

Issue 300

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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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Drug treatment

Ophthalmology. 2016 Oct 1. [Epub ahead of print]

Twelve-Month Outcomes of Ranibizumab vs. Aflibercept for Neovascular Age-Related Macular Degeneration: Data from an Observational Study.

Gillies MC, Nguyen V, Daien V, Arnold JJ, Morlet N, Barthelmes D.

PURPOSE: To directly compare visual acuity (VA) outcomes with ranibizumab vs. aflibercept for eyes with neovascular age-related macular degeneration (nAMD) treated in routine clinical practice.

DESIGN: Database observational study.

PARTICIPANTS: Treatment-naïve eyes with nAMD tracked by the Fight Retinal Blindness outcome registry that commenced anti-vascular endothelial growth factor therapy with ranibizumab or aflibercept between December 1, 2013, and January 31, 2015. Eyes were matched at baseline for VA, age, and choroidal neovascular membrane (CNV) size.

METHODS: Locally weighted scatterplot smoothing curves were used to display VA results. Eyes that switched or discontinued treatment were included with their last observation carried forward.

MAIN OUTCOME MEASURES: Change in mean VA (number of letters read on a logarithm of the minimum angle of resolution chart); number of injections and visits; proportion of eyes with inactive CNV over 12 months.

RESULTS: We identified 394 eyes (197 treated with ranibizumab and 197 with aflibercept) from 372 patients who received treatment from 34 practitioners. Baseline parameters were well matched. The mean (standard deviation [SD]) VA of ranibizumab-treated eyes increased from 58.6 (20.3) letters at baseline to 62.3 (23.9) (+3.7 [95% confidence interval {CI} 1.4-6.1]) letters ($P = 0.001$), compared with 58.9 (19.2) letters at baseline to 63.1 (21.5) (+4.26 [95% CI 2.0-6.5]) letters ($P < 0.001$) for eyes receiving aflibercept. The difference in change in crude VA of 0.6 letters between the 2 groups was not statistically significant ($P = 0.76$), nor was the difference in adjusted mean VA of the 2 groups ($P = 0.26$). In completers, the mean (SD) numbers of injections (8.1 [2.1] vs. 8.0 [2.3]; $P = 0.27$) and visits (9.6 [3.0] vs. 9.5 [3.1]; $P = 0.15$) did not differ between the 2 groups. The adjusted proportion of eyes in which the CNV lesion was graded as inactive during the study was similar between the eyes receiving ranibizumab and aflibercept (74% vs. 77%, respectively; $P = 0.63$).

CONCLUSIONS: Visual acuity outcomes at 12 months did not differ between ranibizumab and aflibercept used for nAMD in this large observational study, nor was a difference in treatment frequency found.

PMID: 27707549

Graefes Arch Clin Exp Ophthalmol. 2016 Oct 7. [Epub ahead of print]

Comparison of two individualized treatment regimens with ranibizumab for diabetic macular edema.

Ebneter A, Waldmeier D, Zysset-Burri DC, Wolf S, Zinkernagel MS.

PURPOSE: To compare outcomes between an as-needed and a treat-and-extend regimen in managing diabetic macular edema with intravitreal ranibizumab.

METHODS: This was a retrospective, single-centre, comparative case series on 46 treatment naive patients with diabetic macular edema. Twenty-two patients were treated following an optical coherence tomography guided treat-and-extend protocol (OCTER), and 24 patients were treated according to a visual acuity guided pro re nata regimen (VAPRN) at a tertiary referral centre. The main outcome measures were best-corrected visual acuity, central retinal thickness, and the number of ranibizumab injections, as well as visits after 12 months of treatment.

RESULTS: After 12 months, the mean gain in best-corrected visual acuity ($\pm$ standard deviation) was 8.3 ± 6.7 versus 9.3 ± 8.9 letters in the VAPRN and OCTER group, respectively ($p = 0.3$). The mean decrease in central retinal thickness was $68.1 \pm 88.0 \mu\text{m}$ in the VAPRN group and $117.6 \pm 114.4 \mu\text{m}$ in the OCTER group ($p = 0.2$). The mean number of ranibizumab injections was significantly different between the VAPRN (5.9 ± 1.8) and the OCTER protocol (8.9 ± 2.0) ($p < 0.001$).

CONCLUSION: The visual acuity driven retreatment regimen resulted in a similar visual acuity outcome like optical coherence tomography guided retreatment for diabetic macular edema. Although the number of visits was similar in both groups, patients in the VAPRN group received significantly fewer intravitreal injections than patients in the OCTER group.

PMID: 27714513

Am J Ophthalmol. 2016 Oct 1. [Epub ahead of print]

Outcomes with As-Needed Aflibercept and Macular Laser Following the Phase III VISTA DME Trial: ENDURANCE 12-Month Extension Study.

Wykoff CC, Le RT, Khurana RN, Brown DM, Ou WC, Wang R, Clark WL, Boyer DS; Endurance Study Group.

PURPOSE: To determine whether the efficacy and safety achieved with 2.0mg intravitreal aflibercept injections (IAI) for diabetic macular edema (DME) during the phase III VISTA DME trial were maintained with individualized, as-needed treatment.

DESIGN: Phase IV, multicenter, open-label extension study.

METHODS: Sixty patients completing VISTA DME elected to enter the ENDURANCE extension study. All patients received IAI in the presence of clinically relevant DME. Patients were observed at 4-, 8-, or 12-week intervals depending on the need for treatment. Main outcome measures were mean IAI given through month 12 (M12), proportion of patients receiving no IAI, and role of macular laser in decreasing treatment burden among patients requiring on-going IAI.

RESULTS: A mean of 4.5 IAI were administered through M12. Eighteen (30%) patients required no IAI and among those who met IAI re-treatment criteria, a mean of 6.0 IAI were administered through M12. BCVA gains achieved during VISTA DME were maintained and stable with individualized dosing during ENDURANCE, fluctuating by less than 1.5 mean letters from the baseline at all time points. Likewise, mean central retinal thickness remained relatively stable during ENDURANCE. Thirty-seven (62%) patients met macular laser criteria at a mean of 19.5 weeks with no significant difference in the frequency of IAI before or after macular laser.

CONCLUSION: Vision gains achieved during the 3-year VISTA DME trial were maintained through 12

months of the ENDURANCE extension study with a reduced treatment frequency, with 30% of patients receiving no IAI. No significant reduction in IAI frequency was observed after macular laser application.

PMID: 27702624

J Med Econ. 2016 Oct 5:1-19. [Epub ahead of print]

Cost-effectiveness of intravitreal aflibercept versus other treatments for wet age-related macular degeneration in Japan.

Yanagi Y, Fukuda A, Barzey V, Adachi K.

OBJECTIVE: This analysis estimated the cost-effectiveness of intravitreal aflibercept injection(s) (IAI) for wet age-related macular degeneration (wAMD) compared with other treatments in Japan.

METHODS: This was a cost-utility analysis based on published data. A state-transition cohort model was constructed with six health states based on best-corrected visual acuity in the better-seeing eye. The cycle time was 4 weeks, and the time horizon was 12 years. The model compared IAI 2mg every 8 weeks (2q8) for 2 years after three initial monthly injections, ranibizumab as needed, ranibizumab 0.5mg every 4 weeks (0.5q4), pegaptanib sodium 0.3mg every 6 weeks, verteporfin photodynamic therapy (PDT), and best supportive care, assumed to include medical management and monitoring but no active therapy. Costs (expressed as Japanese yen [JPY]) and quality-adjusted life years (QALYs) gained were estimated for each treatment and discounted at 2.0%. Input data were obtained from clinical studies, the Japanese drug tariff and social insurance reimbursement schedule, and expert opinion. The analysis was conducted from the societal perspective, including medical costs as well as costs of blindness.

RESULTS: IAI 2q8 was dominant (i.e., more effective in terms of QALYs and less costly) to all other comparators (ranibizumab as needed, ranibizumab 0.5q4, pegaptanib sodium, PDT, and best supportive care) as shown by the incremental cost-utility ratio (i.e. cost per QALY gained).

LIMITATIONS: The strengths of the analysis include the wide range of comparators evaluated and the use of Japanese-specific utility data. The limitations include the use of one eye, inclusion of published data up to 2 years only, and assumptions on disease course over 5 years.

CONCLUSIONS: IAI 2q8 was more effective in terms of QALYs and less costly compared with other treatments for wAMD in Japan.

PMID: 27701921

Clin Ophthalmol. 2016 Sep 22;10:1853-1858. eCollection 2016.

Intravitreal ziv-aflibercept for macular edema following retinal vein occlusion.

Paulose R, Chhablani J, Dedhia CJ, Stewart MW, Mansour AM.

AIM: To report the efficacy of intravitreal ziv-aflibercept injections in eyes with macular edema due to retinal vein occlusions (RVOs).

METHODS: Consecutive patients with persistent or recurrent macular edema (central macula thickness >250 µm) due to RVO were enrolled in this prospective study. Study eyes received intravitreal injections of ziv-aflibercept (1.25 mg/0.05 mL) at baseline. Patients were reassessed monthly for 4 months and given additional injections pro re nata for worsening best-corrected visual acuity (BCVA), intraretinal edema or subretinal fluid seen on spectral domain optical coherence tomography, or central macular thickness (CMT) measurements >250 µm. The primary endpoint was improvement in mean CMT at 4 months. Secondary endpoints included improvement in mean BCVA, and ocular and systemic safety signals.

RESULTS: Nine eyes (five central and four branch RVOs) of nine patients were enrolled. The mean ±

standard deviation CMT decreased from $604 \pm 199 \mu\text{m}$ at baseline to $319 \pm 115 \mu\text{m}$ ($P=0.001$) at 1 month and to $351 \pm 205 \mu\text{m}$ ($P=0.026$) at 4 months. The mean BCVA did not improve significantly from baseline (1.00 LogMAR) to the 1-month (0.74 LogMAR; $P=0.2$) and 4-month (0.71 LogMAR; $P=0.13$) visits. No safety signals were noted.

CONCLUSION: In this small prospective study, intravitreal ziv-aflibercept significantly improved mean CMT in eyes with persistent or recurrent macular edema due to RVOs. Prospective, randomized trials comparing ziv-aflibercept with standard pharmacotherapy are needed to better define efficacy and safety.

PMID: 27703326

BMC Ophthalmol. 2016 Oct 1;16(1):169.

Nurse-administered intravitreal injections of anti-VEGF: study protocol for noninferiority randomized controlled trial of safety, cost and patient satisfaction.

Austeng D, Morken TS, Bolme S, Follestad T, Halsteinli V.

BACKGROUND: Intravitreal injections (IVI) of anti-vascular endothelial growth factor (anti-VEGF) now improve or stabilize visual acuity in a number of previously untreatable eye diseases, of which the main are age-related macular degeneration, retinal vein occlusion and diabetic macular edema. Most patients require multiple injections over lengthy periods of time and the prevalence of treatable conditions is increasing. Anti-VEGF IVI normally administered by physicians, therefore represent a considerable workload on ophthalmologic clinics and will continue to do so in the near future. Nurse-administered IVI may relieve this workload, but the safety, cost and patient satisfaction of such an extended role for nurses in ophthalmologic clinics has not earlier been investigated. To investigate these outcomes following independent anti-VEGF IVI by trained nurses, a noninferiority randomized controlled trial is being conducted.

METHODS/DESIGN: Patients eligible for anti-VEGF treatment, minimum 304, are recruited and randomized to IVI administration by either trained nurses or physicians. The primary outcome is safety, measured by difference in mean change in visual acuity between the two groups during an observation period of 12 months. Secondary outcomes are incidence of ocular adverse events, cost per patient and patient satisfaction.

DISCUSSION: This study protocol describes the design of the first randomized controlled trial of nurse-administered IVI of anti-VEGF. The study is designed to examine safety, cost and patient satisfaction during 12 months follow-up.

PMID: 27716253

Eye (Lond). 2016 Oct 7. [Epub ahead of print]

Risk of geographic atrophy in age-related macular degeneration patients treated with intravitreal anti-VEGF agents.

Gemenetzi M, Lotery AJ, Patel PJ.

Abstract: Anti-vascular endothelial growth factor (VEGF) intravitreal agents are the only successful treatment for wet age-related macular degeneration (AMD). However, there are emerging signals that anti-VEGF treatment can potentially increase development of geographic atrophy (GA). Histopathologic, animal, and clinical studies support this hypothesis although direct proof of a relationship between GA and use of anti-VEGF agents in neovascular AMD is not yet established. This review presents current evidence supporting an association between anti-VEGF therapy and progression of geographic atrophy. The need of exploring alternative methods of treating AMD is indirectly but clearly emphasized.

PMID: 27716750

Ophthalmology. 2016 Oct 1. [Epub ahead of print]

Twenty-four-Month Outcomes of the Ranibizumab for Edema of the Macula in Diabetes - Protocol 3 with High Dose (READ-3) Study.

Sepah YJ, Sadiq MA, Boyer D, Callanan D, Gallemore R, Bennett M, Marcus D, Halperin L, Hassan M, Campochiaro PA, Nguyen QD, Do DV; READ-3 Study Group.

PURPOSE: To compare 2.0 mg ranibizumab (RBZ) injections with 0.5 mg RBZ for eyes with center-involved diabetic macular edema (DME).

DESIGN: Randomized, controlled, double-masked (to the dose), interventional, multicenter clinical trial.

PARTICIPANTS: A total of 152 patients (152 eyes) with DME.

METHODS: Eligible eyes were randomized in a 1:1 ratio to 0.5 mg (n = 77) or 2.0 mg (n = 75) RBZ. Study eyes received 6 monthly mandatory injections followed by as-needed injections until month 24.

MAIN OUTCOME MEASURES: The primary efficacy end point of the study was mean change in best-corrected visual acuity (BCVA) and central foveal thickness (CFT) at month 6. Secondary outcomes included the mean change in BCVA and CFT at month 24, and incidence and severity of systemic and ocular adverse events through month 24.

RESULTS: A total of 152 eyes were randomized in the study. At month 24, the mean improvement from baseline BCVA was +11.06 letters in the 0.5 mg RBZ group (n = 59) and +6.78 letters in the 2.0 mg RBZ group (n = 54) (P = 0.02). The mean numbers of RBZ injections through month 24 were 18.4 and 17.3 in the 0.5 mg and 2.0 mg RBZ groups, respectively (P = 0.08). The mean change in CFT was -192.53 μ m in the 0.5 mg RBZ group and -170.64 μ m in the 2.0 mg RBZ group (P = 0.41). By month 24, 3 deaths had occurred in the 0.5 mg RBZ group and 3 deaths had occurred in the 2.0 mg RBZ group; 5 of these 6 deaths occurred secondary to cardiovascular causes, and 1 death occurred as the result of severe pneumonia. All 5 patients with a cardiovascular cause of death had a history of coronary heart disease.

CONCLUSIONS: At month 24, there were significant visual and anatomic improvements in both groups, with subjects in the 0.5 mg RBZ group gaining more vision. Visual and anatomic gains achieved at month 6 were largely maintained through month 24. No new safety events were identified. In this study population, 2.0 mg RBZ does not appear to provide additional benefit over 0.5 mg RBZ.

PMID: 27707550

JAMA Ophthalmol. 2016 Oct 6. [Epub ahead of print]

Anti-Vascular Endothelial Growth Factor Comparative Effectiveness Trial for Diabetic Macular Edema: Additional Efficacy Post Hoc Analyses of a Randomized Clinical Trial.

Jampol LM, Glassman AR, Bressler NM, Wells JA, Ayala AR; Diabetic Retinopathy Clinical Research Network.

IMPORTANCE: Post hoc analyses from the Diabetic Retinopathy Clinical Research Network randomized clinical trial comparing aflibercept, bevacizumab, and ranibizumab for diabetic macular edema (DME) might influence interpretation of study results.

OBJECTIVE: To provide additional outcomes comparing 3 anti-vascular endothelial growth factor (VEGF) agents for DME.

DESIGN, SETTING, AND PARTICIPANTS: Post hoc analyses performed from May 3, 2016, to June 21, 2016, of a randomized clinical trial performed from August 22, 2012, to September 23, 2015, of 660 participants comparing 3 anti-VEGF treatments in eyes with center-involved DME causing vision impairment.

EXPOSURES: Randomization to intravitreal aflibercept (2.0 mg), bevacizumab (1.25 mg), or ranibizumab (0.3 mg) administered up to monthly based on a structured retreatment regimen. Focal/grid laser treatment was added after 6 months for the treatment of persistent DME.

MAIN OUTCOMES AND MEASURES: Change in visual acuity (VA) area under the curve and change in central subfield thickness (CST) within subgroups based on whether an eye received laser treatment for DME during the study.

RESULTS: Post hoc analyses were performed for 660 participants (mean [SD] age, 61 [10] years; 47% female, 65% white, 16% black or African American, 16% Hispanic, and 3% other). For eyes with an initial VA of 20/50 or worse, VA improvement was greater with aflibercept than the other agents at 1 year but superior only to bevacizumab at 2 years. Mean (SD) letter change in VA over 2 years (area under curve) was greater with aflibercept (+17.1 [9.7]) than with bevacizumab (+12.1 [9.4]; 95% CI, +1.6 to +7.3; $P < .001$) or ranibizumab (+13.6 [8.5]; 95% CI, +0.7 to +6.0; $P = .009$). When VA was 20/50 or worse at baseline, bevacizumab reduced CST less than the other agents at 1 year, but at 2 years the differences had diminished. In subgroups stratified by baseline VA, anti-VEGF agent, and whether focal/grid laser treatment was performed for DME, the only participants to have a substantial reduction in mean CST between 1 and 2 years were those with a baseline VA of 20/50 or worse receiving bevacizumab and laser treatment (mean [SD], -55 [108] μm ; 95% CI, -82 to -28 μm ; $P < .001$).

CONCLUSIONS AND RELEVANCE: Although post hoc analyses should be viewed with caution given the potential for bias, in eyes with a VA of 20/50 or worse, aflibercept has the greatest improvement in VA over 2 years. Focal/grid laser treatment, ceiling and floor effects, or both may account for mean thickness reductions noted only in bevacizumab-treated eyes between 1 and 2 years.

PMID: 27711918

Other treatment & diagnosis

Adv Clin Chem. 2016;77:1-75. Epub 2016 Jul 5.

Overview of Laboratory Testing and Clinical Presentations of Complement Deficiencies and Dysregulation.

Frazer-Abel A, Sepiashvili L, Mbughuni MM, Willrich MA.

Abstract: Historically, complement disorders have been attributed to immunodeficiency associated with severe or frequent infection. More recently, however, complement has been recognized for its role in inflammation, autoimmune disorders, and vision loss. This paradigm shift requires a fundamental change in how complement testing is performed and interpreted. Here, we provide an overview of the complement pathways and summarize recent literature related to hereditary and acquired angioedema, infectious diseases, autoimmunity, and age-related macular degeneration. The impact of complement dysregulation in atypical hemolytic uremic syndrome, paroxysmal nocturnal hemoglobinuria, and C3 glomerulopathies is also described. The advent of therapeutics such as eculizumab and other complement inhibitors has driven the need to more fully understand complement to facilitate diagnosis and monitoring. In this report, we review analytical methods and discuss challenges for the clinical laboratory in measuring this complex biochemical system.

PMID: 27717414

PLoS One. 2016 Oct 6;11(10):e0164419. doi: 10.1371/journal.pone.0164419. eCollection 2016.

Multi-Functional OCT Enables Longitudinal Study of Retinal Changes in a VLDLR Knockout Mouse Model.

Augustin M, Fialová S, Himmel T, Glösmann M, Lengheimer T, Harper DJ, Plasenzotti R, Pircher M,

Macular Disease Foundation Australia Suite 902, 447 Kent Street, Sydney, NSW, 2000, Australia.

Tel: +61 2 9261 8900 | Fax: +61 2 9261 8912 | E: research@mdfoundation.com.au | W: www.mdfoundation.com.au

Hitzenberger CK, Baumann B.

Abstract: We present a multi-functional optical coherence tomography (OCT) imaging approach to study retinal changes in the very-low-density-lipoprotein-receptor (VLDLR) knockout mouse model with a threefold contrast. In the retinas of VLDLR knockout mice spontaneous retinal-choroidal neovascularizations form, having an appearance similar to choroidal and retinal neovascularizations (CNV and RNV) in neovascular age-related macular degeneration (AMD) or retinal angiomatous proliferation (RAP). For this longitudinal study, the mice were imaged every 4 to 6 weeks starting with an age of 4 weeks and following up to the age of 11 months. Significant retinal changes were identified by the multi-functional imaging approach offering a threefold contrast: reflectivity, polarization sensitivity (PS) and motion contrast based OCT angiography (OCTA). By use of this intrinsic contrast, the long-term development of neovascularizations was studied and associated processes, such as the migration of melanin pigments or retinal-choroidal anastomosis, were assessed in vivo. Furthermore, the in vivo imaging results were validated with histological sections at the endpoint of the experiment. Multi-functional OCT proves as a powerful tool for longitudinal retinal studies in preclinical research of ophthalmic diseases. Intrinsic contrast offered by the functional extensions of OCT might help to describe regulative processes in genetic animal models and potentially deepen the understanding of the pathogenesis of retinal diseases such as wet AMD.

PMID: 27711217

Quant Imaging Med Surg. 2016 Aug;6(4):391-401.

Automated registration and enhanced processing of clinical optical coherence tomography angiography.

Camino A, Zhang M, Dongye C, Pechauer AD, Hwang TS, Bailey ST, Lujan B, Wilson DJ, Huang D, Jia Y.

BACKGROUND: Motion artifacts degrade the quality of optical coherence tomography angiography (OCTA). Orthogonal registration can eliminate the majority of these artifacts, but some artifacts persist in most clinical images. We evaluate an automated registration algorithm with selective merging and filtering to remove remaining artifacts and improve the quality of images.

METHODS: A 70 kHz commercial spectral domain OCT was used to obtain 3 mm × 3 mm OCTA in 10 healthy, 5 age-related macular degeneration (AMD), and 31 diabetic retinopathy (DR) participants. Projection artifacts were removed and images were segmented into 3 inner retinal plexuses. Amplitude thresholding identified lines containing a residual artifact and correlation between neighboring lines identified distorted stripes. Then the angiograms were registered and the lines selectively merged. A vesselness filter was applied to the resulting images. The images were evaluated for signal-to-noise ratio (SNR), image entropy, vessel connectivity and vessel density.

RESULTS: Registration and selective merging (RSM) algorithm improved the SNR ($P < 0.02$) compared to orthogonal registration alone. RSM with vesselness filter increased the image entropy ($P < 10^{-8}$) and reduced inter-subject variability (standard error $\leq 3\%$, $n = 10$) in healthy eyes. The method improved vessel details and connectivity in OCTA of healthy, DR and neovascular AMD eyes.

CONCLUSIONS: This automated registration method eliminates residual motion artifacts and enhances the visualization of vessels in OCTA.

PMID: 27709075

J Control Release. 2016 Oct 4. [Epub ahead of print]

Effect of intraocular pressure (IOP) and choroidal circulation on controlled episcleral drug delivery to retina/vitreous.

Li J, Lan B, Li X, Sun S, Lu P, Cheng L.

Abstract: Transscleral drug delivery may become a safe alternative to the intravitreal injection for chronic retinal diseases such as age-related macular degeneration or diabetic macular edema. However, the drug delivered onto the sclera subjects to vigorous clearance by episcleral and choroidal circulation; in addition, the penetration from episclera to retina needs to overcome counter-directional ocular fluid current driven by intraocular pressure (IOP) as well as unfavorable drug disposition exerted by drug transporters before the drug reach retina. It is imperative to understand these processes and quantitate their influence for efficient designing of a sustained formulation or device to achieve efficient transscleral drug delivery. The current study was focused on the effects of intraocular pressure (IOP) and choroidal circulation on transscleral drug delivery using triamcinolone acetonide (TA) as a model drug. Rabbit eye IOP was modulated through cannulation in ex vivo study or through cryopexy of ciliary body in vivo studies before subtenon TA injection or episcleral TA-film implantation. In a subgroup of the rabbit eyes, localized choroid atrophy was induced by cryopexy before TA-film implantation. Each condition had a concurrent control group. The vitreous TA concentration was quantitated by ultra-performance liquid chromatography coupled with tandem mass spectrometry (UPLC/MS/MS). The vitreous TA concentration was compared between the study and control groups for effect of IOP or choroid circulation. For ex vivo studies, higher IOP was a significant effect against TA penetration from episclera towards vitreous. TA was $8.5 \pm 5 \text{ ng/mL}$ in receptor chamber with a cross pressure of 50mmHg versus $15.9 \pm 10 \text{ ng/mL}$ with the cross pressure of 5mmHg; $p=0.001$, t-test. A multivariate regression demonstrated each mmHg of IOP increase would result in 3ng/mL lower concentration in the receptor chamber. Similar IOP effect was also identified in a 3-hour study using euthanized rabbit eyes whose IOP was controlled at 10 or 40mmHg by cannulation ($3261 \pm 1821 \text{ ng/mL}$ vs. $755 \pm 763 \text{ ng/mL}$; $p=0.013$, Wilcoxon test). However, the effect of IOP was not significant in alive animal with the same IOP setting. In vivo chronic study using low IOP (7.7mmHg) versus normal IOP (14.4mmHg), vitreous TA was not statistically significant ($154 \pm 200 \text{ ng/mL}$ vs. $80 \pm 130 \text{ ng/mL}$, $p=0.17$, Wilcoxon test). However, removing of choroidal circulation by local cryopexy significantly enhanced the TA penetration from episclera to vitreous (mean $163 \pm 129.8 \text{ ng/mL}$ for choroidal cryopexy vs. $81.8 \pm 37.2 \text{ ng/mL}$ for ciliary cryopexy or $75.5 \pm 36 \text{ ng/mL}$ for control group, $p=0.007$, regression analysis). In conclusion, the effect of IOP on transscleral drug delivery was not a significant effect in alive rabbit eyes; however, choroidal circulation seems to be a significant effect to affect TA penetration from episclera towards retina and vitreous.

PMID: 27717742

Hum Gene Ther. 2016 Sep 26. [Epub ahead of print]

Lentiviral Vector Gene Transfer of Endostatin/Angiostatin for Macular Degeneration (GEM) Study.

Campochiaro PA, Lauer AK, Sohn EH, Mir TA, Naylor S, Anderton MC, Kelleher M, Harrop R, Ellis S, Mitrophanous KA.

Abstract: Neovascular age-related macular degeneration (NVAMD) is a prevalent cause of vision loss. Intraocular injections of VEGF-neutralizing proteins provide benefit, but many patients require frequent injections for a prolonged period. Benefits are often lost over time due to lapses in treatment. New treatments that sustain anti-angiogenic activity are needed. This study tested the safety and expression profile of a lentiviral Equine Infectious Anemia Virus (EIAV) vector expressing endostatin and angiostatin (RetinoStat®). Patients with advanced NVAMD were enrolled at three centers in the United States, and the study eye received a subretinal injection of 2.4×10^4 ($n = 3$), 2.4×10^5 ($n = 3$), or 8.0×10^5 transduction units (TU; $n = 15$). Each of the doses was well-tolerated with no dose-limiting toxicities. There was little or no ocular inflammation. There was one procedure-related serious adverse event (AE), a macular hole, which was managed without difficulty and resolved. There was a vector dose-related increase in aqueous humor levels of endostatin and angiostatin with high reproducibility among subjects within cohorts. Mean levels of endostatin and angiostatin peaked between 12 and 24 weeks after injection of 2.4×10^5 TU or 8.0×10^5 TU at 57-81 ng/mL for endostatin and 15-27 ng/mL for angiostatin, and remained stable through the last measurement at week 48. Long-term follow-up demonstrated expression was maintained at last measurement (2.5 years in eight subjects and >4 years in two subjects). Despite an apparent reduction in fluorescein angiographic leakage that broadly correlated with the expression levels in the majority of patients, only one subject showed convincing evidence of anti-permeability activity in these late-stage

patients. There was no significant change in mean lesion size in subjects injected with 8.0×10^5 TU. These data demonstrate that EIAV vectors provide a safe platform with robust and sustained transgene expression for ocular gene therapy.

PMID: 27710144

Pathogenesis

Eye (Lond). 2016 Oct 7. [Epub ahead of print]

Structural and molecular changes in the aging choroid: implications for age-related macular degeneration.

Chirco KR, Sohn EH, Stone EM, Tucker BA, Mullins RF.

Abstract: Age-related macular degeneration (AMD) is a devastating disease-causing vision loss in millions of people around the world. In advanced stages of disease, death of photoreceptor cells, retinal pigment epithelial cells, and choroidal endothelial cells (CECs) are common. Loss of endothelial cells of the choriocapillaris is one of the earliest detectable events in AMD, and, because the outer retina relies on the choriocapillaris for metabolic support, this loss may be the trigger for progression to more advanced stages. Here we highlight evidence for loss of CECs, including changes to vascular density within the choriocapillaris, altered abundance of CEC markers, and changes to overall thickness of the choroid. Furthermore, we review the key components and functions of the choroid, as well as Bruch's membrane, both of which are vital for healthy vision. We discuss changes to the structure and molecular composition of these tissues, many of which develop with age and may contribute to AMD pathogenesis. For example, a crucial event that occurs in the aging choriocapillaris is accumulation of the membrane attack complex, which may result in complement-mediated CEC lysis, and may be a primary cause for AMD-associated choriocapillaris degeneration. The actions of elevated monomeric C-reactive protein in the choriocapillaris in at-risk individuals may also contribute to the inflammatory environment in the choroid and promote disease progression. Finally, we discuss the progress that has been made in the development of AMD therapies, with a focus on cell replacement.

PMID: 27716746

Epidemiology

Invest Ophthalmol Vis Sci. 2016 Oct 1;57(13):5273-5277.

Thyroid Dysfunction and Ten-Year Incidence of Age-Related Macular Degeneration.

Gopinath B, Liew G, Kifley A, Mitchell P.

PURPOSE: Epidemiologic evidence of a relationship between thyroid dysfunction and age-related macular degeneration (AMD) is inconsistent and unclear. We aimed to assess the prospective associations between serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4) measurements, as well as thyroid dysfunction (hyperthyroidism and hypothyroidism) and incidence of AMD.

METHODS: Categories of thyroid dysfunction were defined according to a serum TSH screen followed by serum FT4 assessment, and were available in 906 participants (aged 55+ years) at risk of AMD incidence (from 1997-1999 to 2007-2009). Continuous serum FT4 measures were available regardless of TSH screening results in 583 participants at risk of AMD incidence. Age-related macular degeneration was assessed from retinal photographs.

RESULTS: Participants with overt hyperthyroidism compared to those with normal thyroid function at baseline had increased risk of developing any incident AMD, after adjusting for age, sex, smoking, fish consumption, and variants in AMD susceptibility genes (CFH and ARMS2): odds ratio (OR) 3.51 (95%

confidence interval [CI] 1.16-10.65). Participants who reported current use of thyroxine (n = 67; 7.3%) versus those who were not current users (n = 839) had a 68% increased risk of incident AMD, multivariable-adjusted OR 1.68 (95% CI 1.01-2.82). Similarly, participants who had ever been on thyroxine medication (n = 77; 8.4%) compared to those who had never been on thyroxine (n = 829) also had a higher risk of any AMD, multivariable-adjusted OR 1.91 (95% CI 1.18-3.09).

CONCLUSIONS: Overt hyperthyroidism was independently associated with an increased risk of incident AMD. Thyroxine usage in older adults was also positively associated with incidence of AMD.

PMID: 27716857

Hum Mol Genet. 2016 Oct 3. [Epub ahead of print]

Low-frequency coding variants in CETP and CFB are associated with susceptibility of exudative age-related macular degeneration in the Japanese population.

Momozawa Y, Akiyama M, Kamatani Y, et al

Abstract: AMD is a major cause of blindness in the elderly. Previous sequencing studies of AMD susceptibility genes have revealed the association of rare coding variants in CFH, CFI, C3 and C9 in European population; however, the impact of rare or low-frequency coding variants on AMD susceptibility in other populations is largely unknown. To identify the role of low-frequency coding variants on exudative AMD susceptibility in a Japanese population, we analyzed the association of coding variants of 34 AMD candidate genes in the two-stage design by a multiplex PCR-based target sequencing method. We used a total of 2,886 (1st: 827, 2nd: 2,059) exudative AMD cases including typical AMD, polypoidal choroidal vasculopathy, and retinal angiomatous proliferation and 9,337 (1st: 3,247 2nd: 6,090) controls. Gene-based analysis found significant association of low-frequency variants (MAF < 0.05) in CETP, C2 and CFB. The association of CETP remained after conditioned with all known GWAS associated variants. In addition, when we included only disruptive variants, enrichment of rare variants (MAF < 0.01) was also observed after conditioned with all GWAS associated variants ($P = 1.03 \times 10^{-6}$, OR = 2.48). Haplotype and conditional analysis of the C2-CFB-SKIV2L locus showed a low-frequency variant (R74H) in CFB would be individually associated with AMD susceptibility independent of the GWAS associated SNP. These findings highlight the importance of target sequencing to reveal the impact of rare or low-frequency coding variants on disease susceptibility in different ethnic populations.

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Genetics

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Clinical study of the correlation between complement factor H polymorphism and age-related macular degeneration.

Dong HT, Zhang JX, Li QM, Li FZ.

Abstract: This study aimed to investigate the correlation between age-related macular degeneration (AMD) of the liver-kidney yin-deficiency type and complement factor H (CFH) polymorphism, and to determine whether the C allele of the T1277C (Y402H) variant is a risk factor for this condition. We performed a case-control investigation of 60 patients with liver-kidney yin-deficiency AMD and 60 normal control subjects. Peripheral blood was collected from each participant for DNA extraction. Following amplification by polymerase chain reaction, the DNA samples were sequenced, and polymorphism of the CFH gene was examined. Data were analyzed with the chi-square test, with $P < 0.05$ signifying statistical significance. The frequency of the C allele was significantly higher in the wet than in the dry AMD group ($P = 0.044$). In addition, the TC and CC genotypes were markedly more common in the former than in the control group (P

= 0.013), and there was a significant difference in the distribution of the T and C alleles between wet AMD patients and control subjects ($P < 0.05$). Based on this, we conclude that liver-kidney yin-deficiency AMD is associated with the C allele and TC and CC genotypes of the CFH Y402H polymorphism. Among patients with this condition, CFH genotypes were normally distributed. The principal CFH genotypes that induce liver-kidney yin-deficiency AMD are the mutant homozygote CC and heterozygote TC forms. Moreover, C allele carriers are at higher risk of developing this disease.

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Diet, lifestyle & low vision

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Biological and pathophysiological roles of end-products of DHA oxidation.

Yakubenko VP, Byzova TV.

BACKGROUND: Polyunsaturated fatty acids (PUFA) are known to be present and/or enriched in vegetable and fish oils. Among fatty acids, n-3 PUFA are generally considered to be protective in inflammation-related diseases. The guidelines for substituting saturated fatty acids for PUFAs have been highly publicized for decades by numerous health organizations. Recently, however, the beneficial properties of n-3 PUFA are questioned by detailed analyses of multiple randomized controlled clinical trials. The reported heterogeneity of results is likely due not only to differential effects of PUFAs on various pathological processes in humans, but also to the wide spectrum of PUFA's derived products generated in vivo.

SCOPE OF REVIEW: The goal of this review is to discuss the studies focused on well-defined end-products of PUFAs oxidation, their generation, presence in various pathological and physiological conditions, their biological activities and known receptors. Carboxyethylpyrrole (CEP), a DHA-derived oxidized product, is especially emphasized due to recent data demonstrating its pathophysiological significance in many inflammation-associated diseases, including atherosclerosis, hyperlipidemia, thrombosis, macular degeneration, and tumor progression.

MAJOR CONCLUSIONS: CEP is a product of radical-based oxidation of PUFA that forms adducts with proteins and lipids in blood and tissues, generating new powerful ligands for TLRs and scavenger receptors. The interaction of CEP with these receptors affects inflammatory response, angiogenesis, and wound healing.

GENERAL SIGNIFICANCE: The detailed understanding of CEP-mediated cellular responses may provide a basis for the development of novel therapeutic strategies and dietary recommendations. This article is part of a Special Issue entitled: Lipid modification and lipid peroxidation products in innate immunity and inflammation edited by Christoph J. Binder. This article is part of a Special Issue entitled: Lipid modification and lipid peroxidation products in innate immunity and inflammation edited by Christoph J. Binder.

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