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Drug treatment

Eur J Ophthalmol. 2013 Nov 12:0. doi: 10.5301/ejo.5000385. [Epub ahead of print]

One-year outcome of ranibizumab for neovascular age-related macular degeneration: a thorough analysis in a real-world clinical setting.

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Purpose: To verify the safety and efficacy of ranibizumab in neovascular age-related macular degeneration (nAMD) and factors influencing the outcome in a real-world setting.

Methods: Retrospective 12-month follow-up analysis of 100 naive nAMD eyes treated with as-needed ranibizumab. Changes in best-corrected visual acuity (BCVA), central retinal thickness (CRT), lesion, and leakage size were recorded. Type and characteristics of lesions and indicators of protocol adherence were analyzed.

Results: Mean BCVA at baseline was 61.6 ± 14.8 Early Treatment Diabetic Retinopathy Study letters and 59.6 ± 16 at 12 months. Sixty-three eyes maintained or improved BCVA; the number of injections and follow-up visits were 4.8 and 5.1, respectively. First injection and pro re nata retreatments were administered 22.7 and 20.5 days after prescription, respectively. Seventy-two eyes received 3 initial monthly injections. Patients were not reinjected despite BCVA loss >5 letters one or more times in 37% of cases. No adverse events were reported. The CRT diminished by 26 ± 101 μm; choroidal neovascularization size and leakage area increased by 0.53 ± 1.31 mm² and 0.34 ± 1.33 mm², respectively. The BCVA gain was correlated with CRT reduction (r = 0.24, p = 0.016), mean baseline BCVA (r = -0.25, p = 0.01), age (r = -0.25, p = 0.01), and decrease in CNV size and leakage area (r = 0.56 and r = 0.59, respectively, p<0.001).

Conclusions: Our results compare unfavorably with those of controlled trials. Treatment and follow-up regimens in real-world settings seem to have a major role in determining outcome. Lower age and BCVA at baseline were associated with better response to treatment.

PMID: 24242222 [PubMed - as supplied by publisher]

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Intravitreal anti-VEGF therapy for vascularized pigment epithelium detachment in age-related macular degeneration.

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Purpose: To assess the efficacy of intravitreal anti-vascular endothelial growth factor (VEGF) treatment of vascularized pigment epithelial detachment (PED) due to age-related macular degeneration (AMD).

Methods: A total of 26 patients with vascularized PED secondary to AMD were retrospectively analyzed and treated with anti-VEGF intravitreal injections according to a PRN regimen after 3 initial injections. Best-corrected visual acuity (BCVA), optical coherence tomography, and fluorescein angiography were performed at baseline and quarterly.

Results: Mean follow-up ranged from 9 to 26 months (mean 13.5). There was a deterioration in mean BCVA from 0.46 at baseline to 0.79 logMAR at 12 months (p<0.001). The mean PED greatest linear diameter (GLD) increased from 4499 at baseline to 5206 µm at 1-year follow-up (p<0.001). The mean PED maximum height decreased from 669 µm at baseline to 305 µm at 1-year follow-up (p = 0.001). The mean central retinal thickness (CRT) was unchanged (from 277 to 209 µm at 1 year follow-up) (p = 0.099). No effect was seen on the change of VA according to groups of baseline predictors as defined by the medial value: baseline VA, PED height, and CRT (p>0.10).There was a borderline trend (p = 0.064) that GLD affected response to treatment. The mean number of injections was 5.5 (3 to 9). Seven out of 26 (27%) patients developed a retinal pigment epithelium (RPE) tear.

Conclusions: Intravitreal anti-VEGF therapy, with a PRN regimen, did not prevent visual acuity loss or RPE tear.

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Eye (Lond). 2013 Nov 22. doi: 10.1038/eye.2013.245. [Epub ahead of print]

Factors affecting visual outcomes in patients with diabetic macular edema treated with ranibizumab.

Channa R, Sophie R, Khwaja AA, Do DV, Hafiz G, Nguyen QD, Campochiaro PA; The READ-2 Study Group, Abraham P, Green B, Livermont K, Lit ES, Brinton DA, Lee SS, Renslow S, Kruger EF, Yuhas P, Pollack JS, Civantos JM, Ciscato BJ, Do DV, Campochiaro P, Finkelstein D, Goldberg MF, Handa JT, Nguyen QD, Sung JU, Ying H, Zimmer-Galler I, Hafiz G, Azzaro L, Greer L, Shaikh O, Simmons J, Ciulla T, Thukral N, Heier JS, Chieh JJ, Cleary TS, Fenton GL, Liao DS, Topping TM, Wiegand TW, Janzen GP, Shah SP, Chang JA, Williams L, Dugel PU, Sipperley J, Park DW, Liu J, Kunimoto DY, Quinlan EJ, Mollen A, Gaitan JR, Mobley SG, Thach A, Simon R, Parker RJ, Hollifield RD, Loo RH, Yepremyan M, Voo I, Wickens JC, Seybert J, Major C, Davis M, Browder C, Rediker M, Chang TS, Samuel MA, Culotta AJ, Ahmed E, Baghoomian Y, Boyer D, Novack RL, Chu TG, Rahhal FM, Hopkins JJ, Tabandeh H, Roe RH, Gasparyan T, Kurokouchi J, Yoon C, Das A, Schluter M, Nemeth S, Lim J, Eliott D, Padilla M, Campochiaro PA, Heier JS, Nguyen QD, Conway BP, Wilson D, Channa R, Ibrahim M, Sepah Y, Shah SM, Khwaja A, Putzke J, Sepah Y, Hafiz G, Pack V, Sophie R, Khwaja A, Channa R, Sepah Y.

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Purpose: To identify factors associated with visual outcomes in patients with diabetic macular edema (DME) treated with ranibizumab (RBZ) in the Ranibizumab for Edema of the mAcula in Diabetes-Protocol 2 (READ-2) Study.

Patients and methods: Optical coherence tomography scans, fundus photographs, and fluorescein angiograms (FAs) were graded and along with baseline characteristics were correlated with month (M) 24 visual outcome of best-corrected visual acuity (BCVA) ≤20/100 (poor outcome) vs >20/100 (better outcome).

Results: Of 101 patients with a M20 visit or beyond, 27 (27%) had BCVA ≤20/100. Comparison of patients with or without poor outcome showed mean baseline BCVA of 16.8 letters (20/125) in the former compared with 30.4 letters (20/63; P<0.001). Mean change in BCVA between baseline and M24 was -2.6 letters in the poor outcome group compared with +9.8 letters (P<0.001). Foveal thickness (FTH) at M24 was 374.1 µm in the poor outcome group compared with 268.8 µm (P<0.01), a difference driven by 14 patients with mean FTH of 450.3 µm. Foveal atrophy occurred in 65% (11/17) in the poor outcome group compared with 17% (12/71, P=0.001). Persistent edema was noted in 52% (14/27) of patients with poor outcome. Laser scars near foveal center were significantly more common in patients with poor outcome who did not have edema vs those who did (78% (7/9) vs 23% (3/13) P=0.03).

Conclusion: Poor baseline BCVA (≤20/125) in DME patients predicts poor visual outcome (≤20/100) after 2 years of treatment with RBZ and/or focal/grid laser, often due to foveal atrophy and/or persistent edema.Eye advance online publication, 22 November 2013; doi:10.1038/eye.2013.245.

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Br J Ophthalmol. 2013 Nov 18. doi: 10.1136/bjophthalmol-2013-303444. [Epub ahead of print]

Polypoidal choroidal vasculopathy in Caucasian patients with presumed neovascular age-related macular degeneration and poor ranibizumab response.

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AIMS: To determine the prevalence of polypoidal choroidal vasculopathy (PCV) in patients with presumed neovascular age-related macular degeneration (AMD) who were considered poor responders to ranibizumab.

METHODS: Caucasian patients with suspected neovascular AMD, presumed to be choroidal neovascularisation, previously treated with ≥8 intravitreal injections of ranibizumab 0.5 mg (Lucentis; Novartis AG, Basel, Switzerland) administered as required during optical coherence tomography-guided dosing were retrospectively included. Eyes were categorised according to the time from injection 1 to injection 6 (group 1: <12 months; group 2: ≥12 months). Indocyanine green angiography (ICGA) was used to re-evaluate eyes for PCV. Suitable candidates received reduced-fluence photodynamic therapy/ ranibizumab combination therapy supplemented by ranibizumab monotherapy, as required.

RESULTS: 202 eyes were included (group 1: 73.8%; group 2: 26.2%). The prevalence of PCV in group 1 (21.5%) was significantly higher than in group 2 (3.8%; p=0.003). After initiation of combination therapy, 16 eyes with PCV received 3.1±2.5 ranibizumab injections/year vs 8.4±2.4 injections/year before initiation of combination therapy (p<0.001).

CONCLUSIONS: In Caucasian patients with presumed neovascular AMD, PCV prevalence is increased in eyes that respond poorly to ranibizumab monotherapy. ICGA improved PCV diagnosis in poor responders; combination therapy may be beneficial for eyes with PCV.

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Retina. 2013 Nov 14. [Epub ahead of print]

TREAT-AND-EXTEND BEVACIZUMAB FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: The Importance of Baseline Characteristics.

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PURPOSE: To evaluate the factors affecting visual and anatomical outcomes and the number of intravitreal bevacizumab injections required in the treatment of neovascular age-related macular degeneration using a treat-and-extend regimen.

METHODS: Retrospective consecutive case series. The charts of subjects treated with intravitreal bevacizumab for neovascular age-related macular degeneration using a treat-and-extend regimen over a 12-month period were reviewed. The key variables explored were patient age, phakic status, posterior vitreous detachment status, baseline best-corrected visual acuity (BCVA), baseline central macular thickness (CMT), and type of chorodial neovascularization. The primary outcome measures were improvement in BCVA of 3 logMAR lines or more, maintenance of BCVA within 3 logMAR lines of baseline, number of intravitreal injections delivered over a 12-month period, and final CMT on optical coherence tomography.

RESULTS: A total of 230 eyes met the criteria. Mean presenting BCVA was Snellen 20/55 (0.44 logMAR) and mean final BCVA was Snellen 20/44 (0.35 logMAR) ($P < 0.001$). A total of 23.5% (95% confidence interval [CI], 18.5-29.4%) of the subjects demonstrated an improvement in BCVA of 3 or more logMAR lines, whereas 96.5% (95% CI, 93.3-98.2%) of the subjects lost fewer than 3 logMAR lines. Mean CMT on optical coherence tomography changed from a baseline average of 373.1 μm (95%CI, 360.3-386.1 μm) to a final average of 305.5 μm (95% CI, 290.0-316.0 μm). The average number of injections during the 12-month period was 9.2 (95% CI, 9.0-9.4). Posterior vitreous detachment was associated with fewer injections on univariate and multivariate analysis (8.7 injections in the posterior vitreous detachment group versus 9.8 in the non-posterior vitreous detachment group, $P < 0.001$). Patients with poorer presenting BCVA and greater baseline CMTs were more likely to demonstrate a 3 or more logMAR line improvement in BCVA. Thinner final CMTs were independently associated with thinner presenting CMTs and fewer injections.

CONCLUSION: Favorable visual and anatomical outcomes may be achieved with intravitreal bevacizumab in the treatment of neovascular age-related macular degeneration using a treat-and-extend regimen. Our study suggests that posterior vitreous detachment may play a role in the efficacy of intravitreal bevacizumab during the treatment of neovascular age-related macular degeneration.

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Retina. 2013 Nov 14. [Epub ahead of print]

INFLUENCE OF AXIAL LENGTH AND POSTINJECTION REFLUX ON SUSTAINED INTRAOCULAR PRESSURE ELEVATION AS A RESULT OF INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY.

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PURPOSE: To assess an association of axial length (AL) or postinjection reflux with transient or sustained intraocular pressure (IOP) elevation in patients with neovascular age-related macular degeneration receiving anti-vascular endothelial growth factor injections.

METHODS: One hundred and forty-seven eyes from 74 consecutive patients with neovascular age-related macular degeneration who presented to a single physician over a 2-month period had ALs measured by IOLMaster. Twenty-one patients had preinjection and immediate postinjection IOP measured and immediate reflux assessed.

RESULTS: Overall, 9.5% of eyes had been identified with sustained IOP elevation in our previous study. Axial length did not significantly differ between eyes that had (AL, 23.96 ± 0.66 mm; n = 14) and had not experienced sustained IOP elevation (AL, 23.44 ± 1.24 mm; n = 133; P = 0.12, t-test). By linear regression analysis, the relationship between experiencing sustained IOP elevation and AL was not statistically significant (R = 0.0165; P = 0.121). The relationship between AL and immediate postinjection IOP elevation was also not statistically significant (R = 0.0001; P = 0.97). Immediate postinjection IOP increase did differ between eyes without reflux (30.2 ± 9.3 mmHg; n = 12) and those with reflux (1.1 ± 7.2; n = 9; P < 0.001).

CONCLUSION: Axial length does not seem to be a predictor of transient or sustained IOP elevation. Repeated trabecular meshwork trauma related to the absence or presence of reflux and immediate postinjection IOP elevation may be a contributing factor.

PMID: 24240557 [PubMed - as supplied by publisher]

J Comp Eff Res. 2012 Nov;1(6):485-8. doi: 10.2217/cer.12.57.

Anti-VEGF therapies for the treatment of age-related macular degeneration.

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Evaluation of: Martin DF, Maguire MG, Fine SL et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration two-year results. Ophthalmology 119(7), 1388-1398 (2012). Age-related macular degeneration is the leading cause of blindness in European-derived populations. Recently, drugs have been developed that not only reduce the risk of vision loss, but can actually improve visual acuity. This article provides a summary of a recent comparative effectiveness trial evaluating two of these drugs. The study found that visual acuity outcomes were similar for the two drugs and that monthly dosing provided a slight advantage over as-needed treatment. The role of long-term differences in retinal thickening, geographic atrophy and potential differences in serious adverse events between the two drugs need further research.

PMID: 24236467 [PubMed - in process]

Other treatmeht & diagnosis

Doc Ophthalmol. 2013 Nov 22. [Epub ahead of print]

Measurement of cone dark adaptation: a comparison of four psychophysical methods.

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PURPOSE: Dark adaptometry is an important clinical tool for the diagnosis of a range of conditions, including age-related macular degeneration. In order to identify the most robust, clinically applicable technique for the measurement of cone dark adaptation, the repeatability and agreement of four psychophysical methods were assessed.

METHODS: Data were obtained from 31 healthy adults on two occasions, using four psychophysical methods. Participants' pupils were dilated, and 96 % of cone photopigment was bleached before threshold was monitored in the dark using one of the techniques, selected at random. This procedure was repeated for each of the remaining methods. An exponential recovery function was fitted to all threshold recovery data. The coefficient of repeatability (CoR) was calculated to assess the repeatability of the methods, and a repeated-measures analysis of variance was used to compare mean recovery parameters.

RESULTS: All four methods demonstrated a similar level of intersession repeatability for measurement of cone recovery, yielding CoRs between 1.18 and 1.56 min. There were no statistically significant differences in estimates of mean time constant of cone recovery (cone τ) between the four methods ($p = 0.488$); however, significant differences between initial and final cone thresholds were reported ($p < 0.005$).

CONCLUSIONS: All of the techniques were capable of monitoring the rapid changes in visual threshold that occur during cone dark adaptation, and the repeatability of the techniques was similar. This indicates that despite the respective advantages and disadvantages of these psychophysical techniques, all four methods would be suitable for measuring cone dark adaptation in clinical practice.

PMID: 24263533 [PubMed - as supplied by publisher]

Open Ophthalmol J. 2013 Oct 31;7:82-84.

Polypoidal Choroidal Vasculopathy - A Type I Polypoidal Subretinal Neovasculopathy.

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Abstract: This 47 year old female developed the new onset of a polypoidal subretinal neovascular membrane in the left eye 13 years after having polypoidal choroidal vasculopathy (PCV) treated in the right eye. The indocyanine green (ICG) angiography of the left eye at initial presentation showed a normal choroidal vascular pattern without PCV. The new development of a PCV complex on ICG angiography demonstrates that PCV is truly a type of subretinal neovascularization, and not a choroidal vascular abnormality. The optical coherence tomography shows that the polypoidal vascular complex lies above Bruch's membrane and beneath the retinal pigment epithelium, and not within the choroid. Treatment with high dose ranibizumab (2.0 mg) resulted in excellent polyp closure and regression of the branching vascular network. The documented new development of polypoidal subretinal vessels on ICG angiography and the response to ranibizumab supports that PCV is a polypoidal neovasculopathy (PNV).

PMID: 24265653 [PubMed - as supplied by publisher]

Clin Exp Optom. 2013 Nov 20. doi: 10.1111/cxo.12120. [Epub ahead of print]

The ABCs of RVO: A review of retinal venous occlusion.

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Abstract: Retinal vein occlusions are important causes of loss of vision; indeed, they are the second most common retinal vascular disease, following diabetic retinopathy. For this reason alone, primary eye-care providers must be well versed in diagnosis and management. Risk factors, though not universally agreed upon, include but are not limited to advancing age, systemic hypertension, arteriolarsclerosis, diabetes, hyperlipidaemia, blood hyperviscosity, thrombophilia, ocular hypertension and glaucoma. Typically, visual

loss is secondary to macular oedema and/or retinal ischaemia. Treatment modalities have included observation, systemic thrombolysis and haemodilution, radial optic neurotomy, chorioretinal anastomosis, vitrectomy, laser photocoagulation and intravitreal injection of anti-inflammatory and, most recently, anti-vascular endothelial growth factors.

PMID: 24256639 [PubMed - as supplied by publisher]

BMJ Case Rep. 2013 Nov 18;2013. pii: bcr2013201218. doi: 10.1136/bcr-2013-201218.

Long-term fundus changes in acquired partial lipodystrophy.

Jansen J, Delaere L, Spielberg L, Leys A.

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Abstract: We describe long-term fundus changes in a patient with partial lipodystrophy (PL). Retinal pigment alterations, drusen and subretinal neovascularisation were seen without evidence for membranoproliferative glomerulonephritis. Fundus alterations similar to those seen in age-related macular degeneration can occur at an earlier age in patients with PL, even without renal disease. Dysregulation of an alternative complement pathway with low serum levels of C3 has been implicated as a pathogenetic mechanism.

PMID: 24248317 [PubMed - in process]

Exp Eye Res. 2013 Nov 13. pii: S0014-4835(13)00312-6. doi: 10.1016/j.exer.2013.10.023. [Epub ahead of print]

Transplantation of human bone marrow mesenchymal stem cells as a thin subretinal layer ameliorates retinal degeneration in a rat model of retinal dystrophy.

Tzameret A, Sher I, Belkin M, Treves AJ, Meir A, Nagler A, Levkovitch-Verbin H, Barshack I, Rosner M, Rotenstreich Y.

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Abstract: Vision incapacitation and blindness associated with retinal degeneration affect millions of people worldwide. Cell based therapy and specifically transplantation of human adult bone marrow-derived stem cells (hBM-MSCs) present possible treatment strategy. Subretinal transplantation of human or rat BM-MSCs was shown previously to improve retinal function in Royal College Surgeons (RCS) rats. In those studies cells were transplanted via a transscleral-transchoroidal approach, creating a localized subretinal bleb. Limited number cells could be injected and photoreceptor rescue was restricted to areas in proximity to the injection site. Here we describe a new surgical method for subretinal transplantation that facilitates uniform distribution of transplanted cells as a thin layer along most of the subretinal space. We assessed the therapeutic effect of hBM-MSCs on RCS rats when transplanted either subretinally or intravitreally. We also examined whether a second transplantation can prolong the therapeutic effect. A cell suspension of 2.5 × 106 cells in 5 μl was injected subretinally or intravitreally in RCS rats at 28 days postnatal. In the subretinal group, hBM-MSCs were transplanted posterior to the limbus in the superotemporal part of the eye through a longitudinal triangular scleral tunnel reaching the choroid. In the intravitreal group, the cells were injected into the superotemporal part of the vitreous cavity. In cross sections of subretinally transplanted eyes, removed 2 h following transplantation, hBM-MSCs were distributed as a near-homogenous thin layer along most of the subretinal space. In some animals the cells were also detected in the choroid. In the intravitreal injection group, hBM-MSCs were clustered in the vitreous cavity. Transplanted cells could be detected up to 2 weeks after transplantation but not at later time points. Retinal

function and structure were assessed by electroretinogram (ERG) and histology analysis, respectively. Six weeks post transplantation, the mean maximal scotopic ERG b-wave amplitude response recorded in RCS control eyes was 1.2 μV. By contrast, in transplanted eyes mean responses of 56.4 μV and 66.2 μV were recorded in the intravitreally and subretinally transplanted eyes, respectively. In the subretinal group, retinal function was significantly higher in transplanted compared with control eyes up to 20 weeks following transplantation. By contrast, in the intravitreal group, rescue of retinal function persisted only up to 12 weeks following transplantation. Histological analysis revealed that 8 weeks following subretinal transplantation, the retinas of control eyes were dystrophic, with outer nuclear layer (ONL) containing a single cell layer. An extensive photoreceptor rescue was demonstrated in transplanted eyes at this time point, with 3-4 cell layers in the ONL along the entire retina. A second subretinal transplantation at 70 days postnatal did not enhance or prolong the therapeutic effect of hBM-MSCs. No immunosuppressants were used and long-term safety analysis demonstrated no gross or microscopic adverse effects. Taken together our findings suggest that transplantation of hBM-MSCs as a thin subretinal layer enhances the therapeutic effect and the safety of cell transplantation.

PMID: 24239509 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Nov 19;54(12):7637-43. doi: 10.1167/iovs.13-12981.

In vivo visualization of perforating vessels and focal scleral ectasia in pathological myopia.

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PURPOSE: To describe focal scleral ectasia in areas of macular/perimacular patchy chorioretinal atrophy secondary to pathologic myopia.

METHODS: Thirty-nine consecutive patients with pathologic myopia and chorioretinal atrophy in at least one eye, with and without focal scleral ectasia, were analyzed by infrared reflectance (IR) and/or multicolor imaging, enhanced depth imaging optical coherence tomography (EDI-OCT) (39 patients, 78 eyes), and swept source (SS)-OCT (13 out of 39 patients, 26 eyes) cross-sectional scan.

RESULTS: Focal scleral ectasia was found in 12 out of 68 eyes (11 out of 39 consecutive patients, 27 females/12 males; mean age 65.7 ± 11.9 years) with macular/perimacular patchy chorioretinal atrophy, and was always observed inferior or temporal to the macula (mean 1.25 ± 0.38/eye). Focal scleral ectasia, appearing on fundus examination as a deep dark round/oval lesion with well-defined borders, was characterized on EDI-OCT and SS-OCT by an abrupt posterior bow of the sclera with different degrees of scleral schisis on its borders. The retinal pigment epithelium and the choroid were absent in all lesions. IR reflectance and multicolor imaging showed large vessels that seem to emerge from the focal scleral ectasia, and crossing the area of patchy atrophy. EDI-OCT and SS-OCT revealed retrobulbar vessels perforating the sclera at the borders/bottom of the abrupt posterior bow of the sclera (i.e., focal scleral ectasia) and running through the superficial scleral thickness for the whole extension of the atrophic area.

CONCLUSIONS: We showed that perforating vessels are localized at the border/bottom of focal scleral ectasia in pathologic myopia.

PMID: 24194186 [PubMed - in process]

Curr Opin Ophthalmol. 2013 Nov 15. [Epub ahead of print]

Ultraviolet-blocking intraocular lenses: fact or fiction.

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PURPOSE OF REVIEW: Ultraviolet-blocking intraocular lenses (IOLs) are used routinely in cataract surgery and are widely accepted. Blue-blocking IOLs, however, have been much debated since their inception. In this article, we will review the advantages and disadvantages of blue-blocking IOLs.

RECENT FINDINGS: In experimental and animal studies, acute blue light exposure induces retinal damage and the use of blue-blocking IOLs lessens this damage. Many large epidemiologic studies have further investigated this relationship between blue light exposure and the development of age-related macular degeneration, and have shown conflicting results. Visual performance and circadian rhythm disturbances have also been explored in patients with blue-blocking IOLs; no significant negative effects have been shown.

SUMMARY: The current literature on blue-blocking IOLs is contradictory. Studies have failed to conclusively prove that blue-blocking lenses provide photoprotection against age-related macular degeneration or cause any significant detrimental effects on visual function or circadian rhythms.

PMID: 24248095 [PubMed - as supplied by publisher]

Pathogenesis

Trends Endocrinol Metab. 2013 Nov 16. pii: S1043-2760(13)00179-3. doi: 10.1016/j.tem.2013.10.007. [Epub ahead of print]

Eyeballing cholesterol efflux and macrophage function in disease pathogenesis.

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Abstract: Disorders of lipid metabolism are strongly associated with cardiovascular disease. Recently, there has been significant focus on how tissues process lipid deposits. Impaired cholesterol efflux has been shown to be crucial in mediating lipid deposition in atherosclerosis. The inability of macrophages to effectively efflux cholesterol from tissues initiates inflammation, plaque neovascularization, and subsequent rupture. Recent studies suggest that inability to effectively efflux cholesterol from tissues may have global implications far beyond atherosclerosis, extending to the pathophysiology of unrelated diseases. We examine the unifying mechanisms by which impaired cholesterol efflux facilitates tissue-specific inflammation and disease progression in age-related macular degeneration (AMD), a blinding eye disease, and in atherosclerosis, a disease associated with significant cardiovascular morbidity.

PMID: 24252662 [PubMed - as supplied by publisher]

Genetics

PLoS One. 2013 Nov 18;8(11):e78617.

Human Factor H-Related Protein 2 (CFHR2) Regulates Complement Activation.

Eberhardt HU, Buhlmann D, Hortschansky P, Chen Q, Böhm S, Kemper MJ, Wallich R, Hartmann A, Hallström T, Zipfel PF, Skerka C.

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Abstract: Mutations and deletions within the human CFHR gene cluster on chromosome 1 are associated with diseases, such as dense deposit disease, CFHR nephropathy or age-related macular degeneration. Resulting mutant CFHR proteins can affect complement regulation. Here we identify human CFHR2 as a novel alternative pathway complement regulator that inhibits the C3 alternative pathway convertase and terminal pathway assembly. CFHR2 is composed of four short consensus repeat domains (SCRs). Two CFHR2 molecules form a dimer through their N-terminal SCRs, and each of the two C-terminal ends can bind C3b. C3b bound CFHR2 still allows C3 convertase formation but the CFHR2 bound convertases do not cleave the substrate C3. Interestingly CFHR2 hardly competes off factor H from C3b. Thus CFHR2 likely acts in concert with factor H, as CFHR2 inhibits convertases while simultaneously allowing factor H assisted degradation by factor I.

PMID: 24260121 [PubMed - as supplied by publisher]

PLoS One. 2013 Nov 11;8(11):e78274. doi: 10.1371/journal.pone.0078274.

A Novel PRPF31 Mutation in a Large Chinese Family with Autosomal Dominant Retinitis Pigmentosa and Macular Degeneration.

Lu F, Huang L, Lei C, Sha G, Zheng H, Liu X, Yang J, Shi Y, Lin Y, Gong B, Zhu X, Ma S, Qiao L, Lin H, Cheng J, Yang Z.

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PURPOSE: This study was intended to identify the disease causing genes in a large Chinese family with autosomal dominant retinitis pigmentosa and macular degeneration.

METHODS: A genome scan analysis was conducted in this family for disease gene preliminary mapping. Snapshot analysis of selected SNPs for two-point LOD score analysis for candidate gene filter. Candidate gene PRPF31 whole exons' sequencing was executed to identify mutations.

RESULTS: A novel nonsense mutation caused by an insertion was found in PRPF31 gene. All the 19 RP patients in 1085 family are carrying this heterozygous nonsense mutation. The nonsense mutation is in PRPF31 gene exon9 at chr19:54629961-54629961, inserting nucleotide "A" that generates the coding protein frame shift from p.307 and early termination at p.322 in the snoRNA binding domain (NOP domain).

CONCLUSION: This report is the first to associate PRPF31 gene's nonsense mutation and adRP and JMD. Our findings revealed that PRPF31 can lead to different clinical phenotypes in the same family, resulting either in adRP or syndrome of adRP and JMD. We believe our identification of the novel "A" insertion mutation in exon9 at chr19:54629961-54629961 in PRPF31 can provide further genetic evidence for clinical test for adRP and JMD.

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ASSOCIATION OF PLASMA MALONDIALDEHYDE WITH ARMS2 GENETIC VARIANTS AND PHENOTYPES IN POLYPOIDAL CHOROIDAL VASCULOPATHY AND AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: To evaluate the relationships between plasma malondialdehyde (MDA) level and ARMS2 variants and phenotypes in patients with polypoidal choroidal vasculopathy (PCV) and neovascular age-related macular degeneration (nAMD).

METHODS: This study is a retrospective case-control study. Plasma MDA was measured in 84 controls, 62 patients with PCV, and 42 patients with nAMD. Participants were genotyped for ARMS2 polymorphism. Phenotypes including bilaterality and greatest linear dimension based on fluorescein angiography (FA-GLD) and indocyanine green angiography (ICGA-GLD), were evaluated.

RESULTS: Plasma MDA in the PCV and nAMD groups was higher than in the control group ($P < 0.001$, respectively). For ARMS2 variants, plasma MDA of homozygous high-risk genotype (TT) was higher than that of homozygous low-risk genotype (GG) in all groups ($P < 0.001$, respectively). Plasma MDA was higher in homozygous high-risk genotype than in heterozygous genotype in the control, PCV, and nAMD groups ($P = 0.021$, 0.002, and 0.004, respectively). In the nAMD group, there was a correlation between plasma MDA and both FA-GLD ($r = 0.418$, $P = 0.006$) and ICGA-GLD ($r = 0.329$, $P = 0.033$). There was a difference in plasma MDA between patients with unilateral and bilateral lesions in both PCV and nAMD ($P = 0.017$ and 0.019, respectively).

CONCLUSION: This study revealed significant relationships between the plasma MDA level and ARMS2 variants and phenotypes in PCV and nAMD.

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Altered gene expression in dry age-related macular degeneration suggests early loss of choroidal endothelial cells.

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PURPOSE: Age-related macular degeneration (AMD) is a major cause of blindness in developed countries. The molecular pathogenesis of early events in AMD is poorly understood. We investigated differential gene expression in samples of human retinal pigment epithelium (RPE) and choroid from early AMD and control maculas with exon-based arrays.

METHODS: Gene expression levels in nine human donor eyes with early AMD and nine control human donor eyes were assessed using Affymetrix Human Exon ST 1.0 arrays. Two controls did not pass quality control and were removed. Differentially expressed genes were annotated using the Database for Annotation, Visualization and Integrated Discovery (DAVID), and gene set enrichment analysis (GSEA) was performed on RPE-specific and endothelium-associated gene sets. The complement factor H (CFH) genotype was also assessed, and differential expression was analyzed regarding high AMD risk (YH/HH) and low AMD risk (YY) genotypes.

RESULTS: Seventy-five genes were identified as differentially expressed (raw p value <0.01; ≥50% fold change, mean log2 expression level in AMD or control ≥ median of all average gene expression values); however, no genes were significant (adj. p value <0.01) after correction for multiple hypothesis testing. Of 52 genes with decreased expression in AMD (fold change <0.5; raw p value <0.01), 18 genes were identified by DAVID analysis as associated with vision or neurologic processes. The GSEA of the RPE-associated and endothelium-associated genes revealed a significant decrease in genes typically expressed by endothelial cells in the early AMD group compared to controls, consistent with previous histologic and proteomic studies. Analysis of the CFH genotype indicated decreased expression of ADAMTS9 in eyes with high-risk genotypes (fold change = -2.61; raw p value=0.0008).

CONCLUSIONS: GSEA results suggest that RPE transcripts are preserved or elevated in early AMD, concomitant with loss of endothelial cell marker expression. These results are consistent with the notion that choroidal endothelial cell dropout or dedifferentiation occurs early in the pathogenesis of AMD.

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[Contemporary pharmacogenetic approaches to the treatment of age-related macular degeneration]. [Article in Russian]

[No authors listed]

Abstract: A study on the role of CFH, HTRA and IL-8 gene polymorphism in age-related macular degeneration (AMD) development has been conducted. At the first stage of the study genetic testing was done in 69 patients with exudative AMD and 370 random Moscow citizens without the disease. The goal of the second stage was to determine the influence of gene polymorphism on patient's response to endovitreal ranibizumab treatment. For that, visual acuity and foveal thickness were assessed before and after ranibizumab injections in 120 patients with wet AMD. All patients were genotyped for the genes of interest. The results showed that the presence of homozygous 402H polymorphism in CFH gene, as well as homozygous (-625)A mutation in HTRA1 gene, determines certain clinical presentations. Moreover, visual acuity below 0.1 and presence of 402H, (-625)A and (-251)A alleles in both copies of all three genes (CFH, HTRA and IL-8) are negative predictors of disease severity and antiangiogenic treatment response.

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Diet & lifestyle

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Recent advances in the understanding of the role of zinc in ocular tissues.

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Abstract: Zinc levels are high in ocular tissues and the distribution is non-uniform. Zinc is particularly concentrated in the corneal epithelium and posterior stroma. Zinc is the most abundant trace metal in the retina. Bound-zinc is particularly located in the inner nuclear layer, (e.g. forming part of the structure of zinc finger transcription factors), while loosely-bound zinc is prominent in the retinal pigment epithelium and photoreceptor layers. Loosely-bound zinc ions in the photoreceptors might play a role in the phototransduction cascade and rhodopsin regeneration. Loosely-bound zinc is also found in presynaptic vesicles of photoreceptor cells in the outer plexiform and inner plexiform layers and can be synaptically released to affect both ionotropic and metabotropic receptors and also ion channels to modulate neurotransmission. The correct amount of loosely-bound zinc ions is maintained by regulating the function of zinc transporters, sensors and trafficking/storage proteins (i.e. metallothionein). The retinal homeostasis of zinc is dysregulated in systemic zinc depletion, aging and diseases such as age-related macular degeneration. Manipulation of retinal zinc metabolism in these situations might improve visual function.

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Enhanced text spacing improves reading performance in individuals with macular disease.

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Abstract: The search by many investigators for a solution to the reading problems encountered by individuals with no central vision has been long and, to date, not very fruitful. Most textual manipulations, including font size, have led to only modest gains in reading speed. Previous work on spatial integrative properties of peripheral retina suggests that 'visual crowding' may be a major factor contributing to inefficient reading. Crowding refers to the fact that juxtaposed targets viewed eccentrically may be difficult to identify. The purpose of this study was to assess the combined effects of line spacing and word spacing on the ability of individuals with age-related macular degeneration (ARMD) to read short passages of text that were printed with either high (87.5%) or low contrast (17.5%) letters. Low contrast text was used to avoid potential ceiling effects and to mimic a possible reduction in letter contrast with light scatter from media opacities. For both low and high contrast text, the fastest reading speeds we measured were for passages of text with double line and double word spacing. In comparison with standard single spacing, double word/line spacing increased reading speed by approximately 26% with high contrast text ($p < 0.001$), and by 46% with low contrast text ($p < 0.001$). In addition, double line/word spacing more than halved the number of reading errors obtained with single spaced text. We compare our results with previous reading studies on ARMD patients, and conclude that crowding is detrimental to reading and that its effects can be reduced with enhanced text spacing. Spacing is particularly important when the contrast of the text is reduced, as may occur with intraocular light scatter or poor viewing conditions. We recommend that macular disease patients should employ double line spacing and double-character word spacing to maximize their reading efficiency.

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