

Issue 297

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Drug Treatment

Am J Ophthalmol. 2016 Sep 13. [Epub ahead of print]

Real-world outcomes of ranibizumab treatment for diabetic macular edema in a United Kingdom National Health Service setting.

Patrao NV, Antao S, Egan C, Omar A, Hamilton R, Hykin PG, Sivaprasad S, Rajendram R; Moorfields diabetic macular edema study group.

PURPOSE: To determine visual acuity (VA) and spectral domain optical coherence tomography (OCT) outcomes with intravitreal ranibizumab for diabetic macular edema (DME) in a United Kingdom National Health Service clinical setting.

DESIGN: Retrospective interventional case series **PARTICIPANTS:** Consecutive patients with DME, treated with the first ranibizumab injection between August 2013 and March 2014 across 4 sites of Moorfields Eye Hospital, London.

METHODS: 200 eyes of 164 consecutive patients with center-involving DME and VA ≤ 79 ETDRS letters, central subfield macular thickness (CST) $\geq 350\mu\text{m}$ on Topcon 3D OCT 2000 initiated on a loading phase of 3 intravitreal ranibizumab injections and who had at least 6 months follow up were reviewed. Subsequent re-treatment was guided by VA and OCT with the aim of treating to stability. VA, OCT CST and macular volume (MV) were recorded at baseline and monthly to 12 months.

RESULTS: The mean VA, mean CST and mean MV at baseline were $54.4(\pm 15.26)$ letters, $490.16(\pm 116.54)\mu\text{m}$ and $10.46(\pm 2.28)\text{mm}^3$. The mean VA change at 12 months was $+6.6(\pm 13.35)$ letters ($p=0.0003$). 40.3% ($n=77$) of patients gained ≥ 10 letters and 25.1% ($n=48$) gained ≥ 15 letters. 8.9% ($n=17$) lost ≥ 10 letters and 6.3% ($n=12$) lost ≥ 15 letters. At 12 months, the mean change in CST and MV were $-133.9(\pm 160.12)\mu\text{m}$ ($p=0.0001$) and $-1.5(\pm 1.96)\text{mm}^3$ ($p=0.0001$) respectively. An average of $7.2(\pm 2.3)$ injections were given over 12 months.

CONCLUSIONS: Outcomes with three loading injections of 0.5mg ranibizumab given monthly followed by PRN re-treatment in a clinical setting are comparable with outcomes from clinical trials.

PMID: 27637784

Graefes Arch Clin Exp Ophthalmol. 2016 Sep 8. [Epub ahead of print]

A multicenter, 12-month randomized study comparing dexamethasone intravitreal implant with ranibizumab in patients with diabetic macular edema.

Callanan DG, Loewenstein A, Patel SS, Massin P, Corcóstegui B, Li XY, Jiao J, Hashad Y, Whitcup SM.

PURPOSE: To evaluate whether treatment with dexamethasone intravitreal implant (DEX implant) 0.7 mg every 5 months provides a similar average change in best-corrected visual acuity (BCVA) from baseline as ranibizumab 0.5 mg administered as per its European Summary of Product Characteristics in patients with diabetic macular edema (DME).

METHODS: This was a multicenter, open-label, 12-month, randomized, parallel-group, noninferiority study in patients with DME (one eye/patient). The primary efficacy measure was BCVA using the Early Treatment Diabetic Retinopathy Study (ETDRS) method. Secondary efficacy measures included area of leakage on fluorescein angiography and central retinal thickness (CRT) on optical coherence tomography.

RESULTS: Baseline patient characteristics were similar in the two treatment groups (DEX implant, n = 181; ranibizumab, n = 182); mean DME duration was 33 months. The mean average BCVA change from baseline over 12 months was 4.34 letters with DEX implant and 7.60 letters with ranibizumab. The lower limit of the 95 % confidence interval of the between-group difference was -4.74 letters, and therefore, DEX was demonstrated to be noninferior to ranibizumab based on the prespecified noninferiority margin of 5 letters. At monthly follow-up visits, the percentage of patients with ≥ 15 -letter BCVA gain from baseline ranged from 7.2 to 17.7 % with DEX implant and 4.4 to 26.9 % with ranibizumab. Both DEX implant and ranibizumab effectively reduced CRT and reduced the area of fluorescein leakage. Between-group differences in change from baseline CRT favored DEX implant at 1, 2, 6, and 7 months ($p \leq 0.007$) and ranibizumab at 4, 5, 9, and 10 months ($p < 0.001$); the decrease in fluorescein leakage area was greater with DEX implant than ranibizumab at month 12 ($p < 0.001$). Ocular adverse events in the study eye were more frequent in the DEX implant group because of the occurrence of intraocular pressure (IOP) increases and cataract. IOP increases were transient and generally managed with topical medication.

CONCLUSIONS: Both DEX implant and ranibizumab were well tolerated and improved BCVA and anatomic outcomes in patients with DME. DEX implant met the a priori criterion for noninferiority to ranibizumab in average change from baseline BCVA over 12 months. Noninferiority was achieved with an average of 2.85 DEX implant injections and 8.70 ranibizumab injections per patient.

PMID: 27632215

Ophthalmic Surg Lasers Imaging Retina. 2016 Sep 1;47(9):836-9.

Aflibercept for Diabetic Macular Edema in Eyes Previously Treated With Ranibizumab and/or Bevacizumab May Further Improve Macular Thickness.

Shah CP, Heier JS.

BACKGROUND AND OBJECTIVE: To evaluate the short-term anatomic and visual outcomes after aflibercept (Eylea; Regeneron, Tarrytown, NY) in eyes with diabetic macular edema (DME) previously treated with ranibizumab (Lucentis; Genentech, South San Francisco, CA) and/or bevacizumab (Avastin; Genentech, South San Francisco, CA).

PATIENTS AND METHODS: A single-center, retrospective, noncomparative study of 30 eyes in 23 patients with DME treated with prior ranibizumab and/or bevacizumab before switching to aflibercept.

RESULTS: Eyes received an average of 16 prior injections (range: three injections to 31 injections; median: 17 injections). The mean central subfoveal thickness (CST) improved from 453 μm at the time of first anti-vascular endothelial growth factor (VEGF) injection (range: 304 μm to 686 μm ; median: 429 μm), to 374 μm at the time of the switch to aflibercept (range: 267 μm to 547 μm ; median: 361 μm ; $P = .02$), to 332 μm after the first aflibercept injection (range: 242 μm to 545 μm ; median: 318 μm ; $P < .001$). Visual acuity improved after switching to aflibercept at the first follow-up visit (logMAR 0.40 [Snellen equivalent 20/50]) to logMAR 0.35 (Snellen equivalent 20/45) ($P = .044$).

CONCLUSIONS: In eyes with persistent DME treated with ranibizumab and/or bevacizumab, switching to

aflibercept may further improve macular thickness. Given the cost difference between the three drugs, a randomized trial evaluating a stepwise approach may be worthwhile. [Ophthalmic Surg Lasers Imaging Retina. 2016;47:836-839.].

PMID: 27631479

Retina. 2016 Jul 12. [Epub ahead of print]

OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY ASSESSMENT OF VASCULAR EFFECTS OCCURRING AFTER AFLIBERCEPT INTRAVITREAL INJECTIONS IN TREATMENT-NAIVE PATIENTS WITH WET AMD.

Mastropasqua L, Toto L, Borrelli E, Carpineto P, Di Antonio L, Mastropasqua R.

PURPOSE: To investigate vessel changes occurring after aflibercept injections in treatment-naive exudative age-related macular degeneration patients.

METHODS: Fifteen eyes of 15 patients affected by wet age-related macular degeneration were enrolled in the study. All the patients had a diagnosis of Type 1 choroidal neovascularization and were treated with 3 monthly aflibercept intravitreal injections (IVI). Subjects were evaluated by means of optical coherence tomography angiography at baseline, the day after the first injection and one month after both the first and the second IVI. At last, all the patients were followed up to 2 months after the third IVI.

RESULTS: Foveal superficial vascular plexus flow density was 29.01% (21.13-37.32%) at baseline and was significantly reduced as soon as 1 month after the first IVI (median: 20.78%; interquartile range: 14.75-23.13%; $P = 0.017$). Parafoveal superficial vascular plexus flow density was 47.09% (44.91-51.72%) at baseline and significantly decreased as soon as 1 month after the second IVI (median: 44.40%; interquartile range: 41.59-49.29%; $P = 0.034$). Choroidal neovascularization lesion area remained stable throughout the follow-up. Nevertheless, interestingly, choroidal neovascularization flow area was significantly reduced as soon as the next day the first IVI (median: 0.37 mm and interquartile range: 0.27-0.72 mm at baseline; median: 0.30 mm and interquartile range: 0.24-0.64 mm at 1 day after the first IVI; $P = 0.047$).

CONCLUSION: Intravitreal aflibercept injections are associated with a significant change in native retinal and choroidal vasculature. Moreover, the treatment did not cause a reduction in lesion area, but rather reduced the flow in the choroidal neovascularization.

PMID: 27628926

Graefes Arch Clin Exp Ophthalmol. 2016 Sep 14. [Epub ahead of print]

Efficacy of fixed-dosing aflibercept for treating polypoidal choroidal vasculopathy: 1-year results of the VAULT study.

Lee JE, Shin JP, Kim HW, Chang W, Kim YC, Lee SJ, Chung IY, Lee JE; VAULT study group.

PURPOSE: To investigate fixed-dosing aflibercept for treating polypoidal choroidal vasculopathy (PCV).

METHODS: This phase IV, prospective, single-arm, interventional case series was conducted in eight centers. Forty treatment-naïve PCV patients were administered three monthly doses of intravitreal aflibercept (2.0 mg) and an injection every 2 months thereafter. Best-corrected visual acuity (BCVA) and central subfield macular thickness (CSMT) were measured at each visit. Fluorescein and indocyanine green angiography (ICGA) were performed at baseline, 3 and 12 months. The primary outcome measure was the proportion of patients who maintained BCVA (<15 letters loss) at 12 months. Changes in BCVA, macular appearance, and polypoidal lesion appearance were also examined.

RESULTS: Thirty-five eyes (87.5 %) had maintained BCVA at 12 months. Average BCVA was significantly higher at 12 months (20/53, 64.2 letters) than at baseline (20/80, 55.1 letters, 9-letter gain; $P < .001$). Mean CSMT was significantly lower at 12 months (253.6 μm) than at baseline (365.2 μm , $P < .001$). The macula was dry in 32 (76.2 %), 27 (64.3 %), and 24 eyes (60.0 %) at 3, 6, and 12 months respectively. Fourteen eyes (33.3 %) had a fluid recurrence or increase at 6 months, and they had a significantly lower vision gain ($P = .005$) than other patients at 12 months. Complete polyp regression occurred in 26 eyes (66.7 %) at 12 months.

CONCLUSIONS: Fixed-dosing aflibercept showed favorable outcomes in PCV patients at 12 months. However, some patients had worse outcomes because of fluid recurrence during maintenance dosing, and these patients would require additional treatments.

PMID: 27628062

Retina. 2016 Sep 13. [Epub ahead of print]

REGRESSION OF TYPE 2 NEOVASCULARIZATION INTO A TYPE 1 PATTERN AFTER INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Dolz-Marco R, Phasukkijwatana N, Sarraf D, Freund KB.

PURPOSE: To study eyes with Type 2 (subretinal) neovascularization (NV) secondary to neovascular age-related macular degeneration (nAMD) that shows lesion regression into a Type 1 (subretinal pigment epithelium) pattern after treatment with intravitreal anti-vascular endothelial growth factor (VEGF) therapy.

METHODS: Retrospective consecutive case series. Patients showing regression of Type 2 neovascularization into a Type 1 pattern after envelopment by retinal pigment epithelium were included in this analysis. A review of the clinical records and multimodal imaging of these cases was performed at baseline, 1, 3, 6, and 12 months. Demographic data, best-corrected visual acuity (BCVA), color fundus photography, fundus autofluorescence (FAF), fluorescein angiography, near-infrared reflectance (NIR), and structural spectral-domain optical coherence tomography (SD-OCT) were reviewed and analyzed. When available, optical coherence tomography angiography images were analyzed as well.

RESULTS: Ten eyes of 9 patients (6 males) diagnosed with treatment-naïve pure Type 2 neovascularization secondary to nAMD were included. The mean age was 80.7 years ($\text{SD} \pm 4.30$). Mean best-corrected visual acuity expressed in logMAR (Snellen) was 0.45 ± 0.20 (20/55) at baseline and significantly improved to 0.22 ± 0.13 (20/32) at 3-month follow-up (P -value: 0.007). At baseline, color photographs and fundus autofluorescence showed a pigment ring around the neovascular lesion in 6 eyes. A hyperreflective ring was visible on NIR in all eyes at 3-month follow-up. Color photographs showed a tessellated fundus appearance in 9 of the 10 eyes. Serial structural spectral-domain optical coherence tomography scans showed the gradual regression of the Type 2 lesions into a Type 1 pattern with envelopment by the retinal pigment epithelium. En face and cross-sectional optical coherence tomography angiography showed baseline subretinal flow patterns which, after treatment, exhibited reduced flow beneath an intact hyperreflective retinal pigment epithelium (RPE) band.

CONCLUSION: Pure Type 2 lesions are infrequent in nAMD, often leading to poor visual outcomes related to subretinal fibrosis. We describe an alternate regression pattern occurring in eyes with early Type 2 lesions treated with intravitreal anti-vascular endothelial growth factor therapy in which the neovascular tissue is enveloped by retinal pigment epithelium producing a Type 1 pattern. These eyes appear to have better visual outcomes than typically seen with Type 2 lesions related to reduced outer retinal damage.

PMID: 27627752

World J Diabetes. 2016 Aug 25;7(16):333-41.

Treatment of diabetic retinopathy: Recent advances and unresolved challenges.

Stewart MW.

ABSTRACT: Diabetic retinopathy (DR) is the leading cause of blindness in industrialized countries. Remarkable advances in the diagnosis and treatment of DR have been made during the past 30 years, but several important management questions and treatment deficiencies remain unanswered. The global diabetes epidemic threatens to overwhelm resources and increase the incidence of blindness, necessitating the development of innovative programs to diagnose and treat patients. The introduction and rapid adoption of intravitreal pharmacologic agents, particularly drugs that block the actions of vascular endothelial growth factor (VEGF) and corticosteroids, have changed the goal of DR treatment from stabilization of vision to improvement. Anti-VEGF injections improve visual acuity in patients with diabetic macular edema (DME) from 8-12 letters and improvements with corticosteroids are only slightly less. Unfortunately, a third of patients have an incomplete response to anti-VEGF therapy, but the best second-line therapy remains unknown. Current first-line therapy requires monthly visits and injections; longer acting therapies are needed to free up healthcare resources and improve patient compliance. VEGF suppression may be as effective as panretinal photocoagulation (PRP) for proliferative diabetic retinopathy, but more studies are needed before PRP is abandoned. For over 30 years laser was the mainstay for the treatment of DME, but recent studies question its role in the pharmacologic era. Aggressive treatment improves vision in most patients, but many still do not achieve reading and driving vision. New drugs are needed to add to gains achieved with available therapies.

PMID: 27625747

Clin Ophthalmol. 2016 Aug 29;10:1679-84. eCollection 2016.

Contralateral eye-to-eye comparison of intravitreal ranibizumab and a sustained-release dexamethasone intravitreal implant in recalcitrant diabetic macular edema.

Thomas BJ, Yonekawa Y, Wolfe JD, Hassan TS.

OBJECTIVE: To compare the effects of intravitreal ranibizumab (RZB) or dexamethasone (DEX) intravitreal implant in cases of recalcitrant diabetic macular edema (DME).

METHODS: Retrospective, interventional study examining patients with symmetric bilateral, center-involved DME recalcitrant to treatment with RZB, who received DEX in one eye while the contralateral eye continued to receive RZB every 4-5 weeks for a study period of 3 months.

RESULTS: Eleven patients (22 eyes) were included: mean logarithm of the minimal angle of resolution (logMAR) visual acuity (VA) for the DEX arm improved from 0.415 (standard deviation [SD] ± 0.16) to 0.261 (SD ± 0.18) at final evaluation, and mean central macular thickness (CMT) improved from 461 μm (SD ± 156) to 356 μm (SD ± 110 ; net decrease: 105 μm , $P=0.01$). Mean logMAR VA for the RZB arm improved from 0.394 (SD ± 0.31) to 0.269 (SD ± 0.19) at final evaluation. Mean CMT improved from 421 μm (SD ± 147) to 373 μm (SD ± 129 ; net decrease: 48 μm , $P=0.26$).

CONCLUSION: A subset of recalcitrant DME patients demonstrated significant CMT reduction and VA improvement after a single DEX injection.

PMID: 27621587

Retina. 2016 Sep 8. [Epub ahead of print]

TYPE 1 VERSUS TYPE 3 NEOVASCULARIZATION IN PIGMENT EPITHELIAL DETACHMENTS ASSOCIATED WITH AGE-RELATED MACULAR DEGENERATION AFTER ANTI-VASCULAR

ENDOTHELIAL GROWTH FACTOR THERAPY: A Prospective Study.

Chen X, Al-Sheikh M, Chan CK, Hariri AH, Abraham P, Lalezary M, Lin SG, Sadda S, Sarraf D.

PURPOSE: To evaluate the response to aflibercept therapy for Type 1 and Type 3 neovascularization in pigment epithelial detachments associated with treatment-naïve, neovascular age-related macular degeneration.

METHODS: In this multicentered, prospective study, eligible eyes underwent an intravitreal aflibercept injection protocol for 12 months. Visual acuity and morphologic features of the pigment epithelial detachments were compared at baseline and follow-up intervals between eyes with Type 1 versus Type 3 neovascularization.

RESULTS: Thirty-six eyes were analyzed. At 12 months, Type 1 lesions showed a 4.5 ± 23 Early Treatment of Diabetic Retinopathy Study letter improvement ($P = 0.1665$) versus a 14 ± 11 ($P = 0.0072$) letter improvement with Type 3 lesions. Both Type 1 and 3 eyes showed a significant decrease in pigment epithelial detachment size, subretinal fluid, and subretinal hyperreflective material; however, Type 3 eyes had a greater reduction in pigment epithelial detachment size and subretinal hyperreflective material, as well as a reduction in central retinal thickness. Type 1 eyes required an average of 1.636 (range, 1-4) injections to resolve fluid, which was greater than Type 3 eyes, which required an average of 1.143 (range, 1-2) injections ($P = 0.0251$).

CONCLUSION: Intravitreal aflibercept injections were efficacious for pigment epithelial detachments, but baseline and follow-up anatomical and functional outcomes differed in Type 1 versus Type 3 neovascularization. The better response of Type 3 eyes with fewer injections suggests that differentiation of the neovascularization subtype at the initial diagnosis may allow for a more tailored, optimal therapy.

PMID: 27617543

Retina. 2016 Sep 8. [Epub ahead of print]

LONG-TERM OUTCOMES AND INCIDENCE OF RECURRENCE OF NEOVASCULARIZATION IN TREATED EXUDATIVE AGE-RELATED MACULAR DEGENERATION.

Haddad WM, Minous FL, Legeai J, Souied EH.

PURPOSE: To assess the long-term visual outcome and incidence of recurrence of neovascular age-related macular degeneration (NAMMD) treated with intravitreal anti-VEGF injections (IVAI).

METHODS: One hundred and thirty-two consecutive eyes treated with IVAI for NAMMD based on an as-needed regimen with a follow-up ≥ 5 years (mean 7.55, range 5-9.67) were retrospectively reviewed. Main outcome measures included visual acuity, yearly number of IVAI, and occurrence of a long-term remission, defined as no recurrence of NAMMD for ≥ 12 consecutive months.

RESULTS: Mean baseline visual acuity was 20/100. Mean final visual acuity change was -3.41 letters. Mean overall IVAI number was 22.8 ± 17.4 (range 2-71), decreasing from 4.6 during Year 1 to 2.21 during Year 8. A significant positive correlation was found between the number of IVAI during the first year of treatment and the overall number of IVAI during 5 years, 6 years, 7 years, or 8 years follow-up ($r = 0.67$ - 0.70 , $P < 0.0001$). Long-term remission occurred at least once in 83/132 eyes (63%) and was associated with a better visual outcome (-1.04 vs. -7.43 letters, $P = 0.034$). Incidence of yearly remission of NAMMD increased from 28% during Year 2 to 59% during Year 8, fitting along a single straight line ($+5.231\%/year$, $R = 0.9511$).

CONCLUSION: The incidence of recurrence of treated NAMMD decreases slowly but steadily during follow-up. The number of years of follow-up is the main factor to assess the proportion of treated eyes at remission at a given moment. Incidence of recurrence of neovascularization during year 1 and length of follow-up are significant factors when tailoring an optimal long-term follow-up regimen.

PMID: 27617541

Retina. 2016 Sep 8. [Epub ahead of print]

SERUM LEVELS OF VASCULAR ENDOTHELIAL GROWTH FACTOR BEFORE AND AFTER INTRAVITREAL INJECTION OF RANIBIZUMAB OR CONBERCEPT FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Jin E, Bai Y, Luo L, Huang L, Zhu X, Ding X, Qi H, Zhao M.

OBJECTIVE: To investigate the serum levels of vascular endothelial growth factor (VEGF) before and after intravitreal injection of conbercept or ranibizumab for neovascular age-related macular degeneration and polypoidal choroidal vasculopathy patients.

METHODS: This study is a prospective, interventional case series and involved 28 patients, 18 treated with 0.5 mg of conbercept and 10 treated with 0.5 mg of ranibizumab. Serum concentrations of VEGF were determined by enzyme-linked immunosorbent assay before the injection and at 1 day, 1 week, and 1 month after anti-VEGF treatments.

RESULTS: The baseline serum VEGF level of the ranibizumab group was 367.11 ± 311.87 pg/mL, whereas that of the conbercept group was 315.06 ± 170.88 pg/mL ($P = 0.653$). In the conbercept group, VEGF level significantly decreased to 36.32 ± 72.11 pg/mL at 1 day ($P = 0.03$) and returned to 136.55 ± 144.62 pg/mL at 1 week ($P = 0.03$). At 1 month, the concentration increased to 334.48 ± 197.41 pg/mL and showed no significant difference compared with the baseline. In the ranibizumab group, the serum VEGF levels were 292.42 ± 239.80 pg/mL, 282.60 ± 201.36 pg/mL, and 308.83 ± 266.89 pg/mL at 1 day, 1 week, and 1 month after intravitreal injection, respectively. There was no significant difference in the ranibizumab group at each detection time point ($P = 0.45$).

CONCLUSION: Conbercept significantly decreased serum VEGF level 1 day and 1 week after injection, but this effect was not sustained for 1 month. In contrast, ranibizumab had no significant effect on serum VEGF concentration changes. The reduction in serum VEGF by conbercept may affect its systemic safety profile.

PMID: 27617537

Retin Cases Brief Rep. 2016 Sep 8. [Epub ahead of print]

USE OF AFLIBERCEPT FOR THE MANAGEMENT OF REFRACTORY PSEUDOPHAKIC MACULAR EDEMA IN IRVINE-GASS SYNDROME AND LITERATURE REVIEW.

Lin CJ, Tsai YY.

BACKGROUND/PURPOSE: To present the patient treated for pseudophakic cystoid macular edema with intravitreal aflibercept.

METHODS: Interventional case report.

CASE: An 83-year-old woman presented with decreased vision 1 month after uneventful cataract surgery. After failure to respond to posterior subtenons triamcinolone and three Ranibizumab injections, the patient responded to one intravitreal aflibercept injection. Recurrence occurred two months later, and therefore three monthly injections were then given. Again the patient responded although recurrence occurred two months after treatment. The patient refused further treatment.

CONCLUSION: Intravitreal aflibercept may be effective for the treatment of pseudophakic cystoid macular edema.

PMID: 27617392

Eur J Pharm Biopharm. 2016 Sep 8. [Epub ahead of print]

Study of stability and biophysical characterization of ranibizumab and aflibercept.

Moreno MR, Tabitha TS, Nirmal J, Radhakrishnan K, Yee CH, Lim S, Venkatraman S, Agrawal R.

ABSTRACT: The anti-vascular endothelial growth factor (VEGF) agents such as ranibizumab (Lucentis®) and aflibercept (EyLea®) are currently used as monthly or bimonthly intravitreal injections to treat potentially blinding retinal diseases such as wet age-related macular degeneration (AMD) or diabetic macular edema (DME). Because of the complications associated with repeated intra-vitreous injections, there is considerable interest in developing a sustained delivery system. The purpose of this study was to examine the stability of both therapeutic proteins under physiological conditions as well as when incorporated into drug delivery systems (DDS). First, thermotropic properties in physiological conditions and at different pH values were evaluated by differential scanning calorimetry (DSC) to determine the protein denaturation temperature. Second, the effects of pH and incubation time on conformational changes and aggregation were evaluated by circular dichroism (CD), steady-state tryptophan fluorescence spectroscopy, and size-exclusion chromatography (SEC). Also, the ability of both proteins to bind to VEGF was tested in the aforementioned experimental conditions for up to 30 days. Finally, we investigated the stability of both proteins after a rapid screening method that simulates the first homogenizing step during the protein microencapsulation process. This method allowed the development of stable ranibizumab and aflibercept formulations that may be useful to entrap these proteins into microparticles selecting the most convenient organic solvent and protein stabilizers.

PMID: 27615995

Ophthalmology. 2016 Sep 8. [Epub ahead of print]

UK Age-Related Macular Degeneration Electronic Medical Record System (AMD EMR) Users Group Report IV: Incidence of Blindness and Sight Impairment in Ranibizumab-Treated Patients.

Johnston RL, Lee AY, Buckle M, Antcliff R, Bailey C, McKibbin M, Chakravarthy U, Tufail A; UK AMD EMR Users Group.

PURPOSE: To study the incidence of blindness and sight impairment in treatment-naïve patients receiving ranibizumab (Lucentis) for neovascular age-related macular degeneration (nAMD) in the United Kingdom (UK) National Health Service.

DESIGN: Multicenter nAMD database study.

PARTICIPANTS: A total of 11 135 patients who collectively received 92 976 treatment episodes to 12 951 eyes.

METHODS: Data were extracted from 14 UK centers using the same electronic medical record system (EMR). The EMR-mandated collection of a data set (defined before first data entry) including: age, Early Treatment Diabetic Retinopathy Study visual acuity letter score (VA) for both eyes at all visits, and injection episodes. Participating centers used overwhelmingly a pro re nata re-treatment posology at intended monthly follow-up visits following a loading phase of 3 monthly injections.

MAIN OUTCOME MEASURES: Incidence of blindness and sight impairment (VA in the better-seeing eye <38 letters [$\leq 20/200$ Snellen, approximately], and <68 letters [$\leq 20/50$ Snellen, approximately] at 2 consecutive visits, or 1 visit if no further follow-up data) in each year after initiating treatment.

RESULTS: Information from >300 000 clinic visits (2.8 million data points) collected over 5 years was collated from 14 centers. Mean age at first treatment was 79.7 years (standard deviation = 9.19 years), with a female preponderance (63%). The mean (median) VA at baseline in the better-seeing eye was 67.2 (72.0) letters, 20/40- (20/40+) approximate Snellen conversion. The cumulative incidence of new blindness and sight impairment in patients with treated nAMD in at least 1 eye at years 1 to 4 after first injection were 5.1%, 8.6%, 12% and 15.6% for new blindness and 29.6%, 41.0%, 48.7%, and 53.7% for new sight

impairment, but with significant reductions in the rates between year cohorts initiating treatment (blindness [$P = 4.72 \times 10^{-08}$], sight impaired [$P = 3.27 \times 10^{-06}$]).

CONCLUSIONS: To the best of our knowledge, this is the first multicenter real-world study on the incidence of blindness and sight impairment based on VA data in patients treated with ranibizumab for nAMD, and its results show low incidences of both blindness and sight impairment, which both declined during the study period.

PMID: 27615601

Other Treatment and Diagnosis

Meta Gene. 2016 Jul 22;9:249-53. eCollection 2016.

Vascular endothelial growth factor gene polymorphisms and association with age related macular degeneration in Indian patients.

Gupta D, Gupta V, Singh V, Prakash S, Agrawal S, Chawla S, Phadke SR.

BACKGROUND: Age-related macular degeneration (AMD) is an important cause of visual impairment in elderly people. AMD is a multifactorial disease in which both environmental and genetic factors have been implicated. Various single nucleotide polymorphisms (SNPs) have been found to be associated with AMD.

AIM: This study was aimed to investigate the association of polymorphisms in VEGF genes with age related macular degeneration (AMD) in Indian patients.

METHOD: Genotyping for the VEGF - 1154 (G > A), - 2578 (C > A), + 405 (G > C) and - 460 (C > T) SNPs was performed in 100 AMD patients and 100 controls by polymerase chain reaction (PCR), restriction fragment length polymorphism (PCR-RFLP) and sequencing method.

RESULTS: Out of the four SNPs, heterozygous genotypes of VEGF - 1154 G > A (OR = 2.58, $p = 0.0035$), + 460 C > T (OR = 2.90, $p = 0.0046$), and + 405 G > C (OR = 2.02, $p = 0.02$) have shown susceptible association with AMD. However, VEGF - 2578 C > A did not show any statistical significance. Further A-A-G-T haplotype comprising of three mutant alleles revealed risk association (OR = 12.7, $p = 0.0030$) with AMD.

CONCLUSION: The present study suggests significant genetic associations for VEGF - 1154 G > A, + 460 C > T, and + 405 G > C polymorphisms with AMD. Early detection of individuals with risk to these SNPs could lead to strategies for prevention, early diagnosis, and management of AMD.

PMID: 27617226

Retina. 2016 Sep 14. [Epub ahead of print]

CHOROIDAL VASCULARITY INDEX: A Novel Optical Coherence Tomography Based Parameter in Patients With Exudative Age-Related Macular Degeneration.

Wei X, Ting DS, Ng WY, Khandelwal N, Agrawal R, Cheung CM.

PURPOSE: To evaluate choroidal structural changes in exudative age-related macular degeneration (AMD) using choroidal vascularity index computed from image binarization on spectral domain optical coherence tomography with enhanced depth imaging.

METHODS: This prospective case series included 42 consecutive patients with unilateral exudative AMD. Choroidal images were segmented into luminal area and stromal area. Choroidal vascularity index was defined as the ratio of luminal area to total choroid area. Mean choroidal vascularity index and mean

choroidal thickness between study and fellow eyes of the same patient with dry AMD were compared using Student's t-test.

RESULTS: There was a significantly lower choroidal vascularity index in eyes with exudative AMD (60.14 ± 4.55 vs. 62.75 ± 4.82 , $P < 0.01$). Luminal area ($P < 0.01$) was decreased in eyes with exudative AMD but there was no significant difference in total choroid area ($P = 0.05$) and choroidal thickness ($P = 0.93$) between study and fellow eyes.

CONCLUSION: Eyes with exudative AMD demonstrated reduced choroidal vascularity index but insignificant differences in choroidal thickness compared with their fellow eyes. Choroidal vascularity index may be a potential noninvasive tool for studying structural changes in choroid and monitoring choroidal disease in exudative AMD.

PMID: 27632714

Br J Ophthalmol. 2016 Sep 13. [Epub ahead of print]

Association between outer retinal alterations and microvascular changes in intermediate stage age-related macular degeneration: an optical coherence tomography angiography study.

Toto L, Borrelli E, Mastropasqua R, Di Antonio L, Doronzo E, Carpineto P, Mastropasqua L.

AIMS: To investigate associations between changes in retinal vessels and alterations detected by spectral domain optical coherence tomography (SD-OCT) scans in intermediate stage age-related macular degeneration (AMD).

METHODS: Thirty eyes of 30 patients with intermediate dry AMD were enrolled in the study. Of the cohort study, 15 eyes (changes-AMD group) showed OCT changes preceding the development of drusen-associated atrophy. A control group of healthy subjects was selected for statistical comparisons. All patients underwent an ophthalmologic evaluation, including OCT angiography (OCTA) and SD-OCT scans. Main outcome measures were superficial vessel density, deep vessel density, macular thickness.

RESULTS: Foveal macular thickness was 215.2 ± 32.9 μm in changes-AMD patients and was significantly thinner than no changes-AMD patients (248.3 ± 23.3 μm , $p = 0.002$) and healthy subjects (268.1 ± 19.2 μm , $p < 0.0001$). Furthermore, in the parafoveal area, the thicknesses of both the inner retina and the outer retina were reduced in the changes-AMD group, after comparison with the two other groups. Parafoveal superficial vascular plexus flow density was $43.3 \pm 2.7\%$ in changes-AMD patients and was decreased compared with the no changes-AMD group ($48.7 \pm 3.3\%$, $p = 0.003$) and healthy controls ($50.4 \pm 6.1\%$, $p = 0.001$). A direct correlation of the superficial plexus flow density with the inner retina parafoveal macular thickness ($R^2 = 0.761$, $p = 0.028$) was found.

CONCLUSIONS: We demonstrated an association between SD-OCT signs and retinal blood supply in patients with intermediate AMD and we showed that patients with signs predicting development of geographic atrophy have a reduced flow in superficial vascular plexus and damage of the inner and the outer retina.

PMID: 27625163

Am J Ophthalmol. 2016 Sep 13. [Epub ahead of print]

A Perspective on the Nature and Frequency of Pigment Epithelial Detachments.

Tan AC, Simhaee D, Balaratnasingam C, Dansingani KK, Yannuzzi LA.

PURPOSE: To describe and compare the clinical and imaging characteristics of pigment epithelial detachments (PEDs) in age-related macular degeneration (AMD), polypoidal choroidal vasculopathy (PCV)

and central serous chorioretinopathy (CSC) as seen in a clinical setting of a tertiary retinal practice.

DESIGN: A perspective supported by clinical and imaging characteristics of a consecutive, cohort of patients with strictly defined PEDs.

RESULTS: 174 eyes of 113 patients with PEDs were studied with comprehensive clinical retinal examination and multi-modal imaging; PEDs were differentiated into non-vascularized and vascularized forms with 3 main underlying etiologies: AMD (76%), PCV (9%) and CSC (3%). AMD was the most common diagnosis with both non-vascularized PEDs (drusenoid and serous) and vascularized PEDs (type 1 and type 3 neovascularization) associated with drusen and a thin choroid. PCV patients had large, vascularized, peaked PEDs associated with polyps and a variable choroidal thickness, while CSC patients had a thick choroid and predominantly non-vascularized, serous PEDs with an overlying neurosensory detachment. The combined clinical and imaging characteristics form a profile for each PED subtype related to their underlying disease. However, atypical features noted in 11% of patients may complicate the underlying diagnosis.

CONCLUSION: Typical phenotypic manifestations of PEDs and other features seen with multi-modal imaging were associated with specific underlying etiologies. As suggested by our study, identification of these features help clinicians to determine the precise underlying etiology and manage both vascularized PEDs, where evidence based treatment exists, and non-vascularized PEDs, where current treatment is not supported by convincing evidence.

PMID: 27637783

PLoS One. 2016 Sep 15;11(9) eCollection 2016.

Ex Vivo Confocal Spectroscopy of Autofluorescence in Age-Related Macular Degeneration.

Kaluzny J, Purta P1, Poskin Z, Rogers JD, Fawzi AA.

PURPOSE: We investigated the autofluorescence (AF) signature of the microscopic features of retina with age-related macular degeneration (AMD) using 488 nm excitation.

METHODS: The globes of four donors with AMD and four age-matched controls were embedded in paraffin and sectioned through the macula. Sections were excited using a 488 nm argon laser, and the AF emission was captured using a laser scanning confocal microscope (496-610 nm, 6 nm resolution). The data cubes were then analyzed to compare peak emission spectra between the AMD and the controls. Microscopic features, including individual lipofuscin and melanolipofuscin granules, Bruch's Membrane, as well macroscopic features, were considered.

RESULTS: Overall, the AMD eyes showed a trend of blue-shifted emission peaks compared with the controls. These differences were statistically significant when considering the emission of the combined RPE/Bruch's Membrane across all the tissue cross-sections ($p = 0.02$).

CONCLUSIONS: The AF signatures of ex vivo AMD RPE/BrM show blue-shifted emission spectra (488 nm excitation) compared with the control tissue. The magnitude of these differences is small (~4 nm) and highlights the potential challenges of detecting these subtle spectral differences in vivo.

PMID: 27631087

Mol Ther Methods Clin Dev. 2016 Mar 16;5:16011. eCollection 2016.

Ocular and systemic safety of a recombinant AAV8 vector for X-linked retinoschisis gene therapy: GLP studies in rabbits and Rs1-KO mice.

Marangoni D, Bush RA, Zeng Y, Wei LL, Ziccardi L, Vijayasarathy C, Bartoe JT, Palyada K, Santos M,

Hiriyanna S, Wu Z, Colosi P, Sieving PA.

ABSTRACT: X-linked retinoschisis (XLRS) is a retinal disease caused by mutations in the gene encoding the protein retinoschisin (RS1) and is one of the most common causes of macular degeneration in young men. Our therapeutic approach for XLRS is based on the administration of AAV8-scRS/IRBPhRS, an adeno-associated viral vector coding the human RS1 protein, via the intravitreal (IVT) route. Two Good Laboratory Practice studies, a 9-month study in New Zealand White rabbits (n = 124) injected with AAV8-scRS/IRBPhRS at doses of 2E9, 2E10, 2E11, and 1.5E12 vector genomes/eye (vg/eye), and a 6-month study in Rs1-KO mice (n = 162) dosed with 2E9 and 2E10 vg/eye of the same vector were conducted to assess ocular and systemic safety. A self-resolving, dose-dependent vitreal inflammation was the main ocular finding, and except for a single rabbit dosed with 1.5E12 vg/eye, which showed a retinal detachment, no other ocular adverse event was reported. Systemic toxicity was not identified in either species. Biodistribution analysis in Rs1-KO mice detected spread of vector genome in extraocular tissues, but no evidence of organ or tissues damage was found. These studies indicate that IVT administration of AAV8-scRS/IRBPhRS is safe and well tolerated and support its advancement into a phase 1/2a clinical trial for XLRS.

PMID: 27626041

Clin Ophthalmol. 2016 Aug 29;10:1671-8. eCollection 2016.

Macular pigment optical density: repeatability, intereye correlation, and effect of ocular dominance.

Davey PG, Alvarez SD, Lee JY.

PURPOSE: To evaluate short-term repeatability, intereye correlation, and effect of ocular dominance on macular pigment optical density (MPOD) measurements obtained using the QuantifEye Heterochromatic Flicker Photometer.

PATIENTS AND METHODS: A total of 72 study participants were enrolled in this prospective, cross-sectional study. Participants underwent a comprehensive ocular evaluation, including visual acuity, evaluation of ocular dominance, slit lamp examination, intraocular pressure measurement, and optic nerve head and macula analysis using optical coherence tomography and fundus photography. All study participants after initial training underwent MPOD measurement twice in both eyes in a randomized sequence. The repeatability was tested using Altman and Bland plots for first measurements with the second measurements for right eye and left eye and additionally by grouping eyes as a function of ocular dominance. The Pearson correlation coefficient was performed to assess the intereye correlation of MPOD values.

RESULTS: The mean age of study participants was 35.5 years (range 22-68 years). The mean MPOD measurements for OD (right eye) and OS (left eye) were 0.47 and 0.48, respectively, which followed a normal distribution (Shapiro-Wilk test, $P=0.6$ and 0.2). The 95% limits of agreement of Altman and Bland plots for the first and second measurements were -0.12 to $+0.11$ and -0.13 to $+0.12$ for OD and OS, respectively. The correlation coefficient of mean MPOD measurements of OD and OS was r statistic $=0.94$ (Pearson correlation coefficient $P<0.0001$; $r(2)$ 0.89). The 95% limits of agreement of Altman and Bland plots when evaluated by laterality of eye or by ocular dominance were narrow, with limits of agreement ranging from -0.13 to $+0.12$.

CONCLUSION: The MPOD measurements obtained using the QuantifEye show good short-term repeatability. There is excellent intereye correlation, indicating that the MPOD values of one eye data can predict the fellow eye value with 89% accuracy. The ocular dominance had no bearing on the outcome of this psychophysical test in ocular healthy eyes.

PMID: 27621586

Chin Med. 2016 Sep 9;11(1):39. eCollection 2016.

Chi-Ju-Di-Huang-Wan protects rats against retinal ischemia by downregulating matrix metalloproteinase-9 and inhibiting p38 mitogen-activated protein kinase.

Chao HM, Hu L, Cheng JM, Liu XQ, Liu JH, Pan WH, Zhang XM.

BACKGROUND: Retinal ischemia is a retinal disorder related to retinal vascular occlusion, glaucoma, diabetic retinopathy and age-related macular degeneration. The study aimed to evaluate the protective effects and underlying mechanisms of Chi-Ju-Di-Huang-Wan (CJDHW) against retinal ischemia in rats.

METHODS: High intraocular pressure (HIOP)-induced retinal ischemia was established in Wistar rats by raising their intraocular pressure to 120 mmHg for 60 min with in an eye whose anterior chamber was cannulated with a 30-gauge needle adapted to a normal saline bottle through an intravenous line. This ischemic insult was followed by 1 or 7 days of reperfusion. The effects of CJDHW were studied by (i) electroretinogram (ERG); (ii) real-time polymerase chain reaction to determine the retinal mRNA levels of Thy-1 and matrix metalloproteinase-9 (MMP-9); (iii) Western blot analysis to determine the retinal protein levels of B cell lymphoma 2 (Bcl-2), heme oxygenase-1 (HO-1), phosphorylated-p38 mitogen-activated protein kinase (P-p38 MAPK) and MMP-9; (iv) hematoxylin and eosin (HE) staining; (v) fluorogold retrograde labeling; and (vi) terminal deoxynucleotidyl-transferase (TdT)-mediated dUTP nick end-labeling (TUNEL) apoptosis assay. Moreover, after fixation with 4 % paraformaldehyde and 30 % sucrose, the isolated retinas were sectioned and immunolabeled with goat anti-choline acetyltransferase (ChAT) polyclonal antibody, mouse anti-vimentin monoclonal antibody and rabbit anti-glia fibrillary acidic protein (GFAP) polyclonal antibody. The retinal sections were then incubated with rhodamine-conjugated rabbit anti-goat antibody, fluorescein isothiocyanate (FITC)-conjugated goat anti-mouse IgG or FITC-conjugated goat anti-rabbit IgG. A daily oral intake of 3 mL of water (vehicle; Group 2) or CJDHW (2.8 or 4.2 g/kg/day; CJDHW2.8 or CJDHW4.2; Group 3 or 4) was given for 7 consecutive days either before (preischemic drug administration) or after HIOP-induced retinal ischemic injury (postischemic drug administration). In Group 5, an intravitreal injection of 4 μ L of 0.5 mM SB203580 (p38 MAPK inhibitor) was performed on the ischemic eye 15 min before retinal ischemia. The control rats received a sham procedure (Group 1) where the saline reservoir was not raised.

RESULTS: The ischemia-induced changes (Group 2) were significantly modulated by pretreating the rats with 4.2 g/kg/day of CJDHW (Group 4; ERG: $P < 0.001$ on I/R day 7; HE stain: $P < 0.001$ on I/R day 7; TUNEL: $P = 0.05$ on I/R day 7; retrograde labeling: $P = 0.007$ on I/R day 7; Thy-1 mRNA: $P = 0.02$; MMP-9 mRNA: $P < 0.001$; Bcl-2 protein: $P = 0.02$; HO-1 protein: $P = 0.03$; P-p38 MAPK protein: $P < 0.001$; MMP-9 protein: $P = 0.02$). These modulations included the following features (Group 2 vs. 4), increased ERG b-wave amplitudes (0.38 ± 0.04 vs. 0.81 ± 0.03), increased inner retinal thickness (45.08 ± 2.85 vs. 67.98 ± 5.48 μ m), increased ChAT immunolabeling, decreased vimentin/GFAP immunoreactivity, less numerous apoptotic cells in the ganglion cell layer (1.40 ± 0.55 vs. 0.60 ± 0.55), and more numerous retinal ganglion cells (887.73 ± 158.18 vs. 1389.02 ± 53.20). Moreover, increased Thy-1 (0.31 ± 0.15 vs. 0.78 ± 0.32) and decreased MMP-9 mRNA levels were found (4.44 ± 0.84 vs. 1.13 ± 0.34), respectively. Furthermore, the Bcl-2 protein level (0.78 ± 0.08 vs. 1.80 ± 0.34) was increased while the HO-1 (0.99 ± 0.20 vs. 4.15 ± 2.08), P-p38 MAPK (1.12 ± 0.18 vs. 0.57 ± 0.18) and MMP-9 levels were decreased (0.70 ± 0.23 vs. 0.39 ± 0.10). The ischemia-associated increases in P-p38 and MMP-9 protein levels were also attenuated by 0.5 mM SB203580 (P-p38 MAPK: 1.12 ± 0.18 vs. 0.18 ± 0.07 , $P < 0.001$; MMP-9: 0.70 ± 0.23 vs. 0.21 ± 0.07 , $P = 0.002$). This was also the case to the MMP_enzyme activity (Group 2 vs. 4: 5.03 ± 1.57 vs. 1.59 ± 0.47 , $P = 0.002$; Group 2 vs. 5: 5.03 ± 1.57 vs. 1.35 ± 0.41 , $P = 0.001$).

CONCLUSION: Treatment of the rats suffering from retinal ischemia with CJDHW inhibited apoptosis, increased antioxidative activity, downregulated MMP-9 and inhibited p38 MAPK.

PMID: 27617027

Pathogenesis

Eye (Lond). 2016 Sep 16. [Epub ahead of print]

Doyme lecture 2016: intraocular health and the many faces of inflammation.

Dick AD.

ABSTRACT: Dogma for reasons of immune privilege including sequestration (sic) of ocular antigen, lack of lymphatic and immune competent cells in the vital tissues of the eye has long evaporated. Maintaining tissue and cellular health to preserve vision requires active immune responses to prevent damage and respond to danger. A priori the eye must contain immune competent cells, undergo immune surveillance to ensure homeostasis as well as an ability to promote inflammation. By interrogating immune responses in non-infectious uveitis and compare with age-related macular degeneration (AMD), new concepts of intraocular immune health emerge. The role of macrophage polarisation in the two disorders is a tractable start. TNF-alpha regulation of macrophage responses in uveitis has a pivotal role, supported via experimental evidence and validated by recent trial data. Contrast this with the slow, insidious degeneration in atrophic AMD or in neovascular AMD, with the compelling genetic association with innate immunity and complement, highlights an ability to attenuate pathogenic immune responses and despite known inflammasome activation. Yolk sac-derived microglia maintains tissue immune health. The result of immune cell activation is environmentally dependent, for example, on retinal cell bioenergetics status, autophagy and oxidative stress, and alterations that skew interaction between macrophages and retinal pigment epithelium (RPE). For example, dead RPE eliciting macrophage VEGF secretion but exogenous IL-4 liberates an anti-angiogenic macrophage sFLT-1 response. Impaired autophagy or oxidative stress drives inflammasome activation, increases cytotoxicity, and accentuation of neovascular responses, yet exogenous inflammasome-derived cytokines, such as IL-18 and IL-33, attenuate responses. Eye advance online publication, 16 September 2016; doi:10.1038/eye.2016.177.

PMID: 27636226

Aging (Albany NY). 2016 Sep 8. [Epub ahead of print]

PPAR β/δ selectively regulates phenotypic features of age-related macular degeneration.

Choudhary M, Ding JD, Qi X, Boulton ME, Yao PL, Peters JM, Malek G.

ABSTRACT: Peroxisome proliferator-activated receptor- β/δ (PPAR β/δ) is a nuclear receptor that regulates differentiation, inflammation, lipid metabolism, extracellular matrix remodeling, and angiogenesis in multiple tissues. These pathways are also central to the pathogenesis of age-related macular degeneration (AMD), the leading cause of vision loss globally. With the goal of identifying signaling pathways that may be important in the development of AMD, we investigated the impact of PPAR β/δ activation on ocular tissues affected in the disease. PPAR β/δ is expressed and can be activated in AMD vulnerable cells, including retinal pigment epithelial (RPE) and choroidal endothelial cells. Further, PPAR β/δ knockdown modulates AMD-related pathways selectively. Specifically, genetic ablation of Ppar β/δ in aged mice resulted in exacerbation of several phenotypic features of early dry AMD, but attenuation of experimentally induced choroidal neovascular (CNV) lesions. Antagonizing PPAR β/δ in both in vitro angiogenesis assays and in the in vivo experimentally induced CNV model, inhibited angiogenesis and angiogenic pathways, while ligand activation of PPAR β/δ , in vitro, decreased RPE lipid accumulation, characteristic of dry AMD. This study demonstrates for the first time, selective regulation of a nuclear receptor in the eye and establishes that selective targeting of PPAR β/δ may be a suitable strategy for treatment of different clinical sub-types of AMD.

PMID: 27622388

Curr Opin Pulm Med. 2016 Sep 15. [Epub ahead of print]

Eye disorders associated with obstructive sleep apnoea.

West SD, Turnbull C.

PURPOSE OF REVIEW: Obstructive sleep apnoea (OSA) is increasing in prevalence due to rising obesity. Public awareness is also growing. Although OSA is a disorder primarily of the upper airway during sleep, its physiological impact on other parts of the body is now well recognized. There is increasing interest in the association of OSA with various eye disorders. Work in this field has been directed predominantly to OSA prevalence and association studies, but some authors have tried to elucidate the effect of OSA therapies on eye diseases, including continuous positive airway pressure, upper airway surgery or bariatric surgery. This review discusses the publications in this area from the past year.

RECENT FINDINGS: The key ocular disorders featured in the studies and meta-analyses include glaucoma, floppy eyelid syndrome, nonarteritic ischaemic optic neuropathy, keratoconus, age-related macular degeneration and diabetic retinopathy. Associations with OSA were found with all these conditions, but aspects of the studies still leave gaps in our knowledge.

SUMMARY: This review highlights the need for ophthalmologists to consider OSA in their patients and also makes recommendations for future research studies, especially whether therapies for OSA can be effective for ocular disorders also.

PMID: 27635626

Retina. 2016 Sep 8. [Epub ahead of print]

CLINICAL RELEVANCE OF AQUEOUS VASCULAR ENDOTHELIAL GROWTH FACTOR LEVELS IN POLYPOIDAL CHOROIDAL VASCULOPATHY.

Baek J, Lee JH, Lee WK.

PURPOSE: To investigate vascular endothelial growth factor (VEGF) level according to the clinical and imaging features, and to explore its relationship with the responsiveness to anti-VEGF treatment in eyes with polypoidal choroidal vasculopathy.

METHODS: Aqueous samples were collected from 62 eyes of 62 patients with treatment-naïve polypoidal choroidal vasculopathy. Vascular endothelial growth factor levels were measured using enzyme-linked immunosorbent assay. Baseline best-corrected visual acuity, central macular thickness, subfoveal choroidal thickness, greatest linear dimension of the lesion, and the presence of hemorrhage were included in the analysis. The effects of 3 monthly intravitreal ranibizumab injections on best-corrected visual acuity and central macular thickness were assessed.

RESULTS: Baseline VEGF level was negatively correlated with subfoveal choroidal thickness ($r = -0.33$, $P = 0.01$). Other variables had no correlation with VEGF level. The mean change in central macular thickness after anti-VEGF treatment was $-51 \pm 64 \mu\text{m}$, which is positively correlated with VEGF concentration ($r = 0.30$, $P = 0.04$) and negatively correlated with subfoveal choroidal thickness ($r = -0.35$, $P = 0.02$).

CONCLUSION: Vascular endothelial growth factor level demonstrated a negative correlation with baseline subfoveal choroidal thickness and was associated with response to anti-VEGF treatment. These findings suggest that VEGF has a variable contribution to the pathogenesis of polypoidal choroidal vasculopathy depending on choroid thickness.

PMID: 27617539

Exp Cell Res. 2016 Sep 8. [Epub ahead of print]

Induction of Oxidative and Nitrosative Stresses in Human Retinal Pigment Epithelial Cells by All-trans-Retinal.

Zhu X, Wang K, Zhang K, Zhou F, Zhu L.

ABSTRACT: Delayed clearance of free form all-trans-retinal (atRAL) is estimated be the key cause of retinal pigment epithelium (RPE) cells injury during the pathogenesis of retinopathies such as age-related macular degeneration (AMD), however, the underlying molecular mechanisms are far from clear. In this study, we investigated the cytotoxicity effect and underlying molecular mechanism of atRAL on human retinal pigment epithelium ARPE-19 cells. The results indicated that atRAL could cause cell dysfunction by inducing oxidative and nitrosative stress in ARPE-19 cells. The oxidative stress induced by atRAL was mediated through up-regulation of reactive oxygen species (ROS) generation, activating mitochondrial-dependent and MAPKs signaling pathways, and finally resulting in apoptosis of ARPE-19 cells. The NADPH oxidase inhibitor apocynin could partly attenuated ROS generation, indicating that NADPH oxidase activity was involved in atRAL-induced oxidative stress in ARPE-19 cells. The nitrosative stress induced by atRAL was mainly reflected in increasing nitric oxide (NO) production, enhancing iNOS, ICAM-1 and VCAM-1 expressions, and promoting monocyte adhesion. Furthermore, above effects could be dramatically blocked by using a nuclear factor kappa B (NF- κ B) inhibitor SN50, indicated that atRAL-induced oxidative and nitrosative stresses were mediated by NF- κ B. The results provide better understanding of atRAL-induced toxicity in human RPE cells.

PMID: 27616142

Epidemiology

Appl Health Econ Health Policy. 2016 Sep 15. [Epub ahead of print]

Health State Utility Values for Age-Related Macular Degeneration: Review and Advice.

Butt T, Tufail A, Rubin G.

ABSTRACT: Health state utility values are a major source of uncertainty in economic evaluations of interventions for age-related macular degeneration (AMD). This review identifies and critiques published utility values and methods for eliciting de novo utility values in AMD. We describe how utility values have been used in healthcare decision making and provide guidance on the choice of utility values for future economic evaluations for AMD. Literature was searched using PubMed, and health technology assessments (HTA) were searched using HTA agency websites to identify articles reporting utility values or approaches to derive utility values in AMD and articles applying utilities for use in healthcare decision making relating to treatments for AMD. A total of 70 studies qualified for data extraction, 22 of which were classified as containing utility values and/or elicitation methods, and 48 were classified as using utility values in decision making. A large number of studies have elicited utility values for AMD, although those applied to decision making have focused on a few of these. There is an appreciation of the challenges in the measurement and valuation of health states, with recent studies addressing challenges such as the insensitivity of generic health-related quality of life (HRQoL) questionnaires and utility in the worse-seeing eye. We would encourage careful consideration when choosing utility values in decision making and an explicit critique of their applicability to the decision problem.

PMID: 27637920

Stem Cells

Cuad Bioet. 2016 May-Aug;27(90):241-7.

Use of Embryonic Stem Cells to Treat Severe Eye Diseases.

Aznar J, Tudela J.

BACKGROUND: The use of stem cells in regenerative medicine has major therapeutic potential. Recent clinical trials using cells derived from human stem cells are showing encouraging results, although these should be assessed with the necessary caution.

DISCUSSION: Some media have reported the results of these trials without due care, perhaps creating expectations that do not match the reality of the facts. This paper describes some of the recent advances in the use of human stem cells, particularly those made in the area of ophthalmology, and more specifically, in Stargardt's disease and age-related macular degeneration (AMD). We also present promising studies with induced pluripotent stem cells (iPS), aimed at obtaining retinal pigmented epithelium and light-sensitive retinal rods in the aforementioned ocular diseases, with encouraging preclinical and clinical results.

CONCLUSIONS: From a medical point of view, we must not forget that the transplanted retinal epithelium cells may cause tumours, since they have been obtained from Embryonic Stem cells, and may trigger immune rejection problems since they are heterologous. These considerations attest to the ethical uncertainty of the results of these clinical trials, but above all, it must be stressed that whenever Embryonic Stem cells are used, a human embryo must be destroyed to obtain them, which of course has objective ethical difficulties.

PMID: 27637197

Ophthalmic Surg Lasers Imaging Retina. 2016 Sep 1;47(9):869-73.

Retinotomy Closure Following Subretinal Stem Cell Transplant With a 30-Gauge Needle.

Ludwig CA, Leng T.

ABSTRACT: The authors report two cases of posterior retinotomy closure following subretinal stem cell transplantation for age-related macular degeneration with a 30-gauge needle - a larger bore needle than those used in prior studies. Partial retinotomy closure was seen on optical coherence tomography within 24 hours in one patient, whereas complete closure occurred by the 5-month and 1-year follow-up visits. A trace retinal hemorrhage occurred in one case, with resolution by 12 weeks. These findings demonstrate the likelihood of uncomplicated, spontaneous retinotomy closure following subretinal stem cell transplantation with a 30-gauge needle. [Ophthalmic Surg Lasers Imaging Retina. 2016;47:869-873].

PMID: 27631485

Genetics

Mol Vis. 2016 Aug 29;22:1062-76. eCollection 2016.

Whole exome sequencing of extreme age-related macular degeneration phenotypes.

Sardell RJ, Bailey JN, Courtenay MD, Whitehead P, Laux RA, Adams LD, Fortun JA, Brantley MA Jr, Kovach JL, Schwartz SG, Agarwal A, Scott WK, Haines JL, Pericak-Vance MA.

PURPOSE: Demographic, environmental, and genetic risk factors for age-related macular degeneration (AMD) have been identified; however, a substantial portion of the variance in AMD disease risk and heritability remains unexplained. To identify AMD risk variants and generate hypotheses for future studies, we performed

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whole exome sequencing for 75 individuals whose phenotype was not well predicted by their genotype at known risk loci. We hypothesized that these phenotypically extreme individuals were more likely to carry rare risk or protective variants with large effect sizes.

METHODS: A genetic risk score was calculated in a case-control set of 864 individuals (467 AMD cases, 397 controls) based on 19 common ($\geq 1\%$ minor allele frequency, MAF) single nucleotide variants previously associated with the risk of advanced AMD in a large meta-analysis of advanced cases and controls. We then selected for sequencing 39 cases with bilateral choroidal neovascularization with the lowest genetic risk scores to detect risk variants and 36 unaffected controls with the highest genetic risk score to detect protective variants. After minimizing the influence of 19 common genetic risk loci on case-control status, we targeted single variants of large effect and the aggregate effect of weaker variants within genes and pathways. Single variant tests were conducted on all variants, while gene-based and pathway analyses were conducted on three subsets of data: 1) rare ($\leq 1\%$ MAF in the European population) stop, splice, or damaging missense variants, 2) all rare variants, and 3) all variants. All analyses controlled for the effects of age and sex.

RESULTS: No variant, gene, or pathway outside regions known to be associated with risk for advanced AMD reached genome-wide significance. However, we identified several variants with substantial differences in allele frequency between cases and controls with strong additive effects on affection status after controlling for age and sex. Protective effects trending toward significance were detected at two loci identified in single-variant analyses: an intronic variant in FBLN7 (the gene encoding fibulin 7) and at three variants near pyridoxal (pyridoxine, vitamin B6) kinase (PDXK). Aggregate rare-variant analyses suggested evidence for association at ASRGL1, a gene previously linked to photoreceptor cell death, and at BSDC1. In known AMD loci we also identified 29 novel or rare damaging missense or stop/splice variants in our sample of cases and controls.

CONCLUSIONS: Identified variants and genes may highlight regions important in the pathogenesis of AMD and are key targets for replication.

PMID: 27625572

Chem Res Toxicol. 2016 Sep 12. [Epub ahead of print]

Bioactive 4-Oxoheptanedioic Monoamide Derivatives of Proteins and Ethanolaminephospholipids: Products of Docosahexaenoate Oxidation.

Guo J, Hong L, West XZ, Wang H, Salomon RG.

ABSTRACT: Oxidative stress causes lipid-derived oxidative modification of biomolecules that has been implicated in many pathological states. Phospholipids containing polyunsaturated fatty acids are major targets of free radical-initiated oxidation. Phospholipids that incorporate docosahexaenoate (DHA) are highly enriched in important neural structures including the brain and retina, where DHA comprises 40% and 60% of total fatty acids, respectively. Oxidative fragmentation of 2-docosahexaenoyl-1-palmityl-sn-glycerophosphocholine generates esters of 4-hydroxy-7-oxohept-5-enoic acid (HOHA) and 4-keto-7-oxohept-5-enoic acid (KOHA) with 2-lysophosphatidylcholine, HOHA-PC and KOHA-PC. Covalent HOHA adducts that incorporate the primary amino groups of proteins and ethanolamine phospholipids in carboxyethylpyrrole (CEP) derivatives were detected immunologically with anti-CEP antibodies in human tumors, retina and blood. Now, we generated an anti-OHdiA antibody to test the hypothesis that KOHA adducts, which incorporate the primary amino groups of proteins or ethanolamine phospholipids in 4-oxoheptanedioic (OHdiA) monoamide derivatives, are present in vivo. However, whereas the anti-CEP antibody is highly specific and does not cross-react with the OHdiA monoamide epitope, the anti-OHdiA monoamide antibody cross-reacted with CEP epitopes making it of little value as an analytical tool for OHdiA monoamides, but suggesting the possibility that OHdiA monoamides would exhibit receptor-mediated biological activity similar to that of CEP. An LC-MS/MS method was developed that allows quantification of OHdiA derivatives in biological samples. We now find that KOHA-PC forms OHdiA monoamide adducts of proteins and ethanolamine phospholipids and that OHdiA-protein levels are

significantly higher than OHdiA-ethanolamine phospholipid levels in blood from healthy human subjects, 0.45 μM and 0.18 μM respectively ($n = 3$, $p = 0.027$). OHdiA monoamide epitopes are angiogenic, causing TLR2-dependent adhesion and tube formation by human umbilical vein endothelial cells. OHdiA monoamide epitopes are only slightly less potent than CEP epitopes that contribute to the pathological angiogenesis of age-related macular degeneration and tumor growth.

PMID: 27618287

Diet, Lifestyle and Low Vision

Qual Life Res. 2016 Sep 10. [Epub ahead of print]

Reliability, validity and responsiveness of the Greek MacDQoL individualized measure of the impact of macular degeneration on quality of life.

Marakis TP, Koutsandrea C, Chatzistefanou KI, Tountas Y.

PURPOSE: To assess the psychometric properties of the Greek Macular Disease-Dependent Quality of Life Questionnaire (MacDQoL).

METHODS: The MacDQoL was translated in Greek and administered to 191 patients with neovascular age-related macular degeneration (AMD). To assess validity, all patients completed the Greek SF-12 health survey and underwent vision measurements. For test-retest reliability, a subset of twenty participants completed the MacDQoL twice, 2 weeks apart. Responsiveness was assessed on 102 patients who completed the MacDQoL at a follow-up visit, 1 year later. Rasch analysis was used to assess the Greek MacDQoL's response category functioning, precision, unidimensionality, targeting and differential item functioning.

RESULTS: Internal and test-retest reliability of the average weighted impact (AWI) was 0.952 and 0.97, respectively. Test-retest reliability of MacDQoL items ranged from 0.78 to 0.99. Principal component analysis revealed three subscales (activities, embarrassment and family life), which were also confirmed by confirmatory factor analysis. Rasch analysis revealed poor functionality of response categories and that was resolved by collapsing response categories and using the impairment scores only. In terms of convergent validity, the AWI and revised MacDQoL scales showed significant correlations with SF-12 summary scales ($p = 0.21$ - 0.30) and vision assessments ($p = 0.31$ - 0.46). Poorer AMD-related QoL at 1-year follow-up was associated with deterioration in distance visual acuity and worse eye near visual acuity.

CONCLUSIONS: The Greek MacDQoL is a reliable, valid and sensitive to change in vision instrument for assessing AMD patients' perceptions of QoL. However, Rasch analysis revealed that its multiplicative rating scale is flawed. Scientific measurement was restored with a number of revisions to the questionnaire.

KEYWORDS: Age-related macular degeneration; Greece; Psychometric properties; Quality of life; Questionnaire; Rasch analysis

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