns and associated health care costs in Switzerland: findings using real-world claims data.

Reich O, Bachmann LM, Faes L, Böhni SC, Bittner M, Howell JP, Thiel MA, Rapold R, Schmid MK.

BACKGROUND: Little is known about the patterns of actual health care delivery of anti-vascular endothelial growth factor (VEGF) treatment in patients with age-related macular degeneration, diabetic retinopathy, and retinal vein occlusion in Switzerland. The purpose of this study was to describe these treatment patterns, specifically comparing the numbers of anti-VEGF injections and associated expenditures between patients treated with ranibizumab and those treated with aflibercept in Switzerland using claims data.

METHODS: We identified our study patients retrospectively using the Helsana claims database, which includes data on approximately 1.2 million subjects with basic health insurance. Patients qualified for inclusion if ranibizumab or aflibercept had been initiated between December 1, 2012 (when aflibercept was approved by the Federal Office of Public Health) and November 30, 2013. Within this set, patients with at least 12 months of continuous insurance enrolment in the previous year were considered. In univariate analyses, we examined the distribution of demographic data and patient characteristics between those receiving ranibizumab and those receiving aflibercept. Numbers of injections and associated health care expenditures observed during the 6-month follow-up period after incident treatment were the two outcomes considered. In multivariate regression analyses, controlling for possible confounding factors, we compared differences in these two outcomes between patients treated with ranibizumab and those treated with aflibercept.

RESULTS: Of 3,260 patients who were on anti-VEGF treatment for an ophthalmological indication between December 1, 2012 and November 30, 2013, 1,150 qualified for inclusion. Age, geographic region, and number of physician visits in the previous year were significant factors in the number of injections given during the 6-month follow-up period. Frequency of injections and associated health care expenditures were similar between the groups when correcting for differences in patient characteristics.

CONCLUSION: Contrary to the recommendations regarding frequency of injections and the results of clinical studies, aflibercept and ranibizumab are used in a similar fashion in Switzerland, resulting in similar total health care expenditures for both these anti-VEGF agents.

PMID: 25960682 [PubMed] PMCID: PMC4412486

Drug Des Devel Ther. 2015 Apr 22;9:2311-2320.

Profile of conbercept in the treatment of neovascular age-related macular degeneration.

Lu X, Sun X.

Abstract: In developed countries, age-related macular degeneration (AMD) is the leading cause of irreversible blindness in individuals over the age of 65 years. Vascular endothelial growth factor (VEGF) plays a vital role in the formation of neovascular AMD. VEGF regulates angiogenesis, enhances vascular permeability, and drives the formation of choroidal neovascularization. As a result of the introduction of anti-VEGF drugs, the incidence of blindness from neovascular AMD has greatly reduced. Anti-VEGF drugs are used as a first-line treatment for neovascular AMD. The most recent anti-VEGF drug is conbercept, also named KH902, which was approved for the treatment of neovascular AMD by the China Food and Drug Administration in December 2013. In this review, recent clinical information regarding the use of conbercept to treat neovascular AMD is summarized. Conbercept is a soluble receptor decoy that blocks all isoforms of VEGF-A, VEGF-B, VEGF-C, and PlGF, which has a high binding affinity to VEGF and a long half-life in vitreous. Preclinical studies have demonstrated its anti-angiogenesis activity in both ocular neovascular disease models and tumor models. Clinical trials of conbercept have shown its superior efficacy and safety. Patients respond well even with 3-month treatment intervals following loading doses once a month for 3 months. The potential therapeutic effect of conbercept on the treatment of polypoidal choroidal

vasculopathy, a special type of neovascular AMD, is also promising. In summary, conbercept is a new treatment option for ophthalmologists and their patients and may help address the limitations of current anti -VEGF drugs.

PMID: 25960634 [PubMed - as supplied by publisher] PMCID: PMC4410828

Ophthalmology. 2015 May 9. [Epub ahead of print]

Scatter Photocoagulation Does Not Reduce Macular Edema or Treatment Burden in Patients with Retinal Vein Occlusion: The RELATE Trial.

Campochiaro PA, Hafiz G, Mir TA, et al.

PURPOSE: To determine whether scatter and grid laser photocoagulation (laser) adds benefit to ranibizumab injections in patients with macular edema from retinal vein occlusion (RVO) and to compare 0.5-mg with 2.0-mg ranibizumab.

DESIGN: Randomized, double-masked, controlled clinical trial.

PARTICIPANTS: Thirty-nine patients with central RVO (CRVO) and 42 with branch RVO (BRVO).

METHODS: Subjects were randomized to 0.5 mg or 2.0 mg ranibizumab every 4 weeks for 24 weeks and re-randomized to pro re nata ranibizumab plus laser or ranibizumab alone.

MAIN OUTCOME MEASURES: Mean change from baseline best-corrected visual acuity (BCVA) at week 24 for BCVA at weeks 48, 96, and 144 for second randomization.

RESULTS: Mean improvement from baseline BCVA at week 24 was 15.5 and 15.8 letters in the 0.5-mg and 2.0-mg CRVO groups, and 12.1 and 14.6 letters in the 0.5-mg and 2.0-mg BRVO groups. For CRVO, but not BRVO, there was significantly greater reduction from baseline mean central subfield thickness (CST) in the 2.0-mg versus 0.5-mg group (396.1 vs. 253.5 μm; P = 0.03). For the second randomization in CRVO patients, there was no significant difference from week 24 BCVA in the ranibizumab plus laser versus the ranibizumab only groups at week 48 (-3.3 vs. 0.0 letters), week 96 (+0.69 vs. -1.6 letters), or week 144 (+0.4 vs. -6.7 letters), and a significant increase from week 24 mean CST at week 48 (+94.7 vs. +15.2 μm; P = 0.05) but not weeks 96 or 144. For BRVO, there was a significant reduction from week 24 mean BCVA in ranibizumab plus laser versus ranibizumab at week 48 (-7.5 vs. +2.8; P < 0.01) and week 96 (-2.0 vs. +4.8; P < 0.03), but not week 144, and there were no differences in mean CST change from week 24 at weeks 48, 96, or 144. Laser failed to increase edema resolution or to reduce the ranibizumab injections between weeks 24 and 144.

CONCLUSIONS: In patients with macular edema resulting from RVO, there was no short-term clinically significant benefit from monthly injections of 2.0-mg versus 0.5-mg ranibizumab injections and no long-term benefit in BCVA, resolution of edema, or number of ranibizumab injections obtained by addition of laser treatment to ranibizumab.

PMID: 25972260 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2015 May 12. [Epub ahead of print]

Recovery of plasma vascular endothelial growth factor concentrations during aflibercept loading phase and after the transition to bimonthly treatment for neovascular age-related macular degeneration.

Roald AB, Aass HC, Moe MC.

AIMS: To provide data on plasma vascular endothelial growth factor (VEGF) concentration during three consecutive monthly intravitreal aflibercept injections and after transition to bimonthly treatment in patients

with neovascular age-related macular degeneration (nAMD).

METHODS: Sixteen consecutive treatment-naïve Caucasian patients with nAMD were included in the study. The treatment consisted of one intravitreal aflibercept (2 mg) injection every 28 days for three consecutive months followed by a fourth injection 8 weeks later. VEGF plasma concentrations were measured with Luminex on day 0 (baseline, prior to first injection); days 1, 6 and 27 (prior to second injection); day 55 (prior to third injection) and days 97 and 111 (after third injection).

RESULTS: Baseline plasma VEGF concentration was 59.6±13.3 pg/mL. Aflibercept decreased plasma VEGF concentration to 32.5±3 pg/mL on day 1 ($p<0.0001$) and 34.7±6.3 pg/mL on day 6 ($p<0.0001$). On day 27, the VEGF plasma level increased to 50.6±6.5 pg/mL ($p=0.009$) and on day 55 to 52.8±8.8 pg/mL ($p=0.027$). There was no statistically significant difference between mean plasma VEGF concentrations on days 27 and 55 ($p=0.139$). Plasma VEGF concentration recovered completely 6 weeks after the third injection, reaching 57.9±9.6 pg/mL on day 97 ($p=0.600$) and 59.5±11.6 pg/mL on day 111 ($p=0.987$).

CONCLUSIONS: Intravitreal aflibercept decreases plasma VEGF concentration mostly in the first week after treatment. Despite repeated monthly intravitreal injections, there was a monthly increase in plasma VEGF values to near baseline levels, with complete recovery 6 weeks after the third injection.

PMID: 25966740 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Ophthalmology. 2015 May 9. [Epub ahead of print]

Directional Kinetics of Geographic Atrophy Progression in Age-Related Macular Degeneration with Foveal Sparing.

Lindner M, Böker A, Mauschitz MM, Göbel AP, Fimmers R, Brinkmann CK, Schmitz-Valckenberg S, Schmid M, Holz FG, Fleckenstein M; Fundus Autofluorescence in Age-Related Macular Degeneration Study Group.

PURPOSE: To describe the directional kinetics of the spread of geographic atrophy (GA) spread in eyes with age-related macular degeneration and foveal sparing.

DESIGN: Prospective, noninterventional natural history study: Fundus Autofluorescence Imaging in Age-Related Macular Degeneration (FAM; clinicaltrials.gov identifier, NCT00393692).

SUBJECTS: Participants of the FAM study exhibiting foveal sparing of GA.

METHODS: Eyes were examined longitudinally with fundus autofluorescence (FAF; excitation wavelength, 488 nm; emission wavelength, >500 nm) and near infrared (NIR) reflectance imaging (Spectralis HRA+OCT or HRA2; Heidelberg Engineering, Heidelberg, Germany). Areas of foveal sparing and GA were measured by 2 independent readers using a semiautomated software tool that allows for combined NIR reflectance and FAF image grading (RegionFinder; Heidelberg Engineering). A linear mixed effect model was used to model GA kinetics over time.

MAIN OUTCOME MEASURE: Change of GA lesion size over time (central vs. peripheral progression).

RESULTS: A total of 47 eyes of 36 patients (mean age, 73.8±7.5 years) met the inclusion criteria. Mean follow-up time was 25.2±16.9 months (range, 5.9-74.6 months). Interreader agreement for measurements of GA and foveal-sparing size were 0.995 and 0.946, respectively. Mean area progression of GA toward the periphery was 2.27±0.22 mm2/year and 0.25±0.03 mm2/year toward the center. Analysis of square root-transformed data revealed a 2.8-fold faster atrophy progression toward the periphery than toward the fovea. Faster atrophy progression toward the fovea correlated with faster progression toward the periphery in presence of marked interindividual differences.

CONCLUSIONS: The results demonstrate a significantly faster centrifugal than centripetal GA spread in eyes with GA and foveal sparing. Although the underlying pathomechanisms for differential GA progression remain unknown, local factors may be operative that protect the foveal retina-retinal pigment epithelial complex. Quantification of directional spread characteristics and modeling may be useful in the design of interventional clinical trials aiming to prolong foveal survival in eyes with GA.

PMID: 25972258 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2015 May 15. [Epub ahead of print]

Peripapillary choroidal thickness in patients with early age-related macular degeneration and reticular pseudodrusen.

Yun C, Oh J, Ahn SE, Hwang SY, Kim SW, Huh K.

PURPOSE: The purpose of this study was to investigate peripapillary and macular choroidal thickness (CT) in patients with early age-related macular degeneration (AMD) with or without reticular pseudodrusen (RPD).

METHODS: We investigated the medical records of 89 patients (89 eyes) with early AMD. The eyes were grouped into three categories according to the extent of RPD: no RPD, localized RPD, and diffuse RPD. Peripapillary and macular CT were measured with images obtained by spectral domain optical coherence tomography. CT in the peripapillary and macular areas was compared among groups.

RESULTS: Both RPD groups exhibited an older subject age and a greater female predominance compared to the non-RPD group ($P = 0.007$ and $P = 0.030$, respectively). Macular and peripapillary CT were different among the three groups (all, $P < 0.001$), and both RPD groups showed a thinner choroid in all areas compared to the non-RPD group after adjusting for age and sex (all, $P \leq 0.016$). Temporal peripapillary and nasal macular CT at 500 μm and 1500 μm, respectively, from the fovea in eyes with diffuse RPD were significantly thinner than that in eyes with localized RPD ($P = 0.008$, $P = 0.016$ and $P < 0.001$, respectively).

CONCLUSIONS: In addition to the macular area, the peripapillary CT, including the area outside the macula, was thinner in eyes with RPD than in those without RPD. Significant differences in the papillomacular choroid were observed based on RPD distribution type, which suggests that variation in CT is based on the extent of RPD.

PMID: 25971212 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2015 Apr 1;46(4):413-22.

Comparison of Geographic Atrophy Growth Rates Using Different Imaging Modalities in the COMPLETE Study.

Yehoshua Z, de Amorim Garcia Filho CA, Nunes RP, Gregori G, Penha FM, Moshfeghi AA, Sadda S, Feuer W, Rosenfeld PJ.

BACKGROUND AND OBJECTIVE: To compare the measurements and growth rates of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) obtained using different imaging modalities.

PATIENTS AND METHODS: Thirty patients with AMD and GA measuring from 1.25 mm(2) to 18 mm(2) based on spectral-domain optical coherence tomography (SD-OCT) fundus imaging were enrolled. Imaging was performed at baseline and at follow-up months 3, 6, 9, and 12, including autofluorescence (AF) imaging with a fundus camera-based flash system (TRC-50DX; Topcon Medical Systems, Oakland, NJ; AF excitation λ: 535-585 nm; detection λ: 605-715 nm), AF and fluorescein angiography (FA) imaging with a confocal scanning laser ophthalmoscopy (SLO) system (Spectralis; Heidelberg Engineering, Heidelberg, Germany; AF excitation λ: 488 nm; detection λ: > 500 nm), and SD-OCT en face imaging (Cirrus; Carl Zeiss

Meditec, Dublin, CA).

RESULTS: Average baseline square root measurements and enlargement rates of square root areas appeared similar across all modalities; 0.2 mm was the largest difference between any pair of measurement means. The intraclass correlation coefficients (ICC) were essentially equal to 1 for all comparisons of area measurements but were lower for growth rates than area measurements. Comparison of 26-week average enlargement rates showed no significant difference between the SLO AF image and enhanced SD-OCT en face image (mean difference: 0.01 mm; SD: 0.10; P = .70).

CONCLUSION: Agreement among all imaging modalities in measuring the areas of GA at baseline diminished when the growth rates of GA were compared over 26 weeks, likely because each imaging technique identifies different anatomic features along the border of GA, which may appear similar but change at different rates.

PMID: 25970861 [PubMed - in process]

BMJ Open. 2015 May 12;5(5):e007930.

The effect of blue-blocking intraocular lenses on circadian biological rhythm: protocol for a randomised controlled trial (CLOCK-IOL colour study).

Nishi T, Saeki K, Obayashi K, et al

INTRODUCTION: Blue light information plays an important role in synchronising internal biological rhythm within the external environment. Circadian misalignment is associated with the increased risk of sleep disturbance, obesity, diabetes mellitus, depression, ischaemic heart disease, stroke and cancer. Meanwhile, blue light causes photochemical damage to the retina, and may be associated with age-related macular degeneration (AMD). At present, clear intraocular lenses (IOLs) and blue-blocking IOLs are both widely used for cataract surgery; there is currently a lack of randomised controlled trials to determine whether clear or blue-blocking IOLs should be used.

METHODS AND ANALYSIS: This randomised controlled trial will recruit 1000 cataract patients and randomly allocate them to receive clear IOLs or blue-blocking IOLs in a ratio of 1:1. The primary outcomes are mortality and the incidence of cardiovascular disease, cancer and AMD. Secondary outcomes are fasting plasma glucose, triglycerides, cholesterol, glycated haemoglobin, sleep quality, daytime sleepiness depressive symptoms, light sensitivity, the circadian rhythm of physical activity, wrist skin temperature and urinary melatonin metabolite. Primary outcomes will be followed until 20 years after surgery, and secondary outcomes will be assessed at baseline and 1 year after surgery.

ETHICS AND DISSEMINATION: Ethical approval has been obtained from the Institutional Review Board of Nara Medical University (No. 13-032). The findings of this study will be communicated to healthcare professionals, participants and the public through peer-reviewed publications, scientific conferences and the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) home page.

TRIAL REGISTRATION NUMBER: UMIN000014680.

PMID: 25968007 [PubMed - in process]

Cesk Slov Oftalmol. 2015 Spring;71(2):83-6.

[Retinal tubulation].[Article in Czech]

Matušková V.

Abstract: The aim of this study is to present a new retinal structure which is detectable on OCT scans - outer retinal tubulations (ORT). The discovery of these structures is related to more and more perfect retinal imaging using the spectral domain optical coherence tomography (SD OCT). Outer retinal tubulations were

first described by Zweifel et al. in the year 2009 in patients with age-related macular degeneration. These branching tubular structures are localized in the outer nuclear layer of the retina. They are of circular or ovoid shape, with hyporeflectivity in the center, their borders are hyperreflective. Retinal tubulations are mostly seen together with choroid neovasculare membrane or with retinal pigment epithelium atrophy. Typically, they are adjacent to the area of wide damage of the outer retinal structure combined with relatively good preserved photoreceptor layer (respectively junctions between inner and outer photoreceptors segments), often they overlap the area of subretinal fibrosis or RPE (retinal pigment epithelium) damage. In eyes with anti-VEGF (vascular endothelial growth factor) treatment, they do appear in the area, where, before the treatment, the intraretinal fluid was present. These structures may simulate CME or the presence of subretinal fluid, so their determination plays an important role in the indications of next anti-VEGF drugs applications. Their non-detection may cause unneeded re-applications of anti-VEGF drugs into the viterous. This study was presented as a lecture at the Congress of the Czech VitreoRetinal Society in Dolní Morava (Czech Republic, E.U.) in the year 2014.Key words: outer retinal tubulations (ORT), cystoid macular edema (CME), age-related macular degeneration (ARMD), optical coherence tomography (OCT).

PMID: 25962420 [PubMed - in process]

Pathogenesis

PLoS One. 2015 May 11;10(5):e0126592. eCollection 2015.

Quantification of histone deacetylase isoforms in human frontal cortex, human retina, and mouse brain.

Anderson KW, Chen J, Wang M, Mast N, Pikuleva IA, Turko IV.

Abstract: Histone deacetylase (HDAC) inhibition has promise as a therapy for Alzheimer's disease (AD) and other neurodegenerative diseases. Currently, therapeutic HDAC inhibitors target many HDAC isoforms, a particularly detrimental approach when HDAC isoforms are known to have different and specialized functions. We have developed a multiple reaction monitoring (MRM) mass spectrometry assay using stable isotope-labeled QconCATs as internal standards to quantify HDAC isoforms. We further determined a quantitative pattern of specific HDACs expressed in various human and mouse neural tissues. In human AD frontal cortex, HDAC1,2 decreased 32%, HDAC5 increased 47%, and HDAC6 increased 31% in comparison to age-matched controls. Human neural retina concentrations of HDAC1, 2, HDAC5, HDAC6, and HDAC7 decreased in age-related macular degeneration (AMD)-affected donors and exhibited a greater decrease in AD-affected donors in comparison to age-matched control neural retinas. Additionally, HDAC concentrations were measured in whole hemisphere of brain of 5XFAD mice, a model of β-amyloid deposition, to assess similarity to AD in human frontal cortex. HDAC profiles of human frontal cortex and mouse hemisphere had noticeable differences and relatively high concentrations of HDAC3 and HDAC4 in mice, which were undetectable in humans. Our method for quantification of HDAC isoforms is a practical and efficient technique to quantify isoforms in various tissues and diseases. Changes in HDAC concentrations reported herein contribute to the understanding of the pathology of neurodegeneration.

PMID: 25962138 [PubMed - in process]

PLoS One. 2015 May 15;10(5):e0125150.

Interleukin-1β Level Is Increased in Vitreous of Patients with Neovascular Age-Related Macular Degeneration (nAMD) and Polypoidal Choroidal Vasculopathy (PCV).

Zhao M, Bai Y, Xie W, Shi X, Li F, Yang F, Sun Y, Huang L, Li X.

PURPOSE: To examine the expression of pro-interleukin-1β (pro-IL-1β) and interleukin-1β (IL-1β) in the

vitreous body of patients with neovascular age-related macular degeneration(nAMD), polypoidal choroidal vasculopathy (PCV), proliferative diabetic retinopathy (PDR), retinal vein occlusion (RVO) or Eales' disease to further elucidate the role of IL-1β and inflammation in the pathogenesis of neovascular retinal disease.

DESIGN: Prospective clinical laboratory investigation study.

METHODS: All patients enrolled had vitreous hemorrhage due to nAMD, PCV, PDR, RVO or Eales' disease that required vitrectomy. Patients were excluded for any history of active intraocular inflammation, or other ophthalmic surgery besides vitrectomy. Control samples were obtained from patients with idiopathic macular epiretinal membrane. A total of fifty vitreous samples were collected from patient during vitrectomy. Pro-IL-1β and IL-1β expression were measured by enzyme-linked immunosorbent assay (ELISA). Results were analyzed statistically using nonparametric tests.

RESULTS: Expression of pro-IL-1β protein was increased by 2.83-fold and 9.19-fold in PCV and nAMD vitreous samples relative to control, respectively. Expression of IL-β protein was increased by 10-fold and 4.83-fold in PCV and nAMD vitreous samples relative to control, respectively.

CONCLUSIONS: Our results demonstrate that expression of pro-IL-1β and IL-1β proteins is higher in PCV and nAMD. The roles of pro-IL-1β and IL-1β as inflammatory mediators in the development of PCV and nAMD may be associated with photoreceptor degeneration and neovascularization which necessitates further study.

PMID: 25978536 [PubMed - as supplied by publisher]

Genetics

PLoS One. 2015 May 11;10(5):e0126636. eCollection 2015.

Clinical and genetic factors associated with progression of geographic atrophy lesions in age-related macular degeneration.

Grassmann F, Fleckenstein M, Chew EY, Strunz T, Schmitz-Valckenberg S, Göbel AP, Klein ML, Ratnapriya R, Swaroop A, Holz FG, Weber BH.

Abstract: Worldwide, age-related macular degeneration (AMD) is a serious threat to vision loss in individuals over 50 years of age with a pooled prevalence of approximately 9%. For 2020, the number of people afflicted with this condition is estimated to reach 200 million. While AMD lesions presenting as geographic atrophy (GA) show high inter-individual variability, only little is known about prognostic factors. Here, we aimed to elucidate the contribution of clinical, demographic and genetic factors on GA progression. Analyzing the currently largest dataset on GA lesion growth (N = 388), our findings suggest a significant and independent contribution of three factors on GA lesion growth including at least two genetic factors (ARMS2_rs10490924 [P < 0.00088] and C3_rs2230199 [P < 0.00015]) as well as one clinical component (presence of GA in the fellow eye [P < 0.00023]). These correlations jointly explain up to 7.2% of the observed inter-individual variance in GA lesion progression and should be considered in strategy planning of interventional clinical trials aimed at evaluating novel treatment options in advanced GA due to AMD.

PMID: 25962167 [PubMed - in process]

Hum Mol Genet. 2015 May 10. [Epub ahead of print]

Mitochondrial DNA Variants Can Mediate Methylation Status of Inflammation, Angiogenesis and Signaling Genes.

Atilano SR, Malik D, Chwa M, et al

Abstract: Mitochondrial (mt) DNA can be classified into haplogroups representing different geographic and/or racial origins of populations. The H haplogroup is protective against age-related macular degeneration (AMD), while the J haplogroup is high risk for AMD. In the present study, we performed comparison analyses of human retinal cell cybrids, which possess identical nuclei, but mtDNA from subjects with either the H or J haplogroups, and demonstrate differences in total global methylation, expression patterns for two genes related to acetylation and five genes related to methylation. Analyses revealed that untreated-H and -J cybrids have different expression levels for nuclear genes (CFH, EFEMP1, VEGFA and NFkB2). However, expression levels for these genes become equivalent after treatment with a methylation inhibitor, 5-aza-2'-deoxycytidine. Moreover, sequencing of the entire mtDNA suggests that differences in epigenetic status found in cybrids are likely due to single nucleotide polymorphisms (SNPs) within the haplogroup profiles rather than rare variants or private SNPs. In conclusion, our findings indicate that mtDNA variants can mediate methylation profiles and transcription for inflammation, angiogenesis and various signaling pathways, which are important in several common diseases.

PMID: 25964427 [PubMed - as supplied by publisher]

Diet & lifestyle

Eye (Lond). 2015 May 15. [Epub ahead of print]

Sustained supplementation and monitored response with differing carotenoid formulations in early age-related macular degeneration.

Akuffo KO, Nolan JM, Howard AN, Moran R, Stack J, Klein R, Klein BE, Meuer SM, Sabour-Pickett S, Thurnham DI, Beatty S.

Purpose: To compare the impact of sustained supplementation using different macular carotenoid formulations on macular pigment (MP) and visual function in early age-related macular degeneration (AMD).

Patients and methods: Sixty-seven subjects with early AMD were randomly assigned to: Group 1 (20 mg per day lutein (L), 0.86 mg per day zeaxanthin (Z); Ultra Lutein), Group 2 (10 mg per day meso-zeaxanthin (MZ), 10 mg per day L, 2 mg per day Z; Macushield; Macuhealth), Group 3 (17 mg per day MZ, 3 mg per day L, 2 mg per day Z). MP was measured using customised heterochromatic flicker photometry and visual function was assessed by measuring contrast sensitivity (CS) and best-corrected visual acuity (BCVA). AMD was graded using the Wisconsin Age-Related Maculopathy Grading System (AREDS 11-step severity scale).

Results: At 3 years, a significant increase in MP from baseline was observed in all groups at each eccentricity ($P<0.05$), except at 1.75° in Group 1 ($P=0.160$). Between 24 and 36 months, significant increases in MP at each eccentricity were seen in Group 3 ($P<0.05$ for all), and at 0.50° in Group 2 ($P<0.05$), whereas no significant increases were seen in Group 1 ($P>0.05$ for all). At 36 months, compared with baseline, the following significant improvements ($P<0.05$) in CS were observed: Group 2-1.2, 6, and 9.6 cycles per degree (c.p.d.); Group 1-15.15 c.p.d.; and Group 3-6, 9.6, and 15.15 c.p.d. No significant changes in BCVA, or progression to advanced AMD, were observed.

Conclusion: In early AMD, MP can be augmented with a variety of supplements, although the inclusion of MZ may confer benefits in terms of panprofile augmentation and in terms of CS enhancement.

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