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Drug treatment

Ophthalmology. 2015 Jul 18. [Epub ahead of print]

Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies.

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

PURPOSE: To compare efficacy and safety of 2 dosing regimens of intravitreal aflibercept injection (IAI) with macular laser photocoagulation for diabetic macular edema (DME).

DESIGN: Two similarly designed, randomized, phase 3 trials, VISTADME and VIVIDME.

PARTICIPANTS: Patients (eyes; n=872) with type 1 or 2 diabetes mellitus who had DME with central involvement.

METHODS: Eyes received IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 monthly doses (2q8), or laser control.

MAIN OUTCOME MEASURES: The primary end point was mean change from baseline in best-corrected visual acuity (BCVA) at week 52. This report presents the 100-week results including mean change from baseline in BCVA, proportion of eyes that gained ≥ 15 letters, and proportion of eyes with a ≥ 2 -step improvement in the Diabetic Retinopathy Severity Scale (DRSS) score.

RESULTS: Mean BCVA gain from baseline to week 100 with IAI 2q4, IAI 2q8, and laser control was 11.5, 11.1, and 0.9 letters ($P < 0.0001$) in VISTA and 11.4, 9.4, and 0.7 letters ($P < 0.0001$) in VIVID, respectively. The proportion of eyes that gained ≥ 15 letters from baseline at week 100 was 38.3%, 33.1%, and 13.0% ($P < 0.0001$) in VISTA and 38.2%, 31.1%, and 12.1% ($P \leq 0.0001$) in VIVID. The proportion of eyes that lost ≥ 15 letters at week 100 was 3.2%, 0.7%, and 9.7% ($P \leq 0.0220$) in VISTA and 2.2%, 1.5%, and 12.9% ($P \leq 0.0008$) in VIVID. Significantly more eyes in the IAI 2q4 and 2q8 groups versus those in the laser control group had a ≥ 2 step improvement in the DRSS score in both VISTA (37.0% and 37.1% vs. 15.6%; $P < 0.0001$) and VIVID (29.3% and 32.6% vs. 8.2%; $P \leq 0.0004$). In an integrated safety analysis, the most frequent serious ocular adverse event was cataract (2.4%, 1.0%, and 0.3% for 2q4, 2q8, and control).

CONCLUSIONS: In both VISTA and VIVID, the 52-week visual and anatomic superiority of IAI over laser control was sustained through week 100, with similar efficacy in the 2q4 and 2q8 groups. Safety in these studies was consistent with the known safety profile of IAI.

PMID: 26198808 [PubMed - as supplied by publisher]

PLoS One. 2015 Jul 24;10(7):e0133968.

Treatment Frequency and Dosing Interval of Ranibizumab and Aflibercept for Neovascular Age-Related Macular Degeneration in Routine Clinical Practice in the USA.

Ferreira A, Sagkriotis A, Olson M, Lu J, Makin C, Milnes F.

PURPOSE: To compare treatment patterns of intravitreal ranibizumab and aflibercept for the management of neovascular age-related macular degeneration (nAMD) in a real-world setting over the first 12 months of treatment.

METHODS: A proprietary clinical database was used to identify treatment-naïve patients with nAMD in the USA with claims for ranibizumab or aflibercept between November 1, 2011 and November 30, 2013 and with follow-up of at least 12 months. Patients were considered treatment-naïve if they had no anti-VEGF treatment code for 6 months before the index date. Mean numbers of injections and of non-injection visits to a treating physician were compared between the two treatment cohorts (ranibizumab or aflibercept). In addition, the mean interval between doses was also investigated.

RESULTS: Patient characteristics were similar for those receiving either ranibizumab (n = 5421) or aflibercept (n = 3506) at the index date. The mean ($\pm$ standard deviation) numbers of injections received by patients treated with ranibizumab (4.9 ± 3.3) or aflibercept (5.2 ± 2.9) were not clinically different. The mean number of non-injection visits was 2.8 ± 2.8 and 2.1 ± 2.5 for ranibizumab and aflibercept, respectively. Mean dosing interval was 51.0 days (± 41.8 days) in patients receiving ranibizumab and 54.1 days (± 36.0 days) in those receiving aflibercept. Results were robust to sensitivity analyses for definition of treatment-naïve, length of follow-up and treatment in the index eye only.

CONCLUSIONS: Limited data exist regarding real-world treatment patterns of aflibercept for the management of nAMD. Our results suggest that, in routine clinical practice, patients receive a comparable number of injections in the first year of treatment with ranibizumab or aflibercept.

PMID: 26208030 [PubMed - as supplied by publisher]

Ophthalmic Res. 2015 Jul 17;54(2):57-63. [Epub ahead of print]

Optical Coherence Tomography Angiography during Follow-Up: Qualitative and Quantitative Analysis of Mixed Type I and II Choroidal Neovascularization after Vascular Endothelial Growth Factor Trap Therapy.

Coscas G, Lupidi M, Coscas F, François C, Cagini C, Souied EH.

PURPOSE: To report the optical coherence tomography angiography (OCT-A) findings in an exudative age-related macular degeneration (AMD) patient presenting mixed type I and II choroidal neovascularization (CNV) during follow-up after intravitreal vascular endothelial growth factor (VEGF) trap treatment.

METHODS: The clinical assessment included both traditional multimodal imaging, based on fluorescein angiography (FA), indocyanine green angiography (ICGA) and B-scan OCT, and OCT-A at baseline and follow-up. OCT-A images were obtained using a Spectralis OCT-A prototype able to acquire 70,000 A-scans per second, with a resolution of 7 μ m axially and 14 μ m laterally. An amplitude decorrelation algorithm developed by Heidelberg Engineering was applied to a volume scan, on a $15 \times 5^\circ$ area, which was composed of 131 B-scans (35 frames per scan) at a distance of 11 μ m each. The borders of type I and type II CNV were manually outlined and then the areas were analyzed using the provided automated software before and after treatment.

RESULTS: The qualitative approach revealed a substantial decrease in the visibility of tiny branching vessels and anastomoses both in type I and type II components of the neovascular complex, associated with persistence of a clear hyperintense signal coming from the larger trunks, which remained well-perfused. Quantitative analysis confirmed a reduction of the lesion area after VEGF trap treatment: the type

II component decreased from 0.25 to 0.19 mm², while the type I component decreased from 2.03 to 1.80 mm².

CONCLUSIONS: Our study qualitatively and quantitatively demonstrated the response of a mixed type I-II CNV to intravitreal VEGF trap therapy. Although FA remains the gold standard for determining the presence of leakage and OCT easily shows fluid accumulation and its variations, OCT-A offers noninvasive monitoring of the retinal and choriocapillaris microvasculature in patients with CNV, aiding in diagnosis and treatment decisions during follow-up. © 2015 S. Karger AG, Basel.

PMID: 26201877 [PubMed - as supplied by publisher]

Retina. 2015 Jul 21. [Epub ahead of print]

RETROSPECTIVE REVIEW OF LUCENTIS "TREAT AND EXTEND" PATTERNS AND OUTCOMES IN AGE-RELATED MACULAR DEGENERATION.

Chen YN, Powell AM, Mao A, Sheidow TG.

PURPOSE: To assess patterns and outcomes of a "Treat and Extend" dosing regimen of ranibizumab in patients with age-related macular degeneration.

METHODS: Three hundred and thirty two treatment-naïve age-related macular degeneration patients starting therapy with ranibizumab between January 1, 2011, and June 30, 2012, at the Ivey Eye Institute were reviewed, and 79 met inclusion criteria. Patients on Treat and Extend dosing regimen underwent an induction phase with monthly injections and then moved onto an extension phase. Change in visual acuity and central retinal thickness during the induction and extension phases were recorded.

RESULTS: During the induction phase, patients had a significant gain in vision and decrease in central retinal thickness (+8.4 letters, $P < 0.001$ and -81.3 μm , $P < 0.001$). During the extension phase, patients did not have significant change in vision (-0.5 letters, $P = 0.81$) and did not have significant change in central retinal thickness (-11.5 μm , $P = 0.17$). The average extension interval between treatments was 47.7 days, with patients receiving an average of 8.6 injections per year. Cost analysis showed it cost US \$16,659 to treat 1 patient in the first year on Treat and Extend dosing regimen compared with US \$20,614 on monthly dosing.

CONCLUSION: Treat and Extend dosing regimen allows similar visual outcomes to monthly dosing, while reducing the total number of injections, visits, and overall cost.

PMID: 26200511 [PubMed - as supplied by publisher]

Retina. 2015 Jul 21. [Epub ahead of print]

PREDICTING RESPONSE OF EXUDATIVE AGE-RELATED MACULAR DEGENERATION TO BEVACIZUMAB BASED ON SPECTRALIS OPTICAL COHERENCE TOMOGRAPHY.

Segal O, Barayev E, Nemet AY, Mimouni M.

PURPOSE: To identify baseline optical coherence tomography factors in exudative age-related macular degeneration that predict response to bevacizumab injections.

METHODS: Patients underwent spectral domain optical coherence tomography at diagnosis and the width, height, area, and location of the subretinal fluid, intraretinal fluid, pigment epithelial detachment, and subretinal tissue were measured. The location and size of photoreceptor and the loss of retinal pigment epithelium were recorded as well as quantitative retinal measurements. Patients received three consecutive monthly injections of bevacizumab after which their best-corrected visual acuity was recorded.

RESULTS: Overall 105 eyes of 105 patients aging 88 ± 8.6 years were included. In univariate correlational analyses, only subretinal fluid width demonstrated a significant positive correlation with improved best-corrected visual acuity ($R = 0.230$, $P = 0.018$). Eyes with intraretinal fluid ($P = 0.020$) and retinal pigment epithelial loss ($P = 0.009$) located in the subfoveal (as opposed to the juxtafoveal area) demonstrating worst visual outcomes. In stepwise backwards regression, the subretinal fluid width and intraretinal fluid location were the only parameters that remained significant explaining 9.23% of the variation in delta best-corrected visual acuity scores.

CONCLUSION: Improvement in best-corrected visual acuity after three injections of bevacizumab can be predicted from optical coherence tomography measurements. Specifically, the authors identified subretinal fluid width and intraretinal fluid location as significant markers.

PMID: 26200510 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2015 Jul 13;9:1269-74. eCollection 2015.

Evaluation of the effect of intravitreal ranibizumab injections in patients with neovascular age related macular degeneration on retinal nerve fiber layer thickness using optical coherence tomography.

El-Ashry MF, Lascaratos G, Dhillon B.

PURPOSE: To evaluate the effect of repeated intravitreal ranibizumab injections for neovascular age related macular degeneration (nAMD) on the retinal nerve fiber layer (RNFL) thickness using optical coherence tomography.

DESIGN: A prospective observational cohort study of patients with nAMD.

METHODS: Thirty eyes of 30 patients with nAMD were selected. All patients received three ranibizumab injections and underwent scans using the fast RNFL thickness protocol (Stratus optical coherence tomography) before starting the first injection and 1 month after the third injection. The RNFL thickness measurements prior to the injections and after the third injection were used for the analysis. We also evaluated the effect of the lens status as well as the type of choroidal neovascular membrane on RNFL thickness measurements pre- and post-injection. Pre- and post-injection average and individual quadrant RNFL thickness were measured and statistically analyzed.

RESULTS: The mean ($\pm$ standard deviation) pre-injection RNFL thickness was 90.8 ± 18 . The mean ($\pm$ standard deviation) post-injection RNFL thickness was 91.03 ± 15 . The pre- and post-injection values of the mean RNFL thickness were not statistically significant. Likewise, the pre- and post-injection values for RNFL thickness in the different quadrants were not statistically significant. There was no statistical significance for the lens status or the type of choroidal neovascular membrane on the RNFL thickness.

CONCLUSION: Repeated ranibizumab injections in nAMD appear to have no harmful effect on the RNFL thickness in the short term, in spite of the proven neurotrophic effect of vascular endothelial growth factor. Nevertheless, the safety profile of ranibizumab injections in nAMD needs to be further evaluated in a large multicenter trial with special emphasis on the long-term effects on the retina and optic nerve.

PMID: 26203216 [PubMed]

Klin Monbl Augenheilkd. 2015 Jul 21. [Epub ahead of print]

[Comparison of Intravitreal Dexamethasone Implant versus Intravitreal Ranibizumab as a First-Line Treatment of Macular Oedema due to Retinal Vein Occlusion]. [Article in German]

Mayer WJ, Hadjigoli A, Wolf A, Herold T, Haritoglou C.

Purpose: The present study investigated the treatment effect of dexamethasone implant (Ozurdex®, group

1) and anti-VEGF injection (Lucentis®, group 2) in course of macular oedema due to retinal vein occlusion in a retrospective, non-randomised case series.

Material and Methods: Group 1 comprised 60 patients (31 with CRVO and 29 with BRVO) and group 2 included 52 patients, 27 with CRVO and 25 with BRVO) and both groups were further treated in case of recurrence. Preoperative and in monthly intervals best corrected visual acuity (BCVA), central retinal thickness using SD-OCT (Spectralis, Heidelberg Engineering), intraocular pressure, biomicroscopy status and a fundus photo documentation (Optomap) were evaluated. The primary clinical endpoint was visual acuity 12 months after the first intravitreal therapy, while secondary endpoints included the central retinal thickness change and safety of therapy.

Results: In group 1, an increase of BCVA ($\pm$ standard deviation) of 8.4 ($\pm$ 1.9) letters was observed in CRVO patients and a gain of 10.7 ($\pm$ 3.8) letters in BRVO patients after 12 months, while in group 2, an increase of BCVA of 6.9 ($\pm$ 1.9) letters (CRVO) compared to 12.5 ($\pm$ 3.7) letters (BRVO) was observed after the same time span. In both groups a significant reduction in retinal thickness was achieved. An increase of intraocular pressure above 5 mmHg was observed in nearly half of the cases In group 1, but was well controlled by conservative antiglaucomatous therapy. We observed a progression of lens opacity in approximately 50% of the cases in group 1.

Conclusion: The treatment with Ozurdex compared to Lucentis appears to provide a trend towards a better although not significant visual acuity increase after 12 months in CRVO patients. A similar trend favouring anti-VEGF treatment with Lucentis was seen in patients with BRVO. However, the lens status and age of the patient should be taken into account when considering a treatment with Ozurdex.

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Other treatment & diagnosis

Am J Ophthalmol. 2015 Jul 21. [Epub ahead of print]

Lacquer Cracks And Perforating Scleral Vessels in Pathologic Myopia: A Possible Causal Relationship.

Querques G, Corvi F, Balaratnasingam C, Casalino G, Parodi MB, Introini U, Freund KB, Bandello F.

PURPOSE: To describe a possible causal association between the position of perforating scleral vessels and the position of lacquer cracks in eyes with pathologic myopia.

DESIGN: Retrospective case series.

METHODS: Medical records and multimodal imaging results, including confocal scanning laser ophthalmoscopy and spectral-domain optical coherence tomography, were reviewed from patients with lacquer cracks secondary to pathologic myopia who presented between 2010 and 2014 to two institutions. Main outcome measure were the prevalence of perforating scleral vessels at the site of the lacquer crack, the position of the lacquer crack within the macula and the relationships between perforating scleral vessels and retinal-choroidal structures.

RESULTS: A total of 35 eyes of 30 patients with lacquer cracks were included. The average number of lacquer cracks was 1.2 ± 0.5 /eye and in 37 out of 45 lacquer cracks (82%) retrobulbar vessels were found to perforate the sclera at the site of the lacquer crack. Lacquer cracks were more prevalent in the central macula (51%), than in the nasal (19%), temporal (14%), inferior (11%) and superior (5%) macula ($P = 0.001$). Transverse En Face images through the area of lacquer cracks were available for 8 cases and clearly depicted the perforating vessel's course through the sclera and its termination in the choroid, directly beneath the lacquer cracks.

CONCLUSIONS: Perforating scleral vessels are often present beneath the site at which lacquer cracks form in pathologic myopia. We hypothesize that scleral expansion at the location of these perforating

vessels may play a role in the formation of lacquer cracks.

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Am J Ophthalmol. 2015 Jul 21. [Epub ahead of print]

Early Vitrectomy for Spontaneous, Fundus-Obscuring Vitreous Hemorrhage.

Melamud A, Pham H, Stoumbos Z.

PURPOSE: To examine the visual outcomes of early intervention in the setting of fundus-obscuring vitreous hemorrhage (VH) presumed to be due to posterior vitreous detachment.

DESIGN: Retrospective comparative case series.

METHODS: All eyes that presented with a fundus-obscuring VH defined as vision of 20/400 or worse, and requiring a B-scan at presentation from 2003 - 2013, were evaluated. Eyes with any history of retinopathy; macular degeneration; recent trauma; presentation greater than two weeks after onset of symptoms; or follow-up of less than two months were excluded. The main outcome measure studied was final best-correct visual acuity (BCVA) as dependent on the time to surgery.

RESULTS: 92 eyes met inclusion criteria with a mean follow-up of 490 days. Initial BCVA was logMAR 2.218 (Snellen equivalent 20/3000-20/4000 range 20/400- light perception); final BCVA was 0.318 (Snellen equivalent of 20/40-20/50 range 20/20 - light perception, $p < 0.001$). 56 patients (60.8%) had either a retinal tear or a retinal detachment. Patients who underwent surgery within 1 week had no significant improvement over all others, however a significant improvement was found when comparing early versus delayed surgery groups ($p < 0.05$). There was a significantly increased risk of developing a macula-off retinal detachment in patients who did not undergo surgery within one week of presentation.

CONCLUSIONS: Early surgical intervention results in similar visual outcomes compared to a conservative approach. However, early intervention significantly reduces the incidence of severe vision loss related to macula involving retinal detachment. This study highlights the importance of close follow-up given the high risk of retinal detachment in fundus-obscuring vitreous hemorrhage.

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Eye (Lond). 2015 Jul 24. [Epub ahead of print]

Design characteristic of randomised controlled trials for geographic atrophy in age-related macular degeneration: selection of outcomes and sample size calculation.

Krezel AK, Hogg RE, Krezel S, Fallis R, Azuara-Blanco A.

Purpose: The selection of suitable outcomes and sample size calculation are critical factors in the design of a randomised controlled trial (RCT). The goal of this study was to identify the range of outcomes and information on sample size calculation in RCTs on geographic atrophy (GA).

Methods: We carried out a systematic review of age-related macular degeneration (AMD) RCTs. We searched MEDLINE, EMBASE, Scopus, Cochrane Library, www.controlled-trials.com, and www.ClinicalTrials.gov. Two independent reviewers screened records. One reviewer collected data and the second reviewer appraised 10% of collected data. We scanned references lists of selected papers to include other relevant RCTs.

Results: Literature and registry search identified 3816 abstracts of journal articles and 493 records from trial registries. From a total of 177 RCTs on all types of AMD, 23 RCTs on GA were included. Eighty-one clinical outcomes were identified. Visual acuity (VA) was the most frequently used outcome, presented in 18 out of

23 RCTs and followed by the measures of lesion area. For sample size analysis, 8 GA RCTs were included. None of them provided sufficient information on sample size calculations.

Conclusions: This systematic review illustrates a lack of standardisation in terms of outcome reporting in GA trials and issues regarding sample size calculation. These limitations significantly hamper attempts to compare outcomes across studies and also perform meta-analyses.

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Retin Cases Brief Rep. 2015 Jul 21. [Epub ahead of print]

FEEDER VESSEL LASER PHOTOCOAGULATION FOR IDIOPATHIC, SUBFOVEAL POLYPOIDAL CHOROIDAL VASCULOPATHY NOT RESPONDING TO EITHER ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY OR PHOTODYNAMIC THERAPY.

Monés J, Badal J, Biarnés M.

PURPOSE: To describe the management of a subfoveal polypoidal choroidal vasculopathy case refractory to antiangiogenic treatment and to photodynamic therapy.

METHODS: Case report. A 65-year-old male patient presented with a diagnosis of exudative age-related macular degeneration of his left eye and unsuccessful response to eight antiangiogenic injections. Visual acuity was 20/33. Fluorescein angiography, spectral domain optical coherence tomography, and indocyanine green angiography confirmed the diagnosis of polypoidal choroidal vasculopathy. Two photodynamic therapy sessions along with two ranibizumab injections were performed, but no response was obtained. Identification and photocoagulation of the polyp feeder vessels was performed.

RESULTS: Polypoidal structures regressed, intraretinal and subretinal exudation resolved, and visual acuity was preserved with no adverse events.

CONCLUSION: Indocyanine green angiography-guided feeder vessel diode laser photocoagulation in selected cases of polypoidal choroidal vasculopathy may be considered an effective alternative therapy, especially in those refractory to both photodynamic therapy and antiangiogenic therapy.

PMID: 26200385 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2015 Jul 15;9:1299-305. eCollection 2015.

Detection of pigment epithelial detachment vascularization in age-related macular degeneration using phase-variance OCT angiography.

McClintic SM, Kim DY, Fingler J, Garcia S, Zawadzki RJ, Morse LS, Park SS, Fraser SE, Werner JS, Ruggiero JP, Schwartz DM.

PURPOSE: To demonstrate the use of phase-variance optical coherence tomography (PV-OCT) angiography for detection of pigment epithelial detachment (PED) vascularization in age-related macular degeneration (AMD).

PATIENTS AND METHODS: Patients with PEDs and exudative AMD were evaluated by the Retina Services at the University of California, Davis, and the University of California, San Francisco. Each subject underwent fluorescein angiography and structural optical coherence tomography (OCT). Phase-variance OCT analysis was used to create angiographic images of the retinal and choroidal vasculature. PV-OCT-generated B-scans were superimposed on structural OCT B-scans to allow easy identification of perfused vascular structures.

RESULTS: Three patients with vascularized PEDs were imaged with PV-OCT, and each was found to have

a vascular signal extending from the choroid into the hyperreflective substance of the PED. Two patients who had no evidence of PED vascularization on fluorescein angiography did not have vascular signals within their PEDs on PV-OCT.

CONCLUSION: Structural OCT and PV-OCT images can be combined to create composite B-scans that offer high-resolution views of the retinal tissue along with dynamic vascular visualization. This technique offers a fast, noninvasive method for detecting vascularization of PEDs in AMD and may aid in the early detection of neovascular disease.

PMID: 26203220 [PubMed]

Cesk Slov Oftalmol. 2015 Summer;71(3):127-133.

[Functional Magnetic Resonance Imaging in Selected Eye Diseases].[Article in Czech]

Lešták J, Tintěra J.

Abstract: In the study, an actual overview of eyes examinations by means of functional magnetic resonance focused on selected eyes diseases is presented. Special attention is paid to hypertension glaucomas, normotension glaucoma, age-related macular degeneration, and peeling of the epimacular membrane and the internal limiting membrane. The authors point out the decreased activity of the visual cortex in diseases in which the damage of retinal ganglion cells occurs. **Key words:** functional magnetic resonance imaging, glaucomas, age-related macular degeneration, peeling of the epimacular membrane, and peeling the internal limiting membrane.

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Br J Ophthalmol. 2015 Jul 22. [Epub ahead of print]

Volumetric ellipsoid zone mapping for enhanced visualisation of outer retinal integrity with optical coherence tomography.

Itoh Y, Vasanthi A, Ehlers JP.

Abstract: Objective assessment of retinal layer integrity with optical coherence tomography (OCT) is currently limited. The ellipsoid zone (EZ) has been identified as an important feature on OCT that has critical prognostic value in macular disorders. In this report, we describe a novel assessment tool for EZ integrity that provides visual and quantitative assessment across an OCT data set. Using this algorithm, we describe the findings in multiple clinical examples, including normal controls, age-related macular degeneration, drug effects (eg, ocriplasmin, hydroxychloroquine) and effects of surgical manipulation (eg, following membrane peeling using intraoperative OCT). EZ mapping provides both en face visualisation of EZ integrity and EZ-retinal pigment epithelium height. Additionally, volumetric, area and linear measurements are feasible using this assessment tool.

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Retina. 2015 Jul 21. [Epub ahead of print]

ADAPTIVE OPTICS IMAGING OF FOVEAL SPARING IN GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION.

Querques G, Kamami-Levy C, Georges A, Pedinielli A, Capuano V, Blanco-Garavito R, Poulon F, Souied EH.

BACKGROUND: To describe adaptive optics (AO) imaging of foveal sparing in geographic atrophy (GA)

secondary to age-related macular degeneration.

METHODS: Flood-illumination AO infrared (IR) fundus images were obtained in four consecutive patients with GA using an AO retinal camera (rtx1; Imagine Eyes). Adaptive optics IR images were overlaid with confocal scanning laser ophthalmoscope near-IR autofluorescence images to allow direct correlation of en face AO features with areas of foveal sparing. Adaptive optics appearance of GA and foveal sparing, preservation of functional photoreceptors, and cone densities in areas of foveal sparing were investigated.

RESULTS: In 5 eyes of 4 patients (all female; mean age 74.2 ± 11.9 years), a total of 5 images, sized $4^\circ \times 4^\circ$, of foveal sparing visualized on confocal scanning laser ophthalmoscope near-IR autofluorescence were investigated by AO imaging. En face AO images revealed GA as regions of inhomogeneous hyperreflectivity with irregularly dispersed hyporeflective clumps. By direct comparison with adjacent regions of GA, foveal sparing appeared as well-demarcated areas of reduced reflectivity with less hyporeflective clumps (mean 14.2 vs. 3.2; $P = 0.03$). Of note, in these areas, en face AO IR images revealed cone photoreceptors as hyperreflective dots over the background reflectivity (mean cone density $3,271 \pm 1,109$ cones per square millimeter). Microperimetry demonstrated residual function in areas of foveal sparing detected by confocal scanning laser ophthalmoscope near-IR autofluorescence.

CONCLUSION: Adaptive optics allows the appreciation of differences in reflectivity between regions of GA and foveal sparing. Preservation of functional cone photoreceptors was demonstrated on en face AO IR images in areas of foveal sparing detected by confocal scanning laser ophthalmoscope near-IR autofluorescence.

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Pathogenesis

Invest Ophthalmol Vis Sci. 2015 Jul 1;56(8):4644-4652.

Development of Animal Models of Local Retinal Degeneration.

Lorach H, Kung J, Beier C, Mandel Y, Dalal R, Huie P, Wang J, Lee S, Sher A, Jones BW, Palanker D.

Purpose: Development of nongenetic animal models of local retinal degeneration is essential for studies of retinal pathologies, such as chronic retinal detachment or age-related macular degeneration. We present two different methods to induce a highly localized retinal degeneration with precise onset time, that can be applied to a broad range of species in laboratory use.

Methods: A 30- μ m thin polymer sheet was implanted subretinally in wild-type (WT) rats. The effects of chronic retinal separation from the RPE were studied using histology and immunohistochemistry. Another approach is applicable to species with avascular retina, such as rabbits, where the photoreceptors and RPE were thermally ablated over large areas, using a high power scanning laser.

Results: Photoreceptors above the subretinal implant in rats degenerated over time, with 80% of the outer nuclear layer disappearing within a month, and the rest by 3 months. Similar loss was obtained by selective photocoagulation with a scanning laser. Cells in the inner nuclear layer and ganglion cell layer were preserved in both cases. However, there were signs of rewiring and decrease in the size of the bipolar cell terminals in the damaged areas.

Conclusions: Both methods induce highly reproducible degeneration of photoreceptors over a defined area, with complete preservation of the inner retinal neurons during the 3-month follow-up. They provide a reliable platform for studies of local retinal degeneration and development of therapeutic strategies in a wide variety of species.

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Hum Mol Genet. 2015 Jul 21. [Epub ahead of print]

A local complement response by RPE causes early stage macular degeneration.

Fernandez-Godino R, Garland DL, Pierce EA.

Abstract: Inherited and age-related macular degenerations are important causes of vision loss. An early hallmark of these disorders is the formation of sub-retinal pigment epithelium (RPE) basal deposits. A role for the complement system in macular degenerations (MDs) was suggested by genetic association studies, but direct functional connections between alterations in the complement system and the pathogenesis of macular degeneration remain to be defined. We used primary RPE cells from a mouse model of inherited MD due to a p.R345W mutation in EFEMP1 to investigate the role of the RPE in early MD pathogenesis. Efemp1R345W RPE cells recapitulate the basal deposit formation observed in vivo by producing sub-RPE deposits in vitro. The deposits share features with basal deposits, and their formation was mediated by EFEMP1R345W or C3a, but not by C5a. Increased activation of complement appears to occur in response to an abnormal extracellular matrix (ECM), generated by the mutant EFEMP1R345W protein and reduced ECM turnover due to inhibition of matrix metalloproteinase 2 by EFEMP1R345W and C3a. Increased production of C3a also stimulated release of cytokines such as IL-6 and IL-1B, which appear to have a role in deposit formation, albeit downstream of C3a. These studies provide the first direct indication that complement components produced locally by the RPE are involved in the formation of basal deposits. Further, these results suggest that C3a generated by RPE is a potential therapeutic target for treatment of EFEMP1-associated as well as age-related macular degeneration.

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Photochem Photobiol Sci. 2015 Jul 22. [Epub ahead of print]

Photo-damage, photo-protection and age-related macular degeneration.

Marquioni-Ramella MD, Suburo AM.

Abstract: Age-related macular degeneration (AMD) is a degenerative retinal disease that causes blindness in people 60-65 years and older, with the highest prevalence appearing in people 90 years-old or more. Epidemiological estimates indicate that the number of cases is increasing, and will almost double in the next 20 years. Preventive measures require precise etiological knowledge. This is quite difficult, since AMD is a multifactorial condition with intricate relationships between causes and risk factors. In this review, we describe the impact of light on the structure and physiology of the retina and the pigment epithelium, taking into account the continuous exposure to natural and artificial light sources along the life of an individual. A large body of experimental evidence demonstrates the toxic effects of some lighting conditions on the retina and the pigment epithelium, and consensus exists about the importance of photo-oxidation phenomena in the causality chain between light and retinal damage. Here, we analyzed the transmission of light to the retina, and compared the aging human macula in healthy and diseased retinas, as shown by histology and non-invasive imaging systems. Finally, we have compared the putative retinal photo-sensitive molecular structures that might be involved in the genesis of AMD. The relationship between these compounds and retinal damage supports the hypothesis of light as an important initiating cause of AMD.

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Invest Ophthalmol Vis Sci. 2015 Jul 1;56(8):4413-24. doi: 10.1167/iovs.14-16250.

Systemic and Intravitreal Delivery of Dendrimers to Activated Microglia/Macrophage in Ischemia/Reperfusion Mouse Retina.

Kambhampati SP, Clunies-Ross AJ, Bhutto I, Mishra MK, Edwards M, McLeod DS, Kannan RM, Luttly G.

PURPOSE: Microglial activation and associated neuroinflammation play a key role in the pathogenesis of

many diseases of the retina, including viral infection, diabetes, and retinal degeneration. Strategies to target activated microglia and macrophages and attenuate inflammation may be valuable in treating these diseases. We seek to develop dendrimer-based formulations that target retinal microglia and macrophages in a pathology-dependent manner, and deliver drugs, either intravenously or intravitreally.

METHODS: Retinal uptake of cyanine dye (Cy5)-conjugated dendrimer (D-Cy5) was assessed in normal and ischemia/reperfusion (I/R) mouse eyes. Microglia/macrophage uptake of the dendrimer was assessed with immunofluorescence using rabbit Iba-1 antibody with Cy3-tagged secondary antibody (microglia/macrophage). Uptake in retina and other organs was quantified using fluorescence spectroscopy.

RESULTS: Clearance of D-Cy5 from normal eyes was almost complete by 72 hours after intravitreal injection and 24 hours after intravenous delivery. In eyes with activated microglia after I/R injury, D-Cy5 was retained by activated microglia/macrophage (Iba1+ cells) up to 21 days after intravitreal and intravenous administration. In I/R eyes, the relative retention of intravitreal and intravenous D-Cy5 was comparable, if a 30-fold higher intravenous dose was used.

CONCLUSIONS: Intravitreal and systemic dendrimers target activated microglia and show qualitatively similar retinal biodistribution when administered by either route. Results provide proof-of-concept insights for developing dendrimer drug formulations as treatment options for retinal diseases associated with microglia or macrophage activation such as age-related macular degeneration, diabetic retinopathy, and retinal degenerations.

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Targeted fluorescent probes for detection of oxidative stress in the mitochondria.

Yapici NB, Mandalapu S, Michael Gibson K, Bi L.

Abstract: Mitochondrial oxidative stress has been implicated in aging, neurodegenerative diseases, diabetes, stroke, ischemia/reperfusion injury, age-related macular degeneration (AMD) and cancer. Recently, we developed two new mitochondria-targeting fluorescent probes, MitoProbes I/II, which specifically localize in mitochondria and employed both in vivo and in vitro for detection of mitochondrial oxidative stress. Here, we report the design and synthesis of these agents, as well as their utility for real-time imaging of mitochondrial oxidative stress in cells.

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Epidemiology

Ophthalmology. 2015 Jul 21. [Epub ahead of print]

Prevalence and Incidence of Exudative Age-Related Macular Degeneration in South Korea: A Nationwide Population-Based Study.

Park SJ, Kwon KE, Choi NK, Park KH, Woo SJ.

PURPOSE: To determine the prevalence and incidence of exudative age-related macular degeneration (AMD) in South Korea.

DESIGN: Nationwide population-based retrospective study using data from the Korean national health claims database from 2008 through 2012.

PARTICIPANTS: Entire South Korean population 40 years of age or older (n = 22 376 510).

METHODS: We accessed the national health claims database to identify exudative AMD patients using the registration program database for rare intractable diseases, which included ophthalmologist-confirmed exudative AMD, for copayment reduction.

MAIN OUTCOME MEASURES: Prevalence and incidence rates of exudative AMD.

RESULTS: During the 5-year study period, 81 513 patients had exudative AMD (48.2% men) and were included in the prevalence estimates. The prevalence in the general population 40 years of age or older was 36.43 (95% confidence interval [CI], 36.18-36.68) per 10 000 people, that in men was 37.01 (95% CI, 36.65-37.38) per 10 000 people, and that in women was 35.90 (95% CI, 35.56-36.24) per 10 000 people. After excluding prevalent cases during the initial 2-year washout period, 20 196 cases were identified with incident exudative AMD during the final 3-year study period (2010-2012). The incidence in the general population 40 years of age or older was 3.02 (95% CI, 2.98-3.06) per 10 000 person-years, that in men was 3.76 (95% CI, 3.69-3.83) per 10 000 person-years, and that in women was 2.34 (95% CI, 2.29-2.39) per 10 000 person-years. The prevalence and incidence increased with advancing age and peaked at approximately 80 years of age. Both the prevalence and incidence were higher in men than in women in all age groups.

CONCLUSIONS: These detailed estimates of the nationwide, population-based prevalence and incidence of exudative AMD in an Asian population may help to understand the disease pathophysiology and to plan accordingly within the healthcare system.

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Clin Ophthalmol. 2015 Jul 13;9:1275-84. eCollection 2015.

Prevalence of comorbid retinal disease in patients with glaucoma at an academic medical center.

Griffith JF, Goldberg JL.

BACKGROUND: Patients with various retinal diseases and patients who have undergone retinal procedures and surgeries have an increased risk of developing ocular hypertension and glaucoma. Little is known about the epidemiology of comorbid retinal diseases in glaucoma patients. This study evaluated the prevalence of retinal comorbidities in a population of patients with five types of glaucoma.

METHODS: A longitudinal, retrospective study was conducted using International Classification of Disease (ICD-9) billing records from 2003 to 2010 at an academic medical center. Patients were classified as having primary open-angle glaucoma (POAG), low tension open-angle glaucoma (NTG), pigmentary open-angle glaucoma, chronic-angle closure glaucoma (CACG), or pseudoexfoliation glaucoma (PXG) if they had at least three clinic visits with the same ICD-9 code. Patients were classified as having a retinal comorbidity if they had two visits with the same code. Variables were analyzed with the independent t-test, χ^2 (2) test, analysis of variance, or Fisher's exact test.

RESULTS: A total of 5,154 patients had glaucoma, and 14.8% of these had a retinal comorbidity. The prevalence of comorbid retinal disease was higher in patients with POAG (15.7%) than in those with NTG (10.7%), PXG (10.1%), or pigmentary open-angle glaucoma (3.7%; $P < 0.05$). Two hundred and two patients had diabetic retinopathy, with POAG patients (4.5%) having a higher prevalence than those with CACG (1.4%) or PXG (0.6%; $P < 0.001$). There were 297 patients who had macular degeneration and both POAG (2.0%) and PXG patients (2.9%) had a higher prevalence of nonexudative macular degeneration than those with CACG (0%; $P < 0.01$). Patients with comorbid retinal disease had a higher prevalence of blindness and low vision than those without comorbid retinal disease (1.97% versus 1.02%, $P = 0.02$).

CONCLUSION: The high prevalence of comorbid retinal disease and the nearly twofold increase in blindness and low vision in this population demonstrate the need for ophthalmologists to determine if patients have multiple etiologies for their vision loss. The higher prevalence of certain retinal diseases in POAG patients may reflect common pathophysiological processes that warrant further investigation.

PMID: 26203217 [PubMed]

PLoS One. 2015 Jul 22;10(7):e0133043.

Factors Associated with Awareness, Attitudes and Practices Regarding Common Eye Diseases in the General Population in a Rural District in Bangladesh: The Bangladesh Population-based Diabetes and Eye Study (BPDES).

Islam FM, Chakrabarti R, Islam SZ, Finger RP, Critchley C.

BACKGROUND: To assess the awareness, attitudes, and practices associated with common eye diseases and eye care utilization in a rural district of Bangladesh.

METHODS: Data were collected using a multilevel cluster random sampling technique from 3104 adults aged ≥ 30 years from the Banshgram union with a questionnaire assessing the awareness, attitudes and practice about diabetes and common eye diseases, educational attainment, socio-economic status, and medical history.

RESULTS: Participants were aged between 30 and 89 years with a mean (SD) age of 51 (12) years and 65% were female. The majority of participants had heard of cataracts (90%), trachoma (86%) and Pterygium (84%), yet only 4% had heard of diabetic retinopathy (DR), 7% of glaucoma and 8% of Age-related macular degeneration (AMD). However, 58% of participants did not know vision loss could be prevented. Factors associated with lower awareness regarding common eye diseases were increasing age, lack of formal schooling, and lower socio-economic status. A lower proportion (57%) of people with no schooling compared to those who had attained at least secondary school certificate education (72%) reported that they knew that vision loss could be prevented ($p < 0.001$). Overall 51% of people had heard of at least six (67%) out of nine items relating to awareness of common eye diseases. This included 41% of participants aged 65 years or older compared to 61% of those aged 30-35 years ($p < 0.001$). Only 4% had an eye check at least once a year and higher education and better SES were associated with higher frequency of eye checks.

CONCLUSIONS: In rural Bangladesh awareness of cataract, trachoma and pterygium was good but limited in relation to the potentially blinding conditions of glaucoma, DR, and AMD. The results show a large gap between public awareness and treatment practices about common eye diseases. Public health promotion should be designed to address these knowledge gaps.

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Genetics

PLoS One. 2015 Jul 24;10(7):e0134107.

Association Study of Mannose-Binding Lectin Levels and Genetic Variants in Lectin Pathway Proteins with Susceptibility to Age-Related Macular Degeneration: A Case-Control Study.

Osthoff M, Dean MM, Baird PN, Richardson AJ, Daniell M, Guymer RH, Eisen DP.

BACKGROUND: In age-related macular degeneration (AMD) the complement system is thought to be activated by chronic oxidative damage with genetic variants identified in the alternative pathway as susceptibility factors. However, the involvement of the lectin pathway of complement, a key mediator of oxidative damage, is controversial. This study investigated whether mannose-binding lectin (MBL) levels and genetic variants in lectin pathway proteins, are associated with the predisposition to and severity of AMD.

METHODS: MBL levels and single nucleotide polymorphisms (SNPs) in the MBL2 and the ficolin-2 (FCN2) gene were determined in 109 patients with AMD and 109 age- and sex-matched controls.

RESULTS: MBL expression levels were equally distributed in both cases (early and late AMD) and controls ($p > 0.05$). However, there was a trend towards higher median MBL levels in cases with late AMD compared to cases with early AMD (1.0 vs. 0.4 $\mu\text{g/ml}$, $p = 0.09$) and MBL deficiency ($< 0.5 \mu\text{g/ml}$) was encountered

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less frequently in the late AMD group (35% vs 56%, $p = 0.03$). FCN2 and MBL2 allele frequencies were similarly distributed in early and late AMD cases compared with controls ($p > 0.05$ for all analyses) as were MBL2 genotypes. Similarly, there was no significant difference in allele frequencies in any SNPs in either the MBL2 or FCN2 gene in cases with early vs. late AMD.

CONCLUSIONS: SNPs of lectin pathway proteins investigated in this study were not associated with AMD or AMD severity. However, MBL levels deserve further study in a larger cohort of early vs. late AMD patients to elucidate any real effect on AMD severity.

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Diet, lifestyle and low vision

Sci Rep. 2015 Jul 21;5:10585. doi: 10.1038/srep10585.

Homocysteine and the risk of age-related macular degeneration: a systematic review and meta-analysis.

Huang P, Wang F, Kumar Sah B, Jiang J, Ni Z, Wang J, Sun X.

Abstract: Contrasting results have been reported regarding the associations between plasma total homocysteine (tHcy) and B vitamin levels and age-related macular degeneration (AMD) risk. Thus, we aimed to systematically evaluate these associations. Relevant case control studies in English were identified via a thorough search of the PubMed, Medline, and Embase databases from inception to June 2014. The results were pooled using Review Manager 5.2.1. Eleven studies (including 1072 cases and 1202 controls) were eligible for analysis of tHcy levels; additionally, 3 studies (including 152 cases and 98 controls) were eligible for analysis of folic acid and vitamin B12 levels. The cumulative results demonstrated that the plasma tHcy level among the AMD cases was $2.67 \mu\text{mol/L}$ (95% confidence interval [CI], 1.60-3.74) higher than that among the controls. In contrast, the vitamin B12 level among the AMD cases was 64.16 pg/mL (95% CI, 19.32-109.00) lower than that among the controls. Subgroup analyses showed that the folic acid level was 1.66 ng/mL (95% CI, 0.10-3.21) lower for the wet type. Together, the results demonstrated that AMD is associated with elevated tHcy levels and decreased vitamin B12 levels. Plasma tHcy may act as a modulator of the risk for AMD based on the current evidence.

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Exploring new ways of regulation by resveratrol involving miRNAs, with emphasis on inflammation.

Latruffe N, Lançon A, Frazzi R, Aires V, Delmas D, Michaille JJ, Djouadi F, Bastin J, Cherkaoui-Malki M.

Abstract: This review presents recent evidence implicating microRNAs (miRNAs) in the beneficial effects of resveratrol (trihydroxystilbene), a nonflavonoid plant polyphenol, with emphasis on its anti-inflammatory effects. Many diseases and pathologies have been linked, directly or indirectly, to inflammation. These include infections, injuries, atherosclerosis, diabetes mellitus, obesity, cancer, osteoarthritis, age-related macular degeneration, demyelination, and neurodegenerative diseases. Resveratrol can both decrease the secretion of proinflammatory cytokines (e.g., IL-6, IL-8, and TNF- α) and increase the production of anti-inflammatory cytokines; it also decreases the expression of adhesion proteins (e.g., ICAM-1) and leukocyte chemoattractants (e.g., MCP-1). Resveratrol's primary targets appear to be the transcription factors AP-1 and NF- κ B, as well as the gene COX2. Although no mechanistic link between any particular miRNA and resveratrol has been identified, resveratrol effects depend at least in part upon the modification of the expression of a variety of miRNAs that can be anti-inflammatory (e.g., miR-663), proinflammatory (e.g., miR-155), tumor suppressing (e.g., miR-663), or oncogenic (e.g., miR-21).

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Cataract surgery in patients with bilateral advanced age-related macular degeneration: Measurement of visual acuity and quality of life.

Ma Y, Huang J, Zhu B, Sun Q, Miao Y, Zou H.

PURPOSE: To measure the change in visual acuity and vision-related quality of life in patients with both age-related cataract and bilateral age-related macular degeneration (AMD) after cataract surgery.

SETTING: Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University, Shanghai, China.

DESIGN: Prospective case series.

METHODS: Patients with age-related cataract and bilateral advanced AMD who were diagnosed and treated between January 2006 and January 2012 were enrolled. The patients had successful phacoemulsification with foldable posterior chamber intraocular lens implantation. The corrected distance visual acuity (CDVA) and vision-related quality of life measured by the Chinese-version Low Vision Quality of Life (CLVQOL) questionnaire were collected. The Wilcoxon signed-rank test was used to compare the differences. Binary logistic regression analysis was performed to explore potential factors associated with the change in CLVQOL scores.

RESULTS: Sixty eyes of 51 patients were included. The CDVA improved significantly (median difference 0.30 logMAR; range 0 to 1.38 logMAR; $P < .001$). The CLVQOL composite scores and the 4 subscale scores improved significantly (all $P < .001$). A greater increase in the CLVQOL scores was associated with inferior preoperative logMAR CDVA in the more severely affected eye (regression coefficient 3.36; $P < .001$).

CONCLUSIONS: Cataract surgery improved visual acuity and the vision-related quality of life in patients with both age-related cataract and bilateral advanced AMD. Thus, it is beneficial for patients with coexistent advanced AMD to have cataract surgery.

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