

Issue 323

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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

JAMA Ophthalmol. 2017 Apr 6. [Epub ahead of print]

Vascular Safety of Ranibizumab in Patients With Diabetic Macular Edema: A Pooled Analysis of Patient-Level Data From Randomized Clinical Trials.

Zarbin MA, Dunger-Baldauf C, Haskova Z, Koovejee P, Mousseau MC, Margaron P, Snow H, Beaumont PE, Staurenghi G, Francom S.

IMPORTANCE: Patients with diabetic macular edema (DME) are at high risk of vascular complications, including stroke and myocardial infarction (MI). Concerns have been raised that intravitreal dosing of vascular endothelial growth factor inhibitors in DME could be associated with an increase in cardiovascular and cerebrovascular adverse events.

OBJECTIVE: To evaluate the cardiovascular and cerebrovascular safety of ranibizumab, 0.5 mg and 0.3 mg, compared with sham with and without laser in DME.

DATA SOURCES: Patient-level data from 6 randomized, double-masked, sham- and laser-controlled clinical trials.

STUDY SELECTION: Company-sponsored (Genentech or Novartis) studies in DME completed as of December 31, 2013.

DATA EXTRACTION AND SYNTHESIS: Pairwise comparisons (ranibizumab, 0.5 mg, vs sham and laser; ranibizumab, 0.3 mg, vs sham) were performed using Cox proportional hazard regression (hazard ratios, 95% CIs) and rates per 100 person-years. Data analysis was conducted from June 1 to July 15, 2015.

MAIN OUTCOMES AND MEASURES: Standardized Medical Dictionary for Regulatory Activities queries and extended searches were prospectively defined to identify relevant safety end points, including arterial thromboembolic events, MI, stroke or transient ischemic attack, vascular deaths, and major vascular events as defined by the Antiplatelet Trialists' Collaboration (APTC).

RESULTS: Overall, 936 patients were treated with ranibizumab, 0.5 mg; 250 patients with ranibizumab, 0.3 mg; and 581 patients with sham/laser. The hazard ratios associated with all pairwise comparisons included 1 for all key cardiovascular and cerebrovascular safety end points. For ranibizumab, 0.5 mg, vs sham/laser and ranibizumab, 0.3 mg, vs sham, the hazard ratios were, respectively, arterial thromboembolic events, 1.05 (95% CI, 0.66-1.68) and 0.78 (95% CI, 0.43-1.40); MI, 0.84 (95% CI, 0.41-1.72) and 0.94 (95% CI, 0.43-2.06); stroke or transient ischemic attack, 0.94 (95% CI, 0.44-1.99) and 0.53 (95% CI, 0.19-1.42); stroke (excluding transient ischemic attack), 1.63 (95% CI, 0.65-4.07) and 0.59 (95% CI, 0.14-2.46); vascular death, 2.17 (95% CI, 0.57-8.29) and 2.51 (95% CI, 0.49-12.94); and APTC-defined events, 1.09 (95% CI, 0.63-1.88) and 1.00 (95% CI, 0.51-1.96).

CONCLUSIONS AND RELEVANCE: This pooled analysis includes 1 of the largest patient-level data sets on treatment of DME with ranibizumab. Although still underpowered to detect small differences for

infrequent events, such as stroke, the findings suggest that intravitreal ranibizumab does not increase the risk of systemic vascular events. However, uncertainty remains for patients with DME who are at high risk for vascular disease and were not included in these trials.

PMID: 28384675

J Ocul Pharmacol Ther. 2017 Apr 6. [Epub ahead of print]

Incidence and Timing of the First Recurrence in Neovascular Age-Related Macular Degeneration: Comparison Between Ranibizumab and Aflibercept.

Kim JH, Chang YS, Lee DW, Kim CG, Kim JW.

PURPOSE: To compare the incidence and timing of first recurrence between patients who were treated with ranibizumab and aflibercept in neovascular age-related macular degeneration (AMD).

METHODS: This retrospective study included 120 patients who received the diagnosis of treatment-naïve typical neovascular AMD or polypoidal choroidal vasculopathy (PCV) and were treated using either ranibizumab (n = 73) or aflibercept (n = 47). Recurrence within 10 months of the third injection was compared between the 2 treatment groups.

RESULTS: In all 120 patients, there was no difference in recurrence between the ranibizumab and the aflibercept groups (P = 0.846). One hundred five patients completed 12 months follow-up. In typical neovascular AMD, disease recurred in 69.6% (16/23) of patients in the ranibizumab group, with a mean period of 4.4 ± 1.8 months after the third injection. In the aflibercept group, the equivalent values were 68.8% (11/16) and 4.5 ± 1.4 months. In PCV, disease recurred in 72.5% (29/40) of patients in the ranibizumab group, with a mean period of 3.8 ± 1.7 months after the third injection. In the aflibercept group, the equivalent values were 69.2% (18/26) and 4.3 ± 2.0 months.

CONCLUSIONS: Although the incidence of recurrence was slightly higher and the duration between the third injection and the first recurrence was slightly shorter in patients treated using ranibizumab, the differences were not significant. Our results require confirmation in further studies.

PMID: 28384009

Asia Pac J Ophthalmol (Phila). 2017 Mar 29. [Epub ahead of print]

Recommended Guidelines for Use of Intravitreal Aflibercept With a Treat-and-Extend Regimen for the Management of Neovascular Age-Related Macular Degeneration in the Asia-Pacific Region: Report From a Consensus Panel.

Koh A, Lanzetta P, Lee WK, Lai CC, Chan WM, Yang CM, Cheung CM.

PURPOSE: To summarize recommendations for the use of intravitreal aflibercept with a treat-and-extend regimen to manage neovascular age-related macular degeneration (nAMD) in the Asia-Pacific region. Although anti-vascular endothelial growth factor therapies have improved the quality of life of patients with nAMD, a leading cause of blindness and visual impairment, the high treatment frequency recommended by current guidelines places a significant burden on patients and healthcare providers.

DESIGN: Recommended guidelines from a consensus panel.

METHODS: An expert panel formed a consensus on recommendations for use of intravitreal aflibercept as treatment of nAMD in the Asia-Pacific region.

RESULTS: After 3 initial monthly doses, treatment interval could be extended by 4-week increments, to a maximum of 12 weeks, in patients with inactive disease. Conversely, in active disease, treatment intervals

should be shortened, by 4 weeks, or to 4 weeks in cases of severe recurrence. Treatment could be ceased in patients with stable disease activity after 12 months of treatment at 12-week intervals, as a means to prevent over treatment and lifelong injections.

CONCLUSIONS: These recommendations could potentially minimize the number of treatments while maintaining efficacy and improve compliance by reducing the number of clinic visits compared with existing recommendations.

PMID: 28379655

Klin Monbl Augenheilkd. 2017 Apr 4. [Epub ahead of print]

[Retinal Vein Occlusion - Which Treatment When?] [Article in German]

Bajor A, Pielen A, Danzmann L.

Abstract: According to the latest findings, macular oedema due to retinal vein occlusion is best treated safely and effectively with near-term intravitreal anti-VEGF therapy (aflibercept, bevacizumab [off label], ranibizumab). After an initial upload of 3 monthly injections of anti-VEGF, the decision on re-injection should be based on OCT (rather than on visual acuity). After initial monthly injections, the "pro-re-nata" (PRN) and the "treat-and-extend" regimens have been predominantly used in the further course of therapy. Taking into account the side effect spectrum (in particular cataract progression, increased intraocular pressure), intravitreal therapy with a dexamethasone implant may be a reasonable alternative. The prognosis for visual acuity and the decline in macular oedema depend on starting treatment early and continuing it consistently. Before starting treatment, as well as during treatment, fluorescein angiography is necessary to detect ischemic retinal areas. There is evidence that early targeted laser coagulation of ischemic retina may reduce the frequency of necessary injections and improve the response of the oedema to therapy. Significant retinal ischemia may lead to proliferations, rubeosis iridis and secondary glaucoma and therefore requires laser treatment.

PMID: 28376554

Curr Opin Ophthalmol. 2017 May;28(3):213-218.

Impact of intravitreal pharmacotherapies including antivascular endothelial growth factor and corticosteroid agents on diabetic retinopathy.

Wykoff CC.

PURPOSE OF REVIEW: Diabetic retinopathy is common and increasing in prevalence. Pharmacologic management of diabetic macular edema (DME) has improved tremendously over the last decade with the use of two families of intravitreally administered medications: antivascular endothelial growth factor-specific agents and corticosteroids. Clinical evaluation of these pharmaceuticals has demonstrated that they can have a substantial impact on diabetic retinopathy severity levels and the underlying retinal vasculature itself.

RECENT FINDINGS: Phase 3 trials employing ranibizumab, aflibercept, and fluocinolone acetonide enrolling eyes with center-involving DME causing visual acuity loss have demonstrated impressive alteration of the natural history of progressive diabetic retinopathy worsening over time through blunted progression to proliferative diabetic retinopathy, improving diabetic retinopathy severity levels, and slowing progressive retinal nonperfusion, the underlying disease process central to diabetic retinopathy itself.

SUMMARY: Accumulating data indicate that the threshold to initiate ocular-specific pharmacologic treatment for diabetic retinopathy, previously predominately limited to eyes with visual loss because of center-involved DME or proliferative diabetic retinopathy, is being lowered to earlier stages of diabetic

retinopathy. Ongoing clinical trials and secondary analyses continue to further explore the impact and durability of vascular endothelial growth factor blockade and corticosteroids on modification of diabetic retinopathy and the underlying retinal vasculature itself.

PMID: 28376510

Retina. 2017 Mar 30. [Epub ahead of print]

GOOD VISUAL OUTCOME AT 1 YEAR IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION WITH PIGMENT EPITHELIUM DETACHMENT: Factors Influencing the Treatment Response.

de Massoungnes S, Dirani A, Mantel I.

PURPOSE: To evaluate baseline and treatment factors influencing the response of pigment epithelial detachment (PED) in patients with treatment-naïve neovascular age-related macular degeneration after 1 year of intravitreal anti-vascular endothelial growth factor treatment.

METHODS: This retrospective consecutive case series study included 104 eyes (94 patients) with treatment-naïve neovascular age-related macular degeneration and associated PED >150 µm treated with aflibercept (n = 41) or ranibizumab (n = 63) for at least 1 year. Stepwise linear regression was used to assess factors influencing best-corrected visual acuity and PED response.

RESULTS: At 1 year, the best-corrected visual acuity improved from 20/63 (60.8 ± 15.9 Early Treatment of Diabetic Retinopathy Study letters) at baseline to 20/40 (69.0 ± 15.0 letters) (P = 0.001), and PED maximal height decreased from 370.8 ± 205.6 µm to 238.8 ± 178.5 µm (P = 0.001). Multivariate analysis revealed an association of the visual improvement with lower best-corrected visual acuity at baseline (P = 0.001), the presence of foveal subretinal fluid (P = 0.001), and female gender (P = 0.047). Pigment epithelial detachment height reduction was dependent on higher baseline PED height (P = 0.001) and treatment drug (P = 0.008).

CONCLUSION: Visual improvement in neovascular age-related macular degeneration with PED was equally achieved with ranibizumab and aflibercept, influenced mainly by baseline best-corrected visual acuity and foveal subretinal fluid. Pigment epithelial detachment height reduction was influenced by baseline height and the treatment drug, favoring aflibercept for a stronger effect. The clinical significance of this result warrants further studies.

PMID: 28368974

Int J Retina Vitreous. 2017 Apr 3;3:16. doi: 10.1186/s40942-017-0064-0. eCollection 2017.

Effect of intravitreal aflibercept on recalcitrant diabetic macular edema.

Klein KA, Cleary TS, Reichel E.

BACKGROUND: Despite anti-VEGF therapy, some patients develop chronic diabetic macular edema. The objective of this study was to evaluate anatomic and visual outcomes of switching patients with chronic DME from intravitreal bevacizumab or ranibizumab to intravitreal aflibercept injection.

METHODS: In this retrospective observational case series, 11 eyes with recalcitrant diabetic macular edema (DME) were evaluated 6 months prior to and 6 months following initial intravitreal aflibercept injection (IAI). Recalcitrant DME was defined as having a thickened retina (≥350 µm) on spectral domain optical coherence tomography (SD-OCT) with persistent cystic changes (less than a 15% reduction in central retinal thickness) over 6 months prior to intravitreal aflibercept switch despite aggressive treatment for DME during this time.

RESULTS: One hundred and forty-seven patients in total were treated with IAI during this time, and of these, 31 patients were treated with IAI for DME. 18 eyes had less than 4 treatments within the 6 months prior to switch to IAI, 6 patients had a central retinal thickness (CRT) on SD-OCT of less than 350 µm at time of switch to IAI, and 2 patients had a greater than 15% decline in CRT on SD-OCT over the 6 months prior to switch to IAI. A total of 11 patients were included in the study. Over the 6 months prior to switch, the mean change in central retinal thickness was +18.6% and over the 6 months following switch to aflibercept the mean change in central retinal thickness was -27.1%. Switching to a regimen of at least 3 intravitreal aflibercept injections over 6 months resulted in some anatomic improvement and improvement or stabilization of Snellen visual acuity in all eligible patients.

CONCLUSIONS: In patients with recalcitrant diabetic macular edema, switching to intravitreal aflibercept resulted in improved a 25% or more decrease in central retinal thickness in 81% (9/11) patients at 6-month follow-up. Sixty-three percent (7/11) had improvement in Snellen visual acuity after switching to intravitreal aflibercept injection, suggesting some reversibility of functional damage.

PMID: 28373914 PMCID: PMC5376679

Drugs Aging. 2017 Apr 1. [Epub ahead of print]

Aflibercept: A Review in Macular Oedema Secondary to Branch Retinal Vein Occlusion.

Hoy SM.

Abstract: Aflibercept (Eylea®) is a fully human, recombinant fusion protein available in various countries worldwide, including those of the EU, as well as the USA, for intravitreal use in the treatment of macular oedema secondary to branch retinal vein occlusion (BRVO) in adults. Aflibercept acts as a soluble decoy receptor, binding with high affinity to vascular endothelial growth factor (VEGF)-A and placental growth factor (PIGF), preventing these angiogenic factors from binding to and activating their cognate receptors. In a multinational, phase III study in this patient population, aflibercept was associated with a statistically significant and clinically relevant improvement in best-corrected visual acuity (BCVA) [as assessed by the proportion of eyes that gained ≥15 Early Treatment Diabetic Retinopathy Study letters from baseline] relative to macular laser photocoagulation during the first 24-week treatment period (aflibercept injections were administered every 4 weeks). Significant mean improvements from baseline in BCVA and central retinal thickness (CRT) relative to macular laser photocoagulation were also seen. These improvements were maintained relative to macular laser photocoagulation plus rescue aflibercept in a subsequent 24-week period (aflibercept injections were administered every 8 weeks). Aflibercept was generally well tolerated, locally and systemically, in this study, with a tolerability profile generally consistent with the known tolerability profile of the agent in other indications. Thus, intravitreal aflibercept extends the treatment options available for the management of macular oedema secondary to BRVO in adults.

PMID: 28365905

Int Ophthalmol. 2017 Apr 1. [Epub ahead of print]

Vitreous hemorrhage as an early sign of acute bacterial endophthalmitis following intravitreal ranibizumab injection.

Weill Y, Brosh K, Levi-Vineberg T, Hanhart J.

PURPOSE: To report a case of acute bacterial endophthalmitis after antivascular endothelial growth factor injection with a rare presentation of vitreous hemorrhage.

METHODS: An 84-year-old woman presented with sudden painless vision loss in her left eye, 3 days after intravitreal ranibizumab injection for cystoid macular edema due to neovascular age-related macular degeneration. The patient was otherwise asymptomatic. Dense vitreous hemorrhage was observed. At

follow-up the next day, the patient complained on severe left eye pain. After examination, acute endophthalmitis was diagnosed.

RESULTS: Intravitreal injection of vancomycin, ceftazidime and dexamethasone was performed. Vitreous and aqueous cultures grew *Enterococcus faecalis*. After treatment, the inflammation subsided but it took 3 months for the vitreous hemorrhage to totally resorb. Visual acuity was reduced to light perception.

CONCLUSIONS: Vitreous hemorrhage may be an atypical presentation of acute bacterial endophthalmitis occurring after intravitreal injection.

PMID: 28365853

Graefes Arch Clin Exp Ophthalmol. 2017 Apr 7. [Epub ahead of print]

Switching therapy from bevacizumab to aflibercept for the management of persistent diabetic macular edema.

Călugăru D, Călugăru M.

PMID: 28389701

Acta Ophthalmol. 2017 Mar 31. [Epub ahead of print]

One-year treatment outcomes of ziv-aflibercept for treatment-naïve macular oedema in branch retinal vein occlusion.

Chan EW, Eldeeb M, Dedhia CJ, Mansour A, Chhablani J.

PMID: 28371171

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2017 Apr 1;58(4):2079-2086.

Quantitative Analysis of the Ellipsoid Zone Intensity in Phenotypic Variations of Intermediate Age-Related Macular Degeneration.

Gin TJ, Wu Z, Chew SK, Guymer RH, Luu CD.

PURPOSE: Reduction of the ellipsoid zone (EZ) intensity has been reported in eyes with age-related macular degeneration (AMD). This study determined whether overall EZ intensity, in retinal locations undisturbed by pathologic features, is associated with the presence of clinical features, which are known important phenotypic risk factors for disease progression, large drusen, reticular pseudodrusen (RPD), and pigmentary abnormalities.

METHODS: A horizontal B-scan through the foveola on spectral-domain optical coherence tomography (SD-OCT) was performed in both eyes of 75 participants with bilateral intermediate AMD and 10 age-similar control participants. Eyes with AMD were classified as per the presence of large drusen, RPD, and hyperpigmentary changes. The relative EZ intensity profile, up to an eccentricity of 3400 μm , was averaged over seven 1000- μm retinal segments. The association between relative EZ intensity profile over seven retinal segments and AMD pathologic features was analyzed.

RESULTS: The average relative EZ intensities were significantly reduced in eyes with intermediate AMD compared to normal eyes ($P \leq 0.025$) and with increasing age ($P \leq 0.020$). On multivariate analyses, only the presence of hyperpigmentary changes and increasing age were significantly associated with reduced

overall relative intensities ($P \leq 0.024$), but not the presence of large drusen or RPD ($P \geq 0.115$).

CONCLUSIONS: The presence of hyperpigmentary change in the macula in association with large drusen, not large drusen alone, nor large drusen with RPD, was significantly associated with a generalised reduction in EZ intensity. Quantitative assessment of the relative EZ intensity may serve as an effective biomarker of disease severity and progression.

PMID: 28388704

Am J Ophthalmol. 2017 Apr 3. [Epub ahead of print]

Geographic atrophy and foveal sparing changes related to visual acuity in patients with dry age-related macular degeneration over time.

Sayegh RG, Sacu S, Dunavölgyi R, Kroh ME, Roberts P, Mitsch C, Montuoro A, Ehrenmüller M, Schmidt-Erfurth U.

PURPOSE: To correlate the area of geographic atrophy (GA) and residual foveal sparing (FS), and to identify the minimum FS and maximum GA area allowing sufficient visual acuity (VA) for daily tasks.

DESIGN: Prospective cohort study

METHODS: Thirty-six eyes of 25 patients with GA and FS were followed for 18 months using spectral-domain optical coherence tomography and VA tests. Volume scans were imported into software enabling grading of areas in B-scans and computing of planimetric measurements in complete volume scans. Correlation of areas 1 (complete atrophy), 2 (FS in the central millimeter), and 3 (FS in the central 3 mm) with each other and with best-corrected VA (BCVA) were evaluated.

RESULTS: Baseline means of areas 1, 2, and 3 were 6.15 mm², 0.49 mm², and 3.08 mm², respectively. At 1 year, area 1 increased by a mean of 1.33 mm², while areas 2 and 3 were decreased by 0.12 mm² and 0.65 mm², respectively. From baseline to 18 months and from visit-to-visit, all areas and BCVA changed progressively ($p < 0.001$). Significant thresholds in GA size and FS for achieving a BCVA ≥ 70 ETDRS letters were detected (area 1: ≤ 6 mm²; area 2: ≥ 0.48 mm²; and area 3: ≥ 3.28 mm²).

CONCLUSION: GA and FS changed inversely over time. In general, FS highly correlated with BCVA, while GA progression correlated with the central 3-mm FS regression, but not with BCVA. A threshold in GA and FS area could be determined for BCVA necessary for daily activity.

PMID: 28385474

Sci Rep. 2017 Apr 3;7:45847.

Comparing multifocal pupillographic objective perimetry (mfPOP) and multifocal visual evoked potentials (mfVEP) in retinal diseases.

Sabeti F, James AC, Carle CF, Essex RW, Bell A, Maddess T.

Abstract: Multifocal pupillographic objective perimetry (mfPOP) shows regions of slight hypersensitivity away from retinal regions damaged by diabetes or age-related macular degeneration (AMD). This study examines if such results also appear in multifocal visual evoked potentials (mfVEPs) recorded on the same day in the same patients. The pupil control system receives input from the extra-striate cortex, so we also examined evidence for such input. We recruited subjects with early type 2 diabetes (T2D) with no retinopathy, and patients with unilateral exudative AMD. Population average responses of the diabetes patients, and the normal fellow eyes of AMD patients, showed multiple regions of significant hypersensitivity ($p < 0.05$) on both mfPOP and mfVEPs. For mfVEPs the occipital electrodes showed fewer hypersensitive regions than the surrounding electrodes. More advanced AMD showed regions of suppression becoming

centrally concentrated in the exudative AMD areas. Thus, mfVEP electrodes biased towards extra-striate cortical responses (surround electrodes) appeared to show similar hypersensitive visual field locations to mfPOP in early stage diabetic and AMD damage. Our findings suggest that hypersensitive regions may be a potential biomarker for future development of AMD or non-proliferative diabetic retinopathy, and may be more informative than visual acuity which remains largely undisturbed during early disease.

PMID: 28368051 PMCID: PMC5377468

J Curr Ophthalmol. 2017 Mar 21;29(1):1-4. eCollection 2017.

Optical coherence tomography angiography of the retina and choroid; current applications and future directions.

Falavarjani KG, Sarraf D.

PMID: 28367518 PMCID: PMC5362386

Pathogenesis

Sci Rep. 2017 Apr 6;7(1):690.

Multimodal Regulation Orchestrates Normal and Complex Disease States in the Retina.

Olivares AM, Jelcick AS, Reinecke J, Leehy B, Haider A, Morrison MA, Cheng L, Chen DF, DeAngelis MM, Haider NB.

Abstract: Regulation of biological processes occurs through complex, synergistic mechanisms. In this study, we discovered the synergistic orchestration of multiple mechanisms regulating the normal and diseased state (age related macular degeneration, AMD) in the retina. We uncovered gene networks with overlapping feedback loops that are modulated by nuclear hormone receptors (NHR), miRNAs, and epigenetic factors. We utilized a comprehensive filtering and pathway analysis strategy comparing miRNA and microarray data between three mouse models and human donor eyes (normal and AMD). The mouse models lack key NHRs (Nr2e3, RORA) or epigenetic (Ezh2) factors. Fifty-four total miRNAs were differentially expressed, potentially targeting over 150 genes in 18 major representative networks including angiogenesis, metabolism, and immunity. We identified sixty-eight genes and 5 miRNAs directly regulated by NR2E3 and/or RORA. After a comprehensive analysis, we discovered multimodal regulation by miRNA, NHRs, and epigenetic factors of three miRNAs (miR-466, miR1187, and miR-710) and two genes (Eil2 and Entpd1) that are also associated with AMD. These studies provide insight into the complex, dynamic modulation of gene networks as well as their impact on human disease, and provide novel data for the development of innovative and more effective therapeutics.

PMID: 28386079

Klin Monbl Augenheilkd. 2017 Apr 5. [Epub ahead of print]

[Polysialic Acid for Immunomodulation in an Animal Model for Wet Age-Related Macular Degeneration (AMD)]. [Article in German]

Langmann T, Fauser S.

Background: Chronic activation of the innate immune system is a hallmark of retinal degenerative diseases, including age-related macular degeneration (AMD). Overt microglia and macrophage reactivity, as well as dysregulation of the alternative complement system, trigger and sustain retinal degeneration. It is now accepted that there exists a vicious cycle of mononuclear phagocyte reactivity, abnormal intrinsic

complement activation, damage of Bruch's membrane, dysfunction of the retinal pigment epithelium, photoreceptor degeneration and choroidal neovascularization (CNV). Targeting the innate immune system may, therefore, be a complementary approach to anti-angiogenic therapy. This article presents data from polysialic acid treatment experiments in the laser-induced mouse model of wet AMD.

Material and Methods: The laser-CNV mouse model was used to simulate events of neovascular AMD. Polysialic acid was applied by intravitreal injection and microglia activity was assessed with Iba1 staining of retinal and RPE/choroidal flat mounts. Neovascular leakage was determined by fluorescein angiography.

Results: Intravitreal injection of polysialic acid reduced retinal and RPE/choroidal lesion-associated microglia activity in the laser-induced mouse model of AMD. Polysialic acid treatment also diminished vascular leakage at laser spots in this model.

Conclusion: Local retinal immunomodulation with polysialic acid presents a novel concept for treatment of inflammatory conditions related to neovascular AMD.

PMID: 28380648

Sci Rep. 2017 Apr 4;7(1):605.

Systemic frequencies of T helper 1 and T helper 17 cells in patients with age-related macular degeneration: A case-control study.

Singh A, Subhi Y, Krogh Nielsen M, Falk MK, Matzen SM, Sellebjerg F, Sørensen TL.

Abstract: Age-related macular degeneration (AMD) is a degenerative disease of the retina and a leading cause of irreversible vision loss. We investigated the systemic differences in the frequency of T helper (Th) 1 and Th17 cells in patients with non-exudative and exudative AMD and compared to age-matched controls. Flow cytometry was used to determine the systemic frequency of Th1 (CD4+CXCR3+IL12RB2+) and Th17 (CD4+CCR6+IL23R+) cells, and percentage of CD4+ T-cells expressing CXCR3, IL12RB2, CCR6, IL23R, and co-expressing CXCR3 and CCR6. The frequency of Th1 cells and CXCR3+ CD4+ T-cells was lower in patients with exudative AMD. A significant age-dependent decrement in Th1 was observed in controls, but not in non-exudative or exudative AMD. This may be related to the CXCR3+ CD4+ T-cells, which showed similar pattern in controls, but not in non-exudative or exudative AMD. No significant group differences were observed for the frequency of Th17 cells. Correlation networks found several differences between controls and AMD. These data suggests the involvement of the adaptive immune system in AMD and supports the notion of AMD as a systemic disease. Our observations warrant further investigation into the role of the adaptive immune system in the pathogenesis of AMD.

PMID: 28377586

EMBO Mol Med. 2017 Apr 4. [Epub ahead of print]

Ferrochelatase is a therapeutic target for ocular neovascularization.

Basavarajappa HD, Sulaiman RS, Qi X1, Shetty T, Sheik Pran Babu S, Sishtla KL, Lee B, Quigley J, Alkhairy S, Briggs CM, Gupta K, Tang B, Shadmand M, Grant MB, Boulton ME, Seo SY, Corson TW.

Abstract: Ocular neovascularization underlies major blinding eye diseases such as "wet" age-related macular degeneration (AMD). Despite the successes of treatments targeting the vascular endothelial growth factor (VEGF) pathway, resistant and refractory patient populations necessitate discovery of new therapeutic targets. Using a forward chemical genetic approach, we identified the heme synthesis enzyme ferrochelatase (FECH) as necessary for angiogenesis in vitro and in vivo FECH is overexpressed in wet AMD eyes and murine choroidal neovascularization; siRNA knockdown of Fech or partial loss of enzymatic function in the Fech^{m1Pas} mouse model reduces choroidal neovascularization. FECH depletion modulates

endothelial nitric oxide synthase function and VEGF receptor 2 levels. FECH is inhibited by the oral antifungal drug griseofulvin, and this compound ameliorates choroidal neovascularization in mice when delivered intravitreally or orally. Thus, FECH inhibition could be used therapeutically to block ocular neovascularization.

PMID: 28377496

EBioMedicine. 2017 Mar 21. [Epub ahead of print]

Sema3f Protects Against Subretinal Neovascularization In Vivo.

Sun Y, Liegl R, Gong Y, Bühler A, Cakir B, Meng SS, Burnim SB, Liu CH, Reuer T, Zhang P, Walz JM, Ludwig F, Lange C, Agostini H, Böhringer D, Schlunck G, Smith LE, Stahl A.

Abstract: Pathological neovascularization of the outer retina is the hallmark of neovascular age-related macular degeneration (nAMD). Building on our previous observations that semaphorin 3F (Sema3f) is expressed in the outer retina and demonstrates anti-angiogenic potential, we have investigated whether Sema3f can be used to protect against subretinal neovascularization in two mouse models. Both in the very low-density lipoprotein receptor knockout (Vldlr^{-/-}) model of spontaneous subretinal neovascularization as well as in the mouse model of laser-induced choroidal neovascularization (CNV), we found protective effects of Sema3f against the formation of pathologic neovascularization. In the Vldlr^{-/-} model, AAV-induced overexpression of Sema3f reduced the size of pathologic neovascularization by 56%. In the laser-induced CNV model, intravitreally injected Sema3f reduced pathologic neovascularization by 30%. Combined, these results provide the first evidence from two distinct in vivo models for a use of Sema3f in protecting the outer retina against subretinal neovascularization.

PMID: 28373097

Discov Med. 2017 Feb;23(125):129-147.

Salvianolic acid A protects retinal pigment epithelium from OX-LDL-induced inflammation in an age-related macular degeneration model.

Mao K, Shu W, Qiu Q, Gu Q, Wu X.

BACKGROUND: Salvianolic acid A (Sal A), an active monomer of *Salvia miltiorrhiza*, is a phenolic carboxylic acid derivative. The present study was performed to investigate the underlying mechanism of the anti-inflammation effect of Sal A, especially focusing on mTOR-KEAP1-Nrf2 and P2X7R-PKR-NLRP3 signaling pathways.

METHODS: SD mice were divided into four groups: PBS, oxidized-low density lipoprotein (ox-LDL, 3 mg/kg), and ox-LDL (3 mg/kg) + Sal A (5 mg/kg) and + Sal A (10 mg/ml) groups. In vitro experiments, ARPE-19 cells were cultured with serum free medium (SFM) or ox-LDL (100 mg/L), with or without Sal A (5 μM/50 μM) for 24 hours.

RESULTS: Sal A attenuated ox-LDL-induced lipidosis and apoptosis in the retinal pigment epithelium (RPE) layer. Ox-LDL elevated ROS level and induced RPE inflammation, which were inhibited by Sal A pretreatment. Sal A activated PI3K/AKT/mTOR signaling pathway, which further promoted the disassociation of Keap1-Nrf2 complex and the phosphorylation of Nrf2. PI3K and mTOR chemical inhibitors abolished Sal A-induced Nrf2 activation while it had no influence on nlrp3 expression. Sal A also inhibited RPE inflammation by inactivating the P2x7r-Pkr-Nlrp3 signaling pathway.

CONCLUSIONS: The above results indicate that Sal A protects RPE from lipid oxidative damage and chronic inflammation through up-regulating Nrf2 and inactivating the P2x7r-Pkr-Nlrp3 signaling pathway.

PMID: 28371616

Biochemistry (Mosc). 2017 Apr;82(4):426-437.

Formyl Peptide Receptor Polymorphisms: 27 Most Possible Ways for Phagocyte Dysfunction.

Skvortsov SS, Gabdoulkhakova AG.

Abstract: Formyl peptide receptors (FPRs) expressed by mammalian myeloid cells are the important part of innate immunity. They belong to the seven-transmembrane domain class of receptors coupled to heterotrimeric GTP-binding proteins. Binding of the receptor with a wide spectrum of exogenous and endogenous ligands triggers such defensive phagocyte reactions as chemotaxis, secretory degranulation, and respiratory burst, keeping a balance of inflammatory and antiinflammatory processes in the organism. The association between single nucleotide polymorphisms in the gene of FPR1 receptor resulting in disruption of the receptor structure and the development of certain pathologies accompanied with inflammation, such as aggressive periodontitis, macular degeneration, and even gastric cancer (Maney, P., and Walters, J. D. (2009) *J. Periodontol.*, 80, 1498-1505; Liang, X. Y., et al. (2014) *Eye*, 28, 1502-1510; Otani, T., et al. (2011) *Biochem. Biophys. Res. Commun.*, 405, 356-361) has been shown. In this review, we matched the missense mutation of formyl-peptide receptors with their known functional domains and classified them according to their potential significance in pathology.

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Heliyon. 2017 Mar 16;3(3):e00266. eCollection 2017.

Potential protective function of the sterol regulatory element binding factor 1-fatty acid desaturase 1/2 axis in early-stage age-related macular degeneration.

Ashikawa Y, Nishimura Y, Okabe S, Sato Y, Yuge M, Tada T, Miyao H, Murakami S, Kawaguchi K, Sasagawa S, Shimada Y, Tanaka T.

Abstract: Age-related macular degeneration (AMD) is the most common cause of vision loss in elderly individuals throughout the developed world. Inhibitors of vascular endothelial growth factor have been successfully used to treat choroidal neovascularization in late-stage AMD. The pathogenesis of early-stage AMD, however, remains largely unknown, impairing efforts to develop effective therapies that prevent progression to late-stage AMD. To address this, we performed comparative transcriptomics of macular and extramacular retinal pigmented epithelium-choroid (RPE-choroid) tissue from early-stage AMD patients. We found that expression of fatty acid desaturase 1 (FADS1), FADS2, and acetyl-CoA acetyltransferase 2 (ACAT2) is increased in macular but not extramacular tissue, possibly through activation of sterol regulatory element binding factor 1 (SREBF1). Consistent with this, we also found that expression of *Fads1* is increased in RPE-choroid in a mouse model of early-stage AMD. In zebrafish, deletion of *fads2*, which encodes a protein that functions as both *Fads1* and *Fads2* in other species, enhanced apoptosis in the retina upon exposure to intense light. Similarly, pharmacological inhibition of *Srebf1* enhanced apoptosis and reduced *fads2* expression in zebrafish exposed to intense light. These results suggest that the SREBF1-FADS1/2 axis may be activated in macular RPE-choroid as a protective response during early-stage AMD and could thus be a therapeutic target for early-stage AMD.

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J Curr Ophthalmol. 2016 Oct 20;29(1):7-16. eCollection 2017.

Therapeutic targets of renin-angiotensin system in ocular disorders.

Choudhary R, Kapoor MS, Singh A, Bodakhe SH.

PURPOSE: To review current literature on the renin-angiotensin system (RAS)-mediated pathogenic mechanisms and therapeutic targets in ocular diseases.

METHODS: A comprehensive literature survey was performed on PubMed, Scopus, and Google Scholar databases published from 1977 to 2016. The search terms were a RAS, angiotensin, angiotensin receptor, prorenin, pro (renin) receptor, angiotensin converting enzyme inhibitor, angiotensin receptor blocker associated with ocular disorders like cataract, glaucoma, diabetic retinopathy (DR), macular degeneration, and uveitis. Articles were reviewed on the basis of the association between ocular disorders and RAS and relevant articles were discussed.

RESULTS: The literature revealed that the individual RAS components including renin, angiotensins, angiotensin converting enzymes, and RAS receptors have been expressed in the specific ocular tissues like retina, choroid, and ciliary body. The activation of both circulatory and local RAS potentiate the various inflammatory and angiogenic signaling molecules, including vascular endothelial growth factor (VEGF), extracellular signal-regulated kinase, and advanced glycation end products (AGE) in the ocular tissues and leads to several blinding disorders like DR, glaucoma, and macular degeneration. The classical and newer RAS inhibitors have illustrated protective effects on blinding disorders, including DR, glaucoma, macular degeneration, uveitis, and cataract.

CONCLUSIONS: The RAS components are present in the extrarenal tissues including ocular tissue and have an imperative role in the ocular pathophysiology. The clinical studies are needed to show the role of therapeutic modalities targeting RAS in the treatment of different ocular disorders.

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Oxid Med Cell Longev. 2017;2017:4128061. Epub 2017 Mar 7.

Spermidine Oxidation-Mediated Degeneration of Retinal Pigment Epithelium in Rats.

Ohashi K, Kageyama M, Shinomiya K, Fujita-Koyama Y, Hirai SI, Katsuta O, Nakamura M.

Abstract: Retinal pigment epithelium (RPE) degeneration is a crucial event in dry age-related macular degeneration and gyrate atrophy. The polyamine spermidine has been shown to induce RPE cell death in vitro. The present study aimed to establish a novel in vivo model of spermidine-induced RPE degeneration and to determine whether spermidine-induced RPE cell death involves oxidative mechanisms. In this study, spermidine caused ARPE-19 cell death in a concentration-dependent manner. This effect was prevented by removal of serum from the culture medium or treatment with amine oxidase inhibitors, N-acetylcysteine (NAC), or aldehyde dehydrogenase (ALDH). Intravitreal injection of spermidine into rats significantly increased the permeability of the blood-retinal barrier and decreased the amplitudes of scotopic electroretinogram a- and b-waves. Histological analysis revealed that spermidine induced vacuolation, atrophy, and dropout of RPE cells, leading to the disruption of photoreceptor outer segments. Simultaneous intravitreal administration of NAC and ALDH with spermidine prominently inhibited the functional and morphological changes induced by spermidine. In conclusion, this study demonstrated that the intravitreal administration of spermidine induced RPE cell dysfunction and death followed by photoreceptor degeneration in rats. These effects of spermidine are thought to be mediated by oxidative stress and a toxic aldehyde generated during spermidine oxidation.

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J Clin Biochem Nutr. 2017 Mar;60(2):100-107. Epub 2017 Feb 8.

The association of enzymatic and non-enzymatic antioxidant defense parameters with inflammatory markers in patients with exudative form of age-related macular degeneration.

Čolak E, Ignjatović S, Radosavljević A, Žorić L.

Abstract: There are evidence that oxidative stress and inflammation are involved in the pathogenesis of the age-related macular degeneration (AMD). The aim of this study was to analyze the antioxidant defense

parameters and inflammatory markers in patients with exudative form of AMD (eAMD), their mutual correlations and association with the specific forms of AMD. The cross-sectional study, included 75 patients with the eAMD, 31 patients with the early form, and 87 aged-matched control subjects. Significantly lower SOD, TAS and albumin values and higher GR, CRP and IL-6 were found in the eAMD compared to the early form ($p < 0.05$). Significant negative correlations were found between GPx and fibrinogen ($r = -0.254$), TAS and IL-6 ($r = -0.999$) and positive correlations between uric acid and CRP ($r = 0.292$), IL-6 and uric acid ($r = 0.398$) in the eAMD. A significant association of CRP (OR: 1.16, 95% CI: 1.03-1.32, $p = 0.018$), fibrinogen (OR: 2.21, 95% CI: 1.14-4.85, $p = 0.021$), TAS (OR: 7.45, 95% CI: 3.97-14.35, $p = 0.0001$), albumin (OR: 1.25, 95% CI: 1.11-1.41, $p = 0.0001$) and uric acid (OR: 1.006, 95% CI: 1.00-1.02, $p = 0.003$) was found with the eAMD. In conclusion it may be suggested, there is a significant impairment of antioxidant and inflammatory parameter levels in eAMD patients. In addition, significant association exists between the tested inflammatory markers and antioxidant parameters with late-eAMD.

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Mitochondrion. 2017 Mar 29. [Epub ahead of print]

Mitochondrial dysfunction underlying outer retinal diseases.

Lefevre E, Toft-Kehler AK, Vohra R, Kolko M, Moons L, Van Hove I.

Abstract: Dysfunction of photoreceptors, retinal pigment epithelium (RPE) or both contribute to the initiation and progression of several outer retinal disorders. Disrupted Müller glia function might additionally subsidize to these diseases. Mitochondrial malfunctioning is importantly associated with outer retina pathologies, which can be classified as primary and secondary mitochondrial disorders. This review highlights the importance of oxidative stress and mitochondrial DNA damage, underlying outer retinal disorders. Indeed, the metabolically active photoreceptors/RPE are highly prone to these hallmarks of mitochondrial dysfunction, indicating that mitochondria represent a weak link in the antioxidant defenses of outer retinal cells.

PMID: 28365408

Epidemiology

Eye (Lond). 2017 Apr 7. [Epub ahead of print]

Age-related macular degeneration in a South Indian population, with and without diabetes.

Srinivasan S, Swaminathan G, Kulothungan V, Ganesan S, Sharma T, Raman R.

Purpose: To elucidate the prevalence and risk factors of age-related macular degeneration (AMD) in people with diabetes.

Methods: Of the 5495 subjects ≥ 60 years of age recruited in the population-based study in south India, 4791 subjects with gradable images on 30° three-field retinal photographs were analyzed. AMD and diabetic retinopathy (DR) were graded based on the International ARM Epidemiological Study Group classification and International Clinical Diabetic Retinopathy Disease Severity Scale, respectively. All subjects underwent a detailed history, physical examination, and a comprehensive ocular examination.

Results: Of the 4791 subjects, 1256 had diabetes. In those with diabetes, 166 (13.2%) had DR: of which, 9.6% had AMD. Of those with diabetes but no DR, 15.6% had AMD. Presence of DR (OR=0.57, 95% CI: 0.33-0.99, $P=0.046$) was a protective factor for AMD in diabetes. When adjusted for potential confounding factors, those with AMD and diabetes were from urban areas (OR=1.65, 95% CI: 1.09-2.49, $P=0.018$), had raised systolic blood pressure (OR=1.02, 95% CI: 1.00-1.03, $P=0.01$), higher BMI (OR=1.06, 95% CI: 1.02-1.10, $P=0.005$), and higher serum triglycerides (OR=1.00, 95% CI: 1.00-1.01, $P=0.011$). A higher level of

high-density lipoprotein (HDL) (OR=0.98, 95% CI: 0.96-0.99, P=0.038) was a protective factor for AMD in subjects with diabetes.

Conclusions: The presence of DR and higher serum HDL are protective factors whereas obesity and higher systolic blood pressure are risk factors for AMD in subjects with diabetes.

PMID: 28387762

Medicine (Baltimore). 2017 Apr;96(14):e6418.

The association between periodontal disease and age-related macular degeneration in the Korea National health and nutrition examination survey: A cross-sectional observational study.

Shin YU, Lim HW, Hong EH, Kang MH, Seong M, Nam E, Cho H.

Abstract: Periodontal disease (PD) is associated with various systemic diseases. We investigated the association between PD and age-related macular degeneration (AMD). For this population-based, cross-sectional study, we enrolled 13,072 adults at least 40 years of age with gradable retinal fundus photographs and community periodontal index (CPI) data from the Korean National Health and Nutrition Examination Survey (KNHANES) (2008-2010 and 2012). Participants were divided into a middle age group (age ≤ 62 years) and old age group (age > 62 years). PD was divided into 2 categories of mild and severe. Logistic regression analysis was used to evaluate the association between PD and AMD (early and late). The prevalence of PD and AMD in the study population was $37.4\% \pm 0.8\%$ and $5.6\% \pm 0.2\%$, respectively. Overall, there was no significant difference in the proportion of participants with PD between those with and without AMD. Only participants with AMD in the middle age group had more any PD than those without AMD ($P=0.031$). Multivariate logistic regression model after adjusting for all confounding factors showed that PD was not significantly associated with AMD (odds ratio [OR] 1.03, 95% confidence interval [CI] 0.86-1.22). However, according to degree of PD, participants with severe PD in the middle age group were 1.61 times more likely to have AMD (OR 1.61, 95% CI 1.02-2.54). Our data, collected from an Asian population, showed that only severe PD is independently associated with AMD in individuals aged 62 years or younger.

PMID: 28383406

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Absence of Alzheimer Disease Neuropathologic Changes in Eyes of Subjects With Alzheimer Disease.

Williams EA, McGuone D, Frosch MP, Hyman BT, Laver N, Stemmer-Rachamimov A.

Abstract: Alzheimer disease (AD) is the most common cause of dementia in the elderly, and is characterized by extracellular deposition of β -amyloid and intracellular accumulation of hyperphosphorylated tau protein in the brain. These pathologic findings are identified postmortem. Various visual deficits in AD have been reported and there have been conflicting reports, through imaging and pathology studies, regarding the presence of changes in the globe that mirror Alzheimer changes in the brain. Moreover, both macular degeneration and glaucoma have been variously characterized as having AD-related features. We examined one or both eyes from 19 autopsy cases, 17 of which had varying degrees of AD-related changes, and 2 of which were age-matched controls. Three cases had glaucoma and 4 had macular degeneration. Immunohistochemistry for tau, β -amyloid, TDP-43, ubiquitin, and α -synuclein showed no evidence of inclusions, deposits or other protein accumulation in any case, in any part of the globe. This finding suggests that regardless of the severity of changes seen in the brain in AD, there are no similar changes in the globe.

PMID: 28379416

Am J Ophthalmol. 2017 Mar 29. [Epub ahead of print]

Using electronic health records to build an ophthalmological data warehouse and visualize patients' data.

Kortüm KU, Müller M, Kern C, Babenko A, Mayer WJ, Kampik A, Kreutzer TC, Priglinger S, Hirneiss C.

PURPOSE: To develop a near real-time data warehouse (DW) in an academic ophthalmological center to gain scientific use of increasing digital data from electronic medical records (EMR) and diagnostic devices. **Design;** Database development **METHODS:** Specific macular clinic user interfaces within the institutional hospital information system were created. Orders for imaging modalities were sent by an EMR -linked picture-archiving and communications system to the respective devices. All data of 325,767 patients since 2002 were gathered in a DW running on a SQL database. A data discovery tool was developed. An exemplary search for patients with age-related macular degeneration, performed cataract surgery and at least 10 intravitreal (excluding Bevacizumab) injections was conducted.

RESULTS: Data related to those patients (3,142,204 diagnoses [including diagnoses from other fields of medicine], 720,721 procedures [e.g., surgery], and 45,416 intravitreal injections) were stored including 81,274 OCT measurements. A web-based browsing tool was successfully developed for data visualization and filtering data by several linked criteria, e.g., minimum number of intravitreal injections of a specific drug and visual acuity interval. The exemplary search identified 450 patients with 516 eyes meeting all criteria.

CONCLUSIONS: A DW was successfully implemented in an ophthalmological academic environment to support and facilitate research by using increasing EMR and measurement data. The identification of eligible patients for studies was simplified. In future, software for decision support can be developed based on the DW and its structured data. The improved classification of diseases and semi-automatic validation of data via machine learning are warranted.

PMID: 28365240

Genetics

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Gene delivery of calreticulin anti-angiogenic domain attenuates the development of choroidal neovascularization in rats.

Bee YS, Tu L, Sheu SJ, Lin HC, Tang JH, Wang JH, Prea SM, Disting GJ, Wu DC, Zhong J, Bui BV, Tai MH, Liu GS.

Abstract: Choroidal neovascularization (CNV) is a common pathological feature in neovascular age-related macular degeneration which is the leading cause of vision loss amongst elderly populations in developed countries. In this study, we evaluated the effect of a novel endogenous inhibitor of angiogenesis, calreticulin anti-angiogenic domain (CAD), subconjunctivally delivered by an adenoviral vector (Ad-CAD) in a rat model of laser-induced CNV. CAD was expressed in Ad-CAD infected cells and inhibited the angiogenic activity in human umbilical vein endothelial cells in vitro. CAD expression was also found in various ocular tissues after in vivo subconjunctival Ad-CAD injection. Via bioluminescence imaging we show that a single subconjunctival injection of Ad-Luci induced the expression of the transgene in the injected eyes within 24 hours, which lasted for at least 112 days. Forty-two days after subconjunctival Ad-CAD retinal structure and function were unaffected, as measured using optical coherence tomography and electroretinography, respectively. After laser injury, subconjunctival Ad-CAD gene delivery significantly inhibited CNV lesions as measured via choroid flat-mounts (51% reduction at 21 days, $p < 0.001$) as well as by fundus fluorescein angiography (19.3%, 28.2%, 31% and 27.5% reductions at day 21, 28, 35 and 42, $p < 0.05$) in rats. Our data suggests that subconjunctival Ad-CAD gene therapy could effectively inhibit laser-induced CNV and might be an attractive therapeutic approach for the management of choroidal neovascularization.

PMID: 28363247

Diet, lifestyle and low vision

PLoS One. 2017 Apr 5;12(4):e0174910. eCollection 2017.

Evaluation of a gaze-controlled vision enhancement system for reading in visually impaired people.

Aguilar C, Castet E.

Abstract: People with low vision, especially those with Central Field Loss (CFL), need magnification to read. The flexibility of Electronic Vision Enhancement Systems (EVES) offers several ways of magnifying text. Due to the restricted field of view of EVES, the need for magnification is conflicting with the need to navigate through text (panning). We have developed and implemented a real-time gaze-controlled system whose goal is to optimize the possibility of magnifying a portion of text while maintaining global viewing of the other portions of the text (condition 1). Two other conditions were implemented that mimicked commercially available advanced systems known as CCTV (closed-circuit television systems)-conditions 2 and 3. In these two conditions, magnification was uniformly applied to the whole text without any possibility to specifically select a region of interest. The three conditions were implemented on the same computer to remove differences that might have been induced by dissimilar equipment. A gaze-contingent artificial 10° scotoma (a mask continuously displayed in real time on the screen at the gaze location) was used in the three conditions in order to simulate macular degeneration. Ten healthy subjects with a gaze-contingent scotoma read aloud sentences from a French newspaper in nine experimental one-hour sessions. Reading speed was measured and constituted the main dependent variable to compare the three conditions. All subjects were able to use condition 1 and they found it slightly more comfortable to use than condition 2 (and similar to condition 3). Importantly, reading speed results did not show any significant difference between the three systems. In addition, learning curves were similar in the three conditions. This proof of concept study suggests that the principles underlying the gaze-controlled enhanced system might be further developed and fruitfully incorporated in different kinds of EVES for low vision reading.

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