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MD Research News

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Drug treatment

Retina. 2016 May;36(5):881-8.

PIGMENT EPITHELIAL DETACHMENT RESPONSE TO AFLIBERCEPT IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION REFRACTORY TO RANIBIZUMAB: Time Course and Drug Effects.

de Massougnes S, Dirani A, Ambresin A, Decugis D, Marchionno L, Mantel I.

PURPOSE: To investigate the time course of pigment epithelium detachment (PED) height and its change after anti-vascular endothelial growth factor switch from ranibizumab to aflibercept in neovascular age-related macular degeneration.

METHODS: This retrospective study included 60 eyes of 50 consecutive patients with neovascular age-related macular degeneration who showed refractory intraretinal or subretinal fluid (≥9 months) despite monthly ranibizumab treatment and an associated PED (height ≥150 μm). The treatment was switched to aflibercept, and patients were followed-up for at least 9 months. Data on the height and type of PED, exudative fluid, and best-corrected visual acuity were collected at four different time points (two before and two after the drug switch).

RESULTS: The maximal PED height was significantly decreased over time, both under ranibizumab and aflibercept treatment. However, the reduction was significantly greater during the 3 months after the switch to aflibercept, due to two outliers. Visual acuity remained stable. Complete resolution of intraretinal or subretinal fluid was observed in 9 cases (15%) at 3 months after switch, allowing for treatment interval extension.

CONCLUSION: Maximal PED height continuously decreased over time. Switching the intravitreal anti-vascular endothelial growth factor medication from ranibizumab to aflibercept had a significantly stronger short-term effect on PED height reduction, without changes in visual acuity.

PMID: 27115852 [PubMed - in process]

Klin Monbl Augenheilkd. 2016 Apr 28. [Epub ahead of print]

[Switching Therapy from Ranibizumab and/or Bevacizumab to Aflibercept in Neovascular Age-Related Macular Degeneration (AMD): One-Year Results]. [Article in German]

Pfau M, Fassnacht-Riederle HM, Freiberg FJ, Wons JB, Wirth M, Becker MD, Michels S.

Background: The presented study is a retrospective evaluation of switching therapy from ranibizumab and/or bevacizumab to aflibercept in neovascular age-related macular degeneration in patients who had previously given an insufficient response to therapy with ranibizumab and/or bevacizumab. Patients and

Methods: 96 eyes with neovascular age-related macular degeneration (AMD) were included, which had been pretreated with ranibizumab and/or bevacizumab (T&E), but had responded insufficiently. An injection interval of less than six weeks or permanently persisting intra- and/or subretinal fluid or persistent pigment epithelial detachments (PED) were defined as an insufficient response. The patients were followed for 12 months after switching therapy to aflibercept. The change in central retinal thickness (CRT) was defined as the primary endpoint. Other endpoints were the axial height of PEDs and the injection interval.

Results: The primary endpoint, the average CRT, was significantly decreased twelve months after switching therapy to aflibercept (Wilcoxon Nemenyi-McDonald-Thompson post-hoc analysis - 31.36 µm; SD ± 70.64 µm; $p < 0.001$). Another morphological endpoint, the average axial height of PEDs, also decreased significantly (- 34.10 µm; SD ± 91.90 µm, $p < 0.001$) from 207.82 µm (SD ± 148.12 µm) at baseline to 173.72 µm (SD ± 132.30 µm) at month 12. Moreover, the average injection interval increased significantly ($p < 0.001$; Friedman test) from 1.30 months (SD ± 0.19 months) before switching therapy to 1.67 months (SD ± 0.19 months) at month 12 after switching therapy to aflibercept. However, the best corrected visual acuity (BCVA) as a functional endpoint did not significantly improve (+ 0.36 ETDRS letters = 0.0972 p; SD ± 16.94 ETDRS letters).

Conclusion: In patients with neovascular AMD, who had initially exhibited an inadequate response to ranibizumab and/or bevacizumab, switching therapy to aflibercept improves clinical outcome measures. Besides morphological improvements, such as the decrease of the CRT and the axial height of PEDs, the average injection interval was prolonged. However, visual acuity did not improve.

PMID: 27123887 [PubMed - as supplied by publisher]

Klin Monbl Augenheilkd. 2016 Apr;233(4):471-474. Epub 2016 Apr 26.

Long-term Results of Intravitreal Anti-VEGF Injections in Wet AMD: A Meta-Analysis.

Gerding H.

Background: Although intravitreal anti-VEGF medications are widely used in age-related macular degeneration, no systematic data analysis is available on the long-term prognosis of this relatively new therapeutic approach.

Material and Methods: A meta-analysis was performed on available Medline literature. 13 relevant clinical studies (14 case series) could be identified, covering 10 247 treated eyes. The majority of available reports originate from single centre retrospective real-life environments.

Results: The mean improvement in average visual gain was 0.9 ± 0.5 (mean ± 1 standard deviation, median; 0.8 lines) at year 1, 1.2 ± 1.1 (median: 1.1) letters at year 2, 0.7 ± 1.0 (median: 0.7) letters at year 3, and 0.2 ± 0.8 (median: 0.5), 0.4 ± 0.4 (median: 0.5) at years 4 and 5. The drop-out rates in these studies was relatively high. At the end of year 3, the average percentage of observed eyes was 44.3 ± 18.4 % (mean ± 1 standard deviation), at the end of year 4 23.5 ± 23.9 % and after years 6 and 7 below 10 % (8.2 and 7.9 %). The mean treatment frequency of injections in all available studies was highest in year 1 (6.4 ± 1.2, 6.1 - mean ± SD; median), followed by relatively consistent mean values of 4.1 and 5.1 (year (Y)2: 4.4, Y3: 4.3, Y4: 4.7, Y5: 4.1, Y6: 5.1, Y7: 4.7) injections per year.

Conclusions: The results of this meta-analysis clearly indicate that intravitreal anti-VEGF injection therapy is capable of maintaining visual acuity on a long-term basis of at least 4-5 years.

PMID: 27116511 [PubMed - as supplied by publisher]

Klin Monbl Augenheilkd. 2016 Apr;233(4):465-470. Epub 2016 Apr 26.

Effect of Risk Alleles in CFH, C3, and VEGFA on the Response to Intravitreal Bevacizumab in Tunisian Patients with Neovascular Age-related Macular Degeneration.

Habibi I, Kort F, Sfar I, Chebil A, Bouraoui R, Ben Abdallah T, Gorgi Y, El Matri L.

Purpose. The aim of this pharmacogenetic study was to evaluate the impact of high-risk alleles in factor H, factor C3 and vascular endothelial growth factor (VEGF) on the response to intravitreal bevacizumab in patients with neovascular age-related macular degeneration (AMD) in a Tunisian population.

Methods. Ninety patients with active neovascular AMD treated with intravitreal bevacizumab injections were enrolled in the study. Treatment response was evaluated by comparing BCVA at baseline and at 12 months. Patients were classified into either "poor responders" (PR) or "good responders" (GR). Single nucleotide polymorphism (SNP) genotyping was performed for rs1061170 in FH, rs2230199 in C3 andrs699947, rs2010963 and rs3025039 in VEGF. The association between genotype and visual response at 12 months was assessed.

Results. Seventy-seven participants were assigned to the GR group and 13 to the PR group. No correlation was found between FH, C3 and VEGF variant alleles and treatment response. However, haplotype analysis of rs699947 ((- 2578) C/A), rs2010963 ((+ 405) C/G) and rs3025039 ((+ 936) C/T) SNPs revealed that the AGT haplotype was associated with a poor response at 12months (p = 0.048). No association was found between treatment response and the cumulative effect of all high-risk alleles of C3, FH and VEGF. All three types of CNV were found in both groups at a comparable frequency.

Conclusions. The VEGF haplotype TGA could be used as a marker for poor visual prognosis in Tunisian patients with neovascular AMD treated with bevacizumab.

PMID: 27116510 [PubMed - as supplied by publisher]

Adv Ther. 2016 Apr 26. [Epub ahead of print]

Guidelines for the Management of Wet Age-Related Macular Degeneration: Recommendations from a Panel of Greek Experts.

Androudi S, Dastiridou A, Pharmakakis N, Stefaniotou M, Kalogeropoulos C, Symeonidis C, Charonis A, Tsilimbaris M.

PURPOSE: To propose guidelines for the management of patients with wet age-related macular degeneration (wAMD), taking into account the results of large multicenter studies and clinical experience of retina experts.

METHOD: A team of retina experts developed a consensus paper after three consecutive meetings. The group was focused on guidelines to help clinical decision-making around the definition of successful treatment and the definition of non-response to therapy.

RESULTS: Parameters suggestive of a successful response to treatments included: any gain in best corrected visual acuity (BCVA) or vision loss that is less than 5-10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, reduction of central retinal thickness, partial or complete absorption of subretinal fluid (SRF), reduction of intraretinal fluid, reduction of pigment epithelial detachment or restoration of the anatomy of outer retinal layers. Non-response to current treatment was considered in the case of loss of BCVA greater than 10 ETDRS letters, increased retinal edema or increase of SRF as evidenced by optical coherence tomography or new bleeding in biomicroscopy.

CONCLUSION: The introduction of anti-VEGF agents revolutionized the treatment of wAMD. Given the complexity of the disease, the emerging new agents and the difference of cases recruited in clinical trials

compared to those appearing in every-day practice, it is essential to individualize treatment options taking into account the results of clinical trials.

PMID: 27116423 [PubMed - as supplied by publisher]

Dan Med J. 2016 May;63(5).

Non-physician delivered intravitreal injection service is feasible and safe - a systematic review.

Rasul A, Subhi Y, Sørensen TL, Munch IC.

INTRODUCTION: Non-physicians such as nurses are trained to give injections into the vitreous body of the eye to meet the increasing demand for intravitreal therapy with vascular endothelial growth factor inhibitors against common eye diseases, e.g. age-related macular degeneration and diabetic retinopathy. We systematically reviewed the existing literature to provide an overview of the experiences in this transformational process.

METHODS: We searched for literature on 22 September 2015 using PubMed, Embase, the Cochrane Library, CINAHL and the Web of Science. Eligible studies had to address any outcome based on non-physician delivered intravitreal therapy regardless of the study design. Being non-physician was defined as the injecting personnel not being a physician, but no further restrictions were made.

RESULTS: Five studies were included with a total of 31,303 injections having been performed by 16 nurses. The studies found that having nurses perform the intravitreal injections produced to a short-term capacity improvement and liberated physicians for other clinical work. Training was provided through courses and direct supervision. The rates of endophthalmitis were 0-0.40‰, which is comparable to reported rates when the intravitreal therapy is given by physicians.

CONCLUSION: Non-physician delivered intravitreal therapy seems feasible and safe.

PMID: 27127016 [PubMed - in process]

Lasers Surg Med. 2016 Apr 25. [Epub ahead of print]

The short-term effects of aflibercept on the size of choroidal neovascularization lesion in treatment-resistant neovascular age-related macular degeneration as determined by spectral-domain optical coherence tomography.

Abri Aghdam K, Seidensticker F, Pielen A, Framme C, Junker B.

BACKGROUND AND OBJECTIVES: To evaluate the changes in the size of choroidal neovascularization (CNV) lesion using spectral domain-optical coherence tomography (SD-OCT) in patients with treatment-resistant neovascular age-related macular degeneration (AMD) who were switched from ranibizumab to aflibercept.

MATERIALS AND METHODS: In this prospective case-series, 33 eyes of 30 patients with treatment-resistant neovascular AMD were included. Treatment-resistant neovascular AMD was defined as choriodal neovascularization secondary to AMD determined by subretinal fluid and/or intraretinal fluid/cysts after more than 6 months of monthly ranibizumab therapy. Enrolled eyes were received intravitreal aflibercept injections at weeks 0, 4, and 8. Maximum area of CNV lesion in the cross-sectional area in the B-scan was measured using Heidelberg Eye Explorer software. The same cross-sectional sections containing maximum area of CNV lesion were used during the follow-up. CNV subtypes were determined based on fluorescein angiography images prior to ranibizumab therapy. Main outcome measures were changes in best-corrected visual acuity (BCVA), central subfield thickness (CST), and area of CNV lesion.

RESULTS: There were five classic (15%), seven minimally classic (21%), and 21 occult subtypes of CNV (64%). Four weeks after the third injection, BCVA improvement and reduction of the retinal thickness in nine standard ETDRS subfields were significant (both $P < 0.001$). Regarding and regardless of CNV subtypes, mean area of CNV lesion decreased significantly at final visit. Overall, a dry macula was achieved in 21 eyes (64%) and 12 eyes (36%) showed decreased or unchanged edema.

CONCLUSIONS: Switching to aflibercept seems to result in reduction of CNV lesion area in short-term follow-up of patients with treatment-resistant neovascular AMD. Lasers Surg. Med. © 2016 Wiley Periodicals, Inc.

PMID: 27111455 [PubMed - as supplied by publisher]

R I Med J (2013). 2016 May 2;99(5):15-7.

Cost and Selection of Ophthalmic Anti-Vascular Endothelial Growth Factor Agents.

Li E, Greenberg PB, Voruganti I, Krzystolik MG.

Abstract: Anti-vascular endothelial growth factor (anti-VEGF) drugs - ranibizumab, aflibercept, and off-label bevacizumab - are vital to the treatment of common retinal diseases, including exudative age-related macular degeneration (AMD), diabetic macular edema (DME), and macular edema (ME) associated with retinal vein occlusion (RVO). Given the high prevalence of AMD and retinal vascular diseases, anti-VEGF agents represent a large cost burden to the United States (US) healthcare system. Although ranibizumab and aflibercept are 30-fold more expensive per injection than bevacizumab, the two more costly medications are commonly used in the US, even though all three have been shown to be effective and safe for treatment of these retinal diseases. We investigated the availability and content of professional ophthalmic guidelines on cost consideration in the selection of anti-VEGF agents. We found that current professional guidelines were limited in availability and lacked specific guidance on cost-based anti-VEGF drug selection. This represents a missed opportunity to encourage the practice of value-based medicine. [Full article available at http://rimed.org/rimedicaljournal-2016-05.asp, free with no login].

PMID: 27128510 [PubMed - in process]

Klin Monbl Augenheilkd. 2016 Apr 30. [Epub ahead of print]

[Comparison of Functional and Morphological Outcome after Aflibercept or Ranibizumab in Chronic Recurrent Neovascular Age-Related Macular Degeneration]. [Article in German]

Hoffmann AE, Maier M, Lohmann CP, Feucht N.

Background: To assess functional and morphological outcomes in patients with chronic recurrent neovascular age-related macular degeneration (nAMD) previously treated with ranibizumab, who were either switched from ranibizumab to aflibercept or received further ranibizumab injections.

Methods: Retrospective analysis of eyes with recurrent nAMD previously treated with ranibizumab. On recurrence of the macular oedema, patients had received either 3 injections of aflibercept (2.0 mg) or ranibizumab (0.5 mg) at 4 week intervals. Patients were examined before the first injection and four weeks after the last injection. The main outcome measures included change in visual acuity (VA) in logMAR, subfoveal central retinal thickness (CRT), subretinal fluid (SRF) and height of pigment epithelial detachment (PED height), as well as the maximum height of macular subretinal fluid (SRF max) and of macular pigment epithelial detachment (PED height max) in spectral-domain optical coherence tomography (OCT). Changes in VA and OCT were compared between the two groups to investigate differences in the therapeutic effects of aflibercept and ranibizumab.

Results: 60 eyes of 55 patients were included. The aflibercept group (n = 30) and the ranibizumab group (n = 30) showed no statistically significant differences in mean age (p = 0.813), number of prior injections of ranibizumab (p = 0.127) or time since last injection (p = 0.523). Mean VA logMAR improved in both groups, though only in the ranibizumab group was the difference significant (0.50 ± 0.33 to 0.44 ± 0.29 logMAR; p = 0.013; Table 1). CRT decreased in the aflibercept (p = 0.133) and ranibizumab groups (p = 0.043). PED height was reduced in both groups (aflibercept p = 0.068; ranibizumab p = 0.241). SRF, SRF max and PED height max showed statistically significant decreases in both groups. Comparison of the aflibercept and the ranibizumab groups showed no statistically significant differences between the two groups in change in VA logMAR (p = 0.680), CRT (p = 0.882), SRF (p = 0.871), PED height (p = 0.524), SRF max (p = 0.940) or PED height max (p = 0.762).

Conclusions: Aflibercept and ranibizumab were similarly effective in improving visual acuity and morphological parameters of patients with recurrent nAMD after four months. There were no statistically significant differences in the therapeutic effects of the two drugs.

PMID: 27130974 [PubMed - as supplied by publisher]

Mol Vis. 2016 Apr 2;22:294-310. eCollection 2016.

Repurposing an orally available drug for the treatment of geographic atrophy.

Ahmed CM, Biswal MR, Li H, Han P, Ildefonso CJ, Lewin AS.

PURPOSE: Chronic oxidative stress and subacute inflammation have been implicated as causes of age-related macular degeneration (AMD). In this study, we tested whether an orally available 5-OH-tryptamine (5HT) 1a receptor agonist, xaliproden, could protect against retinal pigment epithelium (RPE) cell damage in culture and in a mouse model of geographic atrophy.

METHODS: Paraquat was used to create mitochondrial oxidative stress in ARPE-19 cells, and tumor necrosis factor-α (TNF-α) was used to stimulate the production of inflammatory cytokines in these cells. The production of antioxidant proteins, metallothionein, and inflammatory cytokines was assayed with quantitative real-time PCR. Cell survival was analyzed with microscopy and a cell titer assay. Integrity of the RPE monolayer was determined by measuring the transepithelial electrical resistance (TEER) and with immunocytochemistry with zona occludens protein 1 (ZO-1) antibody. RPE atrophy was studied in mice deleted for Sod2 (the gene for mitochondrial superoxide dismutase) specifically in the RPE. The mice were treated orally with daily doses of xaliproden at 0.5 and 3 mg/kg for 4 months. The retinal structure was analyzed with spectral domain optical coherence tomography (SD-OCT) and with light and electron microscopy. Retinal function was assessed with full-field electroretinography (ERG) and with optokinetic measurements.

RESULTS: Xaliproden led to a dose-dependent increase in cell survival following treatment with paraquat. Synthesis of the antioxidant response genes NqO1, GSTM1, CAT, HO-1, and Nrf2 was increased in response to the drug, as was the zinc chaperone metallothionein. Treatment of cells with TNF-α led to increased production of IL-1β, IL-6, chemokine (C-C motif) ligand 20 (CCL20), and vascular endothelial growth factor (VEGF) by ARPE-19 cells, and this response was attenuated by treatment with xaliproden. TNF-α also led to a decrease in the TEER that was prevented by treatment with the 5HT1a agonist. Daily gavage with xaliproden at either dose induced the production of protective enzymes in the mouse retina, and treatment of the Sod2-deleted mice with the drug showed improved thickness of the outer nuclear layer and improved visual acuity relative to the control-treated mice. There was no significant difference in full-field scotopic ERG among the treatment groups, however. Vacuolization of the RPE and disorganization of the photoreceptor outer segments were reduced at both dose levels of xaliproden.

CONCLUSIONS: Xaliproden protected RPE cells from oxidative and inflammatory insults and protected the mouse RPE and retina from RPE atrophy in the face of excess mitochondrial oxidative stress. These

results suggest that this drug, which had a reasonable safety profile in clinical trials, may be used to prevent the progression of geographic atrophy in humans.

PMID: 27110092 [PubMed - in process] PMCID: PMC4818958

Semin Ophthalmol. 2016 Apr 26:0. [Epub ahead of print]

Ranibizumab (Lucentis) versus bevacizumab (Avastin) for the Treatment of Age-Related Macular Degeneration: An Economic Disparity of Eye Health.

Moreno TA, Kim SJ.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly, and the advent of anti-vascular endothelial growth factor agents (VEGF) has revolutionized treatment for neovascular AMD. Two of the most popular anti-VEGF agents, ranibizumab (Lucentis; Genentech/Roche) and bevacizumab (Avastin; Genentech/Roche), effectively treat neovascular AMD but have a substantial difference in price. Multiple level 1 trials have demonstrated that bevacizumab is noninferior to ranibizumab in the treatment of neovascular AMD and that both have similar safety profiles. The decision to use one drug over the other is multifactorial with influences from industry as well as individual physician biases. However, the additional billions spent on ranibizumab result in a large economic disparity that is not rationalized by cost effectiveness models.

PMID: 27116030 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2016 Apr 1;57(5):ORSFn1-9.

Retinal Structure Measurements as Inclusion Criteria for Stem Cell-Based Therapies of Retinal Degenerations.

Jacobson SG, Matsui R, Sumaroka A, Cideciyan AV.

PURPOSE: We reviewed and illustrated the most optimal retinal structural measurements to make in stem cell clinical trials.

METHODS: Optical coherence tomography (OCT) and autofluorescence (AF) imaging were used to evaluate patients with severe visual loss from nonsyndromic and syndromic retinitis pigmentosa (RP), ABCA4-Stargardt disease, and nonneovascular age-related macular degeneration (AMD). Outer nuclear layer (ONL), rod outer segment (ROS) layer, inner retina, ganglion cell layer (GCL), and nerve fiber layer (NFL) thicknesses were quantified.

RESULTS: All patients had severely reduced visual acuities. Retinitis pigmentosa patients had limited visual fields; maculopathy patients had central scotomas with retained peripheral function. For the forms of RP illustrated, there was detectable albeit severely reduced ONL across the scanned retina, and normal or hyperthick GCL and NFL. Maculopathy patients had no measurable ONL centrally; it became detectable with eccentricity. Some maculopathy patients showed unexpected GCL losses. Autofluorescence imaging illustrated central losses of RPE integrity. A hypothetical scheme to relate patient data with different phases of retinal remodeling in animal models of retinal degeneration was presented.

CONCLUSIONS: Stem cell science is advancing, but it is not too early to open the discussion of criteria for patient selection and monitoring. Available clinical tools, such as OCT and AF imaging, can provide inclusion/exclusion criteria and robust objective outcomes. Accepting that early trials may not lead to miraculous cures, we should be prepared to know why-scientifically and clinically-so we can improve

subsequent trials. We also must determine if retinal remodeling is an impediment to efficacy.

PMID: 27116670 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2016 Apr 1;57(4):2283-9.

Semiautomatic Segmentation of Rim Area Focal Hyperautofluorescence Predicts Progression of Geographic Atrophy Due to Dry Age-Related Macular Degeneration.

Allingham MJ, Nie Q, Lad EM, Izatt DJ, Mettu PS, Cousins SW, Farsiu S.

PURPOSE: To develop image analysis software usable by nonexpert graders to segment geographic atrophy (GA) from dry AMD and to quantify rim area focal hyperautofluorescence (RAFH) surrounding GA on fundus autofluorescence (FAF) images. To compare the GA progression predictions based on RAFH with those of a validated qualitative classification system.

METHODS: Retrospective analysis of serial FAF images from 49 eyes of 30 subjects with GA was performed using MATLAB-based software (MathWorks, Natick, MA, USA). Correlation between RAFH and progression of GA was analyzed using Spearman correlation. Comparisons of lesion growth rate between RAFH tertiles used generalized estimating equations and Kruskal-Wallis testing. Interobserver variability in lesion size, growth rate and RAFH were compared between two expert and one nonexpert grader using Bland-Altman statistics.

RESULTS: Rim area focal hyperautofluorescence was positively correlated with GA progression rate (ρ = 0.49, $P < 0.001$). Subjects in the middle or highest RAFH tertile were at greater risk of progression (P = 0.005 and P = 0.001, respectively). Mean difference in RAFH was 0.012 between expert and -0.005 to 0.017 between expert and nonexperts. Mean difference in lesion size (mm2) was 0.11 between expert and -0.29 to 0.41 between expert and nonexperts. Mean difference in lesion growth rate (mm2/mo) was 0.0098 between expert and -0.027 to 0.037 between expert and nonexperts. Risk stratification based on RAFH tertile was 96% identical across all graders.

CONCLUSIONS: Our semiautomated image analysis software facilitates stratification of progression risk based on RAFH and enabled a nonexpert grader with minimal training to obtain results comparable to expert graders. Predictions based on RAFH were similar to those of a validated qualitative classification system.

PMID: 27127926 [PubMed - in process]

Health Technol Assess. 2016 Apr;20(31):1-108.

Accuracy of fundus autofluorescence imaging for the diagnosis and monitoring of retinal conditions: a systematic review.

Frampton GK, Kalita N, Payne L, Colquitt J, Loveman E.

BACKGROUND: Natural fluorescence in the eye may be increased or decreased by diseases that affect the retina. Imaging methods based on confocal scanning laser ophthalmoscopy (cSLO) can detect this 'fundus autofluorescence' (FAF) by illuminating the retina using a specific light 'excitation wavelength'. FAF imaging could assist the diagnosis or monitoring of retinal conditions. However, the accuracy of the method for diagnosis or monitoring is unclear.

OBJECTIVE: To conduct a systematic review to determine the accuracy of FAF imaging using cSLO for the diagnosis or monitoring of retinal conditions, including monitoring of response to therapy.

DATA SOURCES: Electronic bibliographic databases; scrutiny of reference lists of included studies and relevant systematic reviews; and searches of internet pages of relevant organisations, meetings and trial registries. Databases included MEDLINE, EMBASE, The Cochrane Library, Web of Science and the Medion database of diagnostic accuracy studies. Searches covered 1990 to November 2014 and were limited to the English language.

REVIEW METHODS: References were screened for relevance using prespecified inclusion criteria to capture a broad range of retinal conditions. Two reviewers assessed titles and abstracts independently. Full -text versions of relevant records were retrieved and screened by one reviewer and checked by a second. Data were extracted and critically appraised using the Quality Assessment of Diagnostic Accuracy Studies criteria (QUADAS) for assessing risk of bias in test accuracy studies by one reviewer and checked by a second. At all stages any reviewer disagreement was resolved through discussion or arbitration by a third reviewer.

RESULTS: Eight primary research studies have investigated the diagnostic accuracy of FAF imaging in retinal conditions: choroidal neovascularisation (one study), reticular pseudodrusen (three studies), cystoid macular oedema (two studies) and diabetic macular oedema (two studies). Sensitivity of FAF imaging using an excitation wavelength of 488 nm was generally high (range 81-100%), but was lower (55% and 32%) in two studies using longer excitation wavelengths (514 nm and 790 nm, respectively). Specificity ranged from 34% to 100%. However, owing to limitations of the data, none of the studies provide conclusive evidence of the diagnostic accuracy of FAF imaging.

LIMITATIONS: No studies on the accuracy of FAF imaging for monitoring the progression of retinal conditions or response to therapy were identified. Owing to study heterogeneity, pooling of diagnostic outcomes in meta-analysis was not conducted. All included studies had high risk of bias. In most studies the patient spectrum was not reflective of those who would present in clinical practice and no studies adequately reported how FAF images were interpreted.

CONCLUSIONS: Although already in use in clinical practice, it is unclear whether or not FAF imaging is accurate, and whether or not it is applied and interpreted consistently for the diagnosis and/or monitoring of retinal conditions. Well-designed prospective primary research studies, which conform to the paradigm of diagnostic test accuracy assessment, are required to investigate the accuracy of FAF imaging in diagnosis and monitoring of inherited retinal dystrophies, early age-related macular degeneration, geographic atrophy and central serous chorioretinopathy.

PMID: 27115052 [PubMed - in process]

Curr Eye Res. 2016 Apr 26:1-6. [Epub ahead of print]

The Relationship Between Reticular Macular Disease and Choroidal Thickness.

Cheng H, Kaszubski PA, Hao H, Saade C, Cunningham C, Freund KB, Smith RT.

PURPOSE: Subretinal drusenoid deposits (SDD) are the main structural lesion of reticular macular disease (RMD), a phenotype of age-related macular degeneration (AMD). We aim to demonstrate spatiotemporal relationships between SDD and choroidal thickness (CTh) alterations in RMD+ and RMD- eyes.

METHODS: Thirty-three eyes (26 subjects) with early AMD/no SDD (RMD-) and 18 eyes (16 subjects) with early AMD/SDD (RMD+) underwent enhanced depth imaging spectral domain optical coherence tomography (SD-OCT) for CTh measurements at 11 points per scan, in 5 horizontal B scans, creating a grid of 55 points/eye. The 55 points were treated as a cluster, controlling within-subject correlation. Marginal generalized estimating equation modeling was used to estimate the association between CTh and RMD status. All eyes were divided by their median age (≤82 and >82 years) for stratified analyses.

RESULTS: CTh was not significantly reduced in RMD+ eyes compared with RMD- eyes (mean difference

[MD] -16.84 μm, P = 0.24). Among younger subjects, mean CTh was significantly reduced in RMD+ versus RMD- eyes (MD -53.72 μm, P = 0.01). Conversely, among older subjects, there was no significant difference in CTh between RMD+ and RMD-.

CONCLUSIONS: In RMD, the association of SDD and CTh alterations varies with age but not by macular region. Among younger subjects (<82 years old), CTh was significantly thinner in RMD+ versus RMD- eyes.

PMID: 27115048 [PubMed - as supplied by publisher]

J Ophthalmol. 2016;2016:7521478. Epub 2016 Mar 23.

The Diagnostic Accuracy of Optical Coherence Tomography Angiography for Neovascular Age-Related Macular Degeneration: A Comparison with Fundus Fluorescein Angiography.

Gong J, Yu S, Gong Y, Wang F, Sun X

Purpose: To describe the morphological characteristics and efficacy of OCTA in detecting CNV in nAMD. We retrospectively reviewed 53 patients (86 eyes) with suspected CNV secondary to wet AMD. All the patients underwent a multimodal assessment for CNV. Two independent readers calculated the sensitivity and specificity of OCTA in detecting CNV compared with FA. A qualitative analysis of OCTA was also performed to describe the morphological appearance of CNV. Among 86 eyes of 53 patients, 52 eyes were diagnosed as having CNV based on the FA imaging analysis. According to FA, CNV was classified as classic in 28 eyes, predominantly classic in 6 eyes, minimally classic in 9 eyes, and occult in 9 eyes. In 56 eyes, CNV was visualized on OCTA and corresponding OCT B-scans. In total, 46.4% (26/56) had well-circumscribed vessels, and 53.6% (30/56) showed poorly circumscribed vessels. There were 11 false positives and 7 false negatives using OCTA. The specificity of OCTA for the detection of CNV was 67.6%, with sensitivity of 86.5%. OCTA may help in the noninvasive diagnosis of CNV and may provide a method for monitoring the evolution of CNV.

PMID: 27110394 [PubMed] PMCID: PMC4821972

Comput Biol Med. 2016 Apr 21;73:131-140. [Epub ahead of print]

Novel risk index for the identification of age-related macular degeneration using radon transform and DWT features.

Acharya UR, Mookiah MR, Koh JE, Tan JH, Noronha K, Bhandary SV, Rao AK, Hagiwara Y, Chua CK, Laude A.

Abstract: Age-related Macular Degeneration (AMD) affects the central vision of aged people. It can be diagnosed due to the presence of drusen, Geographic Atrophy (GA) and Choroidal Neovascularization (CNV) in the fundus images. It is labor intensive and time-consuming for the ophthalmologists to screen these images. An automated digital fundus photography based screening system can overcome these drawbacks. Such a safe, non-contact and cost-effective platform can be used as a screening system for dry AMD. In this paper, we are proposing a novel algorithm using Radon Transform (RT), Discrete Wavelet Transform (DWT) coupled with Locality Sensitive Discriminant Analysis (LSDA) for automated diagnosis of AMD. First the image is subjected to RT followed by DWT. The extracted features are subjected to dimension reduction using LSDA and ranked using t-test. The performance of various supervised classifiers namely Decision Tree (DT), Support Vector Machine (SVM), Probabilistic Neural Network (PNN) and k-Nearest Neighbor (k-NN) are compared to automatically discriminate to normal and AMD classes using ranked LSDA components. The proposed approach is evaluated using private and public datasets such as ARIA and STARE. The highest classification accuracy of 99.49%, 96.89% and 100% are reported for private, ARIA and STARE datasets. Also, AMD index is devised using two LSDA components to distinguish

two classes accurately. Hence, this proposed system can be extended for mass AMD screening.

PMID: 27107676 [PubMed - as supplied by publisher]

Ophthalmic Physiol Opt. 2016 May;36(3):303-16.

Infrared reflectance imaging in age-related macular degeneration.

Ly A, Nivison-Smith L, Assaad N, Kalloniatis M.

PURPOSE: The purpose of this article is to describe the appearance of age-related macular degeneration (AMD) phenotypes using infrared (IR) reflectance imaging. IR reflectance imaging of the retina has the potential to highlight specific sub-retinal features and pathology. However, its role in macular disease, specifically AMD, is often underestimated and requires clarification.

RECENT FINDINGS: Recent advances in clinical methods, imaging and scientific knowledge may be integrated to improve the accuracy of disease stratification in AMD. In particular, IR imaging holds an underutilised sensitivity to detect reticular pseudodrusen, which have been repeatedly described as a high-risk sign for late AMD.

SUMMARY: This article provides clinically relevant descriptions of AMD phenotypes using IR reflectance imaging. The findings are integrated with images from cases seen at the Centre for Eye Health. As primary eye-care providers assume a critical role in the detection, diagnosis and management of AMD, we also provide a chair-side reference to assist clinicians in interpreting IR images in AMD.

PMID: 27112225 [PubMed - in process]

Ophthalmic Physiol Opt. 2016 May;36(3):240-65.

Using magnetic resonance imaging to assess visual deficits: a review.

Brown HD, Woodall RL, Kitching RE, Baseler HA, Morland AB.

PURPOSE: Over the last two decades, magnetic resonance imaging (MRI) has been widely used in neuroscience research to assess both structure and function in the brain in health and disease. With regard to vision research, prior to the advent of MRI, researchers relied on animal physiology and human post-mortem work to assess the impact of eye disease on visual cortex and connecting structures. Using MRI, researchers can non-invasively examine the effects of eye disease on the whole visual pathway, including the lateral geniculate nucleus, striate and extrastriate cortex. This review aims to summarise research using MRI to investigate structural, chemical and functional effects of eye diseases, including: macular degeneration, retinitis pigmentosa, glaucoma, albinism, and amblyopia.

RECENT FINDINGS: Structural MRI has demonstrated significant abnormalities within both grey and white matter densities across both visual and non-visual areas. Functional MRI studies have also provided extensive evidence of functional changes throughout the whole of the visual pathway following visual loss, particularly in amblyopia. MR spectroscopy techniques have also revealed several abnormalities in metabolite concentrations in both glaucoma and age-related macular degeneration. GABA-edited MR spectroscopy on the other hand has identified possible evidence of plasticity within visual cortex.

SUMMARY: Collectively, using MRI to investigate the effects on the visual pathway following disease and dysfunction has revealed a rich pattern of results allowing for better characterisation of disease. In the future MRI will likely play an important role in assessing the impact of eye disease on the visual pathway and how it progresses over time.

PMID: 27112223 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2016 Apr 1;57(4):2277-82.

Analysis of Peripapillary Atrophy in Relation to Macular Geographic Atrophy in Age-Related Macular Degeneration.

Chang P, Tan A, Jaffe GJ, Fleckenstein M, Holz FG, Schmitz-Valckenberg S.

PURPOSE: The purpose of this study was to investigate the presence, configuration, and progression of peripapillary atrophy (PPA) relative to macular geographic atrophy (GA) in AMD.

METHODS: Confocal scanning laser ophthalmoscopy images of 413 eyes of 413 patients with GA secondary to AMD (median age, 77.0 years) were evaluated for the presence and configuration of PPA at baseline. In addition, the progression of PPA and the regression of the shortest linear dimension between PPA and GA ("buffer zone") were assessed in 164 eyes that had completed 12 months of follow-up.

RESULTS: At baseline, PPA was present in 357 (86.4%) of 413 eyes, of which 330 eyes (79.9%) were classified as nonconfluent and 27 eyes (6.5%) as confluent PPA. At month 12, eight eyes had transformed from nonconfluent to confluent PPA. The median buffer zone at baseline was significantly smaller in these latter eyes than in eyes where the PPA remained nonconfluent (168.46 vs. 1451.64 μm; $P < 0.001$). The mean regression rate of the buffer zone was 163.0 μm/y (interquartile range, 77.2-281.3).

CONCLUSIONS: Peripapillary atrophy is highly prevalent in eyes with GA due to AMD. Assessment of the buffer zone in eyes with nonconfluent PPA at baseline may be helpful to identify subjects at risk for the progression to confluent PPA. In future interventional clinical trials, it may be useful to exclude any eyes both with confluent PPA at baseline and at risk for development of confluent PPA over time to improve the accuracy of GA lesion size quantification and its enlargement over time.

PMID: 27127925 [PubMed - in process]

Pathogenesis

Biogerontology. 2016 Apr 28. [Epub ahead of print]

Absence of collagen XVIII in mice causes age-related insufficiency in retinal pigment epithelium proteostasis.

Kivinen N, Felszeghy S, Kinnunen AI, Setälä N, Aikio M, Kinnunen K, Sironen R, Pihlajaniemi T, Kauppinen A, Kaarniranta K.

Abstract: Collagen XVIII has the structural properties of both collagen and proteoglycan. It has been found at the basement membrane/stromal interface where it is thought to mediate their attachment. Endostatin, a proteolytic fragment from collagen XVIII C-terminal end has been reported to possess anti-angiogenic properties. Age-related vision loss in collagen XVIII mutant mice has been accompanied with a pathological accumulation of deposits under the retinal pigment epithelium (RPE). We have recently demonstrated that impaired proteasomal and autophagy clearance are associated with the pathogenesis of age-related macular degeneration. This study examined the staining levels of proteasomal and autophagy markers in the RPE of different ages of the Col18a1 -/- mice. Eyes from 3, 6-7, 10-13 and 18 months old mice were enucleated and embedded in paraffin according to the routine protocol. Sequential 5 μm-thick parasagittal samples were immunostained for proteasome and autophagy markers ubiquitin (ub), SQSTM1/p62 and beclin-1. The levels of immunopositivity in the RPE cells were evaluated by confocal microscopy. Collagen XVIII knock-out mice had undergone age-related RPE degeneration accompanied by an accumulation of drusen-like deposits. Ub protein conjugate staining was prominent in both RPE cytoplasm and extracellular space whereas SQSTM1/p62 and beclin-1 stainings were clearly present in the basal part of RPE cell cytoplasm in the Col18a1 -/- mice. SQSTM1/p62 displayed mild extracellular space staining. Disturbed proteostasis regulated by collagen XVIII might be responsible for the RPE degeneration, increased protein

aggregation, ultimately leading to choroidal neovascularization.

PMID: 27125427 [PubMed - as supplied by publisher]

Discov Med. 2016 Mar;21(115):149-58.

Detecting Aβ deposition and RPE cell senescence in the retinas of SAMP8 mice.

Feng L, Cao L, Zhang Y, Wang F.

AIM: Our previous study indicated that Aβ-induced Retinal Pigment Epithelial (RPE) cell senescence may be associated with chronic inflammation in age-related macular degeneration (AMD). The present study was designed to explore whether Aβ deposition and RPE senescence could be found in the senescence-prone mouse strain 8 (SAMP8), which is an animal model for AMD.

METHODS: Eyes of both SAMP8 and age-matched SAMR1 (SAM resistant) mice were examined in vivo by fundus photography and electroretinography (ERG). Retinal morphological features were assessed using light and electron microscopy. Aβ deposition and p16-positive senescent RPE cells were traced using immunofluorescence labeling. P16 expression was detected using western blot. Expressions of IL-6 and IL-8 in RPE/choroid were analyzed using RT-PCR.

RESULTS: In fundus of SAMP8, age-dependent increase of drusen-like lesions and the increase of granular autofluorescent spots were respectively detected using IR (near-infrared) and AF (autofluorescence) imaging of confocal scanning laser ophthalmoscope. The amplitude of the ERGs declined with age in SAMP8 and these changes were paralleled with the significant changes in retinal morphological features examined by funduscopy. Histopathological analysis found significant loss of photoreceptor outer segments (OS) and abnormal localization of RPE cells in aged SAMP8 mice. Degenerative changes in RPE cells of aged SAMP8 mice, including massive vacuoles, thickened Bruch's membrane (BrM), and loss of basal infoldings were further confirmed by electron microscopy. Increased Aβ deposits in OS layer and p16-positive senescent RPE cells were observed using immunofluorescence microscopy. Western blot confirmed that P16 expression was significantly increased in RPE cells of aged SAMP8 mice. Expressions of proinflammatory IL-6 and IL-8 were significantly upregulated in RPE/choroid of aged SAMP8 mice.

CONCLUSIONS: Our results showed that aged SAMP8 mice developed ocular pathology similar to some features of human AMD. In this AMD mouse model, Aβ deposition and RPE senescence may be associated with AMD development, and RPE senescence is likely a mechanistic link between Aβ deposition and inflammation.

PMID: 27115165 [PubMed - in process]

Mol Vis. 2016 Apr 22;22:352-61. eCollection 2016.

Aqueous humor cytokine profiling in patients with wet AMD.

Liu F, Ding X, Yang Y, Li J, Tang M, Yuan M, Hu A, Zhan Z, Li Z, Lu L.

PURPOSE: To investigate the chemokine expression profiles in the aqueous humor of wet age-related macular degeneration (wet AMD) patients and to correlate their levels with clinical findings.

METHODS: Undiluted aqueous humor samples (100-200 µl) were obtained from 16 wet AMD eyes and 12 control eyes. Forty chemokines were measured using a multiplex method. A 6×6 mm area of the macular region centered on the fovea was examined using spectral domain optical coherence tomography (SD-OCT).

RESULTS: The detection rates were 50% or more for 15 chemokines. Compared with the control group, the aqueous humor in wet AMD patients showed a significantly higher expression of CXCL10 (p=0.004), CCL14 (p=0.002), CXCL16 (p=0.013), CXCL7 (p=0.033), and CCL22 (p=0.037), while growth-related oncogene (GRO) was significantly decreased in the wet AMD patients (p=0.001). When compared with treatment-naïve patients, the recurrent group had significant upregulation of CXCL10 (p=0.012) and CCL22 (p=0.002). CXCL16 was positively correlated with lesion size, and CCL22 was higher in patients whose OCT images showed intraretinal fluid (IRF) or hyperreflective foci (HF).

CONCLUSIONS: Elevated levels of inflammation-related chemokines, including CXCL10, CCL14, CXCL16, CXCL7, and CCL22, in the aqueous humor of AMD patients may suggest a pathogenic role for inflammation. CXCL10 and CCL22 were more elevated in eyes with recurrent wet AMD than in treatment-naïve eyes. CXCL16 was positively correlated with lesion size. The increase in CCL22 was correlated with the presence of IRF or HF. These data may be of interest in the search for biomarkers associated with wet AMD and may potentially indicate different treatment strategies.

PMID: 27122966 [PubMed - in process] PMCID: PMC4842003

Biochimie. 2016 Apr 21. [Epub ahead of print]

P2X7-Pannexin-1 and amyloid β-induced oxysterol input in human retinal cell: Role in age-related macular degeneration?

Olivier E, Dutot M, Regazzetti A, Leguillier T, Dargere D, Auzeil N, Laprevote O, Rat P.

PMID: 27109381 [PubMed - as supplied by publisher]

Exp Mol Pathol. 2016 Apr 22. [Epub ahead of print]

Inhibition of RACK1 ameliorates choroidal neovascularization formation in vitro and in vivo.

Liu X, Zhu M, Yang X, Wang Y, Qin B, Cui C, Chen H, Sang A.

Abstract: Choroidal neovascularization (CNV) occurs as a result of age-related macular degeneration (AMD) and causes severe vision loss among elderly patients. The receptor for activated C-kinase 1 (RACK1) serves as a scaffold protein which is recently found to promote angiogenesis. However, the impact of RACK1 on the vascular endothelial growth factor (VEGF) expression in endothelial cells and subsequent choroidal angiogenesis formation remains to be elucidated. In this study, we found that RACK1 and VEGF expression increased, and reached the peak at 7 d in mouse CNV model by laser application. Furthermore, on RPE/choroid cryosections, RACK1 co-localized with CD31, suggesting that RACK1 was expressed in endothelial cells. In vitro, RF/6A cell hypoxia model showed that RACK1 expression was up-regulated in parallel with hypoxia-induced factor 1 (HIF-1α) and VEGF expression, reaching the peak at 6h. Silencing of RACK1 suppressed the invasion and tube formation activity of RF/6A cells in ARPE-19 and RF/6A co-culture system, possibly through VEGF signal pathway. Overexpression of RACK1 showed the opposite effect. Intravitreal injection of anti-RACK1 monoclonal antibody predominantly decreased RACK1 and VEGF expression in mouse laser-induced CNV model. Meanwhile, anti-RACK1 monoclonal antibody intravitreal injection also decreased incidence of CNV and leakage area. These data indicated that RACK1 promoted CNV formation via VEGF pathway. Additionally, anti-RACK1 monoclonal antibody significantly decreased CNV in mouse model and may have therapeutic potential in human CNV.

PMID: 27112838 [PubMed - as supplied by publisher]

Proc Natl Acad Sci U S A. 2016 Apr 25. [Epub ahead of print]

Paired octamer rings of retinoschisin suggest a junctional model for cell-cell adhesion in the retina.

Tolun G, Vijayasarathy C, Huang R, Zeng Y, Li Y, Steven AC, Sieving PA, Heymann JB.

Abstract: Retinoschisin (RS1) is involved in cell-cell junctions in the retina, but is unique among known cell-adhesion proteins in that it is a soluble secreted protein. Loss-of-function mutations in RS1 lead to early vision impairment in young males, called X-linked retinoschisis. The disease is characterized by separation of inner retinal layers and disruption of synaptic signaling. Using cryo-electron microscopy, we report the structure at 4.1 Å, revealing double octamer rings not observed before. Each subunit is composed of a discoidin domain and a small N-terminal (RS1) domain. The RS1 domains occupy the centers of the rings, but are not required for ring formation and are less clearly defined, suggesting mobility. We determined the structure of the discoidin rings, consistent with known intramolecular and intermolecular disulfides. The interfaces internal to and between rings feature residues implicated in X-linked retinoschisis, indicating the importance of correct assembly. Based on this structure, we propose that RS1 couples neighboring membranes together through octamer-octamer contacts, perhaps modulated by interactions with other membrane components.

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Exp Eye Res. 2016 Apr 26. [Epub ahead of print]

Matrigel and Activin A promote cell-cell contact and anti-apoptotic activity in cultured human retinal pigment epithelium cells.

Guo X, Zhu D, Lian R, Han Y, Guo Y, Li Z, Tang S, Chen J.

Abstract: Age-related macular degeneration (AMD) is a leading cause of blindness among the aging population. Currently, replacement of diseased retinal pigment epithelium (RPE) cells with transplanted healthy RPE cells could be a feasible approach for AMD therapy. However, maintaining cell-cell contact and good viability of RPE cells cultured in vitro is difficult and fundamentally determines the success of RPE cell transplantation. This study was conducted to examine the role of Matrigel and Activin A (MA) in regulating cell-cell contact and anti-apoptotic activity in human RPE (hRPE) cells, as assessed by atomic force microscopy (AFM), scanning electron microscope (SEM), immunofluorescence staining, quantitative polymerase chain reaction (qPCR) analysis, Annexin V/propidium iodide (PI) analysis, mitochondrial membrane potential (△Ψ m) assays, intracellular reactive oxygen species (ROS) assays and Western blotting. hRPE cells cultured in vitro could maintain their epithelioid morphology after MA treatment over at least 4 passages. The contact of N-cadherin to the lateral cell border was promoted in hRPE cells at P2 by MA. MA treatment also enhanced the expression of tight junction-associated genes and proteins, such as Claudin-1, Claudin-3, Occludin and ZO-1, as well as polarized ZO-1 protein distribution and barrier function, in cultured hRPE cells. Moreover, MA treatment decreased apoptotic cells, ROS and Bax and increased △Ψ m and Bcl2 in hRPE cells under serum withdrawal-induced apoptosis. In addition, MA treatment elevated the protein expression levels of β-catenin and its target proteins, including Cyclin D1, c-Myc and Survivin, as well as the gene expression levels of ZO-1, β-catenin, Survivin and TCF-4, all of which could be down-regulated by the Wnt/β-catenin pathway inhibitor XAV-939. Taken together, MA treatment could effectively promote cell-cell contact and anti-apoptotic activity in hRPE cells, partly involving the Wnt/β-catenin pathway. This study will benefit the understanding of hRPE cells and future cell therapy.

PMID: 27130547 [PubMed - as supplied by publisher]

Epidemiology

Semin Ophthalmol. 2016 Apr 26:0. [Epub ahead of print]

Eye Care Disparities and Health-Related Consequences in Elderly Patients with Age-Related Eye Disease.

Umfress AC, Brantley MA Jr.

Abstract: The elderly population in the United States (age 65 and older) is growing rapidly, estimated by the U.S. Census Department to reach 83.7 million by 2050.1 Visual impairment increases with age among all racial and ethnic groups.2 In the elderly, the most common culprits for vision loss are cataract, glaucoma, and age-related macular degeneration (AMD).2 In the developed world, vision loss from cataract has been dramatically reduced by increased access to cataract surgery. However, AMD and glaucoma lead to irreversible vision loss without early diagnosis and intervention. In the U.S., cases of AMD are expected to double by 2050, reaching 17.8 million among patients age 50 or older.3 Similarly, cases of glaucoma are expected to reach 5.5 million by 2050, an increase of over 90% from 2014.3 The visually impaired elderly face disparities in access to eye care, and subsequent general medical and psychosocial complications.

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Semin Ophthalmol. 2016 Apr 29:1-8. [Epub ahead of print]

Association between Previous Cataract Surgery and Age-Related Macular Degeneration.

Rim TH, Lee CS, Lee SC, Kim S, Kim SS, Epidemiologic Survey Committee Of The Korean Ophthalmological Society.

PURPOSE: To assess the association between age-related macular degeneration (AMD) and previous cataract surgery.

METHODS: We studied 17,987 randomly selected participants from the Korea National Health and Nutrition Examination Survey who were aged ≥40 years and underwent additional ophthalmologic examinations in 2008–12. The associations between previous cataract surgery and early/late AMD were identified using multivariate logistic regression analysis of data from right or left eyes. Clustered multivariate logistic regression analysis was performed using both eyes to assess inter-eye correlation in same subject. Previous cataract surgery and cataract subtypes were based on slit-lamp examination without pupil dilation. Early and late AMD diagnoses were based on non-mydriatic digital retinal image.

RESULTS: By univariate logistic regression, both early and late AMD prevalence were higher in subjects with pseudophakia/aphakia compared to subjects with cataract as a reference group, or subjects with phakic eye (including clear lens) as a reference group. In univariate logistic regression, both early and late AMD prevalence were higher in eyes with cataract or pseudo/aphakia compared to eyes with clear lens. However, after adjusting for age with multivariate logistic regression, all statistically significant differences in AMD prevalence among subgroups disappeared.

CONCLUSIONS: We found no association between the previous cataract surgery and increased early/late AMD risk in our representative, large, national patient database. This suggests that increasing age, and not cataract surgery history, is predictive of AMD risk. These findings are limited by cross-sectional study and need to be replicated by other longitudinal observational studies.

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JAMA Ophthalmol. 2016 Apr 28. [Epub ahead of print]

Age-Related Macular Degeneration and Quality of Life in Latinos: The Los Angeles Latino Eye Study.

Choudhury F, Varma R, Klein R, Gauderman WJ, Azen SP, McKean-Cowdin R; Los Angeles Latino Eye Study Group.

IMPORTANCE: This study found evidence of a threshold effect in which the presence of bilateral soft drusen and depigmentation of retinal pigment epithelium was associated with substantially low health-related quality of life (HRQoL) in adult Latinos from the United States.

OBJECTIVE: To assess the association of general and vision-specific HRQoL with age-related macular degeneration (AMD), overall and by bilaterality and severity, in adult Latinos.

DESIGN, SETTING, AND PARTICIPANTS: This cross-sectional, population-based study included 4876 participants from the general urban community in 6 US Census tracts in La Puente, California. The data for these analyses were collected as part of a population-based study of ocular diseases in adult Latinos in the Los Angeles Latino Eye Study from February 1, 2000, through May 31, 2003. The analysis was performed from November 2010 to February 2011. Additional analyses were performed in June 2014.

MAIN OUTCOMES AND MEASURES: Mean-adjusted HRQoL scores and effect sizes.

RESULTS: Of the 4876 participants included in the analysis, 4402 (90.3%) had no AMD, and 474 (9.7%) had any AMD, with 453 having early (9.3%) and 21 (0.4%) having late stages of the disease. The mean (SD) age of the cohort was 54.8 (10.7) years. Of the 4876 participants, 2001 (41.0%) were male and 2875 (59.0%) were female. In this cohort of Latinos, participants with AMD had lower vision-specific HRQoL scores. General HRQoL was assessed by the Medical Outcomes Study 12-Item Short-Form Health Survey and self-reported vision-related HRQoL by the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25). Composite NEI-VFQ-25 scores were 59.5 (95% CI, 50.8-68.1) for those with late-stage AMD and 79.4 (95% CI, 72.5-86.1) for those with early-stage AMD, compared with participants without AMD 80.7 (95% CI, 73.9-82.4); $P < .001$. Several lesions of early AMD were associated with lower NEI-VFQ-25 composite scores and 8 to 10 individual scales. Large effect sizes and lower mean scores were observed for those with late AMD lesions, overall and specifically for geographic atrophy and neovascular AMD, compared with those without AMD. With the use of concatenated bilateral severity levels for AMD, decreases in the NEI-VFQ-25 composite and individual scale scores were observed at the transition from a unilateral to bilateral severity level of 40, which corresponds to having bilateral soft drusen (>125 μm in diameter with drusen area ≥196 350 μm2) and depigmentation of retinal pigment epithelium (slope of -19.17 for the NEI-VFQ-25 composite score). Measures of general health, as assessed by the Medical Outcomes Study 12-Item Short-Form Health Survey, were not affected in this cohort.

CONCLUSIONS AND RELEVANCE: In this study of adult Latinos, early AMD lesions are associated with lower self-reported, vision-specific HRQoL but not general HRQoL. Severity and bilaterality of AMD are associated with measurably lower HRQoL scores, with the largest difference in scores occurring for individuals with both eyes affected. A concatenated approach to incorporate bilateral severity might be more useful and provide better insight into the association of AMD and HRQoL.

PMID: 27124819 [PubMed - as supplied by publisher]

Genetics

Invest Ophthalmol Vis Sci. 2016 Apr 1;57(4):2225-31.

Genetic Association Analysis of Drusen Progression.

Hoffman JD, van Grinsven MJ, Li C, Brantley M Jr, McGrath J, Agarwal A, Scott WK, Schwartz SG, Kovach J, Pericak-Vance M, Sanchez CI, Haines JL.

PURPOSE: Age-related macular degeneration is a common form of vision loss affecting older adults. The etiology of AMD is multifactorial and is influenced by environmental and genetic risk factors. In this study, we examine how 19 common risk variants contribute to drusen progression, a hallmark of AMD pathogenesis.

METHODS: Exome chip data was made available through the International AMD Genomics Consortium (IAMDGC). Drusen quantification was carried out with color fundus photographs using an automated drusen detection and quantification algorithm. A genetic risk score (GRS) was calculated per subject by summing risk allele counts at 19 common genetic risk variants weighted by their respective effect sizes. Pathway analysis of drusen progression was carried out with the software package Pathway Analysis by Randomization Incorporating Structure.

RESULTS: We observed significant correlation with drusen baseline area and the GRS in the age-related eye disease study (AREDS) dataset ($\rho = 0.175$, $P = 0.006$). Measures of association were not statistically significant between drusen progression and the GRS ($P = 0.54$). Pathway analysis revealed the cell adhesion molecules pathway as the most highly significant pathway associated with drusen progression (corrected $P = 0.02$).

CONCLUSIONS: In this study, we explored the potential influence of known common AMD genetic risk factors on drusen progression. Our results from the GRS analysis showed association of increasing genetic burden (from 19 AMD associated loci) to baseline drusen load but not drusen progression in the AREDS dataset while pathway analysis suggests additional genetic contributors to AMD risk.

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Stem Cells

Stem Cells Transl Med. 2016 Apr 25. [Epub ahead of print]

Targeting the cAMP and Transforming Growth Factor-β Pathway Increases Proliferation to Promote Re-Epithelialization of Human Stem Cell-Derived Retinal Pigment Epithelium.

Choudhary P, Gutteridge A, Impey E, Storer RI, Owen RM, Whiting PJ, Bictash M, Benn CL.

Abstract: Retinal pigment epithelium (RPE) cell integrity is critical to the maintenance of retinal function. Many retinopathies such as age-related macular degeneration (AMD) are caused by the degeneration or malfunction of the RPE cell layer. Replacement of diseased RPE with healthy, stem cell-derived RPE is a potential therapeutic strategy for treating AMD. Human embryonic stem cells (hESCs) differentiated into RPE progeny have the potential to provide an unlimited supply of cells for transplantation, but challenges around scalability and efficiency of the differentiation process still remain. Using hESC-derived RPE as a cellular model, we sought to understand mechanisms that could be modulated to increase RPE yield after differentiation. We show that RPE epithelialization is a density-dependent process, and cells seeded at low density fail to epithelialize. We demonstrate that activation of the cAMP pathway increases proliferation of dissociated RPE in culture, in part through inhibition of transforming growth factor-β (TGF-β) signaling. This results in enhanced uptake of epithelial identity, even in cultures seeded at low density. In line with these findings, targeted manipulation of the TGF-β pathway with small molecules produces an increase in efficiency of RPE re-epithelialization. Taken together, these data highlight mechanisms that promote epithelial fate acquisition in stem cell-derived RPE. Modulation of these pathways has the potential to favorably impact scalability and clinical translation of hESC-derived RPE as a cell therapy.

SIGNIFICANCE: Stem cell-derived retinal pigment epithelium (RPE) is currently being evaluated as a cell-

replacement therapy for macular degeneration. This work shows that the process of generating RPE in vitro is regulated by the cAMP and transforming growth factor-β signaling pathway. Modulation of these pathways by small molecules, as identified by phenotypic screening, leads to an increased efficiency of generating RPE cells with a higher yield. This can have a potential impact on manufacturing transplantation -ready cells at large scale and is advantageous for clinical studies using this approach in the future.

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Invest Ophthalmol Vis Sci. 2016 Apr 1;57(5):ORSFl1-ORSFl11.

Treatment Paradigms for Retinal and Macular Diseases Using 3-D Retina Cultures Derived From Human Reporter Pluripotent Stem Cell Lines.

Kaewkhaw R, Swaroop M, Homma K, Nakamura J, Brooks M, Kaya KD, Chaitankar V, Michael S, Tawa G, Zou J, Rao M, Zheng W, Cogliati T, Swaroop A.

Abstract: We discuss the use of pluripotent stem cell lines carrying fluorescent reporters driven by retinal promoters to derive three-dimensional (3-D) retina in culture and how this system can be exploited for elucidating human retinal biology, creating disease models in a dish, and designing targeted drug screens for retinal and macular degeneration. Furthermore, we realize that stem cell investigations are labor-intensive and require extensive resources. To expedite scientific discovery by sharing of resources and to avoid duplication of efforts, we propose the formation of a Retinal Stem Cell Consortium. In the field of vision, such collaborative approaches have been enormously successful in elucidating genetic susceptibility associated with age-related macular degeneration.

PMID: 27116668 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2016 Apr 1;57(5):ORSFc1-9.

Subretinal Transplantation of Embryonic Stem Cell-Derived Retinal Pigment Epithelium for the Treatment of Macular Degeneration: An Assessment at 4 Years.

Schwartz SD, Tan G, Hosseini H, Nagiel A.

Abstract: Advanced macular degeneration is an important cause of vision loss in the United States with over 2 million people affected by the disease. Despite substantial progress in the development of new therapies for wet AMD, the severe visual impairment associated with geographic atrophy in dry AMD or Stargardt disease remains untreatable. Recently, two phase I/II studies involving 18 patients with these diseases have demonstrated that it is possible to safely implant human embryonic stem cell-derived RPE (hESC-RPE) in an attempt to rescue photoreceptors and visual function. The anatomical and functional results are encouraging, with more than half of treated patients experiencing sustained improvements in visual acuity and demonstrating evidence of possible cellular engraftment. However, any conclusions remain tempered by the relatively short follow-up time, lack of a formal control group, poor initial visual acuity, and small number of patients. Aside from an instance of postoperative infectious endophthalmitis, no adverse events related to the cell therapy, such as hyperproliferation, tumorigenicity, or rejection-related inflammation were noted in this initial cohort of 18 patients. These first-in-human safety studies have opened the door to future studies enrolling patients with less advanced disease, treating other diseases that result in RPE loss, employing shorter immunosuppressive regimens, and using alternative strategies for RPE transplantation such as sheets of cells with or without scaffolding to mimic Bruch's membrane. The ultimate goal of these initial safety studies is to promote continued translation of complex biological therapies into meaningful treatment strategies that may address unmet medical needs.

PMID: 27116660 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2016 Apr 1;57(5):ORSFb1-3.

Stemming the Tide of Age-Related Macular Degeneration: New Therapies for Old Retinas.

Ramsden CM, da Cruz L, Coffey PJ.

PMID: 27116659 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2016 Apr 1;57(5):ORSFm1-9.

Stem Cell Therapy in Nonneovascular Age-Related Macular Degeneration.

Kashani AH.

Abstract: Age-related macular degeneration (ARMD) is the leading cause of blindness in subjects older than 50 years of age in the developed world. There are two types of ARMD, neovascular (NV) and nonneovascular (NN). While anti-VEGF-based therapies have significantly decreased the visual morbidity associated with NV-ARMD, there are no effective treatments for NN-ARMD. A detailed discussion of NV-ARMD and related therapies is the topic of another section of this special supplement. This review will focus mainly on NN-ARMD. Vision loss in nonneovascular ARMD is highly correlated with the loss of RPE cells and areas of geographic atrophy (GA). Pilot studies using subretinal transplantation of autologous or allogeneic RPE during the past 20 to 30 years have demonstrated that stem cell-derived RPE have the potential to rescue photoreceptor function and restore vision. New methods of differentiating RPE from human embryonic stem cells (hESC) and induced pluripotent stem cells (iPSC) have created a potentially unlimited supply of RPE cells to meet the demands of future commercially viable stem cell products. Thanks to fundamental advances in stem cell biology, vitreoretinal surgery, and noninvasive retinal imaging, stem cell-based therapies for NN-ARMD are emerging and several clinical trials are in progress. However, there are major regulatory, safety, and technical challenges that remain. This review will focus on summarizing the most promising aspects of stem cell-based therapy for NN-ARMD and highlighting areas that require further research.

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Diet, lifestyle & low vision

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The Association Between Serum Vitamin D Levels and Age-Related Macular Degeneration: A Systematic Meta-Analytic Review.

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PURPOSE: We conducted a meta-analysis of individual studies reporting an association between serum vitamin D levels and AMD.

METHODS: Relevant studies evaluating the association between serum vitamin D levels and AMD risk were identified by systematically searching four electronic literature databases (Ovid Medline, PubMed, EMBASE, and ISI Web of Science) censored by June 2015. Due to the heterogeneity of studies in categorizing serum vitamin D levels, all individual odds ratios (ORs) were recalculated and transferred for an increase of serum vitamin D levels by 10 ng/ml. Summary ORs and 95% confidence intervals (CIs) of AMD risk per 10-unit increase of serum vitamin D were obtained using standard meta-analysis. Publication bias was evaluated using funnel plots and Kendall's rank correlation tests.

RESULTS: Ten individual studies were included and pooled in this meta-analysis. Meta-analysis of studies

on AMD risk led to a pooled OR (95% CI) of 0.91 (0.69-1.22) for an increase of 25-hydroxy vitamin D by 10 ng/mL (P = 0.12). No indication for publication bias was found, but substantial heterogeneity was obtained (I2 = 79.7%, P < 0.01). Estimates from subgroup analyses also did not show statistically significant associations of serum vitamin D levels with different stages (early AMD, late AMD, and advanced AMD) and subtypes of AMD (neovascular AMD and nonneovascular AMD; P > 0.05).

CONCLUSIONS: There is no evidence to indicate an inverse association between serum vitamin D levels and any stages and subtypes of AMD risk, but opposite results from the United States and Korea resulted in this nonsignificance. Potential difference across various study designs might exist, based on few studies reporting in heterogeneous manners so far. More studies are needed to further confirm the causality of vitamin D and AMD, especially longitudinal studies.

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