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MD Research News

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Drug treatment

Int J Retina Vitreous. 2016 Feb 1;2:3. eCollection 2016.

Fusion proteins for treatment of retinal diseases: aflibercept, ziv-aflibercept, and conbercept.

de Oliveira Dias JR, de Andrade GC, Novais EA, Farah ME, Rodrigues EB.

Abstract: In the last few years, monoclonal antibodies have revolutionized the treatment of retinal neovascular diseases. More recently, a different class of drugs, fusion proteins, has provided an alternative treatment strategy with pharmacological differences. In addition to commercially available aflibercept, two other drugs, ziv-aflibercept and conbercept, have been studied in antiangiogenic treatment of ocular diseases. In this scenario, a critical review of the currently available data regarding fusion proteins in ophthalmic diseases may be a timely and important contribution. Aflibercept, previously known as VEGF Trap Eye, is a fusion protein of VEGF receptors 1 and 2 and a treatment for several retinal diseases related to angiogenesis. It has firmly joined ranibizumab and bevacizumab as an important therapeutic option in the management of neovascular AMD-, DME- and RVO-associated macular edema. Ziv-aflibercept, a systemic chemotherapeutic agent approved for the treatment of metastatic colorectal cancer, has recently drawn attention because of its potential for intravitreal administration, since it was not associated with ERG-related signs of toxicity in an experimental study and in human case reports. Conbercept is a soluble receptor decoy that blocks all isoforms of VEGF-A, VEGF-B, VEGF-C, and PlGF, which has a high binding affinity for VEGF and a long half-life in vitreous. It has been studied in a phase three clinical trial and has shown efficacy and safety. This review discusses three fusion proteins that have been studied in ophthalmology, aflibercept, ziv-aflibercept and conbercept, with emphasis on their clinical application for the treatment of retinal diseases.

PMID: 27847621 PMCID: PMC5088480

Int J Retina Vitreous. 2016 Jan 25;2:2. eCollection 2016.

Conversion back to bevacizumab or ranibizumab for recurrent neovascular activity with aflibercept in age-related macular degeneration: a case series.

Slean GR, Hemarat K2, Khurana RN3, Stewart JM4.

BACKGROUND: Neovascular age-related macular degeneration often requires chronic therapy with anti-VEGF agents, and patients with recurrent disease are challenging to manage.

METHODS: This retrospective case series evaluates patients who were switched from bevacizumab or ranibizumab to aflibercept and then back again because of recurrent fluid on optical coherence tomography (OCT) by reporting changes in OCT measurements over the course of medication changes.

RESULTS: Twenty-one eyes in nineteen patients received an average of 20.7 bevacizumab and/or

ranibizumab injections and then an average of 7.2 aflibercept injections before being switched back to bevacizumab or ranibizumab because of recurrent fluid on OCT. Median central macular thickness improved on transition from bevacizumab or ranibizumab (317 μm) to aflibercept (285 μm; p = 0.034), then worsened over the course of aflibercept treatment (296 μm; p = 0.080), but improved again with transition from aflibercept back to bevacizumab or ranibizumab (283 μm; p = 0.016). The total volume of subretinal fluid, intraretinal fluid, and pigment epithelial detachments also decreased on transition from bevacizumab or ranibizumab (2.56 mm3) to aflibercept (2.44 mm3; p = 0.080), then worsened over the course of aflibercept treatment (3.18 mm3; p = 0.019), and improved again on transition back to bevacizumab or ranibizumab (2.11 mm3; p = 0.016).

CONCLUSIONS: While aflibercept appears initially effective, some patients develop recurrent fluid with aflibercept that improves with transition back to bevacizumab or ranibizumab. Rotating anti-VEGF agents may be beneficial with recurrent neovascular activity.

PMID: 27847620 PMCID: PMC5088459

Int J Retina Vitreous. 2015 Nov 9;1:22. eCollection 2015.

Triple combination therapy and zeaxanthin for the treatment of neovascular age-related macular degeneration: an interventional comparative study and cost-effectiveness analysis.

Olk RJ, Peralta E, Gierhart DL, Brown GC, Brown MM.

BACKGROUND: Reports of triple combination therapy for neovascular age-related macular degeneration (AMD) suggest a benefit, as do reports for zeaxanthin. An interventional comparative study was thus undertaken to evaluate the efficacy of triple combination therapy with and without zeaxanthin, as well as the economic viability of the therapies.

METHODS: The cases of 543 consecutive eyes of 424 patients with subfoveal choroidal neovascularization (CNV) secondary to AMD were reviewed. All eyes were treated with triple combination therapy (triple therapy) consisting of: (1) reduced-fluence photodynamic therapy with verteporfin, (2) intravitreal bevacizumab and (3) intravitreal dexamethasone. Therapy was repeated as necessary. One cohort of patients was also given supplementation with 20 mg of oral zeaxanthin (Zx) daily.

RESULTS: The triple therapy group without Zx received a mean of 2.8 treatment cycles and 87 % of patients had stable or improved vision at 24 months. In the triple therapy group with Zx, the mean number of treatment cycles was 2.1, with 83 % of patients having stable or improved vision at 24 months. At 24 months, CNV developed in 12.5 % of fellow eyes treated with triple therapy alone; CNV developed in 6.25 % of eyes treated with triple therapy with Zx (p = 0.03). An average cost-utility analysis revealed that triple therapy was cost-effective with a cost-utility ratio of $26,574/QALY, while triple therapy with Zx was more cost-effective with an average cost-utility ratio of $19,962/QALY. The incremental cost-utility analysis assessing the addition of Zx to triple therapy disclosed Zx supplementation was very cost-effective at $5302/QALY. When it was assumed that triple therapy with Zx reduced fellow eye CNV development by 30.3 %, the incremental cost-utility dropped to (-$6332/QALY), indicating that adding Zx to triple therapy yielded greater patient value, and was also less expensive than using triple therapy alone.

CONCLUSIONS: Triple therapy is comparatively effective and cost-effective. Considerably less treatment is needed than reported in monotherapy studies. The addition of oral Zx appears to further reduce the treatment cycles required, and possibly reduce the risk of CNV development in the fellow eye.

PMID: 27847615 PMCID: PMC5088486

Ophthalmic Surg Lasers Imaging Retina. 2016 Nov 1;47(11):1-18.

Ranibizumab 0.3 mg for Persistent Diabetic Macular Edema After Recent, Frequent, and Chronic Bevacizumab: The ROTATE Trial.

Fechter C, Frazier H, Marcus WB, Farooq A, Singh H, Marcus DM.

BACKGROUND AND OBJECTIVE: To evaluate the safety and efficacy of 0.3 mg ranibizumab (Lucentis; Genentech, South San Francisco, CA) in eyes with persistent diabetic macular edema (DME) after recent, chronic, and frequent bevacizumab (Avastin; Genentech, South San Francisco, CA).

PATIENTS AND METHODS: Open-label, prospective study of 0.3 mg ranibizumab for eyes with persistent DME after bevacizumab. Thirty eyes randomized to a sustained group or a pro re nata (PRN) dosing group.

RESULTS: The mean change in ETDRS best-corrected visual acuity from baseline to 1 year was +6.7 letters in the sustained group, +6.4 letters in the PRN group, and +6.5 letters overall. There was an overall mean reduction of 116 µm from baseline central subfield thickness at 1 year, with -92 µm and -127 µm decreases in the sustained and PRN groups, respectively. Adverse events included two deaths; one patient with multiple cardiopulmonary comorbidities, myocardial infarction, stroke, osteomyelitis; and mild posterior subcapsular cataracts in two eyes.

CONCLUSION: Ranibizumab 0.3 mg demonstrated improved visual and anatomic outcomes in patients with persistent DME following bevacizumab. [Ophthalmic Surg Lasers Imaging Retina. 2016;47:1030-1037.].

PMID: 27842191

Invest Ophthalmol Vis Sci. 2016 Nov 1;57(14):6234-6241.

Association of Circulating Markers With Outcome Parameters in the Bevacizumab and Ranibizumab in Diabetic Macular Edema Trial.

Fickweiler W, Klaassen I, Vogels IM, Hooymans JM, Wolffenbuttel BH, Los LI, Schlingemann RO; BRDME Research Group.

PURPOSE: The purpose of this study was to evaluate selected candidate biomarkers as potential markers for patients with diabetic macular edema (DME) who receive antivascular endothelial growth factor (VEGF) therapy.

METHODS: Selected biomarkers included blood levels of messenger RNA (mRNA) of retinoschisin, RPE65, rhodopsin, and endothelial progenitor cell markers CD34 and CD133. Blood samples were obtained from 89 patients with DME according to the study protocol of the Bevacizumab and Ranibizumab in Diabetic Macular Edema (BRDME) study. During each monthly visit, patients underwent optical coherence tomography scanning and visual acuity was measured. Anti-VEGF injections were administered at fixed monthly intervals over 6 months. Analyses of covariance using simplified and linear mixed models were used to examine the correlations between candidate markers and changes in visual acuity and central subfield thickness.

RESULTS: Plasma mRNA levels of retinoschisin were negatively associated with visual acuity, and plasma mRNA levels of rhodopsin were positively associated with visual acuity in patients with DME ($P < 0.01$ and $P < 0.05$, respectively). In addition, changes in central subfield thickness between baseline and months 1, 2, and 3 during anti-VEGF treatment were associated with mRNA levels of retinoschisin, rhodopsin, and the ratio of retinoschisin-to-rhodopsin ($P < 0.01$, all).

CONCLUSIONS: This prospective, multicenter study found that circulating mRNA levels of retinoschisin and rhodopsin are associated with visual acuity and changes in central subfield thickness during anti-VEGF

therapy in patients with DME. (ClinicalTrials.gov number: NCT01635790.).

PMID: 27842163

Indian J Ophthalmol. 2016 Sep;64(9):643-647.

Long-term effect of anti-vascular endothelial growth factor injections on intraocular pressure.

Nariani A, Williams B, Hariprasad SM.

OBJECTIVE: There is a substantial debate in the ophthalmology community about whether anti-vascular endothelial growth factor (VEGF) injections result in a long-term increase in intraocular pressure (IOP).

DESIGN: We performed a retrospective study to investigate how the number and timing of intravitreal injections in patients with age-related macular degeneration (AMD) and diabetic macular edema (DME) affect IOP over time.

METHODS: We collected long-term IOP data on patients receiving anti-VEGF injections at our institution. Patients over the age of 40 years who received injections for AMD (n = 76) or DME (n = 55) were included. Patients were grouped according to indication as well as number of injections received (1-3, 4-6, 7-9, or 10+ injections). IOP measurements were then placed into time points (0-6, 6-12, 12-18, 18-24, or 24+ months) and compared to the preinjection average IOP.

RESULTS: For patients with DME, average preinjection IOP was 15.7 mmHg. At 24+ months after injection, the average IOP was 15.2 (P = 0.68) for patients receiving 1-3 injections, 16.8 (P = 0.23) for 4-6 injections, and 14.4 (P = 0.66) for 7-9 injections. For patients with AMD, average initial IOP was 15.6 mmHg. At 24+ months after injection, the average IOP was 12.6 (P = 0.97) for 1-3 injections, 14.9 (P = 0.96) for 4-6 injections, 14.8 (P = 0.84) for 7-9 injections, and 15.7 (P = 0.56) for 10+ injections.

CONCLUSIONS: There was no increase in IOP over time for AMD or DME patients, regardless of how many injections they received. For patients receiving unilateral injections, there was no increase in IOP in the injected eye when compared to the noninjected eye.

PMID: 27853011

Semin Ophthalmol. 2016 Nov 14:1-6. [Epub ahead of print]

Intravitreal Bevacizumab and Ranibizumab in the Treatment of Acute Central Serous Chorioretihopathy: A Single Center Retrospective Study.

Tekin K, Sekeroglu MA, Cankaya AB, Teke MY, Doguizi S, Yilmazbas P.

OBJECTIVES: To evaluate and compare the anatomical and functional outcomes of patients with acute central serous chorioretinopathy (CSC) who did not receive any intervention or treatment with intravitreal bevacizumab or ranibizumab.

METHODS: A single-center retrospective comparative study. Seventy eyes of 70 patients were recruited for the study; 27 patients were only observed without any medication or intervention (observation group), 23 were treated with intravitreal bevacizumab (IVB group), and the remaining 20 were treated with intavitreal ranibizumab (IVR group). The best-corrected visual acuity (BCVA) and central macular thickness (CMT) obtained by spectral-domain optical coherence tomography were compared between the groups.

RESULTS: There were no significant differences between the groups with regard to age, sex, and follow-up periods (p>0.05). The mean time from baseline to initial complete resolution of subretinal fluid was 3.52±1.64 months in the observation group, 1.19±0.60 months in the IVB group, and 1.11±0.47 months in

the IVR group; the resolution time was significantly longer in the observation group (p<0.001). While the CMT was significantly thicker in the observation group when compared to the IVB and IVR groups in the first month (p=0.001), it was similar between the groups in the third, sixth, and twelfth months (p>0.05). Additionally, pairwise comparisons of the IVB and IVR groups revealed that there were no significant differences between these groups regarding CMT at any follow-up time (p>0.05).

CONCLUSIONS: Compared with observation alone, neither IVB nor IVR had a positive effect in terms of anatomical and functional outcomes for acute CSC. Although the resolution time of SRF is shorter by using ranibizumab, both the ranibizumab and bevacizumab could be effective in achieving rapid resolution of serous detachment in patients with acute CSC.

PMID: 27841949

Int J Retina Vitreous. 2016 Aug 23;2:20. eCollection 2016.

Aflibercept in branch retinal vein occlusion as second line therapy: clinical outcome 12 months after changing treatment from bevacizumab/ranibizumab-a pilot study.

Wirth MA, Becker MD, Graf N, Michels S.

PURPOSE: To evaluate the effect of aflibercept (as second line therapy) on the clinical outcome in patients with chronic macular edema secondary to branch retinal vein occlusion (BRVO) insufficiently responding to prior treatment with bevacizumab and/or ranibizumab.

METHODS: Ten eyes of ten patients (n = 10) with chronic macular edema secondary to BRVO were included in a retrospective analysis. These patients received aflibercept after an insufficient response to treatment with ranibizumab and/- or bevacizumab. All intravitreal injections were administered according to a "treat and extend" regimen. Insufficient response was defined as the necessity of injection intervals of 6 weeks or less. The primary outcome of the study was the change in mean injection interval from baseline (prior switching to aflibercept) to month 12 after conversion to aflibercept. Secondary outcomes included the change in best corrected visual acuity (BCVA), central retinal thickness (CRT), central retinal volume (CRV) and intraocular pressure (IOP).

RESULTS: All patients completed 12 months follow-up. In total, patients received a mean of 15.5 injections of ranibizumab and/or bevacizumab over a mean period of 23.1 months prior to switching to aflibercept. The primary endpoint indicated a significant increase in the injection interval from 5.0 weeks at baseline to 8.3 weeks at month 12 (p = 0.002). Secondary outcomes showed favorable results. Mean BCVA increased from 72.7 letters at baseline to 77.9 letters at month 12 after treatment initiation with aflibercept (+5.2 letters, p = 0.375). Correspondingly, CRT values decreased by 61.7 µm (p = 0.344) and the mean CRV (6 mm diameter) by 0.86 mm3 (p = 0.021) from baseline to 1 year after treatment initiation with aflibercept. During the treatment period with aflibercept no significant changes in intraocular pressure were registered (p = 0.238).

CONCLUSIONS: Changing treatment to aflibercept in patients with chronic macular edema secondary to BRVO showed a statistically significant extension of the retreatment interval as well as beneficial anatomic changes in our study group. Our data do not allow a definite conclusion since the study was not controlled.

PMID: 27847638 PMCID: PMC5088487

Int J Retina Vitreous. 2016 Jul 11;2:16. eCollection 2016.

Initiation of intravitreal aflibercept injection treatment in patients with diabetic macular edema: a review of VIVID-DME and VISTA-DME data.

Ziemssen F, Schlottman PG, Lim JI, Agostini H, Lang GE, Bandello F.

BACKGROUND: Diabetic macular edema (DME) shows a gradual and sustained functional and morphologic response to anti-vascular endothelial growth factor (VEGF) drugs, but the optimal schedule for initiation of anti-VEGF therapy is not known. This study evaluates the treatment response behavior of DME in the Phase 3 trials of intravitreal aflibercept, with 5 initial intravitreal aflibercept injections (IAI), 2 mg every 4 weeks (2q4), in the upload phase.

METHODS: This post hoc pooled analysis of the VISTA-DME (NCT01363440) and VIVID-DME (NCT01331681) trials evaluated the change in best-corrected visual acuity (BCVA) and central retinal thickness (CRT) during the upload phase, using pooled data from both IAI treatment groups [2q4 and 2 mg every 8 weeks (2q8)]. The mean visit-to-visit change in BCVA and CRT, and the respective rate of gainers and losers was calculated for each successive visit. A secondary analysis compared the visit-to-visit change in BCVA between the 2q4 and 2q8 treatment arms during the upload period and the first year treatment period.

RESULTS: The majority of eyes showed a continuing improvement of BCVA after the first IAI. The proportions of eyes gaining BCVA (≥5 letters) at each visit compared with the previous visit during the IAI 2q4 upload phase were 60 (4-weeks), 19 (8-weeks), 16 (12-weeks), 15 (16-weeks), and 14 % (20-weeks). In contrast, the proportions of eyes losing BCVA (≥5 letters) were 3 (4-weeks), 7 (8-weeks), 7 (12-weeks), 9 (16-weeks), and 8 % (20-weeks), respectively. The odds of BCVA (≥5 letters) gain/loss exceeded 1.7 at each visit (range 1.7-20). Overall, the proportion of patients with BCVA gain ≥5 letters at week 20 (compared with baseline) was 76 and 80 % in the 2q4 and 2q8 groups, respectively. The proportions of eyes showing a visit-to-visit decrease in CRT of ≥30 µm during the first 5 IAI were 77 (4-weeks), 27 (8-weeks), 21 (12-weeks), 17 (16-weeks), and 12 % (20-weeks). In the secondary analysis, the BCVA outcomes were similar for the 2q8 and 2q4 treatment arms.

CONCLUSIONS: The data presented here are consistent with continual functional and anatomic improvement following the fourth and fifth initial 2q4 injections, suggesting that an intensive and sufficiently long upload may be beneficial. Trial registration VIVID-DME: Clinicaltrials.gov: NCT01331681; VISTA-DME: Clinicaltrials.gov: NCT01363440.

PMID: 27847634 PMCID: PMC5088462

Sci Rep. 2016 Nov 16;6:36870.

Treatment of polypoidal choroidal vasculopathy by photodynamic therapy, aflibercept and dexamethasone triple therapy.

Ho M, Woo DC, Chan VC, Young AL, Brelen ME.

Abstract: Polypoidal choroidal vasculopathy is a relatively common type of degenerative macular disease among the Chinese population. This study aims to describe the therapeutic responses to combination therapy with photodynamic therapy, intravitreal aflibercept and intravitreal dexamethasone in patients with polypoidal choroidal vasculopathy. A prospective series of 17 eyes of 13 patients suffering from treatment-naïve polypoidal choroidal vasculoapathy were recruited. All cases received triple therapy with photodynamic therapy, intravitreal aflibercept and intravitreal dexamethasone and one year outcomes were reported. The baseline visual acuity was 0.65logMAR +/- 0.38 (Snellen 20/80 to 20/100). The visual acuity at 1 week, 3 months, 6 months and one year after treatment were significantly improved to 0.522logMAR+/-0.365 ($P < 0.04$) (Snellen 20/70), 0.363logMAR+/-0.382 (Snellen 20/50;$P < 0.001$), 0.377logMAR +/- 0.440 (Snellen 20/50;$p = 0.005$), and 0.35logMAR +/- 0.407 (Snellen 20/40;$P < 0.001$), respectively. The baseline central foveal thickness (CFT) on optical coherence tomography (OCT) was 394.7 +/- 70.6 µm. CFT at 6 months and 1 year after treatment were significantly reduced to 259 +/- 54 µm ($p = 0.004$) and 271 +/- 49.7 µm($p = 0.016$), respectively. Triple therapy with photodynamic therapy, intravitreal aflibercept and intravitreal dexamethasone is an effective treatment for polypoidal choroidal vasculopathy. The majority of

cases responded well with significant responses observed as early as 1 week after initiation of therapy.

PMID: 27848983

Am J Ophthalmol. 2016 Nov 11. [Epub ahead of print]

Long-Term Results of Pro Re Nata Regimen of Aflibercept Treatment in Persistent Neovascular Age -Related Macular Degeneration.

Călugăru D, Călugăru M.

PMID: 27842696

Eur J Ophthalmol. 2016 Oct 22:0. [Epub ahead of print]

Author's reply to comments to: Ranibizumab for persistent diabetic macular edema after bevacizumab treatment.

Katz G.

PMID: 27854373

Other treatment & diagnosis

Int J Retina Vitreous. 2015 Dec 1;1:20. eCollection 2015.

Early detection of age related macular degeneration: current status.

Schwartz R, Loewenstein A.

Abstract: Early diagnosis and treatment of choroidal neovascularization (CNV), a main cause of severe vision loss in age related macular degeneration (AMD), is crucial in order to preserve vision and the quality of life of patients. This review summarizes current literature on the subject of early detection of CNV, both in the clinic setting and mainly in the patient's home. New technologies are evolving to allow for earlier detection and thus vision preservation in AMD patients.

PMID: 27847613 PMCID: PMC5088451

Invest Ophthalmol Vis Sci. 2016 Nov 1;57(14):6256-6264.

Choroidal Thickness and Choroidal Vessel Density in Nonexudative Age-Related Macular Degeneration Using Swept-Source Optical Coherence Tomography Imaging.

Zheng F, Gregori G, Schaal KB, Legarreta AD, Miller AR, Roisman L, Feuer WJ, Rosenfeld PJ.

PURPOSE: To analyze the relationship between choroidal thickness and the distribution of choroidal blood vessels in eyes with nonexudative AMD.

METHODS: Eyes with a diagnosis of nonexudative AMD were imaged using a prototype 100-kHz swept-source (SS) optical coherence tomography (OCT) instrument (Carl Zeiss Meditec, Dublin, CA, USA) with a central wavelength of 1050 nm. We used an OCT cube scan pattern consisting of 512 × 512 A-scans over a 12 × 12 mm retinal area. The eyes were partitioned into two groups based on the presence or absence of reticular pseudodrusen (RPD). All scans were segmented using an automated algorithm. In addition, five

eyes from each of the two groups were randomly chosen for manual segmentation. Binary choroidal vessels maps were generated from suitable OCT choroidal slabs, and the relationship between the density of large choroidal vessels and choroidal thickness was analyzed using an Early Treatment Diabetic Retinopathy Study-like target centered on the fovea.

RESULTS: Twenty-five eyes were enrolled in each group. The automated algorithm produced accurate choroidal thickness maps with an average difference between the manual and automated segmentations of 13.7 μm. There was a significant and stable correlation between choroidal thickness and choroidal vessel density across the two groups. Both average choroidal thickness and vessel density were significantly lower in eyes with RPD.

CONCLUSIONS: Our fully automated choroidal segmentation algorithm was able to capture the different patterns of choroidal thickness over a wide area. Choroidal thickness has a clear relationship with the density of large choroid vessels in our sample, irrespective of the presence or absence of RPD.

PMID: 27849311

Int J Retina Vitreous. 2015 Apr 15;1:5. eCollection 2015.

A review of optical coherence tomography angiography (OCTA).

de Carlo TE, Romano A, Waheed NK, Duker JS.

Abstract: Optical coherence tomography angiography (OCTA) is a new, non-invasive imaging technique that generates volumetric angiography images in a matter of seconds. This is a nascent technology with a potential wide applicability for retinal vascular disease. At present, level 1 evidence of the technology's clinical applications doesn't exist. In this paper, we introduce the technology, review the available English language publications regarding OCTA, and compare it with the current angiographic gold standards, fluorescein angiography (FA) and indocyanine green angiography (ICGA). Finally we summarize its potential application to retinal vascular diseases. OCTA is quick and non-invasive, and provides volumetric data with the clinical capability of specifically localizing and delineating pathology along with the ability to show both structural and blood flow information in tandem. Its current limitations include a relatively small field of view, inability to show leakage, and proclivity for image artifact due to patient movement/blinking. Published studies hint at OCTA's potential efficacy in the evaluation of common ophthalmologic diseases such age related macular degeneration (AMD), diabetic retinopathy, artery and vein occlusions, and glaucoma. OCTA can detect changes in choroidal blood vessel flow and can elucidate the presence of choroidal neovascularization (CNV) in a variety of conditions but especially in AMD. It provides a highly detailed view of the retinal vasculature, which allows for accurate delineation of the foveal avascular zone (FAZ) in diabetic eyes and detection of subtle microvascular abnormalities in diabetic and vascular occlusive eyes. Optic disc perfusion in glaucomatous eyes is notable as well on OCTA. Further studies are needed to more definitively determine OCTA's utility in the clinical setting and to establish if this technology may offer a non-invasive option of visualizing the retinal vasculature in detail.

PMID: 27847598 PMCID: PMC5066513

Int J Retina Vitreous. 2016 Nov 1;2:25. eCollection 2016.

Novel perspectives on swept-source optical coherence tomography.

Lavinsky F, Lavinsky D.

Abstract: Technologies for multimodal digital imaging of vitreoretinal diseases have improved the accuracy of diagnosis and the depth of the knowledge of the mechanisms of disease and their response to treatments. Optic coherence tomography (OCT) has become a mandatory tool for the management and for the follow-up of retinal pathologies. OCT technology evolved in the last two decades from time-domain to

spectral domain and recently to the swept-source OCTs (SS-OCT). SS-OCT improved the depth of imaging and the scan speed, thus adding novel algorithms and features such as for vitreous and vitreoretinal interface evaluation, choroid segmentation and mapping, OCT angiography and En-face OCT. The multimodal approach using SS-OCT is expected to advance the understanding of retinal pathologies such as age related macular degeneration, diabetic maculopathy, central serous chorioretinopathy, the pachychoroid spectrum and macular telangiectasia. Surgical vitreoretinal diseases such as vitreo-macular traction syndrome, epiretinal membrane, retinal detachment, proliferative vitreoretinal retinopathy and diabetic traction retinal detachment also will be better understood and documented with SS-OCT. This technology also provides great utility for a broad spectrum of ophthalmic pathologies including glaucoma, uveitis, tumors and anterior segment evaluation.

PMID: 27847643 PMCID: PMC5088466

Ophthalmic Surg Lasers Imaging Retina. 2016 Nov 1;47(11):1038-1043.

Plenoptic Ophthalmoscopy: A Novel Imaging Technique.

Adam MK, Aenchbacher W, Kurzweg T, Hsu J.

Abstract: This prospective retinal imaging case series was designed to establish feasibility of plenoptic ophthalmoscopy (PO), a novel mydriatic fundus imaging technique. A custom variable intensity LED array light source adapter was created for the Lytro Gen1 light-field camera (Lytro, Mountain View, CA). Initial PO testing was performed on a model eye and rabbit fundi. PO image acquisition was then performed on dilated human subjects with a variety of retinal pathology and images were subjected to computational enhancement. The Lytro Gen1 light-field camera with custom LED array captured fundus images of eyes with diabetic retinopathy, age-related macular degeneration, retinal detachment, and other diagnoses. Post-acquisition computational processing allowed for refocusing and perspective shifting of retinal PO images, resulting in improved image quality. The application of PO to image the ocular fundus is feasible. Additional studies are needed to determine its potential clinical utility. [Ophthalmic Surg PMID: 27842198

Int J Retina Vitreous. 2016 Jun 1;2:14. eCollection 2016.

Changes of macular pigment optical density in elderly eyes: a longitudinal analysis from the MARS study.

Meyer Zu Westrup V, Dietzel M, Zeimer M, Pauleikhoff D, Hense HW.

BACKGROUND: Macular pigment (MP) has been related to the occurrence of age related macular degeneration (AMD). We investigated prospectively in eyes of elderly individuals how magnitude and spatial distribution of MP had changed after 4 years.

METHODS: The study included 380 eyes from 237 participants of the Münster Ageing and Retina Study cohort which were free of advanced stages of AMD. MP optical density (MPOD) was measured in density units (D.U.) at eccentricities of 0.25°, 0.5°, 1.0° and 2.0° from the fovea using dual-wavelength autofluorescence; ring-like MP distributions were identified from MP density profiles. Changes were assessed with mixed linear models.

RESULTS: The study participants' mean age at baseline was 70.5 years. Early AMD was present in 150 study eyes (39.5 %) and a ring-like distribution of MPOD was found in 87 study eyes (22.9 %). After a median follow-up time of 3.96 years, the MPOD averaged over all eyes was slightly raised at the central fovea (from 0.658 to 0.670 D.U. (relative change +1.8 %), $p = 0.08$) and most markedly at 2.0° (from 0.157 to 0.172 D.U. (+9.5 %), $p < 0.001$). Multivariate analyses, adjusting for sex, body mass and carotenoid supplement intake, revealed that MPOD increments, at any distance from the fovea, were slightly less pronounced in older eyes. Serum concentrations of lutein at follow-up, presumably reflecting recent intake

of antioxidant supplements, raised MPOD levels significantly at 1.0° and 2.0° (both $p < 0.01$) but not in the central fovea. Early AMD at baseline and ring-like MPOD distribution did not significantly impact on MPOD changes over time. A ring-like spatial distribution of MPOD persisted in over 80 % of the affected eyes.

CONCLUSIONS: Overall, the magnitude and spatial arrangement of MPOD was remarkably stable over time in elderly eyes. Significant MPOD rises in perifoveal regions probably indicate effects of lutein containing supplements. The persistence of ring-like MPOD distributions over time seems to suggest their determination by anatomical structures.

PMID: 27847632 PMCID: PMC5088485

Int J Retina Vitreous. 2016 Apr 8;2:12. eCollection 2016.

Clinical applications of fundus autofluorescence in retinal disease.

Yung M, Klufas MA, Sarraf D.

Abstract: Fundus autofluorescence (FAF) is a non-invasive retinal imaging modality used in clinical practice to provide a density map of lipofuscin, the predominant ocular fluorophore, in the retinal pigment epithelium. Multiple commercially available imaging systems, including the fundus camera, the confocal scanning laser ophthalmoscope, and the ultra-widefield imaging device, are available to the clinician. Each offers unique advantages for evaluating various retinal diseases. The clinical applications of FAF continue to expand. It is now an essential tool for evaluating age related macular degeneration, macular dystrophies, retinitis pigmentosa, white dot syndromes, retinal drug toxicities, and various other retinal disorders. FAF may detect abnormalities beyond those detected on funduscopic exam, fluorescein angiography, or optical coherence tomography, and can be used to elucidate disease pathogenesis, form genotype-phenotype correlations, diagnose and monitor disease, and evaluate novel therapies. Given its ease of use, non-invasive nature, and value in characterizing retinal disease, FAF enjoys increasing clinical relevance. This review summarizes common ocular fluorophores, imaging modalities, and FAF findings for a wide spectrum of retinal disorders.

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Pathogenesis

Mol Med Rep. 2016 Oct 26. [Epub ahead of print]

Tristetraprolin regulates the decay of the hypoxia-induced vascular endothelial growth factor mRNA in ARPE-19 cells.

Ryu J, Seong H, Yoon NA, Seo SW, Park JW, Kang SS, Park JM, Han YS.

Abstract: The aim of the present study was to investigate the effects of tristetraprolin (TTP) on the vascular endothelial growth factor (VEGF) mRNA and protein expression levels in retinal pigment epithelial cells under hypoxic conditions, and to consider the possibility of using TTP as a novel treatment tool for neovascular age‑related macular degeneration (AMD). Overexpression of TTP reduced the expression and secretion levels of VEGF in ARPE‑19 cells under hypoxic conditions. TTP destabilized the VEGF mRNA by binding to adenosine and uridine‑rich elements regions in its 3'‑untranslated region. Furthermore, conditioned medium (CM) from TTP‑overexpressing ARPE‑19 cells suppressed the tube formation in human umbilical vein endothelial cells compared with hypoxic CM. These findings indicate that regulation of TTP expression may be a promising therapeutic tool for neovascular AMD, however, further research is required.

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Type 1 neovascularization may confer resistance to geographic atrophy amongst eyes treated for neovascular age-related macular degeneration.

Dhrami-Gavazi E, Balaratnasingam C, Lee W, Freund KB.

BACKGROUND: To report a series of age-related macular degeneration (AMD) patients in whom progression to geographic atrophy (GA) in one eye receiving frequent intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) therapy for type 1 neovascularization (NV) was slower than that of the fellow eye with non-neovascular AMD.

METHODS: Retrospective, observational case series examining the clinical course and GA progression rate in four consecutive patients in which one eye harbored type 1 neovascular AMD and was receiving anti -VEGF therapy, while the fellow eye manifested signs of non-neovascular AMD only. Eligibility criteria included anti-VEGF therapy duration of over 4 years and over 50 injections. Lesion evolution was documented via multimodal imaging. GA at baseline and final visits was quantified and GA progression rate for each eye was determined.

RESULTS: Four consecutive patients were followed for a mean interval of 94 months (range 62-120). One eye harbored type 1 NV while the fellow eye remained non-neovascular. The former received a mean of 65.5 ± 15.2 anti-VEGF injections. Mean rate of GA progression in non-neovascular eyes was 0.076 ± 0.024 mm2/month and in type 1 NV eyes was 0.004 ± 0.005 mm2/month. Difference in GA progression rate between type 1 and non-neovascular eyes was found to be statistically significant (P = 0.001).

CONCLUSIONS: These findings support previous hypotheses that, unlike type 2 and 3 lesions, type 1 NV may represent a neovascular AMD subtype more resilient to GA formation. This may have implications for anti-VEGF regimens in the management of type 1 NV.

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Continuous exposure to non-lethal doses of sodium iodate induces retinal pigment epithelial cell dysfunction.

Zhang XY, Ng TK, Brelén ME, Wu D, Wang JX, Chan KP, Yung JS, Cao D, Wang Y, Zhang S, Chan SO, Pang CP.

Abstract: Age-related macular degeneration (AMD), characterized by progressive degeneration of retinal pigment epithelium (RPE), is the major cause of irreversible blindness and visual impairment in elderly population. We previously established a RPE degeneration model using an acute high dose sodium iodate to induce oxidative stress. Here we report findings on a prolonged treatment of low doses of sodium iodate on human RPE cells (ARPE-19). RPE cells were treated continuously with low doses (2-10 mM) of sodium iodate for 5 days. Low doses (2-5 mM) of sodium iodate did not reduce RPE cell viability, which is contrasting to cell apoptosis in 10 mM treatment. These low doses are sufficient to retard RPE cell migration and reduced expression of cell junction protein ZO-1. Phagocytotic activity of RPE cells was attenuated by sodium iodate dose-dependently. Sodium iodate also increased expression of FGF-2, but suppressed expression of IL-8, PDGF, TIMP-2 and VEGF. Furthermore, HTRA1 and epithelial-to-mesenchymal transition marker proteins were downregulated, whereas PERK and LC3B-II proteins were upregulated after sodium iodate treatment. These results suggested that prolonged exposure to non-lethal doses of oxidative stress induces RPE cell dysfunctions that resemble conditions in AMD. This model can be used for future drug/treatment investigation on AMD.

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α-Lipoic Acid Treatment Improves Vision-Related Quality of Life in Patients with Dry Age-Related Macular Degeneration.

Tao Y, Jiang P, Wei Y, Wang P, Sun X, Wang H.

Abstract: Dry form of age-related macular degeneration (AMD) constitutes 90% of AMD cases, and it is characterized by the formation of drusen under the retina and the slow breakdown of the light-sensing cells in the macula, which causes a gradual loss of central vision. Since oxidative stress is involved in the pathogenesis of dry AMD, α-lipoic acid (LA) with antioxidant properties was selected, and its effect on anti-oxidative markers and visual quality in patients with dry AMD was assessed. A total of 100 dry AMD patients (60-83 years old) were randomly assigned to LA treatment group (n = 50) and placebo control group (n = 50). We measured the serum superoxide dismutase (SOD) activity, an important marker of antioxidant defense, best-corrected visual acuity (BCVA), contrast sensitivity, and Chinese-Version Low Vision Quality of Life (CLVQOL) before and after LA or placebo intervention. Pearson correlation coefficients were calculated to explore the relationship between contrast sensitivity values and CLVQOL scores. There was a statistically significant increase in serum SOD activity after LA intervention. The CLVQOL score was improved significantly after LA treatment. The contrast sensitivity measured at middle and low spatial frequency was significantly higher after LA treatment. CLVQOL scores were positively correlated with contrast sensitivity at low spatial frequency (3 cyc/degree) in LA-treated group. These results indicate that LA treatment improves vision-related quality of life in patients with dry AMD probably by increasing antioxidant activity. Thus, LA can be regarded as a promising agent for the treatment of AMD.

PMID: 27840374

Epidemiology

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Does the use of acetylsalicylic acid have an influence on our vision?

Michalska-Małecka K, Regucka A, Śpiewak D, Sosnowska-Pońska M, Niewiem A.

PURPOSE: Acetylsalicylic acid (ASA) is one of the most commonly used drugs in the world due to its anti-inflammatory, analgesic, and antipyretic properties. This review aims to describe the relationship between acetylsalicylic acid and age-related macular degeneration (AMD) - a chronic disease that causes deterioration of visual acuity and is one of the most common ophthalmological diseases these days.

METHODS: Data presented in this review were collected from both research and review articles concerning ophthalmology and pharmacology.

RESULTS: The results of the studies analyzed in this review are not unambiguous. Moreover, the studies are not homogenous. They differed from one another in terms of the number of patients, the age criteria, the ASA dose, and the duration of control period. The reviewed studies revealed that ASA therapy, which is applied as a protection in cardiovascular diseases in patients with early forms of AMD and geographic atrophy, should not be discontinued.

CONCLUSION: On the basis of the present studies, it cannot be unequivocally said whether ASA influences people's vision and if people endangered with AMD progression or who are diagnosed with AMD should use this drug. It may increase the risk of AMD, but it can also reduce the risk of life-threatening conditions. The authors suggest that in order to avoid possible risks of AMD development, people who frequently take ASA should have their vision checked regularly.

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[A cross-sectional study of moderate or severe visual impairment and blindness in residents with type 2 diabetes living in Xinjing Town, Shanghai]. [Article in Chinese]

Bai XL, Xu X, Lu M, He JN, Xu X, Du X, Zhang B, He XG, Lu LN, Zhu JF, Zou HD, Zhao JL.

Objective: To investigate the prevalence, underlying causes and risk factors of moderate or severe visual impairment and blindness in a population with type 2 diabetes in Xinjing Town, Shanghai, China. Methods: A cross-sectional survey among local Han adult residents, who were previously diagnosed as type 2 diabetes, was conducted between October 2014 and January 2015. The survey was preceded by a pilot study; operational methods were refined and quality assurance evaluation was carried out. The best corrected visual acuity was recorded and classified following the modified World Health Organization grading system. Assigned ophthalmic doctors assured the leading causes of every blind or visually impaired eye. Binary logistic regression analysis was used to determine the related factors of blindness and moderate or severe visual impairment. Results: A total of 2 216 type 2 diabetic residents were enrolled, and 166 eyes (3.7%, 166/4 432) were blind. Cataract was the leading cause of blindness (39.8%); macular degeneration (18.0%) and eyeball atrophy (11.4%) were the second and third leading causes of blindness, respectively. Moderate or severe visual impairment was found in 376 eyes (8.5%, 376/4 432), and the most frequent cause was cataract (65.7%), followed by diabetic retinopathy (9.8%) and macular degeneration (9.4%). Older age, female gender, earlier onset diabetes and a lower spherical equivalent in the better eye were associated with best corrected visual acuity<20/63 in the better eye. Conclusion: The prevalences of moderate or severe visual impairment and blindness in our population with type 2 diabetes were high. (Chin J Ophthalmol, 2016, 52: 825-830).

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Genetics

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A Value-Based Medicine cost-utility analysis of genetic testing for neovascular macular degeneration.

Brown GC, Brown MM, Lieske HB, Lieske PA, Brown KS.

BACKGROUND: There is a dearth of patient, preference-based cost-effectiveness analyses evaluating genetic testing for neovascular age-related macular degeneration (NVAMD).

METHODS: A Value-Based Medicine, 12-year, combined-eye model, cost-utility analysis evaluated genetic testing of Category 3 AMD patients at age 65 for progression to NVAMD. The benefit of genetic testing was predicated upon the fact that early-treatment ranibizumab therapy (baseline vision 20/40-20/80) for NVAMD confers greater patient value than late-treatment (baseline vision ≤20/160). Published genetic data and MARINA Study ranibizumab therapy data were utilized in the analysis. Patient value (quality-of-life gain) and financial value (2012 US real dollar) outcomes were discounted at 3 % annually.

RESULTS: Genetic testing-enabled, early-treatment ranibizumab therapy per patient conferred mean 20/40 -1 vision, a 0.845 QALY gain and 14.1 % quality-of-life gain over sham therapy. Late-treatment ranibizumab therapy conferred mean 20/160+2 vision, a 0.250 QALY gain and 4.2 % quality-of-life gain over sham therapy. The gain from early-treatment over late-treatment was 0.595 QALY (10.0 % quality-of-life gain). The per-patient cost for genetic testing/closer monitoring was $2205 per screened person, $2.082 billion for the 944,000 estimated new Category 3 AMD patients annually. Genetic testing/monitoring costs per early-treatment patient totaled $66,180. Costs per early-treatment patient included: genetic testing costs: $66,180 + direct non-ophthalmic medical costs: -$40,914 + caregiver costs: -$172,443 + employment costs: -$14,098 = a net societal cost saving of $160,582 per early treatment patient. When genetic screening

facilitated an incremental 12,965 (8.0 %) of the 161,754, new annual NVAMD patients aged ≥65 in the US to undergo early-treatment ranibizumab therapy, each additional patient treated accrued an overall, net financial gain for society of $160,582. Genetic screening was cost-effective, using World Health Organization criteria, when it enabled an incremental 4.1 % (6634) of 161,754 annual NVAMD patients ≥65 years to receive early-treatment ranibizumab therapy.

CONCLUSIONS: Genetic screening-enabled, early-treatment ranibizumab therapy for NVAMD is cost-effective if it enables an incremental 4.1 % of the annual US cohort of new-onset NVAMD patients ≥65 to undergo early-treatment with ranibizumab.

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Protective effects of an HTRA1 insertion-deletion variant against age-related macular degeneration in the Chinese populations.

Ng TK, Liang XY, Lu F, Liu DT, Yam GH, Ma L, Tam PO, Chen H, Cen LP, Chen LJ, Yang Z, Pang CP.

Abstract: Age-related macular degeneration (AMD) is a leading cause of visual impairment and irreversible blindness in most developed countries, affecting about 50 million elderly people worldwide. Retinal pigment epithelial (RPE) cell degeneration is the pathophysiological cause of AMD, leading to geographic atrophy and choroidal neovascularization. We and others have previously identified several polymorphisms on chromosome 10q26 (HTRA1 rs11200638 as well as LOC387715 rs10490924 and c.372_815del443ins54) associated with AMD. In this study, we confirmed the association of our previously identified HTRA1 insertion-deletion (indel) variant (c.34delCinsTCCT) in 195 exudative AMD patients and 390 controls from the Hong Kong Chinese cohort with additional 168 patients and 210 controls from the Chengdu Chinese cohort and followed by studying its biological functions in RPE cells. Genetic analysis verified the higher prevalence of c.34delCinsTCCT allele in control subjects (8.0%) than in AMD patients (1.9%; P=7.87 × 10-5, odds ratio=0.229). This protective effect was validated as the haplotype of the c.34delCinsTCCT allele existed independent of the risk haplotype (P=1.17 × 10-5). In vitro studies showed that recombinant HTRA1 c.34delCinsTCCT variant protein was more localized in the endoplasmic reticulum of RPE cells compared with the wild-type protein, and its secretion was delayed. Moreover, ARPE-19 cells expressing HTRA1 c.34delCinsTCCT variant had higher cell viability, lower cell apoptosis and were less responsive to anoikis, supporting its protective role. We revealed a protective AMD-associated HTRA1 variant in Chinese populations and the biological role of HTRA1 in RPE cell degeneration, indicating its involvement in AMD pathogenesis.Laboratory Investigation advance online publication, 14 November 2016; doi:10.1038/labinvest.2016.117.

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Diet, lifestyle & low vision

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Nitroxide free radicals protect macular carotenoids against chemical destruction (bleaching) during lipid peroxidation.

Zareba M, Widomska J, Burke JM, Subczynski WK.

Abstract: Macular xanthophylls (MXs) lutein and zeaxanthin are dietary carotenoids that are selectively concentrated in the human eye retina, where they are thought to protect against age-related macular degeneration (AMD) by multiple mechanisms, including filtration of phototoxic blue light and quenching of singlet oxygen and triplet states of photosensitizers. These physical protective mechanisms require that

MXs be in their intact structure. Here, we investigated the protection of the intact structure of zeaxanthin incorporated into model membranes subjected to oxidative modification by water- and/or membrane-soluble small nitroxide free radicals. Model membranes were formed from saturated, monounsaturated, and polyunsaturated phosphatidylcholines (PCs). Oxidative modification involved autoxidation, iron-mediated, and singlet oxygen-mediated lipid peroxidation. The extent of chemical destruction (bleaching) of zeaxanthin was evaluated from its absorption spectra and compared with the extent of lipid peroxidation evaluated using the thiobarbituric acid assay. Nitroxide free radicals with different polarity (membrane/water partition coefficients) were used. The extent of zeaxanthin bleaching increased with membrane unsaturation and correlated with the rate of PC oxidation. Protection of the intact structure of zeaxanthin by membrane-soluble nitroxides was much stronger than that by water-soluble nitroxides. The combination of zeaxanthin and lipid-soluble nitroxides exerted strong synergistic protection against singlet oxygen-induced lipid peroxidation. The synergistic effect may be explained in terms of protection of the intact zeaxanthin structure by effective scavenging of free radicals by nitroxides, therefore allowing zeaxanthin to quench the primary oxidant, singlet oxygen, effectively by the physical protective mechanism. The redox state of nitroxides was monitored using electron paramagnetic resonance spectroscopy. Both nitroxide free radicals and their reduced form, hydroxylamines, were equally effective. Obtained data were compared with the protective effects of α-tocopherol, which is the natural antioxidant and protector of MXs within the retina. The new strategies employed here to maintain the intact structure of MXs may enhance their protective potential against AMD.

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