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MD Research News

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Drug treatment

Ophthalmology. 2014 Jul 9. pii: S0161-6420(14)00429-1. doi: 10.1016/j.ophtha.2014.05.009. [Epub ahead of print]

Twenty-four-Month Efficacy and Safety of 0.5 mg or 2.0 mg Ranibizumab in Patients with Subfoveal Neovascular Age-Related Macular Degeneration.

Ho AC, Busbee BG, Regillo CD, Wieland MR, Van Everen SA, Li Z, Rubio RG, Lai P; for the HARBOR Study Group.

OBJECTIVE: To evaluate the 24-month efficacy and safety of intravitreal ranibizumab 0.5 mg and 2.0 mg administered monthly or as needed (pro re nata [PRN]) in patients with neovascular age-related macular degeneration (wet AMD).

DESIGN: Twenty-four-month, multicenter, randomized, double-masked, active treatment-controlled phase 3 trial.

PARTICIPANTS: Patients (n = 1098) ≥50 years of age with treatment-naïve subfoveal wet AMD.

METHODS: Patients were randomized to receive intravitreal injections of ranibizumab 0.5 mg or 2.0 mg monthly or PRN after 3 monthly loading doses.

MAIN OUTCOME MEASURES: The primary efficacy end point was the mean change in best-corrected visual acuity (BCVA) from baseline at month 12. Key secondary end points included mean change in BCVA from baseline at month 24, proportion of patients who gained ≥15 letters in BCVA, mean number of ranibizumab injections, and mean change in central foveal thickness from baseline over time by spectral-domain optical coherence tomography. Ocular and systemic safety events also were evaluated through month 24.

RESULTS: At month 24, the mean change from baseline in BCVA was (letters) +9.1 (0.5 mg monthly), +7.9 (0.5 mg PRN), +8.0 (2.0 mg monthly), and +7.6 (2.0 mg PRN). The change in mean BCVA from month 12 to 24 was (letters) -1.0, -0.3, -1.2, and -1.0, respectively. The proportion of patients who gained ≥15 letters from baseline in BCVA at month 24 was 34.5%, 33.1%, 37.6%, and 34.8%, respectively. The mean number of ranibizumab injections through month 24 was 21.4, 13.3, 21.6, and 11.2, respectively; 5.6 and 4.3 mean injections were required in year 2 in the 0.5 mg and 2.0 mg PRN groups, respectively. The average treatment interval in the 0.5 mg PRN group was 9.9 weeks after 3 monthly loading doses, and 93% of these patients did not require monthly dosing. Ocular and systemic safety profiles over 2 years were similar among all 4 treatment groups and were consistent with previous ranibizumab trials in AMD.

CONCLUSIONS: At month 24, mean BCVA improvements were clinically meaningful and similar among all 4 ranibizumab treatment groups. The 0.5 mg PRN group achieved a mean gain of 7.9 letters at month 24 with an average of 13.3 injections (5.6 injections in year 2). No new safety events were identified over 24 months.

PMID: 25015215 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2014 Jul 7. pii: bjophthalmol-2014-305252. doi: 10.1136/bjophthalmol-2014-305252. [Epub ahead of print]

Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD.

Avery RL, Castellarin AA, Steinle NC, Dhoot DS, Pieramici DJ, See R, Couvillion S, Nasir MA, Rabena MD, Le K, Maia M, Visich JE.

BACKGROUND: Data comparing systemic exposure and systemic vascular endothelial growth factor (VEGF) suppression of ranibizumab, bevacizumab and aflibercept following intravitreal injection are lacking.

METHODS: Fifty-six patients with wet age-related macular degeneration received intravitreal ranibizumab (0.5 mg), bevacizumab (1.25 mg), or aflibercept (2.0 mg). Serum pharmacokinetics and plasma free VEGF were evaluated after the first and third injections.

RESULTS: Following the first dose, systemic exposure to aflibercept was 5-, 37-, and 9-fold higher than ranibizumab, whereas, bevacizumab was 9-, 310-, and 35-fold higher than ranibizumab, based on geometric mean ratio of peak and trough concentrations and area under the curve, respectively. The third dose showed accumulation of bevacizumab and aflibercept but not ranibizumab. Aflibercept substantially suppressed plasma free VEGF, with mean levels below lower limit of quantitation (10 pg/mL) as early as 3 h postdose until ≥7 days postdose. Mean free (unbound) VEGF levels with ranibizumab were largely unchanged, with mean trough level of 14.4 pg/mL compared with baseline of 17 pg/mL.

CONCLUSIONS: There are notable differences in systemic pharmacokinetics and pharmacodynamics among anti-VEGF treatments after intravitreal administration. All three agents rapidly moved into the bloodstream, but ranibizumab very quickly cleared, whereas bevacizumab and aflibercept demonstrated greater systemic exposure and produced a marked reduction in plasma free VEGF.

PMID: 25001321 [PubMed - as supplied by publisher]

Retina. 2014 Jul 3. [Epub ahead of print]

INTRAVITREAL RANIBIZUMAB FOR NAIVE EXTRAFOVEAL CHOROIDAL NEOVASCULARIZATION SECONDARY TO AGE-RELATED MACULAR DEGENERATION.

Parodi MB, Iacono P, La Spina C, Iuliano L, Lo Giudice G, Introini U, Bandello F.

PURPOSE: To investigate the effect of intravitreal ranibizumab on extrafoveal choroidal neovascularization secondary to age-related macular degeneration.

METHODS: Eighteen eyes affected by extrafoveal choroidal neovascularization secondary to age-related macular degeneration were prospectively enrolled in this study. After an initial intravitreal ranibizumab, all patients were reevaluated monthly over 12 months of follow-up. Further retreatments were performed on a pro re nata basis, depending on detection of any type of fluid on optical coherence tomography and/or the presence of leakage on fluorescein angiography. Primary outcome measures were mean changes in best-corrected visual acuity and the proportion of eyes gaining at least 15 letters (3 Early Treatment Diabetic Retinopathy Study [ETDRS] lines) at the end of the follow-up. Secondary outcome measures were central

macular thickness variations and changes in choroidal neovascularization size.

RESULTS: Mean best-corrected visual acuity presented a significant improvement during the follow-up period, being 0.3 ± 0.2 logMAR at baseline and 0.2 ± 0.2 logMAR at the 12-month examination (P < 0.001). An improvement of at least 3 EDTRS lines was achieved by 6 eyes (33.3%), whereas 6 patients (33.3%) gained 1 to 2 lines. The mean central macular thickness at baseline was 314 ± 87 μm, changing to 268 ± 65 μm at the 12-month examination (P = 0.003). The mean lesion size was 1.4 ± 1.4 mm and remained stable throughout the follow-up, being 1.8 ± 2.9 mm at 12 months (P = 0.64).

CONCLUSION: Intravitreal ranibizumab administered after a pro re nata regimen with monthly evaluation is a beneficial approach for the management of extrafoveal choroidal neovascularization secondary to age-related macular degeneration over 12 months of follow-up. Further studies are warranted to confirm our preliminary results.

PMID: 24999724 [PubMed - as supplied by publisher]

Retina. 2014 Jul 3. [Epub ahead of print]

RESPONSE TO AFLIBERCEPT AS SECONDARY THERAPY IN PATIENTS WITH PERSISTENT RETINAL EDEMA DUE TO CENTRAL RETINAL VEIN OCCLUSION INITIALLY TREATED WITH BEVACIZUMAB OR RANIBIZUMAB.

Eadie JA, Ip MS, Kulkarni AD.

BACKGROUND: Recent advances have given practitioners options for the treatment of macular edema secondary to central retinal vein occlusion. These options include steroid injections and implants as well as anti-vascular endothelial growth factor medications. However, there is little in the medical literature to guide secondary therapy when an initial treatment strategy is insufficient. The authors present encouraging results from the treatment of six consecutive cases of central retinal vein occlusion treated with aflibercept as a secondary therapy for macular edema refractory to repeated intravitreal bevacizumab or ranibizumab injections.

METHODS: A retrospective review of six consecutive cases of central retinal vein occlusion with persistent macular edema despite regular anti-vascular endothelial growth factor injections that were transitioned to aflibercept was conducted. Optical coherence tomography and visual acuity data were examined.

RESULTS: All six eyes from the six patients included showed either complete or near complete resolution of macular edema with one or two injections of aflibercept. The improvement in edema was accompanied by lasting modest visual gains in three of the six patients and in subjective visual improvement in four of the six patients.

CONCLUSION: The six eyes in this series all responded favorably to aflibercept as a secondary therapy. Although the sample size is too small to draw definitive conclusions, the results are encouraging.

PMID: 24999721 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Jul 7. pii: S0161-6420(14)00426-6. doi: 10.1016/j.ophtha.2014.05.006. [Epub ahead of print]

Intravitreal Aflibercept for Diabetic Macular Edema.

Korobelnik JF, Do DV, Schmidt-Erfurth U, Boyer DS, Holz FG, Heier JS, Midena E, Kaiser PK, Terasaki H, Marcus DM, Nguyen QD, Jaffe GJ, Slakter JS, Simader C, Soo Y, Schmelter T, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Zeitz O, Metzig C, Brown DM.

PURPOSE: A head-to-head comparison was performed between vascular endothelial growth factor blockade and laser for treatment of diabetic macular edema (DME).

DESIGN: Two similarly designed, double-masked, randomized, phase 3 trials, VISTADME and VIVIDDME.

PARTICIPANTS: We included 872 patients (eyes) with type 1 or 2 diabetes mellitus who presented with DME with central involvement.

METHODS: Eyes received either intravitreal aflibercept injection (IAI) 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 initial monthly doses (2q8), or macular laser photocoagulation.

MAIN OUTCOME MEASURES: The primary efficacy endpoint was the change from baseline in best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters at week 52. Secondary efficacy endpoints at week 52 included the proportion of eyes that gained ≥15 letters from baseline and the mean change from baseline in central retinal thickness as determined by optical coherence tomography.

RESULTS: Mean BCVA gains from baseline to week 52 in the IAI 2q4 and 2q8 groups versus the laser group were 12.5 and 10.7 versus 0.2 letters ($P < 0.0001$) in VISTA, and 10.5 and 10.7 versus 1.2 letters ($P < 0.0001$) in VIVID. The corresponding proportions of eyes gaining ≥15 letters were 41.6% and 31.1% versus 7.8% ($P < 0.0001$) in VISTA, and 32.4% and 33.3% versus 9.1% ($P < 0.0001$) in VIVID. Similarly, mean reductions in central retinal thickness were 185.9 and 183.1 versus 73.3 μm ($P < 0.0001$) in VISTA, and 195.0 and 192.4 versus 66.2 μm ($P < 0.0001$) in VIVID. Overall incidences of ocular and nonocular adverse events and serious adverse events, including the Anti-Platelet Trialists' Collaboration-defined arterial thromboembolic events and vascular deaths, were similar across treatment groups.

CONCLUSIONS: At week 52, IAI demonstrated significant superiority in functional and anatomic endpoints over laser, with similar efficacy in the 2q4 and 2q8 groups despite the extended dosing interval in the 2q8 group. In general, IAI was well-tolerated.

PMID: 25012934 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Jul 4. pii: S0161-6420(14)00432-1. doi: 10.1016/j.ophtha.2014.05.012. [Epub ahead of print]

Pharmacokinetics of Ranibizumab after Intravitreal Administration in Patients with Retinal Vein Occlusion or Diabetic Macular Edema.

Zhang Y, Yao Z, Kaila N, Kuebler P, Visich J, Maia M, Tuomi L, Ehrlich JS, Rubio RG, Campochiaro PA.

OBJECTIVE: To describe the systemic pharmacokinetics of ranibizumab after intravitreal administration in patients with retinal vein occlusion (RVO) or diabetic macular edema (DME).

DESIGN: A population approach of nonlinear mixed-effect pharmacokinetics modeling based on serum concentrations of ranibizumab measured at various times after intravitreal administration.

PARTICIPANTS: Patients with RVO (n = 441) and DME (n = 435) from 4 large, randomized, phase 3 clinical trials of monthly ranibizumab intravitreal administration.

METHODS: A 1-compartment pharmacokinetics model with first-order absorption and elimination rate constants previously developed in patients with age-related macular degeneration (AMD) was fitted separately to RVO and DME data. Population pharmacokinetic parameters and interindividual variability were estimated for each model. Baseline covariates were evaluated for potential effects on systemic pharmacokinetics. Model performance was validated using general diagnostic plots and a visual predictive check.

MAIN OUTCOME MEASURES: Ranibizumab disposition was determined in RVO and DME patients and

compared with that previously seen in AMD patients.

RESULTS: The AMD pharmacokinetics model correctly predicted the measured serum ranibizumab concentration data for RVO and DME patients. Most observed data points were within the simulated 90% confidence interval, indicating that systemic ranibizumab concentrations were comparable among AMD, RVO, and DME patients. No disease-related covariates were identified by the population pharmacokinetics analysis.

CONCLUSIONS: The systemic pharmacokinetics of ranibizumab were similar among patients with AMD, RVO, or DME. Disease-related differences and patient demographics, measured in this study, did not lead to variability in ocular elimination or in systemic exposure of ranibizumab after intravitreal administration. In all disease processes tested, ranibizumab exits the eye slowly and then is eliminated rapidly from the circulation, thus minimizing systemic exposure.

PMID: 25001159 [PubMed - as supplied by publisher]

BioDrugs. 2014 Jul 11. [Epub ahead of print]

EXTEND II: An Open-Label Phase III Multicentre Study to Evaluate Efficacy and Safety of Ranibizumab in Chinese Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration.

Zhao J, Li X, Tang S, Xu G, Xu X, Zhang F, Zhang M, Shamsazar J, Pilz S, Nieweg A.

PURPOSE: To evaluate the efficacy and safety of monthly ranibizumab 0.5 mg in Chinese patients with subfoveal choroidal neovascularization (CNV) secondary to neovascular age-related macular degeneration (nAMD).

METHODS: A 12-month open-label single-arm multicenter phase III study that included treatment-naïve (study eye) patients with primary/recurrent subfoveal CNV secondary to AMD. Patients (N = 114) aged ≥50 years with best-corrected visual acuity (BCVA) of 73-24 letters were treated with monthly ranibizumab for 12 months. Main outcomes were mean BCVA change from baseline to month 4 (primary endpoint) and over time to month 12, effects of ranibizumab treatment on retinal structure (months 4 and 12), and safety.

RESULTS: Ranibizumab led to significant improvements in mean BCVA ± standard error (SE) at both months 4 and 12 versus baseline (+9.5 ± 1.10 letters, 95 % confidence interval [CI] 7.3-11.7, and +12.7 ± 1.14 letters, 95 % CI 10.4-14.9, respectively, both P < 0.0001). Ranibizumab prevented loss of vision (≥0 letters BCVA gain) in 91.2 % of patients. Mean central retinal thickness ± SE reduced from baseline to month 12 (-119.9 ± 12.97 µm, 95 % CI -145.59 to -94.20, P < 0.0001). No new safety findings were reported in this study.

CONCLUSION: Ranibizumab administered monthly over 12 months was effective in improving BCVA and was well-tolerated in Chinese nAMD patients.

PMID: 25012926 [PubMed - as supplied by publisher]

Retina. 2014 Jul 9. [Epub ahead of print]

OPTICAL COHERENCE TOMOGRAPHY-BASED RANIBIZUMAB MONOTHERAPY FOR RETINAL ANGIOMATOUS PROLIFERATION IN KOREAN PATIENTS.

Shin JY, Yu HG.

PURPOSE: To evaluate the visual outcome of optical coherence tomography-based ranibizumab monotherapy in Korean patients with retinal angiomatous proliferation and identify prognostic factors of

visual outcome.

METHODS: A prospective single-arm clinical study of 31 retinal angiomatous proliferation patients who underwent 3 consecutive monthly intravitreal ranibizumab injections was conducted. Additional treatment was given based on optical coherence tomography at monthly follow-ups over 24 months.

RESULTS: Best-corrected visual acuity improved from 48.7 ± 19.3 to 56.3 ± 19.1 letters at 24 months (P = 0.010). Total cumulative numbers of injection were 5.5 ± 2.2 and 7.7 ± 3.4 times at 12 and 24 months, respectively. Older age, larger choroidal neovascularization size, and poor initial best-corrected visual acuity were associated with poor visual outcome. Final best-corrected visual acuity was significantly worse with Stage 3 disease (70.4 ± 5.1, 62.3 ± 11.6, 46.2 ± 22.3 letters improved in each stage; P = 0.015). Among factors associated with poor visual outcome, only the stage of retinal angiomatous proliferation remained statistically significant on multiple linear regression analysis (P = 0.006). Although baseline best-corrected visual acuity was similar, Stage 3 patients exhibited limited visual improvement despite anatomical improvement, and more recurrences requiring more injections.

CONCLUSION: Retinal angiomatous proliferation may be successfully managed with ranibizumab monotherapy in Korean patients, with the number of treatments required comparable to other forms of neovascular age-related macular degeneration. However, visual improvement was limited in late-stage RAP.

PMID: 25011025 [PubMed - as supplied by publisher]

Med Sci Monit. 2014 Jul 9;20:1168-75. doi: 10.12659/MSM.890671.

Combination of bevacizumab and bromfenac therapy in age-related macular degeneration: A pilot study.

Wyględowska-Promieńska D, Piotrowska-Gwóźdź A, Piotrowska-Seweryn A, Mazur-Piotrowska G, Rokicki W.

Background: According to recent studies, the newest strategy for the treatment of exudative age-related macular degeneration is to combine anti-VEGF agents with non-steroid anti-inflammatory drugs (NSAIDs) such as nepafenac and bromfenac to decrease the frequency of intravitreal injections. Since most research has focused on ranibizumab, the aim of this study is to evaluate whether an alternative drug such as bevacizumab could lead to similar outcomes.

Material and Methods: The study was conducted on a group of 26 patients who were administered intravitreal bevacizumab and topical bromfenac (study group) and 26 patients with single bevacizumab therapy (control group). Cases that were not qualified for ranibizumab therapy were included in the study group.

Results: The study revealed that the visual acuity and parameters observed in OCT improved more in the study group than in the control group. However, the correlations between the above factors and the frequency of intravitreal injections were statistically significant only in visual acuity.

Conclusions: We recommend the combined therapy of bevacizumab and bromfenac as an alternative and beneficial method of treatment in patients with exudative AMD who do not qualify for ranibizumab therapy. This combined therapy might efficiently reduce the number of intravitreal injections of bevacizumab.

PMID: 25006692 [PubMed - in process]

Pathogenesis

Prog Retin Eye Res. 2014 Jul 3. pii: S1350-9462(14)00039-1. doi: 10.1016/j.preteyeres.2014.06.004. [Epub ahead of print]

Role of crystallins in ocular neuroprotection and axonal regeneration.

Thanos S, Böhm MR, Meyer Zu Hörste M, Prokosch-Willing V, Hennig M, Bauer D, Heiligenhaus A.

Abstract: Neuroprotection is an emerging challenge in ophthalmology due to the particularly exposed location of retinal neurons and to the steadily increasing rate of intraocular surgical and pharmacological treatments applied to various eye diseases. Within few decades neuroprotection has developed from strongly contested approaches to being recognized and introduced as a potentially clinical application. One of the groups of putative substances for neuroprotection comprises αA- and αB-crystallins, which are types of heat-shock proteins and are considered to be molecular chaperones. The β/γ-crystallins form their own superfamily and are characterized as proteins with a distinct structure containing four Greek key motifs. Besides being abundant in the ocular lens, crystallins are also expressed in both the developing and mature retina. Crystallins are dramatically up-regulated in numerous retinal pathologies, including mechanical injury, ischemic insults, age-related macular degeneration, uveoretinitis, and diabetic retinopathy. Crystallins of the α family are thought to play a crucial role in retinal neuron survival and inflammation. Crystallins of the β/γ superfamily are also small proteins with a possible emerging role in retinal tissue remodeling and repair. One of the typical retinal diseases associated with crystallins is the experimental glaucomatous neuropathy that is characterized by their expression. Another typical retinal disease is the atrophy that occurs after mechanical injury to the optic nerve, which is associated with the need to regrow retinal axons. We have shown in regenerative models in vivo and in vitro that βB2-crystallin actively supports the regenerative growth of cut retinal axons, thereby offering targets for neuroprotective and regenerative treatments. In this review we discuss the discovery that βB2-crystallin is clearly up-regulated in the regenerating retina in vitro. βB2-Crystallin is produced and secreted during axon elongation, while β/γ-crystallins promote axon growth both in vivo and in vitro by acting either directly by uptake into cells, or indirectly by enhancing the production of ciliary neurotrophic factor from astrocytes to synergistically promote axon regrowth. We also discuss methods to induce the continuous production of crystallins at the site of injury and repair based on the use of transfected neural progenitor cells. This review ultimately leads to the conclusion that the postinjury fate of neurons cannot be seen merely as inevitable, but instead should be regarded as a challenge to shaping the neuroprotective and regenerative conditions that promote cell survival and axon repair.

PMID: 24998680 [PubMed - as supplied by publisher]

J Zhejiang Univ Sci B. 2014 Jul;15(7):661-9. doi: 10.1631/jzus.B1300194.

Effects of organic solvents on two retinal pigment epithelial lipofuscin fluorophores, A2E and all-trans-retinal dimer.

Jin QX, Dong XR, Chen JM, Yao K, Wu YL.

Abstract: Gene and drug therapies are being developed to alleviate vision loss in patients with Stargardt's disease and age-related macular degeneration (AMD). To evaluate the therapeutic effects of these treatments, organic solvents are routinely used to extract and quantify bisretinoid lipofuscin constituents, such as N-retinylidene-N-retinyl-ethanolamine (A2E) and all-trans-retinal dimer (ATR-dimer). By high-performance liquid chromatography (HPLC), we found that A2E and ATR-dimer were both altered by tetrahydrofuran (THF) and chloroform, but were stable in dimethyl sulfoxide (DMSO) or methanol (MeOH). In addition, cyclohexane and ethanol (EtOH) did not alter ATR-dimer, whereas an alteration of A2E occurred in EtOH. On the basis of these findings, we designed processes II-IV, generated by modifications of process I, a routine method to measure bisretinoid compounds in vivo. Extra amounts of either ATR-

dimer or A2E in mouse eyecups were released by processes II-IV versus process I. Efforts to clarify the effects of organic solvents on lipofuscin pigments are important because such studies can guide the handling of these fluorophores in related experiments.

PMID: 25001225 [PubMed - in process]

Epidemiology

Exp Ther Med. 2014 Aug;8(2):371-376. Epub 2014 May 26.

A population-based study of macular choroidal neovascularization using optical coherence tomography in Eastern China.

Zhao J, Hu J, Lu H, Yang L.

Abstract: The aim of the present study was to investigate the pathomorphological and functional variations of choroidal neovascularization (CNV) in age-related macular degeneration (AMD) in a Chinese population using optical coherence tomography (OCT). This population-based study enrolled 59 patients (age, >45 years; eyes, 70) with early and intermediate-stage AMD from Youyi Road Community, Baoshan District, Shanghai, China. Comprehensive standardized ophthalmic examinations included visual acuity, anterior segment analysis using a slit lamp, dilated fundus evaluation by direct ophthalmoscopy, 90D handheld lens analysis, fundus photography, fundus fluorescein angiography (FFA) and fast optic disk scans using OCT. The macular CNV characteristic profiles in early and intermediate-stage AMD were determined by OCT. Data were obtained on the first visit and the follow-up period ranged between 6 and 24 months, where FFA and OCT outcomes of early and intermediate-stage AMD patients were analyzed. Three profiles of early and intermediate-stage AMD were created from the OCT and FFA results, each with a different prognosis. Firstly, drusens with unclear boundaries and evident pigment proliferation, as well as hypofluorescence around the drusens, was observed via FFA. A slight small arch field located in the retinal pigment epithelium (RPE)/choriocapillary layer (CCL) was shown on OCT scans, indicating exudative AMD. Secondly, RPE detachments of >1 pupillary distance, without CNV in the macular area, indicated geographic chorioretinitis atrophy. Finally, drusens with clear boundaries and few pigment proliferations and no certain surrounding fluorescence was observed via FFA, while a clear RPE/CCL band on the OCT scans indicated slow progress. The results of the present study demonstrated that combined OCT and FFA was the most efficient method for identifying CNV and diagnosing AMD. If the two techniques are not available concurrently, then OCT is a safer and more reliable technique to follow-up early and intermediate-stage AMD patients.

PMID: 25009585 [PubMed]

JAMA Ophthalmol. 2014 Jul 1;132(7):906-7. doi: 10.1001/jamaophthalmol.2014.1785.

Age-related macular degeneration and early diagnosis of dementia.

Al-Salem KM, Schaal S.

PMID: 25010180 [PubMed - in process]

JAMA Ophthalmol. 2014 Jul 1;132(7):907. doi: 10.1001/jamaophthalmol.2014.1797.

Age-related macular degeneration and early diagnosis of dementia-reply.

Keenan TD, Goldacre R, Goldacre MJ.

PMID: 25010182 [PubMed - in process]

Genetics

Curr Opin Ophthalmol. 2014 Jul 10. [Epub ahead of print]

Genome-wide association study success in ophthalmology.

Mackey DA, Hewitt AW.

PURPOSE OF REVIEW: Much progress in our understanding of the genetic profile of many ophthalmic diseases has been made over the last decade. Identification of novel gene associations allows insight into the mechanisms of disease and potentially enables the identification of individuals at increased risk, as well as facilitating the development of new treatments. We highlight key recent discoveries using the genome-wide association study design.

RECENT FINDINGS: Over the last 2 years, we have seen major international collaborations successfully conduct genome-wide association study to identify genetic pathways associated with eye diseases, such as myopia, age-related macular degeneration and glaucoma. Similarly other studies have identified and confirmed genes associated with ocular biometry or disease-specific endophenotypes.

SUMMARY: Our understanding of the genetic architecture of common eye diseases, such as myopia, age-related macular degeneration and glaucoma, is rapidly expanding. With reducing costs of next-generation sequencing, we expect a transition to large-scale interrogation at the whole exome and genome level, which will enable the identification of rare variants which confer a level of sensitivity and specificity to predict risk that will allow us to further understand, predict and intervene in genetic-based eye diseases.

PMID: 25014751 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Jul 11. pii: IOVS-14-14494. doi: 10.1167/iovs.14-14494. [Epub ahead of print]

Set-based joint test of interaction between SNPs in the VEGF pathway and exogenous estrogen finds association with age-related macular degeneration.

Courtenay MD, Cade W, Schwartz SG, Kovach JL, Agarwal A, Wang G, Haines JL, Pericak-Vance MA, Scott WK.

Purpose: Age-Related Macular Degeneration (AMD) is the leading cause of irreversible visual loss in developed countries. Its etiology includes genetic and environmental factors. Although VEGFA variants are associated with AMD, the joint action of variants within the VEGF pathway and their interaction with non-genetic factors has not been investigated.

Methods: Affymetrix 6.0 chipsets were used to genotype 668,238 SNPs in 1,207 AMD cases and 686 controls. Environmental exposures were collected by questionnaire. A set-based test was conducted using the chi-square statistic at each SNP derived from Kraft's 2df joint test. Pathway and gene-based test statistics were calculated as the mean of all independent SNP statistics. Phenotype labels were permuted 10,000 times to generate an empirical p-value.

Results: While a main effect of the VEGF pathway was not identified, the pathway was associated with neovascular AMD in women when accounting for birth control pill (BCP) use (P= 0.017). Analysis of VEGF's subpathways found that SNPs in the Proliferation subpathway were associated with neovascular AMD (P=0.029) when accounting for BCP use. Nominally significant genes within this subpathway were also observed. Stratification by BCP use revealed novel significant genetic effects in women who had taken BCPs.

Conclusions: These results illustrate that some AMD genetic risk factors may only be revealed when considering complex relationships among risk factors. This shows the utility of exploring pathways of

previously associated genes to find novel effects. It also demonstrates the importance of incorporating environmental exposures in tests of genetic association at the SNP, gene, or pathway level.

PMID: 25015356 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2014 Jul 10. doi: 10.1001/jamaophthalmol.2014.1752. [Epub ahead of print]

The Relationship Between Hepatic Lipase Gene Variant and Advanced Age-Related Macular Degeneration: A Meta-analysis.

Lou LX, Hu KM, Jin K, Zhang SZ, Ye J.

Importance: To date, no consistency exists across studies that have evaluated the relationship between hepatic lipase gene (LIPC) rs10468017 variant and advanced age-related macular degeneration (AMD).

Objective: To summarize all relevant evidence for a relationship between LIPC variant and advanced AMD.

Data Sources: The PubMed and Embase databases were searched for studies potentially eligible in any language published up to September 15, 2013.

Study Selection: Case-control studies of 2 or more comparison groups that included patients with advanced AMD (choroidal neovascularization or geographic atrophy).

Data Extraction and Synthesis: Allele frequencies and genotype distributions of rs10468017 variant.

Main Outcomes and Measures: Summary odds ratios (ORs) and 95% CIs were estimated under different genetic models using meta-analytic methods. A stratified analysis by advanced AMD subtypes and race/ethnicity was performed, as well as a sensitivity analysis.

Results: Data from 10 case-control studies were included in the meta-analysis. The rs10468017 variant (C→T) showed significant summary ORs of 0.81 (95% CI, 0.75-0.88), 0.83 (95% CI, 0.70-0.98), and 0.60 (95% CI, 0.44-0.81) under the allelic (T vs C), heterozygous (TC vs CC), and homozygous (TT vs CC) models, respectively. Carrying at least 1 copy of the T allele decreased the risk of choroidal neovascularization and geographic atrophy by 20% (OR, 0.80; 95% CI, 0.74-0.87) and 29% (OR, 0.71; 95% CI, 0.59-0.86), respectively. The pooled OR for white race/ethnicity under an allelic model was 0.80 (95% CI, 0.74-0.87). The sensitivity analysis indicated the robustness of our findings, and no evidence of publication bias was observed in our meta-analysis.

Conclusions and Relevance: Our meta-analysis indicates that LIPC rs10468017 variant is associated with a reduced risk of advanced AMD. This finding may lead to insights regarding the pathogenesis, prevention, and treatment of AMD.

PMID: 25010633 [PubMed - as supplied by publisher]

Optom Vis Sci. 2014 Jul 10. [Epub ahead of print]

Cone Structure in Subjects with Known Genetic Relative Risk for AMD.

Land ME, Cooper RF, Young J, Berg E, Kitchner T, Xiang Q, Szabo A, Ivacic LC, Stepien KE, Page CD, Carroll J, Connor T Jr, Brilliant M.

PURPOSE: Utilize high-resolution imaging to examine retinal anatomy in patients with known genetic relative risk (RR) for developing age-related macular degeneration (AMD).

METHODS: Forty asymptomatic subjects were recruited (9 men, 31 women; age range, 51 to 69 years; mean age, 61.4 years). Comprehensive eye examination, fundus photography, and high-resolution retinal

imaging using spectral domain optical coherence tomography and adaptive optics were performed on each patient. Genetic RR scores were developed using an age-independent algorithm. Adaptive optics scanning light ophthalmoscope images were acquired in the macula extending to 10 degrees temporal and superior from fixation and were used to calculate cone density in up to 35 locations for each subject.

RESULTS: Relative risk was not significantly predictive of fundus grade ($p = 0.98$). Only patients with a high RR displayed drusen on Cirrus or Bioptigen OCT. Compared to an eye with a grade of 0, an eye with a fundus grade equal to or greater than 1 had a 12% decrease in density ($p < 0.0001$) and a 5% increase in spacing ($p = 0.0014$). No association between genetic RR and either cone density ($p = 0.435$) or spacing ($p = 0.538$) was found. Three distinct adaptive optics scanning light ophthalmoscope phenotypical variations of photoreceptor appearance were noted in patients with grade 1 to 3 fundi. These included variable reflectivity of photoreceptors, decreased waveguiding, and altered photoreceptor mosaic overlying drusen.

CONCLUSIONS: Our data demonstrate the potential of multimodal assessment in the understanding of early anatomical changes associated with AMD. Adaptive optics scanning light ophthalmoscope imaging reveals a decrease in photoreceptor density and increased spacing in patients with grade 1 to 3 fundi, as well as a spectrum of photoreceptor changes, ranging from variability in reflectivity to decreased density. Future longitudinal studies are needed in genetically characterized subjects to assess the significance of these findings with respect to the development and progression of AMD.

PMID: 25014365 [PubMed - as supplied by publisher]

Diet & lifestyle

Aust Fam Physician. 2014 Jul;43(7):447-50.

Eye care in the elderly.

Green C, Goodfellow J, Kubie J.

BACKGROUND: Eye disease and visual impairment are common in the elderly and are associated with social and functional decline, the need to access community support services, depression, falls, nursing home placement and increased mortality.

OBJECTIVE: To provide guidance for general practitioners in the detection and recommended management of the most important eye conditions in the elderly in Australia: refractive error, cataract, diabetic retinopathy, age-related macular degeneration and glaucoma.

DISCUSSION: Timely detection and treatment of eye disease can greatly reduce its morbidity. Elderly patients should be encouraged to undergo eye testing every 2 years. Health professionals, including general practitioners, optometrists and ophthalmologists should work collaboratively to ensure patients have access to appropriate disease detection and treatment.

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Inverse Relationship between High Blood 25-Hydroxyvitamin D and Late Stage of Age-Related Macular Degeneration in a Representative Korean Population.

Kim EC, Han K, Jee D.

Purpose: To investigate the association of 25-hydroxyvitamin D with AMD.

Methods: A population-based, cross-sectional study using a nationwide, systemic stratified, multistage clustered sampling method involved a total of 17,045 subjects aged >40 years who participated in the Korean National Health and Nutrition Examination Survey 2008-2012. All participants underwent standardized interviews, evaluation of blood 25-hydroxyvitamin D levels, and comprehensive ophthalmic examinations. A 45° digital fundus photograph of both eyes was taken under physiologic mydriasis. All fundus photographs were graded using the international classification and grading system.

Results: Blood 25-hydroxyvitamin D levels were 17.5 ng/mL in women and 20.0 ng/mL in men. After adjusting for potential confounders including age, sex, smoking status, hypertension, heart problems, stroke, and sunlight exposure time, the odds ratio (OR) for late AMD significantly decreased in the highest blood 25-hydroxyvitamin D quintile (OR, 0.32; 95% confidence interval [CI], 0.12-0.81; P for trend =0.018) compared with the lowest quintile in men, but not in women. Early AMD was not associated with blood 25-hydroxyvitamin D levels in either sex.

Conclusions: High level of blood 25-hydroxyvitamin D was inversely associated with late AMD in men but not women. Considering anti-angiogenic and anti-fibrotic action of vitamin D, association between two variables warrants further studies.

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Size or spacing: Which limits letter recognition in people with age-related macular degeneration?

Chung ST.

Abstract: Recent evidence suggests a double dissociation of size and spacing limit on letter recognition - it is limited by size in the fovea and critical spacing in the normal periphery. Here, we evaluated whether size or spacing limits letter recognition in people with age-related macular degeneration (AMD) who must use their peripheral vision. We measured the size threshold for recognizing lowercase letters presented alone, or flanked by two letters at various center-to-center nominal letter spacings (multiples of letter size) for 11 observers with AMD. For comparison, similar measurements were obtained at 5 and 10° eccentricity in the nasal and lower visual fields in three older adults with normal vision. Single-letter size thresholds were worse for observers with AMD than at comparable retinal locations in the normal periphery. For flanked letters, size threshold improved with larger nominal spacing up to the critical spacing, beyond which size threshold was unaffected by the flankers. Seven AMD observers had a nominal critical spacing between 1.25× and 1.80×, values close to those in the normal fovea, suggesting that their letter recognition is size-limited; two had a nominal critical spacing of 3-4×, values close to those in the normal periphery, implying that their letter recognition is limited by spacing; and another two had a nominal critical spacing of ~2.3×, implying that their letter recognition is limited by both size and spacing. The wide range of nominal critical spacings observed in our AMD observers may reflect the degree of completeness of their adaptation process to vision loss.

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JAMA Ophthalmol. 2014 Jul 1;132(7):904. doi: 10.1001/jamaophthalmol.2014.1768.

Experimental design issue for assessment of carotenoids lutein and zeaxanthin in age-related eye disease study 2 formulation for age-related macular degeneration.

Benke KK, Benke KE.

PMID: 25010177 [PubMed - in process]

JAMA Ophthalmol. 2014 Jul 1;132(7):904-5. doi: 10.1001/jamaophthalmol.2014.1783.

Experimental design issue for assessment of carotenoids lutein and zeaxanthin in age-related eye disease study 2 formulation for age-related macular degeneration-reply.

Chew EY, Clemons TE.

PMID: 25010178 [PubMed - in process]